CLINICAL REVIEW

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Reviewer Name: Joseph M. Porres, MD, PhD
Through: Daiva Shetty, MD
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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

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: SPF15 Water Resistant (NDA 21-501, approved 10/2/06), SPF 15 lotion (NDA 21-502, approved 7/21/06), and SPF 20 Water Resistant (NDA 21-471, approved 10/6/06) .

The following table compares the formulations of the various products:

TABLE 1. FORMULATION OF THE PRODUCTS				
Product name	Helioblock SX SPF40 Cream	SPF 20 W/R Cream	SPF 15 Daily Use Cream	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%	-	-

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 SPF15 W/R Cream in the addition of titanium dioxide, and from the approved SPF20 W/R Cream in the content of ecamsule (3% in HSX as opposed to 2% in SPF20 W/R) and in the content of titanium dioxide (5% in HSX as opposed to 2% in SPF20 W/R).

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

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. Phase1
V99.1203	Dermal absorption of C^{14} 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 SPF 15 Daily Use Cream
750.02	Open label long term safety of SPF 15 W/R Cream

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

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 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.

On 3/1/06 L'Oreal submitted IND 57,850, serial #30, indicating that the HSX's formulation was changing from the pigmentary (formulation) to the 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.

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 titanium dioxide were compared.

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.

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.

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 ≥ 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.

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.

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.

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.

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

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:

- SPF15 Water Resistant (NDA 21-501, approved 10/2/06)
- SPF 15 lotion (NDA 21-502, approved 7/21/06)
- 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.
2. ANTHELIOS 40
3.

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:

- SPF15 Water Resistant (NDA 21-501, approved 10/2/06)
- SPF 15 lotion (NDA 21-502, approved 7/21/06)
- 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.

The sponsor states that variations among the four ecamsule containing formulations in the 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 and 1 Helioblock NDAs). This reviewer concurs with this conclusion.

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 units of sunscreen products containing ecamsule in combination with other EU approved UV filters have been sold in Europe and globally.

3. SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

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 embryolethality 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)
- [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.

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.

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^{14} 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 [redacted] formulations, as follows:

TABLE 4. STUDIES WITH ECAMSULE CONTAINING SUNSCREENS			
750.01	Open label long term safety of [redacted] SPF 15 Daily Use Cream	248	708 subjects
750.02	Open label long term safety of [redacted] SPF 15 W/R Cream	246	
750.03	Open label long term safety of [redacted] SPF 20 W/R Cream	79	
750.04	Long term safety with [redacted] Titanium dioxide	135	
110.01	Repeat Insult Patch test	223	1232 subjects
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

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

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

- 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 [redacted] development program, as shown in Table 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 [redacted] formulations that share ingredients with HSX.). All SAEs were considered unrelated to study medication.

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

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.

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

TABLE 5. SUBJECT DISPOSITION. 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.

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[1]:

- 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.

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:

TABLE 6. SUMMARY OF AES IN STUDY PEN.750.04		
	Subjects (n=135)	
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:

TABLE 7. SUMMARY OF AES IN PHASE 1, 2, AND 3 CLINICAL STUDIES

Study #	N	No. of AEs	Subjects with AEs	Types of AEs (cases)
Phase 1 Local Tolerance Studies				
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

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
Phase 2 Combination Policy Studies				
PEN.810.05	50	1	1	Sore throat
PEN.810.06	100	1	1	Headache
PEN.910.02	70	0	0	--
Phase 3 UVA/UVB Protection Studies				
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	--
Total	1155	125	86	

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 (%)
Total		145	39 (15.7)
Body as Whole	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
Cardiovascular System	Hypertension	3 (1.2)	0
Digestive System	Dyspepsia	4 (1.6)	0
	Gastrointestinal disorder	3 (1.2)	0
	Nausea	3 (1.2)	0
	Tooth disorder	6 (2.4)	0
Musculo-Skeletal System	Bone disorder	3 (1.2)	0
Nervous System	Depression	3 (1.2)	0
	Dizziness	5 (2.0)	0
	Neuralgia	4 (1.6)	0
Respiratory system	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
Skin and Appendages	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)

	Erythema	10 (4.0)	3 (1.2)
	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)
Special Senses	Conjunctivitis	6 (2.4)	2 (0.8)
	Taste perversion	3 (1.2)	1 (0.4)
Urogenital System	Urinary tract infection	5 (2.0)	0

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 (%)
Total		167	18 (7.3)
Body as Whole	Abdominal pain	5 (2.0)	0
	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
Digestive System	Gastritis	8 (3.3)	0
	Vomiting	9 (3.7)	0
Hemic/Lymphatic	Ecchymosis	5 (2.0)	0
Musculo-Skeletal System	Myalgia	4 (1.6)	0
Respiratory system	Asthma	4 (1.6)	0
	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
Skin and Appendages	Bite	9 (3.7)	0
	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)
Special Senses	Conjunctivitis	6 (2.4)	1 (0.4)
	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
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.

