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*APPLICATION NUMBER:*

**22-009**

**MEDICAL REVIEW(S)**

**Clinical Review**

Joseph M. Porres MD, PhD  
NDA 22009, N-000  
Helioblock-SX

**CLINICAL REVIEW (addendum)**

Application Type: NDA

Submission Number: 22-009

Submission Code: N-000

Letter Date: February 8, 2008

Stamp Date: February 8, 2008

PDUFA Goal Date: March 31, 2008

Reviewer Name: Joseph M. Porres, MD, PhD

Through: Daiva Shetty, MD

Review Completion Date: March 19, 2008

Established Name: Helioblock SX

(Proposed) Trade Name: Anthelios 40

Therapeutic Class: Sunscreen

Applicant: L'Oreal USA

Priority Designation: S

Formulation: cream

Dosing Regimen: as needed

Indication: Prevention of sunburn

Intended Population: adults and children older than 6months

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Helioblock-SX

This is a review of the 120-day Safety Update, submitted by the sponsor on February 8, 2008, after the completion of the review of the NDA, and update on pediatric issues.

L'Oréal has not conducted any new preclinical studies on the formulation subject to this application nor on ecamsule.

The sponsor states that formulations covered by the approved NDA's 21-501, 21-502, 21-471, or by the pending NDA 22-009 are not being marketed anywhere else in the world.

**1. The safety update.**

This update covers the period from May 31, 2007 to January 31, 2008, and it contains the following information:

- Adverse events from L'Oréal sponsored clinical trials conducted under IND 57,850 on the formulation subject to the pending NDA during the time period noted above. All clinical study adverse events were non-serious and there were no drop-outs due to AE's. This information is summarized in the following table:

Study #	N#	Subject #	AE Type	Causality Status	Severity Status	Drop Outs due to AE
PEN 550.02	46	110	Neck Pain	Unrelated	Non serious	0
		118	Throat Inf.	Unrelated	Non serious	
		120	Pimples	Possibly Related	Non serious	
PEN 810.07	17	07	Severe Erythema	Possibly Related	Non serious	0
PEN 810.08	25	09	Runny Nose	Unrelated	Non serious	0
		09	Sore Throat	Unrelated	Non serious	
PEN 910.03	12					0

L'Oreal had submitted to the IND the following protocols:

Date	Protocols included	Protocol objective	Phase	subjects	Formulation
3/30/07	810.07	SPF determination	3	20	<del>_____</del> TiO2
	910.03	UVA determination	3	10	<del>_____</del> TiO2
	910.04	UVA determination	3	10	<del>_____</del> TiO2
6/5/07	550.02	comedogenicity	3	49	<del>_____</del> TiO2

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The sponsor states that these protocols were intended for an eventual request for a formulation change to the new formulation containing \_\_\_\_\_ titanium dioxide. This reviewer has not been able to identify a submission for protocol 810.08, for which

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AEs are reported in the 120 day safety update. No finalized reports have been submitted for any of these studies

- Spontaneous adverse events on products marketed in the US by L'Oréal under NDA's 21-501, 21-502 and 21-471, from launch through January 31, 2008, with the majority being included in the respective Quarterly Period Safety Updates submitted by L'Oréal. There have been no Serious Adverse Events (SAE's) and therefore no 15-day reports have been made. This information is summarized in the following table:

NDA #	Brand	Launch To 01/31/08	4Q '07	Total Reports	AE per Body System*		
					Eye	Skin	LoE**
21-501	Vichy Capital Soleil 15	1	0	1			
	LRP Anthelios 15	1	1	1			
					0	4	1
21-502	Kiehl's UV Protective	1	1	1			
	LRP Anthelios SX	103	11	103			
	L'Oreal Revitalift UV	30	19	30			
	Vichy UV Active	0	0	0			
					33	90	7
21-471	Lancome UV Expert 20	15	2	15			
	Kiehl's UV Protective Suncare	0	0	0			
<b>TOTALS</b>		<b>151</b>	<b>34</b>	<b>151</b>	<b>5</b>	<b>12</b>	<b>4</b>

NOTE: There have been NO serious adverse events reported

\* Some reports encompassed multiple AE Terms

\*\* Lack of Effect

- L'Oréal markets numerous other ecamsule-containing formulations globally, and their safety is monitored via the L'Oréal's cosmetovigilance system. Two serious AEs have been reported, both of which resulted in hospitalization:
  - 2006LO002964. UK. 25/April/06. A 50 year old female developed an allergic reaction and swollen eyes 3-days after using Ambre Solaire Ultra Moisturizing Protection Spray SPF 15 (formula 292924/2) and 1-day after using Ambre Solaire Clear Protect SPF 10 (formula 293806) on the face. The products carry a warning that they should not to be sprayed directly on the face. The female recovered after discontinuing the product. Patch tests with the ingredients were negative and cutaneous allergy could not be confirmed. The investigator consider the AE unrelated to treatment.

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*Reviewer comment: This report from the UK probably does not represent an allergic reaction but this reviewer considers that a treatment related irritant reaction cannot be ruled out.*

- 2007LO008727. Netherlands. ———. A 69 year old male developed itch and a burning sensation, and chapped skin on arms and body 15 minutes after using both Ambre Solaire Spray SPF 15 (formula 293984/2) and Ambre Solaire UV Sensitive SPF 50 (formula 736819) on a first day of sun exposure. Later, arms and hands swelled and the skin thickened and became chapped. Five days later the subject was hospitalized for 8 days, and the manifestations did not resolve rapidly upon discontinuation of the products. A positive patch test was obtained with one of the products (unspecified), but repeated Open Application Test was negative. A provisional diagnosis of actinic reticuloid was adopted. The subject had had a similar reaction 3 years earlier. The investigator consider the AE unrelated to treatment.

**b(6)**

*Reviewer comment: This reviewer concurs that the report from The Netherlands probably does not represent a treatment-related AE.*

The 120-day safety update does not include a review of the recent literature. L'Oreal send a submission dated February 26, 2008, in which the sponsor states that a literature search has been extended to January 31, 2008, and has not found new information that would impact the safety or safety labeling of ecamsule containing sunscreen products.

*Reviewer comment: This reviewer has conducted a PubMed search for safety related publications on ecamsule and found no new publications.*

In conclusion, the safety data that has been submitted in the 120-day safety update does not preclude the approval of Helioblock SX SPF40.

**2. Pediatric issues:**

**2.1 Extrapolation of efficacy to the pediatric population:**

The efficacy of Helioblock SX in protecting against UVB and UVA was reviewed by Michael L. Koenig Ph.D., on January 4, 2008.

UVB protection is measured by determining the SPF (sun protecting factor) value (i.e., effectiveness). In the US, the determination of SPF for OTC sunscreen drug products is detailed in 21 CFR part 352 subpart D. SPF is recognized by FDA and other regulatory bodies around the world as a valid and appropriate measure of sunscreen effectiveness against UVB radiation. Furthermore, U.S. consumers recognize SPF as the measure of protection against sunburn, which is caused primarily by UVB radiation.

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A standard sunscreen with a known SPF value is tested concurrently with each test formulation to ensure the test results are valid. Subjects are exposed to a geometric series of increasing amounts of radiation (§ 352.73(b)) in the absence or presence of a sunscreen to determine the MEDUS (MED unprotected skin) or MEDPS (MED protected skin), respectively. MED (minimum erythema dose) is defined as the amount of light energy required to produce the "first perceptible, redness reaction with clearly defined borders 22 to 24 hours after exposure" (§ 352.73(c)). SPF is defined as the ratio of MEDPS to MEDUS (§ 352.73(c)). Thus, sunscreen effectiveness directly correlates to the SPF value. SPF values are determined for each subject enrolled in the study, and a mean SPF value is calculated for the group.

The testing procedure in the monograph suggests that studies should include males and females. Ideally, the studies would enroll equal numbers of males and females as well as pediatric subjects. The studies actually included more females than males, some studies including only females. However, Dr. Koenig concluded that it does not seem unreasonable to extrapolate the findings to males or to children over 6 months (as labeled under the sunscreen monograph), and that there is no apparent anatomical or physiological difference between female and male skin or the skin of adults and children (over 6 months) that suggest there may be significant differences in protection provided by a sunscreen for these groups. Based on the review of five clinical and one in vitro studies, the reviewer concluded that Helioblock SX cream provides effective protection from skin damage due to both UVB and UVA radiation, and that, consistent with the OTC sunscreen drug monograph (21 CFR part 352), these formulations are effective for children older than 6 months of age.

The mechanism of action of a sunscreen is based on its functioning as a barrier to light and this effect should be independent of the age of the subject. This reviewer considers it appropriate to extrapolate efficacy down to 6 months of age.

#### 2.2 Pediatric safety:

The sponsor has requested a waiver from supplying use information in the pediatric population under 6 months of age for Helioblock SX Cream in the prevention of sunburn and skin damage following chronic exposure to ultraviolet radiation. The sponsor states that a partial waiver is requested because Helioblock SX is very similar in composition and identical in indication for use to three other L'Oreal sunscreen products containing combinations of the same three or four sunscreen active ingredients in varying amounts that were granted PREA partial waivers for the following reasons:

- a) In children less than 6 months of age non-chemical protection should be the main modality used to protect young infants from sun exposure, and
- b) the use of sunscreen products in infants less than 6 months of age may lead to inappropriately high systemic levels of the ingredients and pose safety concerns.

The sponsor further states that the use of Helioblock SX would be inappropriate in children under 6 months for the following reasons:

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1. Infants under 6 months of age should not be exposed to the sun.
2. Infants are extremely sensitive to UV damage and the adverse events of solar exposure. Furthermore, they are unable to respond to injury by movement or gaining parental attention.
3. Sunscreen application in infants has the potential to increase exposure to UV radiation and solar heat due to parents' confidence in its protective properties.
4. Infants have skin barrier and metabolic properties that may expose them inappropriately to proportionally high levels of sunscreen chemicals. Their skin barrier is not fully developed, and its relative size to weight can contribute to excessive blood levels of active and inactive ingredients. Infants' sweating mechanisms can be negatively affected by topical products, leading to overheating.
5. An FDA panel specifically reviewing sunscreen ingredients highlighted the inappropriateness of their use on children under the age of 6 months because of potential underdevelopment of systems which metabolize and excrete drugs absorbed through their skin.<sup>1</sup> The FDA sunscreen monograph recommends avoiding all sunscreen use before 6 months of age<sup>2</sup>.

In response to an earlier request by the Agency to conduct PK studies in children, the sponsor states that PK studies in children younger than 6 months would be impractical and place these children at unacceptable risk because:

1. Infants would be exposed to potentially inappropriate levels of chemicals based on their physiologic skin absorptive characteristics.
2. Methods requiring blood draws and the use of radioactive markers have unknown risks making it unethical to conduct pk studies, and it is believed that parents and IRBs would not provide consent for such exposure.
3. Very few prospective scientific studies on infant vulnerability to sun or sunscreen exposure have been performed due to the ethical considerations of infant testing

The sponsor further states that efficacy studies would also be impractical because infants would need to be exposed to UV radiation with the potential for AEs (heat, pain, erythema, swelling, overheating, dehydration, and contribute to melanoma development later in life) and limited, if any, benefit.

Dr. Hari Sachs, from the Office of New Drugs, Immediate Office Pediatric and Maternal Health Staff, was consulted regarding the need for additional studies in children. She commented that "Consideration should be given to requesting both pharmacokinetic and "actual use" safety studies in patients less than 6 months of age presuming that the studies in older children do not reveal any safety concerns. She further states that:

- Pharmacokinetic studies have not been performed in children as the lack of systemic absorption has been inferred from adult and preclinical data. Thus, consideration should be given to obtaining pharmacokinetic data in pediatric age groups 6 months to 12 years to confirm that drug is not systemically absorbed when used in this combination as the extent of absorption has not been directly tested. PMHS acknowledges that designing and conducting these studies may be

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quite challenging. In particular, ethical constraints may complicate the performance of these studies in otherwise healthy infants. In the waiver request, the Sponsor argued that conduct of PK studies would require blood sampling in infants and exposure to radioactive labels. A subset of the PK studies in adults did not require the use of radioactive labels for ecamsule. Therefore, as long as blood drawing limits are closely adhered to, a properly-designed, sparse sampling or population PK study would be ethical. A single blood draw is usually considered to be "minimal risk."

- An "actual use" open-label, safety study such as the one performed in older children 6 months to 12 years would not require sun exposure in "untreated" children and if the population was selected properly, infants who would otherwise be at risk by virtue of sun-exposure (e.g., while on vacation or at the swimming pool) could be enrolled. Existing clinical guidelines would need to be followed (e.g., avoid peak sun, use clothing, umbrellas, etc.) so that studies are conducted according to an appropriate pediatric standard of care. The product would need to be used according to labeled directions (e.g., apply only to face and hands) without mandating exposure to excessive levels of the product (which would be unethical).

*Reviewer comment: If PK studies were conducted in children younger than 6 months and showed high absorption of ecamsule, the products would remain labeled for use by children 6 months and older; if PK levels were not high, it would not affect labeling because there are other safety concerns in children younger than 6 months: Children of that age are likely to inadvertently smear the sunscreen in the eyes, possibly causing irritation, or in their mouths, causing the ingestion of small amounts of sunscreen. If PK studies would not produce useful data, it would be difficult to justify performing venipunctures in small children.*

*If actual use studies were to be conducted, their design would be difficult because one would have to decide whether to conduct the study with sun exposure, which is not recommended for children younger than 6 months of age, and what area of application should be chosen. Here, the monograph does not recommend the use of sunscreens below 6 months of age, let alone maximal exposure. If a safety signal was detected under maximal exposure, it would not change the recommendation to not use below 6 months of age. And if no safety signal is found in that age group, still labeling would not be changed because there are other reasons for not using sunscreen in that age group, as stated in the previous paragraph.*

*For these reasons, this reviewer considers that little potential benefit could be expected from the conduct of PK or actual use studies to justify performing venipunctures in small children.*

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Conclusions:

As stated in my review of this NDA, Section 8.4 Pediatrics, the pediatric exposure includes adults and children down to 6 months of age, and this reviewer concludes that there is sufficient safety data down to 6 months of age. In the review of the safety data submitted with the NDA and with the 120 day safety update, this reviewer has not identified any adverse events reported in children younger than 6 months.

This reviewer recommends the partial waiver be granted because in children under 6 months of age, PK studies would be highly impractical and unlikely to produce safety data that would be useful or that would lead to changes in labeling.

Actual use studies in children under 6 months of age would be of difficult to design, of questionable value if performed in the absence of sun exposure, and should not be performed under sun exposure conditions because it is not recommended that children younger than 6 months of age be exposed to the sun, and sunscreens are not recommended for that age under the sunscreen monograph.

This reviewer recommends that labeling retains the recommendation to avoid using the product in children under 6 months of age because without such wording, parents may be more inclined to use sunscreen liberally in this population, possibly leading to at least inadvertent eye irritation.

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<sup>1</sup> Federal Register: Sunscreen drug products for over-the-counter human use. Tentative final monograph. 1993 May 12; 58 (90): 28194-28241.

<sup>2</sup> Meurer LN et al. What is the appropriate use of sunscreen for infants and children? J. of Fam Practice 2006. 55 (5): 437, 440, 444.

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/s/

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3/20/2008 09:22:17 AM  
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NDA 22009, N-000  
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## CLINICAL REVIEW

Application Type: NDA  
Submission Number: 22-009  
Submission Code: N-000

Letter Date: May 31, 2007  
Stamp Date: May 31, 2007  
PDUFA Goal Date: March 31, 2008

Reviewer Name: Joseph M. Porres, MD, PhD  
Through: Daiva Shetty, MD  
Review Completion Date: February 7, 2008

Established Name: Helioblock SX  
(Proposed) Trade Name: Anthelios 40  
Therapeutic Class: Sunscreen  
**Applicant: L'Oreal USA**

Priority Designation: S

Formulation: cream  
Dosing Regimen: as needed  
Indication: Prevention of sunburn  
Intended Population: adults and children older than 6months

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## 1. EXECUTIVE SUMMARY

**L'Oreal USA is seeking approval for OTC marketing** of Helioblock-SX SPF40 Sunscreen Cream (HSX) for adults and children older than 6 months, for the prevention of sunburn.

### 1.1 Recommendation on Regulatory Action

Upon review of the submitted safety data, the safety profile is acceptable. From the safety perspective, Helioblock-SX SPF40 Sunscreen Cream (ecamsule 3%, avobenzone USP 2%, octocrylene USP 10%, and titanium dioxide USP 5%) may be approved for OTC marketing. Final approvability depends on the recommendations of the reviewers of the data submitted for efficacy, preclinical, biopharmaceutics, chemistry, and labeling.

This reviewer recommends that Helioblock-SX SPF40 Sunscreen Cream be approved for use as needed for the prevention of sunburn in adults and in children 6 months of age and older.

### 1.2 Recommendation on Postmarketing Actions

#### 1.2.1 Risk Management Activity

No postmarketing risk management activities are recommended.

#### 1.2.2 Required Phase 4 Commitments

None.

#### 1.2.3 Other Phase 4 Requests

None.

### 1.3 Summary of Clinical Findings

#### 1.3.1 Brief Overview of Clinical Program

**L'Oreal is seeking approval for OTC marketing** of Helioblock SX SPF 40 Sunscreen Cream (HSX) for adults and children older than 6 months, for the prevention of sunburn.

HSX contains 4 sunscreen ingredients, three of which (avobenzone USP 2%, octocrylene USP 10%, and titanium dioxide USP 5%) are sunscreen ingredients already marketed in the US under

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the Final Monograph for Sunscreen Drug Products for OTC Human Use. The fourth, ecamsule, has been marketed outside the U.S. since 1993, and it is an ingredient in three sunscreens approved in the US for OTC use, for daily use in adults and children six months of age and older: [redacted] SPF15 Water Resistant (NDA 21-501, approved 10/2/06), [redacted] SPF 15 lotion (NDA 21-502, approved 7/21/06), and [redacted] SPF 20 Water Resistant (NDA 21-471, approved 10/6/06) .

b(4)

The following table compares the formulations of the various [redacted] products:

b(4)

TABLE 1. FORMULATION OF THE [redacted] PRODUCTS				
Product name	Helioblock SX SPF40 Cream	[redacted] SPF 20 W/R Cream	[redacted] SPF 15 Daily Use Cream	[redacted] SPF 15 W/R Cream
Formula #	760.001	539.106	539.009	760.006
IND #	57,850	59,126	59,126	59,126
NDA	22-009	21-471	21-502	21-501
Active ingredient:				
Ecamsule	3%	2%	2%	3%
Avobenzone	2%	2%	2%	2%
Octocrylene	10%	10%	10%	10%
Titanium dioxide	5%	2%	-	-

b(4)

The safety of ecamsule as a 2% formulation has been assessed in NDA 21-471, and as a 3% formulation in NDA 21-501. HSX differs from the approved [redacted] SPF15 W/R Cream in the addition of titanium dioxide, and from the approved [redacted] SPF20 W/R Cream in the content of ecamsule (3% in HSX as opposed to 2% in [redacted] SPF20 W/R) and in the content of titanium dioxide (5% in HSX as opposed to 2% in [redacted] SPF20 W/R).

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b(4)

In support of this application, the sponsor has submitted data from several studies, conducted under the [redacted] IND 57,850, as shown in the following table:

b(4)

TABLE 2. LIST OF STUDIES SUBMITTED TO SUPPORT THE APPLICATION	
Study	Objective
2604	Contact sensitization and irritation. Phase 1
2605	Phototoxicity. Phase 1
2606	Photosensitization. Phase 1
2607	Pharmacokinetics. Phase 1
V99.1203	Dermal absorption of C <sup>14</sup> ecamsule. Phase 2
V3156	Urinary excretion of ecamsule. Phase 2
2612	SPF determination of Helioblock SX. Phase 2
18045	SPF determination of Helioblock SX and its triads. Phase 2
2613	Determination of UVA Protection Factor of Helioblock SX and its triads. Phase 2
2614	Determination of UVA Protection Factor of Helioblock SX and its triads using the 8-MOP method. Phase 2
2639	SPF determination of Helioblock SX by two different methods. Phase 2
2616	Safety and efficacy of Helioblock SX vs. a triad and a pair of filters. Phase 3
18057	Safety and efficacy of Helioblock SX vs. two triads of filters. Phase 3
18047	Open label long term safety of Helioblock SX in patients with PLE.
750.01	Open label long term safety of [redacted] SPF 15 Daily Use Cream
750.02	Open label long term safety of [redacted] SPF 15 W/R Cream

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750.03	Open label long term safety of [redacted] SPF 20 W/R Cream
1010.02	Transepidermal water loss
750.04	Long term safety with [redacted] Titanium dioxide

b(4)

All of these studies have already been submitted and reviewed under NDA 21-501, NDA 21-502, and NDA 21-471.

The sponsor is also submitting data from two new studies, PEN1010.02 (transepidermal water loss), and PEN750.04 (a safety study in children), that are reviewed in the Appendix. The sponsor has also submitted data from 14 uncontrolled (cosmetic) EU pediatric safety studies that were not part of the [redacted] IND 57,850, and were not always in compliance with full GMP for manufacturing of study drug. These EU studies are summarized in the Appendix.

b(4)

On 3/1/06 L'Oreal submitted IND 57,850, serial #30, indicating that the HSX's formulation was changing from the pigmentary (formulation [redacted]) to the [redacted] version of titanium dioxide (formulation 283419), which is coated with aluminum and stearic acid, and that the sponsor was conducting in Canada clinical studies with the new formulation to assess photoallergy, phototoxicity, comedogenicity, repeat insult patch testing, and moisturization. It included Protocol 750.04 to assess long-term safety in 135 subjects age 6 months to 12 years. This study is summarized in the Appendix.

b(4)

[redacted]

b(4)

The new clinical study PEN.1010.02 included in the application, to support the cosmetic claim of moisturizing, is the only study in which both a pigmentary and a [redacted] titanium dioxide were compared.

b(4)

### 1.3.2 Efficacy

The sponsor is seeking approval to market HSX for the prevention of sunburn.

In support of product efficacy, the sponsor has submitted results of five controlled clinical studies. These studies include the following:

- Three sun protection factor (SPF) determination studies.
- Two studies for the determination of UVA (PFA) protection factor.

All of these studies have already been submitted and reviewed under NDA 21-501, NDA 21-502, NDA 21-471.

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**1.3.3 Safety**

A total of 3208 subjects have been exposed to ecamsule containing sunscreen formulations as follows:

- 1268 subjects have been exposed to the HSX formulation in Phase 1, 2, and 3 clinical studies (studies 1-15, Table 3). There were no drug-related deaths or drug-related serious adverse events reported among the participants in clinical trials. In these studies, 86 subjects reported a total of 125 AEs. Seven adverse events (skin infection, pruritus, and eczema) were assessed as probably or possibly related to treatment; all were mild and non-serious. A total of 31 subjects in clinical studies discontinued due to adverse events (AEs). Out of those, 12 were assessed as probably, possibly or definitely related to study drug. All of these 12 AEs were related to local skin irritation and all of them resolved. A total of 475 subjects were exposed to HSX during a long-term safety study (RD.06.SRE.18047). Long-term study RD.06.SRE.18047 has been reviewed in detail under NDA 21-501, and NDA 21-502. According to the clinical reviewers, except for sunburn, adverse events that were considered to be possibly related to the study products were of low incidence and minor severity.
- Additionally, 1940 subjects (Table 4) were exposed to other ecamsule-containing sunscreen drug products, as follows:
  - 708 subjects during long-term safety studies with ecamsule containing formulations (248 subjects in 750.01, with [redacted] SPF 15, Daily use cream; 246 subjects in 750.02, with [redacted] 15 W/R Cream; 79 in 750.03, with [redacted] SPF 20 W/R Cream; 135 subjects in 750.04, with a HSX-like formulation containing [redacted] titanium dioxide).
  - 1232 in other safety and efficacy studies (Table 4) in the [redacted] development program.

b(4)

b(4)

Drug-related adverse events reported during these long-term [redacted] clinical studies were limited to Skin and Appendages Body System and Special Senses. A total of 66 drug related AEs were reported in Skin and Appendages System and four in the Special Senses System. None of these events were assessed by the investigator as serious and all of them resolved. The profile of drug-related AEs was consistent across the three long-term studies, except for PEN.750.01 where a higher number of acne events were reported. The following AEs were the most common (incidence of  $\geq 1\%$  in individual studies) treatment-related AEs in the three long-term [redacted] studies: acne, dermatitis, dry skin, eczema, erythema, pruritus, skin discomfort, and sunburn.

b(4)

b(4)

Study PEN 750.04 (reviewed in detail in the Appendix) was a long term safety study conducted in 135 children 6 months to 12 years, and it was conducted with a formulation containing a [redacted] titanium dioxide [redacted] titanium dioxide. The study called for treatment up to six months and it defined as treatment compliant those subjects who used the sunscreen for at least 14 sun exposure days. In the study, 80 % of subjects used treatment for less than 80 days, 50% of subjects used the sunscreen for less than 50 days, and 30% of subjects for less than 30 days. Although the study objective was met regarding compliance with 14 days of sun exposure, this reviewer considers that the length treatment exposure in the study is insufficient for the assessment of long term safety in a 6-month study. Nevertheless, the study does provide some useful safety data and revealed no safety concerns.

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The long term safety studies (750.01, 750.02, and 750.03) conducted with other ecamsule containing [REDACTED] formulations containing some of the same ingredients found in HSX support the safety of HSX. The EU Pediatric Cosmetic Use studies in 363 children , 6 month to 12 years of age, support the safety of ecamsule. b(4)

Postmarketing AEs reported to the sponsor did not reveal any serious safety issues. The most common AEs in the postmarketing database are consistent with the AE profile from the clinical trials.

### 1.3.4 Dosing Regimen and Administration

The proposed dosing directions for HSX are:

- apply liberally 15 minutes before sun exposure
- reapply as needed or after towel drying, swimming, or perspiring
- children under 6 months of age: ask a doctor

### 1.3.5 Drug-Drug Interactions

No formal drug-drug interaction studies have been conducted with HSX. The sponsor states that ecamsule and its combination formulations are poorly absorbed (<1%) when topically applied to the skin, and therefore, it is unlikely that interactions with systemic medications would occur. Subjects who participated in the clinical trials were allowed to use any systemic or topical treatments. There were no safety signals noted due to a particular drug-drug interaction.

### 1.3.6 Special Populations

Exposure to treatment in pediatric population has been limited. Nevertheless, there did not appear to be a specific association of adverse reactions with pediatric use of the other [REDACTED] sunscreens. This issue is discussed in detail in Section 8.4. b(4)

Based on the preclinical pharmacology data, ecamsule is a Pregnancy Category B drug. The proposed labeling does not carry any pregnancy warning.

## 2. INTRODUCTION AND BACKGROUND

This is a medical safety review of HSX.

### 2.1 Product Information

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HSX is a combination of two mainly UVB (octocrylene 10% and titanium dioxide 5%) and two mainly UVA (ecamsule 3%, avobenzone 2%) ultraviolet filters. The rationale for the combination of the four filters is to provide a strong and continuous protection across the entire ultraviolet spectrum. Avobenzone, octocrylene, and titanium dioxide are Category 1 sunscreens in the Final Monograph for OTC sunscreen drug products. The monograph permits the use of octocrylene and titanium dioxide in a single sunscreen product in approved concentrations, and the concentrations of these ingredients in HSX are within the approved ranges. Ecamsule has been marketed outside the U.S. since 1993, and it is an ingredient in three sunscreens approved in the US for OTC marketing, for daily use in adults and children six months of age and older:

- [redacted] SPF15 Water Resistant (NDA 21-501, approved 10/2/06) b(4)
- [redacted] SPF 15 lotion (NDA 21-502, approved 7/21/06)
- [redacted] SPF 20 Water Resistant (NDA 21-471, approved 10/6/06)

The sponsor is requesting to market the HSX formulation under three different brand names:

1. [redacted] b(4)
2. ANTHELIOS 40
3. [redacted]

**2.2 Currently Available Treatment for Indications**

The Final Monograph for Sunscreen Drug Products for OTC Human Use includes 16 active sunscreen ingredients currently available for US marketing for the prevention of sunburn. Ecamsule is an ingredient in three sunscreens approved in the US for OTC use.

**2.3 Availability of Proposed Active Ingredient in the United States**

Three of the four active ingredients contained in HSX are available in the US under the Final Monograph for Sunscreen Drug Products for OTC Human Use. The fourth, ecamsule, has been marketed outside the U.S. since 1993, and it is an ingredient in three sunscreens approved in the US for OTC marketing, for daily use in adults and children six months of age and older:

- [redacted] SPF15 Water Resistant (NDA 21-501, approved 10/2/06)
- [redacted] SPF 15 lotion (NDA 21-502, approved 7/21/06) b(4)
- [redacted] SPF 20 Water Resistant (NDA 21-471, approved 10/6/06)

**2.4 Important Issues With Pharmacologically Related Products**

There are no known serious safety issues with pharmacologically related products.

**2.5 Presubmission Regulatory Activity**

Ecamsule was studied under IND 57,850 to assess dermal safety, and to assess sun protecting factor for UVA and UVB. All of these studies have already been submitted and reviewed under NDA 21-501, NDA 21-502, and NDA 21-471. [redacted]

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[REDACTED]

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The sponsor states that variations among the four ecamsule containing formulations in the [REDACTED] development plan, other than the quantity of active ingredients, are minor, and as such, much of the safety information is common to all four new drug applications (3 [REDACTED] and 1 Helioblock NDAs). This reviewer concurs with this conclusion.

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The sponsor sought regulatory guidance and advice from FDA on several occasions during the development phase of the products. The present NDA was submitted without a PRE-NDA meeting.

## **2.6 Other Relevant Background Information**

Ecamsule (terephthalydene dicamphor sulfonic acid) has been marketed as a sunscreen ingredient under the trademark name Mexoryl ® SX. It is a broad spectrum UVA filter with an optimum absorbance at 344 nm, and fills the gap of spectrophotometric absorbance between octocrylene (peak absorbance at 303 nm) and avobenzone (peak absorbance at 358nm). Its combination with the other three UV filters is complementary and provides continuous protection across the entire UV spectrum (290-400 nm).

**L'Oreal states that the EEC Cosmetics Directive** Annex VII authorizes the use of ecamsule, expressed as an acid, for use up to a maximum concentration of 10%. Ecamsule was registered with the Australian health Authorities in 1995 and with the Canadian Health Protection Bureau in 1994. Ecamsule containing formulations are beginning to be marketed in those countries but with formulations that are different from HSX (see Table 1 for differences in formulation).

