

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-502**

**MEDICAL REVIEW**



**MEMORANDUM**

Department Of Health and Human Services  
Food and Drugs Administration  
Center for Drug Evaluation and Research  
**Division of Nonprescription Clinical Evaluation**

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**Date:** July 11, 2006

**From:** Andrea Leonard-Segal, M.D.  
Director

**Subject:** [ ]

NDA 21-502 [ ] SPF 15 Sunscreen Daily Cream  
[ecamsule 2% (Mexoryl®); avobenzone 2%; octocrylene 10%]

**Sponsor:** L'Oreal USA Products, Inc.

**RECOMMENDATIONS:**

Each of these [ ] NDAs should be approved if the sponsor resolves the respective remaining labeling issues by the PDUFA date. If labeling issues remain unresolved, then the NDA(s) should be approvable.

As a Phase 4 commitment to address the Pediatric Research Equity Act, the sponsor should be asked to perform safety and pharmacokinetics studies in babies < 6 months of age for [ ] [ ] NDA 21-502.

**Introduction:**

The subject of this review is the May 18, 2006 resubmission of NDA [ ] 21-502. (Refer to my memorandum dated March 6, 2006.) The Class I complete response for each of these NDAs included new proposed labeling and a safety update.

**Background:**

[ ] [ ] NDA 21-502 is for a SPF 15 sunscreen cream (ecamsule 2%; avobenzone 2%; octocrylene 10%).

L'Oreal is seeking approval for the nonprescription marketing of these — sunscreen drug products for daily use by adults and children at least 6 months of age. The sponsor states that the products are indicated “for the prevention of sunburn [ ] — [ ] following [ ] — [ ] exposure to ultraviolet radiation.”

The sponsor has developed the combination of active ingredients in these sunscreen products in an attempt to provide products that absorb UV radiation across a relatively broad range of the spectrum. These — sunscreens protect against both ultraviolet (UV) B and UVA radiation. The products — contain ecamsule, an active ingredient that has been marketed since 1993 in Europe where the allowed concentration of ecamsule is up to 10%. Ecamsule has also been approved since 1994 in Canada, and since 1995 in Australia. Ecamsule is a new molecular entity in the United States. The other active ingredients in the sunscreens (avobenzone and octocrylene) are among the 16 generally recognized as safe and effective sunscreen active ingredients listed in the over-the-counter (OTC) drug sunscreen drug monograph ( 21 CFR 352). The concentrations of the avobenzone and octocrylene in the L'Oreal products are concentrations that the monograph allows.

On March 10, 2006, the FDA issued an approvable letter covering the — NDAs citing deficiencies in labeling and concerns about the proposed trade names of the formulations. In the letter, the FDA also told the sponsor that the Agency must conduct an inspection of the manufacturing facilities referenced in the applications to determine satisfactory compliance with cGMPs. At the time of the approvable letter, the cGMP inspection of the [ ] — [ ] manufacturing facility had not been completed.

**Chemistry:**

On March 16, 2006, Office of Compliance gave an “acceptable” recommendation for all facilities used in the manufacture and control of the drug substance and drug product for [ ] — [ ] NDA 21-502.

With — of the resubmissions, the sponsor revised the drug product specification to reflect changes in the acceptance criteria of ecamsule related impurities. The chemists found the revisions to be acceptable. Thus, in the July 7, 2006 review, Dr. Sue Ching Lin recommended that the NDA [ ] — [ ] 21-502 could be approved from a chemistry perspective. No Phase 4 commitments were recommended.

**Safety Update:**

Dr. Daiva Shetty reviewed the safety update information submitted as part of the complete response to the approvable letter for the NDAs. The safety data covered — [ ] — [ ] NDA 21-502 and generated no safety concerns. Dr. Shetty’s original recommendation that the — NDAs could be approved was not changed by the safety update in the resubmissions.

**Labeling:**

As of the date of this review, there are outstanding labeling issues to be resolved for these — NDAs.

**Pediatrics:**

Refer to my March 6, 2006 memorandum for a discussion related to the need for pediatric studies for these NDAs to fulfill the requirements of the Pediatric Research Equity Act. As per that memorandum, as a Phase 4 commitment, the sponsor will be asked to perform safety and pharmacokinetics studies in babies < 6 months of age.

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Andrea Segal  
7/11/2006 11:43:40 AM  
MEDICAL OFFICER

MEDICAL REVIEW (DERMATOLOGY)

NDA [ — ] 21-502

[ — ] SPF 15 Daily Use Moisturizer Sunscreen Cream

June 29, 2006

L'Oreal USA Products, Inc., the applicant for these — NDA products has submitted a complete response to the prior Approvable letters for the respective NDAs dated March 10, 2006.

No new information was submitted regarding the efficacy of the drug products. However, revised labeling is submitted. The labeling considerations were the primary reason for not approving these products during the prior review cycle. Several claims requested by the sponsor were unsubstantiated in the information submitted to the Agency. In addition, a safety update is submitted, which is the subject of review by Drs. Shetty and Feibus in the Division of Nonprescription Clinical Evaluation (dated 6/7/2006).

For relevant review of efficacy, please refer to prior reviews by Dr. Phyllis Huene, Medical Officer, Dermatology, which recommend approval of these sunscreen products from the standpoint that sufficient efficacy has been demonstrated. Please also refer to the reviews of the SPF and UVA studies by Mr. Koenig of the non-prescription drug review division.

The labeling claims were reviewed upon resubmission by Mr. Koenig and the clinical team and the following items were communicated with the sponsor in the Discipline Review letter dated June 13, 2006:

1. [ ]

2.

1   Page(s) Withheld

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

  ✓   § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

It is the recommendation of the reviewing dermatologist that this product be approved with labeling that is appropriate and substantiated, which will include addressing the ten items listed above that have been conveyed to the sponsor.

Markham C. Luke, M.D., Ph.D.  
Lead Medical Officer, Dermatology

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Markham Luke  
6/29/2006 08:21:13 AM  
MEDICAL OFFICER

Labeling review to be done by Non-Prescription drugs in  
collaboration with DDDP.

Susan Walker  
7/10/2006 08:14:23 PM  
DIRECTOR



## MEDICAL OFFICER REVIEW

Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
**Division of Nonprescription Clinical Evaluation**

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**NDA #:** [redacted] 21-502  
**Drug name:** [redacted] Sunscreen Cream  
[redacted] SPF 15 Daily Use Moisturizer Sunscreen Cream  
**Sponsor:** L'Oreal USA Products, Inc.  
**Pharmacologic Category:** Sunscreen  
**Proposed Indications:** Prevention of sunburn [redacted] due to sun exposure  
**Dosage Form:** Cream  
**Route of Administration:** Topical  
**Submission Date:** May 18, 2006  
**Review Date:** June 3, 2006  
**Reviewer:** Daiva Shetty, MD

### Introduction:

This is a clinical review of the safety update for [redacted] combination sunscreen drug products submitted under [redacted] different NDA. [redacted] 21-502.

NDA [redacted] 21-502 were originally submitted by L'Oreal USA Products, Inc in May of 2005. [redacted] of the NDAs have been reviewed by FDA and were assessed as approvable because of deficiencies in labeling and delayed manufacturing facility inspection. The current submission is the sponsor's response to the 3/10/2006 Approvable Letter. It includes new proposed labeling and a safety update.

For detailed review of the [redacted] sunscreen drug products refer to the original medical officer reviews. This review addresses only the safety update portion of the submission. Since the clinical data to support the marketing of [redacted] the products are the same, the [redacted] NDAs will be reviewed together. An interdisciplinary scientist in the Division of Nonprescription Regulation Development is reviewing formatting and content changes to the re-proposed labeling.

**Background:**

NDA 21-502 is for the \_\_\_\_\_ SPF 15 Daily Use Moisturizer Sunscreen Cream. \_\_\_\_\_  
SPF 15 cream is a topical combination sunscreen composed of the following three active  
sunscreen ingredients:

- Avobenzone 2%
- Octocrylene 10%
- Ecamsule (Mexoryl®) 2%

The sponsor is requesting to market this formulation under \_\_\_\_\_ different brand names:

\_\_\_\_\_  
\_\_\_\_\_  
— ANTHELIOS SX  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

The sponsor is proposing to market \_\_\_\_\_ of the combination sunscreen products in the  
OTC setting for daily use in children six months of age and older and in adults in  
accordance with all requirements of the existing OTC sunscreen product regulations, 21  
CFR Part 352.

**Safety Update Review:**

The Safety Update consists of the latest safety information collected by L'Oreal for their  
ecamsule-containing sunscreen products through year end 2004. This information has  
been compared to previous information reported in NDA \_\_\_\_\_ '21-502 through  
2002 and the additional information submitted in the 120 day Safety Update Report on  
September 9, 2005.

The sponsor states that no additional non-clinical or clinical data have been generated  
with \_\_\_\_\_ formulations or with ecamsule since the original submission of the \_\_\_\_\_  
NDAs. Safety information in this submission comes from two sources: L'Oreal's  
postmarketing cosmetovigilance database and literature.

Results of the literature search since the update reported September 8, 2005 through March, 2006, consist of one article.<sup>1</sup> The article reported two cases of contact dermatitis in 3- and 10-year-old children, following application of sunscreen products containing 10% octocrylene. Both children underwent contact allergy testing and were found to be allergic to the octocrylene component of the sunscreens. Severity and outcomes of the cases were not reported in the article.

*Comment:*

*Contact sensitivity to a topically applied sunscreen products is not an unusual adverse reaction. Labeling for — of the sunscreens under this review already carry a warning to stop use the product if rash or irritation develops or lasts.*

L'Oreal Postmarketing Pharmacovigilance/Cosmetovigilance Data Review

The original submission covered cosmetovigilance information received for the period through year end 2002 and the 120 day Safety Update of September 8, 2005 reported information through 2003. This update contains postmarketing adverse event data through 2004 with a special focus on adverse events reported between 2003 and 2004.

From 2003 through year end 2004, more than [ — ] ecamsule or [ — ] solution have been produced. Approximately

[ — ] countries where the cosmetovigilance system is in place through 2004.

For all reported spontaneous adverse reactions, a conservative estimate of 54 adverse events per — units sold of all ecamsule-containing product formulations has been reported during 12 years of marketing through 2004, an overall adverse event incidence of 0.0054% [ — ] spontaneous adverse events reported during the same time period and — \ units sold). The incidence of adverse reports is relatively stable over time.

In the database, there are a total of 3837 spontaneous adverse event reports in children reported through 2004. The database defines children as individuals 16 years of age and younger. Over an 11-year period, the incidence of adverse events among children is 0.0142% with 14 adverse events per — \ units sold. It is assumed that most reactions occurred while using children's products.

Summary of incidence of adverse events associated with use of ecamsule-containing products for children and all subjects presented in Table 1 below.

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<sup>1</sup> Madan V and Beck MH. Contact allergy to octocrylene in a sunscreen with recurrence from passive transfer of cosmetic. Contact Dermatitis 2005;53:2141-42.

**Table 1. Summary of Incidence of AEs Associated with Use of Ecamsule-Containing Products for Children and for all Subjects**

Adverse Event Term	Incidence of all AEs per — units sold 1993- 2004*	Incidence of children's AEs per — units sold 1993- 2004**
	Number of AEs and % of units sold for each subgroup	
All adverse events	54.4 (0.0054)	142 (0.142)
Erythema	11.9 (0.0012)	38.9 (0.0040)
Dermatitis	10.3 (0.0010)	35.6 (0.0036)
Skin Discomfort	7.8 (0.00078)	9.5 (0.0010)
Pruritus	6.5 (0.00065)	18.4 (0.0018)
Edema Skin	4.7 (0.00047)	16.6 (0.0017)
Irritation	3.5 (0.00035)	5.2 (0.00052)
Dry Skin	1.9 (0.00019)	4.3 (0.00043)
Desquamation	1.3 (0.00013)	1.1 (0.00011)
Eczema	1.3 (0.00013)	2.5 (0.00025)
Allergic Local Reaction	0.92 (0.00009)	0.96 (0.00010)
Conjunctivitis	0.98 (0.00010)	0.78 (0.00008)
Photosensitivity	0.56 (0.00006)	0.52 (0.00005)
Lacrimation Disorder	0.59 (0.00006)	0.74 (0.00007)
Skin Burn	0.61 (0.00006)	1.6 (0.00016)
Sunburn	0.34 (0.00003)	1.3 (0.00013)
Urticaria	0.30 (0.00003)	2.1 (0.00021)
Skin Discoloration	0.20 (0.00002)	0.37 (0.00004)
Acne	0.21 (0.00002)	0.04 (0.000004)
Edema Conjunctival	0.16 (0.00002)	0.81 (0.00008)

Table 2 lists the frequency of adverse events in descending order as a percentage of all adverse reactions reported for two groups – children and adults > 16 years of age for the specific year 2004 and for the time period 1993 through 2003 for comparison.

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**Table 2. Summary of AEs as % of All Terms in Descending Order Associated with Use of Ecamsule-Containing Products: Frequency of AEs > 0.2%**

Adverse Event Term	Frequency of AEs as % of all AEs in adults for the year 2004	Frequency of AEs as % of all AEs in adults for years 1993-2003	Frequency of AEs as % of all AEs in children for the year 2004	Frequency of AEs as % of all AEs in children for years 1993-2003
	Number of Adverse events as % of all adverse events in each subgroup			
<b>All adverse events</b>	<b>100%</b>	<b>100%</b>	<b>100%</b>	<b>100%</b>
Erythema	25.20	20.50	31.30	27.00
Dermatitis	13.00	18.30	24.70	25.10
Skin discomfort	14.80	15.30	3.80	7.00
Pruritus	10.00	11.90	10.70	13.20
Edema skin	9.40	7.90	12.50	11.60
Irritation	6.40	7.20	6.60	3.30
Dry skin	3.70	3.70	3.00	3.00
Desquamation	2.70	2.70	0.00	0.84
Eczema	1.80	2.60	1.80	1.70
Allergic local reaction	0.57	2.10	0.00	0.75
Conjunctivitis	4.30	1.90	1.00	0.49
Photosensitivity	0.40	1.30	0.25	0.38
Lacrimation disorder	2.40	1.10	1.30	0.44
Skin burn	2.30	0.92	1.00	1.10
Sunburn	0.34	0.59	0.76	0.93
Urticaria	0.17	0.36	0.51	1.60
Skin discoloration	0.28	0.39	0.25	0.26
Acne	1.30	0.39	0.00	0.03
Edema conjunctival	0.45	0.21	0.00	0.64
Eye pain	0.28	0.08	0.00	0.06

The sponsor states that for the year 2004, there were no serious adverse events reported into the cosmetovigilance database. Serious adverse events reported prior to 2004, were discussed in the NDA [redacted] 21-502 safety review.

**Conclusions:**

*The updated postmarketing data for ecamsule-containing sunscreen drug products did not reveal new serious adverse events. The safety profile of these sunscreens is consistent with that from previous years. Most frequently reported adverse events were local application skin reactions (erythema, dermatitis, pruritus, edema, dry skin, skin irritation, etc.) or signs of eye irritation. The incidences of these reactions were not significantly different in children compared to adults.*

The proposed [redacted] SPF 15 Daily Use Moisturizer Sunscreen Cream have an acceptable safety profile for over-the-counter marketing.

**Recommendation:**

Based of the safety profile, [redacted] SPF 15 Daily Use Moisturizer Sunscreen Cream should be approved for over-the-counter marketing.

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Daiva Shetty  
6/7/2006 09:15:33 AM  
MEDICAL OFFICER

Karen Feibus  
6/12/2006 01:12:11 PM  
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

**Memorandum**

Department Of Health and Human Services  
Food and Drugs Administration  
Center for Drug Evaluation and Research  
Office of New Drugs  
Office of Nonprescription Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266  
(301) 796-2060

Date: 7-21-06

From: Charles J. Ganley, M.D. \_\_\_\_\_  
Director, Office of Nonprescription Products (HFD-560)  
Office of New Drugs  
Center for Drug Evaluation and Research

Subject: NDA 21-502 / Anthelios Sx

NDA 21-502 is a sunscreen product that includes three sunscreen ingredients. Originally, the sponsor (Loreal) submitted numerous labels with different trade names and package configurations. Within the past week, the [ ] requested some changes in the proposed label because of some concerns about implied claims for [ ]. The sponsor decided to withdraw the labeling for many of the products except for one with the trade name Anthelios Sx.

Anthelios Sx is configured as a 3.4 oz bottle with labeling that suggests this product is to be marketed primarily as a moisturizer with a sunscreen. It is likely this product is to be directed at women who would apply it to their face or hands in the morning. There are several cosmetic statements on the principle display panel that could be misleading if it were to be used as "beach" sunscreen. The statements include: 1) Daily Moisturizing Cream; 2) Daily Use Moisturizer; 3) 24 hr long lasting moisturizer. These statements could be misleading for a sunscreen product because they suggest that the product will last the entire day. If used primarily as a sunscreen, these statements could lead someone to believe the sunscreen will provide protection throughout the day without reapplication (Drug Facts directions state to reapply as needed). This could be a problem if the sponsor increases the package size amount.

In order to make it clear that the approval applies to this specific product, the approval letter should include a statement that instructs the sponsor to submit a prior approval supplement if the package size is increased. If they want to increase the package amount, there may need to be clarifying language on the principle display panel that makes it clear that reapplication may be necessary for sun protection.

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Charles Ganley  
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MEDICAL OFFICER



It should be noted that clinical pharmacology studies were not conducted with the \_\_\_\_\_ products. The Sponsor provided clinical pharmacology data for a related product, \_\_\_\_\_

\_\_\_\_\_ the three active ingredients contained in \_\_\_\_\_ lotion. These data demonstrated minimal systemic exposure in the human after single and repeated topical administration of \_\_\_\_\_ cream. Specifically, data were submitted from a maximum exposure study, \_\_\_\_\_ conducted in healthy adult male volunteers after single and multiple applications of about 15g of \_\_\_\_\_ cream per application (approximately 1 mg/cm<sup>2</sup>). The plasma levels of ecamsule were below the quantification limit (1 ng/ml) in all but 2 of 154 samples. The maximum concentration of ecamsule obtained was 1.95 ng/ml. The Sponsor also submitted data from two supportive studies also conducted in healthy adult male volunteers using different formulations of ecamsule. These studies also demonstrated minimal systemic absorption of ecamsule. The first was a pharmacokinetic (PK) study, \_\_\_\_\_ using 2% radio-labeled ecamsule. The systemic absorption after a single topical application, estimated from the radioactivity levels in the urine, feces and skin was less than 0.1% of the applied dose. In the second PK study, \_\_\_\_\_ conducted with a non radio-labeled 4.95% ecamsule formulation, for a five-day repeated topical application, unchanged ecamsule was not detected in the urine.

The Clinical Pharmacology reviewer stated that based on the maximum systemic exposure of ecamsule in man (~2 ng/ml) and the estimated maximal exposure level demonstrated in two animal species treated orally with ecamsule without showing toxic effects (~1,000 ng/ml), the safety margin for the systemic exposure of ecamsule in the adult is ~500-fold. The review further stated that given the higher body surface area to weight in children, the safety margin in adults should be divided by a factor of 1.3-1.4 to estimate the safety margin in children (Nohynel et al, 2001). Based on this factor, the safety margin in children would be >350-fold. However, the Pharmacology/Toxicology reviewer stated that adequate data were not available to determine the safety margin in humans. Nevertheless, as elucidated below, the safety of ecamsule and \_\_\_\_\_ cream from the preclinical perspective was demonstrated.

The Pharmacology/Toxicology reviewer concluded that the nonclinical studies showed that the new active ingredient, ecamsule, and \_\_\_\_\_ cream had low acute and repeat dose toxicity. Essentially no toxicity was observed after chronic topical dosing of ecamsule solutions (up to 24%) or \_\_\_\_\_ cream in minipigs or after chronic oral dosing with ecamsule in rats. The reviewer noted that the NOAEL for oral ecamsule in rats after 26 weeks was at least 1,000 mg/kg/day. Ecamsule appeared to be negative for genotoxic potential and it was negative, at concentrations up to 26%, in a 2-year dermal carcinogenicity study in mice. The reproductive toxicology studies demonstrated a slight but statistically significant decrease in the percentage of implantation sites with live concepti and a slight but statistically significant increase in post-implantation loss in female rats at the 1,000 mg/kg dose but no effect was seen at the 100 and 300 mg/kg doses. There was no other evidence of adverse effects on reproductive and developmental parameters in rats and rabbits.

The product clinical program to demonstrate efficacy enrolled adult subjects while the safety program also included pediatric subjects at the request of FDA. The Medical Officer's review of the safety profile of

SPF 15 lotion (NDA 21-502) demonstrated that these sunscreen products are safe for OTC use in children, 6 months of age and older, and in adults. Information was primarily extracted from the Clinical Safety Review of NDA 21-502 by Dr. D. Shetty, dated 1/6/06. When information was extracted from the MO review by Dr. P. Huene for cream, that was so indicated.

*Overview of the Clinical Safety Program:*

19 Phase 1, 2 and 3 clinical studies that enrolled 1,155 adult subjects (i.e. >18 years of age). 1,094 subjects completed these studies;  
 4 Phase 3 long-term safety studies that enrolled a total of 1,048 adult and pediatric subjects and with 730 completers and  
 5 supportive studies that enrolled 336 adult subjects of whom 317 were completers.

*Total number of death in all studies:* in the entire clinical safety program, there was only 1 death- an intentional injury in a 13 year old female that was unrelated to study treatment.

*Any serious adverse event, except death, reported in any clinical study:* according to the MO safety reviewer, Dr. D. Shetty, a total of 32 subjects experienced serious adverse events. All occurred in the long-term safety studies. The review does not specify the nature of these adverse events but states that all of them were unrelated to study treatment.

(Note: per the MO review of study which was submitted under NDA 18 subjects experienced serious adverse events. One was dermatological and 17 were non-dermatological. The specific nature of these adverse events was not specified).

*Treatment-emergent adverse events:*

In the Phase 1, 2 and 3 clinical studies, 7 (0.6%) adverse events (skin infection, pruritus and eczema) were assessed as possibly or probably related to treatment. All were non-serious and of mild severity.

In the three long-term studies (750.01, 750.02 and 750.03), which enrolled a total of 573 patients, there were 60 treatment-related adverse events reported in the Skin and Appendages System. These included 16 (2.8%) dermatitis; 12 (2.1%) acne; 6 (1.0%) sunburn; 5 (0.9%) each of eczema, erythema, pruritus and skin discomfort; 3 (0.5%) dry

skin; 2 (0.3%) seborrhea and 1 (0.2%) rosacea. There were 4 treatment-emergent adverse events in the Special Senses System: 3 (0.5%) conjunctivitis and 1 (0.2%) taste perversion. None of these adverse events were assessed by the investigator as serious and all of them resolved.