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 [redacted] clinical safety studies.

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.

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

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.

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 comes 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

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.

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.

7.2.1.2 Demographics

7.2.1.2.1 Phase 1, 2, and 3 Clinical Studies

Subject demographics and baseline characteristics across the Phase1, 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

- 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).

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

TABLE 13. DEMOGRAPHICS AND BASELINE CHARACTERISTICS IN LONG TERM STUDIES

		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	> 0.5 to < 2	0 (0)	57 (23.17)	24 (30.38)	0
(years)	> 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	Male	58 (23.39)	101 (41.06)	26 (32.91)	83 (17.5)
(N[%])	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	I	17 (6.85)	14 (5.69)	6 (7.59)	87 (18.3)
phototype	II	52 (20.97)	96 (39.02)	27 (34.18)	179 (37.7)
(N[%])	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	Yes	97 (39.11)	159 (64.63)	45 (56.96)	--
subjects	No	151 (60.89)	87 (35.37)	34 (43.04)	--
	PLME	0	0	0	475 (100)

Subjects enrolled into the [redacted] 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 [redacted] 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

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

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^2. 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
Phase 1 Local Tolerance Studies			
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.GC.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
Phase 1 Pharmacokinetic Studies			
1.CG.03.SRE.2607	6	15 g applied twice daily 9 days	18 whole body applications
V99.1203	5	0.2 g ([^{14}C]-ecamsule, 2%) 100 cm^2 area	4 hours on volar forearm
V3156	8	10 g, 4.95% ecamsule	5 consecutive days
Phase 2 Combination Policy Studies			
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
Phase 3 UVA/UVB Protection Studies			

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
		N=248	N=246	N=79	N=475
Treatment Duration	N	248	246	79	475
(days)	Mean (SD)	307.1 (110.3)	88.4 (96.9)	37.3 (34.3)	258.3 (125.8)
	Median	356.0	44.5	31.0	335.0
	Range	1.0-376.0	1.0-363.0	1.0-225.0	1.0-393.0
Total Usage (g)	N	237	237	74	445
	Mean (SD)	570.6 (474.0)	256.6 (249.9)	143.0)106.8)	302.3 (297.4)
	Median	433.4	174.5	122.0	211.6
	Range	27.9-3141.8	0.1-1650.8	6.8-532.0	-1.5-2006.0
Daily Usage (g/day)	N	235	235	72	445
	Mean (SD)	2.0 (2.6)	4.2 (3.6)	4.8 (4.5)	1.3 (1.9)
	Median	1.6	3.1	3.7	0.9
	Range	0.16-35.5	0.07-26.85	0.86-29.6	-1.0-26.1
Product Application	N	239	237	75	453
(total number)	Mean (SD)	417.4 (180.0)	145.9 (295.2)	55.9 (55.5)	303.1 (171.3)
	Median	388.0	57.0	42.0	342.0
	Range	1.0-1029.0	1.0-2687.0	0.0-421.0	1.0-1158.0
Daily Application	N	239	237	73	453
(number/day)	Mean (SD)	1.3 (0.4)	1.4 (0.8)	1.5 (0.5)	1.1 (0.4)
	Median	1.1	1.2	1.3	1.1
	Range	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

(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:

- 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:

TABLE 17. TREATMENT DURATION FOR DIFFERENT AGE GROUPS (FOUR LONG-TERM STUDIES)

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.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

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 [redacted] 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.

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.

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

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

TABLE 18. 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 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		41 (8.7)	49 (14.4)	46 (19.6)	136 (13.0)
TRAE					
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/	Dermatitis	6 (1.3)	8 (2.4)	2 (0.9)	16 (1.5)
Irritation	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)
Photosensitizatio	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)

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:

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

		Drug Related AEs	
Demographic Subgroup		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%)

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 [redacted] 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.

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 [redacted] LONG-TERM STUDIES BY PREDISPOSING CONDITIONS

	Drug Related AEs	
Predisposing Conditions	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%)

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 [redacted] 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

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.

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 form 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:

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_2	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

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.

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].

The sponsor states that there are no safety concerns with titanium dioxide, avobenzone, 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.

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.

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)[2] 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.

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 uopdate 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.

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.

9.5 Comments to Applicant

No comments.

10. APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Study [redacted].1010.02

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_2, the other was "extremely similar" except for including [redacted] TiO_2; 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.

Investigator: [redacted]

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 ≥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^2 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.