Sunscreen products are considered cosmetics in all other countries with the exception of Canada and Australia.

Since its commercial introduction in 1993, nearly [REDACTED] units of sunscreen products containing ecamsule in combination with other EU approved UV filters have been sold in Europe and globally.

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## **3. SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES**

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### 3.1 CMC (and Product Microbiology, if Applicable)

There are no outstanding CMC issues pending from earlier reviews.

### 3.2 Animal Pharmacology/Toxicology

The sponsor conducted a total of 87 animal and toxicology studies under the HSX development program. Neither ecamsule, nor HSX was teratogenic, carcinogenic, or photocarcinogenic. There was no embryoletality or reproductive toxicity associated with ecamsule alone or with the other active sunscreen ingredients contained in the proposed drug product. The acute oral toxicity dose in the rat was 5000 mg/kg and in the mouse, 2000 mg/kg.

## 4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

### 4.1 Sources of Clinical Data

The sponsor has provided a series of studies to support the safety of the HSX formulation as shown in Table 2.

The sponsor has also conducted other supportive studies with the following formulations:

- [REDACTED] SPF 15 W/R Lotion (NDA 21-501)
- [REDACTED] SPF 15 Daily Lotion (NDA 21-502)      **b(4)**
- [REDACTED] SPF 20 W/R Lotion (NDA 21-471)

These formulations include some of the HSX sunscreen filters, as shown in Table 1. These studies have been submitted and reviewed previously for other NDAs and will not be reviewed here.

The sponsor has also conducted in Europe 14 uncontrolled (cosmetic) pediatric safety studies in 363 children with 526 exposures (some children participated in more than one study). These studies were conducted with formulations containing the same four sunscreen ingredients found in HSX but could contain additional ingredients or higher concentrations of the same four filters. These studies were not part of the original [REDACTED] IND program but were completed in response to revised cosmetic EU regulations requiring safety testing of the to-be-marketed products in the targeted population. The sponsor states that although these studies were conducted according to cosmetic guidelines and not always in compliance with full GMP for manufacturing of study drug, the studies do support the safe use of HSX in pediatrics. These studies are summarized in the Appendix. **b(4)**

The sponsor has submitted data from two new clinical studies: Study PEN.1010.02, to support the cosmetic claim of moisturizing, and PEN750.04, a safety study in children. These are reviewed in the Appendix.

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## 4.2 Tables of Clinical Studies

The sponsor has studied the HSX formulation in the following studies:

TABLE 3. STUDIES WITH HSX SUBMITTED TO SUPPORT THE APPLICATION			
#	Study	Objective	Subjects
1	2604	Contact sensitization and irritation	207
2	2605	Phototoxicity	30
3	2606	Photosensitization	112
4	2607	Pharmacokinetics	6
5	V99.1203	Dermal absorption of C <sup>14</sup> ecamsule	5
6	V3156	Urinary excretion of ecamsule	7
7	2612	SPF determination of Helioblock SX	23
8	18045	SPF determination of Helioblock SX and its triads	41
9	2613	Determination of UVA Protection Factor of Helioblock SX and its triads	60
10	2614	Determination of UVA Protection Factor of Helioblock SX and its triads using the 8-MOP method	11
11	2639	SPF determination of Helioblock SX by two different methods	25
12	2616	Safety and efficacy of Helioblock SX vs. a triad and a pair of filters.	87
13	18057	Safety and efficacy of Helioblock SX vs. two triads of filters. Phase 3	144
14	18047	Open label long term safety of Helioblock SX in patients with PLE	475
15	1010.02	Transepidermal water loss	35
		Total	1268

Additionally, ecamsule has been studied in other [ ] formulations, as follows:

b(4)

TABLE 4. STUDIES WITH ECAMSULE CONTAINING SUNSCREENS			
750.01	Open label long term safety of [ ] SPF 15 Daily Use Cream	248	708 subjects
750.02	Open label long term safety of [ ] SPF 15 W/R Cream	246	
750.03	Open label long term safety of [ ] SPF 20 W/R Cream	79	
750.04	Long term safety with [ ] Titanium dioxide	135	1232 subjects
110.01	Repeat Insult Patch test	223	
210.01	Photoallergy	137	
250.01	Phototoxicity	26	
570.01	Comedogenicity	44	
570.02	Comedogenicity	30	
810.05	SPF	50	
810.06	SPF	100	
910.02	UVA	70	
810.01	SPF	21	
810.02	SPF	20	
820.01	SPF	21	
820.02	SPF	25	
910.01	UVA	32	
920.01	UVA	14	
99001	SPF	24	
1010.01	Moisturization	32	
EU	Pediatric Cosmetic Studies	363	
	Total		1940

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A total of 3208 subjects have used an ecamsule containing sunscreen at least once in a clinical study.

**4.3 Review Strategy**

This review covers safety data submitted to support NDA 22-009, which were previously submitted to support NDA 21-501, NDA 21-502, and NDA 21-471, and which have been reviewed by the reviewers in the Division of Dermatologic and Dental Drug Products (DDDDP), and by the medical reviewers and the interdisciplinary scientist in the Office of Nonprescription Products (ONP).

**4.4 Data Quality and Integrity**

Most of the studies submitted to support the application were previously submitted to support NDA 21-501, NDA 21-502, and NDA 21-471 and were reviewed at that time. Two additional studies have been included for this submission, PEN.1010.02, and PEN.750.04. During the review, there were no discrepancies noted either in data or its analyses. No new DSI audits have been conducted for this NDA.

**4.5 Compliance with Good Clinical Practices**

All clinical studies were conducted under the sponsorship of the applicant and its affiliates and were reviewed and approved by Independent Ethics Committees and Institutional Review Boards. Informed consent from participants was obtained in accordance with 21 CFR parts 50 and 56 or 312.120. The full clinical program was performed in compliance with Good Clinical Practice (GCP) including archiving of essential study documents.

The sponsor states that 14 cosmetic studies were conducted outside of the U.S. with a study product not manufactured according to Good Manufacturing Practices.

**4.6 Financial Disclosures**

The sponsor submitted Form 3454 certifying that the investigators lacked of any significant financial interest in these products for the following clinical studies: 2612, 2613, 2614, 18045, 2639, 2616, 18057, 18047. The sponsor lists several investigators for which only partial disclosure was available.

**5. CLINICAL PHARMACOLOGY****5.1 Pharmacokinetics**

Three in vivo (1.CG.03.SRE.2607, V99.1203, and V3156) pharmacokinetic studies showed low

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percutaneous absorption of ecamsule using different methodologies and analysis methods. For detailed review of the studies, refer to the discipline-specific reviews.

## **5.2 Pharmacodynamics**

There are no pharmacodynamic data submitted to this NDA.

## **5.3 Exposure-Response Relationships**

There are no exposure-response studies submitted to this NDA.

# **6. INTEGRATED REVIEW OF EFFICACY**

## **6.1 Indication**

The sponsor is seeking to market OTC the HSX sunscreen drug product for the prevention of sunburn.

In support of product efficacy, the sponsor submitted results of five controlled clinical studies. These studies include the following:

- Three sun protection factor (SPF) determination studies.
- Two studies to determine the UVA (PFA) protection factor.

All of these studies have been reviewed by other reviewers in ONP. The reviewer of the efficacy data concluded that based on the clinical and in vitro studies submitted to support the NDA, HSX provides effective protection from both UVA and UVB radiation.

# **7. INTEGRATED REVIEW OF SAFETY**

## **7.1 Methods and Findings**

Safety data to support the NDA comes from different sources:

- Phase 1, 2, and 3 clinical studies

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- Phase 3 long-term safety studies
- Post-marketing safety data
- Review of the literature

Table 3 lists the supporting studies.

All the studies were conducted on healthy subjects except for the following studies that were conducted in subjects with polymorphous light eruption: 2616 (Phase 2 safety and efficacy study in PLE subjects), 18057 (Phase 3 safety and efficacy study in subjects with PLE), and 18047 (long term safety assessment study in PLE subjects). PLE subjects used sunscreen for the prevention of flare-ups rather than as treatment for the condition, and it is therefore reasonable to consider them as healthy subjects at the time of study.

All of these studies, except for PEN.1010.02 and PEN.750.04 have been reviewed previously for NDA 21-501, NDA 21-502, and NDA 21-471, and those reviewers concluded that the safety of the HSX formulation had been adequately established. Previous reviewers concluded that the dermal safety studies, 2604, 2605, and 2607, were adequate to conclude that there was little or no potential for significant irritation, contact sensitization, phototoxicity, or photosensitization.

To support the safety of the HSX formulation the sponsor quotes other studies conducted with other ecamsule containing formulations in the [ ] development program, as shown in Table 4. **b(4)**

#### 7.1.1 Deaths

There were no deaths in the Phase 1, 2, and 3 clinical studies conducted with HSX.

#### 7.1.2 Other Serious Adverse Events

There were no serious adverse events related to treatment in the clinical studies submitted to support the application.

There were 32 subjects with serious adverse events in the four long-term safety studies (18047, conducted with the HSX formulation, and 750.01, 750.02, and 750.03, conducted with other [ ] formulations that share ingredients with HSX.). All SAEs were considered unrelated to study medication. **b(4)**

There was one SAE in the HSX study, RD.06.SRE.18057. Subject 143, a 50- year-old Caucasian woman, was diagnosed with thyroid cancer. The event occurred prior to the start of treatment and was assessed as unrelated to study drug.

#### 7.1.3 Dropouts and Other Significant Adverse Events

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7.1.3.1 Overall profile of dropouts

This information has been reviewed earlier for NDA 21-501, NDA 21-502, and NDA 21-471. The majority of discontinuations were not related to adverse events.

The only studies that have not been reviewed earlier are 1010.02, for the assessment of transepidermal water loss, which enrolled 31 subjects and had no dropouts, and PEN.750.04, conducted with a formulation containing [redacted] titanium dioxide instead of pigmentary titanium dioxide. These two studies are reviewed in the Appendix.

b(4)

The following table summarizes the subject disposition in study PEN.750.04:

	Subjects	
Enrolled	136	100.00%
Completed	135	99.26%
Safety population	135	99.26%
Discontinued	11	8.00%
Due to AEs	6	4.41%
Subject request	2	2.20%
Protocol violation	0	0.00%
Lost to follow up	2	2.20%

In study PEN.750.04, 136 subjects were enrolled and 135 completed the study. Eleven (8%) subjects discontinued early for the following reasons:

- Subject 21-29 was lost to follow up after the first application.
- Subject 20-21 was dropped from the study because a sibling (20-12) participating in the study had an AE and was discontinued.
- Six subjects were dropped because of application site reaction: 19-05, 19-06, 20-12, 20-17, 21-17, and 21-22.

7.1.3.2 Adverse events associated with dropouts

Except for the two new studies, this information has been reviewed earlier for NDA 21-501, NDA 21-502, and NDA 21-471. Discontinuation due to adverse events was infrequent. Only 12 subjects overall discontinued due to AEs, most of them in study 2604 (irritancy and sensitization). All of these 12 AEs were related to local skin irritation and all of them resolved.

In study PEN.750.04, six subjects dropped because of application site reaction: 19-05, 19-06, 20-12, 20-17, 21-17, and 21-22. None were severe.

There were no dropouts in Study 1010.02.

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#### 7.1.3.3 Other significant adverse events

None.

#### 7.1.4 Other Search Strategies

Not applicable.

#### 7.1.5 Common Adverse Events

Historically, common treatment-related events associated with sunscreen use include the following reactions<sup>1</sup>:

- Rash
- No drug effect
- Application site reaction
- Pruritus
- Paresthesia
- Skin discoloration
- Allergic reaction
- Facial edema
- Pain
- Photosensitivity
- Urticaria
- Contact dermatitis
- Hyperesthesia

#### 7.1.5.1 Eliciting adverse events data in the development program

During clinical studies, at each follow-up visit, the investigator:

- examined all areas of skin where the subject applied study drug, specifically looking for cutaneous signs of irritation, sensitization, or photosensitivity.
- asked the subject an open question regarding their health and medical status since the last visit.
- reviewed the **subject's** diary for any information indicating a change in status from baseline or any adverse events.

Subjects were encouraged to come to the study site any time if they experienced a severe adverse event.

#### 7.1.5.2 Appropriateness of adverse event categorization and preferred terms

AE reports observed during clinical studies were grouped by preferred terms using the COSTART dictionary in some studies and by using MedDRA in others.

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## 7.1.5.3 Incidence of common adverse events

The incidences of adverse events in clinical studies conducted in support of earlier NDAs were relatively low. The most common AEs were related to local reactions at the site of application of the study product.

In study PEN.750.04, there were no deaths, pregnancies, or severe treatment-related AEs. The safety profile from the study is summarized in the following table:

	Subjects (n=135)	
	Count	Percentage
Subjects reporting AES	86	64%
Mild	50	37%
Moderate	33	24%
Severe	3	2%
Subjects reporting at least one treatment related AE	8	6%
Dermatological	8	6%
Non-Dermatological	1	<1%
Subjects with AEs leading to discontinuation	6	4%

Most treatment related AEs were dermatological. Two subjects also had eye irritation.

Table 32 summarizes the AEs in PEN 750.04 by MedDRA term.

## 7.1.5.4 Common adverse event table

The following tables (7,8,9 & 10) summarize the AES in studies previously reviewed:

Study #	N	No. of AEs	Subjects with AEs	Types of AEs (cases)
<b>Phase 1 Local Tolerance Studies</b>				
PEN.110.01	223	18	14	Headache, head cold, teeth extraction, cough, fatigue, upset stomach, fever, back spasm, acid reflux, right knee surgery, toothache, pain in mouth, neck sprain, back sprain
PEN.210.01	137	5	4	Headache, sinus infection, backache
PEN.250.01	26	0	0	--
1.GC.03.SRE.2604	225	66	53	Flu syndrome, pharyngitis, cold (coryza), headache, sore throat, tooth disorders, GI events, general pruritus, itchiness around eyes, 3 reactions to Scanpore tape
1.CG.03.SRE.2605.R01	30	0	0	--
1.CG.03.SRE.2606	118	4	4	Pharyngitis, asthenia, cold, tendonitis

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Phase 1	Studies			
1.CG.03.SRE.2607	6	18	6	Dizziness, headache, pruritus, eczema, infected skin
V99.1203	5	6	3	Toothache, myalgia, right shoulder pain, abdominal cramps, nausea
V3156	8	1	1	Joint disorder
<b>Phase 2 Combination Policy Studies</b>				
PEN.810.05	50	1	1	Sore throat
PEN.810.06	100	1	1	Headache
PEN.910.02	70	0	0	--
<b>Phase 3 UVA/UVB Protection Studies</b>				
PEN.810.01	21	0	0	--
PEN.810.02	20	0	0	--
PEN.820.01	21	0	0	--
PEN.820.02	25	0	0	--
PEN.910.01	32	0	0	--
PEN.920.01	14	3	3	Headache, sore throat
PEN.99001.01COS	24	0	0	--
<b>Total</b>	<b>1155</b>	<b>125</b>	<b>86</b>	

TABLE 8. STUDY PEN.750.01: SUMMARY OF AES THAT OCCURRED IN >1% OF SUBJECTS (N=248)

Body System	Preferred Term	All AEs N (%)	TRAEs* N (%)
<b>Total</b>		<b>145</b>	<b>39 (15.7)</b>
<b>Body as Whole</b>	Accidental injury	16 (6.5)	0
	Allergic Reaction	10 (4.0)	0
	Back pain	4 (1.6)	0
	Fever	6 (2.4)	0
	Flu symptoms	40 (16.1)	0
	Headache	31 (12.5)	0
	Infection	11 (4.4)	0
	Pain	6 (2.4)	0
	Surgical/medical procedure	5 (2.0)	0
<b>Cardiovascular System</b>	Hypertension	3 (1.2)	0
<b>Digestive System</b>	Dyspepsia	4 (1.6)	0
	Gastrointestinal disorder	3 (1.2)	0
	Nausea	3 (1.2)	0
	Tooth disorder	6 (2.4)	0
<b>Musculo-Skeletal System</b>	Bone disorder	3 (1.2)	0
<b>Nervous System</b>	Depression	3 (1.2)	0
	Dizziness	5 (2.0)	0
	Neuralgia	4 (1.6)	0
<b>Respiratory system</b>	Asthma	4 (1.6)	0
	Bronchitis	5 (2.0)	0
	Cough increased	3 (1.2)	0
	Pharyngitis	7 (2.8)	0
	Rhinitis	10 (4.0)	0
	Sinusitis	8 (3.2)	0
<b>Skin and Appendages</b>	Acne	17 (6.9)	12 (4.8)
	Contact dermatitis	3 (1.2)	0
	Dermatitis	14 (5.6)	7 (2.8)
	Dry skin	8 (3.2)	3 (1.2)
	Eczema	3 (1.2)	3 (1.2)

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	<b>Erythema</b>	<b>10 (4.0)</b>	<b>3 (1.2)</b>
	Excoriation	3 (1.2)	0
	Pruritus	7 (2.8)	5 (2.0)
	Rosacea	3 (1.2)	1 (0.4)
	Seborrhea	4 (1.6)	2 (0.8)
	Skin burn	4 (1.6)	0
	Skin discomfort	4 (1.6)	3 (1.2)
	Sunburn	10 (4.0)	2 (0.8)
<b>Special Senses</b>	<b>Conjunctivitis</b>	<b>6 (2.4)</b>	<b>2 (0.8)</b>
	Taste perversion	3 (1.2)	1 (0.4)
<b>Urogenital System</b>	<b>Urinary tract infection</b>	<b>5 (2.0)</b>	<b>0</b>

Note: TRAE: treatment related AEs.

**TABLE 9. STUDY PEN.750.02: SUMMARY OF AES THAT OCCURRED IN >1% OF SUBJECTS (N=246)**

Body System	Preferred Term	All AEs N (%)	TRAEs N (%)
<b>Total</b>		<b>167</b>	<b>18 (7.3)</b>
<b>Body as Whole</b>	<b>Abdominal pain</b>	<b>5 (2.0)</b>	<b>0</b>
	Accidental injury	33 (13.4)	0
	Allergic Reaction	10 (4.1)	0
	Fever	29 (11.8)	0
	Flu symptoms	52 (21.1)	0
	Headache	17 (6.9)	0
	Infection	23 (9.3)	0
	Pain	16 (6.5)	0
	Surgical/medical procedure	3 (1.2)	0
<b>Digestive System</b>	<b>Gastritis</b>	<b>8 (3.3)</b>	<b>0</b>
	Vomiting	9 (3.7)	0
<b>Hemic/Lymphatic</b>	<b>Ecchymosis</b>	<b>5 (2.0)</b>	<b>0</b>
<b>Musculo-Skeletal System</b>	<b>Myalgia</b>	<b>4 (1.6)</b>	<b>0</b>
<b>Respiratory system</b>	<b>Asthma</b>	<b>4 (1.6)</b>	<b>0</b>
	Bronchitis	4 (1.6)	0
	Cough increased	21 (8.5)	0
	Lung disorder	5 (2.0)	0
	Pharyngitis	7 (2.8)	0
	Rhinitis	29 (11.8)	0
	Sinusitis	12 (4.9)	0
<b>Skin and Appendages</b>	<b>Bite</b>	<b>9 (3.7)</b>	<b>0</b>
	Contact dermatitis	3 (1.2)	0
	Dermatitis	20 (8.1)	7 (2.8)
	Eczema	6 (2.4)	1 (0.4)
	Erythema	8 (3.3)	2 (0.8)
	Miliaria	3 (1.2)	0
	Skin discomfort	3 (1.2)	2 (0.8)
	Skin infection	3 (1.2)	0
	Sunburn	13 (5.3)	4 (1.6)
<b>Special Senses</b>	<b>Conjunctivitis</b>	<b>6 (2.4)</b>	<b>1 (0.4)</b>
	Ear pain	6 (2.4)	0
	Otitis media	25 (10.2)	0

Note: TRAEs: treatment related AEs

TABLE 10. STUDY PEN.750.03: SUMMARY OF AES THAT OCCURRED IN >1% OF SUBJECTS (N=79)				
Body System	Preferred Term	All AEs N (%)	TRAEs N (%)	
Total		55 (69.6)	3 (3.8)	
Body as Whole	Accidental injury	18 (22.8)	0	
	Allergic Reaction	3 (3.8)	0	
	Fever	13 (16.5)	0	
	Flu symptoms	32 (40.5)	0	
	Headache	4 (5.1)	0	
	Infection	5 (6.3)	0	
	Neck rigidity	1 (1.3)	0	
	Pain	5 (6.3)	0	
Digestive System	Constipation	1 (1.3)	0	
	Diarrhea	3 (3.8)	0	
	Gastritis	2 (2.5)	0	
	Gastroenteritis	1 (1.3)	0	
	Ulcerative colitis	1 (1.3)	0	
	Vomiting	3 (3.8)	0	
	Lymphangitis	1 (1.3)	0	
Hemic/Lymphatic System	Lymphangitis	1 (1.3)	0	
Metabolic/Nutritional	Dehydration	1 (1.3)	0	
Nervous System	Anxiety	1 (1.3)	0	
Respiratory system	Asthma	2 (2.5)	0	
	Bronchitis	2 (2.5)	0	
	Cough increased	11 (13.9)	0	
	Lung disorder	1 (1.3)	0	
	Pharyngitis	2 (2.5)	0	
	Rhinitis	9 (11.4)	0	
	Sinusitis	4 (5.1)	0	
	Skin and Appendages	Acne	3 (3.8)	0
		Bite	5 (6.3)	0
Dermatitis		11 (13.9)	2 (2.5)	
Desquamation		1 (1.3)	0	
Dry skin		1 (1.3)	0	
Eczema		2 (2.5)	1 (1.3)	
Erythema		5 (6.3)	0	
Melanosis		3 (3.8)	0	
Skin edema		1 (1.3)	0	
Skin hypertrophy		1 (1.3)	0	
Skin infection		2 (2.5)	0	
Skin neoplasm		9 (11.4)	0	
Sunburn		2 (2.5)	0	
Special Senses		Conjunctivitis	2 (2.5)	0
	Ear pain	1 (1.3)	0	
	Otitis media	8 (10.1)	0	
Urogenital System	Kidney calculus	1 (1.3)	0	
	Kidney pain	1 (1.3)	0	

The following table provides a comparison of related dermatological AEs for subjects in all 4 long-term studies, combined and by treatment duration:

TABLE 11. COMPARISON OF TREATMENT-RELATED DERMATOLOGICAL AES FOR SUBJECTS IN ALL FOUR LONG-TERM STUDIES COMBINED AND BY TREATMENT DURATION

		Treatment duration			
		1 to < 180 days (N=473)	180 to < 360 days (N=340)	≥ 360 days (N=235)	All subjects combined (N=1048)
Subjects with at least 1 AE		295 (62.4)	244 (71.8)	182 (77.4)	721 (68.8)
Subjects with at least 1 TRAE		44 (9.3)	53 (15.6)	50 (21.3)	147 (14.0)
Subjects with at least 1 skin and appendage AE		137 (29.0)	136 (40.0)	102 (43.4)	375 (35.8)
Subjects with at least 1 skin and appendage TRAE		41 (8.7)	49 (14.4)	46 (19.6)	136 (13.0)
Skin Conditions	Acne	4 (0.8)	8 (2.4)	9 (3.8)	21 (2.0)
	Eczema	1 (0.2)	2 (0.6)	2 (0.9)	5 (0.5)
	Seborrhea	0 (0)	1 (0.3)	1 (0.4)	2 (0.2)
	Folliculitis	1 (0.2)	1 (0.3)	0 (0)	2 (0.2)
	Rosacea	0 (0)	1 (0.3)	0 (0)	1 (0.1)
	Skin neoplasm	0 (0)	1 (0.3)	0 (0)	1 (0.1)
	Pimples	0 (0)	1 (0.3)	0 (0)	1 (0.1)
	Herpes simplex	0 (0)	0 (0)	1 (0.4)	1 (0.1)
	Hirsutism	0 (0)	1 (0.3)	0 (0)	1 (0.1)
	Miliaria	1 (0.2)	0 (0)	0 (0)	1 (0.1)
Dermatitis/Irritation	Dermatitis	6 (1.3)	8 (2.4)	2 (0.9)	16 (1.5)
	Irritant dermatitis	4 (0.8)	1 (0.3)	4 (1.7)	9 (0.9)
	Irritation skin	2 (0.4)	1 (0.3)	2 (0.9)	5 (0.5)
	Skin irritation	2 (0.4)	0 (0)	0 (0)	2 (0.2)
	Allergic contact dermatitis	1 (0.2)	0 (0)	1 (0.4)	2 (0.2)
	Irritant contact dermatitis	0 (0)	1 (0.3)	0 (0)	1 (0.1)
Photosensitization	Photosensitivity rash	4 (0.8)	4 (1.2)	10 (4.3)	18 (1.7)
	Photosensitivity	0 (0.0)	0 (0)	3 (1.3)	3 (0.3)
	Photoallergic reaction	1 (0.2)	0 (0)	0 (0)	1 (0.1)
Inflammation	Sunburn	6 (1.3)	4 (1.2)	7 (3.0)	17 (1.6)
	Erythema	4 (0.8)	3 (0.9)	3 (1.3)	10 (1.0)
	Skin infection	0 (0)	2 (0.6)	0 (0)	2 (0.2)
	Skin edema	0 (0)	1 (0.3)	0 (0)	1 (0.1)
Dry/Oily Skin	Dry skin	1 (0.2)	8 (2.4)	2 (0.9)	11 (1.0)
	Desquamation	0 (0)	1 (0.3)	0 (0)	1 (0.1)
	Oily skin	0 (0)	1 (0.3)	0 (0)	1 (0.1)
	Dryness skin	0 (0)	0 (0)	2 (0.9)	2 (0.2)
	Drying	1 (0.2)	0 (0)	0 (0)	1 (0.1)
Skin Sensation	Pruritus	3 (0.6)	4 (1.2)	1 (0.4)	8 (0.8)
	Itching skin	2 (0.4)	5 (1.5)	1 (0.4)	8 (0.8)
	Skin discomfort	0 (0)	4 (1.2)	1 (0.4)	5 (0.5)
	Discomfort skin	1 (0.2)	0 (0)	1 (0.4)	2 (0.2)
	Stinging sensation	2 (0.4)	0 (0)	1 (0.4)	3 (0.3)
	Burning sensation skin	1 (0.2)	1 (0.3)	0 (0)	2 (0.2)
Skin Coloration	Skin discoloration	0 (0)	1 (0.3)	0 (0)	1 (0.1)
	Discoloration skin	0 (0)	0 (0)	1 (0.4)	1 (0.1)
	Blotching	1 (0.2)	0 (0)	0 (0)	1 (0.1)
	Hyperpigmentation skin	0 (0)	0 (0)	1 (0.4)	1 (0.1)

In study PEN.750.04, there were 5 severe non treatment related AEs, all in the 6 month to 2 years old group (fatigue, pyrexia, and nasopharyngitis) and in the 6-12 years old group (pneumonia, back pain). Of the 135 subjects, 86 (64%) experienced at least one AE. Eight subjects (6%) experienced a cutaneous AE at least possibly related. Table 32 summarizes the AEs by MedDRA term.

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#### 7.1.5.5 Identifying common and drug-related adverse events

All adverse events that were reported as probably or possibly related to treatment in Phase 1, 2, and 3 clinical trials were assessed as mild and non-serious. The reviewers stated that adverse events possibly related to the study products were of low incidence and minor severity, with the exception of sunburn.

A total of 66 drug related AEs were reported in Skin and Appendages System and four in the Special Senses System. None of these events were assessed by the investigator as serious and all of them resolved. The profile of drug-related AEs was consistent across the 5 long-term safety studies except for PEN.750.01 where a higher incidence of acne was reported. This increased incidence may be related to a higher number of adolescents enrolled.

#### 7.1.5.6 Additional analyses and explorations

There were no additional analyses or extrapolations performed by the sponsor.

#### 7.1.6 Less Common Adverse Events

The number of adverse events in the clinical studies was too small to assess the incidence of less common AEs.

#### 7.1.7 Laboratory Findings

Except for urine pregnancy testing, there were no routine laboratory tests performed in the clinical safety studies with HSX.

Laboratory evaluations were performed in the pharmacokinetic Study 2607, which evaluated percutaneous absorption of ecamsule when tested under maximized conditions. Laboratory evaluations included hematology, serum chemistries, and urinalysis, at baseline and the end of the study. No laboratory abnormalities appeared during the study.

In study 18047 (the Phase 3, open-label study) in subjects with polymorphous light eruption (PLME), routine laboratory tests (hematology, serum chemistry and urinalysis) were performed at screening, Month-6 and Month-12 or at study discontinuation. There were no clinically significant changes in the incidences of pathological laboratory parameters from screening to final visit. For detailed review of these studies, see NDA 21-501.

#### 7.1.8 Vital signs

There was no vital sign monitoring in the  clinical safety studies.

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7.1.9 Electrocardiograms (ECGs)

There were no ECGs performed during any of the clinical studies.

7.1.10 Immunogenicity

Immunogenicity of the tested sunscreen formulations was not assessed.

7.1.11 Human Carcinogenicity

There were no data on human carcinogenicity submitted to this application.

7.1.12 Special Safety Studies

Special safety studies have been conducted to assess cumulative irritancy, contact sensitizing potential, photosensitivity, and photoallergenicity. These studies have been reviewed by reviewers in the Division of Dermatologic and Dental Drug Products, and will not be discussed in this review.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There is no reason to believe that sunscreen drug products have the potential to be abused.

7.1.14 Human Reproduction and Pregnancy Data

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

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

Six pregnancies were reported during the long term safety study 18047, three discontinued because of their pregnancy, two resulted in delivery of normal healthy babies.

Three of six infants were normal at birth but subsequently developed vascular lesions, approximately three months after birth. All three lesions (two hemangiomas and one nevus flammeus) were reported as serious adverse events (congenital anomaly). Family history was negative in two cases and positive in one (nevus flammeus). An earlier reviewer commented that

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ecamsule is not a teratogen and does not have an effect on reproductive function in animals, and that no information is available for the other two monograph active ingredients (avobenzone and octocrylene), which are not contraindicated during pregnancy, and the reviewer agreed with the **sponsor's conclusion that vascular** lesions noted in newborns whose mothers were exposed to ecamsule during their pregnancy did not appear to be unusual and could have occurred by chance alone.

The Pregnancy Lactation Team (PLT) did not find the need for additional safety data monitoring in pregnant women or their babies, and concluded that there is no need for a pregnancy warning on  sunscreen drug products.

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7.1.15 Assessment of Effect on Growth

There were no assessments of effect on growth in this application.