The review of the long-term safety study, [ ] submitted with [ ] did not specifically address treatment-emergent adverse events other than to state that the reviewer did not consider any of the serious adverse events to be related to [ ]

In the [ ] supportive studies, there were 7 (2.1%) events of erythema/edema that were considered to be probably related and 4 (1.2%) of papules that were considered to be possibly related to study treatment.

*Specific Information Provided for the Long-term Studies which Included Pediatric Patients:*

A total of 358 pediatric subjects, aged 6 months to 18 years of age, were included in the four long-term safety studies. The study numbers, total sample size (N), formulation used and the number of subjects enrolled by age subsets are depicted in the table below:

	750.01 N= 248	750.02 N= 246	750.03 N= 79	 N= 475
<i>Formulation</i>	SPF 15	SPF 15	SPF	cream <sup>b</sup>
<i># (%) patients enrolled by age:</i>				
0.5 to ≤2 yrs.	0 (0%)	57 (23.2%)	24 (30.4%)	0 (0%)
>2 to ≤6 years	0 (0%)	60 (24.4%)	32 (40.5%)	0 (0%)
>6 to ≤12 years	0 (0%)	62 (25.2%)	8 (10.1%)	0 (0%)
12 to ≤18 years	78 (31.5%)	24 (9.8%)	2 (2.5%)	11 (2.3%)
>18 yrs. (adult)	170 (68.5%)	43 (17.5%)	13 (6.5%)	464 (97.7%)

The treatment duration in these 3 long-term safety studies combined were, by age, as follows:

Age Group	Mean $\pm$ S.D. (days)	Median (range) days
0.5 to $\leq$ 2 years	57.79 $\pm$ 68.92	31.0 (1-312)
2 to $\leq$ 6 years	67.45 $\pm$ 80.32	36.0 (1-363)
6 to $\leq$ 12 years	87.59 $\pm$ 99.05	37.5 (1-350)
12 to $\leq$ 18 years	247.67 $\pm$ 145.40	344.0 (1-371)
18 to $\leq$ 65years	250.24 $\pm$ 142.51	346.0 (1-376)
>65 years	308.31 $\pm$ 117.58	360.5 (2-372)

Comment: The above table demonstrates that treatment duration was shorter for children (aged  $\leq$ 12 years) than for adolescents and adults and that duration of exposure of adolescents to sunscreen was comparable to adults.

The MO safety reviewer stated that a total of 19 subjects discontinued the long-term studies due to adverse events. 6 of these 19 were pediatric subjects. The adverse events were death in one subject (intentional injury in a 13 year old female, unrelated to study treatment), rash in 3 subjects (assessed as definitely related), one photosensitivity (possibly related) and one urticaria (unlikely related).

The MO safety reviewer compared the incidence of treatment related adverse events by age subsets in the 3 — long-term safety studies as follows:

	Drug Related Adverse Events	
	Dermatological	Non-Dermatological
<i>Age subgroup:</i>		
0.5 to $\leq$ 2 years (n= 81)	3 (3.7%)	1 (1.2%)
>2 to $\leq$ 6 years (n= 92)	8 (8.7%)	0 (0%)
>6 to $\leq$ 12 years (n= 70)	5 (7.1%)	0 (0%)
>12 to $\leq$ 18 years (n= 104)	7 (6.7%)	0 (0%)
>18 years (n= 226)	31 (18.8%)	7 (6.8%)

Comment on the above table:

The incidence of drug-related adverse events, both dermatological and non-dermatological, were lower in pediatric subjects (0.5 to 18 years) compared to adults. Specifically, the incidence of drug related dermatological adverse events was 6.6% in pediatric subjects compared to 13.7% in adults. The corresponding incidences for drug related non-dermatological adverse events were 0.3% and 3.1%. Dr. Shetty mentioned that these differences in incidence may be related to differences in duration of use.

*Predisposing conditions:*

The MO safety review also mentioned that the — products should be applied only to healthy skin. The reviewer provides data (Table 24, pp. 43) that demonstrated a higher incidence of adverse events, the majority of which were dermatological, when these products were applied to the skin of subjects with predisposing conditions such as atopic/dry skin. An example is provided of a 14 month old boy with a history of eczema who experienced worsening eczema on the back of the neck upon application of . — SPF . — to this site. The event resolved with topical hydrocortisone. When the

sunscreen was subsequently applied to other areas of the body, no sequelae were observed.

*Post-marketing adverse events:*

Per Dr. Shetty's review, there were no new safety signals.

The annual incidence of adverse events spontaneously reported to the L'Oreal Cosmetovigilance System for all ecamsule-containing products over the period 1993-2003 was relatively stable over time, ranging from 0.011% in 1993 to 0.002% in 1995, with an incidence rate of 0.0045% in 2003. The nature of the adverse events was similar to those reported in the clinical studies (see Dr. Shetty's review, Table 13, pp. 29). Six serious adverse events were retrospectively identified. Four of these were reported in children and included erythema and edema of the skin; edema of the face and eyes with rash; breathing difficulty and swelling of the face and eyes in a child with a history of asthma; and sore throat (strep)/swollen eyes and rash. The remaining 2 cases were an anaphylactic reaction (swollen eyes and tightness of the chest and throat) in an adult and urticaria in a subject of unspecified age.

The Sponsor also submitted pediatric adverse events spontaneously reported to the L'Oreal Cosmetovigilance System with use of sunscreens containing any of the ingredients found in the — products (octocrylene, Mexoryl SX, avobenzone —  
 [ — ] A total of 386 adverse events were reported in children, aged 1 to 16 years, between 1996 (when the products were first marketed) and 2004. There was a gradual increase in the number of adverse event reports, from 1 in 1996 to 102 in 2004. The Sponsor associated this increasing trend with increased use of sunscreen products. The majority of reactions occurred within several hours after the first application and the majority resolved within 3 days. No permanent sequelae were reported. All the reactions were limited to the sunscreen application site. The most common adverse events (in decreasing order of frequency) were erythema, papules, edema, dryness, "eczema" and urticaria-like lesions. In some cases, these symptoms were accompanied by pruritus or a "burning sensation".

A search of the AERS database conducted by Dr. S. McCune (see her review dated 1/31/06 in response to a consult requested from The Pregnancy and Lactation Team) for ecamsule, avobenzone, octocrylene, [ — ] and — revealed a total of 61 reports. There were no AERS mentions for any children between 0-1 years of age.

*Literature Review:*

The MO safety reviewer summarizes several articles submitted by the Sponsor highlighting the occurrence of photoallergic reactions to the active ingredients in sunscreens. Dr. Shetty mentions that photoallergic reactions to sunscreens are a well known adverse effect.

Literature review by DPDD:

The American Academy of Pediatrics (AAP)<sup>1</sup> states that the safety of sunscreen use in infants less than 6 months of age is controversial. Concerns cited include the possibility of different absorptive characteristics of skin in infants younger than 6 months and immaturity of biological systems that metabolize and excrete drugs. However, the AAP points out that the Australian Cancer Society, supported by the Australian College of Dermatologists, has concluded that there is no evidence to suggest that using sunscreen on small areas of a baby's skin is associated with any long-term effects. They recommend their use when physical protection, e.g. clothing, hats and shade, is not adequate<sup>2</sup>. The AAP states that on reflective surfaces, an umbrella or canopy may reduce UVR exposure by only 50%. The AAP urges that parents be informed of the importance of avoiding high-risk sun exposure. They further state that it may be reasonable to apply sunscreen to small areas of the infant's skin that is not adequately protected by clothing, such as the face and backs of the hands.

The updated version of the Australian Cancer Society's Position Statement on this issue<sup>3</sup> again reiterates that there is no evidence that using sunscreen in infants is harmful<sup>4</sup>. They recommend that infants, 0-12 months of age, be kept out of the sun as much as possible. They state: "If infants are kept out of the sun or are well protected from UV radiation by clothing, hats and shade, then sunscreen need only be used occasionally on very small areas of an infant's skin." The Australian Cancer Society's recommendations are specifically as follows:

- minimize the infant's exposure to the sun, particularly between 10 am and 3 pm;
- cover the infant's skin as much as possible with loose-fitting clothes and tightly woven wraps;
- choose a hat that will protect the baby's face, neck and ears;
- make use of available full shade and use material that will cast a dark shadow to shade the infant's pram, stroller or play area;
- regular check the infant's clothing, hat and shade positioning to ensure that the infant continues to be well protected from UV radiation;
- apply a SPF 30+ broad spectrum water resistant sunscreen to small areas of skin that cannot be protected by clothing (e.g. face, ears, backs of hands). Apply sunscreen 20 minutes before going outside and reapply every couple of hours or more often if it has been wiped or washed off.

Potential side effects of sunscreen use in infants that are mentioned in this position statement include minor skin irritation and allergic contact dermatitis from preservatives or perfumes in the product. They mention that sunscreen milks or creams formulated for sensitive skin usually contain titanium dioxide or zinc oxide and are less likely to contain alcohol or fragrances that may irritate the skin. They recommend that use be stopped immediately in the event of occurrence of an unusual reaction.

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<sup>1</sup> American Academy of Pediatrics Committee on Environmental Health. Ultraviolet Light: A Hazard to Children. *Pediatrics* 1999;104(2):328-333.

<sup>2</sup> Australian Cancer Society. *Policy Statement: Babies and Sunscreen*. Sydney, Australia: Australian Cancer Society; 1998.

<sup>3</sup> Cancer Council Australia and The Australian College of Dermatologists. *Position Statement. Sun Protection and Infants (0-12 months)*. May 2005.

<sup>4</sup> Marks R. The Use of Sunscreens in the Prevention of Skin Cancer. *Cancer Forum* 1996;20:211-215.

Marks (see reference 4) mentions that when sunscreen is applied to small areas of infant skin, it is unlikely that there will be enough absorption of sunscreen to constitute an excess load for hepatic metabolism.

Robinson JK et al<sup>5</sup> emphasize the importance of not directly exposing infants to the sun before 6 months of age. Morelli JG and Weston WL<sup>6</sup> make the point that there is no compelling reason for infants less than 6 months of age to have sun exposure prolonged enough to require sunscreens. They further mention that sunscreen use in infants may give parents a false sense of security and make it more likely that the infant will be exposed to the sun for longer periods of time than without sunscreen. It is, therefore, imperative that the guidelines as outlined by the AAP and the Australian Cancer Society are followed if sunscreen is applied to young infants.

De Simone<sup>7</sup> mentions that there is "little data" available to help healthcare providers make informed decisions regarding the best sunscreen products to use in infants less than 6 months of age although the Sunscreen OTC monograph recommends that a physician be consulted regarding use of sunscreen in this age group.

#### **Conclusions and Recommendations** (note: recommendations are bolded below)

Both the AAP and The Australian Cancer Society acknowledge that sunscreen may need to be *occasionally applied to small areas of infant skin* such as the face or backs of the hands. They do emphasize the importance of non-chemical protective measures and avoiding/minimizing exposure of young infants to the sun as the primary protective measures. While there is no evidence that sunscreens are harmful to infants under 6 months of age, there is no direct evidence that they are safe in this age group. The safety of the \_\_\_\_\_ sunscreen products has been adequately demonstrated from both a preclinical and clinical perspectives in subjects 6 months of age and older. **The safety of these products needs to be demonstrated in those infants younger than 6 months of age.** As pointed-out by Dr. D. Shetty, **it is important that these products be studied in infants with healthy skin** because skin conditions such as eczema which is prevalent in young infants may be exacerbated by application of sunscreen to affected areas. Although absorption of these products appears to be minimal, detectable blood levels of a comparable sunscreen drug product, [ \_\_\_\_\_ ] was detected in 2 adult subjects. Also, given that clinical pharmacology studies have not been conducted with \_\_\_\_\_ products in any age group and that there is greatest potential for systemic absorption in young infants given their high body surface area to body weight ratio, **it is recommended that pharmacokinetic data also be obtained in this age group.** The data obtained from the pharmacokinetic and safety studies will be critical to practitioners

<sup>5</sup> Robinson JK et al. Meeting Report. Executive summary of the national "Sun Safety: Protecting Our Future" Conference: American Academy of Dermatology and Centers for Disease Control and Prevention. New York, New York, May 1 and 2, 1997. Journal of the American Academy of Dermatology 1998;38 (no. 5, part 1):774-780.

<sup>6</sup> Morelli JG and Weston WL. What Sunscreen Should I Use for My 3-Month-Old Baby? Pediatrics 1993;9(6):882.

<sup>7</sup> DeSimone EM. FDA Proposes Changes in Sunscreen Regulations. American Pharmacy 1994; volume NS34, No.6:26-31.

who are consulted by parents and caregivers regarding use of sunscreen products in infants less than 6 months of age. **Furthermore, consideration should be given to providing additional precautions in OTC labeling of sunscreen products if they are approved for use in infants less than 6 months of age so that parents and caregivers understand the appropriate place of these products in protecting young infants from UV radiation.**

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3/21/2006 02:52:26 PM  
MEDICAL OFFICER  
Concur



MEMORANDUM

Department Of Health and Human Services  
Food and Drugs Administration  
Center For Drug Evaluation and Research  
**Division of Nonprescription Clinical Evaluation**

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**Date:** March 6, 2006

**From:** Andrea Leonard-Segal, M.D.  
Acting Director

**Subject:**

[ — ]  
**NDA 21-502 [ — ] SPF 15 Sunscreen Daily Lotion**  
**[ecamsule 2% (Mexoryl®); avobenzone 2%; octocrylene 10%]**

**Sponsor:** L'Oreal USA Products, Inc.

**RECOMMENDATIONS:**

- [ — ] NDA 21-502 should be approved if:
- the chemistry inspection is completed and the site is found to be acceptable before the PDUFA date
  - the labeling is revised before the PDUFA date in accordance with the FDA comments sent by FAX to the sponsor

Otherwise the sponsor should receive an approvable letter.

As a Phase 4 commitment to address the Pediatric Research Equity Act, the sponsor should be asked to perform safety and pharmacokinetics studies in babies < 6 months of age.

[ — ]  
[ — ]

**BACKGROUND:**

L'Oreal is seeking approval for the nonprescription marketing of [redacted] sunscreen drug products for daily use by adults and children at least 6 months of age. The sponsor states that the [redacted] products are indicated "for the prevention of sunburn [redacted] following [redacted] exposure to ultraviolet radiation." This indication includes both an ultraviolet (UV) B and a UVA radiation protection claim. The UVB claim is "helps prevent sunburn/protects against UVB radiation." This UVB claim is allowed for nonprescription sunscreens marketed under the monograph system (21 CFR 352.52(b)(1).

The sponsor has developed the combination of active ingredients in these sunscreen products in an attempt to provide a product that absorbs UV radiation across a relatively broad range of the spectrum.

- NDA 21-502 is a SPF 15 sunscreen lotion (ecamsule 2%; avobenzone 2%; octocrylene 10%)

The sponsor requests that this formulation be marketed under [redacted] brand names. The sponsor intends to market this formulation in tubes [redacted] (See page 8 of Dr. Michael Koenig's efficacy review.)

The clinical data to support the marketing of the [redacted] products are the same, so the [redacted] NDAs have been evaluated concurrently by the reviewers and will be treated similarly in this division director memorandum. Each of these [redacted] products contains ecamsule, an active ingredient that has been marketed since 1993 in Europe where the allowed concentration range of ecamsule is up to 10%. Ecamsule has also been approved since 1994 in Canada, and since 1995 in Australia. Ecamsule is a new molecular entity in the United States.

The other active ingredients in these sunscreens (avobenzone, octocrylene, [redacted]) are among the 16 generally recognized as safe and effective sunscreen active ingredients listed in the over-the-counter (OTC) drug sunscreen drug monograph (21 CFR 352). The concentrations of the avobenzone, octocrylene [redacted] in the L'Oreal products are concentrations that the monograph allows. The sunscreen

monograph was finalized on May 21, 1999 and did not include the combination of avobenzone \ as an acceptable combination of active ingredients because data demonstrating the combination is effective was lacking. However, FDA issued a stay of the effective date on Dec. 31, 2001. The effective date is stayed until FDA publishes the UVA testing and labeling components of the monograph.

The sponsor opened IND 59,126 on October 15, 1999 to study the [ — ] sunscreen formulations. The pharmacology/toxicology section of this IND submission contained studies that had been reviewed under IND [

**DISCUSSION:**

**Chemistry:**

See the reviews by Dr. Sue-Ching Lin [ — ] for NDA 21-502. For NDAs Dr. Lin recommends that, if the inspection at the — facility is acceptable, the applications could be approved from a chemistry standpoint. — is one of the avobenzone drug substance manufacturing sites and the inspection is pending as of the date of the Division Director Memo. The NDA cannot be approved without an "acceptable" recommendation from the Office of Compliance for all the manufacturing and control facilities.

There are no recommended Phase 4 commitments for these — NDAs from the chemists.

**Pharmacology/Toxicology:**

Shetty's review.) The pharmacology/toxicology review for these applications is duplicated or adapted from [redacted].

Ecamsule absorbs light at wavelengths from approximately 290 to 400 nm with a maximum absorption at 344 nm. The review of the data shows that the new active ingredient, ecamsule, has low acute and repeat dose toxicity. Essentially no toxicity was observed in rats after chronic oral dosing with ecamsule or after chronic topical dosing with the ecamsule in minipigs. Ecamsule appears to be negative for genotoxic potential and was negative in a 2-year dermal carcinogenicity assay in mice. UV induction of skin tumor formation in hairless mice was not increased by ecamsule, the sunscreens containing three active ingredients, [redacted]. The conclusions of the Carcinogenicity Assessment Committee that met August 30, 2005 to consider were that an adequate carcinogenicity study was performed and that there were no drug-related tumor findings.

Based upon the preclinical data, ecamsule is not a teratogen. In a fertility study in rabbits treated with ecamsule, a slight but statistically significant decrease in the percentage of implantation sites with live concepti and a slight but statistically significant increase in post-implantation loss were observed in females but no evidence of adverse effects on reproductive and developmental parameters in rats and rabbits was noted. No sensitization was detected in guinea pigs tested with ecamsule in aqueous solution.

Dr. Yao concluded that the NDA is approvable from a pharmacology/toxicology perspective and that no additional non-clinical studies are needed.

**Microbiology:**

See the review by Dr. Stephen E. Langille. The drug products are all non-sterile topical creams containing methylparaben and propylparaben preservatives and no deficiencies were noted by the reviewer. He recommended approval from the standpoint of product microbiology quality and did not recommend the need for any Phase 4 studies.

**Clinical Pharmacology/Biopharmaceutics:**

See the following reviews by Dr. Abimbola Adebawale:

- o NDA [redacted] 21-502 [redacted] dated February 21, 2006

The applicant provided the previously submitted in vivo data for [redacted] cream and the previously submitted in vitro permeation data to evaluate the impact of reformulation [redacted] on the bioavailability of ecamsule. The agency found this approach acceptable (documented in the minutes for the end of Phase 2 meeting held on January 24, 2001).

The pharmacokinetic data based upon single and multiple topical applications of [redacted] to the trunk, arms and legs demonstrated minimal systemic exposure. For 152 of 154 samples obtained in the study of six male healthy volunteers, the plasma concentration of ecamsule was below the limit of quantitation (1 ng/ml). Two

of the samples indicated that the potential systemic absorption of ecamsule following topical application of [redacted] cream for 8 days resulted in plasma concentrations < 2 ng/mL, which Dr. Adebowale concluded was also minimal systemic exposure.

In vitro percutaneous absorption studies demonstrated that 0.83% of ecamsule penetrated the skin following topical application of [redacted] cream. [redacted] formulations that were the subject of IND 59,126 were also studied. The mean percentage of the applied dose of ecamsule that penetrated the skin was 1.1% for [redacted] cream, [redacted]

Dr. Adebowale concludes that the totality of the clinical pharmacology data for ecamsule, the non-clinical toxicity data, the in vitro data, and the safety data obtained from the clinical studies and post-marketing studies all combined together indicate that the systemic exposure of ecamsule following the topical application of the [redacted] formulations is minimal. Dr. Adebowale also notes that the effect of ecamsule on the systemic exposure of the combination of the three other active ingredients is minimal and unlikely to be clinically relevant from a safety perspective.

**Division of Scientific Investigation:**

A request was submitted to the Division of Scientific Investigation (DSI) to inspect the [redacted]. This study center we selected for inspection because 8 of the 12 clinical studies and one of the 3 in vitro studies were conducted there. The results of the inspection are pending.

**Statistics:**

No statistical review was performed.

**Clinical:**

**Efficacy:**

See the review and memorandum to the file by Dr. Michael Koenig. His review evaluates the 12 clinical efficacy studies submitted under NDA [redacted] 21-502, [redacted]

[redacted] Nine clinical studies were submitted to demonstrate that the [redacted] formulations provide protection against UVB radiation. Six of the studies examined static [redacted] UVB protection [redacted]

[redacted] Three studies were submitted to demonstrate the UVA radiation protection for all [redacted] formulations. In addition to the clinical studies, there were three in vitro studies submitted to demonstrate that the [redacted] formulations absorb UVA light at wavelengths  $\geq 360$  nm.

Dr. Koenig comments that the efficacy studies for protecting against UVB radiation are adequate and well-controlled as defined in 21 CFR 314.126 since they strictly adhere to the SPF testing procedures outlined in the OTC sunscreen drug monograph

(21 CFR 352 subpart D). ☐

FDA has not published a final rule specifying testing procedures for evaluating the UVA radiation protection of sunscreens. However, FDA has published comments regarding UVA protection. As stated in the 1993 TFM, a sunscreen can bear a claim that it provides UVA protection if it meets two criteria (58 FR 28194 at 28233):

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

There have been additional TFM amendments published on UVA testing. In a 1998 TFM amendment, FDA found a method based on determination of a minimal response dose (MRD) which uses pigment darkening rather than erythema (as used in SPF testing) to be an acceptable testing method (63 FR 56584 at 56587). Dr. Koenig comments that two of the sponsor's UVA clinical studies were conducted using the persistent pigment darkening method (PPD) which is nearly identical to the MRD method. As stated in that 1998 TFM, until FDA proposes a UVA protection test method, FDA "considers testing procedures similar to the UVA protection factor method...and those methods described by R.W. Gange et al. and N. J. Lowe et al. as adequate for determining the UVA protection potential of a finished OTC sunscreen drug product" (63 FR 56584 at 56587). Dr. Koenig states that the sponsor's third clinical UVA study was conducted using the 8-methoxypsoralen (8-MOP) method, which is comparable to the FDA-accepted methods of Lowe, et al. and Gange, et al. In studies using synthetic human skin, the sponsor demonstrated that all — formulations effectively absorb UV light at wavelengths  $\geq 360$  nm.