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

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

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:

TABLE 22. STUDY SCHEDULE. PEN 750.04

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[1]		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

[1] 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:

- 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 titanium dioxide. The following table compares this formulation to the HSX formulation used for the other studies in the NDA:

TABLE 23. COMPOSITION OF FORMULATIONS. PIGMENTARY VERSUS TITANIUM DIOXIDE

Composition (w/w%)	Pending NDA 22-009 formula Helioblock® SX Cream (pigmentary TiO_2)	IND 57,850 PEN.750.04 formula (TiO_2)
Active Ingredients		
Avobenzone USP	2.00	2.00
Ecamsule*	3.00	3.00
Octocrylene USP	10.00	10.00
Titanium Dioxide USP	5.00	5.00
Inactive Ingredients		
Carbomer 940 NF		
Carbomer 1342 NF		
Cyclomethicone NF		
Dimethicone NF, 200-350 cst		
Edetate Disodium USP		
Glycerin USP		
Hydroxypropyl Methylcellulose USP		
Isopropyl Palmitate NF		
Methylparaben NF		
Phenoxyethanol Ph. Eur.		
Polyvinylpyrrolidone Eicosene copolymer		
Propylene Glycol USP		
Propylparaben NF		
Stearic Acid NF		
Aluminum Hydroxide		
Stearoyl Macroglycerides Ph. Eur.,		
Stearyl Alcohol NF		
Trolamine NF		
Purified Water USP		

The sponsor comments that both formulations are "extremely similar" , and that the titanium [redacted] 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.

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:

TABLE 24. BASELINE DEMOGRAPHICS AND BACKGROUND CHARACTERISTICS

	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 (%)[1] 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	5 (11)	12 (27)	9 (20)	26 (19)
Self assessed	1 (20)	2 (17)	2 (22)	5 (19)
Atopic background	4 (80)	11 (92)	7 (78)	22 (85)
Previous intolerance to topical products	1 (20)	0 (0)	0 (0)	1 (4)

[1] 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:

TABLE 25. 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 dairy	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.

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

TABLE 26. EXTENT OF EXPOSURE BY AGE. PEN 750.04

	6 Months to ≤ 2 Years Old	> 2 Years to ≤ 6 Years Old	> 6 Years to ≤ 12 Years Old	Total
Number of Subjects	46	44	45	135
Number of Days Subject had Sun Exposure				
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
Total Length of Sun Exposure (Hours)				
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
Number of Applications				
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
Number of Days Product Used				
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
Total Product Used (g)				
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
Dosing Compliant[a]				
Yes	42 (93%)	39 (89%)	45 (100%)	126 (94%)
No	3 (7%)	5 (11%)	0 (0%)	8 (6%)

[a] A subject was considered compliant with the dosing regimen if they applied study product at least 14 days while enrolled in the study.

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

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:

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:

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:

TABLE 30. STUDY SUBJECT COMPLETION AND DISCONTINUATIONS

	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
Premature Study Discontinuation Reason				
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[a]	1	0	0	1

[a] Subject 20-11: Dropped as per PI, due to siblings adverse even

SOURCE: [redacted])

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:

TABLE 31. PROTOCOL DEVIATIONS

	Subjects (N=135)
Deviation	
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:

TABLE 32. AES BY MEDRA ORGAN CLASS AND PREFERRED TERM

SYSTEM ORGAN CLASS / Preferred Term	No.	%
INFECTIONS & INFESTATIONS	46	34
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
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	31	23
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
METABOLISM & NUTRITION DISORDERS	1	1
Dehydration	1	1
MUSCULOSKELETAL & CONNECTIVE TISSUE DISORDERS	2	1
Back pain	1	1
Myalgia	1	1
NEOPLASMS BENIGN, MALIGNANT & UNSPECIFIED	1	1
Melanocytic nevus	1	1
NERVOUS SYSTEM DISORDERS	3	2
Headache	2	1
Tension headache	1	1
RESPIRATORY, THORACIC & MEDIASTINAL DISORDERS	19	14
Allergic cough	1	1
Asthma	1	1
Cough	8	6

SYSTEM ORGAN CLASS / Preferred Term	No.	%
Nasal congestion	4	3
Pharyngolaryngeal pain	2	1
Pulmonary congestion	1	1
Rhinitis allergic	1	1
Rhinorrhea	3	2
SKIN & SUBCUTANEOUS TISSUE DISORDERS	41	30
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.

The following table summarizes the dermatological AEs by severity:

TABLE 33. DERMATOLOGICAL AES BY SEVERITY

	Mild	Moderate	Severe
6 Months to ≤ 2 Years Old (N=46)			
Number of Events Reported	36	4	0
System Organ Class[1]			
General disorders and administration site conditions	1 (2%)	0 (0%)	0 (0%)
Application site rash	1 (2%)	0 (0%)	0 (0%)
Infections and infestations	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%)
Injury, poisoning and procedural complications	2 (4%)	2 (4%)	0 (0%)
Contusion	0 (0%)	1 (2%)	0 (0%)
Excoriation	2 (4%)	1 (2%)	0 (0%)
Skin and subcutaneous tissue disorders	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.