7.1.16 Overdose Experience

Given the intended route of administration (topical) and the low level of percutaneous absorption, overdosage is unlikely. Overdosage has not been reported in any of the clinical studies.

7.1.17 Postmarketing Experience

At the time of writing this review, the sponsor had not submitted the 120 day safety update. Postmarketing safety data for ecamsule-containing products should come from these sources:

- L'Oreal cosmetovigilance
- Galderma pharmacovigilance
- Literature

**The sponsor's postmarketing safety** database will be reviewed in this section. The literature review is discussed in Section 8.6 of this review.

**L'Oreal postmarketing pharmacovigilance/cosmetovigilance** data review:

This application includes the same safety information that has already been reviewed for NDA 21-471.

There are two working databases, one is the **Galderma (an affiliate of L'Oreal) pharmacovigilance system and the second is the L'Oreal cosmetovigilance system**. As marketing has been discontinued by Galderma in 2001 and no reports of adverse events have been received by Galderma in at least the past three years, the Galderma database did not have an update.

**The L'Oreal cosmetovigilance system is designed** to identify adverse reactions that may be related to cosmetic products. In preparation of this report, the sponsor reviewed all ecamsule-containing products. These products may contain ecamsule in combination with other US approved OTC sunscreen filters, but also may contain ecamsule in combination with filters not approved in the US but listed in the EEC Cosmetic Directive Annex VII. COSTART preferred

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terms were used for classification of all AEs reported to L'Oreal postmarketing system.

From 1993 through 2005, more than [redacted] of active dry ecamsule or [redacted] of the 33% solution have been produced by the L'Oreal subsidiary, CHIMEX, S.A. for commercial use. Approximately [redacted] units of ecamsule containing products (including beach sunscreen products, daily-use moisturizers with sunscreens and makeup products) have been sold to countries where the cosmetovigilance system is in place. The sponsor makes a conservative estimate, for all reported spontaneous adverse reactions, of 52 adverse events per [redacted] units sold of all ecamsule-containing product formulations has been reported during 12 years of marketing through 2005, an overall adverse event incidence of 0.0052%, all of which may or may not be associated with ecamsule. Although this estimate is of limited value because units sold does not equate with units used, and because gross underreporting can be expected, it does provide some measure of safety.

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b(4)

From cosmetovigilance information, there have been four cases of allergic reactions (positive patch test) to ecamsule, two of which were also allergic to other ingredients. During the 12 years of marketing experience, there were 6 serious AEs possibly related to ecamsule, 4 of which were pediatric, all of which were reported as resolved successfully.

## 7.2 Adequacy of Patient Exposure and Safety Assessments

This item has been addressed in the reviews of the other NDAs.

### 7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) used to evaluate Safety.

#### 7.2.1.1 Study type and design/patient enumeration

Table 3 summarizes the patient exposure to HSX, and Table 4 summarizes the exposure to ecamsule containing sunscreens. Table 21 summarizes the pediatric exposure to HSX and to other [redacted] sunscreens sharing some of the same ingredients. A total of 1268 subjects have been exposed to the HSX formulation, and a total of 3208 subjects have been exposed at least once to ecamsule containing sunscreens in clinical studies.

b(4)

#### 7.2.1.2 Demographics

##### 7.2.1.2.1 Phase 1, 2, and 3 Clinical Studies

Subject demographics and baseline characteristics across the Phase 1, 2, and 3 clinical studies were similar (Table 12). The majority of subjects were Caucasians, middle-aged females, except in the pharmacokinetic studies where subjects were male and slightly younger. The predominant skin type was type II (sensitive skin) and III (normal skin), with no evidence of active skin abnormalities.

Classification of the skin phototypes:

- **Type I – always burns easily; never tans**

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- Type II – always burns easily; tans minimally
- Type III – burns minimally; tans gradually
- Type IV – burns minimally; always tans well
- Type V – rarely burns; tans profusely
- Type VI – never burns; deeply pigmented

TABLE 12. DEMOGRAPHIC AND BASELINE CHARACTERISTICS OF SUBJECTS IN PHASE 1, 2 & 3 STUDIES						
	N	Mean Age	Gender	Race	Major Skin	
Phase 1 Local Tolerance Studies						
PEN.110.01	223	4 (18-91)	74%	82% Caucasian	31% type III	
PEN.210.01	137	4 (16-68)	77%	93% Caucasian	58% type III	
PEN.250.01	26	4 (18-63)	85%	81% Caucasian	73% type III	
1.GC.03.SRE.2604	225	4 (16-85)	68%	100%	52% type III	
1.CG.03.SRE.2605.R0	30	2 (18-53)	73%	100%	70% type II	
1.CG.03.SRE.2606	118	3 (18-62)	64%	100%	66% type II	
Phase 1						
	Studie					
1.CG.03.SRE.2607	6	3 (23-55)	100	100%	83% type III	
V99.1203	5	2 (19-29)	100	Not specified	Not done	
V3156	8	2 (19-41)	100	100%	Not done	
Phase 2 Combination Policy Studies						
PEN.810.05	50	3 (18-65)	68%	96% Caucasian	72% type II	
PEN.810.06	100	3 (18-63)	66%	99% Caucasian	57% type II	
PEN.910.02	70	3 (18-62)	57%	77% Hispanic	50% type III&IV	
Phase 3 UVA/AVB Protection Studies						
PEN.810.01	21	4 (26-58)	95%	100%	XX% type III	
PEN.810.02	20	3 (18-52)	56%	100%	96% type III	
PEN.820.01	21	4 (26-58)	95%	100%	71% type III	
PEN.820.02	25	3 (18-52)	56%	100%	56% type III	
PEN.910.01	32	4 (18-65)	53%	66% Caucasian	63% type III	
PEN.920.01	14	4 (35-65)	86%	100%	79% type III	
PEN.99001.01COS	24	3 (19-47)	75%	100%	46% type III	
Helioblock SX Cream Studies						
RD.06.SRE.18057	1	4 (18-73)	8	98% Caucasian	50% type II	
RD.06.SRE.2616	8	4 (18-65)	9	100%	41% type II	

*7.2.1.2.2 Phase 3 Long-Term Safety Studies*

FDA requested that the sponsor enroll 100 children, 6 months to 12 years of age, in PEN.750.03 and 100 children between 6 months and 12 years of age in PEN.750.02. Only 64 children were included in the safety population in PEN.750.03. However, 179 children 6 months to 12 years of age (73% of all subjects) were enrolled and 69% of them (124/179) completed PEN.750.02. PEN.705.02 was conducted on the [redacted] formula (760-006).

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The demographic and baseline characteristics for subjects in the long-term safety studies are presented in the following table:

		Study			
		PEN.750.01	PEN.750.02	PEN.750.03	Study 18047
Characteristic		N=248	N=246	N=79	N=475
Age (years)	Mean	35.79 (19.37)	10.98 (12.56)	8.69 (12.05)	45.6 (13.48)
	Median	35.44	6.69	3.69	46.0
	Range	12.04-83.43	0.5-67.95	0.64-48.15	12-85
Age group (years)	> 0.5 to < 2	0 (0)	57 (23.17)	24 (30.38)	0
	> 2 to < 6	0 (0)	60 (24.39)	32 (40.51)	0
	> 6 to < 12	0 (0)	62 (25.20)	8 (10.13)	0
	12 to < 18	78 (31.45)	24 (9.76)	2 (2.53)	11 (2.3)
	18 to 65	145 (58.47)	42 (17.07)	13 (16.46)	428 (90.1)
	> 65	25 (10.08)	1 (0.41)	0	36 (7.6)
Gender (N[%])	Male	58 (23.39)	101 (41.06)	26 (32.91)	83 (17.5)
	Female	190 (76.61)	145 (58.94)	53 (67.09)	392 (82.5)
Race (N[%])	Caucasian	193 (77.82)	193 (78.46)	66 (83.54)	431 (90.7)
	Black	23 (9.27)	8 (3.25)	0	10 (2.1)
	Hispanic	26 (10.48)	21 (8.54)	6 (7.59)	25 (5.3)
	Asian/Pacific	5 (2.02)	2 (0.81)	4 (5.06)	4 (0.8)
	Other	1 (0.40)	22 (8.94)	3 (3.80)	5 (1.1)
Skin phototype (N[%])	I	17 (6.85)	14 (5.69)	6 (7.59)	87 (18.3)
	II	52 (20.97)	96 (39.02)	27 (34.18)	179 (37.7)
	III	90 (36.29)	82 (33.33)	30 (37.97)	153 (32.2)
	IV	44 (17.74)	33 (13.41)	12 (15.19)	42 (8.8)
	V	29 (11.69)	17 (6.91)	2 (2.53)	13 (2.7)
	VI	16 (6.45)	4 (1.63)	2 (2.53)	1 (0.2)
Sensitive	Yes	196 (79.03)	207 (84.15)	67 (84.81)	--
	No	52 (20.97)	39 (15.85)	12 (15.19)	--
Predisposed subjects	Yes	97 (39.11)	159 (64.63)	45 (56.96)	--
	No	151 (60.89)	87 (35.37)	34 (43.04)	--
	PLME	0	0	0	475 (100)

Subjects enrolled into the [ ] studies were younger than subjects enrolled into Study RD.06.SRE.18047 (PLE patients). Women outnumbered men in all studies. Nearly twice as many women compared with men were enrolled in the [ ] studies PEN.750.01 and PEN.750.03. Slightly more women than men were enrolled in PEN.750.02 (59% women and 41% men), and in Study RD.06.SRE.18047, the ratio of women to men was nearly 5:1 (85% women vs. 18% men). The majority of subjects in each study were Caucasian (78% or more). Most subjects had skin phototype II or III.

The overall safety population for this integrated safety summary consisted of:

- 243 pediatric subjects 6 months to 12 years of age
- 115 adolescent subjects
- 628 adults
- 62 elderly subjects

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The demographics of the long term safety study, 750.04, conducted with a  titanium dioxide formulation, are summarized in Table 24 in the Appendix.

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7.2.1.3 Extent of exposure (dose/duration)

7.2.1.3.1 Phase 1, 2, and 3 Clinical Studies

Extent of exposure for subjects who participated in the Phase 1, 2, and 3 clinical studies was wide ranging, spanning from hours to weeks depending on the study design. The body surface area covered varied from patch application to whole body application. The usual amount of product applied was 2 mg/cm<sup>2</sup>. The largest amounts of sunscreen formula applied (15 grams twice daily and 10 grams once daily) were in two pharmacokinetic studies (1.CG.03.SRE.2607 and V3156). Extent of exposure data is summarized in the following table:

TABLE 14. EXTENT OF EXPOSURE FOR SUBJECTS IN PHASE 1, 2 & 3 CLINICAL STUDIES			
Study Number	N	Amount of Application	Length of Exposure
<b>Phase 1 Local Tolerance Studies</b>			
PEN.110.01	223	0.2 mL to sites 8 mm in diameter under occlusive conditions	4 weeks, 12-24 hrs (3 weeks); 72 hrs (3 weekends); 1-48 hrs (1 week)
PEN.210.01	137	0.2 mL to each 0.75 in x 0.75 in test site each time	24-hr applications 2x week, 3 consecutive weeks (induction phase); challenge with single 24-hr application
PEN.250.01	26	0.2 mL to each of 8 sites under occlusive conditions	Single exposure; 24 hours
1.CG.03.SRE.2604	225	50 µL under occlusive conditions	4 24-hr & 1 72-hr applications/week, 3 weeks; 1 48-hr application after 2-week rest period
1.CG.03.SRE.2605.R01	30	50 µL of product	24 hours
1.CG.03.SRE.2606	118	50 µL of product	Twice daily for 3 weeks + 1 single dose
<b>Phase 1 Pharmacokinetic Studies</b>			
1.CG.03.SRE.2607	6	15 g applied twice daily 9 days	18 whole body applications
V99.1203	5	0.2 g ([ <sup>14</sup> C]-ecamsule, 2%) 100 cm <sup>2</sup> area	4 hours on volar forearm
V3156	8	10 g, 4.95% ecamsule	5 consecutive days
<b>Phase 2 Combination Policy Studies</b>			
PEN.810.05	50	100 mg	Single exposure; 22-24 hours
PEN.810.06	100	100 mg	Single exposure; 22-24 hours
PEN.910.02	70	70 mg	Single exposure; 3 hours
<b>Phase 3 UVA/UVB Protection Studies</b>			

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PEN.810.01	21	120 mg	Single exposure; 22-24 hours
PEN.810.02	20	100 mg	Single exposure; 22-24 hours
PEN.820.01	21	120 mg	Single exposure; 22-24 hours
PEN.820.02	25	100 mg	Single exposure; 22-24 hours
PEN.910.01	32	70 mg	Single exposure; 22-24 hours
PEN.920.01	14	100 mg	Single exposure; 72 hours
PEN.99001.01COS	24	100 mg	Single exposure; 22-24 hours

The following table summarizes the extent of exposure in the Phase 3 studies:

TABLE 15. EXTENT OF EXPOSURE FOR SUBJECTS IN THE PHASE 3 STUDIES WITH HSX			
Study Number	N	Amount of Application	
RD.06.SRE.1805	144	Median 7g (range 5-11)	To whole body for 6 days
RD.06.SRE.2616	86	Median 8-9g (range 6.7-12)	To whole body for 6 days

*7.2.1.3.2 Phase 3 Long-Term Safety Studies*

Exposure to study treatments for subjects enrolled in the four long-term safety studies is summarized in the following table:

TABLE 16. SUMMARY OF TREATMENT DURATION, STUDY DRUG USE AND PRODUCT APPLICATION IN THE LONG-TERM SAFETY STUDIES					
		PEN.750.01	PEN.750.02	PEN.750.03	Study 18047
		<b>N=248</b>	<b>N=246</b>	<b>N=79</b>	<b>N=475</b>
<b>Treatment Duration (days)</b>	<b>N</b>	248	246	79	475
	<b>Mean (SD)</b>	307.1 (110.3)	88.4 (96.9)	37.3 (34.3)	258.3 (125.8)
	<b>Median</b>	356.0	44.5	31.0	335.0
	<b>Range</b>	1.0-376.0	1.0-363.0	1.0-225.0	1.0-393.0
<b>Total Usage (g)</b>	<b>N</b>	237	237	74	445
	<b>Mean (SD)</b>	570.6 (474.0)	256.6 (249.9)	143.0 (106.8)	302.3 (297.4)
	<b>Median</b>	433.4	174.5	122.0	211.6
	<b>Range</b>	27.9-3141.8	0.1-1650.8	6.8-532.0	-1.5-2006.0
<b>Daily Usage (g/day)</b>	<b>N</b>	235	235	72	445
	<b>Mean (SD)</b>	2.0 (2.6)	4.2 (3.6)	4.8 (4.5)	1.3 (1.9)
	<b>Median</b>	1.6	3.1	3.7	0.9
	<b>Range</b>	0.16-35.5	0.07-26.85	0.86-29.6	-1.0-26.1
<b>Product Application (total number)</b>	<b>N</b>	239	237	75	453
	<b>Mean (SD)</b>	417.4 (180.0)	145.9 (295.2)	55.9 (55.5)	303.1 (171.3)
	<b>Median</b>	388.0	57.0	42.0	342.0
	<b>Range</b>	1.0-1029.0	1.0-2687.0	0.0-421.0	1.0-1158.0
<b>Daily Application (number/day)</b>	<b>N</b>	239	237	73	453
	<b>Mean (SD)</b>	1.3 (0.4)	1.4 (0.8)	1.5 (0.5)	1.1 (0.4)
	<b>Median</b>	1.1	1.2	1.3	1.1
	<b>Range</b>	0.95-3.01	1.0-7.78	1.0-2.8	0.01-3.0

Total amount of study medication used was highest for the daily-use study PEN.750.01 (570.6 grams) followed by study RD.06.SRE.18047 (301.3 grams), PEN.750.02 (256.6 grams) and PEN.750.03

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(143 grams). Daily usage in grams was highest for [redacted] studies PEN.750.02 and PEN.750.03 (4.2 grams and 4.8 grams, respectively). On the days that subjects used sunscreen treatment, the number of applications was similar for subjects in all studies (1.1 to 1.5 applications/day). The average length of treatment for all studies combined was 213 days and ranged from 1 to 393 days. Exposure to study treatment for all subjects (N=1048) in the long-term safety studies combined by duration of treatment was as follows:

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- 473 subjects treated for 1 to <180 days (average 62.5 days)
- 340 subjects treated for 180 to <360 days (average 315.9 days)
- 235 subjects treated for more than one year (average 368.2 days)

Treatment duration assessed for age subgroups in three long-term studies (750.01, 750.02, and 750.03), revealed that the pediatric age subgroups had the shortest treatment duration, as shown in the following table:

Age groups	Mean	SD	Median	Range
0.5 to ≤ 2 years (N=81)	57.79	68.92	31.0	1-312
2 to ≤ 6 years (N=92)	67.45	80.32	36.0	1-363
6 to ≤ 12 years (N=70)	87.59	99.05	37.5	1-350
12 to ≤ 18 years	247.67	145.40	344.0	1-371
18 to ≤ 65 years	250.24	142.51	346.0	1-376
> 65 years (N=26)	308.31	117.58	360.5	2-372

In study PEN.750.02, each subject was to plan for at least 14 days with outdoor activities, such as a beach vacation or weekend gardening or sport activities, where the use of a sunscreen was required. A total of 14.2% of the study PEN.750.02 population did not use study drug for the required 14 days and also did not have the 14 days of sun exposure required by the protocol.

**7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety**

Safety data submitted from the literature is discussed in section 8.6 of this review.

**7.2.3 Adequacy of Overall Clinical Experience**

A long marketing experience in foreign countries, in addition to several clinical studies, has not revealed any serious safety signals for ecamsule-containing drug products. The available data supports the safety of ecamsule containing sunscreens for over-the-counter marketing. The following ecamsule containing sunscreens have been approved: [redacted] SPF 15 W/R Lotion (NDA 21-501), [redacted] SPF 15 Daily Lotion (NDA 21-502), and [redacted] SPF 20 W/R Lotion (NDA 21-471). [redacted] SPF 20 W/R Lotion also contains 3% ecamsule.

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**7.2.4 Adequacy of Special Animal and/or In Vitro Testing**

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The adequacy of preclinical data is being assessed by pharmtox reviewers. Refer to discipline specific reviews. Earlier reviews have not identified any pending safety issues.

**7.2.5 Adequacy of Routine Clinical Testing**

The sponsor has conducted all the required studies requested by FDA.

**7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup**

The sponsor has submitted all the required data to characterize the pharmacological profile of this combination product.

**7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study**

This reviewer considers the safety of HSX has been reasonably established for adults and children older than 6 months. Pediatric waivers for studies below 6 months have been granted for similar sunscreens.

The Division of Pediatric and Maternal Health has made several recommendations, as follows:

- That the sponsor provides a rationale for extrapolating efficacy from adults to children
- Presuming that studies in older children do not reveal any safety concerns, that consideration be given to :
  - Obtaining pharmacokinetic data in the pediatric age groups 6 months to 12 years to confirm that drug is not systemically absorbed when used in this combination as the extent of absorption has not been directly tested.
  - Requesting an actual use study in patients less than 6 months of age, that could be similar to the study conducted in children 6 months to 12 years of age, using the product according to label, and obtaining pk data.

**7.2.8 Assessment of Quality and Completeness of Data**

From a clinical safety perspective, this application is adequate for approval.

**7.2.9 Additional Submissions, Including Safety Update**

A four-month safety update was due to be submitted by the sponsor as required by 21 CFR 314.50 (d) (5)(vi)(b). In the safety update for NDA 21-471, the sponsor stated that there were no new animal, non-clinical, or clinical studies initiated or completed with the three-active ingredients in [ ] formulations after the submission of NDA 21-501 and NDA 21-502 on May 16, 2005. In that update, there was no additional information in the literature on adverse reactions to ecamsule from the reporting date of October 2004 in the NDA 21-501 through August 31, 2005.

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The safety update included only global cosmetovigilance data on formulas containing the new chemical entity, ecamsule.

**7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions**

**7.4 General Methodology**

**7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence**

A total of 3208 subjects were exposed at least once to an ecamsule-containing sunscreen product during the development phase of these sunscreens. It is inappropriate to combine safety data from all the clinical studies because of differences in the formulation, design, and methodology used in different studies.

**7.4.1.1 Pooled data vs. individual study data**

For the incidence of AEs in individual studies, see section 7.1.5 of the review.

**7.4.1.2 Combining data**

Only data gathered during the three [redacted] and one Helioblock long-term studies were combined to assess the predictive factors. A total of 1048 subjects participated in those four studies.

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**7.4.2 Explorations for Predictive Factors**

Analyses of safety data were performed for patient-predictive factors such as demographics, skin phototype, and duration of product use. Drug-related adverse events were limited to skin. These data have been previously reviewed for NDAs 21-501, 21-502, and 21-471.

**7.4.2.1 Explorations for dose dependency for adverse findings**

There was no assessment of dose dependency performed.

**7.4.2.2 Explorations for time dependency for adverse findings**

This data has been submitted and reviewed for the other NDAs.

The following table provides a comparison of related dermatological adverse events for subjects

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in all four long-term studies, combined and by treatment duration.

		Treatment duration			
		1 to <180 days (N=473)	180 to <360 days (N=340)	≥360 days (N=235)	All combined (N=1048)
Subjects with at least 1 AE		295 (62.4)	244 (71.8)	182 (77.4)	721 (68.8)
Subjects with at least 1 TRAE		44 (9.3)	53 (15.6)	50 (21.3)	147 (14.0)
Subjects with at least 1 skin and appendage AE		137 (29.0)	136 (40.0)	102 (43.4)	375 (35.8)
Subjects with at least 1 skin and appendage TRAE		41 (8.7)	49 (14.4)	46 (19.6)	136 (13.0)
Skin Conditions					
	Acne	4 (0.8)	8 (2.4)	9 (3.8)	21 (2.0)
	Eczema	1 (0.2)	2 (0.6)	2 (0.9)	5 (0.5)
	Seborrhea	0 (0)	1 (0.3)	1 (0.4)	2 (0.2)
	Folliculitis	1 (0.2)	1 (0.3)	0 (0)	2 (0.2)
	Rosacea	0 (0)	1 (0.3)	0 (0)	1 (0.1)
	Skin neoplasm	0 (0)	1 (0.3)	0 (0)	1 (0.1)
	Pimples	0 (0)	1 (0.3)	0 (0)	1 (0.1)
	Herpes simplex	0 (0)	0 (0)	1 (0.4)	1 (0.1)
	Hirsutism	0 (0)	1 (0.3)	0 (0)	1 (0.1)
	Miliaria	1 (0.2)	0 (0)	0 (0)	1 (0.1)
Dermatitis/Irritation					
	Dermatitis	6 (1.3)	8 (2.4)	2 (0.9)	16 (1.5)
	Irritant dermatitis	4 (0.8)	1 (0.3)	4 (1.7)	9 (0.9)
	Irritation skin	2 (0.4)	1 (0.3)	2 (0.9)	5 (0.5)
	Skin irritation	2 (0.4)	0 (0)	0 (0)	2 (0.2)
	Allergic contact dermatitis	1 (0.2)	0 (0)	1 (0.4)	2 (0.2)
	Irritant contact dermatitis	0 (0)	1 (0.3)	0 (0)	1 (0.1)
Photosensitization					
	Photosensitivity rash	4 (0.8)	4 (1.2)	10 (4.3)	18 (1.7)
	Photosensitivity	0 (0.0)	0 (0)	3 (1.3)	3 (0.3)
	Photoallergic reaction	1 (0.2)	0 (0)	0 (0)	1 (0.1)
Inflammation					
	Sunburn	6 (1.3)	4 (1.2)	7 (3.0)	17 (1.6)
	Erythema	4 (0.8)	3 (0.9)	3 (1.3)	10 (1.0)
	Skin infection	0 (0)	2 (0.6)	0 (0)	2 (0.2)
	Skin edema	0 (0)	1 (0.3)	0 (0)	1 (0.1)
Dry/Oily Skin					
	Dry skin	1 (0.2)	8 (2.4)	2 (0.9)	11 (1.0)
	Desquamation	0 (0)	1 (0.3)	0 (0)	1 (0.1)
	Oily skin	0 (0)	1 (0.3)	0 (0)	1 (0.1)
	Dryness skin	0 (0)	0 (0)	2 (0.9)	2 (0.2)
	Drying	1 (0.2)	0 (0)	0 (0)	1 (0.1)
Skin Sensation					
	Pruritus	3 (0.6)	4 (1.2)	1 (0.4)	8 (0.8)
	Itching skin	2 (0.4)	5 (1.5)	1 (0.4)	8 (0.8)
	Skin discomfort	0 (0)	4 (1.2)	1 (0.4)	5 (0.5)
	Discomfort skin	1 (0.2)	0 (0)	1 (0.4)	2 (0.2)
	Stinging sensation	2 (0.4)	0 (0)	1 (0.4)	3 (0.3)
	Burning sensation skin	1 (0.2)	1 (0.3)	0 (0)	2 (0.2)
Skin Coloration					
	Skin discoloration	0 (0)	1 (0.3)	0 (0)	1 (0.1)
	Discoloration skin	0 (0)	0 (0)	1 (0.4)	1 (0.1)
	Blotching	1 (0.2)	0 (0)	0 (0)	1 (0.1)
	Hyperpigmentation skin	0 (0)	0 (0)	1 (0.4)	1 (0.1)

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During the first 360 days of treatment all AEs were dermatological.  
 The long term safety study 750.04 is reviewed in the Appendix.

7.4.2.3 Explorations for drug-demographic interactions

No formal drug-demographic interaction studies have been performed on any of the [ ] formulations. The following table summarizes the distribution of AEs according to gender, race, skin phototype and age of the subjects:

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TABLE 19. TREATMENT RELATED AES BY DEMOGRAPHICS IN THE FOUR [ ] LONG-TERM STUDIES

Demographic Subgroup		Drug Related AEs	
		Dermatologica	Non-Dermatological
Gender	Males (N=185)	21 (11.4%)	1 (0.5%)
	Females (N=388)	33 ( 8.5%)	7 (1.8%)
Race	Asian (N=11)	2 (18.2%)	0 (0.0%)
	Black (N=31)	7 (22.6%)	1 (3.2%)
	White (N=452)	38 ( 8.4%)	5 (1.5%)
	Hispanic (N=53)	7 (13.2%)	0 (0.0%)
	Other (N=26)	0 ( 0.0%)	0 (0.0%)
Skin Phototype	Type I (N=37)	0 ( 0.0%)	0 (0.0%)
	Type II (N=175)	23 (13.1%)	3 (1.7%)
	Type III (N=202)	19 ( 9.4%)	3 (1.5%)
	Type IV (N=89)	5 ( 5.6%)	1 (1.1%)
	Type V (N=48)	5 (10.4%)	0 (0.0%)
	Type VI (N=22)	2 ( 9.1%)	1 (4.5%)
Age	0.5 to < 2 yrs (N=81)	3 ( 3.7%)	1 (1.2%)
	> 2 to < 6 yrs (N=92)	8 ( 8.7%)	0 (0.0%)
	> 6 to < 12 yrs (N=70)	5 ( 7.1%)	0 (0.0%)
	> 12 to < 18 yrs (N=104)	7 ( 6.7%)	0 (0.0%)
	> 18 to < 65 yrs (N=200)	30 (15.0%)	6 (3.0%)
	> 65 yrs (N=26)	1 ( 3.8%)	1 (3.8%)

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Even though number of subjects in some of the demographic subgroups was low, there was no obvious difference in the incidence of drug related adverse events among subgroups of subjects with different skin phototypes, race, gender, and skin sensitivity.

For the three combined [ ] long-term studies, 60 of the 573 subjects (10.5% incidence) reported treatment-related adverse events and 54 (90%) of them were dermatologic. Of these, 17 were reported by pediatric subjects. Subjects in the youngest pediatric subgroup experienced the lowest incidence (3.7%) of treatment related dermatologic adverse reactions. There were 3 events among 81 children, ages 6 months and 2 years. Among 2 to 6 year old children, the incidence was 8.7% (8 events among 92 children) closely followed by an incidence of 7.1% (5/70 subjects) among 6 to 12 year olds, and an incidence of 6.7% (7/140) among adolescents. In the adults, the incidence of treatment related dermatologic AEs was considerably higher, 15%. On average, adult subjects used sunscreens for longer treatment durations than pediatric subjects because most adults participated in the 12 months daily use study. The difference in adverse event incidence rates between children and adults may be related to differences in duration of use.

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There did not appear to be a specific association of adverse reactions with pediatric use of the sunscreens.

7.4.2.4 Explorations for drug-disease interactions

No analysis on drug-disease interactions was performed for any study. All studies were performed on healthy individuals except for the following studies that were conducted in subjects with polymorphous light eruption: 2616 (Phase 2 safety and efficacy study in PLE subjects), 18057 (Phase 3 safety and efficacy study in subjects with PLE), and 18047 (long term safety assessment study in PLE subjects). When not undergoing a flare-up, these subjects could be considered to have "normal" appearing skin. The adverse events reported by subjects in these studies did not indicate a new, emergent pattern of adverse events unique to individuals with PLME. The presence of PLME in the subject population did not change the safety profile of the study treatments in these predisposed subjects.

The following table summarizes the treatment related AEs in the long term studies by predisposing conditions:

TABLE 20. TREATMENT RELATED AEs IN THE FOUR [ ] LONG-TERM STUDIES BY PREDISPOSING CONDITIONS

Predisposing Conditions	Drug Related AEs	
	Dermatological	Non-Dermatological
Asthma/Allergy (N=106)	22 (20.8%)	1 (0.9%)
Atopic/Dry Skin (N=75)	13 (17.3%)	2 (2.7%)
Acne/Rosacea (N=99)	11 (11.1%)	1 (1.0%)
Sensitive Skin (N=103)	12 (11.7%)	5 (4.9%)
All predisposed subjects (N=272)	32 (11.8%)	5 (1.8%)

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The sponsor analyzed the incidence of adverse events reported among a subgroup of predisposed subjects (those with a history of or current atopic/dry skin, asthma/allergy, acne/rosacea, and/or sensitive skin) who participated in the three long-term [ ] studies. A higher incidence of adverse events was reported for the predisposed subjects (69.1%) than for subjects without a predisposing medical condition (59.5%). The incidence of treatment-related AEs was also higher in subjects with predisposing conditions (12.9%) than subjects without them (10.5%). The

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majority of treatment-related adverse events were dermatological, and all were mild or moderate in severity.

Subjects with predisposing dermatological conditions had a higher incidence of cutaneous adverse event. The proposed label appropriately directs consumers to stop use the product if rash or irritation develops and lasts.