The monograph allows for labeling of sunscreens for adults and children at least 6 months of age but does not specify the ages of study participants that need to enroll in the efficacy studies. The monograph states that male and female subjects need to be enrolled, but does not state that they must be enrolled in equal numbers, just that they must have fair skin with skin types I, II, and III (21 CFR 352.72). The populations enrolled in the efficacy studies had a preponderance of females and an age range of 18 years to 65 years. Dr. Koenig notes that there is no apparent anatomical or physiological difference between male and female skin, or the skin of adults and children (at least 6 months old) to suggest that there may be a difference in the efficacy of a sunscreen for these groups.

Dr. Koenig concludes that the effectiveness of the — sunscreen formulations containing ecamsule in combination with the other generally recognized as safe and effective sunscreen active ingredients is acceptable for OTC marketing. The formulations provide effective protection against UVB and UVA radiation. ☐

The Division of Dermatologic and Dental Products (DDDP) was requested to provide oversight on the clinical efficacy review of the \_\_\_\_\_ sunscreen products. The DDDP concluded that Dr. Koenig's recommendation that these products should be approved for OTC use for the prevention of \_\_\_\_\_ induced by UVB and UVA radiation should be implemented.

**Dermal Safety Studies:**

See the review by Dr. Phyllis A. Huene.

The sponsor conducted an irritation and contact sensitization study, a photosensitization study, and a phototoxicity study using the \_\_\_\_\_ sunscreen formulations. Dr. Huene concludes that the dermal safety studies are adequate to show that there is little or no potential for irritation, phototoxicity, or photosensitization under the conditions of proposed usage. She comments that although there were no sensitization reactions at challenge, one subject in the sensitization study was apparently pre-sensitized to the test products prior to study initiation. Thus, there is some potential for sensitization and the product labeling should address this.

For the acnegenicity/comedogenicity study (\_\_\_\_\_ 570.01), the sponsor used only the formulation which is the subject of NDA 21-502 (active ingredients: ecamsule 2%, avobenzone 2%, and octocrylene 10%). The sponsor concludes that the results indicate that this formulation is non-acnegenic and non-comedogenic. Dr. Huene disagrees, noting that although the mean values for acne lesions and comedones decreased from baseline, there were increased lesions of both types in one or more subjects, as indicated by the range of values. She suggests that there may be a subset of subjects in which the test product might be acnegenic/comedogenic.

The sponsor also conducted a comedogenicity study to assess the comedogenicity potential of \_\_\_\_\_ of the formulations \_\_\_\_\_ by determining the densities of microcomedones on follicular biopsies after repeated patch applications. Microcomedones are microscopically visible precursors of comedones and their presence is determined by stereomicroscopic examination of follicular biopsies. The evaluation of comedogenicity was based on a comparison of the mean microcomedone score between the test material and the untreated control. The sponsor concluded that, under the conditions of the study, \_\_\_\_\_ formulations were non-comedogenic. Dr. Huene concluded that the study is interesting from a theoretical standpoint, but has no regulatory utility, as it did not utilize clinical parameters. Dr. Huene states that the acnegenicity/comedogenicity studies are not adequate to conclude that the test products are not acnegenic or comedogenic. \_\_\_\_\_

**Safety:**

See the review by Dr. Daiva Shetty.

The sponsor submitted safety data from a total of 28 clinical studies. The sponsor organized the studies into three groups:

- o Phase 1, 2, 3
- o Long term

- o Supportive

The sponsor states that variations among the — formulations addressed in this review and .L — J are minor, and, as such, much of the safety information is common to all. Since the safety data provided to support the marketing of all L — J formulations is the same, Dr. Shetty reviewed the data for the different NDAs en mass.

A total of 2539 study subjects were exposed at least once to an ecamsule-containing sunscreen product during the development phases of these sunscreens. There were no drug-related deaths or drug-related serious adverse events (AE) reported among the participants in the clinical trials. A total of 31 subjects in the clinical studies discontinued due to AEs. Twelve of them discontinued because of AEs that may have been drug related. All of these possibly, probably, or definitely drug related AEs were local skin irritations and all resolved.

Eighty-six of the 1155 subjects in the Phase 1, 2, and 3 clinical studies experienced 125 AEs. Of these, seven (skin infection, pruritis, eczema) were assessed as probably or possibly related to treatment and they were all mild and non-serious. A total of 1048 subjects had long-term exposure (12-month studies) to one of the ecamsule-containing sunscreen formulations. The average combined long term exposure for the long term studies for the — formulations that are the subject of this review plus the — was 213 days (range 1 – 393 days).

For the L — J formulations, 66 drug-related AEs were reported (skin and appendages system) and 4 additional drug-related AEs occurred in the Special Senses System. None were assessed as serious and all resolved. The profile of drug-related AE was consistent across the 3 long-term — studies, except for — 750.01 (ecamsule 2%; avobenzone 2%; octocrylene 10%) in which a higher number of acne events were reported. Dr. Shetty states that this may have been related, in part, to the higher number of adolescents enrolled in this study. (Also relevant may be Dr. Huene's observation, in her dermal safety review, that there may be a subset of the population in which the product is acnegenic.) The most common treatment-related AEs in these three long-term — studies were: acne, dermatitis, dry skin, eczema, erythema, pruritus, skin discomfort and sunburn. Among 336 subjects in the supportive . — studies, were seven reports of probably related erythema/edema and four possibly related reports of papules.

Dr. Shetty notes that the sunscreen products were inadvertently applied to abnormal skin in some study participants. These participants had a higher incidence of cutaneous adverse events. Dr. Shetty states that the proposed label appropriately directs consumers to stop use of the product if a rash or irritation develops and lasts, but she recommends that the labeling should also carry a warning to use caution when applying the sunscreen on damaged skin.

Dr. Shetty comments that the L — J 12-month safety study .L — J was reviewed in detail under NDA — by Dr. Huene on January 29, 2004. Except for

sunburn, adverse events which were considered to be possibly related to the study products were of low incidence and minor severity. Four vascular birthmarks in infants born to pregnant women who participated in this study were noted. (See the Pregnancy section below).

Dr. Shetty's review reflects that post marketing AEs reported to the sponsor did not reveal serious safety issues and the most common AEs in the post marketing database were consistent with the AE profile from the clinical trials. Dr. Shetty's review of the medical literature did not reveal new safety concerns.

### Pediatrics:

The efficacy studies did not enroll subjects under the age of 18 years. Dr. Koenig notes that, ideally, the studies would have enrolled pediatric subjects, however, it is not unreasonable to extrapolate the findings to children 6 months or older as labeled under the sunscreen monograph. There is no apparent anatomical or physiological difference between the skin of adults and children 6 months or older that suggests there may be significant differences in protection provided by a sunscreen.

FDA requested that the sponsor enroll 100 children, ages 6 months to 12 years of age in the long term safety study assessing the SFP 15. In fact, 179 children 6 months to 12 years enrolled of whom 57 were 2 years of age or younger. An additional 24 children between 12 and 17 years also participated in this study. FDA also requested that the sponsor enroll 100 children ages 6 months to 12 years of age in the long term safety study assessing the SFP 15; the sponsor enrolled 64 children under twelve of whom 24 were 2 years of age or younger. The long term safety study assessing the SFP 15 product (NDA 21-502) enrolled 78 children ages 12 - 17. The overall pediatric population for the integrated safety summary included 243 children ages 6 months to 12 years and an additional 115 adolescents. No specific association between adverse reactions and pediatric use was noted by Dr. Shetty.

The Division of Nonprescription Clinical Evaluation consulted the Division of Pediatric Drug Development for their advice concerning the need for pediatric studies in infants less than 6 months of age for the sunscreen products (NDA 21-502). (See the consultation from Dr. Lisa Mathis.) Because the American Academy of Pediatrics and the Australian Cancer Society acknowledge that sunscreen may need to be occasionally applied to small areas of infant skin such as the face and back of hands, and there is no evidence that sunscreens are safe in the age group < 6 months, Dr. Mathis recommends that the safety of the new sunscreen products be demonstrated in infants < 6 months of age. Also, given that clinical pharmacology studies have not been conducted with sunscreen products in infants and that there is greatest potential for systemic absorption in young infants given their high body surface area to body weight ratio, she recommends that pharmacokinetic data be obtained in infants < 6 months of age. She comments that it is important that these products be studied in infants with

healthy skin. She also recommends that “consideration should be given to providing additional precautions in OTC labeling of sunscreen products approved for use in babies < 6 months of age so that parents and caregivers understand the appropriate place of these products in protecting young infants from UV radiation.” I concur with Dr. Mathis’ recommendations to study infants, however it would not be surprising if the sponsor has trouble enrolling young infants for the requested pharmacokinetic studies because of the multiple blood sampling needed.

**Pregnancy:**

The monograph labeling for sunscreens does not include a pregnancy warning (21 CFR 352.52). The proposed labeling for the [ ] NDAs does not carry a pregnancy warning. Ecamsule is Pregnancy Category B, based upon pre-clinical data.

Eleven study participant women became pregnant. Four infants of mothers using [ ] developed birthmarks: two with hemangiomas, one with a nevus flammeus and one with a café au lait spot. Because of hemangiomas in two infants that were born to mothers using the [ ] product while pregnant, in her review, Dr. Shetty recommends a Phase IV controlled study in pregnant women to evaluate the relationship between sunscreen exposure during pregnancy and vascular skin abnormalities in babies. She makes this recommendation despite the negative animal teratogenicity and reproductive function studies, the lack of human systemic absorption of ecamsule under maximized conditions of exposure, and the high background incidence of vascular skin abnormalities in babies.

Drs. Phyllis Huene and Jonathan Wilkin in their reviews of the [ ] NDA comment on the vascular lesions seen in infants born to women in the long term safety study. Dr. Wilkin notes that vascular formations are fairly common in neonates and that estrogen has been theorized to play a role. He states that although some sunscreens have been weakly positive in bioassays of estrogenicity, ecamsule has not been evaluated beyond standard reproductive toxicology studies, avobenzone is considered inactive in estrogenicity tests, and no data are available for the other two filters regarding estrogenicity. In her review, Dr. Huene recommends that there should be a post-marketing commitment to evaluate children of mothers exposed to the product during pregnancy for cutaneous vascular abnormalities. Dr. Wilkin’s division director memo recommends that the applicant should evaluate post-marketing data in other jurisdictions to see whether there is a signal for congenital vascular neoplasms/malformations associated with the use of component UV filters or chemically-related UV filters as part of the [ ] resubmission. In his division director memorandum, Dr. Wilkin did not consider the congenital vascular lesions in infants to be an approvability issue.

Post-marketing data in other jurisdictions was submitted as part of the safety data supplied to the NDAs for the [ ] sunscreen formulations and Dr. Shetty did not pick up any safety signals regarding vascular lesions in neonates. It is important to note that the ecamsule-containing products are marketed as a cosmetic in most foreign jurisdictions, and as a drug in Canada and Australia. It is unclear how effective the post-marketing reporting systems, especially in those markets where the sunscreens are

cosmetics, would be in capturing an association between sunscreen use and vascular skin lesions. Dr. Shetty's review of the medical literature did not reveal safety signals for vascular lesions.

The Division of Nonprescription Clinical Evaluation consulted the Division of Pediatric Drug Development and the Pregnancy and Lactation Team (PLT) to provide feedback on whether or not the sponsor should conduct studies to evaluate children of mothers exposed to the new sunscreen formulations during pregnancy for cutaneous vascular abnormalities and for advice as to whether the OTC labeling for these new sunscreen products should carry any pregnancy warnings. See the consultation from Drs. Susan McCune and Diane Kennedy.

Upon a review of study data, the FDA adverse events reporting system data, and the medical literature, the Division of Pediatric Drug Development and the PLT concluded, in their January 31, 2006 review, that cutaneous vascular abnormalities occur frequently in newborns. The literature suggests that hemangiomas are seen in approximately 7-10% of the newborn population. The PLT consultation states that unless the two cases of hemangiomas reported in the one study [redacted] which was reviewed for the [redacted] are unusual for some reason, e.g., very large, life threatening, deep, etc., the PLT does not see a need for a pregnancy exposure registry.

One of the two babies had two small hemangiomas; one was raised and the other was flat. These were considered to be of mild severity. The second baby had a strawberry hemangioma the investigator considered to be of moderate severity. The lesion was located in the perianal area and the baby received pulse-dye laser treatment which slowed the lesion's growth. The child was said to be developing well.

Dr. Lawrence Eichenfield, M.D., Chief, Pediatric and Adolescent Dermatology, Children's Hospital and Health Center and the University of California, San Diego School of Medicine also reviewed the neonate vascular lesion cases. He stated that hemangiomas occur in 10% to 13% of children in the first year of life, and to the best knowledge of experts, have not been reported to be induced by exogenous factors such as drugs or chemicals. He concluded that the vascular birthmarks reported in the [redacted] trials were probably random findings not related to the use of the cream during pregnancy. After internal discussion with Dr. Shetty, a pediatrician, as well as the medical reviewer who looked at the safety data, neither of these lesions appears to meet the unusual criteria defined by the PLT that would trigger the need for a pregnancy exposure registry.

The PLT concluded that the nevus flammeus case was considered of unlikely relationship to the study treatment and note that this lesion is present in approximately half of all newborns. Café au lait spots are seen in approximately 10% of all newborns.

With regard for the need for a pregnancy warning on the OTC label, the PLT did not recommend that a pregnancy warning be included. They made this recommendation for the following reasons:

- o Negative reproductive toxicology findings in animals
- o < 1% systemic absorption of ecamsule
- o No evidence of reproductive toxicity for [redacted] ecamsule, avobenzone, or octocrylene in the literature
- o No literature reports or AERS reports of hemangiomas associated with the use of [redacted] ecamsule, avobenzone, or octocrylene.

Considering the totality of the available data, I support this recommendation and do not see the need for a pregnancy registry or other types of Phase 4 studies targeted to assess pregnancy-related adverse events.

**Labeling:**

See the labeling review by Dr. Michael Koenig for NDA [redacted] 21-502. The sponsor submitted labeling for the [redacted] sunscreens to be marketed under [redacted] trade names. The [redacted] sunscreens have identical trade names in [redacted] cases, and thus [redacted] novel trade names have been proposed for the [redacted] NDAs. He recommends that the [redacted] trade names proposed for these products are acceptable.

The Division sent the sponsor many labeling comments based upon the clinical recommendations of the reviewers, the recommendations of the Division of Medication Errors and Technical Support, and also the need to comply with the formatting requirements of the Drug Facts label for NDA [redacted] 21-502. These comments are detailed in Dr. Koenig's review and I concur with them.

**CONCLUSION:**

The data supports that these [redacted] sunscreen formulations are safe and effective when used as directed. There are no unsettled issues related to pharmacology/toxicology, microbiology, or clinical pharmacology/biopharmaceutics. The products are effective. However, the NDA 21-502 [redacted] SPF 15 Sunscreen is not water resistant. This product should include the labeling to reapply as needed after towel drying, swimming, or perspiring [redacted] so consumers achieve desired efficacy over the course of the day.

The products may be more irritating if applied to damaged skin and so the labeling should include a warning not to use on broken skin or serious burns. Further, application of the product to skin where the barrier has been compromised may impact the pharmacokinetics of the creams. The data does not support [ — ] labeling.

Based upon the clinical pharmacology and biopharmaceutical data, the pharmacology/toxicology data, the lack of signal in the post-marketing data, the lack of signal in the published literature, and the recommendations by the PLT, it does not appear that the sunscreen NDAs need a pregnancy warning, phase IV studies to assess vascular lesions in babies of pregnant women, or a pregnancy exposure registry.

The sponsor should study the pharmacokinetic and safety of these products in infants < 6 months of age because infants in this age category could benefit from availability of a nonprescription sunscreen. Currently nonprescription sunscreens are labeled down to the age of 6 months. Thus the sponsor should not be granted a waiver for this age category.

The chemistry analyses and labeling were performed for the — NDA [ — ] 21-502. The chemistry analysis supports that these are creams, [ — ] and the labeling should reflect this. The — inspection is not yet complete and must be acceptable for the — NDAs to be approved. The sponsor has many labeling deficiencies to correct before this product can be approved.

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Andrea Segal  
3/6/2006 12:16:04 PM  
MEDICAL OFFICER



Oversight of Clinical Efficacy review  
Phyllis A. Huene, M.D.  
NDA: \_\_\_\_\_ 21-502, \_\_\_\_\_  
\_\_\_\_\_ Sunscreens

The Division of Dermatologic and Dental Products has been requested to provide oversight on the clinical efficacy review of the [ ] sunscreen products (NDA [ ] 21-502, [ ]), done by Michael Koenig, Ph.D.

On review of Dr. Koenig's evaluation of the test data on protection from UVB and UVA radiation, it is apparent that the standards for approval differ for prescription and for OTC sunscreen products in such particulars as the demonstration of the contribution of each ingredient, description of the methodology, the number of subjects tested, independent confirmation of the results, and more.

However, Dr. Koenig's review appears to be in conformance with the OTC regulations and review policies for sunscreen products, and so his recommendations that these products should be approved for OTC use for the prevention of [ ] should be implemented.

Phyllis A. Huene, M.D.

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Phyllis Huene  
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Markham Luke  
2/15/2006 09:36:27 AM  
MEDICAL OFFICER  
Efficacy Review Addendum on SPF and UVA protection -  
Dermatology Evaluation

Stanka Kukich  
2/15/2006 05:59:28 PM  
MEDICAL OFFICER

Clinical review  
Phyllis A. Huene, M.D.  
NDA 21-502  
           Sunscreen 539-009

## CLINICAL REVIEW

Application Type	NDA
Submission Number	21-502
Submission Code	N-000
Letter Date	May 12, 2005
Stamp Date	Stamp date: May 12, 2005
PDUFA Goal Date	March 16, 2006
Reviewer Name	Phyllis A. Huene, M.D.
Review Completion Date	October 17, 2005
Established Names	Ecamsule, Avobenzone, Octocrylene
(Proposed) Trade Name	<input type="checkbox"/> <input checked="" type="checkbox"/> SPF 15 Daily Use Moisturizing Sunscreen
Therapeutic Class	Sunscreen agent
Priority Designation	S
Formulation	<u>          </u>
Dosing Regimen	Application 15 minutes before sun exposure
Indication	Sun protection
Intended Population	Age 6 months and older

Clinical review  
Phyllis A. Huene, M.D.  
NDA 21-502  
Sunscreen 539-009

2

MEDICAL OFFICER'S REVIEW OF NDA 21-502  
ORIGINAL SUBMISSION

SPONSOR: L'Oreal USA Products, Inc.

PRODUCT:   SPF 15 Daily Use Moisturizing Sunscreen  
(539-009)

Active ingredients: Active ingredients: ecamsule\* 2%,  
avobenzone 2%, octocrylene 10%.

\*Trade name for ecamsule is Mexoryl SX.

MATERIAL REVIEWED: Phase 1 studies. The other portions of the NDA submissions are to be reviewed by the Division of OTC Drug Products.

REVIEWER'S EVALUATION OF PHASE 1 STUDIES: The dermal safety studies are adequate to show that there is little or no potential for irritation, phototoxicity, or photosensitization under the conditions of proposed usage. There is some potential for sensitization. The acnegenicity/comedonegenicity studies are not adequate to conclude that the test products are not acnegenic or comedogenic.

Study 110.01 Irritation and contact sensitization

This study was conducted at the facilities of   at its sites at   The investigators were   M.D., at the former site and   M.D., at the latter site.

It was performed on 223 adult subjects, of which 217 subjects completed the study. Six subjects discontinued for non-related reasons and one was lost to followup.

The test products were

formula 539-009, the subject of the current application, and petrolatum as a control. The active ingredients were as follows.

Formulation	Ecamsule	Avobenzone	Octocrylene
<input type="checkbox"/>			<input checked="" type="checkbox"/>
539-009 (lotion)	2%	2%	10%
<input type="checkbox"/>			<input checked="" type="checkbox"/>
White petrolatum	-	-	-

The patching devices were 8 mm diameter flexible [ ] centered on a measured strip of [ ], making an occlusive patch. Approximately 0.15 ml of the test materials were applied to the patches immediately prior to application. The patches were randomly applied to the test sites, and the investigator was blinded to the identification of the test products.

During the induction phase, applications were made to the same skin sites on the back, five times a week for three weeks. The patches were applied for a period of 24 hours on Mondays through Thursdays, and for 72 hours on Fridays, remaining in place until Monday. Skin reactions were evaluated immediately after patch removal. If a score of 3 or greater occurred at a patch site, an alternate skin site was used for subsequent applications.

After a rest period of one week, occlusive challenge applications were made to naive skin sites for 48 hours. Skin reactions were graded at patch removal and at 24 and 48 hours later. At one center the subjects were to be evaluated at day 8 if there were an equivocal reaction at 48 hours, while at the other center all subjects were evaluated at day 8.

Reactions were scored on the following scale:

0	No visible skin reaction
1	Redness, faint to moderate, with partial involvement of exposure area
2	Redness, moderate to intense, with total involvement of exposure area
3	Redness, intense, all of contact area involved
4	Redness, moderate to intense, plus edema or papules
5	Redness, moderate to intense, plus vesicles, blisters, or bullae
6	Redness, infiltration, plus extension of effect beyond area of contact

Other local reactions were recorded as follows.

O	Edema	Definite swelling
P	Papules	Many small, red, solid elevations; surface of reaction has granular feel
V	Vesiculation	Small (<0.5 cm) circumscribed elevations having translucent surfaces so that fluid is visible
B	Blisters	Bullae; large (>0.5 cm) circumscribed elevations with visible fluid
Pu	Pustules	Inflammatory small elevations containing yellow-white exudates
H	Hyperpigmentation	An increase of the usual pigmentation limited on the patch test area
W	Weeping/oozing	May be a sign of vesiculation or blisters (epidermal damage) and manifest as crusting
S	Spreading of reaction beyond patch site	Reaction where no product came in contact with the skin.
Se	Superficial erosion	Slight to moderate removal of epidermis

Other skin reactions such as dryness, cracking, peeling, were noted as comments.

At the end of the challenge phase the investigators assessed the occurrence of possible contact sensitization as negative, equivocal, or positive. Signs and symptoms such as pruritus, vesicles, spreading or crescendo reactions were considered as possibly positive reactions. Any subject whose reaction was judged as equivocal at challenge was to be re-challenged after a two week rest period.