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

TABLE 34. SUBJECTS WITH STUDY DRUG RELATED AES BY AGE

Subject No.	Subject Age	Preferred Term (number of occurrences)	Severity	Related to Study Drug	Subject Discontinued Due to the AE(s)?
6 months to 2 years old					
21-31	0.63	lacrimation increased (1)	mild	definitely	No
21-33	1.73	application site rash (1)	mild	probably	Yes
>2 to 6 years old					
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
>6 to 12 years old					
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:

TABLE 35. TREATMENT RELATED AES. PEN 750.04

SYSTEM ORGAN CLASS / Preferred Term	No.	%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**7**	**5**
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
EYE DISORDERS	**2**	**1**
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), pruritus (5%, all mild), and application site rash (2% mild + 7% moderate).

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:

TABLE 36. SUMMARY OF AES. PEN 750.04

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

[1] 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

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:

TABLE 37. COMPARISON OF UV ACTIVE INGREDIENTS IN HELIOBLOCK SX CREAM SPF 40 TO THE SUNSCREEN FORMULATIONS USED IN THE 14 PEDIATRIC COSMETIC USE STUDIES BY INCREASING PERCENTAGES OF ECAMSULE

Study	SPF	Active Ingredient (%)			
		Ecamsule	Avobenzone	Octocrylene	TiO_2
Helioblock® SX Cream SPF 40					
RD.06.SRE.18047	40	3	2	10	5
Pediatric Cosmetic Use					
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[a]	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

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

TABLE 38. SEQUENCE OF PEDIATRIC COSMETIC USE STUDIES

Study	Date First Subject Enrolled	Date Last Subject Completed	Number of Subjects That Used Sunscreen at least Once
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:

TABLE 39. DURATION OF EXPOSURE TO ECAMSULE-CONTAINING SUNSCREENS IN THE PEDIATRIC COSMETIC USE STUDIES

Study	≤ 7 days	8 to 14 days	15 to 21 days	22 to 28 days
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)
All Studies	**13(2.5)**	**36 (6.8)**	**216 (41.1)**	**261 (49.6)**

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
Supportive Cosmetic Pediatric Use Safety Studies on Related Sunscreens							
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/cm2, 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 subjectw with related AEs (16.1%), 3 erythema, 1 dermatitis, 1 skin discomfort, 1 dryness, 1 pruritis, 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 expcept 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 40completed	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 wserious 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 acceptabiligy: no related AEs. No serious AEs. No discontinuations due to 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
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 COLORÉ 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

	All Studies (N=526)	
Adverse Event	**No.**	**%**
Any Dermatologic Adverse Event	**36**	**6.8**
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 %.

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

TABLE 42. ADVERSE EVENTS IN SUBJECTS WHO USED SUNSCREEN ≥14 DAYS DURING THE PEDIATRIC COSMETIC USE STUDIES BY PERCENTAGE OF ECAMSULE IN THE FORMULATION

Adverse Event	Number (%) of Subjects	
	<3% Ecamsule N=188	≥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 ≥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[a]	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	27Sep2004/180ct2004	4.5%	1	Erythema Skin discomfort Dryness
I	IEUT 3058	60	10Nov2003/02Dec2003	>6%	37	Dermatitis Dryness
	IEUT 4052	60	27Sep2004/180ct2004	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	27Sep2004/180ct2004	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	27Sep2004/180ct2004	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	27Sep2004/180ct2004	4.5%	21	None
BN	IEUT 3058	60	10Nov2003/02Dec2003	>6%	21	None
	IEUT 3066	60	18Mar2004/07Apr2004	3%	13	Acne
	IEUT 4052	60	27Sep2004/180ct2004	4.5%	22	Erythema Pruritus
BP	IEUT 3066	60	18Mar2004/07Apr2004	3%	15	None
	IEUT 4053	60	050ct2004/260ct2004	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	27Sep2004/180ct2004	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	27Sep2004/180ct2004	4.5%	32	None

[a] 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

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:

Page 69 redacted for the following reason:
- -

Page 70 redacted for the following reason:
- -

An interdisciplinary scientist in the ONP is reviewing the proposed labeling for the products.

REFERENCES

[1] Sunscreen drug products for over-the-counter human use; Amendment to the tentative final monograph. Food and Drug Administration. Federal Register 61(180):48645-48655, September 16, 1996

[2] American Academy of Pediatrics. Ultraviolet Light: A Hazard to Children. Pediatr 1999;104(2): 328-333

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/s/

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

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2/8/2008 08:05:46 AM
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