#### 7.4.2.5 Explorations for drug-drug interactions

No formal drug-drug interaction studies have been conducted with HSX. The sponsor states that ecamsule and its combination formulations are poorly absorbed (<1%) when topically applied to the skin, and therefore, it is unlikely that interactions with systemic medications would occur.

#### 7.4.3 Causality Determination

The sponsor has not performed special causality assessments.

## **8. ADDITIONAL CLINICAL ISSUES**

### **8.1 Dosing Regimen and Administration**

The proposed dosing directions for HSX include:

- apply liberally 15 minutes before sun exposure
- reapply as needed or after towel drying, swimming, or perspiring
- children under 6 months of age: ask a doctor

The proposed dosing directions are consistent with the FM for Sunscreen Drug Products for OTC Human Use.

### **8.2 Drug-Drug Interactions**

No formal drug-drug interaction studies have been conducted with HSX. The sponsor states that ecamsule and its combination formulations are poorly absorbed (<1%) when topically applied to the skin, and therefore, it is unlikely that interactions with systemic medications would occur. Subjects who participated in the clinical trials were allowed to use any systemic or topical treatments. There were no safety signals noted due to a particular drug-drug interaction.

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### 8.3 Special Populations

HSX is indicated for healthy individuals. One safety concern that surfaced from the available clinical data is the use of sunscreens in subjects with predisposing dermatological conditions (see Section 7.4.2.4). The proposed labeling carries a warning to use caution when applying the sunscreen on damaged skin.

### 8.4 Pediatrics

The sponsor is requesting to market HSX in the OTC setting for daily use in children six months of age and older and in adults, and is requesting a waiver from the requirement to conduct studies in children younger than 6 months.

The following table shows the pediatric exposure to HSX and to other [redacted] sunscreen formulations containing some of its ingredients:

b(4)

TABLE 21. PEDIATRIC EXPOSURE TO HSX AND ITS INGREDIENTS IN OTHER [redacted] SUNSCREENS

Study	Formulation	N. subjects	Ages	Duration	Study type
18047	Helioblock SX	475 entered 278 completed	11 subjects (12-18 y.o.) 464 subjects (≥18 y.o.)	137 subjects for ≥12 months 187 subjects for 6-12 months 92 subjects for <6 months	Open label safety Self application
18057	Helioblock SX	144	≥18		Phase 3
2616	Helioblock SX	87	≥18		Phase 2
750.03	593-106 -471, [redacted] SPF 20 W/R	79	24 (6m-2 y.o.) 32 (2-6 y.o.) 8 (6-12 y.o.) 2 (12-18 y.o.) 13 (>18 y.o.)	Intermittent up to 6 months Average duration 40 days	
750.02	760.006 NDA 21-501, [redacted] SPF 15W/R	246	57 (5m-2 y.o.) 60 (2-6 y.o.) 62 (6-12 y.o.) 24 (12-18y.o.) 43 (>18y.o.)	Intermittent up to 12 months Average duration 4 months	
750.01	539.009 NDA 21-502, [redacted] SPF 15	248	78 (12-18 y.o.) 170 (>18y.o.)	Intermittent up to 12 months Average duration 10 months	
750.04	HSX [redacted] TiO <sub>2</sub>	135	46 (6m-2 years) 44 (2-6 years) 45 (6-12 years)	Intermittent up to 6 months Average duration	
EU Pediatric Cosmetic	Various	526*	207 (3-6 years) 319 (6-12 years)	>90% of subjects used sunscreen at least 15 days	

\* There were 363 subjects, some of which participated in more than one study.

The sponsor has not conducted long term safety studies in children younger than 12 years of age with the HSX formulation but is supplying safety data from studies conducted with the formulation 539.106 of the approved [redacted] SPF 20, which has the same four UV filters but at a

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slightly lower concentration (see Table 1 showing a comparison of the formulations). The medical reviewers for [REDACTED] SPF 20 considered that there was sufficient safety data in the 6 month to 12 years of age to support approval of the application without additional safety studies. b(4)

Study PEN.750.02, with the 3% ecamsule formulation, enrolled 179 children 6 months to 12 years of age (73% of all subjects), of which 69% of them (124/179) completed the study.

Study PEN.750.03, with a formulation containing only 2% ecamsule but containing also 2% titanium dioxide, included 64 children.

The sponsor claims that establishing the safety of ecamsule in the 3 approved formulations also establishes the safety of ecamsule for the HSX formulation. The HSX formulation not only contains a higher concentration of ecamsule but it also contains a higher concentration of titanium dioxide. Other OTC sunscreen and cosmetic products are currently being marketed containing that amount of titanium dioxide, such as Blue Lizard Baby formula and Solbar Shield, or even higher (8%) such as [REDACTED]. b(4)

The sponsor states that there are no safety concerns with titanium dioxide, avobenzene, and octocrylene because they are used according to the Final Monograph 21 CFR part 352. Regarding ecamsule, the sponsor states that several pharmacokinetic studies, reviewed for earlier [REDACTED] NDAs, show that the application of topical formulations containing 2-4.95% ecamsule showed virtually no absorption. b(4)

The sponsor has conducted a 6-month safety study (PEN.750.04) in children 6 months to 12 years of age but with a formulation slightly different from HSX, containing [REDACTED] titanium dioxide [REDACTED] used in the other studies in the NDA. In this study, 80% of the subjects used the product for less than 85 days, 50% for less than 50 days, and 30% for less than 30 days, and although this reviewer considers that this exposure is not appropriate to assess long term safety, no safety signal was detected in the study. b(4)

The EU Pediatric Cosmetic Use studies conducted with sunscreen formulations similar to HSX but which contained additional ingredients or higher concentrations of the same 4 ingredients in HSX support the safety of the HSX formulation.

Ecamsule has been marketed for children in Europe since 1996. In the opinion of this reviewer, there is an adequate extent of exposure and no unusual safety signals noted in the pediatric population down to 6 months of age. Clinical practice guidelines published by the American Academy of Pediatrics (AAP)<sup>2</sup> do not recommend using sunscreens in children less than 6 months of age. Nevertheless, many sunscreens are promoted for use in babies and there is probably wide use of these products in small children.

For NDAs 21-501 and 21-502, pediatric studies in children younger than 6 months were initially deferred (7/21/2006) and later waived (2/23/2007).

In the opinion of this reviewer, the HSX formulation should be labeled as requested by the sponsor for the use in children six months and older.

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See Section 7.2.7 for recommendations by the Division of Pediatric and Maternal Health.

## **8.5 Advisory Committee Meeting**

There is no advisory committee meeting planned for this NDA.

## **8.6 Literature Review**

A 120-day safety update has not been submitted at the time of writing this review. To support NDAs 21-501, 21-502, and 21-471, the sponsor had conducted a scientific literature search on all three active sunscreen ingredients up to January 2006, including the following databases: Medline, Embase, Biosis, Toxline, Hazardous Substances Data Bank, ToxFile, CancerLit, Pascal, HSELINE (Health and Safety), Allied and Complimentary Medicine, CA Search (Chemical Abstracts), and Global Health. The following is a summary of the findings:

Titanium dioxide: Nash J. Human safety and efficacy of ultraviolet filters and sunscreen products. *Dermatol Clinics* 2006; 24:35-51. Summary: A recent review of publications showing lack of cutaneous absorption.

Octocrylene: Madan V. Beck H. Contact allergy to octocrylene in sunscreen with recurrence from passive transfer of a cosmetic. *Contact Dermatitis*. 2005; 53: 241-242. Summary: two cases of allergy to octocrylene were reported in children, a 3 year old who had a reaction from a sunscreen and from a moisturizer containing octocrylene with positive delayed sensitization tests, and a 10 year old who had an allergic reaction to a sunscreen containing octocrylene.

This reviewer has identified one additional publication describing contact sensitization to octocrylene, as follows:

Delplace D, Blondeel A. Octocrylene: really non-allergenic? *Contact dermatitis* 2006; 54: 295. Summary: After several patients with a suggestive history of allergy to sunscreen products had negative tests with a sunscreen series but positive test results to sunscreen products, the sunscreen patch test series was modified to include octocrylene. Since then four patients were identified, three who had positive photoallergy testing and one who had positive delayed hypersensitivity testing to octocrylene and to sunscreen formulations containing the ingredient.

## **8.7 Postmarketing Risk Management Plan**

There is no postmarketing management plan.

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## **8.8 Other Relevant Materials**

There are no other relevant materials submitted for the review.

## **9. OVERALL ASSESSMENT**

### **9.1 Conclusions**

The safety profile of Helioblock SX SPF 40 Sunscreen Cream, containing ecamsule in combination with three monograph sunscreen ingredients is acceptable for OTC marketing.

### **9.2 Recommendation on Regulatory Action**

The proposed Helioblock SX SPF 40 Sunscreen Cream (Avobenzone 2%+Octocrylene 10%+Ecamsule (Mexoryl®) 3%, titanium dioxide 5.0%) has an acceptable safety profile, and therefore, is approvable for OTC marketing from the safety stand point. Final approvability depends on the outcome of the efficacy, preclinical, and chemistry data, which are being reviewed by other reviewers.

### **9.3 Recommendation on Postmarketing Actions**

#### **9.3.1 Risk Management Activity**

No special postmarketing risk management activities are recommended.

#### **9.3.2 Required Phase 4 Commitments**

No special postmarketing risk management activities are recommended.

#### **9.3.3 Other Phase 4 Requests**

None.

### **9.4 Labeling Review**

The proposed labeling for Helioblock SX SPF40 is included in Section 10.2. The labeling review is being done by the interdisciplinary scientist in the Office of Nonprescription Products. The sponsor incorporated all the important warnings for sunscreen drug products.

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**9.5 Comments to Applicant**

No comments.

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## 10. APPENDICES

### 10.1 Review of Individual Study Reports

#### 10.1.1 Study [redacted].1010.02      b(4)

This was a single-center, randomized, evaluator-blinded, intraindividual assessment of the skin moisturizing ability of two sunscreen formulations: One formulation was HSX with pigmentary TiO<sub>2</sub>, the other was "extremely similar" except for including [redacted] TiO<sub>2</sub>; both were compared to an untreated control site, using capacitance measures to assess transepidermal water loss (TEWL). Although the assessment of TEWL does not have regulatory utility, the study provides some safety data. b(4)

Investigator: [redacted]      b(4)

The study was conducted from 8/2006 to 10/2006.

There were 31 enrolled subjects (3 male, 28 female), 18-55 years old, with a dry skin score of  $\geq 2$  on the Stanfield Grading System on the skin of the forearms.

The 9-day study included 7 days of conditioning, in which forearms were washed twice daily with a provided soap and were not moisturized, and 2 days for product evaluation. Then study products were applied on day-8, for 24 hours, at the rate of 2 mg/cm<sup>2</sup> to 5x10 cm test sites, with one untreated control.

The primary parameter of the study was a change from baseline in capacitance as measured by a corneometer. The secondary parameter was a change from baseline in transepidermal water loss from the skin, as measured by a [redacted] evaporimeter, and readings were conducted through days 8 and 9. b(4)

The sponsor concludes that both formulations significantly moisturized the skin when compared to an untreated site, with no significant difference between the two formulations. No subjects were discontinued from the study and no AEs were reported.

#### 10.1.2 Study PEN 750.04. Long term safety study.

This protocol was submitted to IND 57,850 and reviewed in the Division of Dermatological Drug Products. The following are the reviewer comments conveyed to the sponsor:

1. The application of test product should not be required to be performed under supervision, in order to reflect true market usage in the large population who would benefit from frequent sunscreen use. Written instructions with diagrams should be sufficient, and incorporated into any planned future labeling.
2. The proposed subject instructions should be improved to reinforce the concept that sunscreen

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use is not a substitute for sun avoidance in peak conditions, and that sunscreen use is important for non-sunny days and non-beach areas as well.

3. Please specify the study centers to assure that disparate geographic areas will be represented, and how adequate sun exposure in those areas is obtained as well.

It appears the sponsor adopted these recommendations into the protocol.

Study Title: Clinical Safety Trial of Long-Term intermittent use of Helioblock ® SX Cream Formula 2834192.

Principal Investigators:

Study center 19	Irwin Kantor, MD.	Great Neck, NY
20	Elyse Rafal, MD	Huntington, NY
21	David Rodriguez, MD	Coral Gables, FL
22	Elaine Sigfrid, MD	St. Louis, MO

Institutional Review Board: Chesapeake Research Review, Inc.

Number of Subjects: 135.

Ages of Subjects: 6 months to 12 years inclusive.

Inclusion Criteria:

1. Male or female subjects of any race or skin type, 6 months to 12 years of age inclusive, willing to use the test product for six months. During the 6-month period, each subject had to plan for at least 14 days with outdoor activities, such as a beach vacation or swimming and outdoor sports activities, where the use of sunscreen is required.
2. Subjects who have signed an informed consent.
3. Subjects who are willing and capable of cooperating to the extent and degree required by the protocol, especially in regards to compliance with the long term dosing requirements.

Exclusion Criteria:

1. Subjects with a condition, or in a situation, which in the **investigator's opinion, may suggest a significant hazard for the subject, may confound the study results, or may interfere with the subject's participation** in the study.
2. Subjects who are lactating or pregnant.
3. Subjects with known sensitivities to any of the study ingredients.
4. Subjects who have participated in a clinical research study, including consumer product studies, within 30 days of enrollment.

Withdrawal Criteria:

Reasons for withdrawal could have included any of the following:

1. **Either at the investigator's request, for safety reasons (e.g. severe adverse reactions, or conditions that may jeopardize the subject's health if they were to continue in the trial), or at the**

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**subject's request.**

2. When the requirements of the protocol are not respected.
3. When a subject is lost to follow-up, despite the outlined attempts to contact the subjects.

Study Design: Multicenter, 6-month open label safety study

Study Objective: Determine the safety potential of Helioblock SX cream in long term intermittent use conditions for six months.

Study Plan: Thirty four pediatric subjects were enrolled in each of 4 independent centers to total 135 subjects, 45 in each of the following subgroups: 6 months to = 2 years; > 2 years to = 6 years; and > 6 years to = 12 years.

The following table summarizes the study schedule:

Procedure	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6 or Early Termination
	Baseline Visit	Visit 1	Visit 2	Telephone contact	Visit 3	Telephone contact	Visit 4 / Final Visit
Informed Consent	X						
Collect Demographic Information	X						
Inclusion/Exclusion Criteria	X						
Continuation Criteria <sup>1</sup>		X	X	X	X	X	
Medical History	X						
Dermatological Examination	X	X	X		X		X
Dispense Subject Diary	X	X	X		X		
Collect Subject Diary		X	X		X		X
Complete CRF Subject Questionnaire	X		X		X		X
Study Drug Weighed and Dispensed	X	X	X		X		
Study Drug Collected and Weighed		X	X		X		X
Concomitant Therapies Recorded	X	X	X		X		X
Urine Pregnancy Test*	X	X	X		X		X
Adverse Events		X	X		X		X
Exit Form							X

<sup>1</sup> Review inclusion/exclusion criteria (with the exception of age) and assure that the subject complies with the requirements of the protocol.  
 \*Urine Pregnancy Test was performed if subject was of childbearing potential or had begun menses since the last visit.

A protocol amendment 01 was approved by Chesapeake Research Review on 3/20/2006, with the following revisions:

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- A row was added to the study flow chart for Continuation Criteria to be completed during the study at months 1, 2, 3, 4, and 5, with review of inclusion criteria except for age.
- The sentence “subject must be using an acceptable form of birth control if the subject is sexually active” was added to the exclusion criteria.

Qualified subjects received Helioblock SX Sunscreen Cream in 100 ml tubes, formula 2843192, with [redacted] titanium dioxide. The following table compares this formulation to the HSX formulation used for the other studies in the NDA:

b(4)

TABLE 23. COMPOSITION OF FORMULATIONS. PIGMENTARY VERSUS [redacted] TITANIUM DIOXIDE

Composition (w/w%)	Pending NBA 22-009 formula Helioblock <sup>®</sup> SX Cream (pigmentary TiO <sub>2</sub> )	IND 57,850 PEN.750.04 formula [redacted] TiO <sub>2</sub>
<b>Active Ingredients</b>		
Avobenzene USP	2.00	2.00
Ecamsule*	3.00	3.00
Octocrylene USP	10.00	10.00
Titanium Dioxide USP	5.00	5.00
<b>Inactive Ingredients</b>		
Carbomer 940 NF	[redacted]	[redacted]
Carbomer 1342 NF	[redacted]	[redacted]
Cyclomethicone NF	[redacted]	[redacted]
Dimethicone NF, 200-350 cst	[redacted]	[redacted]
Edetate Disodium USP	[redacted]	[redacted]
Glycerin USP	[redacted]	[redacted]
Hydroxypropyl Methylcellulose USP	[redacted]	[redacted]
Isopropyl Palmitate NF	[redacted]	[redacted]
Methylparaben NF	[redacted]	[redacted]
Phenoxyethanol Ph. Eur.	[redacted]	[redacted]
Polyvinylpyrrolidone Eicosene copolymer	[redacted]	[redacted]
Propylene Glycol USP	[redacted]	[redacted]
Propylparaben NF	[redacted]	[redacted]
Stearic Acid NF	[redacted]	[redacted]
Aluminum Hydroxide	[redacted]	[redacted]
Stearyl Macroglycerides Ph. Eur.	[redacted]	[redacted]
Stearyl Alcohol NF	[redacted]	[redacted]
Trolamine NF	[redacted]	[redacted]
Purified Water USP	[redacted]	[redacted]

b(4)

b(4)

b(4)

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The sponsor comments that both formulations are **“extremely similar”**, and that the titanium  result in a slightly different inactive ingredient formulation. The sponsor believes that the formulation utilized in the study represents a **“worse case” scenario in terms of any untoward effects** and, therefore, considers that the study should adequately address the request to provide safety information in the adolescent population as the formulation used in the study would represent equal to or greater safety exposure issues than the formulation in HSX. Although one cannot predict how formulation changes of this type can affect the safety of a product, this reviewer considers that the **sponsor’s conclusion is acceptable**.

b(4)

The product was applied to sun exposed areas of the skin, approximately 15 minutes before each sun exposure, and reapplied during longer sun exposures and after swimming. The minimum exposure required was 14 days with outdoor exposure.

Investigators educated subjects regarding unnecessary and long term sun exposure and adequate sun protection (staying out of the sun at midday and seeking shaded areas, wearing clothing, hats, sunglasses). Subjects received verbal and written instructions as to the proper dosing and test product application techniques, and were showed at the baseline visit how to use the test product as **“homogeneously as possible to all sun exposed areas.”**

Subjects were seen at 1, 2, 4, and 6 months to monitor adverse events, dermatologic changes, and to collect diary information regarding sun exposure and product usage.

Concomitant products including other drug and cosmetic products were recorded. The only laboratory testing was urine pregnancy tests at baseline, 1, 2, 4, and 6 months. Only one subject was post-menses and administered pregnancy tests.

Compliance was tracked by diary and container weights.

**Safety Evaluation:**

Subjects had a dermatologic evaluation at baseline and at each follow-up visit, documenting skin type, and signs of irritation, sensitization, or photosensitivities. Adverse events were monitored and recorded by investigator interview and subject diary review.

**Statistical Analysis:**

All study statistics for the primary endpoints were descriptive, and no formal statistical hypotheses were tested.

**Results:**

The following table summarizes the demographic data for the enrolled subjects:

	6 mo – 2 yrs	> 2 – 6 yrs	> 6 – 12 yrs	Total
N	46	44	45	135
Age (years)				
Mean	1.77	4.88	9.57	5.39
SD	0.75	1.16	1.62	3.45
Range	0.63-2.98	3.02-6.96	7.04-12.95	0.63-12.95
	Number (%) <sup>1</sup> of Subjects			
Gender				
Male	28 (61)	27 (61)	27 (60)	82 (61)
Female	18 (39)	17 (39)	18 (40)	53 (39)
Race				
Caucasian	39 (85)	36 (82)	36 (80)	111 (82)
Black	2 (4)	1 (2)	2 (4)	5 (4)
Hispanic	2 (4)	7 (16)	6 (13)	15 (11)
Other	3 (7)	0 (0)	1 (2)	4 (3)
Skin Type				
Oily	0 (0)	0 (0)	0 (0)	0 (0)
Normal	39 (85)	27 (61)	33 (73)	99 (73)
Dry	7 (15)	17 (39)	11 (24)	35 (26)
Combination	0 (0)	0 (0)	1 (2)	1 (1)
Skin Phototype				
I	1 (3)	1 (3)	3 (7)	5 (4)
II	9 (24)	12 (30)	9 (20)	30 (25)
III	20 (54)	21 (53)	24 (53)	65 (53)
IV	4 (11)	4 (10)	6 (13)	14 (11)
V	3 (8)	2 (5)	3 (7)	8 (7)
VI	0 (0)	0 (0)	0 (0)	0 (0)
Sensitive Skin				
Self assessed	5 (11)	12 (27)	9 (20)	26 (19)
Atopic background	1 (2)	2 (17)	2 (22)	5 (19)
Previous intolerance to topical products	4 (8)	11 (92)	7 (78)	22 (85)
	1 (20)	0 (0)	0 (0)	1 (4)

<sup>1</sup> Denominator is the number of subjects in that age group, with the exception of the basis for sensitive skin assessment (last 3 rows), for which the denominator is the number of subjects with sensitive skin in that age group.  
 Data Source: Summary Table 14.1.6

Subjects were enrolled at 4 study centers (n=136, at 34 each), evenly distributed among the 3 age groups. A slight majority of subjects were female. The mean age of subjects was 5.39 years. Less than twenty per cent of subjects had sensitive skin, most of which were in the 2-6 years old group.

The sponsor states the study was conducted under GCP.

The following table summarizes protocol deviations:

Deviation	No. subjects (135)
Lost or discarded study drug, or failed to return	19 (14.1%)
Lost or did not return study diary	3 (2.2%)
Application site not documented in diary	1 (0.7%)
Early termination visit not conducted	5 (3.7%)
Visit 2 or 3 not as scheduled	15 (11.1%)
Fewer than 14 days sun exposure	10 (7.4%)
Due to early discontinuation	7 (5.2%)
Lost to follow up	1 (0.7%)
Normal completion with <14 days	2 (1.5%)

Additionally, 4 subjects returned the study medication more than 24 hour late.

Subject 21-29 was lost to follow-up and never returned the medication.

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The following table summarizes the extent of exposure during the study:

<b>TABLE 26. EXTENT OF EXPOSURE BY AGE. PEN 750.04</b>				
	<u>6 Months to ≤ 2 Years Old</u>	<u>&gt; 2 Years to ≤ 6 Years Old</u>	<u>&gt; 6 Years to ≤ 12 Years Old</u>	<u>Total</u>
Number of Subjects	46	44	45	135
<b>Number of Days Subject had Sun Exposure</b>				
n	45	44	45	134
Mean	71.56	71.80	87.69	77.05
STD	48.25	52.49	51.73	51.03
Range	1-160	1-168	17-168	1-168
<b>Total Length of Sun Exposure (Hours)</b>				
n	45	41	45	131
Mean	147.58	167.29	209.07	174.87
STD	103.04	121.08	147.77	127.18
Range	2-458	2-643	13-816	2-816
<b>Number of Applications</b>				
n	45	44	45	134
Mean	99.89	102.43	137.47	113.34
STD	79.84	89.51	99.01	90.78
Range	1-383	1-377	21-488	1-488
<b>Number of Days Product Used</b>				
n	45	44	45	134
Mean	68.49	68.73	87.76	75.04
STD	47.00	51.19	51.68	50.44
Range	1-160	1-168	17-172	1-172
<b>Total Product Used (g)</b>				
n	46	44	44	134
Mean	256.85	325.23	393.55	324.19
STD	243.66	360.33	325.38	315.36
Range	2-1040	2-1825	44-1596	2-1825
<b>Dosing Compliant<sup>a</sup></b>				
Yes	42 ( 93%)	39 ( 89%)	45 (100%)	126 ( 94%)
No	3 ( 7%)	5 ( 11%)	0 ( 0%)	8 ( 6%)

<sup>a</sup> A subject was considered compliant with the dosing regimen if they applied study product at least 14 days while enrolled in the study.

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The following table shows the number of days treatment was used by each subject:

TABLE 27. USE OF SUNSCREEN FOR EACH SUBJECT IN DAYS AND IN NUMBER OF APPLICATIONS							
Center	Subject	No. Applications	Days of use	Center	Subject	No. Applications	Days of use
19	1	62	51	20	1	180	121
	2	63	51		2	433	172
	3	13	10		3	114	77
	4	89	64		4	196	115
	5	4	3		5	135	82
	6	3	3		6	28	28
	7	44	27		7	19	19
	8	248	72		8	151	95
	9	112	75		9	148	95
	10	155	195		10	148	95
	11	146	138		11	1	1
	12	70	57		12	1	1
	13	110	72		13	38	37
	14	83	83		14	118	73
	15	80	80		15	111	70
	16	87	54		16	42	31
	17	70	45		17	1	1
	18	71	44		18	72	39
	19	79	50		19	73	40
	20	181	85		20	250	78
	21	134	76		21	252	79
	22	84	68		22	254	79
	23	86	70		23	81	68
	24	85	59		24	68	58
	25	71	46		25	86	70
	26	62	47		26	83	57
	27	11	10		27	92	58
	28	11	10		28	104	83
	29	161	156		29	142	109
	30	152	148		30	143	109
	31	156	151		31	116	87
	32	136	84		32	194	131
	33	136	84		33	115	45
	34	179	118		34	122	47

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TABLE 27. USE OF SUNSCREEN FOR EACH SUBJECT IN DAYS AND IN NUMBER OF APPLICATIONS (CONTINUATION)							
Center	Subject	No. Applications	Days of use	Center	Subject	No. Applications	Days of use
21	1	255	166	22	1	45	34
	2	200	141		2	45	34
	3	283	166		3	90	61
	4	197	155		4	24	18
	5	208	159		5	24	18
	6	488	154		6	175	134
	7	174	119		7	158	130
	8	175	119		8	44	30
	9	47	17		9	21	21
	10	191	150		10	20	19
	11	182	167		11	69	57
	12	114	109		12	56	47
	13	117	113		13	53	45
	14	179	119		14	37	33
	15	377	158		15	62	52
	16	383	158		16	62	52
	17	23	22		17	37	37
	18	221	167		18	30	30
	19	235	166		19	16	16
	20	183	162		20	15	15
	21	199	160		21	22	17
	22	223	123		22	23	18
	23	57	42		23	29	24
	24	58	48		24	45	27
	25	136	99		25	52	29
	26	136	98		26	44	41
	27	275	168		27	41	36
	28	267	166		28	48	41
	29	0	0		29	38	28
	30	69	55		30	34	30
	31	183	160		31	32	27
	32	194	160		32	23	18
	33	0	0		33	28	23
	34	225	153		34	27	33

The following table summarizes the cumulative number of subjects who used treatment for each duration of treatment. The numbers on the third column show the number of subjects who used treatment for fewer than the number of days shown on the first column:

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**TABLE 28. CUMULATIVE USAGE OF SUNSCREEN. DAYS. PEN 750.04**

Days of use	Number of subjects	% of 135 subjects with treatment shorter than the number of days on column #1	Days of use	Number of subjects	% of 135 subjects with treatment shorter than the number of days on column #1
0	2	1.48	45	57+5=62	45.88
1	2+6=8	5.92	46	62+1=63	46.62
3	8+2=10	7.40	47	63+3=66	48.84
10	10+3=13	9.62	48	66+1=67	49.58
15	13+1=14	10.36	50	67+1=68	50.32
16	14+1=15	11.10	51	68+2=70	51.80
17	15+2=17	12.58	52	70+2=72	53.28
18	17+4=21	15.54	54	72+1=73	54.02
19	21+3=24	17.76	55	73+1=74	54.76
21	24+1=25	18.50	57	74+3=77	56.98
22	25+1=26	19.24	58	77+2=79	58.46
23	26+1=27	19.98	59	79+1=80	59.20
24	27+3=30	22.20	61	80+1=81	59.94
27	30+3=33	24.42	64	81+1=82	60.68
28	33+3=36	26.64	68	82+3=85	62.90
29	36+1=37	27.38	70	85+3=88	65.12
30	37+3=40	29.60	72	88+3=91	67.34
31	40+1=41	30.34	73	91+2=93	68.82
33	41+2=43	31.82	75	93+1=94	69.56
34	43+2=45	33.30	76	94+1=95	70.30
36	45+1=46	34.04	77	95+1=96	71.04
37	46+2=48	35.52	78	96+1=97	71.78
38	48+1=49	36.26	79	97+2=99	73.26
39	49+1=50	37.00	80	99+1=100	74.00
40	50+1=51	37.74	81	100+1=101	74.74
41	51+2=53	39.22	82	101+1=102	75.48
42	53+2=55	40.70	83	102+3=105	77.70
44	55+2=57	42.18	84	105+2=107	79.18
			85	107+1=108	79.92

Although the study was labeled as a Clinical Safety trial of Long-Term intermittent use, the protocol only required a minimum treatment of 14 days of sun exposure to declare the subject as treatment compliant. Eighty % of the subjects used sunscreen for less than 85 days. Fifty % of subjects used the sunscreen for less than 50 days. Thirty % of subjects used the sunscreen for less than 30 days. This reviewer considers that the treatment exposure in the study is insufficient for the assessment of long term safety. Nevertheless, the study does provide some useful safety data.

The following table summarizes the cumulative number of subjects who used treatment for each number of treatment applications. The numbers on the third column show the number of subjects who used treatment for fewer than the number of applications shown on the first column:

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TABLE 29. CUMULATIVE USAGE OF SUNSCREEN. APPLICATIONS. PEN 750.04					
Applications	N umber of subjects	% of 135 subjects that had a number of applications fewer than the number of applications on column #1	Applications	N umber of subjects	% of 135 subjects that had a number of applications fewer than the number of applications on column #1
0	2	1.26	48	40+1=41	30.34
1	2+3=5	3.70	52	41+1=42	31.08
3	5+1=6	4.44	53	24+1=43	31.82
4	6+1=7	5.18	56	43+1=44	32.56
11	7+2=9	6.66	57	44+1=45	33.30
13	9+1=10	7.40	58	45+1=46	34.04
15	10+1=11	8.14	62	46+6=49	36.26
16	11+1=12	8.88	63	49+2=51	37.74
19	12+1=13	9.62	68	51+1=52	38.48
20	13+1=14	10.36	69	52+2=54	39.96
21	14+1=15	11.10	70	54+2=56	41.44
22	15+2=17	12.58	71	56+2=58	42.92
23	17+3=20	14.80	72	58+1=59	43.66
24	20+2=22	16.28	73	59+1=60	44.40
27	22+1=23	17.02	79	60+1=61	45.15
28	23+2=25	18.50	80	61+1=62	45.88
29	25+1=26	19.24	81	62+1=63	46.62
30	26+1=27	19.98	83	63+2=65	48.10
34	27+1=28	20.72	84	65+1=66	48.84
37	28+2=30	22.20	85	66+1=67	49.58
38	30+2=32	23.68	86	67+2=69	51.06
41	32+1=33	24.42	87	69+1=70	51.8
42	33+1=34	25.16	89	70+1=71	52.54
44	34+3=37	27.38	90	71+1=72	53.28
45	37+3=40	29.60	92	72+1=73	54.00

Fifty percent of subjects used fewer than 86 applications.