Results were as follows.

Of the 223 subjects enrolled, 6 subjects were discontinued from the study. Five subjects discontinued for non-medical reasons, and 1 subject was lost to followup. Analyses were conducted on 218 subjects.

- 1) Induction phase: Skin irritation was found in 3 subjects during the induction phase.

One subject had grade 1 reactions on the first day of week 2 at the

three test product sites, which subsequently increased to grade 4 reactions during week 2. At the start of week 3, three alternate sites were patched, and at the end of week 3 the subject had grade 1-2 reactions to the three test products at the new test sites, and the original sites continued to show grade 4 reactions. No reactions were seen at the control site. The investigator concluded that the subject had entered the study pre-sensitized to the test products, and the subject was discontinued from the study.

Two subjects had grade 4 reactions, both at the C lotion (539-009) sites, one on the fourth day of week 2 and one at the last application on the first day of week 4. The first subject was patched at an alternate site during week 3, and no further reactions occurred. The second subject showed grade 1 reactions during the next two days. The two subjects had also shown transient grade 1 reactions to the cream test products. Both subjects completed the study, and neither showed sensitization during the challenge phase.

The Mean Cumulative Irritancy Index for all three test products was 0.01.

- 2) Challenge phase: There were no reactions in any subjects to any of the test products.

*Reviewer's evaluation: This study was adequately designed and executed, except that the usual requirement for a cumulative irritation study is that it be of 21 days duration. However, based on the results in the induction phase under conditions of exaggerated exposure, the test products would be expected to have little potential for irritation under conditions of normal use. No sensitization or other reactions were found in the challenge phase; however, one subject was apparently sensitized to the test products prior to initiation of the study. There is therefore some potential for sensitization with the test product.*

Study — 210.01 - Photosensitization

The investigator for this study was Robert Shanahan, Ph.D., of Consumer Product Testing Co., Fairfield, NJ. The subject population was 106 evaluable subjects.

The test products were C

U formula 539-009, the subject of the current application, and petrolatum as a control. The active ingredients were as follows.

Formulation	Ecamsule	Avobenzone	Octocrylene		
[			]	/	
539-009 (lotion)	2%	2%	10%		
[			]		
White petrolatum	-	-	-		

The light sources used were a UVA radiation source and a full spectrum radiation source. The UVA radiation source was a [ - ] solar simulator, filtered to remove radiation below 320 nm. The full spectrum radiation source was a [ - ] solar simulator with a continuous emission spectrum in the UVA and UVB range from 290 to 400 nm.

The minimal erythema dose (MED) of full spectrum radiation was determined for each subject prior to test applications. During the induction phase, 0.2 ml of the test products were applied under occlusive patches to skin sites on the back for 24 hours, twice weekly on Mondays and Thursdays, for 3 weeks. At each patch removal the sites were irradiated with 2 MEDs of full spectrum irradiation during the first week and with 3 MEDs during the second and third weeks. An untreated control site was included. Skin reactions were assessed at 30 minutes after patch removal, prior to irradiation.

The induction period was followed by a two week rest period. In the challenge phase, two sets of the test products were applied to naive skin sites under occlusion for 24 hours. After patch removal one set of sites was irradiated with 10 J/cm<sup>2</sup> of UVA irradiation followed by 0.8 MED of full spectrum radiation. The other set of sites served as treated, non-irradiated controls. An untreated control site was also included. Skin reactions were scored before irradiation, and at 48 and 72 hours after irradiation. A 96 hour evaluation was to be done if reactions were equivocal.

The following scale was used for grading reactions during the induction and challenge phases.

0	No visible skin reaction
0.5	Barely perceptible or spotty erythema
1	Mild erythema
2	Moderate erythema, possible presence of edema
3	Marked erythema, possible edema
4	Severe erythema, possible, edema, vesiculation, bullae and/or ulceration

Other local reactions were recorded as follows.

0	Edema	Definite swelling
P	Papules	Many small, red, solid elevations; surface of reaction has granular feel
V	Vesiculation	Small (<0.5 cm) circumscribed elevations having translucent surfaces so that fluid is visible
B	Blisters	Bullae; large (>0.5 cm) circumscribed elevations with visible fluid
Pu	Pustules	Inflammatory small elevations containing yellow-white exudates
H	Hyperpigmentation	An increase of the usual pigmentation limited on the patch test area
W	Weeping/oozing	May be a sign of vesiculation or blisters (epidermal damage) and manifest as crusting
S	Spreading of reaction beyond patch site	Reaction where no product came in contact with the skin.
Se	Superficial erosion	Slight to moderate removal of epidermis

Other skin reactions such as dryness, cracking, peeling, were noted as comments.

Immediate skin responses to irradiation consisting of tanning, reddening, or heat were evaluated as present or absent, using the following definitions.

Tanning: immediate darkening or tanning, typically greyish or purplish in color, fading in 30 to 60 minutes, attributed to photo-oxidation of existing melanin granules.

Reddening: immediate reddening, fading rapidly and viewed as a normal response of capillaries and venules to heat, and visible and IR radiation.

Heat response: immediate generalized heat response, resembling prickly heat rash, fading in 30 to 60 minutes, and apparently caused by heat and moisture generally irritating the skin surface.

Results were as follows.

137 subjects were enrolled into the study, of which 106 were evaluable for photosensitization reactions. The following subjects were discontinued from the study: 14 subjects were enrolled into another study concurrently or within 30 days of the start of this study; 4 subjects were taking an exclusionary medication; 2 subjects had disqualifying medical conditions; 1 subject was over the age limit of 65 years, and 11 subjects were discontinued at their request.

During the induction phase, erythema was seen in about 25% of the active product sites and in over 80% of the petrolatum sites during the third week. There were no reactions in the challenge phase.

Reviewer's evaluation: This study was adequately designed and executed. No sensitization or other reactions were found in the challenge phase, and the products would be expected to have little or no potential for photosensitization.

Study 250.01 - Phototoxicity

The investigator for this study was Robert Shanahan, Ph.D., of Consumer Product Testing Co., Fairfield, NJ. The subject population was 26 evaluable subjects.

The test products

☐ formula 539-009, the subject of the current application, and petrolatum as a control. The active ingredients were as follows.

Formulation	Ecamsule	Avobenzone	Octocrylene
☐	—	—	☐
539-009 (lotion)	2%	2%	10%
☐	—	—	☐
White petrolatum	-	-	-

The light source was a ☐ — ☐ solar simulator for full spectrum radiation, which was filtered to produce UVA radiation.

The minimal erythema dose (MED) of full spectrum radiation was determined for each subject prior to test applications. 0.2 ml of the test products were applied in two sets of occlusive patches to skin sites on the back for 24 hours. Two additional sites were untreated and occluded to serve as controls. At 60 minutes after patch removal, one set of test sites were irradiated with 20 Joules/cm<sup>2</sup> of UVA light, and were then exposed to 0.8 MED of full spectrum radiation. The patches were evaluated for reactions immediately following irradiation and at 24 and 48 hours later.

The following scale was used to grade erythema reactions.

0	No visible skin reaction
0.5	Barely perceptible or spotty erythema
1	Mild erythema
2	Moderate erythema, possible presence of edema
3	Marked erythema, possible edema
4	Severe erythema, possible, edema, vesiculation, bullae and/or ulceration

If any other local reactions were found, they were to be noted as in the photosensitization study.

Results were as follows.

26 subjects were enrolled into, and completed the study. There were no erythema or local reactions observed for any of the subjects at any observation time. The investigator concluded that no phototoxic reactions had occurred.

Reviewer's evaluation: This study was adequately designed and executed, except that the Agency generally requires 30 evaluable subjects in a phototoxicity study. No reactions were found after irradiation, and the products would be expected to have little or no potential for phototoxicity.

Study — 570.01 - Acnegenicity/Comedogenicity

The objective of this study was to determine the acnegenicity and comedogenicity potential of the test product. The study was conducted in an open fashion on 44 subjects. The sole test product was [ — ] Sunscreen (539-009), the subject of this application, having as active ingredients 2% ecamsule, 2% avobenzene, and 10% octocrylene.

The principal investigator was Robert Shanahan, Ph.D., of Consumer Product Testing Co., Fairfield, NJ. The evaluations and readings were performed by [ — ] M.D., a dermatologist.

The subjects were males and females of 18 to 40 years of age. Approximately half of the subjects were considered to be acne prone, with 10 or fewer acne lesions, while the other half had more than 10 acne lesions. Subjects were excluded from enrollment if they were currently receiving or had received systemic acne treatment within the prior six months, or had received topical acne treatment within the prior four weeks, or if they had started or changed dosage or brands of oral contraceptives within the prior six months, or if they had a menstrual cycle-dependent flare of acne lesions.

Applications of the test product were made twice daily to the face for 6 weeks. The subjects were instructed to discontinue use of their regular facial lotion/moisturizer. Other than lipstick and mascara, no cosmetic products were to be used on the face. No systemic medications were to be taken nor topical medications applied without prior consultation with the investigator. Treatment with concomitant medications was permitted if in the investigator's opinion it did not interfere with the conduct of the study or the interpretation of the results.

The number of acne lesions was counted at baseline and at return visits at weeks 4 and 6. For this evaluation the face was divided into six sites, consisting of the right and left forehead, cheeks, and chin. The number of non-inflammatory lesions (comedones) and inflammatory lesions (papules and pustules) were counted in these sites and recorded in the case report form.

A statistical analysis for acnegenicity was performed, whereby the paired t-test was used to test the null hypothesis that the mean number of lesions at baseline for all subjects was equal to the mean number of lesions for all subjects at the final visit. An analysis for comedogenicity compared the mean comedone counts in the same manner.

Results were as follows.

44 subjects were enrolled in the study, of which 40 subjects were analyzed for acnegenicity/comedogenicity. One subject was excluded for a protocol violation, and 3 subjects did not complete the study for unrelated reasons.

The baseline characteristics of all subjects enrolled were as follows.

Baseline characteristics n=44	
<u>Gender</u>	
Male	24 (55%)
Female	20 (45%)
<u>Race</u>	
Caucasian	32 (82%)
Black	3 (7%)
Asian	2 (5%)
Hispanic	3 (7%)
<u>Skin type</u>	
I	2 (5%)
II	7 (16%)
III	13 (30%)
IV	12 (27%)
V	8 (18%)
VI	2 (5%)

The mean acne lesion counts and the comedone counts at baseline and return visits were as follows.

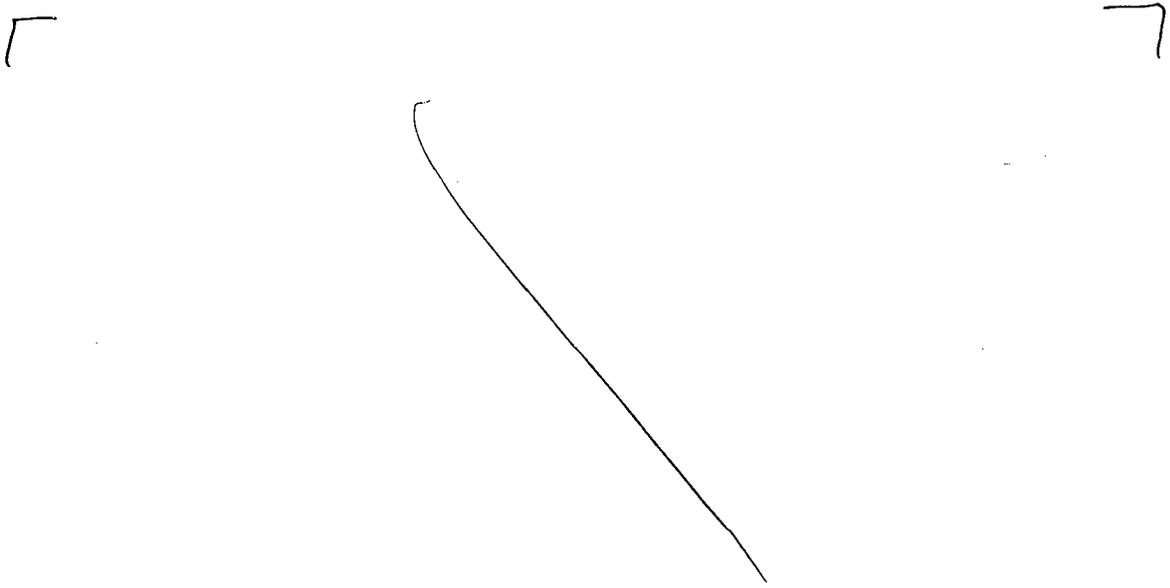
Acne lesion counts		
	Mean	Range
Baseline	7.7	1-24
Week 4	6.9	1-35
Week 6	6.6	1-36

Comedone counts		
	Mean	Range
Baseline	3.2	0-20
Week 4	2.6	0-32
Week 6	3.0	0-33

There were no statistically significant differences between the baseline and final lesion counts, nor between the baseline and final comedone counts.

The sponsor's conclusion was that, according to the results of this study, ☐ ☐ Sunscreen (539-009) can be considered non-acnegenic and non-comedogenic.

Reviewer's evaluation: Although the mean values for acne lesions and comedones decreased from baseline, there were increased lesions of both types in one or more subjects, as indicated by the ranges of values. The individual subject data need to be examined to determine whether there is a subset of subjects in which the test product might be acnegenic/comedogenic.



3 Page(s) Withheld

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

§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process

Reviewer's overall evaluation of Phase 1 studies: The dermal safety studies are adequate to show that there is little or no potential for irritation, phototoxicity, or photosensitization under the conditions of proposed usage. Although there were no sensitization reactions at challenge, one subject in the sensitization study was apparently pre-sensitized to the test products prior to initiation of the study. There is therefore some potential for sensitization.

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Markham Luke  
1/13/2006 05:05:29 PM  
MEDICAL OFFICER  
Dermatology review of dermal safety. See OTC MO review  
for overall safety and UV sunscreen evaluation by  
OTC.

Stanka Kukich  
3/7/2006 11:16:11 AM  
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 31, 2006

FROM: Susan McCune, MD  
Division of Pediatric Drug Development, OCTAP

Dianne L. Kennedy, MPH, RPH  
Pregnancy & Lactation Team, OND

THROUGH: Sandra Kweder, MD  
Deputy Director, OND

TO: Elaine Abraham, RPM  
DNCE

SUBJECT: Combination OTC Sunscreens (Investigational Name - [redacted] and Use During Pregnancy  
NDA [redacted] 21-502 [redacted] (L'Oreal USA Products)

Consult received by the PLT: December 8, 2005  
Due date: January 31, 2006

**I. EXECUTIVE SUMMARY**

L'Oreal USA Products is seeking approval to market — new sunscreen products with three — sunscreen ingredients in differing concentrations. These ingredients are avobenzone, octocrylene, [redacted] (all — monograph ingredients) and ecamsule (a new ingredient). Eleven women became pregnant during three studies, four infants developed birthmarks: two with hemangiomas, one with a nevus flammeus and one with a café au lait spot.

The Pregnancy & Lactation Team (PLT) was consulted to

1. Provide feedback on whether or not the sponsor should conduct studies to evaluate children of mothers exposed to the new sunscreen formulations during pregnancy for cutaneous vascular abnormalities.
2. Advise whether the OTC labeling for these new sunscreen products should carry any pregnancy warnings.

The PLT recommends that the sponsor be requested to provide more descriptive information on the seriousness and extent of vascular involvement for the two

cases of hemangiomas as well as the dose and duration of exposure to the drug. Given that hemangiomas develop postnatally frequently (7 – 10% of infants) and most are small and involute, the PLT does not recommend setting up a pregnancy exposure registry unless there is something unusual about the two cases, e.g., very large, life-threatening, deep, etc.

The PLT does not recommend requiring a pregnancy warning on the OTC labeling for these products for the following reasons:

- Ecamsule is a Pregnancy Category B drug according to the Pharm/Tox review.
- PK studies show that <1% of ecamsule is absorbed systemically
- There is no evidence of reproductive toxicity for [redacted], ecamsule, avobenzone or octocrylene in the literature although the data are sparse.
- There are no reports in the literature or in AERS of hemangiomas associated with the use of [redacted] ecamsule, avobenzone or octocrylene.

## II. BACKGROUND

The following was information provided in the written consult request:

“The sponsor is requesting approval to market [redacted] new sunscreen drug products [redacted] in the over-the-counter setting (NDA [redacted] 21-502 [redacted]). All [redacted] sunscreens contain three [redacted] active sunscreen ingredients in different concentrations: avobenzone, octocrylene, [redacted] (all [redacted] monograph ingredients) and ecamsule (a new ingredient). [redacted]

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

Four women became pregnant in Study [redacted] 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. All four women delivered normal healthy babies.

Six pregnancies were reported during Study [redacted]. Of the six women who reported pregnancy, three discontinued because of their pregnancy. Two of the six pregnancies resulted in a delivery of normal healthy babies. One infant developed a café au lait spot 1 to 2 weeks after birth. Since isolated café au lait spots occur in up to 10-20% of the normal population, the event was assessed

by the sponsor as of no pathological significance. Three of six infants were normal at birth but subsequently developed vascular lesions approximately three months after birth. All three events of birthmarks (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). For the two cases of hemangioma, the events were considered possibly related to study treatment; the case of nevus flammeus was considered of unlikely relationship to study treatment.

According to the pharmacology review, ecamsule is a Pregnancy Category B drug. Based on the preclinical data, ecamsule is not a teratogen and does not have an effect on reproductive function in animals. The division does not have data for the other two monograph active ingredients (avobenzone and octocrylene), which are not contraindicated in pregnancy. The number of women exposed to the sunscreen formulations containing ecamsule is small. Three congenital vascular adverse events occurred in subjects with \_\_\_\_\_ could have occurred by chance alone. Nevertheless, the exposure to drug product could be significant if used as directed. PK studies show that <1% of ecamsule (active ingredient) is absorbed systemically.”

### III. REVIEW OF DATA

The following materials were reviewed:

- Medical Officer review [ ]
- Pharm/Tox review [ ]
- Reprotox information in the online Micromedex Intergrated Index including Teris – The Teratogen Information System, the Reprotox System and Shepard’s Catalog of Teratogenic Agents
- AERs database
- Pubmed for 1. reproductive effects with avobenzone, octocrylene [ ] or ecamsule and 2. hemangiomas. The following articles were retrieved.
  - Blei F. Basic science and clinical aspects of vascular anomalies. *Current Opinion in Pediatrics* 2005;17:5011-9.
  - Chiller KG, Frieden IJ, Arbiser JL. Molecular pathogenesis of vascular anomalies: Classification into three categories based upon clinical and biochemical characteristics. *Lymphatic Research and Biology* 2003;1(4):267-81.
  - Chang MW. Updated classification of hemangiomas and other vascular anomalies. *Lymphatic Research and Biology* 2003;1(4)259-65.

The medical officer review and the pharm/tox review are from the previous submission [ ]. There is no information from the current submission other than what is included in the written consult. It appears that 3 studies contained women who became pregnant (N=11). One woman in study [ ] became pregnant and

discontinued her participation in the trial. Four women in study — 750.02 became pregnant and all delivered healthy babies. Six pregnancies were reported in study [ — ] Of the 6 pregnancies, 3 infants developed "vascular lesions" approximately 3 months after birth. One was a nevus flammeus and two were reported as hemangiomas. There was no description of the hemangiomas. Dr. Eichenfield at UCSD stated that nevus flammeus is present in half of all newborns and hemangiomas occur in 10-13% of children in the first year of life. He was unaware of any reports that hemangiomas have been induced by exogenous factors such as drugs or chemicals. He felt that the hemangiomas were random findings and not related to the use of the sunscreen.

The consult mentions another patient with a cafe au lait spot but that is not discussed in the medical officer review [ — ]. According to the consult, the cafe au lait spot was felt to be of no pathological significance "since isolated cafe au lait spots occur in up to 10-20% of the normal population".

In the Pharm/Tox review [ — ] there was an oncogenicity study by dermal application of ecamsule to CD-1 mice for 104 weeks (p.45-51). They concluded, "The relative incidence of hemangiosarcomas compared to controls was higher in the high dose males and females. The relative incidence of hemangiomas in treated females was also increased over control. However, hemangiomas and hemangiosarcomas are not rare in the historical control data from the testing laboratory and the values from the current study appear to be within historical control ranges."

There is no evidence of reproductive toxicology for [ — ] ecamsule, avobenzone or octocrylene in the literature although the data are sparse.

There are no reports in the literature of hemangiomas associated with ecamsule, avobenzone, octocrylene [ — ]

In a search of the AERS database for ecamsule, avobenzone, octocrylene, [ — ] [ — ], there were a total of 61 reports. None of them mentioned hemangioma. There were no AERS reports for any children between 0-1 year of age, and there were no reports of congenital anomalies.

The literature supports the assessment that nevus flammeus occurs in approximately half of all newborns, cafe au lait spots in approximately 10 % of infants and hemangiomas in approximately 7-10% of the newborn population. Hemangiomas are more common in female infants and premature infants. They tend to grow postnatally for several months and then spontaneously involute. There are many varieties of hemangiomas in the newborn period and there was no description of the type of hemangioma in the study report. The etiology of vascular anomalies in the newborn period is unclear and likely represents a multifactorial process.

#### IV. CONCLUSIONS

Cutaneous vascular abnormalities occur frequently in the newborns. Unless the two cases of hemangiomas reported in the study are unusual for some reason, e.g., very large, life-threatening, deep, etc. the PLT does not see a need for a pregnancy exposure registry.

Based on the materials reviewed the PLT does not recommend a pregnancy warning be included in the OTC labeling.

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Susan McCune, MD  
Division of Pediatric Drug Development,  
OCTAP

---

Dianne L. Kennedy, MPH, RPh  
Pregnancy & Lactation Team,  
OND

Cc: OND: Kweder, Kennedy  
DPPD: Mathis, McCune  
DNCE: Leonard Segal, Abraham

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/s/

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Matthew Bacho  
2/1/2006 01:55:32 PM  
CSO  
PLT Consult for NDA. 

  21-502.

Sandra L. Kweder  
2/8/2006 05:42:15 PM  
MEDICAL OFFICER

**CLINICAL EFFICACY REVIEW**

Application Type NDA  
Submission Number            21-502,            (IND 59,126)  
Submission Code N000

Letter Date               
May 12, 2005 (NDA 21-502)

Stamp Date                
May 12, 2005 (NDA 21-502)

PDUFA Goal Date                
              
March 12, 2006 (NDA 21-502)

Reviewer Name Michael L. Koenig, Ph.D.  
Review Completion Date December 27, 2005

Established Name               
          ,           ,             
**NDA 21-502: Ecamsule, 2%; avobenzone, 2%; octocrylene, 10%**  
              
           

(Proposed) Trade Name Several  
Therapeutic Class Sunscreen  
Applicant L'Oreal USA Products Inc.

Priority Designation S

Formulation           

Dosing Regimen

Clinical Efficacy Review

Michael L. Koenig

NDA 21-502: SPF 15 sunscreen lotion

☐

☐

**NDA 21-502:** Apply evenly ☐ — ☐  
before sun exposure ☐ — ☐

Indication Prevention of sunburn ☐ — ☐ due  
to sun exposure by providing broad  
spectrum protection from UVB and UVA  
radiation

Intended Population Adults and children 6 months of age and  
older

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NDA 21-502: SPF 15 sunscreen lotion

## 1 EXECUTIVE SUMMARY

### 1.1 Recommendation on Regulatory Action

Based on effectiveness, the following products should be approved for over-the-counter (OTC) use for prevention of skin damage induced by UVB and UVA radiation:

- SPF 15 sunscreen lotion (NDA 21-502)

Final approvability depends on the outcome of the preclinical and clinical safety and chemistry studies being evaluated by other reviewers in the Office of Nonprescription Products and Division of Dermatologic and Dental Drug Products.

### 1.2 Recommendation on Postmarketing Actions

#### 1.2.1 Risk Management Activity

This review only considers the effectiveness of the [redacted] formulations in NDA [redacted] 21-502, [redacted]. Therefore, this section is not applicable.

#### 1.2.2 Required Phase 4 Commitments

There are no phase 4 requirements with respect to efficacy.

#### 1.2.3 Other Phase 4 Requests

None.

### 1.3 Summary of Clinical Findings

#### 1.3.1 Brief Overview of Clinical Program

L'Oreal is seeking approval to market [redacted] OTC sunscreen drug products for daily use by adults and children six months of age and older:

- SPF 15 sunscreen lotion (NDA 21-502)

[redacted] (21-502) include 2% avobenzone, 10% octocrylene, and the new molecular entity ecamsule at different concentrations.

Each sunscreen product contains the new molecular entity, ecamsule. Although it has been marketed outside the United States since 1993, ecamsule is a new molecular entity in the United States. The other active ingredients (octocrylene, avobenzone, ) are among the 16 generally recognized as safe and effective (GRASE) sunscreen active ingredients listed in the OTC sunscreen drug monograph (21 CFR part 352).

In support of its submission, the sponsor has submitted data from a total of three pre-clinical and 12 clinical studies. Since the pre-clinical and clinical data to support the marketing of the products are the same, the NDAs are being evaluated concurrently for efficacy in this review.

### 1.3.2 Efficacy

Based on my review of the twelve clinical and three in vitro studies submitted in these NDAs, this reviewer concludes that all formulations provide effective protection from due to both UVB and UVA radiation. The formulations meet the criteria for UVB radiation protection in 21 CFR 352.20(a) in that:

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

Because the formulations meet these criteria, they may be labeled as providing effective UVB protection.

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

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

The products to be marketed under NDA 21-502, may bear UVA protection claims, such as "broad spectrum" or "protects against UVA rays or radiation" (58 FR 28194 at 28233), but they may make no claims as to the degree of UVA protection.

Clinical Efficacy Review

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NDA 21-502: SPF 15 sunscreen lotion

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### 1.3.3 Safety

More than 2500 subjects were exposed at least once to an ecamsule-containing sunscreen product during the clinical studies conducted for these sunscreens. There were no drug-related deaths or drug-related serious adverse events reported among the participants in clinical trials. In addition, postmarketing AEs reported to the sponsor did not reveal any serious safety issues. All of the safety data are being evaluated by other reviewers in the Office of Nonprescription Products and Division of Dermatological and Dental Drug Products.

### 1.3.4 Dosing Regimen and Administration

The proposed dosing directions for the SPF 15 sunscreen lotion (NDA 21-502) are as follows:

- apply evenly before sun exposure
- children under 6 months of age: ask a doctor

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

### 1.3.5 Drug-Drug Interactions

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

### 1.3.6 Special Populations

There are not special population related to effectiveness. Special populations related to safety are discussed as part of the safety review conducted by other reviewers in the Office of Nonprescription Products and Division of Dermatological and Dental Drug Products.

## 2 INTRODUCTION AND BACKGROUND

This is a clinical efficacy review of sunscreen combination drug products submitted under NDA 21-502. Because the clinical data to support the marketing of the products are the same, the NDAs are being evaluated concurrently in this review.

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NDA 21-502: SPF 15 sunscreen lotion

## 2.1 Product Information

NDA 21-502 was submitted for the SPF 15 sunscreen lotion. This product is a topical sunscreen composed of the same three active ingredients in formulation

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

The only difference between this product and formulation is the concentration of ecamsule (and inactive ingredient). The sponsor requests that this formulation be marketed under brand names:

ANTHELIOS

The products/brand names will be marketed in tubes. Throughout this review, SPF 15 sunscreen lotion is referred to as formulation 539-009.

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

## 2.2 Currently Available Treatment for Indications

There are a total of 16 sunscreen active ingredients generally recognized as safe and effective (GRASE) under the OTC sunscreen drug monograph (21 CFR part 352). All sunscreens currently available for OTC use in the United States are marketed under the sunscreen monograph. — of the active ingredients included in these sunscreen formulations (avobenzone, octocrylene, — — —) are listed as GRASE in the sunscreen monograph both as single active ingredients and in combination with other sunscreen active ingredients.

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

As mentioned in section 2.2, three of the active ingredients contained in the sunscreen formulations are currently available in the United States OTC market. The only ingredient not currently available in the United States is ecamsule.

## 2.4 Important Issues With Pharmacologically Related Products

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

## 2.5 Presubmission Regulatory Activity

The — formulations were developed under IND 59,126. In addition to IND 59,126, the sponsor studied ecamsule under IND —

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The sponsor sought regulatory guidance and advice from FDA on several occasions during the development of these — formulations. All issues raised by FDA during pre-NDA meetings have been adequately addressed by the sponsor.

## 2.6 Other Relevant Background Information

In 1991, ecamsule was included in the European Economic Community (EEC) Cosmetic Directory, Annex VII, "List of UV Filters Which Cosmetic Products May Contain." Subsequently, marketing of sunscreen products containing ecamsule began in Europe and other parts of the world in 1993. According to the sponsor, over — units of sunscreen products containing ecamsule have been sold worldwide during that time.

Sunscreen products, also known as UV filters, are regulated as cosmetics in all other countries except Canada and Australia. Ecamsule was registered with the Canadian Health Protection Bureau in 1994 and with the Australian Health Authorities in 1995.

## 3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

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

The CMC review is pending.

### 3.2 Animal Pharmacology/Toxicology

The sponsor conducted a total of 87 animal and toxicology studies as part of the — development program —. These studies did not demonstrate that ecamsule was teratogenic, carcinogenic, or photocarcinogenic. There was no embryolethality or reproductive toxicity associated with ecamsule alone or in combination with other sunscreen active ingredients. The acute oral toxicity dose is 5000 mg/kg in the rat and 2000 mg/kg in the mouse.

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

### 4.1 Sources of Clinical Data

Clinical data to support the effectiveness of the — formulations was submitted in NDA — 21-502 (volumes 74-80) —. Data include 12 single center, controlled, randomized, double-blinded studies. Eight of the studies were conducted under the supervision of Dr. Robert W. Shanahan at the Consumer Product Testing

Company, Inc. (CPTC) in Fairfield, NJ. Four of the studies were conducted under the supervision of Dr. Alan H. Greenspan at TKL Research, Inc. (TKL) in Paramus, NJ.

In response to a request from FDA (End of Phase 2 Meeting Minutes, April 16, 2001), the sponsor also submitted in vitro (i.e., non-clinical) studies designed to demonstrate that the absorption spectra of the formulations extend to wavelengths  $\geq 360$  nm (i.e., long-wavelength UVA). One of the studies was conducted under the supervision of Dr. Robert W. Shanahan at CPTC in Fairfield, NJ. The other two studies were conducted at L'Oreal Applied Research and Development Laboratories in Clichy and Chevilly-Larue, France.

As additional evidence that the formulations are effective UVB and UVA sunscreens, the sponsor references seven clinical studies submitted on May 29, 2003, to support the effectiveness of the cream. Cream contains the same active ingredients contained in the formulations currently under review.

Data supporting the safety of the formulations is included in the 12 clinical effectiveness studies. Safety data is also derived from nine clinical studies designed specifically to evaluate the safety of the formulations that are the subject of this review and four safety studies conducted to support the safety of the formulations.

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

Table 1. UVB Protection

Study	Formulation 539-009 (NDA 21-502)	Study Center
810.01	✓	TKL
810.02	✓	CPTC
810.03		TKL
810.04		CPTC
810.05	✓	CPTC
810.06	✓	CPTC

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#### 4.5 Compliance with Good Clinical Practices

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

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

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

#### 4.6 Financial Disclosures

The sponsor submitted Form 3454 certifying that the investigators of all but three clinical studies had no financial interests in these products, the studies, or the companies conducting the studies. The three studies for which certifications were not provided were previously reviewed under [redacted]. None of the studies are pivotal for the evaluation of either efficacy or safety for the [redacted] sunscreen formulations submitted under NDA [redacted] 21-502 [redacted].

### 5 CLINICAL PHARMACOLOGY

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

#### 5.1 Pharmacokinetics

Pharmacokinetics studies are not pertinent to this review of efficacy. Three in vivo and four in vitro pharmacokinetics studies are being evaluated by other reviewers.

#### 5.2 Pharmacodynamics

No pharmacodynamic data were submitted in the [redacted] NDAs.

#### 5.3 Exposure-Response Relationships

The [redacted] NDAs did not include studies exploring exposure-response relationships.

## 6 INTEGRATED REVIEW OF EFFICACY

### 6.1 Indication

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

#### 6.1.1 Methods

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

The method for determining the SPF value (i.e., effectiveness) of an OTC sunscreen drug product marketed in the United States is detailed in 21 CFR part 352 subpart D. As indicated in § 352.72, at least 20 evaluable subjects must complete the study. Sunscreen formulations are applied to  $\geq 50$  cm<sup>2</sup> test sites on each subject’s back. Each test site is further subdivided into at least 3 subsites no less than 1 cm<sup>2</sup> in size. Each subsite is exposed to a different amount of simulated solar radiation. Sunscreen formulations are applied to the entire test site using a finger cot to ensure an even distribution of 2 mg/cm<sup>2</sup>. Subjects are not exposed to UV radiation for at least 15 minutes after applying sunscreen formulations.

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

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

Subjects are exposed to a geometric series of increasing amounts of radiation (§ 352.73(b)) in the absence or presence of a sunscreen to determine the MED<sub>US</sub> (MED unprotected skin) or MED<sub>PS</sub> (MED protected skin), respectively. MED is defined as the amount of light energy required to

produce the “first perceptible, redness reaction with clearly defined borders 22 to 24 hours after exposure” (§ 352.73(c)). Therefore,  $MED_{US}$  is always lower than  $MED_{PS}$ , because less UV radiation is required to produce redness (i.e., erythema) in the absence of a sunscreen than in the presence of a sunscreen.

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

### 6.1.2 General Discussion of Endpoints

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

### 6.1.3 Study Design

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

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

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

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

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

The submitted studies include more female than male subjects, with some studies enrolling only females. The ages of subjects evaluated in these studies range from 18 to 65. Ideally, the studies would enroll equal numbers of males and females as well as pediatric subjects. However, it does not seem unreasonable to extrapolate the findings to males or to children over 6 months (as labeled under the sunscreen monograph). There is no apparent anatomical or physiological difference between female and male skin or the skin of adults and children (over 6 months) that suggest there may be significant differences in protection provided by a sunscreen for these groups.

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

#### 6.1.4 Efficacy Findings

##### 6.1.4.1 Study — 810.01

This phase 3 study was conducted under the supervision of Dr. Alan H. Greenspan at TKL Research Inc. in Paramus, NJ. The study began on April 26, 2000, and concluded on June 9, 2000. A total of 21 evaluable subjects completed the study. All of the subjects were female with an age range of 22 to 58 years (average age of 42 years). The subjects had skin type I, II, or III.

This study evaluates the effectiveness of formulation 539-009 (NDA 21-502) which consists of the following active ingredients:

- 2% ecamsule
- 10% octocrylene
- 2% avobenzone

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

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

The mean SPF of the standard sunscreen was reported to be 4.44 with a standard deviation (SD) of 0.69. This falls within the acceptable range specified in 21 CFR 352.70(a), which is  $4.47 \pm 1.279$ . The mean SPF  $\pm$  SD of test formulation 539-009 was  $16.65 \pm 3.57$ . The 95% confidence interval ranged from 15.3 to 17.9, resulting in a labeled SPF of 15 (21 CFR 352.73(d)).

Test formulation 539-009 appears to be an effective sunscreen against UVB radiation on adult females. It is expected that the formulation is also effective on males and children (over two years). The formulation meets the criterion specified in 21 CFR 352.20(a) that it have an

SPF value greater than 2 times the number of active ingredients (i.e.,  $15 > 2 \text{ times } 3$ ). The contribution of each active ingredient to the effectiveness of the finished product, as required by 21 CFR 352.20(a), is addressed in studies — 810.05 and — 810.06.

#### 6.1.4.2 Study 1 — 810.02

This phase 3 study was conducted under the supervision of Dr. Robert Shanahan at the CPTC in Fairfield, NJ. The study began on July 31, 2000, and concluded on August 16, 2000. A total of 20 evaluable subjects completed the study. Fifteen subjects were female and five were male. The subjects ranged in age from 19 to 55 years (average age 33.3 years) and had skin type I, II, or III.

As in study — 810.01, this study evaluates the effectiveness of formulation 539-009 and includes the concomitant testing of an 8% homosalate standard sunscreen.

The principal investigator reports only one deviation from the IRB-approved protocol. Subject 03/ — had their MED evaluated approximately 25 hours after exposure to irradiation. The investigator notes that this evaluation should have occurred between 22 and 24 hours after irradiation (21 CFR 352.72(h)). This reviewer does not consider this minor deviation to have affected the study results.

The mean SPF  $\pm$  SD of the standard sunscreen was reported to be  $4.44 \pm 0.45$ . This falls within the acceptable range specified in 21 CFR 352.70(a), which is  $4.47 \pm 1.279$ . The mean SPF  $\pm$  SD of test formulation 539-009 was  $17.45 \pm 2.78$ . The 95% confidence interval ranged from 16.15 to 18.75, resulting in a labeled SPF of 16 (21 CFR 352.73(d)).

Test formulation 539-009 appears to be an effective sunscreen against UVB radiation in both males and females. It is expected that the formulation is also effective on children (over 6 months of age). The formulation meets the criterion specified in 21 CFR 352.20(a) that it have an SPF value greater than 2 times the number of active ingredients (i.e.,  $16 > 2 \text{ times } 3$ ). The contribution of each active ingredient to the effectiveness of the finished product, as required by 21 CFR 352.20(a), is addressed in studies — 810.05 and — 810.06.

#### 6.1.4.3 Study 2 — 810.03

1   Page(s) Withheld

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

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

Clinical Efficacy Review

Michael L. Koenig

NDA 21-502: SPF 15 sunscreen lotion

6.1.4.5 — 810.05

This phase 2 study was conducted under the supervision of Dr. Robert Shanahan at the CPTC in Fairfield, NJ. The study began on April 2, 2002, and concluded on April 24, 2002. A total of 49 evaluable subjects completed the study. Thirty-three subjects were female and sixteen were male. The subjects ranged in age from 18 to 65 years (average age 36.1 years). They had skin type I, II, or III. Each subject was randomly assigned three test products and the standard sunscreen, such that each of six test products was tested on at least 20 subjects.

This study was designed to evaluate the effectiveness of six test formulations containing various combinations of the active ingredients in formulations — 539-009, —  
— All test formulations consisted of the same vehicle, with the only difference being the active ingredients. [

> The following table outlines the composition of each test formulation and the number of subjects tested with each formulation. — of the test formulations represent final formulations submitted under NDA — 21-502, —

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**Table 5. Composition of Test Formulations in Study 810.05**

Test Formulation	10% Octocrylene		2% Avobenzone	2% Ecamsule		Number of subjects
A	✓					25
B	✓		✓			25
C	✓		✓	✓		24
D (539-009)	✓		✓	✓		24

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

The principal investigator reports four deviations from the IRB-approved protocol:

- The MED for one subject was scored 24.5 hours post-irradiation.
- The MED for one subject was scored 21 hours and 52 minutes post-irradiation.
- The MED for one subject was scored at 25 hours and 20 minutes post-irradiation.
- One subject ingested two tablets of Tylenol Cold and Flu medicine during the study.

This reviewer agrees with the principal investigator that these deviations do not interfere with the study results.

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

**Table 6. SPF Values for Formulations Tested in — 810.05**

Test Formulation	Mean SPF ±SD	Labeled SPF	Standard Sunscreen Mean SPF ± SD
A	8.50 ± 1.13	8	4.47 ± 0.85
B	12.47 ± 1.33	12	4.68 ± 0.89
C	17.55 ± 2.57	16	4.69 ± 0.77
D (539-009)	18.55 ± 2.64	17	4.7 ± 0.95

The mean SPF ± SD of the standard sunscreen ranged from 4.47 ± 0.85 to 4.70 ± 0.95. These values fall within the acceptable range specified in 21 CFR 352.70(a). Therefore, the study results are valid.

This study evaluated the effectiveness of individual active ingredients contained in formulations — 539-009 —. According to 21 CFR 352.20(a), the SPF of the final formulation must be equal to or greater than two times the number of active ingredients. Formulations — 539-009 (test formulation D) contain three active ingredients, requiring an SPF of at least 6. Formulation — 539-009 both produced SPF values of 17.

Thus, all — formulations meet one of the two effectiveness criteria specified in 21 CFR 352.20(a).

In addition, 21 CFR 352.20(a) requires that each active ingredient contribute a minimum SPF of not less than 2 to the finished product. In this study, formulation 539-009 (test formulation D) produced an SPF of 17. Comparing this formulation to test formulation B indicates that 2% ecamsule contributes an SPF of 5 to formulation 539-009. By comparing test formulation A to test formulation B, it appears that 2% avobenzone contributes an SPF of 4. Finally, test formulation A produced an SPF of 8, indicating that 10% octocrylene contributes an SPF of 8 to formulation 539-009. Thus, formulation 539-009 meets both criteria in 21 CFR 352.20(a) and, therefore, is effective. It is also interesting to note that, as evidenced by comparing test formulation D to test formulation C, — is not an active ingredient

6.1.4.6 Study — 810.06

This phase 2 study was conducted under the supervision of Dr. Robert Shanahan at the CPTC in Fairfield, NJ. The study began on June 26, 2002, and concluded on August 15, 2002. A total of 97 evaluable subjects completed the study. Of the original 100 subjects enrolled in the study, 66 subjects were female and 34 were male. One subject (#90, — ) requested to be withdrawn from the study, and two subjects (#5, — and #53, — ) were excluded because they were taking exclusionary concomitant medications. The subjects ranged in age from 18 to 63 years (average age 36.9 years) and had skin type I, II, or III. Each subject was randomly assigned two test products and two standard sunscreens, such that each of the seven test products was tested on at least 20 subjects.

This study was designed to evaluate the effectiveness of seven test products containing various combinations of the individual active ingredients in formulation. — 539-009,

— All test formulations consisted of the same vehicle, —

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**Table 7. Composition of Test Formulations in Study — 810.06**

Test Formulation	10% Octocrylene		2% Avobenzone	2% Ecamsule		Number of subjects
607-76A	✓		✓			23
607-12A	✓		✓			24
607-20A	✓		✓	✓		25
607-27A (539-009)	✓		✓	✓		25
[ ]						
607-67A	✓		✓			23

In accordance with the 21 CFR 352.70, a standard sunscreen was tested concomitantly. In this study, the standard sunscreen consisted of an 8% homosalate preparation (SPF 4). The study also included an SPF 15 standard sunscreen to ensure that determinations of SPF greater than 15 were valid.

The principal investigator reports 34 deviations from the IRB-approved protocol. Twenty-six subjects had different evaluators assess MED<sub>US</sub> and MED<sub>PS</sub>. Six subjects had readings outside the 22-24 hour post-irradiation window (five had readings ranging from 7 to 40 minutes early; one had a reading 25 hours post-irradiation). One subject was exposed to slightly lower doses of UV radiation than others in the test group, but an SPF could still be accurately determined. One subject was incorrectly irradiated at one subsite. This reviewer concurs with the principal investigator's assertion that none of these deviations would have significantly affected the study results.

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

Table 8. SPF Values for Different Formulations Tested in 810.06

Test Formulation	Mean SPF ± SD	Labeled SPF	SPF 4 Sunscreen Mean SPF ± SD	SPF 15 Sunscreen Mean SPF ± SD
607-76A	17.24 ± 1.89	16	4.33 ± 0.48	15.07 ± 1.57
607-12A	11.16 ± 1.69	10	4.38 ± 0.60	15.52 ± 1.75
607-20A	17.10 ± 2.84	16	4.37 ± 0.57	15.13 ± 1.30
607-27A (539-009)	16.14 ± 2.16	15	4.40 ± 0.65	15.03 ± 1.59
607-67A	10.99 ± 1.04	10	4.41 ± 0.49	15.97 ± 1.59

The mean SPF ± SD of the SPF 4 standard sunscreen ranged from 4.38 ± 0.60 to 4.47 ± 1.279. These values fall within the acceptable range specified in 21 CFR 352.70(a), which is 4.47 ± 1.279. The mean SPF ± SD of the SPF 15 standard sunscreen ranged from 15.03 ± 1.59 to 15.97 ± 1.59. These standard sunscreens indicate that the study results are valid.

Like 810.05, this study evaluated the effectiveness of individual active ingredients contained in formulations 539-009. According to 21 CFR 352.20(a), the SPF of the final formulation must be equal to or greater than two times the number of active ingredients. Formulation 539-009 (test formulation 607-20A) contain three active ingredients, requiring an SPF of at least 6. Formulation 539-009 produced SPF values of 15 and 16, respectively.

Therefore, all formulations meet one of the two effectiveness criteria specified in 21 CFR 352.20(a).