This reviewer considers that the use of treatment in this study, either expressed as total number of days of treatment or as total number of treatment applications is not adequate for the study of long term safety, but nevertheless the study provides useful safety data.

Exposure ranged from 1 to 172 days (mean=75.04). Ninety four % of subjects were dosing compliant, i.e. they used study drug for at least 14 days, as specified by the protocol.

The following table summarizes the study discontinuations:

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	6 Months to < 2 Years Old	> 2 Years to < 6 Years Old	> 6 Years to < 12 Years Old	Total
Number of Subjects Enrolled	46	45	45	136
Number of Subjects Included in AST Analyses	46	44	45	135
Subjects with Normal Study Completion	42	39	44	125
<b>Premature Study Discontinuation Reason</b>				
Adverse Event	1	5	0	6
Subject's Request	2	0	0	2
Protocol Violation	0	0	0	0
Lost to Follow-up	0	1	1	2
Other <sup>a</sup>	1	0	0	1

<sup>a</sup> Subject 20-11: Dropped as per PI, due to siblings adverse even  
 SOURCE: [REDACTED]

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Eleven (8%) subjects discontinued early:

- Subject 21-29 was lost to follow up after the first application.
- Subject 20-21 was dropped from the study because a sibling (20-12) participating in the study had an AE.
- Six subjects because of application site reaction: 19-05, 19-06, 20-12, 20-17, 21-17, and 21-22.

There were some minor protocol violations, as summarized in the following table:

Deviation	Subjects (N=135)
Failure to return medication	19 (14.1%)
Failure to return diary	3 (2%)
Fewer than 14 days sun exposure	10 (7.4%)
Early termination visit not conducted	5 (3.7%)

The most common protocol violation was failure to return medication, followed by fewer than 14 days of sun exposure in 10 subjects of which 8 were either lost to follow up or discontinued from the study, and the remaining two had 10-days of sun exposure each (19-27 and 19-28).

Adverse events:

No deaths, pregnancies, or serious treatment-related AEs were recorded during the study. Three subjects experienced 5 severe non treatment related AEs, all in the 6 month to 2 years old group (fatigue, pyrexia, and nasopharyngitis) and in the 6-12 years old group (pneumonia, back pain). Of the 135 subjects, 86 (64%) experienced at least one AE. Eight subjects (6%) experienced a cutaneous AE at least possibly related.

The following table summarizes the number of subjects in the safety population (N=135) with AEs by MEDRA organ class and preferred terms:

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<b>TABLE 32. AES BY MEDRA ORGAN CLASS AND PREFERRED TERM</b>		
<b>SYSTEM ORGAN CLASS / Preferred Term</b>	<b>No.</b>	<b>%</b>
<b>INFECTIONS &amp; INFESTATIONS</b>	<b>46</b>	<b>34</b>
Bronchitis	2	1
Bronchopneumonia	1	1
Coxsackie viral infection	1	1
Ear infection	9	7
Erythema infectiosum	1	1
Fungal rash	1	1
Furuncle	1	1
Gastroenteritis viral	4	3
Hand, foot & mouth disease	1	1
Impetigo	1	1
Lice infestation	1	1
Molluscum contagiosum	3	2
Nasopharyngitis	16	12
Otitis externa	1	1
Otitis media	2	1
Pharyngitis streptococcal	4	3
Rhinitis	1	1
Roseola	1	1
Sinusitis	2	1
Skin infection	1	1
Tooth abscess	2	1
Upper respiratory tract infection	6	4
Urinary tract infection	1	1
Viral infection	5	4
<b>INJURY, POISONING AND PROCEDURAL COMPLICATIONS</b>	<b>31</b>	<b>23</b>
Arthropod bite	13	10
Contusion	1	1
Excoriation	15	11
Injury	1	1
Periorbital hematoma	1	1
Post-traumatic pain	2	1
Skin laceration	1	1
Sunburn	5	4
Tooth fracture	1	1
Wound	1	1
<b>METABOLISM &amp; NUTRITION DISORDERS</b>	<b>1</b>	<b>1</b>
Dehydration	1	1
<b>MUSCULOSKELETAL &amp; CONNECTIVE TISSUE DISORDERS</b>	<b>2</b>	<b>1</b>
Back pain	1	1
Myalgia	1	1
<b>NEOPLASMS BENIGN, MALIGNANT &amp; UNSPECIFIED</b>	<b>1</b>	<b>1</b>
Melanocytic nevus	1	1
<b>NERVOUS SYSTEM DISORDERS</b>	<b>3</b>	<b>2</b>
Headache	2	1
Tension headache	1	1
<b>RESPIRATORY, THORACIC &amp; MEDIASTINAL DISORDERS</b>	<b>19</b>	<b>14</b>
Allergic cough	1	1
Asthma	1	1
Cough	8	6

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<b>SYSTEM ORGAN CLASS / Preferred Term</b>	<b>No.</b>	<b>%</b>
Nasal congestion	4	3
Pharyngolaryngeal pain	2	1
Pulmonary congestion	1	1
Rhinitis allergic	1	1
Rhinorrhea	3	2
<b>SKIN &amp; SUBCUTANEOUS TISSUE DISORDERS</b>	<b>41</b>	<b>30</b>
Blister	1	1
Café au lait spots	1	1
Dermatitis	1	1
Dermatitis allergic	1	1
Dermatitis contact	3	2
Dermatitis diaper	4	3
Dermatosis	1	1
Dry skin	4	3
Ecchymosis	2	1
Eczema	13	10
Ephelides	1	1
Erythema	3	2
Keratosis pilaris	2	1
Livedo reticularis	1	1
Nail dystrophy	1	1
Pityriasis alba	2	1
Pityriasis rosea	1	1
Pruritis	2	1
Rash	4	3
Rash macular	1	1
Rash papular	2	1
Rash pruritic	1	1
Scab	1	1
Skin chapped	1	1
Skin exfoliation	1	1
Skin nodule	1	1
Urticaria	1	1

*Data Source: Summary Table 14.3.3.2*

The greatest number of subjects reported events in the infections and infestations class (34%), followed by skin and subcutaneous disorders (30%), injury, poisoning and procedural complications (23%). Most events were reported by a single subject or by only 1% of subjects. Most AEs were mild or moderate. The most common was nasopharyngitis (12%). The majority of treatment related AEs were cutaneous. No racial or skin type group showed a predominance of AEs.

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The following table summarizes the dermatological AEs by severity:

<b>TABLE 33. DERMATOLOGICAL AES BY SEVERITY</b>			
	<u>Mild</u>	<u>Moderate</u>	<u>Severe</u>
<b>6 Months to ≤ 2 Years Old (N=46)</b>			
<b>Number of Events Reported</b>	<b>36</b>	<b>4</b>	<b>0</b>
<b>System Organ Class<sup>1</sup></b>			
<b>General disorders and administration site conditions</b>			
Application site rash	1 ( 2%)	0 ( 0%)	0 ( 0%)
<b>Infections and infestations</b>	2 ( 4%)	1 ( 2%)	0 ( 0%)
Erythema infectiosum	0 ( 0%)	1 ( 2%)	0 ( 0%)
Fungal rash	1 ( 2%)	0 ( 0%)	0 ( 0%)
Molluscum contagiosum	1 ( 2%)	0 ( 0%)	0 ( 0%)
<b>Injury, poisoning and procedural complications</b>	2 ( 4%)	2 ( 4%)	0 ( 0%)
Contusion	0 ( 0%)	1 ( 2%)	0 ( 0%)
Excoriation	2 ( 4%)	1 ( 2%)	0 ( 0%)
<b>Skin and subcutaneous tissue disorders</b>	17 ( 37%)	1 ( 2%)	0 ( 0%)
Dermatitis	1 ( 2%)	0 ( 0%)	0 ( 0%)
Dermatitis contact	1 ( 2%)	0 ( 0%)	0 ( 0%)
Dermatitis diaper	4 ( 9%)	0 ( 0%)	0 ( 0%)
Dry skin	2 ( 4%)	0 ( 0%)	0 ( 0%)
Ecchymosis	1 ( 2%)	0 ( 0%)	0 ( 0%)
Eczema	4 ( 9%)	0 ( 0%)	0 ( 0%)
Erythema	1 ( 2%)	1 ( 2%)	0 ( 0%)
Keratosis pilaris	1 ( 2%)	0 ( 0%)	0 ( 0%)
Pityriasis alba	1 ( 2%)	0 ( 0%)	0 ( 0%)
Rash	2 ( 4%)	0 ( 0%)	0 ( 0%)
Scab	1 ( 2%)	0 ( 0%)	0 ( 0%)
Skin chapped	1 ( 2%)	0 ( 0%)	0 ( 0%)
Skin nodule	1 ( 2%)	0 ( 0%)	0 ( 0%)
Urticaria	1 ( 2%)	0 ( 0%)	0 ( 0%)

The majority of cutaneous AEs were mild and occurred predominantly in the 6 month to 2-year-old age group. Only 6 were treatment related (rash, exfoliation, pruritus, erythema, edema, and papules). One subject developed mild urticaria that resolved without treatment.

A comparison of dermatological treatment AEs by subject predisposing background showed only one subject (20-17, atopic) who had a mild application site AE.

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The following table summarizes the AEs and the relationship to study drug:

Subject No.	Subject Age	Preferred Term (number of occurrences)	Severity	Related to Study Drug	Subject Discontinued Due to the AE(s)?
<b>6 months to 2-years old</b>					
21-31	0.63	lacrimation increased (1)	mild	definitely	No
21-33	1.73	application site rash (1)	mild	probably	Yes
<b>&gt;2 to 6 years old</b>					
19-06	3.79	application site rash (3)	mild	possibly	Yes
		application site rash (2)	moderate	possibly	Yes
		application site exfoliation (2)	mild	possibly	Yes
20-12	4.09	application site pruritis (2)	moderate	definitely	Yes
		application site erythema (2)	moderate	definitely	Yes
		application site oedema (2)	moderate	definitely	Yes
		application site papules (1)	moderate	definitely	Yes
19-05	4.87	application site exfoliation (2)	mild	possibly	Yes
		application site rash (1)	mild	possibly	Yes
		application site rash (2)	moderate	possibly	Yes
		eye pruritis (1)	mild	possibly	Yes
20-17	5.88	application site rash (2)	mild	possibly	Yes
21-17	6.27	application site rash (2)	moderate	probably	Yes
		application site pruritis (1)	moderate	probably	Yes
<b>&gt;6 to 12 years old</b>					
19-22	8.26	application site rash (1)	mild	possibly	No

Data Source: Listing 16.2.7

Because of the small number of AEs, no age trend could be shown.

The following table summarizes the treatment related AEs:

SYSTEM ORGAN CLASS / Preferred Term	No.	%
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</b>	<b>7</b>	<b>5</b>
Application site erythema	1	1
Application site exfoliation	2	1
Application site edema	1	1
Application site papules	1	1
Application site pruritis	2	1
Application site rash	6	4
<b>EYE DISORDERS</b>	<b>2</b>	<b>1</b>
Eye pruritis	1	1
Lacrimation increased	1	1

Data Source: Listing 16.2.7

Most treatment related application site events occurred in the 2-6 years old group (5 subjects or 11%), but the significance of this finding is of difficult interpretation because of the small number of subjects (n=8) reporting treatment related AEs. The most common cutaneous AE in this group were eczema (14%, all of them mild), application site reaction (5%, all mild), pruritis (5%, all mild), and application site rash (2% mild + 7% moderate).

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The 6-12 years old group had the fewest application site AEs (2%) and skin and subcutaneous tissue disorders (2%), eczema being the most common (7%). Only one subject had a treatment related application site rash.

The following table summarizes the AEs:

	<b>No.</b>	<b>%</b>
<b>Subjects in the Safety Population</b>	<b>135</b>	<b>100</b>
<b>Subjects reporting at least one adverse event</b>	<b>86</b>	<b>64</b>
Mild	50	37
Moderate	33	24
Severe	3	2
<b>Subjects reporting at least one treatment-related AE<sup>1</sup></b>	<b>8</b>	<b>6</b>
Dermatological	8	6
Non-Dermatological	1	<1
<b>Subjects with an AE leading to discontinuation</b>	<b>6</b>	<b>4</b>
Dermatological	6	4
Non-Dermatological	0	0

<sup>1</sup> Assessed by the Investigator as definitely, probably or possibly related to the study drug.  
 Data Source: Summary Table 14.3.3.1, Listing 16.2.7, Listing 16.2.9.4

The majority of subjects experienced mild (37%) or moderate (24%) AEs. Only 2% experienced severe AEs. Eight (6%) subjects experienced AEs considered by the investigator to be possibly, probably or definitely treatment related, all of them cutaneous (application site rash, exfoliation, pruritus, edema or papules), two of them ocular (lacrimation, eye pruritus). In 6 of the 8, the AE event led to study

discontinuation.

**Summary and conclusions:**

In this long term safety study, there were no deaths or serious treatment related AE. There were 5 serious AEs but they were not treatment related.

Sixty four % of subjects experienced at least one AE. Eight (6%) subjects reported AEs that could have some relationship to treatment, all of them dermatological and two ocular, all of them mild or moderate, and in 6 of them the AE led to study discontinuation. All AEs resolved.

The highest incidence of cutaneous reactions occurred in the 6 month-2 years old group but only two of these were related to treatment.

Overall, Helioblock SX Cream appears to have been well tolerated in the study.

**10.1.3 EU Pediatric Cosmetic Use Studies.**

During End-of-Phase II discussions, FDA suggested that the [redacted] formulations be studied in 100 pediatric subjects <12 years of age in long term use studies. In order to address the FDA request for safety data in pediatric subjects <12 years of age, L'Oréal has completed two such studies that enrolled pediatric subjects (PEN.750.02 and PEN.750.03), and has also summarized safety data from 14 pediatric (cosmetic) use studies that were conducted outside of the United States for the non-US marketing of qualitatively similar sunscreen products. The 14 pediatric non-US cosmetic safety studies used the same 4 active ingredients (octocrylene, avobenzone, ecamsule, and titanium dioxide) as Helioblock SX Cream SPF 40. A comparison of the active

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ingredients in the formulations used in the 14 pediatric cosmetic use studies as compared to Helioblock SX Cream SPF 40 is shown in the following table:

Study	SPF	Active Ingredient (%)			
		Ecamsule	Avobenzone	Octocrylene	TiO <sub>2</sub>
<b>Helioblock® SX Cream SPF 40</b>					
RD.06.SRE.18047	40	3	2	10	5
<b>Pediatric Cosmetic Use</b>					
IEUT 04005	60	1.5	2.5	10	6.5
ECUT 04011	30	1.5	3	10	8.25
ECUT 04012	40	1.5	3	10	16.7
ECUT 04013	20	1.5	2.5	10	2.8
ECUT 04014	40	1.5	3	10	8.25
IEUT 03066	60	3	3	10	4
IEUT 04026	30	3	3	3.5	4
IEUT 03074	30	4.5	2	9	3
IEUT 04004	60	4.5	3	10	4
IEUT 04052	60	4.5	3.5	3.5	5.94
IEUT 04053	60	4.5	3	5	5.94
ECUT 04010	60	>6	3.5	10	5
ECUT 04017	45	>6	2	3.5	5
IEUT 03058*	60	>6	3	10	6

Seven of the formulations contained ecamsule at a higher concentrations than in HSX. Four of the formulation studied contained a higher concentration of titanium dioxide than HSX.

In 13 of these studies, the subjects were required to have continuous use of the sunscreen for at least 21 days with applications at least twice daily during the period of strongest sun for the region.

The sponsor states that, taken together, the long-term and short-term continuous daily use of sunscreen cover the range of sunscreen use patterns that would be expected for Helioblock SX Cream SPF 40. This reviewer concurs with this conclusion.

Some subjects in the pediatric cosmetic use studies participated in more than one of these studies. A total 363 subjects participated in these studies, with 107 subjects participating in more than one study. Therefore, the total number of exposures by pediatric subjects in these 14 studies was 526 (207 (3-6 years old), 319 (6-12 years old)).

The 14 Pediatric Cosmetic Use studies were open-label and single-center, in children 3-12 years old, and were conducted with IRB approval in one of four countries: Argentina (7 studies), Spain (2 studies), France (4 studies), or Brazil (1 study), between 2003 and 2005. In 13 of the studies, subjects were required to apply sunscreen twice daily for at least 21 days. The following table

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summarizes the time of enrollment and completion date and the number of subjects in each study:

<b>Study</b>	<b>Date First Subject Enrolled</b>	<b>Date Last Subject Completed</b>	<b>Number of Subjects That Used Sunscreen at least Once</b>
IEUT 03058	10 November 2003	2 December 2003	48
IEUT 03074	10 February 2004	1 March 2004	41
IEUT 04004	19 February 2004	10 March 2004	30
IEUT 04005	9 March 2004	29 March 2004	33
IEUT 03066	18 March 2004	7 April 2004	30
ECUT 04010	14 April 2004	27 July 2004	41
ECUT 04011	5 May 2004	30 June 2004	38
IEUT 04026	4 June 2004	25 June 2004	40
ECUT 04017	14 June 2004	3 August 2004	39
ECUT 04013	21 June 2004	19 July 2004	40
ECUT 04014	23 June 2004	12 March 2005	42
ECUT 04012	1 September 2004	13 October 2004	40
IEUT 04052	27 September 2004	18 October 2004	31
IEUT 04053	5 October 2004	26 October 2004	33

The following tables summarizes the duration of exposure in these studies:

<b>Study</b>	<b>≤ 7 days</b>	<b>8 to 14 days</b>	<b>15 to 21 days</b>	<b>22 to 28 days</b>
IEUT 03058	10 (20.8)	36 (75.0)	2 (4.2)	0 (0.0)
IEUT 03066	0 (0.0)	0 (0.0)	30 (100.0)	0 (0.0)
IEUT 03074	0 (0.0)	0 (0.0)	41 (100.0)	0 (0.0)
IEUT 04004	0 (0.0)	0 (0.0)	30 (100.0)	0 (0.0)
IEUT 04005	0 (0.0)	0 (0.0)	33 (100.0)	0 (0.0)
IEUT 04052	2 (6.5)	0 (0.0)	1 (3.2)	28 (90.3)
IEUT 04053	1 (3.0)	0 (0.0)	0 (0.0)	32 (97.0)
IEUT 04026	0 (0.0)	0 (0.0)	40 (100.0)	0 (0.0)
ECUT 04010	1 (2.4)	0 (0.0)	26 (63.4)	14 (34.1)
ECUT 04011	0 (0.0)	0 (0.0)	26 (68.4)	12 (31.6)
ECUT 04012	0 (0.0)	0 (0.0)	22 (55.0)	18 (45.0)
ECUT 04017	0 (0.0)	0 (0.0)	11 (28.2)	28 (71.8)
ECUT 04013	0 (0.0)	0 (0.0)	18 (45.0)	22 (55.0)
ECUT 04014	3 (7.1)	2 (4.8)	36 (85.7)	1 (2.4)
<b>All Studies</b>	<b>13(2.5)</b>	<b>36 (6.8)</b>	<b>216 (41.1)</b>	<b>261 (49.6)</b>

*Data Source: Item 8 Section 14 Appendix C Table 1, 1*

Over all studies, more than 90% of the subjects used sunscreen for at least 15 days. The exception was Study IEUT 03058, where the majority of subjects used sunscreen for 8 to 14 days. The following table summarizes the study design of the Pediatric Cosmetic Use studies:

**TABLE 40. SUMMARY OF PEDIATRIC COSMETIC USE STUDIES**

Study No. Formula #	Study Design	No. Subjects	Age/Sex/ Other	Dosage	Duration of Exposure	Status	Results
<b>Supportive Cosmetic Pediatric Use Safety Studies on Related Sunscreens</b>							
IEUT 03058 CRÈME SOLAIRE SPF60 #293406	Cosmetic short term use, single center, open label safety study	48 enrolled 48 completed	Range 3 – 12 X=7.8 years 48% female 4.2% sensitive skin 25% atopic	2 mg/cm <sup>2</sup> , 1.2 g face, 0.6 g neck, twice daily	8 days	Complete	Sunscreen was safe and well tolerated: 5 subject with related AEs (10.4%), all mild or moderate; 4 acne, 2 dermatitis, 1 dryness, 1 erythema, 2 pruritus. No serious AEs. 1 discontinuation due to unrelated AE.
IEUT 03066 LAIT SOLAIRE IP 60 #293540	Cosmetic short term use, single center, open label safety study	32 enrolled 30 completed	Range 3 – 12 X=7.9 years 43% female 43% sensitive skin face, 27% body 40% atopic	As much as necessary to cover exposed areas. Use at least twice daily	21 days	Complete	Sunscreen was safe and well tolerated: 2 subjects with related AEs (6.7%), all mild; 2 acne, 1 skin discomfort. No discontinuations due to AEs. No serious AEs.
IEUT 03074 LAIT SOLAIRE IP 30 #293546	Cosmetic short term use, single center, open label safety study	42 enrolled 41 completed	Range 3 – 12 X=8.2 years 59% female 51% sensitive skin face, 34% body 54% atopic	As much as necessary to cover exposed areas. Use at least twice daily	21 days	Complete	Sunscreen was safe and well tolerated: 1 subjects with related mild AE (2.4%), 1 erythema. No discontinuations due to AEs. No serious AEs.
IEUT 05005 LAIT SOLAIRE IP 60 #293611	Cosmetic short term use, single center, open label safety study	32 enrolled 30 completed	Range 3 – 12 X=7.2 years 43% female 60% sensitive skin face, 23% body 6.7% atopic	As much as necessary to cover exposed areas. Use at least twice daily	21 days	Complete	Sunscreen was safe and well tolerated: 2 subjects with related mild AEs (6.7%), 1 erythema; 1 ocular erythema, 1 ocular discomfort, 1 ocular heat. No discontinuations due to AEs. No serious AEs.
IEUT 04005 LAIT SOLAIRE IP 60 #293401	Cosmetic short term use, single center, open label safety study	35 enrolled 33 completed	Range 3 – 12 X=7.9 years 43% female 43% sensitive skin face, 27% body 40% atopic	As much as necessary to cover exposed areas. Use at least twice daily	21 days	Complete	Sunscreen was safe and well tolerated: 3 subjects with related mild AEs (9.1%), 2 erythema; 1 dryness, 1 acne. No discontinuations due to AEs. No serious AEs.

**TABLE 40. SUMMARY OF PEDIATRIC COSMETIC USE STUDIES (CONTINUED)**

Study No. Formula #	Study Design	No. Subjects	Age/Sex/ Other	Dosage	Duration of Exposure	Status	Results
IEUT 04052 LAIT SOLAIRE SPF 60 #736089	Cosmetic short term use, single center, open label safety study	31 enrolled 31 completed	Range 3 – 12.6 X=8.3 years 42% female 77% sensitive skin face, 68% body 39% atopic	As much as necessary to cover exposed areas. Use at least twice daily	21 days	Complete	Sunscreen was very well tolerated in 26 subjects and not well tolerated in 2 subjects: 5 subjects with related AEs (16.1%), 3 erythema, 1 dermatitis, 1 skin discomfort, 1 dryness, 1 pruritus, 1 acne; 2 subjects with severe AEs; others mild or moderate. No serious AEs. 2 discontinuations due to AEs, both related.
IEUT 04053 LAIT SOLAIRE SPF 60 #736013/1	Cosmetic short term use, single center, open label safety study	33 enrolled 33 completed	Range 3 – 11 X=7.5 years 42% female 57% sensitive skin face, 97% body 49% atopic	As much as necessary to cover exposed areas. Use at least twice daily	21 days	Complete	Sunscreen was safe and well tolerated in all except 1 subject: 3 subjects with related mild or moderate AEs (9.1%), 1 erythema, 1 dermatitis, 1 acne. No serious AEs. 1 discontinuation due to related AEs.
IEUT 04026 LAIT SOLAIRE IP 30 #293636/2	Cosmetic short term use, single center, open label safety study	45 enrolled 40 completed	Range 3 – 12 X=7.0 years 53% female 100% sensitive skin face, 63% body 30% atopic	As much as necessary to cover exposed areas. Use at least twice daily	21 days	Complete	Sunscreen was safe and well tolerated: 3 subjects with related mild AEs (7.5%), 1 erythema, 1 ocular discomfort, 1 eye tearing. No serious AEs. 1 discontinuation due to unrelated AE.
ECUT 04010 (IK 177) LAIT SOLAIRE SPF 60 #293445/2	Cosmetic short term use, single center, open label safety study	41 enrolled 40 completed	Range 3 – 12 X=7.2 years 54% female 100% sensitive skin face, 63% body 66% atopic	Apply to face and body by massage until complete penetration; use at least twice daily	21 days	Complete	Sunscreen had moderate acceptability being very good in 39 of 41 subjects: 2 subjects with moderate related AEs (4.9%), 2 irritant dermatitis. No serious AEs. 1 discontinuation due to related AE
ECUT 04011 (IK 181) SPRAY SOLAIRE SPF 30 #293565	Cosmetic short term use, single center, open label safety study	40 enrolled 38 completed	Range 3 – 12 X=7.6 years 65% female 100% sensitive skin 53% atopic	Apply to face and body by massage until complete penetration; use at least twice daily	21 days	Complete	Sunscreen was safe and had very good acceptability: no related AEs. No serious AEs. No discontinuations due to AEs.

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**TABLE 40. SUMMARY OF PEDIATRIC COSMETIC USE STUDIES (CONTINUED)**

Study No. Formula #	Study Design	No. Subjects	Age/Sex/ Other	Dosage	Duration of Exposure	Status	Results
ECUT 04012 (IK 182) SPRAY SOLAIRE IP 40 #293527	Cosmetic short term use, single center, open label safety study	40 enrolled 40 completed	Range 3 – 12 X=6.8 years 50% female 100% sensitive skin 53% atopic	Apply to face and body by massage until complete penetration; use at least twice daily	21 days	Complete	Sunscreen was safe and had very good acceptability: no related AEs. No serious AEs. No discontinuations due to AEs.
ECUT 04017 (IK 335) LAIT SOLAIRE SPF 45 #293637	Cosmetic short term use, single center, open label safety study	41 enrolled 39 completed	Range 3 – 12 X=6.9 years 49% female 100% sensitive skin 61% atopic	Apply to face and body by massage until complete penetration; use at least twice daily	21 days	Complete	Sunscreen was safe and had very good acceptability: no related AEs. No serious AEs. No discontinuations due to AEs.
ECUT 04013 (EF Pk 030) SPRAY SOLAIRE COLORE IP 20 #293658	Cosmetic short term use, single center, open label safety study	41 enrolled 41 completed	Range 3 – 12 X=7.4 years 46% female 98% sensitive skin 20% atopic	Apply to face and body by massage until complete penetration; use at least twice daily	21 days	Complete	Sunscreen was safe and had very good acceptability: no related AEs. No serious AEs. No discontinuations due to AEs.
ECUT 04014 (Pk 031) SPRAY SOLAIRE SPF 40 #293568/2	Cosmetic short term use, single center, open label safety study	42 enrolled 38 completed	Range 3 – 12 X=6.4 years 57% female 100% sensitive skin 26% atopic	Apply to face and body by massage until complete penetration; use at least twice daily	21 days	Complete	Sunscreen had moderate acceptability being very good in 38 of 41 subjects: 3 subjects with severe related AEs (7.0%), 1 dermatitis, 2 erythema, 3 pruritus. No serious AEs. 3 discontinuations due to related AEs.

**Adverse Events:**

Non-related adverse events were not systematically captured in any of the 14 studies. AEs were collected by using a predefined clinical signs page but the page was not identical for all studies. Eleven captured information on ocular signs and symptoms. The following table summarizes the AEs:

**TABLE 41. DERMATOLOGIC ADVERSE EVENTS IN THE PEDIATRIC COSMETIC USE STUDIES**

Adverse Event	All Studies (N=526)	
	No.	%
<b>Any Dermatologic Adverse Event</b>	<b>36</b>	<b>6.8</b>
Erythema	22	4.2
Acne	9	1.7
Pruritus	6	1.1
Dermatitis	5	1.0
Dryness Irritant	3	0.6
Dermatitis Skin	2	0.4
Discomfort	2	0.4
Desquamation	1	0.2

*Data Source: Item 8 Section 14 End of Text Tables - Table 2. 1; Pediatric Cosmetic Use Safety Report Listing 3 Adverse Events*

Thirty-six subjects (6.8%) across all EU pediatric cosmetic use studies reported dermal adverse events. Of the subjects who had dermal adverse events, most had only one. Erythema was the most frequent; acne was the second followed next by pruritus and dermatitis. The remaining dermal adverse events were reported at an incidence less than 1 %.

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The following table summarizes the AEs by content of ecamsule in the sunscreen used:

TABLE 42. ADVERSE EVENTS IN SUBJECTS WHO USED SUNSCREEN $\geq$ 14 DAYS DURING THE PEDIATRIC COSMETIC USE STUDIES BY PERCENTAGE OF ECAMSULE IN THE FORMULATION		
Adverse Event	Number (%) of Subjects	
	<3% Ecamsule N=188	$\geq$ 3% Ecamsule N=283
Erythema	2 (1.1)	14 (4.9)
Acne	1 (0.5)	5 (1.8)
Pruritus	0 (0.0)	2 (0.7)
Dermatitis	0 (0.0)	1 (0.4)
Dryness	1 (0.5)	1 (0.4)
Irritant Dermatitis	0 (0.0)	1 (0.4)
Skin Discomfort	0 (0.0)	1 (0.4)
Desquamation	0 (0.0)	0 (0.0)

*Data Source: Item 8 Section 14 End of Text Tables - Table 2.3*

Among the subjects who applied sunscreen for at least 14 days, erythema and acne were reported by most subjects. In general, in the subjects who applied sunscreen for at least 14 days, the number of adverse events reported was higher with sunscreens containing  $\geq$ 3% ecamsule.