In addition, 21 CFR 352.20(a) requires that each active ingredient contribute a minimum SPF of not less than 2 to the finished product. In this study, formulation 539-009 (test formulation 607-27A) produced an SPF of 15. Comparing this formulation to test formulation 607-67A indicates that 2% ecamsule contributes an SPF of 5 to formulation 539-009. The individual contributions of 10% octocrylene and 2% avobenzone cannot be determined in this study, but from the results for study 810.05, it seems that these ingredients contribute SPFs greater than 2 in the same vehicle. Thus, formulation 539-009 meets both criteria in 21 CFR 352.20(a) and, therefore, is effective. It is also interesting to note that, as evidenced by comparing formulation 539-009 to test formulation 607-20A, is not an active ingredient.

### 6.1.5 Clinical Microbiology

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

### 6.1.6 Efficacy Conclusions

A total of six studies were conducted to evaluate the effectiveness of formulation 539-009, in protecting against UVB radiation. The test method derives from the sunscreen monograph (i.e., 21 CFR part 352 subpart D). The studies adequately demonstrate that all formulations are effective in helping prevent sunburn by providing protection against UVB radiation.

**Table 10. Labeled SPF Values for Formulation 539-009 (NDA 21-502)**

Study	Labeled SPF	Number of subjects
.810.01	15	21
.810.02	16	20
.810.05	17	24
.810.06	15	25

A total of 90 evaluable subjects participated in four studies designed to demonstrate that formulation 539-009 is effective in protecting against UVB radiation. The submitted labeling for this formulation claims an SPF of 15. The data support this claim. The mean labeled SPF ranges from 15 to 17.

## 6.2 Indication

### 6.2.1 Methods

4 Page(s) Withheld

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

§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process

### 6.3 Indication

The proposed labeling for the — formulations includes claims regarding protection against UVA radiation. A UVA claim of “broad spectrum protection” is allowed for OTC sunscreens marketed under the sunscreen monograph, but PFA values are not currently allowed (*Federal Register* vol. 64, p. 27672).

#### 6.3.1 Methods

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

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

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

test method except that the endpoint (i.e., "response") is pigment darkening rather than erythema (63 FR 56584 at 56587).

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

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

The PPD method used in studies — 910.01 and — 910.02 is nearly identical to the MRD testing method. According to the MRD method, each subject is exposed to increasing amounts of simulated solar radiation in the absence or presence of a sunscreen. The MRD for protected and unprotected skin is determined for each subject. MRD represents the lowest radiation dose that causes pigment darkening that lasts 22-24 hours, because UVA radiation primarily causes the skin to darken (rather than redden). The protection factor for UVA, termed PFA, is then calculated as the ratio of MRD (protected skin) to MRD (unprotected skin). Thus, UVA protection increases with increasing PFA. A minimum of 20 subjects are required to complete the study according to the MRD protocol identified as acceptable by FDA (63 FR 56584 at 56587). As with the SPF test method, a sunscreen standard is tested concurrently to validate the study results.

The 8-methoxypsoralen (8-MOP) method was used in Study — 920.01. According to this method, an alcohol solution containing 0.1% 8-MOP is applied to the skin of each subject. The 8-MOP photosensitizes the skin to UVA radiation, such that UVA radiation produces erythema instead of pigment darkening. Approximately 45 minutes after application of 8-MOP, each subject is irradiated with increasing doses of UVA radiation. Seventy-two hours post-irradiation, the skin is evaluated for erythema to determine a minimal phototoxic dose (MPD).

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

### 6.3.2 General Discussion of Endpoints

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

### 6.3.3 Study Design

These studies were designed in accordance with FDA's published comments regarding UVA protection. As stated in the 1998 TFM, until we propose a UVA protection test method, FDA

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

### 6.3.4 Efficacy Findings

Three studies were submitted to support a claim of effectiveness in protecting against UVA radiation. The three studies determined protection factors (PFA values) for formulation 539-009, 910.01 and 910.02) and then the study conducted according to the 8-MOP method (920.01).

#### 6.3.4.1 Study 910.01

This phase 3 study was conducted under the supervision of Dr. Robert Shanahan at the CPTC in Fairfield, NJ. The study began on September 31, 2000, and concluded on October 10, 2000. Thirty-two subjects enrolled in the study. Seventeen of the enrolled subjects were female, and fifteen were male. The subjects ranged in age from 18 to 65 years (average age 41.7 years) and had skin type II, III, or IV. A total of 30 evaluable subjects completed the study.

This study evaluates the effectiveness of formulation 539-009 in protecting against UVA radiation. In this study, the standard sunscreen was the JCIA 2 UVA Standard, with an expected PFA value of 3.75.

The principal investigator reports minor deviations for all subjects. Each subject had one of the test products and the UVA control product applied randomly to two sites rather than the protocol-specified randomized application of all 3 test products and the UVA control product to four sites. This resulted in only ten subjects being evaluated for each test formulation rather than required 20 subjects. Because the variation about the mean PFA values is relatively small, this reviewer does not consider the protocol deviation to have substantially affected the study results. Even though these deviations may decrease the accuracy of the PFA values, as discussed below, this review only evaluates the UVA studies to determine whether the formulations are effective (not the level of effectiveness).

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

**Table 14. PFA Values for Different Formulations Tested in Study . — 910.01**

Test Formulation	Mean PFA ± SD	Standard Mean PFA ± SD
539-009	19.53 ± 3.39	4.05 ± 0.59

The expected PFA of 3.75 falls within the 95% confidence interval of the PFA for the standard sunscreen in each trial. These results for the standard indicate that study results are valid. The mean PFA ± SD of formulation 539-009 is 19.53 ± 3.39.

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

The PFAs of all formulations greatly exceed two times the number of active ingredients. Thus, the sunscreens provide effective UVA protection in both women and men, and it is expected that the formulations will also be effective on children (over 6 months of age).

#### 6.3.4.2 Study . — 910.02

This phase 2 study was conducted under the supervision of Dr. Robert Shanahan at the CPTC in Fairfield, NJ. The study began on June 26, 2002, and concluded on July 26, 2002. Seventy evaluable subjects completed the study. Forty of the enrolled subjects were female, and thirty were male. The subjects ranged in age from 18 to 62 years (average age 34.7 years) and had skin type III or IV. Each subject was randomly assigned one test formulation and the standard sunscreen, such that each of seven test products was tested on 10 subjects.

This study was designed to evaluate the effectiveness of seven test formulations containing various combinations of active ingredients in formulation. 539-009. These are the same test formulations evaluated for UVB protection in Study .810.06. The JCIA 2 UVA standard sunscreen was evaluated concurrently.

**Table 15. Composition of Test Formulations in Study .910.02**

Test Formulation	10% Octocrylene	2% Avobenzone	2% Ecamsule			
607-76A	✓	✓				
607-12A	✓	✓				
607-20A	✓	✓	✓			
607-27A (539-009)	✓	✓	✓			
607-67A	✓		✓			

The principal investigator reports four deviations from the IRB-approved protocol:

- The MRD for subject 16/FRR was determined less than two hours after irradiation (rather than the required  $3 \pm 1$  hour post-irradiation).
- Evaluators differed on successive days for three subjects (2, 29, and 66).

This reviewer agrees with the principal investigator that these deviations do not interfere with the study results.

The expected PFA of 3.75 falls within the 95% confidence interval of the PFA for the standard sunscreen in each trial. These results for the standard indicate that study results are valid. The mean PFA  $\pm$  SD for each test product and concurrently run standard sunscreen are presented in the table below.

Table 16. PFA Values for Different Formulations Tested in Study — .910.02

Test Formulation	Mean PFA ± SD	Standard Mean PFA ± SD
607-76A	12.85 ± 3.02	3.96 ± 0.55
607-12A	8.25 ± 2.13	4.57 ± 0.96
607-20A	12.05 ± 2.84	4.45 ± 0.86
607-27A (539-009)	15.84 ± 3.34	4.34 ± 0.71
607-67A	6.75 ± 0.96	3.86 ± 0.49

This study demonstrates that the — formulations provide effective protection against UVA radiation. The formulations produced PFA values ranging from 15.84 (539-009) —

In addition, this study demonstrates the effectiveness of each active ingredient contained in formulation — 539-009 — For example, comparing the PFA value for formulation 607-27A — with the PFA value for formulation 607-20A shows that 2% ecamsule provides a PFA value of 3. Comparing formulation 607-20A with formulation 607-12A demonstrates that 2% avobenzone contributes a PFA value of 4 to the PFA of the formulation — Likewise, comparing formulation — with

This study does not provide information about the possible contribution of 10% octocrylene to the formulation PFA values. Octocrylene would not be expected to provide protection against UVA radiation because the ingredient absorbs light almost exclusively in the UVB region of the spectrum.

6.3.4.3 Study — 920.01

This phase 3 study was conducted under the supervision of Dr. Alan H. Greenspan at TKL Research Inc. in Paramus, NJ. The study began on September 27, 2000, and concluded on October 12, 2000. A total of 14 subjects enrolled in the study. Twelve of the subjects were female, and two were male. The age range of the subjects was 35 to 65 years (average age 46.5 years), and subjects had skin type II or III. Ten subjects were evaluable for formulation — Eleven subjects were evaluable for formulation 539-009. Twelve subjects were evaluable for formulation — The number of subjects included in this study is considerably lower than the number of subjects included in the studies by Lowe et al. (Ref. 1) and Gange et al. (Ref. 2).

This study evaluates the effectiveness of formulation. — 539-009 — in protecting against UVA radiation using the 8-MOP method (Refs. 1 and 2). No standard sunscreen preparation was utilized. Effectiveness was measured against untreated (control) sites.

The principal investigator reports nine minor deviations from the IRB-approved protocol. Four subjects had different evaluators assess MPDs on different test days. Four subjects took exclusionary medications (approved by the sponsor). One subject was inadvertently exposed to slightly higher doses of UVA radiation than others in his test group. This reviewer concurs with the principal investigator that these deviations are not likely to affect the study results.

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

**Table 17. PFA Values for Different Formulations Tested in Study — 920.01**

Test Formulation	Mean PFA $\pm$ SD
539-009	27.65 $\pm$ 10.91

In the absence of a concomitantly run standard, it is not possible to validate these results. Furthermore, the numbers of subjects tested with each formulation is low compared with the numbers enrolled in the two reference studies. Because of the low enrollment, the standard deviation values are high (greater than 25% of the mean values). The PFA values calculated using the 8-MOP method in this study are consistently higher than but comparable to the PFA values calculated using the PPD method (Study — 910.01). The mean PFA value for formulation — is higher than the mean PFA values of formulations — 539-009, and the mean PFA values for formulations — 539-009 are very similar.

Even though there is substantial variation about the mean PFA values calculated in this study, the PFA values are clearly greater than two times the number of active ingredients in each formulation. Thus, this study supports the effectiveness of the — formulations in protecting against UVA radiation.

### 6.3.5 Clinical Microbiology

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

### 6.3.6 Efficacy Conclusions

A total of three clinical studies were conducted to demonstrate that formulation — 539-009, — effectively protect against UVA radiation. Two studies were conducted using the PPD method (Studies — 910.01 and — 910.02). This method is comparable to the MRD method previously cited by FDA as acceptable (63 FR 56584 at 56587). The other study was conducted using the 8-MOP method, which is comparable to the FDA-accepted methods of Lowe et al. (Ref. 1) and Gange et al. (Ref. 2). In all three studies, UVA protection is defined by a PFA value, which is analogous to an SPF value for UVB protection. The — formulations appear to be effective in providing protection against UVA radiation.

**Table 18. Mean PFA Values for Each Sunscreen Formulation**

Study	539-009 (NDA 21-502)
.910.01	19.53
.910.02	15.84
.920.01	27.65

A total of 110 evaluable subjects participated in the three clinical studies. PFA values are comparable in the PPD ( — 910.01 and — 910.02) and 8-MOP studies ( — 920.01). The submitted data support the claim that each of these sunscreen formulations protects against UVA radiation. Formulation — seems to provide the greatest amount of protection, with mean PFA values ranging from — . Formulations — 539-009 also seem to be effective, with mean PFA values greater than — 15, respectively.

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

general UVA protection claim of “broad spectrum” does not specify which active ingredients are contributing to UVA protection effectiveness.

The PFAs of all — formulations greatly exceeded two times the number of active ingredients. Thus, the sunscreens provide effective UVA protection in both women and men, and it is expected that the formulations will also be effective on children (over 6 months of age).

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

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

Stating a UVA rating such as PFA on a sunscreen label is likely to lead to consumer confusion. First, it is a new term that U.S. consumers are not familiar with and would only appear on the product label of the — formulations in these NDAs. Second, FDA may propose different UVA testing and labeling under the monograph. It would be detrimental to the public health to have different UVA rating systems in the United States.

## 6.4 Indication

### 6.4.1 Methods

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

### 6.4.2 General Discussion of Endpoints

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

### 6.4.3 Study Design

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

### 6.4.4 Efficacy Findings

#### 6.4.4.1 Study S01-0205

This in vitro study was conducted under the supervision of Dr. Robert Shanahan at the CPTC in Fairfield, NJ. The study began on April 10, 2001, and concluded on April 11, 2001.

Critical wavelengths for each of the — test formulations are presented in the table below.

**Table 21. Mean Critical Wavelengths for Different Formulations Tested in Study S01-0205**

Test Formulation	Mean Critical Wavelength (nm)
539-009	378

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

#### 6.4.4.2 Study D20041030

This in vitro study was conducted by Mlle Marjorie Boudet at the L'Oreal Laboratory in Chevilly-Larue, France. The study involved the same formulations included in studies — 810.06 and — 910.02.

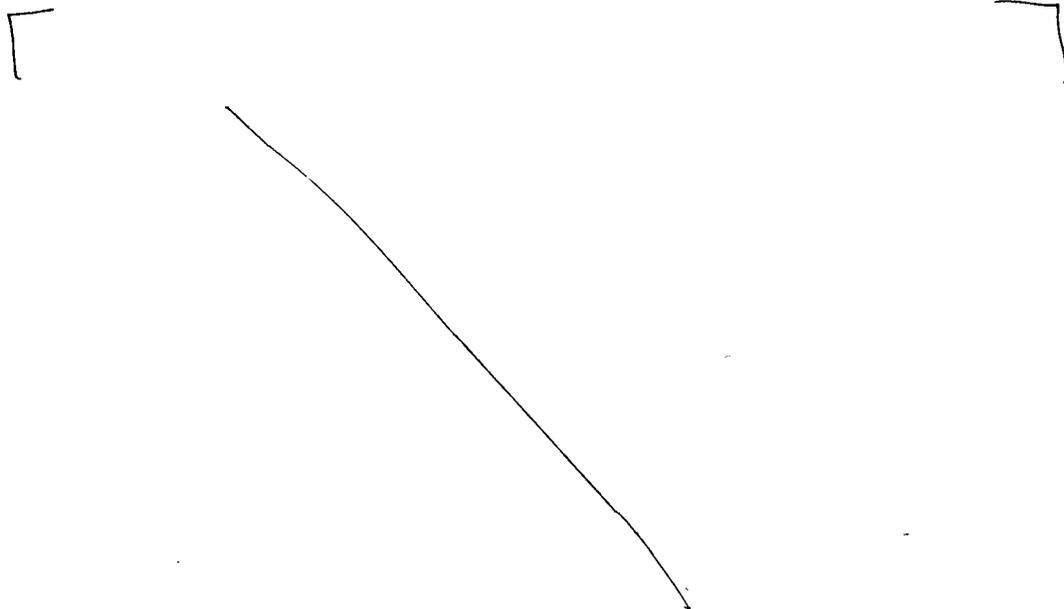
Critical wavelengths for each of the — test formulations that are the subject of this review are presented in the table below.

**Table 21. Mean Critical Wavelengths for NDA Formulations Tested in Study D20041030**

Test Formulation	Mean Critical Wavelength (nm)
607-27A (539-009)	380

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

6.4.4.3 Study



## 7 INTEGRATED REVIEW OF SAFETY

The safety of the — formulations is being evaluated separately by reviewers in the Office of Nonprescription Products and the Division of Dermatological and Dental Drug Products.

## 8 ADDITIONAL CLINICAL ISSUES

### 8.1 Dosing Regimen and Administration

The proposed dosing directions for the SPF 15 sunscreen lotion are as follows:

- apply evenly \_\_\_\_\_ before sun exposure \_\_\_\_\_
- children under 6 months of age: ask a doctor

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

### 8.2 Drug-Drug Interactions

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

### 8.3 Special Populations

There are no special populations related to effectiveness. Special populations related to safety are discussed as part of the safety review conducted by other reviewers in the Office of Nonprescription Products and Division of Dermatological and Dental Drug Products.

Clinical Efficacy Review

Michael L. Koenig

NDA 21-502: SPF 15 sunscreen lotion

#### 8.4 Pediatrics

These formulations are effective for children older than 6 months of age. This is consistent with the OTC sunscreen drug monograph (21 CFR part 352). The safety of the formulations for children is pending evaluation by reviewers in the Office of Nonprescription Products and Division of Dermatological and Dental Drug Products.

#### 8.5 Advisory Committee Meeting

No advisory committee meeting is necessary to evaluate effectiveness of the — formulations.

#### 8.6 Literature Review

A literature review was conducted as part of the safety review by Daiva Shetty, M.D., in the Office of Nonprescription Products.

#### 8.7 Postmarketing Risk Management Plan

The need for a postmarketing risk management plan is pending safety evaluation by other reviewers in the Office of Nonprescription Products and Division of Dermatological and Dental Drug Products.

#### 8.8 Other Relevant Materials

There are no other relevant materials submitted for review.

### 9 OVERALL ASSESSMENT

#### 9.1 Conclusions

The effectiveness of the — sunscreen formulations containing ecamsule in combination with other GRASE sunscreen active ingredients is acceptable for OTC marketing. The formulations provide effective protection against UVB and UVA radiation. ☐

Clinical Efficacy Review

Michael L. Koenig

NDA 21-502: SPF 15 sunscreen lotion

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## 9.2 Recommendation on Regulatory Action

Based on effectiveness, the following sunscreens should be approved for over-the-counter (OTC) use for prevention of \_\_\_\_\_ induced by UVB and UVA radiation:

- SPF 15 sunscreen lotion

Final approvability depends on the outcome of the preclinical and clinical safety and chemistry studies being evaluated by other reviewers.

## 9.3 Recommendation on Postmarketing Actions

### 9.3.1 Risk Management Activity

This review only considers the effectiveness of the \_\_\_\_\_ formulations in NDA \_\_\_\_\_, 21-502, \_\_\_\_\_. Therefore, this section is not applicable.

### 9.3.2 Required Phase 4 Commitments

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

### 9.3.3 Other Phase 4 Requests

None.

## 9.4 Labeling Review

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

## 9.5 Comments to Applicant

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

## 10 APPENDICES

No appendices are included.

Clinical Efficacy Review

Michael L. Koenig

NDA 21-502: SPF 15 sunscreen lotion

---

## REFERENCES

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

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/s/

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Michael Koenig  
1/6/2006 02:29:54 PM  
INTERDISCIPLINARY

Matthew has reviewed and OKed edits

Charles Ganley  
1/9/2006 08:14:10 AM  
MEDICAL OFFICER

## CLINICAL REVIEW

Application Type NDA  
Submission Number \_\_\_\_\_ 21-502 (IND 59,126)  
Submission Code N 000

Letter Date [ \_\_\_\_\_ ]  
May 12, 2005 (NDA 21-502)

Stamp Date  
PDUFA Goal Date [ \_\_\_\_\_ ]  
March 12, 2006 (NDA 21-502)

Reviewer Name Daiva Shetty, MD  
Review Completion Date January 6, 2006

Established Names [ \_\_\_\_\_ ]  
Ecamsule 2%/avobenzone2%/  
octocrylene 10% (NDA 21-502)

(Proposed) Trade Name Several  
Therapeutic Class Sunscreen  
Applicant L'Oreal USA Products, Inc.

Priority Designation S

Formulation  
Dosing Regimen [ \_\_\_\_\_ ]

For NDA 21-502: Apply evenly \_\_\_\_\_  
before sun exposure \_\_\_\_\_

Indication Prevention of sunburn \_\_\_\_\_  
due to sun exposure \_\_\_\_\_

Intended Population Children 6 months and older and  
adults

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## 1 EXECUTIVE SUMMARY

### 1.1 Recommendation on Regulatory Action

The proposed [ ] SPF 15 lotion (Avobenzone 2%+Octocrylene 10%+Ecamsule (Mexoryl®) 2%) have an acceptable safety profile. They are approvable for over-the-counter (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.

### 1.2 Recommendation on Postmarketing Actions

#### 1.2.1 Risk Management Activity

No special postmarketing risk management activities are recommended.

#### 1.2.2 Required Phase 4 Commitments

If these NDAs are approved, a controlled study in pregnant women should be conducted to evaluate the relationship between sunscreen exposure during pregnancy and vascular skin abnormalities in babies.

#### 1.2.3 Other Phase 4 Requests

None.

### 1.3 Summary of Clinical Findings

#### 1.3.1 Brief Overview of Clinical Program

L'Oreal is seeking approval to market [ ] new combination sunscreen drug products, [ ] SPF 15 lotion (NDA 21-502), in the OTC setting for daily use in adults and children six months of age and older.

[ ] products contain three active ingredients [ ] Two out of three (octocrylene and avobenzone) are sunscreen ingredients already marketed in the US under the Tentative Final Monograph for Sunscreen Drug Products for OTC Human Use. The third ingredient, ecamsule, is a new molecular entity in the US, even though it has been marketed in Europe, and other parts of the world since 1993.

In support of their submission, the sponsor has submitted data from a total of 28 clinical studies. Since the clinical data to support the marketing of the products are the same, the NDAs are reviewed together.

### 1.3.2 Efficacy

The sponsor is seeking to market the sunscreen drug products for the prevention of sunburn.

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

- Seven sun protection factor (SPF) determination studies
- Two protection factor for UVA (PFA) determination studies (one by the persistent pigment darkening PPD method and one by a similar method but using the photosensitizer 8-MOP)

All of these studies are being reviewed by other reviewers in the Office of Nonprescription Products and Division of Dermatological and Dental Drug Products. Only safety findings from these studies pertinent to the sunscreen drug products will be discussed in this review.

### 1.3.3 Safety

A total of 2539 subjects were exposed at least once to an ecamsule-containing sunscreen product during the development phase of these sunscreens.

There were no drug-related deaths or drug-related serious adverse events reported among the participants in clinical trials.

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.

Clinical studies that contributed to the safety database were classified into three groups:

- Phase 1,2, and 3 clinical studies
- Long-term safety studies
- Supportive studies

Of the 1155 subjects in the Phase 1, 2, and 3 clinical 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 1048 subjects were exposed to one of the ecamsule-containing sunscreen drug products during long-term safety studies (573 in studies and 475 in a study). Drug-related adverse events reported during the three long-term 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 3 long-term studies, except for 750.01 where a higher number of acne events were reported. This increased incidence could be partly related to a higher number of adolescents enrolled. The following AEs were the most common (incidence of  $\geq 1\%$  in individual studies) treatment-related AEs in the three long-term studies: acne, dermatitis, dry skin, eczema, erythema, pruritus, skin discomfort, and sunburn.

Long-term study has been reviewed in detail under the According to the clinical reviewer, except for sunburn, adverse events which were considered to be possibly related to the study products were of low incidence and minor severity.

Seven reports of erythema/edema were considered probably related and four reports of papules possibly related in supportive studies. A total number of subjects in these studies were 336.

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 15 lotion are:

- apply evenly before sun exposure
- 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 formulations. The sponsor states that ecamsule and its combination formulations are poorly absorbed ( $<1\%$ ) when topically applied to the skin; 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

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

Based on the preclinical pharmacology data, ecamsule is a Pregnancy Category B drug. The proposed labeling does not carry any pregnancy warning. Eleven pregnant women were exposed to ecamsule-containing drug products during clinical development program, and three of them delivered babies with vascular congenital defects. In the opinion of this reviewer, the product labeling should alert pregnant or nursing women to consult a physician prior to the use of these sunscreens. The sponsor should also conduct a post-marketing controlled study in pregnant women to evaluate the relationship between the sunscreen exposure during pregnancy and vascular skin abnormalities in their babies.

## 2 INTRODUCTION AND BACKGROUND

This is a medical safety review of — sunscreen combination drug products, submitted under — NDA number — 21-502. Since the clinical data to support the marketing of — the products are the same, the — NDAs will be reviewed together.

### 2.1 Product Information

☐  
☐  
☐  
☐  
NDA 21-502 is for the — SPF 15 lotion. — SPF 15 lotion is a topical combination sunscreen composed of the following three active sunscreen ingredients:

- Avobenzone 2%
- Octocrylene 10%
- Ecamsule (Mexoryl®) 2%

For the purposes of this review, — SPF 15 lotion will be also referred as SPF 15 or as its formulation code 539-009.

The sponsor is requesting to market this formulation under — different brand names:

[ ANTHELIOS ]  
[ ]  
[ ]

The sponsor is proposing to market — the combination sunscreen products in the OTC setting for daily use in children six months of age and older and in adults in accordance with all requirements of the existing OTC sunscreen product regulations, 21 CFR Part 352.

### 2.2 Currently Available Treatment for Indications

There are a total of 16 active sunscreen ingredients currently available for the prevention of sunburn to US consumers. All of them are marketed under the Tentative Final Monograph (TFM) for Sunscreen Drug Products for OTC Human Use. [ ] are marketed in the US under the TFM as single ingredients or in combination with others.

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

As mentioned above, two out of three active ingredients contained in the [ ] 15 lotion are available in the US. The third ingredient, ecamsule, is new to the US market.

### 2.4 Important Issues With Pharmacologically Related Products

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

### 2.5 Presubmission Regulatory Activity

In addition to the — products under current review [ ]

## 2.6 Other Relevant Background Information

Ecamsule was included in the European Economic Community (EEC) Cosmetic Directory, Annex VII, "List of UV Filters Which Cosmetic Products May Contain" in 1991 and commercialization of ecamsule-containing sunscreen products began throughout Europe and other parts of the world in 1993. Over \_\_\_\_\_ units of sunscreen products containing ecamsule have been sold worldwide. Sunscreen products are considered cosmetics in all other countries with the exception of Canada and Australia. Ecamsule was registered with the Canadian Health Protection Bureau in 1994 and the Australian Health Authorities in 1995.

## 3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

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

CMC review is pending.

### 3.2 Animal Pharmacology/Toxicology

The sponsor conducted a total of 87 animal and toxicology studies under the \_\_\_\_\_ cream development program. Neither ecamsule, nor \_\_\_\_\_ cream was teratogenic, carcinogenic, or photocarcinogenic. There was no embryolethality or reproductive toxicity associated with ecamsule alone or with 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

Clinical data to support the proposed drug products come from:

- 22 studies designed to evaluate safety and efficacy of various \_\_\_\_\_ sunscreen products containing ecamsule,
- 12 studies conducted under the \_\_\_\_\_ and \_\_\_\_\_
- several supportive studies that contributed to safety data.

There are — related formulations for which the sponsor is submitting NDAs for the indication of prevention of sunburn:

- —
- — SPF 15 Daily Lotion (NDA 21-502), and
- —

Safety data supporting the — OTC sunscreen products reviewed in this document come from clinical studies conducted with the — formulations listed above and with —

— A comparison between the — related formulations is presented in Table 1 below.

**Table 1. Comparative Active Sunscreen Ingredients in Different Formulations**

Active Ingredients	—	SPF 15 (539-009) NDA 21-502	—	—
Ecamsule	—	2.0%	—	—
Avobenzone	—	2.0%	—	—
Octocrylene	—	10.0%	—	—

#### 4.2 Tables of Clinical Studies

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### 4.3 Review Strategy

This review covers safety data submitted to support the NDA 21-502. Efficacy data, dermal tolerance studies, and studies to support cosmetic claims for the products will be reviewed by the reviewers in the Division of Dermatologic and Dental Drug Products (DDDDP) and the interdisciplinary scientist in the Office of Nonprescription Products (ONP).

### 4.4 Data Quality and Integrity

Even though ecamsule is a new molecular entity, it has been marketed for more than a decade in Europe and other countries. During the review, there were no discrepancies noted either in data or its analyses. Therefore, there were no DSI audits conducted for the study sites or data analyses.

### 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 and/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 15 cosmetic studies were not run according to GCP standards with a study product not manufactured according to Good Manufacturing Practices. These studies were performed in Europe on cosmetic sunscreens and were not included in the Integrated Summary of Safety Analysis.

### 4.6 Financial Disclosures

The sponsor submitted Form 3454 certifying that the investigators of all but three clinical studies did not have any significant financial interests in these products, conducted studies, or the company conducting the studies. Three of the studies for which certification was not provided, were previously reviewed under NDA 21-502. None of these studies are pivotal for the evaluation of efficacy or safety of the sunscreen products submitted under NDA 21-502.

## 5 CLINICAL PHARMACOLOGY

The sponsor submitted a total of six clinical studies and seven pharmacokinetic studies (four in vitro studies and three in vivo studies) to assess pharmacology of the sunscreen drug products. The clinical studies include the following:

- three dermal tolerance studies (one contact sensitization, 110.01, one photoallergy, 210.01, one phototoxicity, 250.01)

- three Phase 2 OTC Sunscreen Monograph Drug Combination Policy Rule studies (two SPF, — 810.05 & — .810.06, and one PFA. — 910.02)

All of the studies submitted under this section are being reviewed by other reviewers in DDDDP and ONP. Clinical safety findings from these studies pertinent to the — sunscreen drug products being reviewed are discussed in Section 7 of this review.

### 5.1 Pharmacokinetics

Three in vivo ☐ — ☐

☐ and four in vitro (☐ — ☐)

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 these NDAs.

### 5.3 Exposure-Response Relationships

There are no data on exposure-response relationships submitted to these NDAs.

## 6 INTEGRATED REVIEW OF EFFICACY

The sponsor is seeking to market — sunscreen drug products for the prevention of sunburn.

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

- Seven sun protection factor (SPF) determination studies ☐ — ☐
- Two protection factor for UVA (PFA) determination studies (one by the persistent pigment darkening PPD method and one by a similar method but using the photosensitizer 8-MOP)

All of these studies are being reviewed by other reviewers in ONP and DDDDP. Only safety findings from these studies pertinent to — sunscreen drug products will be discussed in the next section of this review.

## 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

For the purposes of this review, clinical studies to support safety are classified into three groups:

1. Phase 1, 2, and 3 clinical studies:

- |          |          |
|----------|----------|
| • 110.01 | • 810.06 |
| • 210.01 | • 910.02 |
| • 250.01 | • 810.01 |
| • _____  | • 810.02 |
| • _____  | • 820.01 |
| • _____  | • 820.02 |
| • _____  | • 910.01 |
| • _____  | • 920.01 |
| • _____  |          |
| • 810.05 |          |

2. Phase 3 long-term safety studies:

- 750.01
- 750.02
- 750.03
- \_\_\_\_\_

3. Other supportive studies:

- 1570.01
- \_\_\_\_\_
- 1010.01
- \_\_\_\_\_
- \_\_\_\_\_

The first group of studies will be reviewed in detail by other reviewers. The safety data gathered during those studies are included in this review. The second group of studies includes three long-term safety studies (750.01, 750.02, and 750.03) and one safety study. Safety results gathered during these four studies will be reviewed together. Details of the three long-term studies are discussed in the Appendices 10.1.1 through 10.1.3 of this review. For detailed review of the long-term safety study

### 7.1.1 Deaths

There were no deaths in the Phase 1, 2, and 3 clinical studies or the supportive cream studies.

In the four long-term safety studies, there was one death (intentional injury) reported in Study 750.01, which was unrelated to study medication.

### 7.1.2 Other Serious Adverse Events (SAE)

There were no serious adverse events in the Phase 1, 2, and 3 clinical studies or supportive studies.

There were 32 subjects with serious adverse events among the four long-term safety studies. All SAEs were considered unrelated to study medication.

There was one SAE in the Cream study, 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

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

Completion rates were high in the Phase 1, 2, and 3 clinical studies. Overall, 1155 subjects were enrolled and 1094 (94.7%) completed the studies. Sixty-two (5.5%) subjects discontinued. The most frequent reason for discontinuation in these studies was protocol violation (18 subjects, 1.8%), followed by subject request (16 subjects, 1.4%).

Summary of subject disposition in Phase 1, 2, and 3 clinical studies is listed in Table 3 below.

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**Table 3. Summary of Subject Disposition in Phase 1, 2, & 3 Clinical Studies**

Study #	Enroll	Complete	Discontinuation Reason					
			AE	Protocol violation	Non-medical	Lost to f/u	Subject request	Other
<b>Phase 1 Local Tolerance Studies</b>								
110.01	223	217	0	0	5	1	0	0
210.01	137	107	1	18	0	0	11	0
250.01	26	26	0	0	0	0	0	0
	225	210	7	0	0	0	2	6
	30	30	0	0	0	0	0	0
	118	112	4	0	0	0	2	0
<b>Phase 1 Pharmacokinetic Studies</b>								
	6	6	0	0	0	0	0	0
	5	5	0	0	0	0	0	0
	8	7	1	0	0	0	0	0
<b>Phase 2 Combination Policy Studies</b>								
810.05	50	49	0	0	0	0	0	1*
810.06	100	99	0	0	0	0	1	0
910.02	70	70	0	0	0	0	0	0
<b>Phase 3 UVA/UVB Protection Studies</b>								
810.01	21	21	0	0	0	0	0	1
810.02	20	20	0	0	0	0	0	0
	21	21	0	0	0	0	0	0
	25	24	0	0	0	0	0	1**
910.01	32	32	0	0	0	0	0	0
920.01	14	14	0	0	0	0	0	0
	24	24	0	0	0	0	0	0
<b>Total</b>	<b>1155</b>	<b>1094</b>	<b>13</b>	<b>18</b>	<b>5</b>	<b>1</b>	<b>16</b>	<b>9</b>

\* Used exclusionary medication; \*\* Failure to complete Day 2 visit

Discontinuation due to adverse events in these studies was 1.1% (13 subjects). One subject in the Phase 1 local tolerance studies (Study — 210.01) withdrew due to an AE. Subject 116 was discontinued from the study — 210.01 due to a severe sinus infection that began on November 11, 2000 and required exclusionary concomitant medication. The sinus infection resolved on November 13, 2000.

One subject in PK study — withdrew from the study due to a joint disorder that was considered mild and unrelated to treatment.

In the [ ] Cream study [ ] there were four subjects who discontinued due to adverse events (one with mild cold, one with mild asthenia, one with severe pharyngitis, and one with moderate tendonitis). The investigator considered all adverse events non-serious and unrelated to study treatment. All adverse events resolved.

Seven of 225 subjects in Study [ ] discontinued due to adverse events. Six events were assessed as unrelated to study treatment. One mild general pruritus event was assessed as possibly related to study treatment.

**Phase 3 Long-Term Studies**

Subject disposition in four long-term safety studies is summarized in Table 4.

**Table 4. Subject Disposition in Long-Term Safety Studies**

Status	Number (%) of Subjects			
	.750.01 Daily Use (N=248)	750.02		750.03 (N=475)
		Intermittent Use (N=246)		
Subjects enrolled	248 (100%)	246 (100%)	80 (100%)	475 (100%)
Subjects completed	205 (82.66%)	180 (73.17%)	67 (83.80%)	278 (58.5%)
Subjects discontinued	43 (17.34%)	66 (26.83%)	13 (16.25%)	197 (41.5%)
Adverse events	4 ( 9.30%)	3 ( 4.55%)	0 ( 0.00%)	12 ( 2.5%)
Subject request	16 (37.21%)	24 (36.36%)	3 (23.08%)	117 (24.6%)
Protocol violation	4 ( 9.30%)	1 ( 1.52%)	0 ( 0.00%)	4 ( 0.8%)
Lost to follow-up	18 (41.86%)	18 (27.27%)	9 (69.23%)	40 ( 8.4%)
Other	1 ( 2.33%)	20 (30.30%)	1 ( 7.69%)	21 ( 4.4%)
Subjects in Safety Population	248 (100%)	246 (100%)	79 (98.75%)	475 (100%)

Completion rates in — long-term studies ranged from 73% to 84% of subjects. Discontinuation rates ranged from 16% to 27%. The most frequent reasons for discontinuation were subject request and lost to follow-up. The incidence of discontinuation due to adverse events in the — studies was less than 10% in each study. Higher overall discontinuation rate (42%) was seen in study —, however, discontinuation due to adverse events was low (2.5%) during this study.

There were 19 (6%) discontinuations due to AEs across the three studies, four in — .750.01, three in — 750.02, and 12 in — Table 5 summarizes these subjects.

**Table 5. Summary of Subjects Who Discontinued due to AEs in Long-Term Studies**

Study #	Subject #	Age/ Gender	Event	Relationship	Outcome
—750.01	6-12	13/F	Intentional injury	Unrelated	Death
	8-33	58/F	Arthritis	Unlikely	Ongoing
	10-12	60/F	Erythema and hives (3 days)	Probably	Resolved
	10-34	58/F	Facial itching (1 day)	Probably	Resolved
— 750.02	12-10	4/M	Rash (3 days)	Definitely	Resolved
	16-04	8/M	Rash (2 days)	Definitely	Resolved
	16-05	5/M	Rash (2 days)	Definitely	Resolved
—	157	13/F	Photosensitivity	Possibly	Resolved
	251	43/F	Abnormal liver function tests	Unlikely	Ongoing
	314	38/F	Acne	Possibly	Resolved
	367	52/F	Increased serum creatinine	Unlikely	Resolved
	490	79/F	Pruritus	Possibly	Resolved
	497	61/F	Skin discomfort	Probably	Resolved
	515	49/F	Photosensitivity	Unlikely	Resolved
	573	58/F	Pruritus	Probably	Ongoing
	757	34/F	Miliaria	Possibly	Resolved
	759	62/F	Colon Cancer	Unlikely	Resolved
	784	59/F	Nosocomial infection	Unlikely	Resolved
	806	12/F	Urticaria	Unlikely	Resolved

## Other Supportive Studies

Completion rates were high in both types of supportive studies, cream (Table 6).

**Table 6. Summary of Subject Disposition in Other Supportive Studies**

Study #	Enroll	Complete	Discontinuation Reason					
			AE	Protocol Violation	Non-Medical	Lost-to-f/u	Subject Request	Other
<b>Cosmetic Support Studies</b>								
570.01	44	40	0	0	0	0	0	4
570.02	30	26	0	0	0	0	4	0
1010.01	32	32	0	0	0	0	0	0
<b>Other Formulations Containing Ecamsule Cream Studies</b>								
	144	140	4	0	0	0	0	0
	86	79	6	1	0	0	0	1
<b>Total</b>	<b>336</b>	<b>317</b>	<b>10</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>4</b>	<b>5</b>

No subjects in the supportive studies (570.01, 570.02 or 1010.01) discontinued due to adverse events.

Ten subjects discontinued due to adverse events in the two Cream supportive studies in subjects with F. The events were as follows: sunburn, accidental injury, arthritis, dyspnea, and chest pain. All adverse events were assessed as unlikely related to study treatment.

## 7.1.3.1 Overall profile of dropouts

The majority of discontinuations were not related to adverse events.

## 7.1.3.2 Adverse events associated with dropouts

A total of 31 subjects in clinical studies discontinued due to adverse events. 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 resolved.

## 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 drug-related events associated with sunscreen use include the following reactions:<sup>1</sup>

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

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

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

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

Subject were encouraged to come to the study site any time they experienced a severe adverse drug 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.

#### 7.1.5.3 Incidence of common adverse events

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

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<sup>1</sup> 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

## 7.1.5.4 Common adverse event tables

Tables 7 through 11 display AEs reported during clinical studies.

**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)
<b>Phase 1 Local Tolerance Studies</b>				
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
210.01	137	5	4	Headache, sinus infection, backache
250.01	26	0	0	--
	225	66	53	Flu syndrome, pharyngitis, cold (coryza), headache, sore throat, tooth disorders, GI events, general pruritus, itchiness around eyes, 3 reactions to — tape*
	30	0	0	--
	118	4	4	Pharyngitis, asthenia, cold, tendonitis
<b>Phase 1 Pharmacokinetic Studies</b>				
	6	18	6	Dizziness, headache, pruritus, eczema, infected skin
	5	6	3	Toothache, myalgia, right shoulder pain, abdominal cramps, nausea
	8	1	1	Joint disorder
<b>Phase 2 Combination Policy Studies</b>				
810.05	50	1	1	Sore throat
810.06	100	1	1	Headache
910.02	70	0	0	--
<b>Phase 3 UVA/UVB Protection Studies</b>				
810.01	21	0	0	--
810.02	20	0	0	--
820.01	21	0	0	--
820.02	25	0	0	--
910.01	32	0	0	--
920.01	14	3	3	Headache, sore throat
99001.01COS	24	0	0	--
<b>Total</b>	<b>1155</b>	<b>125</b>	<b>86</b>	

\* — tape is a part of an adhesive patch used for the application of test drugs in sensitization studies

**Table 8. Study — 750.01: Summary of AEs that Occurred in >1% of Subjects (N=248)**

Body System	Preferred Term	All AEs N (%)	TRAEs* N (%)
<b>Total</b>		<b>145 (58.5)</b>	<b>39 (15.7)</b>
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

\* TRAE: treatment related adverse event

**Table 9. Study — .750.02: Summary of AEs that Occurred in >1% of Subjects (N=246)**

Body System	Preferred Term	All AEs N (%)	TRAEs* N (%)
<b>Total</b>		<b>167 (67.9)</b>	<b>18 (7.3)</b>
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 System	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

\* TRAE: treatment related adverse events

**Table 10. Study — 750.03: Summary of AEs that Occurred in >1% of Subjects (N=79)**

Body System	Preferred Term	All AEs N (%)	TRAEs N (%)
<b>Total</b>		<b>55 (69.6)</b>	<b>3 (3.8)</b>
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

**Table 11. Summary of AEs in Supportive Studies**

Study No.	N	AEs	Subjects with AEs	Types of AEs (cases)
570.01	44	0	0	--
570.02	30	13	7	Erythema/edema, erythema, papules, ankle sprain, head cold
010.01	32	0	0	--
<b>Total</b>	<b>106</b>	<b>13</b>	<b>7</b>	

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

A total of seven adverse events (skin infection, pruritus and eczema) probably or possibly related to treatment were reported in Phase 1, 2, and 3 clinical trials (see Table 7, section 7.1.5.4). All events were assessed as mild and non-serious.

Drug-related adverse events reported during the three long-term clinical safety 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 3 long-term safety studies except for 750.01 where a higher incidence of acne was reported. This increased incidence may be related to a higher number of adolescents enrolled.

Long-term study was reviewed in detail under The reviewer stated that adverse events possibly related to the study products were of low incidence and minor severity, with the exception of sunburn.

Seven reports of erythema/edema were considered probably related and four reports of papules possibly related to the use of study drug in supportive studies.

#### 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 were 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 for the potential OTC sunscreen products, subject of the NDAs.

Laboratory evaluations were performed in Study Cream, 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 (the Phase 3, open-label study) in subjects with , routine laboratory tests (hematology, serum chemistry and urinalysis) were performed at screening, Month 6 and Month 12 or at study discontinuation.

Overall, 58 (12.2%) patients had 77 laboratory AEs. The most prevalent abnormalities were hyperlipidemia including hypertriglyceridemia (12 patients, 2.5%) and hypercholesterolemia (9 patients, 1.9%). No fasting conditions were required by the protocol, explaining some of the variation observed during the study. Two patients (# 251 and 367) discontinued due to an increase in liver function tests (which were present at screening) and elevated creatinine. 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

#### 7.1.8 Vital Signs

There were no vital sign monitoring in the 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 are being 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 \_\_\_\_\_ formulas or similar formulations. One woman (Subject #60) in Study \_\_\_\_\_ 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 \_\_\_\_\_ 750.02 and \_\_\_\_\_). There were no pregnancies reported during any other studies.

Four women became pregnant in Study \_\_\_\_\_ 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 Study \_\_\_\_\_. Of the six women who reported pregnancy, three discontinued because of their pregnancy. Two of the six pregnancies resulted in delivery of normal healthy babies. One infant developed a café au lait spot 1 to 2 weeks after birth. Since isolated café au lait spots occur in up to 10-20% of the normal population, the sponsor considered the event of no pathological significance. 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). For the two cases of hemangioma, the events were considered possibly related to study treatment; the case of nevus flammeus was considered of unlikely relationship to study treatment.