The following table summarizes all the non-cutaneous AEs in the pediatric cosmetic studies:

TABLE 43. NON-CUTANEOUS ADVERSE EVENTS IN THE PEDIATRIC COSMETIC USE STUDIES: ALL SUBJECTS		
AE (N=6)	All subjects (N=526) (1.1%)	
Discomfort	2	0.4%
Allergic reaction	1	0.2%
Eye tearing	1	0.2%
Ocular discomfort	1	0.2%
Ocular erythema	1	0.2%
Ocular heat	1	0.2%

Six subjects reported 7 non-cutaneous adverse events across all studies, all of which occurred in fewer than 1 % of subjects. Ocular discomfort, ocular erythema, and ocular heat were all reported by a single subject in Study IEUT 04004. **According to the child's mother**, these events occurred when the sunscreen inadvertently entered the child's eyes.

Some subjects participated in more than one study, as shown in the following table:

TABLE 44. ADVERSE EVENTS FOR SUBJECTS WHO PARTICIPATED IN MULTIPLE PEDIATRIC COSMETIC USE STUDIES

Subject Designation <sup>a</sup>	Study No.	SPF	Duration of Study: Date First Subject Enrolled/ Date Last Subject Completed	Concentration of Ecamsule	Subject No.	Adverse Event(s)
A	IEUT 3058	60	10Nov2003/02Dec2003	>6%	45	None
	IEUT 3074	30	10Feb2004/01Mar2004	4.5%	22	None
	IEUT 4052	60	27Sep2004/18Oct2004	4.5%	1	Erythema Skin discomfort Dryness
I	IEUT 3058	60	10Nov2003/02Dec2003	>6%	37	Dermatitis Dryness
	IEUT 4052	60	27Sep2004/18Oct2004	4.5%	6	None
U	IEUT 3058	60	10Nov2003/02Dec2003	>6%	23	None
	IEUT 3074	30	10Feb2004/01Mar2004	4.5%	34	None
	IEUT 4005	60	09Mar2004/29Mar2004	1.5%	18	Acne
Q	IEUT 3074	30	10Feb2004/01Mar2004	4.5 %	44	None
	IEUT 4005	60	09Mar2004/29Mar2004	1.5%	13	None
	IEUT 4052	60	27Sep2004/18Oct2004	4.5%	10	Dermatitis
T	IEUT 3074	30	10Feb2004/01Mar2004	4.5%	35	None
	IEUT 4005	60	09Mar2004/29Mar2004	1.5%	17	None
	IEUT 4052	60	27Sep2004/18Oct2004	4.5%	12	Acne
AW	IEUT 3058	60	10Nov2003/02Dec2003	>6%	1	Desquamation
	IEUT 3074	30	10Feb2004/01Mar2004	4.5%	10	Erythema
BM	IEUT 3058	60	10Nov2003/02Dec2003	>6%	20	None
	IEUT 3066	60	18Mar2004/07Apr2004	3%	12	Acne Skin discomfort
	IEUT 4052	60	27Sep2004/18Oct2004	4.5%	21	None
BN	IEUT 3058	60	10Nov2003/02Dec2003	>6%	21	None
	IEUT 3066	60	18Mar2004/07Apr2004	3%	13	Acne
	IEUT 4052	60	27Sep2004/18Oct2004	4.5%	22	Erythema Pruritus
BP	IEUT 3066	60	18Mar2004/07Apr2004	3%	15	None
	IEUT 4053	60	05Oct2004/26Oct2004	4.5%	4	Acne
CT	IEUT 3058	60	10Nov2003/02Dec2003	>6%	33	None
	IEUT 4004	60	19Feb2004/10Mar2004	4.5 %	26	Erythema
	IEUT 3066	60	18Mar2004/07Apr2004	3%	27	None
	IEUT 4052	60	27Sep2004/18Oct2004	4.5%	31	None
CU	IEUT 3058	60	10Nov2003/02Dec2003	>6%	34	None
	IEUT 4004	60	19Feb2004/10Mar2004	4.5 %	27	Erythema
	IEUT 3066	60	18Mar2004/07Apr2004	3%	28	None
	IEUT 4052	60	27Sep2004/18Oct2004	4.5%	32	None

<sup>a</sup> A letter designation was assigned to identify each subject who participated in more than 1 study (See Item 8 Section 14 Appendix B Table B.2 for a complete list of subjects who participated in more than 1 study).

Seven subjects in 4 studies discontinued treatment because of AEs, erythema and itching in all instances, usually around day 2-3, and all resolved in a few days. In 2 of 3 subjects who were re-challenged, the reaction recurred. One subject discontinued treatment on the face but was able to

**Clinical Review**

Joseph M. Porres MD, PhD

NDA 22009, N-000

Helioblock-SX

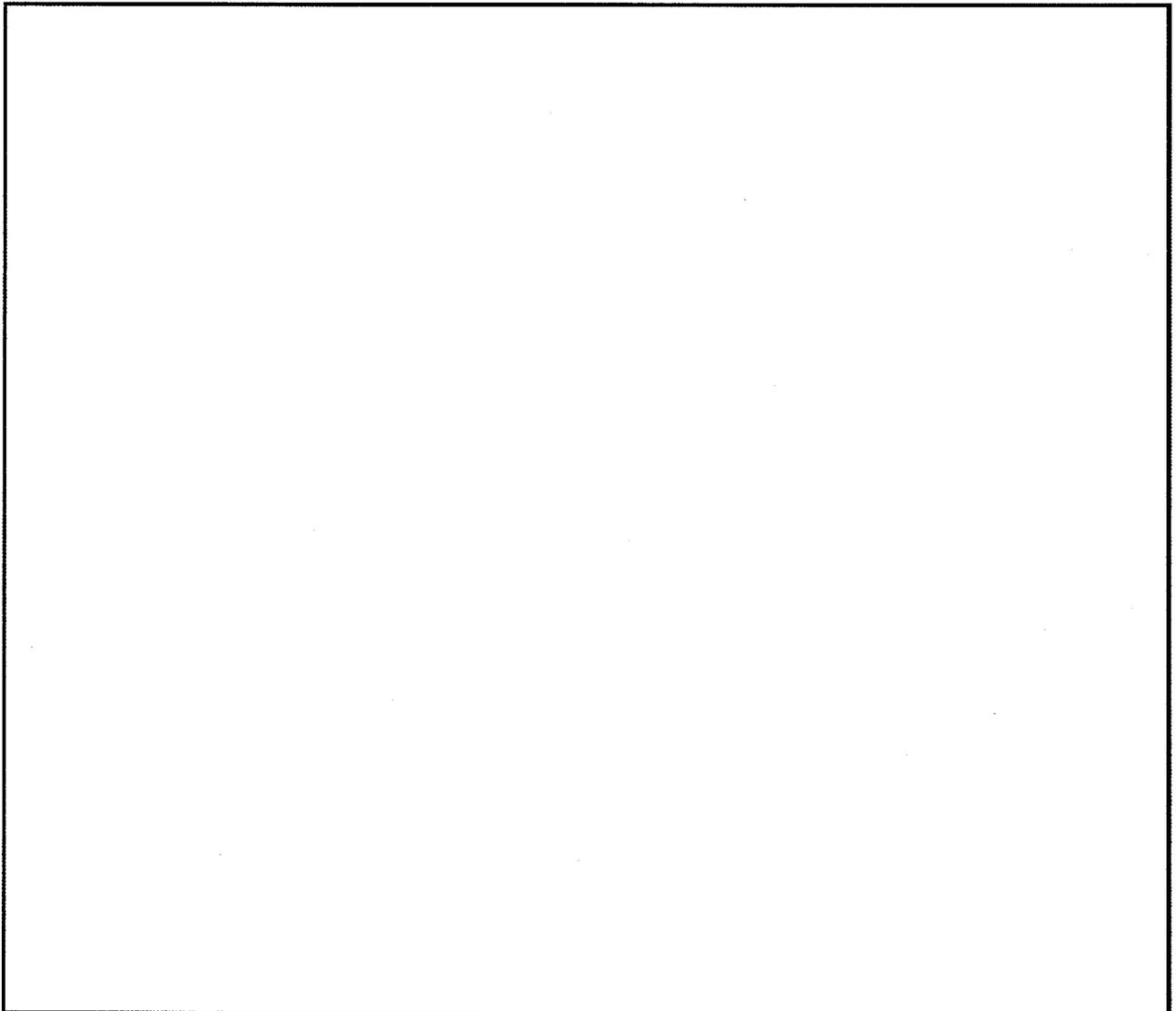
continue treatment on body areas.

In conclusion, 36 subjects reported AEs across all the EU pediatric cosmetic use studies. Of the subjects with AEs, most had only one. The most common AE was erythema, followed by acne and pruritus. The remaining AEs were reported by less than 1% of subjects. AEs were rare and sunscreens were generally well tolerated. There were no deaths or serious AEs during these studies.

In conclusion, these EU Pediatric Cosmetic Use studies provide some support to the safety of HSX.

**10.2 Line-by-Line Labeling Review**

**L'Oreal has submitted the following draft labeling:**



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/s/

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Joseph Porres  
2/7/2008 01:51:25 PM  
MEDICAL OFFICER

Daiva Shetty  
2/8/2008 08:05:46 AM  
MEDICAL OFFICER



**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

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Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Silver Spring MD 20993

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**M E M O R A N D U M**

**Date:** February 19, 2008

**From:** David Kettl, MD, Medical Officer, DDDP

**Through:** Markham Luke, MD, PhD, Dermatology Team Leader, DDDP  
Susan Walker, MD, Division Director, DDDP

**To:** Andrea Leonard Segal, MD, Division Director, DNCE

**CC:** Julie Beitz, MD, Director, ODE 3, CDER  
Bronwyn Collier, ADRA, ODE 3, CDER  
Joel Schiffenbauer, Deputy Director, DNCE  
Margo Owens, Supervisory Project Manager, DDDP  
Daiva Shetty, MD, Medical Officer, DNCE  
Joseph Porres, MD, Medical Officer, DNCE  
Elaine Abraham, Regulatory Health Project Manager, DAVP  
Hari Cheryl Sachs, MD, Medical Officer, PMHS, OND

**Re: DDDP Consult #1063 NDA 22-009**

**Materials Evaluated:**

**Consult Request**

Clinical Review, Joseph Porres, MD, DNCE, NDA 22-009, February 7, 2008  
Pediatric and Maternal Staff Consult, Hari Cheryl Sachs, MD, January 14, 2008

**Background:**

The proposed drug formulation, Helioblock SX Cream, SPF 40, contains ecamsule 3%, avobenzone 2%, octocrylene 10%, and titanium dioxide 5%. The requested indication is

for the prevention of sunburn. DDDP has been requested to comment on recommended pediatric studies for this product. Specifically, DDDP has been asked whether the skin of children six months of age is similar to adults in the ability to absorb or block the absorption of topical products.

Avobenzone (up to 3%), octocrylene (up to 10%) and titanium dioxide (up to 25%) are OTC monograph ingredients (21 CFR 352). These monograph products are permitted to be used in combination as long as the product provides an SPF at least as high as 2 times the number of ingredients. In addition, they can be used in children down to 6 months of age. Ecamsule was a NME that was approved in July 21, 2006 under NDA 21-502 (Anthelios SX cream).

The primary safety reviewer, Dr. Porres, “considers the safety of Helioblock SX has been reasonably established for adults and children older than 6 months”. He adds that “Pediatric waivers for studies below 6 months have been granted for similar sunscreens.”

The Division of Pediatric and Maternal Health has made several recommendations, as follows:

- That the sponsor provides a rationale for extrapolating efficacy from adults to children
- Presuming that studies in older children do not reveal any safety concerns, that consideration be given to :
  - Obtaining pharmacokinetic data in the pediatric age groups 6 months to 12 years to confirm that drug is not systemically absorbed when used in this combination as the extent of absorption has not been directly tested.
  - Requesting an actual use study in patients less than 6 months of age, that could be similar to the study conducted in children 6 months to 12 years of age, using the product according to label, and obtaining PK data.

The previous reviews for these sunscreen applications suggested that an adequate safety exposure margin level was demonstrated, though the PMHS reviewer, Dr. Sachs, commented that “*exposure has not been directly measured in pediatric patients but inferred from the animal and adult pharmacokinetic data.*”

Dr. Sachs goes on to argue that “*...systemic absorption of topical products may be increased in children due to their relatively high body surface area...*”

DDDP has been asked to comment on the differences in skin absorption in the infant age group, and the age at which infant skin characteristics are considered mature and similar

to the skin of adults. Specifically, the question posed by DNCE is whether the skin of six month old infants is similar to adult skin.

Review:

Human skin serves various roles including mechanical protection, thermoregulation, immuno-surveillance, and maintenance of a barrier that prevents the loss of body fluids. The development and growth of human skin is dependent on a variety of interactions of the numerous cell types that compose the organ. These evolving changes also vary with gestational and post-natal ages.

A specific age cannot be pinpointed where the development of skin or any organ is complete since multiple structural and functional aspects of development occur gradually over the first years of life. Likewise the scientific literature does not provide a specific answer to the question of developmental skin maturity. Most of the published literature compares differences in the skin of pre-term infants versus term newborns and the developmental changes which occur in the first month of life.

The following discussion highlights several critical developmental phases which are pertinent to the current application.

The epidermis, or outer layer of the skin, is divided into five layers: the stratum corneum, (the upper most layer) stratum lucidum, stratum granulosum, stratum spinosum and stratum basale (the lowest layer, above the dermis). It is well accepted that the stratum corneum is the major rate limiting barrier to molecular diffusion through mammalian epidermis.

The stratum corneum itself is made up of 10 to 20 microscopic layers in the term infant, similar to that seen in an adult. Infants born before 32 weeks gestation have a very thin stratum corneum, between two to three layers. In extremely premature infants, of less than 23 gestational weeks, the stratum corneum may be virtually non-existent.

The epidermis and its underlying basement membrane are relatively flat during fetal development. The rete ridges which eventually project into the dermis layer are not fully developed until six months of age. The dermis layer also matures with its complex functions about six months of age. Thus histologically, infant skin is similar to adult skin at the age of six months for infants born at term.

More important than the post-natal age of the infant is the relationship of mass to body surface area. The vast differences in body surface area between children and adults and its implication on sunscreen use seems critical to this reviewer. An infant's ratio of body surface area to weight is up to 5 times that of an adult. A drug with minimal absorption in adults may have different implications for an infant where the product is applied to a relatively larger surface area even though the actual percutaneous absorption is similar. This could be addressed in labeling following consultation with PMHS and Biopharmaceutics.

Cutaneous absorption also varies with the type of product which is applied. Absorption of drugs applied topically is influenced by both physical and chemical properties of the drug as well as the barrier properties of the skin. Most literature reports of cutaneous toxicity are from the neonatal period, but some reports involving drugs such as topical anesthetics and lindane highlight the fact that there can be differences in systemic levels which relate to body surface area treated and differences in cutaneous absorption in infants and young children compared with adults, even though the skin is histologically similar.

David Kettl, MD  
Medical Officer

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/s/  
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David Kettl  
2/19/2008 04:04:07 PM  
MEDICAL OFFICER

Markham Luke  
2/22/2008 04:40:42 PM  
MEDICAL OFFICER

Sunscreens for pediatric use should be evaluated thoroughly in children as needed prior to marketing. Sunscreen use in peds should be part of a complete sun protective regimen including hat and clothing, so body surface area of exposure can be minimized.

Susan Walker  
3/3/2008 01:18:37 PM  
DIRECTOR



**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

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Food and Drug Administration  
Office of New Drugs - Immediate Office  
Pediatric and Maternal Health Staff  
Silver Spring, MD 20993  
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**M E M O R A N D U M**

Date: January 14, 2008

From: Hari Cheryl Sachs, MD, Medical Officer  
Office of New Drugs - Immediate Office  
Pediatric and Maternal Health Staff

Through: Lisa Mathis, MD, OND Associate Director  
Office of New Drugs - Immediate Office  
Pediatric and Maternal Health Staff

To: Joe Porres, MD, Medical Officer  
Daiva Shetty, MD, Team Leader  
Andrea Leonard-Segal, Division Director  
Division of Nonprescription Clinical Evaluation

Re: Helioblock SX (3% ecamsule/2% avobenzone/10% octocrylene/ 5% titanium dioxide), NDA 22-009

**Materials Reviewed**

Consult request

L'oreal Pediatric Study Synopses ("Clinical Safety Trial of Long-Term (Intermittent Use of Helioblock SX cream Formula 2834192), November 2007

PREA partial waiver granted NDA 21-501, 21-502, Feb 2007

Pediatric Waiver request consult for NDA 21-501, Jean Temeck Nov 2006

Approval letters for NDA 21-501, 21-502, 21-247

Pediatric consult for NDA 21-501 and 21-502, Jean Temeck March 2006

Medical officer review NDA 21-501, 21-502, 21-247), Michael Koenig, December 2005

Safety review NDA 21-501, 21-502, Daiva Shetty Jan 2006

Division director memo, NDA 21-471 Andrea Leonard-Segal, October 2006

**Background/product description:**



measures (e.g., clothing, hats, shade) as the primary protective measures and the desire to avoid the misconception that infants would be protected if sunscreen is used.

**Information regarding submission**

Drug: Helioblock SX

Sponsor: L'Oreal

Proposed Indication in Adults: prevention of sunburn

Proposed dosing: apply liberally 15 minutes before sun exposure. Reapply after 40 minutes of swimming or perspiring and after towel drying.

Proposed indication in Pediatrics: prevention of sunburn in children down to 6 months

Proposed dosing: same

**Brief Summary of Previous Studies**

According to the excellent summary (see Table II) provided in the consult request, the current formulation \_\_\_\_\_ has been studied in mostly adults with pediatric exposure limited to 11 patients (12 to 18 years). The product containing 3% ecamsule (NDA 21-501) has been studied in approximately 203 pediatric patients, including 57 children less than 2 years of age and 122 patients ages 2 to 12 years. A total of 358 pediatric patients were enrolled in the four long-term safety studies of any ecamsule-containing product (see Table III). b(4)

Table II: Summary of ecamsule studies  
(Extracted from consult request, page 3 and 4)

Study	Formulation	N. subjects	Ages	Duration	Study type
18047	Helioblock SX	475 entered 278 completed	11 subjects (12-18 y.o.) 428 subjects (≥18 y.o.)	137 subjects for ≥12 months 187 subjects for 6-12 months 92 subjects for <6 months	Open label safety Self application
18057	Helioblock SX	144	≥18		Phase 3
2616	Helioblock SX	87	≥18		Phase 2
750.03	593-106 NDA 21-471, approved	79	6m-2 y...24 2-6 y...32 6-12 y...8 12-18 y...2 >18 y...13	Intermittent up to 6 months Average duration 40 days	
750.02	760.006 NDA 21-501, approved		5m-2 y...57 2-6 y...60 6-12 y...62	Intermittent up to 12 months Average duration 4	

			12-18y...24 >18y...43	months	
750.01	539.009 NDA 21-502, Approved as Anthelios SX	248	12-18 y...78 >18y...170	Intermittent up to 12 months Average duration 10 months	



were lower in pediatric patients compared with adults, perhaps related to lower duration of use. No unique safety concerns, deaths or serious AEs related to study drug were identified in 243 pediatric and 115 adolescent patients (p34 Daiva Shetty) receiving these sunscreen products. In addition, postmarketing AEs reported to the Sponsor for ecamsule did not appear to reveal any serious safety issues other than allergic reactions and the common AEs were consistent with the AE profile observed in clinical trials (p31). Dermal safety studies for the only other product with all four ingredients (NDA 21-417) showed little or no potential for skin irritation, phototoxicity or photosensitization. However, these dermal safety studies did not include any pediatric patients.

In March 2006, an IND was submitted by L'Oreal (IND 57,850, protocol PEN 750.04) describing an actual use, long-term, intermittent use, clinical safety trial of Helioblock SX in 135 pediatric patients 6 months to 12 years of age. The study has been completed and a synopsis submitted November 2007. According to the synopsis, 136 patients were enrolled with approximately 45 patients in each age cohort (6 months to 2 years, >2 to 6 years and >6 to 12 years of age.) Minimum exposure was to be 14 days over the 6 month trial period, however, actual exposure ranged from 1 to 172 days, with 94% of patients using the product for the required minimum period of 2 weeks. According to L'Oreal, no deaths and few SAEs (2%) occurred during the study period and the majority of AEs were mild (37%) or moderate (24%). Most of the AEs related to the drug appeared to be dermatological, with the highest incidence in the youngest age cohort (6 months to 2 years). The Sponsor concluded that the study demonstrated that use of Helioblock SX cream is safe and well tolerated in children age 6 months to 12 years. The study has not yet been reviewed by the division.

*Reviewer comment: The Sponsor's conclusions will need to be confirmed. The DNCE reviewer notes that these studies were conducted with a newer formulation using a \_\_\_\_\_ titanium dioxide as opposed to all the previous studies which were performed with the non- \_\_\_\_\_ form. Whether or not this is acceptable will be a review issue.*

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**Specific Questions posed by Review Division:**

1. Please advise if L'Oreal needs to provide safety data for pediatric patients 6 months to 12 years of age for the Helioblock SX product for the prevention of sunburn?

If no, can we label the product for prevention of sunburn down to 6 months of age?

If yes, what kind of studies, and in what age categories should studies be conducted and could it be a postmarketing commitment?

*Answer: The Sponsor appears to have submitted safety data and DNCE will determine whether or not the safety data from the "actual use study" is acceptable. The safety data is particularly important since systemic absorption of topical products may be increased in children due to their relatively high body surface area (Hengge 2006) and the fact that extrapolation has been used to support both the efficacy and lack of systemic absorption. Therefore, since efficacy is to be extrapolated from adult data, the rationale for doing so must be provided. Under the new regulations, a brief documentation of the scientific data supporting the ability to extrapolate shall be included in any pertinent reviews of an*

*application. Moreover, pharmacokinetic studies have not been performed in children as the lack of systemic absorption has been inferred from adult and preclinical data. Thus, consideration should be given to obtaining pharmacokinetic data in pediatric age groups 6 months to 12 years to confirm that drug is not systemically absorbed when used in this combination as the extent of absorption has not been directly tested.*

Additional comment regarding the partial waiver of pediatric studies in children less than 6 months of age:

Studies in this age group appear to be waived, in part, because “the use of sunscreen products in infants less than 6 months of age may lead to inappropriately high systemic levels of the ingredients and pose safety concerns.” If existing data demonstrate that use of sunscreen products containing ecamsule and titanium dioxide leads to excess levels of the ingredients in infants and thus poses a safety risk so that studies need to be waived, the fact that studies were waived for safety concerns as well as the risk will need to be conveyed in labeling. However, the extent of absorption of ecamsule in this concentration and with this combination has not been directly tested for any age pediatric patient, much less in infants less than 6 months of age.

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Since the degree of exposure from these ingredients is unknown, the issue of requesting pediatric studies in children less than 6 months of age should be revisited. Although PMHS concurs that “non-chemical protection should be the main modality used to protect young infants from sun exposure,” clinical recommendations do not preclude the use of sunscreen when sun exposure is unavoidable or other measures are impossible. The American Academy of Pediatrics states that when adequate shade or clothing is not available, the use of sunscreen in infants less than 6 months may be safe (AAP 1999). A recent evidence-based review concluded that the risks and benefits for sunscreen use under the age of 6 months are unknown; however “as research is lacking for this age group, and the risk of harm due to sunburn is real, it would be reasonably prudent to use sunscreen when physical protection from the sun is impossible” (Meurer 2006). Consequently, sunscreen products are marketed and used in infants. A recent survey of products available in the UK identified 10 products marketed for infants (Wahie 2007). Similar products are available in the United States (e.g., Water BABIES®). Parents (and some physicians) believe that sun exposure is beneficial to infants for bone development, rickets prevention, and as adjunctive treatment of jaundice or diaper dermatitis (Aladag 2006). For these reasons, consideration should be given to requesting both pharmacokinetic and “actual use” safety studies in patients less than 6 months of age presuming that the studies in older children do not reveal any safety concerns.

*Reviewer comment: Reviewer comment: PMHS acknowledges that designing and conducting these studies may be quite challenging. In particular, ethical constraints may complicate the performance of these studies in otherwise healthy infants. In the waiver request, the Sponsor argued that conduct of PK studies would require blood sampling in infants and exposure to radioactive labels. A subset of the PK studies in adults did not require the use of radioactive labels for ecamsule. Therefore, as long as blood drawing limits are closely adhered to, a properly-designed, sparse sampling or population pK study would be ethical. A single blood draw is usually considered to be “minimal risk.” The Sponsor also stated efficacy studies would require exposure of treated and control*

*skin to UV radiation sufficient to induce burning, which clearly is inappropriate and unethical. However, an "actual use" open-label, safety study such as the one performed in older children 6 months to 12 years would not require sun exposure in "untreated" children and if the population was selected properly, infants who would otherwise be at risk by virtue of sun-exposure (e.g., while on vacation or at the swimming pool) could be enrolled. Existing clinical guidelines would need to be followed (e.g., avoid peak sun, use clothing, umbrellas, etc.) so that studies are conducted according to an appropriate pediatric standard of care. The product would need to be used according to labeled directions (e.g., apply only to face and hands) without mandating exposure to excessive levels of the product (which would be unethical). Finally, parents could not be unduly influenced into enrolling into the study due to compensation. In that manner, the parental decision to use sunscreen would be based on concern to minimize the risk of sunburn to the infant and independent of the research. For these reasons, FDA could request that these studies be performed under BPCA even if they are not required under PREA.*

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Wahie S, Loyd J and Farr P. Sunscreen ingredients and labeling: a survey of products available in the UK. *Clin Exp Dermatol* 2007; 32(4): 359-364.

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## CLINICAL EFFICACY REVIEW

Application Type	NDA
Submission Number	22,009
Submission Code	N000
Letter Date	May 31, 2007
Stamp Date	May 31, 2007
PDUFA Goal Date	March 31, 2008
Reviewer Name	Michael L. Koenig, Ph.D.
Review Completion Date	January 4, 2008
Established Name	Ecamsule, 3%; avobenzone, 2%; octocrylene, 10%, titanium dioxide, 5%
(Proposed) Trade Name	ANTHELIOS 40
Therapeutic Class	Sunscreen
Applicant	L'Oreal USA Products Inc.
Priority Designation	S
Formulation	Cream
Dosing Regimen	Apply evenly 15 minutes before sun exposure and reapply as needed or after towel drying, swimming, or perspiring
Indication	Prevention of sunburn and skin damage due to sun exposure by providing broad spectrum protection from UVB and UVA radiation
Intended Population	Adults and children 6 months of age and older

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## **1 EXECUTIVE SUMMARY**

### **1.1 Recommendation on Regulatory Action**

Based on effectiveness, ANTHELIOS 40 sunscreen cream (NDA 22-009) should be approved for over-the-counter (OTC) use for prevention of sunburn and skin damage induced by UVB and UVA radiation.

Final approvability depends on the outcome of the preclinical and clinical safety and chemistry studies being evaluated by other reviewers in the Divisions of Nonprescription Clinical Evaluation, Dermatologic and Dental Drug Products, and Pre-Marketing Assessment II.

### **1.2 Recommendation on Postmarketing Actions**

#### **1.2.1 Risk Management Activity**

This review only considers the effectiveness of the formulation in NDA 22-009. Therefore, this section is not applicable.

#### **1.2.2 Required Phase 4 Commitments**

There are no phase 4 requirements with respect to efficacy.

#### **1.2.3 Other Phase 4 Requests**

None.

### **1.3 Summary of Clinical Findings**

#### **1.3.1 Brief Overview of Clinical Program**

L'Oreal is seeking approval to market ANTHELIOS 40 sunscreen cream (NDA 22-009) for daily use by adults and children six months of age and older.

The sunscreen includes 2% avobenzone, 10% octocrylene, 5% titanium dioxide, and 3% ecamsule. The product contains ecamsule, an ingredient approved for use as a sunscreen ingredient under NDAs 21-501, 21-502, and 21-471. The other active ingredients (octocrylene, avobenzone, and titanium dioxide) are among the 16 generally recognized as safe and effective (GRASE) sunscreen active ingredients listed in the OTC sunscreen drug monograph (21 CFR part 352).

In support of its submission, the sponsor submitted data from one in vitro and five clinical studies that include ANTHELIOS 40. The sponsor also submitted numerous supportive studies that include formulations similar to ANTHELIOS. Because these supportive studies do not include ANTHELIOS 40, they are not included in this review.

### 1.3.2 Efficacy

Based on my review of the five clinical and one in vitro studies submitted in the NDA, this reviewer concludes that ANTHELIOS 40 sunscreen cream provides effective protection from skin damage due to both UVB and UVA radiation. The formulation meets the criteria for UVB radiation protection in 21 CFR 352.20(a) in that:

- the concentration of each active ingredient contributes a minimum SPF of not less than 2 to the finished products
- each finished product has an SPF value that exceeds the number of sunscreen active ingredients in the product multiplied by 2

Because the formulation meets these criteria, it may be labeled as providing effective UVB protection.

The formulation also meets the criteria outlined in the 1993 tentative final monograph (TFM) for OTC sunscreen drug products making claims of UVA protection. In that rulemaking, FDA stated that a sunscreen can bear a claim that it provides UVA protection if it meets two criteria (58 FR 28194 at 28233):

- the absorption spectrum extends to 360 nm or above in the UVA range
- UVA protection is demonstrated using an appropriate testing procedure

The products to be marketed under NDA 22-009 may bear UVA protection claims, such as “broad spectrum” or “protects against UVA rays or radiation” (58 FR 28194 at 28233), but they may make no claims as to the degree of UVA protection.

### 1.3.3 Safety

Subjects were exposed to an ecamsule-containing sunscreen product during the clinical studies conducted for this sunscreen. There were no drug-related deaths or drug-related serious adverse events reported among the participants in clinical trials. In addition, postmarketing AEs reported to the sponsor did not reveal any serious safety issues. The safety data are being evaluated separately by Dr. Joseph Porres in the Division of Nonprescription Clinical Evaluation, Office of Nonprescription Products.

### 1.3.4 Dosing Regimen and Administration

The proposed dosing directions for the product are as follows:

- apply liberally 15 minutes before sun exposure
- reapply as needed or after towel drying, swimming, or perspiring
- children under 6 months of age: ask a doctor

The proposed dosing directions are consistent with the OTC sunscreen drug monograph (21 CFR part 352).

### 1.3.5 Drug-Drug Interactions

Potential drug-drug interactions are discussed as part of the safety review conducted by other reviewers in the Office of Nonprescription Products and Division of Dermatological and Dental Drug Products.

### 1.3.6 Special Populations

There are no special populations related to effectiveness. Special populations related to safety are discussed as part of the safety review conducted by Dr. Joseph Porres in the Division of Nonprescription Clinical Evaluation, Office of Nonprescription Products.

## 2 INTRODUCTION AND BACKGROUND

This is a clinical efficacy review of ANTHELIOS 40 Sunscreen Cream submitted under NDA 22-009.

### 2.1 Product Information

NDA 22-009 was submitted for ANTHELIOS 40 Sunscreen Cream. This product is a topical sunscreen composed of the following four active ingredients:

- Avobenzone, 2%
- Octocrylene, 10%
- Ecamsule (Mexoryl<sup>®</sup>), 3%
- Titanium dioxide, 5%

The sponsor requests that this formulation be marketed by three different distributors under three different brand names:

1. ANTHELIOS 40 (reference trade name)
2. UV EXPERT 40
3. CAPITAL SOLEIL 40

These products will be marketed in tubes containing 50 g (1.7 oz) of product.

The sponsor is proposing to market the products in the OTC setting for daily use by adults and children six months of age and older. The sponsor states that the products will be marketed in accordance with OTC sunscreen drug monograph (21 CFR part 352).

### 2.2 Currently Available Treatment for Indications

There are a total of 16 sunscreen active ingredients generally recognized as safe and effective (GRASE) under the OTC sunscreen drug monograph (21 CFR part 352). Nearly all sunscreens

currently available for OTC use in the United States are marketed under the sunscreen monograph. Three of the active ingredients included in this sunscreen formulation (avobenzone, octocrylene, and titanium dioxide) are listed as GRASE in the sunscreen monograph as single active ingredients. Two (octocrylene and titanium dioxide) are classified as GRASE in combination with other sunscreen active ingredients. Avobenzone is not currently classified as GRASE in combination with titanium dioxide.

### **2.3 Availability of Proposed Active Ingredient in the United States**

As mentioned in section 2.2, three of the active ingredients contained in the sunscreen formulation are currently available in the United States OTC market. The ingredient ecamsule is available in the United States under NDAs 21-501, 21-502, and 21-471.

### **2.4 Important Issues With Pharmacologically Related Products**

There are no known serious safety or efficacy issues with pharmacologically related products.

### **2.5 Presubmission Regulatory Activity**

This formulation was developed under IND 57,850 and submitted to FDA as an NDA \_\_\_\_\_ (May 29, 2003). FDA issued an approvable letter on March 31, 2004. The approvable letter indicated \_\_\_\_\_

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On March 1, 2006, the sponsor indicated that it intended to submit the information developed under IND 57,850 to support a new NDA "for a traditional sunscreen indication." This NDA was submitted on May 31, 2007.

### **2.6 Other Relevant Background Information**

Not applicable.

## **3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES**

### **3.1 CMC (and Product Microbiology, if Applicable)**

The CMC review is pending.

### **3.2 Animal Pharmacology/Toxicology**

The sponsor conducted a total of 87 animal and toxicology studies as part of the \_\_\_\_\_ development program \_\_\_\_\_. These studies did not demonstrate that ecamsule was

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teratogenic, carcinogenic, or photocarcinogenic. There was no embryoletality or reproductive toxicity associated with ecamsule alone or in combination with other sunscreen active ingredients. The acute oral toxicity dose is 5000 mg/kg in the rat and 2000 mg/kg in the mouse.

## 4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

### 4.1 Sources of Clinical Data

Data to support the effectiveness of ANTHELIOS 40 Sunscreen Cream were submitted in six volumes (1.101 – 1.104, 1.155, and 1.156). Clinical data submitted include five single center, controlled, randomized, double-blinded studies. Two of the studies (1.CG.03.SRE.2612 and 1.CG.03.SRE.2613) were conducted under the supervision of Dr. Robert W. Shanahan at the Consumer Product Testing Company, Inc. (CPTC) in Fairfield, NJ. The other studies were conducted outside the United States at different centers with different principal investigators:

Study	Principal Investigator	Study Site
1.CG.03.SRE.2614	Anne Parneix-Spake, M.D.	ASTER Cosmetology, Paris, France
1.GUS.05.SRE.2639	Lynda Arnaud-Boissel	Institut d'Expertise Clinique (IEC), Lyon, France
1.GUS.SRE.18045.R01	John W.P. Toole, M.D.	Hill Top Research, Winnipeg, Canada

The sponsor also submitted one in vitro (i.e., non-clinical) study designed to demonstrate that the absorption spectra of the formulation extends to wavelengths  $\geq 360$  nm (i.e., long-wavelength UVA). The study was conducted at the L'Oreal Applied Research and Development Laboratory in Clichy, France.

Data supporting the safety of the formulation is included in the five clinical effectiveness studies.

### 4.2 Tables of Clinical Studies (Efficacy Only)

Table 1. UVB Protection

Study	Method	Volume	Page
1.CG.03.SRE.2612	SPF	1.101	218
1.GUS.05.SRE.2639	SPF	1.104	191
1.GUS.SRE.18045.R01	SPF	1.102	105

Table 2. UVA Protection

Study	Method	Volume	Page
1.CG.03.SRE.2613	PPD	1.103	123
1.CG.03.SRE.2614	8-MOP	1.104	001

**Table 3. In Vitro UVA Absorption Study**

Study	Method	Volume	Page
SOL-DP1-97-021	$\lambda_c^1$	1.155	184

<sup>1</sup>Critical Wavelength

### 4.3 Review Strategy

Safety data are being reviewed separately by Joseph Porres, M.D., in the Division of Nonprescription Clinical Evaluation, Office of Nonprescription Products.

This review evaluates the five clinical and one non-clinical efficacy studies submitted under NDA 22-009. The review will first evaluate three clinical studies submitted to demonstrate that ANTHELIOS 40 provides protection against UVB radiation (section 6.1). After evaluating UVB protection, the review discusses two clinical studies submitted to demonstrate UVA radiation protection (section 6.2). The in vitro study submitted to demonstrate that ANTHELIOS 40 absorbs UVA light at wavelengths  $\geq 360$  nm is discussed in section 6.3.

### 4.4 Data Quality and Integrity

During the review of previously submitted NDA 21-471, a request was submitted to the Division of Scientific Investigations (DSI) to inspect the Consumer Product Testing Co., Inc. (CPTC) in Fairfield, NJ. This study center was selected for inspection because eight of the 12 clinical studies and one of the three in vitro studies included in that NDA were conducted by CPTC. CPTC conducted two of the five clinical studies reviewed in this application. FDA inspected the facility between February 21 and March 6, 2006. Although protocol deviations and one instance of discrepant recordkeeping were noted, the inspector found that the data were "satisfactory in support of" NDA 21-471.

### 4.5 Compliance with Good Clinical Practices

Institutional Review Boards (IRBs), as defined in 21 CFR part 56, approved the protocols and informed consent forms (ICFs) for all clinical studies. No changes in the conduct of the studies were allowed without prior written approval from the sponsor and approval by the IRB.

The sponsor indicates that study investigators obtained written consent from all subjects in accordance with 21 CFR 50.20, 50.25, and 50.27. The sponsor further states that the study investigator or a delegated staff member explained the nature of the study, including any associated risks, to each subject before the subject signed the ICF. The explanations of the study occurred privately with adequate time to answer any questions from study subjects.

The sponsor states that all of the studies were conducted in accordance with the ethical principles originating from the Declaration of Helsinki and Good Clinical Practice and were in compliance with local, state, and federal regulatory requirements.

#### **4.6 Financial Disclosures**

The sponsor submitted Form 3454 certifying that the investigators in all clinical studies had no financial interests in these products, the studies, or the companies conducting the studies.

### **5 CLINICAL PHARMACOLOGY**

Clinical pharmacology studies are not pertinent to this review of efficacy. These studies are being evaluated by other reviewers.

#### **5.1 Pharmacokinetics**

Pharmacokinetics studies are not pertinent to this review of efficacy. These studies are being evaluated by other reviewers.

#### **5.2 Pharmacodynamics**

No pharmacodynamic data were submitted in this NDA.

#### **5.3 Exposure-Response Relationships**

The NDA does not include studies exploring exposure-response relationships.

### **6 INTEGRATED REVIEW OF EFFICACY**

#### **6.1 Indication**

The sponsor states that this product is indicated "for prevention of sunburn and skin damage following chronic exposure to ultraviolet radiation." This indication includes both a UVB and UVA radiation protection claim. The UVB claim is essentially "helps prevent sunburn/protects against UVB radiation." This UVB claim is allowed for OTC sunscreens marketed under the OTC drug monograph system (21 CFR 352.52(b)(1)).

##### **6.1.1 Methods**

An assessment of the effectiveness of a sunscreen formulation in protecting against UVB radiation is based on the criteria outlined in the OTC sunscreen final monograph published on May 21, 1999 (*Federal Register*, vol. 64, pp. 27666-27693). In accordance with 21 CFR 352.10 and 352.20, OTC sunscreen drug products must have a minimum SPF value of not less than the total number of sunscreen active ingredients in the formulation multiplied by two. For example, an OTC sunscreen drug product containing four active ingredients must have an SPF of at least 8 (i.e., 4 multiplied by 2). In addition, each active ingredient must contribute an SPF of at least 2 to the SPF of the finished product.

The method for determining the SPF value (*i.e.*, effectiveness) of an OTC sunscreen drug product marketed in the United States is detailed in 21 CFR part 352 subpart D. As indicated in § 352.72, at least 20 evaluable subjects must complete the study. Sunscreen formulations are applied to  $\geq 50$  cm<sup>2</sup> test sites on each subject's back. Each test site is further subdivided into at least three subsites no less than 1 cm<sup>2</sup> in size. Each subsite is exposed to a different amount of simulated solar radiation. Sunscreen formulations are applied to the entire test site using a finger cot to ensure an even distribution of 2 mg/cm<sup>2</sup>. Subjects are not exposed to UV radiation for at least 15 minutes after applying sunscreen formulations.

A standard sunscreen with a known SPF value is tested concurrently with each test formulation to ensure the test results are valid. A standard formulation containing 8 percent homosalate is prepared as described in § 352.70. The SPF of this standard formulation should be  $4.47 \pm 1.28$  and the 95 percent confidence interval for the mean SPF of the standard formulation should include the value 4.

Solar radiation is simulated with a light source emitting UV radiation over the range of 290 to 400 nm (*i.e.*, UVB and UVA radiation). The solar simulator must be calibrated periodically to ensure that subjects are exposed to the spectrum of UV radiation defined in § 352.71.

Subjects are exposed to a geometric series of increasing amounts of radiation (§ 352.73(b)) in the absence or presence of a sunscreen to determine the MED<sub>US</sub> (MED unprotected skin) or MED<sub>PS</sub> (MED protected skin), respectively. MED is defined as the amount of light energy required to produce the "first perceptible, redness reaction with clearly defined borders 22 to 24 hours after exposure" (§ 352.73(c)). Therefore, MED<sub>US</sub> is always lower than MED<sub>PS</sub>, because less UV radiation is required to produce redness (*i.e.*, erythema) in the absence of a sunscreen than in the presence of a sunscreen.

SPF is defined as the ratio of MED<sub>PS</sub> to MED<sub>US</sub> (§ 352.73(c)). Thus, sunscreen effectiveness directly correlates to the SPF value. SPF values are determined for each of the subjects enrolled in the study, and a mean SPF value is calculated for the group. Variability about the mean is estimated by calculating the standard deviation and the 95% confidence interval. The labeled SPF value of a test formulation is the largest whole number less than the lower limit of the 95% confidence interval.

### 6.1.2 General Discussion of Endpoints

The endpoint in these studies is erythema (redness) induced by simulated solar radiation. By determining the amount of radiation necessary to produce erythema on each subject's back in the presence and absence of a sunscreen, an SPF value can be calculated for the sunscreen. The SPF was first allowed by FDA over thirty years ago (*Federal Register*, vol. 43, pp. 38206-38269). SPF is recognized by FDA and other regulatory bodies around the world as a valid and appropriate measure of sunscreen effectiveness against UVB radiation. Furthermore, U.S. consumers recognize SPF as the measure of protection against sunburn, which is caused primarily by UVB radiation.

### 6.1.3 Study Design

These studies were designed to strictly adhere to the SPF testing procedures outlined in the OTC sunscreen drug monograph (21 CFR part 352 subpart D). According to the monograph, study subjects must meet all of the following criteria:

- Be fair-skinned (i.e., skin type I, II, or III)
- In good health
- Not taking medicines that might produce abnormal sunlight response
- Have no "sunburn, suntan, scars, active dermal lesions, [or] uneven skin tones" on the parts of the back to be tested

Skin types are defined in 21 CFR 352.72(a)(1):

- Type I: always burns easily; never tans
- Type II: always burns easily; tans minimally
- Type III: burns moderately; tans gradually (light brown)
- Type IV: burns minimally; always tans well (moderate brown)
- Type V: rarely burns; tans profusely (dark brown)
- Type VI: never burns; deeply pigmented

Thus, the study design appropriately excludes U.S consumers that do not frequently sunburn. The testing procedure in the monograph suggests that studies should include males and females, but does not specify the numbers of males and females required or any other demographic criteria.

The submitted studies include more female than male subjects. The ages of subjects evaluated in these studies range from 18 to 62. Ideally, the studies would enroll equal numbers of males and females as well as pediatric subjects. However, it does not seem unreasonable to extrapolate the findings to males or to children over 6 months (as labeled under the sunscreen monograph). There is no apparent anatomical or physiological difference between female and male skin or the skin of adults and children (over 6 months) that suggest there may be significant differences in protection provided by a sunscreen for these groups.

Because FDA developed the OTC sunscreen drug monograph, the studies are adequate and well-controlled as defined in 21 CFR 314.126. Therefore, the study design provides a reasonable assessment of benefit.

### 6.1.4 Efficacy Findings

#### 6.1.4.1 Study 1.CG.03.SRE.2612

This phase 2 study was conducted under the supervision of Dr. R.W. Shanahan at the Consumer Product Testing Company in Fairfield, NJ. The study began on April 26, 1999, and concluded on June 5, 1999. A total of 25 subjects were enrolled and 19 evaluable subjects completed the study. Twenty of the enrolled subjects were female and five were male with an age range of 18 to 61 years (average age of 36 years). The subjects had skin type I (16%), II (60%), or III (24%).

In accordance with the 21 CFR 352.70, an 8% homosalate standard sunscreen was tested concomitantly.

The principal investigator reports one deviation from the IRB-approved protocol. The time between the UV exposure and the visual evaluation of erythema was 21.45 hours for one subject (i.e., not 22 – 24 hours post-exposure as specified in 21 CFR 352.72(h)). The investigator asserts that the deviation did not “interfere with the study results,” and I concur.

The mean SPF of the standard sunscreen was reported to be 4.1 with a standard deviation (SD) of 0.5. This falls within the acceptable range specified in 21 CFR 352.70(a), which is  $4.47 \pm 1.279$ . The mean SPF  $\pm$  SD of ANTHELIOS 40 (test formulation 760.001) was  $45.2 \pm 6.5$ . The 95% confidence interval ranged from 42.0 to 48.3, resulting in a labeled SPF of 42 (21 CFR 352.73(d)).

Test formulation 760-001 appears to be an effective sunscreen against UVB radiation. The formulation meets the criterion specified in 21 CFR 352.20(a) that it have an SPF value greater than 2 times the number of active ingredients (i.e.,  $42 > 2 \text{ times } 4$ ). The contribution of each active ingredient to the effectiveness of the finished product, as required by 21 CFR 352.20(a), is addressed in study 1.GUS.SRE.18045.R01.

#### 6.1.4.2 Study 1.GUS.05.SRE.2639

This phase 2 study was conducted under the supervision of Lynda Arnaud-Boissel at the Institut d'Expertise Clinique (IEC) in Lyon, France. The study began on September 28, 1999, and concluded on October 20, 1999. A total of 25 subjects were enrolled, and 22 evaluable subjects completed the study. Nineteen of the enrolled subjects were female and six were male. The subjects ranged in age from 19 to 49 years (average age for males 32 and for females 27 years) and had skin type I (16%), II (36%), or III (48%).

As in study 1.CG.03.SRE.2612, this study evaluates the effectiveness of formulation 760-001 and includes the concomitant testing of an 8% homosalate standard sunscreen.

The principal investigator reports two deviations from the IRB-approved protocol. Readings for one subject were made 20 hours after irradiation (i.e., less than the 22 to 24 hours specified in 21 CFR 352.72(h)). This was considered a minor deviation. The determination of erythema for another subject was made 4 days after irradiation. The investigator states that the data for this subject were included because “it did not significantly change the SPF values.”

The mean SPF  $\pm$  SD of the standard sunscreen was reported to be  $4.2 \pm 0.8$ . This falls within the acceptable range specified in 21 CFR 352.70(a), which is  $4.47 \pm 1.279$ . The mean SPF  $\pm$  SD of test formulation 760-001 was  $45.9 \pm 10.1$ . The 95% confidence interval ranged from 42.2 to 49.6, resulting in a labeled SPF of 42 (21 CFR 352.73(d)).

Test formulation 760-001 appears to be an effective sunscreen against UVB radiation in both males and females. It is expected that the formulation is also effective on children (over 6

months of age). The formulation meets the criterion specified in 21 CFR 352.20(a) that it have an SPF value greater than 2 times the number of active ingredients (i.e.,  $16 > 2 \text{ times } 3$ ). The contribution of each active ingredient to the effectiveness of the finished product, as required by 21 CFR 352.20(a), is addressed in study 1.GUS.SRE.18045.R01.

#### 6.1.4.3 1.GUS.SRE.18045.R01

This phase 2 study was conducted under the supervision of Dr. John W. P. Toole at Hilltop Research Inc. in Winnipeg, Manitoba, CA. The study began on August 31, 1999, and concluded on October 1, 1999. A total of 41 evaluable subjects completed the study. Thirty-one of the subjects were female and 10 were male with an age range of 18 to 62 years (average = 38) and skin type I (15%), II (46%), or III (39%).

Each subject was randomly assigned three test products and the standard sunscreen, such that each of five test products was tested on at least 20 subjects.

This study was designed to evaluate the effectiveness of five test formulations containing various combinations of the active ingredients in formulations 760-001. All test formulations consisted of the same vehicle. The following table outlines the composition of each test formulation and the number of subjects tested with each formulation.

**Table 4. Composition of Test Formulations in Study 1.GUS.SRE.18045.R01**

Test Formulation	10% Octocrylene	2% Avobenzone	3% Ecamsule	5% Titanium dioxide	Number of subjects
760.001	✓	✓	✓	✓	20
760.008	✓		✓	✓	22
760.003	✓	✓		✓	21
760.006	✓	✓	✓		23
760.009		✓	✓	✓	23

In accordance with 21 CFR Section 352.70, an 8% homosalate standard sunscreen was tested concomitantly.

The principal investigator reports deviations from the IRB-approved protocol in terms of the time elapsed between irradiation and MED evaluations. This time interval should be 22 to 24 hours (21 CFR 352.72(h)) but in every case, the time interval was less than 22 hours or greater than 24 hours. Actual elapsed time ranged from 20 hours and four minutes to 24 hours and 43 minutes. In the majority of cases, the elapsed time was within one hour of the 22 – 24 hour time frame. The report states that these deviations occurred because the length

of UV exposure time exceeded 2 hours and, as a result, follow-up evaluation appointments for the subjects did not fall within 22 – 24 hours of exposure. The principal investigator did not feel that these deviations interfered with the test results, and this reviewer concurs.

The mean SPF  $\pm$  SD for each test formulation and concurrently run standard sunscreen are presented in the table below. The table also includes the labeled SPF value for each test formulation. In accordance with 21 CFR 352.73(d), the labeled SPF equals the largest whole number less than the lower limit of the 95% confidence interval.

**Table 5. SPF Values for Formulations Tested in Study 1.GUS.SRE.18045.R01**

<b>Test Formulation</b>	<b>Missing Active Ingredient</b>	<b>Mean SPF <math>\pm</math>SD</b>	<b>Lower 95% Confidence Interval</b>	<b>Labeled SPF</b>
760.001	None	42.5 $\pm$ 6.2	40.1	40
760.008	Avobenzone	38.7 $\pm$ 4.3	37.1	37
760.003	Ecamsule	28.5 $\pm$ 4.7	26.7	26
760.006	Octocrylene	10.2 $\pm$ 1.6	9.6	9
760.009	Titanium Dioxide	20.9 $\pm$ 3.9	19.5	19

The mean SPF  $\pm$  SD of the standard sunscreen ranged from 4.1  $\pm$  0.5 to 4.5  $\pm$  0.8. These values fall within the acceptable range specified in 21 CFR 352.70(a). Therefore, the study results are valid.

This study evaluated the effectiveness of individual active ingredients contained in formulation 760-001. According to 21 CFR 352.20(a), the SPF of the final formulation must be equal to or greater than two times the number of active ingredients. Formulation 760-001 contains all four active ingredients, requiring an SPF of at least 8. The labeled SPF for this formulation was determined to be 40. This formulation meets one of the two effectiveness criteria specified in 21 CFR 352.20(a).

Combination products must also meet the requirement that each active ingredient contribute a minimum SPF of not less than 2 to the finished product. In this study, formulation 760-001 (all active ingredients) produced an SPF of 40. Comparing this formulation to formulation 760.008 (lacking avobenzone) indicates that 2% avobenzone contributes an SPF of 3 to the final formulation. By comparing formulation 760.003 (lacking ecamsule) to the final formulation, it appears that 3% ecamsule contributes an SPF of 14. Similarly, comparing formulation 760.006 (lacking titanium dioxide) to the final formulation indicates that 5% titanium dioxide produces an SPF of 31 and comparing formulation 760.009 (lacking octocrylene) to the final formulation indicates that 10% octocrylene produces an SPF of 21.

In summary, formulation 760.001 meets both criteria in 21 CFR 352.20(a) and, therefore, is effective.

### 6.1.5 Clinical Microbiology

No antimicrobial claims are made. Therefore, this section is not applicable.

### 6.1.6 Efficacy Conclusions

A total of three studies were conducted to evaluate the effectiveness of ANTHELIOS 40 (formulation 760-001) in protecting against UVB radiation. The test method derives from the sunscreen monograph (i.e., 21 CFR part 352 subpart D). The studies adequately demonstrate that this formulation is effective in helping prevent sunburn by providing protection against UVB radiation.

**Table 6. Labeled SPF Values for ANTHELIOS 40**

Study	Labeled SPF	Number of subjects
1.CG.03.SRE.2612	42	19
1.GUS.05.SRE.2639	42	22
1.GUS.SRE.18045.R01	40	20

A total of 61 evaluable subjects participated in three studies designed to demonstrate that formulation 760-001 is effective in protecting against UVB radiation. The submitted labeling for this formulation claims an SPF of 40. The data support this claim.

## 6.2 Indication

The proposed labeling for ANTHELIOS 40 includes claims regarding protection against UVA radiation. A UVA claim of "broad spectrum protection" is allowed for OTC sunscreens marketed under the sunscreen monograph (*Federal Register* vol. 64, p. 27672).

### 6.2.1 Methods

FDA has not yet published a final rule specifying testing procedures for evaluating the UVA radiation protection of sunscreens. In the 1993 TFM for OTC sunscreen drug products, FDA states that a sunscreen can bear a claim that it provides UVA protection if it meets two criteria (58 FR 28194 at 28233):

- the absorption spectrum extends to 360 nm or above in the UVA range
- UVA protection is demonstrated using an appropriate testing procedure

In the same document, FDA states that we believe a testing method similar to the one described by Lowe et al. (Ref. 1) could be used to demonstrate that a sunscreen provides protection against UVA radiation (58 FR 28194 at 28250). A 1996 amendment to the TFM reaffirms FDA's belief that the method of Lowe et al. is an appropriate test. In addition, FDA stated that the testing procedure described by Gange et al. (Ref. 2) is adequate (61 FR 48645 at 48652). The methods described by Lowe et al. and Gange et al. are similar to each other. In a 1998 amendment to the TFM, FDA found a third testing procedure to be adequate for evaluating UVA protection. This

method is based on determination of a minimal response dose (MRD) and is similar to the SPF test method except that the endpoint (i.e., "response") is pigment darkening rather than erythema (63 FR 56584 at 56587).

The sponsor submitted results from UVA effectiveness studies conducted according to two test methods:

- (1) the persistent pigment darkening (PPD) method
- (2) a method similar to the methods of Lowe et al. and Gange et al.

The PPD method used in study 1.CG.03.SPR.2613 is nearly identical to the MRD testing method. According to the MRD method, each subject is exposed to increasing amounts of simulated solar radiation in the absence or presence of a sunscreen. The MRD for protected and unprotected skin is determined for each subject. MRD represents the lowest radiation dose that causes pigment darkening that lasts 22-24 hours, because UVA radiation primarily causes the skin to darken (rather than redden). The protection factor for UVA, termed PFA, is then calculated as the ratio of MRD (protected skin) to MRD (unprotected skin). Thus, UVA protection increases with increasing PFA. A minimum of 20 subjects are required to complete the study according to the MRD protocol identified as acceptable by FDA (63 FR 56584 at 56587). As with the SPF test method, a sunscreen standard is tested concurrently to validate the study results.

The 8-methoxypsoralen (8-MOP) method was used in Study 1.CG.03.SRE.2614. According to this method, an alcohol solution containing 0.1% 8-MOP is applied to the skin of each subject. The 8-MOP photosensitizes the skin to UVA radiation, such that UVA radiation produces erythema instead of pigment darkening. Approximately 45 minutes after application of 8-MOP, each subject is irradiated with increasing doses of UVA radiation. Seventy-two hours post-irradiation, the skin is evaluated for erythema to determine a minimal phototoxic dose (MPD).

After determining the MPD for each subject, a phototoxic protection factor (PPF) is identified for different sunscreen formulations. The PPF is calculated as the ratio of MPD (protected skin) to MPD (unprotected skin). Thus, a larger PPF represents greater protection against UVA radiation. The number of subjects required in 8-MOP studies varies. Lowe et al. enrolled 26 subjects in each study (Ref. 1), whereas Gange et al. enrolled 41 (Ref. 2).

## 6.2.2 General Discussion of Endpoints

The endpoints according to the two UVA protection methods differ. The PPD (MRD) method utilizes pigment darkening, whereas the 8-MOP method utilizes erythema. According both methods, the endpoints are used to calculate protection factors. Both PFA and PPF values reflect the degree of UVA radiation provided by a sunscreen. Therefore, for consistency, the sponsor defines protection against UVA radiation using the term PFA for all UVA protection studies.

## 6.2.3 Study Design

These studies were designed in accordance with FDA's published comments regarding UVA protection. As stated in the 1998 TFM, until we propose a UVA protection test method, FDA "considers testing procedures similar to the UVA protection factor method...and those methods

described by R.W. Gange et al. and N.J. Lowe et al. as adequate for determining the UVA protection potential of a finished OTC sunscreen drug product” (63 FR 56584 at 56587). Inclusion and exclusion criteria are as defined in these methods. The submitted studies conform to these methods except where noted below. In general, the inclusion and exclusion criteria are similar to those of the SPF test. The only significant difference concerns the skin types of study subjects. The SPF test method requires skin types I, II, and III. The PPD method utilizes skin types II, III, and IV, which allow pigment darkening (rather than erythema).

#### 6.2.4 Efficacy Findings

Two studies were submitted to support a claim of effectiveness in protecting against UVA radiation. The two studies determined protection factors (PFA values) for the full formulation (760-001, containing all four active ingredients) and for triad formulations (containing three of the four active ingredients). This review first discusses the study conducted according to the PPD/MRD method (1.CG.03.SPR.2613) and then the study conducted according to the 8-MOP method (1.CG.03.SRE.2614).

##### 6.2.4.1 Study 1.CG.03.SPR.2613

This phase 2 study was conducted under the supervision of Dr. Robert Shanahan at the CPTC in Fairfield, NJ. The study began on September 8, 1999, and concluded on October 6, 1999. Sixty subjects enrolled in the study. Forty-four of the enrolled subjects were female, and sixteen were male. The subjects ranged in age from 18 to 59 years and had skin type II, III, or IV. A total of 55 evaluable subjects completed the study.

This study evaluates the effectiveness of the full formulation (760-001) and four triad formulations, each lacking one of the four active ingredients, in protecting against UVA radiation. In this study, the standard sunscreen was the JCIA 2 UVA Standard, with an expected PFA value of 3.75.

The principal investigator reports that data from 5 subjects were not suitable for evaluation. In addition, there were 15 deviations from protocol in that visual evaluation of pigment darkening did not occur at the planned 120, 180, and 240 minute time intervals and three protocol deviations due to the time between recording of pigmentation in one test site and the previous test site not being exact. These deviations should not have interfered with the study results.

The mean PFA  $\pm$  SD for each test formulation and concurrently run standard sunscreen are presented in the table below.

**Table 7. PFA Values for Different Formulations Tested in Study 1.CG.03.SPR.2613**

<b>Test Formulation</b>	<b>Missing Active Ingredient</b>	<b>Mean PFA ± SD</b>
760-001	None	23.2 ± 5.6
760-008	Avobenzone	13.2 ± 3.2
760-003	Ecamsule	15.3 ± 2.8
760-009	Octocrylene	11.9 ± 1.7
760-006	Titanium Dioxide	22.0 ± 4.2

The expected PFA of 3.75 falls within the 95% confidence interval of the PFA for the standard sunscreen in each trial. These results for the standard indicate that study results are valid.

Although PFA values are given, FDA has not yet published a final monograph establishing a rating scale for UVA protection. Therefore, this review only evaluates the UVA studies to determine whether the sunscreen formulations are effective UVA protectants (not the degree of UVA protection). Because PFA values are calculated in a manner analogous to SPF values, this reviewer is evaluating effectiveness in UVA protection based on the effectiveness criteria for UVB protection (21 CFR 352.20(a)). The final formulation is found to provide effective UVA protection if the PFA equals or exceeds two times the number of active ingredients. This reviewer does not think that the formulations need to meet the second criterion for UVB protection effectiveness (i.e., each active ingredient contributes a PFA of at least two to the final formulation). This criterion is included in the OTC sunscreen monograph for SPF determinations because sunscreen product labeling attributes UVB protection (i.e., sunburn protection) to each active ingredient. In contrast, a general UVA protection claim of “broad spectrum” does not specify which active ingredients are contributing to effective UVA protection. Thus, not every active ingredient must contribute to UVA radiation protection.

The PFA of formulation 760-001 (i.e., containing all four active ingredients) is  $23.2 \pm 5.6$ . This is greater than two times the number of active ingredients (2 times 4 = 8). Thus, the sunscreen provides effective broad spectrum UVA protection in both men and women, and it is expected that the formulations will also be effective on children (over 6 months of age).

#### 6.2.4.2 Study 1.CG.03.SRE.2614

This phase 2 study was conducted under the supervision of Dr. Anne Parneix-Spake at ASTER Cosmetology in Paris, France. The study began on September 3, 1999, and concluded on October 2, 1999. A total of 14 subjects enrolled in the study. Eight of the subjects were female, and six were male. The age range of the subjects was 18 to 55 years (average age 26.1 years), and subjects had skin type II or III. Eleven subjects were evaluable for formulation 760-001 (i.e., containing all four active ingredients) and the four triad formulations, each lacking one of the four active ingredients.. The number of subjects

included in this study is considerably lower than the number of subjects included in the studies by Lowe et al. (Ref. 1) and Gange et al. (Ref. 2).

This study evaluates the effectiveness of formulation 760-001, containing all 4 active ingredients, and four triads in protecting against UVA radiation using the 8-MOP method (Refs. 1 and 2). No standard sunscreen preparation was utilized. Effectiveness was measured against untreated (“control”) sites.

The principal investigator reports no deviations from the IRB-approved protocol.

The mean PFA values  $\pm$  SD for each of the three test products are presented below.

**Table 8. PFA Values for Different Formulations Tested in Study 1.CG.03.SRE.2614**

<b>Test Formulation</b>	<b>Missing Active Ingredient</b>	<b>Mean PFA <math>\pm</math> SD</b>
760-001	None	28.5 $\pm$ 3.3
760-008	Avobenzone	13.1 $\pm$ 3.0
760-003	Ecamsule	17.6 $\pm$ 4.0
760-009	Octocrylene	13.3 $\pm$ 1.9
760-006	Titanium Dioxide	24.7 $\pm$ 5.3

In the absence of a concomitantly run standard, it is not possible to validate these results. Furthermore, the numbers of subjects tested with each formulation is low compared with the numbers enrolled in the two reference studies. The PFA values calculated using the 8-MOP method in this study are generally higher than but comparable to the PFA values calculated using the PPD method (Study 1.CG.03.SPR.2613).

Even though no concurrent control was included in this study, the PFA value for the full formulation (760-001) is clearly greater than two times the number of active ingredients. Thus, this study suggests that ANTHELIOS 40 is effective in protecting against UVA radiation.

### 6.2.5 Clinical Microbiology

No antimicrobial claims are made. This section is not applicable.

### 6.2.6 Efficacy Conclusions

A total of two clinical studies were conducted to demonstrate that ANTHELIOS 40 (test formulation 760-001) effectively protects against UVA radiation. One study was conducted using the PPD method (Study 1.CG.03.SPR.2613). This method is comparable to the MRD method previously cited by FDA as acceptable (63 FR 56584 at 56587). The other study was conducted using the 8-MOP method, which is comparable to the FDA-accepted methods of Lowe et al. (Ref. 1) and Gange et al. (Ref. 2). In both studies, UVA protection is defined by a

PFA value, which is analogous to an SPF value for UVB protection. ANTHELIOS 40 appears to be effective in providing protection against UVA radiation.

**Table 9 Mean PFA Values for ANTHELIOS 40**

Study	PFA
1.CG.03.SPR.2613	23.2 ± 5.6
1.CG.03.SRE.2614	28.5 ± 3.3

A total of 66 evaluable subjects participated in the two clinical studies. PFA values are comparable in the PPD (1.CG.03.SPR.2613) and 8-MOP studies (1.CG.03.SRE.2614). The submitted data support the claim that ANTHELIOS 40 protects against UVA radiation.

Because PFA values are calculated in a manner analogous to SPF values, this reviewer is determining UVA protection effectiveness based on the effectiveness criteria for UVB protection (21 CFR 352.20(a)). Thus, the final formulation is found to provide effective UVA protection if the PFA equals or exceeds two times the number of active ingredients. This reviewer does not think that the formulations need to meet the second criterion for UVA protection effectiveness (i.e., each active ingredient contributes a PFA of at least two to the final formulation). This criterion is included in the OTC sunscreen monograph because sunscreen product labeling attributes UVB protection (i.e., sunburn protection) to each active ingredient. In contrast, a general UVA protection claim of “broad spectrum” does not specify which active ingredients are contributing to UVA protection effectiveness.

The PFAs determined in the two studies greatly exceeded two times the number of active ingredients. Thus, ANTHELIOS 40 provides effective UVA protection in both men and women, and it is expected that the formulation will also be effective on children (over 6 months of age).

The sunscreen monograph does not allow PFA values to be included on product labeling. Currently, the sunscreen monograph allows sunscreens that protect against UVA radiation to bear claims such as the following (58 FR 28194 at 28233):

- “broad spectrum”
- “protects against UVA rays or radiation”

FDA published a proposed rule in August 2007 that incorporates UVA testing and labeling into the sunscreen monograph. Until this proposed rule becomes finalized, all OTC sunscreen products should only be allowed claims such as those listed above. Stating a UVA rating such as PFA on a sunscreen label is likely to lead to consumer confusion. First, it is a new term that U.S. consumers are not familiar with and would only appear on the product label of the three formulations in these NDAs. Second, FDA has proposed different UVA testing and labeling under the monograph. It would be detrimental to the public health to have different UVA rating systems in the United States.

### 6.3 Indication

The submitted labeling for all three formulations includes claims regarding protection against UVA radiation. The submitted labeling includes PFA values. A UVA claim of "broad spectrum protection" is allowed for OTC sunscreens marketed under the OTC drug monograph system, but PFA values are not currently allowed (*Federal Register* vol. 64, p. 27672).

#### 6.3.1 Methods

To substantiate a claim of protection against UVA radiation, FDA requires that two criteria be met (see section 6.3.1). The sponsor has demonstrated that ANTHELIOS 40 meets the first criterion of providing UVA protection according to appropriate clinical testing procedures (section 6.3.6). To meet the second criterion, the sponsor submitted data from one study to demonstrate that a prototype ANTHELIOS 40 formulation absorbs light at wavelengths  $\geq 360$  nm (i.e., long wavelength UVA).

#### 6.3.2 General Discussion of Endpoints

The endpoint in this study is light absorption at each UVB and UVA wavelength. This data is then used to calculate a critical wavelength for each sunscreen formulation. Critical wavelength adequately demonstrates the ability of a sunscreen to absorb long-wavelength UVA radiation.

#### 6.3.3 Study Design

The critical wavelength is useful in determining the ability of a sunscreen to absorb long-wavelength UVA radiation, as a longer critical wavelength implies greater protection against long-wavelength UVA radiation (i.e.,  $\geq 360$  nm). Although the studies use synthetic human skin, the results can be extrapolated to human use. The absorption spectra will be different on different skin types, so it is impossible to determine a single spectrum for all consumers under actual use conditions. Rather, synthetic human skin can be expected to provide an approximation of the spectrum under conditions of OTC use.

#### 6.3.4 Efficacy Findings

##### 6.3.4.1 Study SOL-DP1-97-021

This in vitro study was conducted by M. Joël Bover at the L'Oreal Laboratory in Clichy, France. The study included several formulations. Two of the formulations are prototype formulations of ANTHELIOS 40 and are therefore relevant to this review. Formulation 427926 contains ecamsule, avobenzene, octocrylene, and a \_\_\_\_\_ titanium dioxide \_\_\_\_\_ grade). Formulation 427929 contains the same ingredients but the titanium dioxide is USP grade. Although only formulation 47929 is being considered for approval under this NDA, the two formulations are essentially identical and the critical wavelengths for both formulations are presented in the table below.

b(4)

**Table 10. Mean Critical Wavelengths for Prototype Formulations 427926 and 427929 in Study SOL-DP1-97-021**

Test Formulation	Mean Critical Wavelength (nm)
427926 (USP grade TiO <sub>2</sub> )	379
427929 (USP grade TiO <sub>2</sub> )	382

b(4)

Both formulations exhibited critical wavelengths of approximately 380 nm. Therefore, the two formulations meet the criterion of protecting against UVA radiation  $\geq 360$  nm.

### 6.3.5 Clinical Microbiology

No antimicrobial claims are made. This section is not applicable.

### 6.3.6 Efficacy Conclusions

Both formulations effectively absorb UV light at wavelengths  $\geq 360$  nm. Thus, the two formulations meet both criteria specified in the 1993 tentative final monograph (TFM) for OTC sunscreen drug products. The formulations may bear UVA protection claims, such as the following (58 FR 28194 at 28233):

- “broad spectrum”
- “protects against UVA rays or radiation”

## 7 INTEGRATED REVIEW OF SAFETY

The safety of ANTHELIOS 40 is being evaluated separately by Dr. Joseph Porres in the Division of Nonprescription Clinical Evaluation, Office of Nonprescription Products.

## 8 ADDITIONAL CLINICAL ISSUES

### 8.1 Dosing Regimen and Administration

The proposed dosing directions for ANTHELIOS 40 are as follows:

- apply liberally 15 minutes before sun exposure
- reapply as needed or after towel drying, swimming, or perspiring
- children under 6 months of age: ask a doctor

The proposed dosing directions are consistent with the OTC sunscreen drug monograph (21 CFR part 352).

## **8.2 Drug-Drug Interactions**

Potential drug-drug interactions are discussed as part of the safety review conducted by Dr. Joseph Porres in the Division of Nonprescription Clinical Evaluation, Office of Nonprescription Products..

## **8.3 Special Populations**

There are no special populations related to effectiveness. Special populations related to safety are discussed as part of the safety review conducted by Dr. Joseph Porres in the Division of Nonprescription Clinical Evaluation, Office of Nonprescription Products..

## **8.4 Pediatrics**

These formulations are effective for children older than 6 months of age. This is consistent with the OTC sunscreen drug monograph (21 CFR part 352). The safety of the formulations for children is pending evaluation by Dr. Joseph Porres in the Division of Nonprescription Clinical Evaluation, Office of Nonprescription Products..

## **8.5 Advisory Committee Meeting**

No advisory committee meeting is necessary to evaluate effectiveness of ANTHELIOS 40.

## **8.6 Literature Review**

A literature review was conducted as part of the safety review by Dr. Joseph Porres in the Division of Nonprescription Clinical Evaluation, Office of Nonprescription Products..

## **8.7 Postmarketing Risk Management Plan**

The need for a postmarketing risk management plan is pending safety evaluation by Dr. Joseph Porres in the Division of Nonprescription Clinical Evaluation, Office of Nonprescription Products.

## **8.8 Other Relevant Materials**

There are no other relevant materials submitted for review.

# **9 OVERALL ASSESSMENT**

## **9.1 Conclusions**

The effectiveness of ANTHELIOS 40 is acceptable for OTC marketing. The formulation provides effective protection against both UVB and UVA radiation.

## **9.2 Recommendation on Regulatory Action**

Based on effectiveness, ANTHELIOS 40 should be approved for over-the-counter (OTC) use for prevention of skin damage induced by UVB and UVA radiation. Final approvability depends on the outcome of the preclinical and clinical safety and chemistry studies being evaluated by other reviewers.

## **9.3 Recommendation on Postmarketing Actions**

### **9.3.1 Risk Management Activity**

This review only considers the effectiveness of ANTHELIOS 40. Therefore, this section is not applicable.

### **9.3.2 Required Phase 4 Commitments**

There are no required phase 4 commitments with respect to efficacy.

### **9.3.3 Other Phase 4 Requests**

None.

## **9.4 Labeling Review**

Evaluation of the proposed labeling is being done in a separate review.

## **9.5 Comments to Applicant**

This review does not have any comments to convey to the applicant.

## **10 APPENDICES**

No appendices are included.

## **REFERENCES**

1. Lowe et al., "Indoor and outdoor efficacy testing of broad spectrum sunscreen against UVA radiation in psoralin-sensitized subjects," *J. Am. Acad. Dermatol.* 17:224-230, 1987.
2. Gange R.W. et al., "Efficacy of a sunscreen containing butyl methoxydibenzoylmethane against ultraviolet A radiation in photosensitized subjects," *J. Am. Acad. Dermatol.* 15:494-499, 1986.

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**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

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**M E M O R A N D U M**

**Date:** September 21, 2007

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**Re: DDDP Consult #996:** Please review the sections related to the dermal safety studies for NDA 22-009, Helioblock SX SPF 40 (760.001).

**Material Reviewed:**

Study 1.CG.03.SRE.2604 irritation and contact sensitization  
Study 1.CG.03.SRE.2605. R01 phototoxicity  
Study 1.CG.03.SRE.2606 photoallergy

Study PEN.110.01 cumulative irritation and sensitization  
Study PEN.210.01 photosensitization  
Study PEN 250.01 phototoxicity

**Conclusion:**

The results of these studies are adequate to conclude that significant irritation, contact sensitization, phototoxicity or photosensitization did not occur during conduct of dermal safety battery studies with the product or related products. No additional dermal safety studies are recommended at this juncture. However, complete review of the safety during actual use conditions in other studies may be relevant in determining future evaluations for sunscreen safety. Such review is being conducted by the medical review staff in the Office of Non-prescription Products by prior agreement.

**Review:**

The proposed drug formulation, Helioblock SX Cream, SPF 40, contains ecamsule 3%, avobenzone 2%, octocrylene 10%, and titanium dioxide 5%. The requested indication is for the prevention of sunburn. DDDP has been requested to evaluate the dermal safety studies submitted to support the safety evaluation of the NDA.

Helioblock SX Cream was originally developed as a prescription product and was previously submitted May 30, 2003, in ' \_\_\_\_\_ , for ' \_\_\_\_\_

(The related IND was \_\_\_\_\_

The clinical reviewer, Dr.

Huene, felt that the safety of Helioblock SX has been adequately demonstrated. Of the dermatological adverse events which appeared to be possibly related to Helioblock SX, the most frequent was photosensitivity (PMLE), which occurred in 110 (23%) patients. This probably was felt to be due to inadequate applications. The remainder of the dermatological events occurred in 5% or less of patients and was generally mild to moderate in severity. There were no apparent drug-related changes in hematological parameters or in clinical chemistries.

Included in the submission are studies performed on related products which have been approved for the prevention of sunburn in separate NDA's. They are presented as supporting information for the current product and include formulations which contain slightly different formulations of the four sunscreen ingredients.

(Helioblock SX) cream is a combination of two mainly UVB and two mainly UVA ultraviolet filters. The rationale for the combination of the four filters, namely, ecamsule, avobenzone, octocrylene, and titanium dioxide, is to provide a strong and continuous protection across the entire ultraviolet spectrum.

Ecamsule and avobenzone are primarily UVA filters, and octocrylene and titanium dioxide are UVB filters. Avobenzone, octocrylene, and titanium dioxide are Category 1 sunscreens in the final monograph for OTC sunscreen drug products. The monograph permits the use of octocrylene and titanium dioxide in a single sunscreen product in

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approved concentrations; the concentrations of these ingredients in Helioblock SX are within the approved ranges.

Ecamsule was first approved in the United States on July 21, 2006 in NDA 21-502 for Anthelios SX Cream, a combination of ecamsule 2%, avobenzone 2%, and octocrylene 10%.

#### Dermal Safety Studies:

Provocative studies to evaluate dermal safety of topical drug products are needed prior to marketing and should be conducted with the final to-be-marketed drug formulation. They typically include assessments of cumulative irritation, sensitization, phototoxicity, and photo allergenicity.

The following studies were submitted in support of the current application for Helioblock SX Cream:

1. CG.03.SPR.2604 Irritation and contact sensitization—Number of subjects: 207
1. CG.03.SRE.2605 Phototoxicity – Number of subjects: 30
1. CG.03.SRE.2606 Photosensitization – Number of subjects: 112

The following studies were also submitted (in related IND 59,126) as supportive dermal safety evidence but did not use the to-be-marketed formulation which is the subject of the current NDA application:

PEN.110.01 Cumulative irritation and sensitization  
PEN.210.01 Photosensitization  
PEN 250.01 Phototoxicity

The studies which actually reviewed the dermal safety for Helioblock SX Cream (the 2604, 2605, and 2606 studies listed above) were previously reviewed by Dr. Huene during the review of \_\_\_\_\_ dated March 15, 2004. Excerpts of her review are reproduced here in support of the current NDA application:

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#### **Study 1.CG.03.SPR.2604**

This study was conducted by Dr. R.D. Scholefield, Quintiles Consumer Product Evaluation, Ledbury Herefordshire, England.

Study Title: Evaluation of the Cutaneous Contact Sensitization and Cumulative Irritancy Potential of Helioblock SX Cream, its Corresponding Triads and its Vehicle Following Repeated Applications to the Skin of Humans.

Study population: 207 evaluable subjects.

Study design and procedures: This was a randomized, investigator blind, intra-individual comparison of seven test products, which were as follows:

Helioblock SX cream  
Helioblock SX-E cream (without ecamsule)  
Helioblock SX-O cream (without octocrylene)  
Helioblock SX-T cream (without titanium dioxide)  
Helioblock SX-A cream (without avobenzone)  
Helioblock cream vehicle  
White petrolatum

During the induction period the test products were applied under occlusive dressings to the same skin sites on the back of each subject, for 24 hours four times weekly (Monday through Thursday) and for 72 hours once weekly (on Friday), for three weeks. Patch sites were changed if there were an excessive site reaction, defined as severe erythema and/or oozing, crusting and/or superficial erosion. Skin reactions were assessed at 15 to 30 minutes after each patch removal.

After a rest period of two weeks, challenge patches with each product were applied to naive sites under occlusion for 48 hours. Skin reactions were assessed at 15 to 30 minutes and at 48 and 72 hours after patch removal. A patched untreated site served as a control during the induction and challenge periods. Reactions were graded on the following scale:

Erythema	
0	No reaction
0.5	Erythema barely visible
1	Mild erythema
2	Moderate erythema
3	Severe erythema
Other reactions	
0	Oedema
P	Papules (many small, red solid elevations, surface or reaction has granular feeling)

V	Vesiculation (small <0.5 cm circumscribed elevations with visible fluid)
B	Blisters (bullae; large >0.5 cm circumscribed elevations with visible fluid)
Pu	Pustules (inflammatory small elevations containing yellow-white exudate)
H	Hyperpigmentation (an increase of the usual pigmentation limited on the patch test area)
W	Weeping/oozing (may be a sign of vesiculation or blisters (epidermal damage) and manifest as crusting)
S	Spreading of reaction beyond patch study site (i.e. reaction where no product came in contact with the skin)

Study results: 225 subjects were enrolled in the study, of which 224 participated in the induction period and 210 completed the study. The reasons for withdrawal were adverse events (7), subject request (2), and other (6). None of the adverse events leading to withdrawal was related to the test products.

The maximum erythema scores during the induction period were as follows:

Maximum erythema scores - induction period					
	0	0.5	1	2	3
Helioblock SX	65 (29%)	60 (27%)	64 (29%)	27 (12%)	8 (4%)
Helioblock SX-E	121 (54%)	55 (25%)	37 (17%)	9 (4%)	2 (1%)
Helioblock SX-A	69 (31%)	55 (25%)	56 (25%)	35 (16%)	9 (4%)
Helioblock SX-T	90 (40%)	52 (23%)	50 (22%)	26 (12%)	6 (3%)
Helioblock SX-O	43 (19%)	58 (26%)	62 (28%)	42 (19%)	19 (9%)
Helioblock SX vehicle	139 (62%)	51 (23%)	26 (12%)	6 (3%)	2 (1%)
Petrolatum	136 (61%)	53 (24%)	62 (28%)	42 (19%)	19 (9%)
Untreated patch	69 (31%)	73 (33%)	75 (34%)	7 (3%)	0

The incidence of other reactions during the induction period was as follows:

Other reactions - induction period				
	Edema	Papules	Pustules	Weeping/ oozing
Helioblock SX	1 (0.4%)	1 (0.4%)	1 (0.4%)	6 (3%)
Helioblock SX-E	0	0	1 (0.4%)	0
Helioblock SX-A	4 (4%)	2 (1%)	0	5 (2%)
Helioblock SX-T	4 (2%)	3 (1%)	1 (0.4%)	2 (1%)
Helioblock SX-O	12 (5%)	1 (0.4%)	1 (0.4%)	9 (4%)
Helioblock SX vehicle	2 (1%)	0	1 (0.4%)	1 (0.4%)
Petrolatum	1 (0.4%)	1 (0.4%)	2 (1%)	0
Untreated patch	2 (1%)	0	2 (1%)	0

The mean cumulative irritation index was as follows:

Mean cumulative irritation index	
Helioblock SX	0.20
Helioblock SX-E	0.08
Helioblock SX-A	0.24
Helioblock SX-T	0.16
Helioblock SX-O	0.32
Helioblock SX vehicle	0.05
Petrolatum	0.07
Untreated patch	0.12

The number of subjects per product that had the patch site changed due to excessive irritation was as follows:

Subjects with excessive irritation	
Helioblock SX	14
Helioblock SX-E	2
Helioblock SX-A	14
Helioblock SX-T	9
Helioblock SX-O	32
Helioblock SX vehicle	3
Petrolatum	3
Untreated patch	2

The results of the challenge patch are reported as the percentage of subjects with no reaction immediately after challenge and at 48 and 72 hours after challenge, as follows:

Percentage with no reaction to challenge			
	Immediate	48 hr	72 hr
Helioblock SX	96.6	98.1	99.0
Helioblock SX-E	99.0	99.5	100
Helioblock SX-A	98.1	98.6	99.5
Helioblock SX-T	96.6	98.6	99.5
Helioblock SX-O	93.8	97.6	99.0
Helioblock SX vehicle	97.6	99.0	99.5
Petrolatum	93.3	99.5	100
Untreated patch	84.1	98.6	99.5

The reactions at challenge were a maximum erythema score of 1 in a few subjects in each treatment group. There were no edema, papules, vesiculation, or spreading of reaction beyond the patch site reported.

A total of 66 adverse events were experienced by 53 subjects during the study. Nine were moderate, and 57 were mild in severity. No serious adverse events were reported. Seven subjects discontinued participation due to adverse events, but none of these were

related to study medication. One subject developed pruritus which was possibly related to the study drug, but no other specific adverse event was related to treatment.

Reviewer's comments: Helioblock SX showed an excessive irritation, defined as severe erythema and/or oozing, crusting and/or superficial erosion, in about 6% of subjects. The earliest time of this reaction in any subject was day 7. This was primarily due to the components avobenzone and octocrylene. It is felt that this level of irritation under these conditions of exaggerated exposure indicates a low potential for significant irritation under conditions of normal usage.

The sponsor stated that no reactions indicative of contact sensitization were found.

### **Study 1.CG.03.SRE.2605.R01**

This study was conducted by Anne Parneix-Spake, M.D., Aster Cosmetology, Paris, France.

Study title: Evaluation of the Phototoxicity Potential of Helioblock SX Cream, its Corresponding Triads and its Vehicle.

Study population: 30 evaluable subjects.

Study design and procedures: This was a randomized, investigator blind, intra-individual comparison of seven test products, which were as follows:

- Helioblock SX cream
- Helioblock SX-E cream (without ecamsule)
- Helioblock SX-O cream (without octocrylene)
- Helioblock SX-T cream (without titanium dioxide)
- Helioblock SX-A cream (without avobenzone)
- Helioblock cream vehicle
- White petrolatum

The seven test products were applied under occlusive patches to two sets of patch sites on the back of each subject. An additional patch site in each set was an untreated control. After 24 hours one set of patches was irradiated with 20 Joules/cm<sup>2</sup> of UVA, followed by a sub-erythema dose (0.8 MED) of UVA/UVB light. The other set of patches were covered and served as non-irradiated controls.

Skin reactions were evaluated at 15-30 minutes and at 24 and 48 hours after patch removal.

Reactions were graded on the following scale:

Erythema	
0	No reaction
0.5	Erythema barely visible
1	Mild erythema
2	Moderate erythema
3	Severe erythema
Other reactions	
0	Oedema

P	Papules (many small, red solid elevations, surface or reaction has granular feeling)
V	Vesiculation (small <0.5 cm circumscribed elevations having translucent surfaces so that fluid is visible)
B	Blisters (bullae; large >0.5 cm circumscribed elevations with visible fluid)
Pu	Pustules (inflammatory small elevations containing yellow-white exudate)
H	Hyperpigmentation (an increase of the usual pigmentation limited on the patch test area)
W	Weeping/oozing (may be a sign of vesiculation or blisters (epidermal damage) and manifest as crusting)
S	Spreading of reaction beyond patch study site (i.e. reaction where no product came in contact with the skin)

Study results: 30 subjects were enrolled in the study, all of whom completed the study. The mean erythema scores and range of erythema scores for the eight patch sites were as follows:

Erythema scores		
	Mean	Range
<u>Helioblock SX</u>		
Immediate	0.00	-
24 hours	0.02	0.0-0.5
48 hours	0.00	-
<u>Helioblock SX-E</u>		
Immediate	0.00	-
24 hours	0.10	0.0-1.0
48 hours	0.05	0.0-1.0
<u>Helioblock SX-O</u>		
Immediate	0.00	-
24 hours	0.25	0.0-2.0
48 hours	0.08	0.0-1.0
<u>Helioblock SX-T</u>		
Immediate	0.00	-
24 hours	0.05	0.0-0.5
48 hours	0.02	0.0-0.5
<u>Helioblock SX-A</u>		
Immediate	0.00	-
24 hours	0.12	0.0-1.0
48 hours	0.02	0.0-0.5
<u>Vehicle</u>		
Immediate	0.00	-
24 hours	0.32	0.0-2.0
48 hours	0.17	0.0-2.0
<u>Petrolatum</u>		
Immediate	0.00	-
24 hours	0.30	0.0-2.0
48 hours	0.15	0.0-2.0
<u>Untreated site</u>		
Immediate	0.00	-
24 hours	0.32	0.0-2.0
48 hours	0.18	0.0-2.0

No subject showed erythema on the non-irradiated side. Other local reactions consisted of hyperpigmentation at 24 and 48 hours after irradiation.

The sponsor's conclusion was that no phototoxic reactions occurred with the test products.

**Study 1.CG.03.SRE.2606**

This study was conducted by Anne Parneix-Spake, M.D., Aster Cosmetology, Paris, France.

Study title: Evaluation of the Photoallergic Potential of Helioblock SX Cream, its Corresponding Triads and its Vehicle Following Repeated Applications to the Skin of Humans.

Study population: 112 evaluable subjects.

Study design and procedures: This was a randomized, investigator blind, intra-individual comparison of seven test products, which were as follows:

- Helioblock SX Cream
- Helioblock SX-E cream (without ecamsule)
- Helioblock SX-O cream (without octocrylene)
- Helioblock SX-T cream (without titanium dioxide)
- Helioblock SX-A cream (without avobenzone)
- Helioblock cream vehicle
- White petrolatum

The seven test products were applied to the back of each subject under occlusive patches for 24 hours twice weekly for three weeks. At each patch removal the sites were irradiated with UVA/UVB light. Dosage was 2 MED during the first week and 3 MED during the second and third week. Skin reactions were evaluated prior to applications or before irradiation of the sites.

After a two week rest period, in the challenge phase the test products were applied under occlusion for 24 hours in two sets of patches. After patch removal one set of patches was irradiated and the other was a non-irradiated control. The irradiation dose was 0.8 MED of UVA/UVB light followed by 10 Joules/cm<sup>2</sup> of UVA light. An untreated irradiated site and a treated non-irradiated site served as controls. Skin reactions were evaluated at 15 to 30 minutes, 48 hours, and 72 hours after irradiation.

Reactions were graded on the following scale:

Erythema	
0	No reaction
0.5	Erythema barely visible
1	Mild erythema
2	Moderate erythema
3	Severe erythema

Other reactions	
O	Oedema
P	Papules (many small, red solid elevations, surface or reaction has granular feeling)
V	Vesiculation (small <0.5 cm circumscribed elevations having translucent surfaces so that fluid is visible)
B	Blisters (bullae; large >0.5 cm circumscribed elevations with visible fluid)
Pu	Pustules (inflammatory small elevations containing yellow-white exudate)
H	Hyperpigmentation (an increase of the usual pigmentation limited on the patch test area)
W	Weeping/oozing (may be a sign of vesiculation or blisters (epidermal damage) and manifest as crusting)
S	Spreading of reaction beyond patch study site (i.e. reaction where no product came in contact with the skin)

Study results: 118 subjects were enrolled in the study, of which 112 completed the study. Four subjects discontinued due to unrelated adverse events, and two were discontinued at their request.

During the induction phase the incidence and severity of erythema were higher at the untreated, vehicle, and petrolatum sites than at the Helioblock SX and Triads sites. One subject had papulation at the Helioblock SX-E site, one had edema at the Helioblock SX-T site, and one had papulation and vesiculation at the vehicle site. The frequency of hyperpigmentation increased during the induction period, but was slightly faster at the untreated, vehicle and petrolatum sites than at the Helioblock SX and Triads sites.

Reactions in the challenge phase were a low incidence of mild to moderate erythema at the Helioblock SX and Triads sites. One subject had papulation at the Helioblock SX site, and one subject had papulation at the vehicle site. The sponsor's conclusion was that under the conditions of the study, no photoallergic reactions were reported in any of the subjects.

Four adverse events, two mild, one moderate, and one severe, were experienced by four subjects but were assessed to be unlikely related to study drug products. These adverse events were severe pharyngitis, moderate tendonitis, cold, and mild asthenia. No adverse events were likely related to study drug.

Reviewer's evaluation of Studies 2604, 2605, and 2606: The results of these studies are adequate to conclude that there is little or no potential for significant irritation, contact sensitization, phototoxicity or photosensitization.

\_\_\_\_\_ Studies:

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Study PEN.110.01 cumulative irritation and sensitization

Study PEN.210.01 photosensitization

Study PEN 250.01 phototoxicity

The sponsor has included dermal safety studies for the \_\_\_\_\_ sunscreen product development program, though the formulations of these sunscreens are different than the Helioblock SX formulations. As such, they are not directly applicable to the current NDA application.

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Three of the \_\_\_\_\_ formulations were included and compared to a treated control, white petrolatum. Two of the three \_\_\_\_\_ compounds did not include titanium dioxide at all, while the third contained 2% titanium dioxide and only 2% ecamsule.

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These studies have been previously reviewed by Dr. Huene in October, 2005, as part of the review of NDA 21-502, previously entered into DFS on January 9, 2006. Her conclusion was:

“The dermal safety studies are adequate to show that there is little or no potential for irritation, phototoxicity, or photosensitization under the conditions of proposed usage. Although there were no sensitization reactions at challenge, one subject in the sensitization study was apparently pre-sensitized to the test products prior to initiation of the study. There is therefore some potential for sensitization.”

These \_\_\_\_\_ studies are supportive since they utilized related sunscreen formulations, but the conclusions are less relevant since the formulations are different from the subject of this application.

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David Kettl, MD  
Medical Officer

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