According to the pharmacology review, ecamsule is a Pregnancy Category B drug. Following are the conclusions from the pharmacology review:

*“Embryofetal toxicity studies have been conducted in rats with oral doses of ecamsule of up to 300 mg/kg (2 times the maximum human dose based on a body surface area comparison) and with topical application in rabbits with doses of up to 600 mg/kg (8 times the maximum human dose based on a body surface area comparison) and have revealed no evidence of harm to the fetus.*

*A pre- and postnatal developmental study has been conducted in rats with oral doses of ecamsule of up to 1000 mg/kg (6.5 times the maximum human dose based on a body surface area comparison) and has revealed no effects on the reproductive parameters in F0 females and no effects on the physical or behavioral development of the F1 generation. The F1 generation also had normal reproductive function after reaching sexual maturity.*

*There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.*

*Ecamsule did not reveal any potential to impair fertility or to induce embryo-fetal abnormalities. Development of off-spring was not affected by treatment with high doses of ecamsule."*

*Comments:*

*Based on the preclinical data, ecamsule is not a teratogen and does not have an effect on reproductive function in animals. We do not have data for the other two monograph active ingredients (avobenzone and octocrylene), which are not contraindicated during pregnancy. In addition, percutaneous absorption study [ ] did not reveal percutaneous penetration of ecamsule in most subjects when tested under maximized conditions. However, the number of women exposed to the sunscreen formulations containing ecamsule is small. Three congenital vascular adverse events occurred in subjects with [ ] could have occurred by chance alone. Nevertheless, the exposure to drug product could be significant if used as directed. Therefore, in the opinion of this reviewer, the product labeling should carry a pregnancy warning as specified in the 21 CFR 201.63 (a): "If pregnant or breast-feeding, ask a healthcare professional before use." The sponsor should also conduct a Phase 4 controlled study in pregnant women to evaluate the relationship between the sunscreen exposure during pregnancy and vascular skin abnormalities in their babies.*

#### 7.1.15 Assessment of Effect on Growth

There were no assessments of effects 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. No reports of overdosage have been reported in any of the clinical studies.

#### 7.1.17 Postmarketing Experience

Postmarketing safety data for ecamsule-containing products comes from two sources:

- L'Oreal Cosmetovigilance, and
- Literature

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

#### L'Oreal Postmarketing Pharmacovigilance/Cosmetovigilance Data Review

The original [ ] NDA 21-502 submissions covered cosmetovigilance safety information from 1993 through 2002. On September 13, 2005 the sponsor submitted the 120 day safety update, where safety data from the same postmarketing system was updated for the additional one year, between 2002 and the end of 2003. The sponsor did not analyze this updated information separately; rather it was discussed in a context of all 11 years together.

Therefore, all the postmarketing information (original and updated) will be discussed together in this section of the review.

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 2003, more than \_\_\_\_\_ of active \_\_\_\_\_ ecamsule or \_\_\_\_\_ metric tons of the 33% solution have been produced by the L'Oreal subsidiary, CHIMEX, S.A. for commercial use. Approximately \_\_\_\_\_ units of ecamsule containing products (including beach sunscreen products, daily-use moisturizers with sunscreens and makeup products) have been sold in 15 countries where the cosmetovigilance system is in place.

For all reported spontaneous adverse reactions, a conservative estimate of 55 adverse events per \_\_\_\_\_ units sold of all ecamsule-containing product formulations has been reported during 11 years of marketing through 2003, an overall adverse event incidence of 0.0055% (derived from a total of 20,484 spontaneous adverse events reported during the same time period and \_\_\_\_\_ units sold). The incidence of adverse reports is relatively stable over time. A summary of incidence of AEs by year reported in the cosmetovigilance system for ecamsule containing products is presented in Table 12 below.

**Table 12. Summary of Incidence of AEs by Year Reported in the Cosmetovigilance System for Ecamsule Containing Products**

Years	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
%	0.011	0.0042	0.002	0.0029	0.004	0.0067	0.0048	0.0056	0.0095	0.0078	0.0045

In the database, there have been a total of 3444 spontaneous adverse event reports in children reported through 2003. The database defines children as individuals 16 years of age and younger. Over a ten year period, the incidence of adverse events among children is 0.0148% with 148 adverse events per \_\_\_\_\_ units sold. It is assumed that most reactions occurred while using children's products.

Summary of incidence of adverse events associated with use of ecamsule-containing products for children and all subjects presented in Table 13.

**Table 13. Summary of Incidence of AEs Associated with Use of Ecamsule-Containing Products for Children and for all Subjects**

Adverse Event Term	Incidence of all AEs per units sold 1993-2003*	Incidence of children's AEs per units sold 1993-2003**	Frequency of AEs as % of all reported AEs in adults through 2003	Frequency of AEs among children as % of all children's AEs through 2003
	Number of AEs and % of units sold for each subgroup		Number of AEs as % of all AEs in each subgroup	
All adverse events	55 (0.0055)	148 (0.148)	100%	100%
Erythema	11.8 (0.0012)	39.9 (0.0040)	21.5	27.0
Dermatitis	10.6 (0.0011)	37.1 (0.0037)	19.2	25.1
Skin Discomfort	8.0 (0.00080)	10.4 (0.0010)	14.5	7.00
Pruritus	6.6 (0.00066)	19.6 (0.0020)	12.1	13.2
Edema Skin	4.7 (0.00047)	17.1 (0.0017)	8.40	11.6
Irritation	3.6 (0.00036)	4.9 (0.00049)	6.50	3.30
Dry Skin	2.0 (0.00020)	4.5 (0.00045)	3.60	3.00
Desquamation	1.3 (0.00013)	1.2 (0.00012)	2.30	0.84
Eczema	1.4 (0.00014)	2.6 (0.00026)	2.50	1.70
Allergic Local Reaction	1.0 (0.00010)	1.1 (0.00011)	1.80	0.75
Conjunctivitis	0.90 (0.00009)	0.73 (0.00007)	1.60	0.49
Photosensitivity	0.62 (0.00006)	0.56 (0.00006)	1.10	0.38
Lacrimation Disorder	0.54 (0.00005)	0.64 (0.00006)	0.97	0.44
Skin Burn	0.57 (0.00006)	1.7 (0.00017)	1.00	1.10
Sunburn	0.36 (0.00004)	1.4 (0.00014)	0.65	0.93
Urticaria	0.32 (0.00003)	2.3 (0.00023)	0.58	1.60
Skin Discoloration	0.20 (0.00002)	0.38 (0.00004)	0.37	0.26
Acne	0.18 (0.00002)	0.04 (0.000004)	0.32	0.03
Edema Conjunctival	0.16 (0.00002)	0.94 (0.00009)	0.28	0.64

**Comments:**

*There are several deficiencies in the L'Oreal cosmetovigilance database. The causality of the AEs in relation to the drug/cosmetic product was not assessed. The estimate of the incidence or frequency of AEs in pediatric/adolescent population is flawed. Denominator to assess the incidence in pediatric population, chosen by the sponsor, is the number of adolescent products sold. It is not known if only adolescent products were used by children. Also we don't know if adolescent products were used by adults. Therefore, the sponsor's estimate of the incidence of AEs in children based on the total number of adolescent products sold may not be accurate.*

Since the cosmetovigilance system was designed for postmarketing surveillance of cosmetic products, the criteria of serious adverse events have not been entered into the database. For the purpose of this NDA, a retrospective search was conducted by the sponsor to look for potentially serious cases. A total of six serious adverse events were discovered. Brief description of those events is presented below:

- One spontaneous report was considered serious (anaphylactic reaction) by the reporting physician and a causal relationship cannot be ruled out. A 43-year woman in Singapore experienced an anaphylactic reaction (puffy eyelids, tightness of chest and throat) 15

minutes after her first application of [redacted] Cream, containing ecamsule, avobenzone, [redacted]

[redacted] No concomitant treatment was given, and the reaction resolved within 2 hours.

- Case #11548. A 12 year old female developed redness and edema 12 hours after using the ecamsule-containing product. The subject was hospitalized for 2 days and treated with a topical steroid. No patch testing was done but a relationship to ecamsule cannot be ruled out.
- Case #17718. A 7 year old child, with a history of asthma, experienced breathing difficulties and swelling of the face and eyes four hours after applying the product. The child was treated with a nebulizer and antihistamines and was detained for 5 hours in the hospital. A dermatologist was consulted and suggested the reaction may have been to the nuts she ate for lunch. Given the multifactorial nature of her medical history and the timing of the reaction, a causal role of the sunscreens is unlikely but cannot be ruled out.
- Subject # 17614- [redacted] experienced an urticarial reaction two days after using an ecamsule-containing sunscreen. She was hospitalized and treated with antihistamines and steroids. A relationship to use of the ecamsule-containing sunscreen is possible.
- Case # 17846- [redacted] An 8 year old child applied an ecamsule-containing sunscreen in the morning at 8:30 and by 3:00 pm developed a swollen face and eyes and a rash over the entire body. The child was hospitalized 24 hours and treated with steroids. The child had a history of eczema and had used the product one year earlier without reaction. A relationship is possible given the timing of the reaction, but a specific ingredient cannot be incriminated due to the absence of patch testing.
- Case #19642- [redacted] A 5 year old female used [redacted] for the first time and developed swollen eyes, sore throat, and a raised rash involving her torso, arms and bottom. The child was taken to a doctor who prescribed penicillin and Piriton. On the evening of the same day, she experienced generalized swelling, including her tonsils. The subject was taken to the hospital and treated with penicillin, Piriton, and steroids. Five days later [redacted] was again applied to the child's body and the child's eyes again became swollen. The sponsor assessed a relationship to the ecamsule-containing sunscreen as unlikely, and related the symptoms to infectious strep throat. In the opinion of this reviewer, a relationship to the ecamsule-containing sunscreen is still probable.

The incidence of AEs associated with the use of ecamsule-containing drug products [redacted] units sold) is similar to that of avobenzone, the UV filter most recently recognized/proposed as safe and effective for use in an OTC Drug Product (sunscreens). The incidence of adverse events reported for avobenzone in the Federal Register Notice was 0.0067% of units sold (or 67 adverse events [redacted] units sold). This was based on [redacted] units sold over a three year period.

*Comment:*

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.

## 7.2 Adequacy of Patient Exposure and Safety Assessments

### 7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

A total of 2539 subjects were exposed at least once to an ecamsule-containing sunscreen product during the development phase of these sunscreens.

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

A list of all clinical studies to support safety is presented in Table 14 below.

**Table 14. List of Studies to Support Safety**

	Study #	Study Type	# of subjects
Phase 1 Local Tolerance Studies	110.01	Repeat insult patch	223
	210.01	Photoallergy	137
	250.01	Phototoxicity	26
		Contact sensitization and irritancy	225
		Phototoxicity	30
		Photoallergy	118
Phase 1 Pharmacokinetic Studies		Maximized exposure PK	6
		Dermal absorption	5
		Urinary excretion after repeat application	8
Phase 2 Combination Policy Studies	810.05	SPF	50
	810.06	SPF	100
	910.02	UVA	70
Phase 3 UVA/AVB Protection Studies	810.01	SPF	21
	810.02	SPF	20
		SPF	21
		SPF	25
	910.01	UVA	32
	920.01	UVA	14
		SPF	24
Phase 3 Long-Term Studies	750.01	12 Months Clinical Safety	248
	750.02	12 Months Clinical Safety	246
	750.03	12 Months Clinical Safety	79
		Clinical safety in PLME	475
Other Supportive Studies	570.01	Acnegenicity/comedogenicity	44
		Comedogenicity	30
	1010.01	Moisturization	32
Other Formulations Containing Ecamsule		Efficacy/Safety	144
		Efficacy/Safety	86

Studies evaluating safety of the [redacted] have been previously evaluated by the reviewers in HFD-540. Therefore, studies with [redacted] are not being discussed in detail in this review.

### 7.2.1.2 Demographics

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

Subject demographics and baseline characteristics across the Phase 1, 2, and 3 clinical studies were similar (Table 15). 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 15. Demographic and Baseline Characteristics of Subjects in Phase 1, 2, & 3 Clinical Studies**

	N	Mean Age	Gender	Race	Major Skin Type
<b>Phase 1 Local Tolerance Studies</b>					
110.01	223	48 (18-91)	74% female	82% Caucasian	31% type III
210.01	137	43 (16-68)	77% female	93% Caucasian	58% type III
250.01	26	40 (18-63)	85% female	81% Caucasian	73% type III
[redacted]	225	43 (16-85)	68% female	100% Caucasian	52% type III
[redacted]	30	28 (18-53)	73% female	100% Caucasian	70% type II
[redacted]	118	33 (18-62)	64% female	100% Caucasian	66% type II
<b>Phase 1 Pharmacokinetic Studies</b>					
[redacted]	6	37 (23-55)	100% male	100% Caucasian	83% type III
[redacted]	5	22 (19-29)	100% male	Not specified	Not done
[redacted]	8	26 (19-41)	100% male	100% Caucasian	Not done
<b>Phase 2 Combination Policy Studies</b>					
.810.05	50	36 (18-65)	68% female	96% Caucasian	72% type II
.810.06	100	37 (18-63)	66% female	99% Caucasian	57% type II
.910.02	70	35 (18-62)	57% female	77% Hispanic	50% type III&IV
<b>Phase 3 UVA/AVB Protection Studies</b>					
.810.01	21	43 (26-58)	95% female	100% Caucasian	XX% type III
.810.02	20	38 (18-52)	56% female	100% Caucasian	96% type III
[redacted]	21	43 (26-58)	95% female	100% Caucasian	71% type III
[redacted]	25	38 (18-52)	56% female	100% Caucasian	56% type III
.910.01	32	42 (18-65)	53% female	66% Caucasian	63% type III
.920.01	14	47 (35-65)	86% female	100% Caucasian	79% type III
[redacted]	24	33 (19-47)	75% female	100% Caucasian	46% type III

## 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 —.750.03 and 100 children between 6 months and 12 years of age in —.750.02. Only 64 children were included in the safety population in —.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 —.750.02.

—.750.02 was conducted on the — SPF 15 lotion formula —. The demographic and baseline characteristics for subjects in the long-term safety studies are presented in Table 16 below.

Table 16. Demographics and Baseline Characteristics for Subjects in the Long-Term Safety Studies

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

Subjects enrolled into the — studies were younger than subjects enrolled into Study — ( — ). Women outnumbered men in all studies. Nearly twice as many women compared with men were enrolled in the — studies — 750.01 and —.750.03. Slightly more women than men were enrolled in —.750.02 (59% women and

41% men), and in Study [redacted], 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

#### 7.2.1.2.3 Other Supportive Studies

The majority of subjects who enrolled in the supportive studies were Caucasian females with a mean age of about 40 years. The baseline and demographic characteristics of subjects in both the [redacted] and the [redacted] Cream studies were similar (Table 17).

**Table 17. Demographic and Baseline Characteristics of Subjects in Other Supportive Studies**

Study	N	Age Mean (range)	Gender	Race	Major Skin Type
<b>Penipro Cosmetic Claim Support Studies</b>					
570.01	44	(18-40)*	45% female	80% Caucasian	30% type III
[redacted]	30	42 (20-59)	93% female	97% Caucasian	Not done
1010.01	32	41 (20-59)	66% female	84% Caucasian	Not done
<b>Other Formulations Containing Ecamsule [redacted] Cream Studies)</b>					
[redacted]	144	40 (18-73)	82% female	98% Caucasian	50% type II
[redacted]	86	41 (18-65)	92% female	100% Caucasian	41% type II

\* Mean age not provided in the report

#### 7.2.1.3 Extent of exposure (dose/duration)

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

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

[redacted] Extent of exposure data is summarized in Table 18 below.

**Table 18. Extent of Exposure for Subjects in Phase 1, 2, & 3 Clinical Studies**

Study Number	N	Amount of Application	Length of Exposure
<b>Phase 1 Local Tolerance Studies</b>			
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)
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
250.01	26	0.2 mL to each of 8 sites under occlusive conditions	Single exposure; 24 hours
	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
	30	50 µL of product	24 hours
	118	50 µL of product	Twice daily for 3 weeks + 1 single dose
<b>Phase 1 Pharmacokinetic Studies</b>			
	6	15 g applied twice daily 9 days	18 whole body applications
	5	0.2 g ([ <sup>14</sup> C]-ecamsule, 2%) 100 cm <sup>2</sup> area	4 hours on volar forearm
	8	10 g, 4.95% ecamsule	5 consecutive days
<b>Phase 2 Combination Policy Studies</b>			
810.05	50	100 mg	Single exposure; 22-24 hours
810.06	100	100 mg	Single exposure; 22-24 hours
910.02	70	70 mg	Single exposure; 3 hours
<b>Phase 3 UVA/UVB Protection Studies</b>			
810.01	21	120 mg	Single exposure; 22-24 hours
810.02	20	100 mg	Single exposure; 22-24 hours
	21	120 mg	Single exposure; 22-24 hours
	25	100 mg	Single exposure; 22-24 hours
910.01	32	70 mg	Single exposure; 22-24 hours
920.01	14	100 mg	Single exposure; 72 hours
	24	100 mg	Single exposure; 22-24 hours

*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 Table 19.

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**Table 19. Summary of Treatment Duration, Study Drug Use and Product Application in the Long-Term Safety Studies**

		750.01 N=248	750.02 N=246	750.03 N=79	Study N=475
<b>Treatment Duration (days)</b>	N	248	246	79	475
	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
<b>Total Usage (g)</b>	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
<b>Daily Usage (g/day)</b>	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
<b>Product Application (total number)</b>	N	239	237	75	453
	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
<b>Daily Application (number/day)</b>	N	239	237	73	453
	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 750.01 (570.6 grams) followed by study 750.02 (301.3 grams), 750.02 (256.6 grams) and 750.03 (143 grams). Daily usage in grams was highest for studies 750.02 and 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).

*Comment:*

*The reasons why the usage of sunscreen was so different in these long-term studies, could be explained by differences in directions for use. In study 750.01, subjects were instructed to apply the lotion to the face, neck, and arms daily. In studies 750.02 and 750.03, subjects were instructed to apply the product to all sun-exposed areas and to reapply as needed during extended outdoor usage.*

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 (Table 20).

**Table 20. Treatment Duration for Different Age Groups (three 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 (N=104)	247.67	145.40	344.0	1-371
18 to ≤ 65 years (N=200)	250.24	142.51	346.0	1-376
> 65 years (N=26)	308.31	117.58	360.5	2-372

In study — 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 — .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.

#### 7.2.1.3.3 Other Supportive Studies

A wide range of exposure times and applications were observed in the supportive studies. Table 21 summarizes data on extent of exposure in the five supportive studies.

**Table 21. Extent of Exposure for Subjects in the Other Supportive Studies**

Study Number	N	Amount of Application	Length of Exposure
<b>Cosmetic Claim Support Studies</b>			
570.01	44	Entire face (excluding lips and eye area), twice daily	6 weeks
570.02	33	0.3 mL/300mg topically to sites 3cm x 3cm (total 12 applications)	4 weeks, 48-72 hours each application
.1010.01	32	80 mg on volar forearm	Single exposure; 24 hours
<b>Other Formulations Containing Ecamsule — Cream Studies)</b>			
	144	Median 7g (range 5-11)	To whole body for 6 days
	86	Median 8-9g (range 6.7-12)	To whole body for 6 days

## 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, does not reveal any serious safety signals for ecamsule-containing drug products. Data supports the safety of these products for over-the-counter marketing.

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

Adequacy of preclinical data is being assessed by pharmtox reviewers. Refer to discipline-specific reviews.

### 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. Studies to support the contribution of each ingredient to the efficacy of the products are being reviewed by the interdisciplinary scientist in the Office of Nonprescription Products.

### 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

From a clinical safety perspective, a study in pregnant women is recommended (see section 7.1.14 of this review).

The need for studies in children below 6 months of age will be addressed by the Division of Pediatric Development.

### 7.2.8 Assessment of Quality and Completeness of Data

From a clinical safety perspective, this application is adequate for approval but not complete.

### 7.2.9 Additional Submissions, Including Safety Update

A four-month safety update was submitted by the sponsor as required by 21 CFR 314.50 (d)(5)(vi)(b). The sponsor states that there were no new animal, non-clinical or clinical studies initiated or completed with the three-active ingredients in — formulations after submission of [ ] NDA 21-502 on May 16, 2005. There was no additional information in the literature on adverse reactions to ecamsule since reporting date of [ ]. Therefore, the safety update included only global cosmetovigilance data on formulas containing the new chemical entity, ecamsule. Since the sponsor did not analyze this updated safety information separately, it was incorporated into the postmarketing experience section of the review (see Section 7.1.17).

### **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 2539 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 formulations and 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 \_\_\_\_\_ and one \_\_\_\_\_ 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. Since drug-related adverse events were limited to skin, only dermatological AEs are discussed in this part of the review.

###### **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**

Table 22 below provides a comparison of related dermatological adverse events for subjects in all four long-term studies combined and by treatment duration.

**Table 22. 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)

With a few exceptions (acne, photosensitivity and sunburn), most subjects reported treatment-related dermatological AEs during the first 360 days of treatment. Acne and photosensitivity were reported more often by subjects treated for a longer time intervals.

#### 7.4.2.3 Explorations for drug-demographic interactions

No formal drug-demographic interaction studies have been performed on any of the formulas. Across the four long-term clinical studies used in support of safety, skin phototypes (Type I – Type VI), age (6 months to no upper limit), race, gender, and sensitive versus non-sensitive type subgroups have been represented. Subjects with AEs in each subgroup were summarized by numbers and percentages in each individual clinical study report. The sponsor did not provide combined data drug-demographics interactions for all four long term studies. Therefore, table 23 summarizes treatment related adverse events in the long-term studies by demographics.

**Table 23. Treatment Related AEs by Demographics in the Long-Term Studies**

Demographic Subgroup		Drug Related AEs	
		Dermatological	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 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.

The sponsor submitted pediatric adverse events spontaneously reported to the L'Oreal Cosmetovigilance System following use of sunscreens containing any sunscreen ingredients (octocrylene, Mexoryl SX, avobenzone,  $\square$   $\text{---}$   $\square$ ). There were a total of 386 adverse event reports in children aged 1 to 16 years between 1996, when the products were first marketed, and 2004. Distribution of AEs by age is as follows:

- 81% of the children were 7 years-old or younger
- 15% of the children were older than 7 years
- 4% were unidentified

The number of reports per year is as follows:

1996	-	1
1997	-	9
1998	-	11
1999	-	35
2000	-	40
2001	-	61
2002	-	49
2003	-	78
2004	-	102

Despite some fluctuations there is a trend towards a gradual increase in the number of reactions that the sponsor associates with an increase in use of sunscreen products during this time.

In the majority of cases, reactions occurred within several hours after first application, and the majority resolved in less than 3 days. No permanent sequelae were reported. All of the reactions were limited to the sunscreen application site. The predominant manifestation was erythema (74% of cases), followed by papules (49%), edema (32%), dryness (8%), "eczema" (6%), urticaria-like lesions (2%). These manifestations were accompanied by pruritus in 35% and by "burning sensation" in 6% of cases.

*Comments:*

*From the available clinical and post-marketing data, it does not appear that pediatric patients are more likely to develop cutaneous adverse reactions than adults. There were no unusual adverse events noted in children exposed to the sunscreen products containing ecamsule.*

## 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 with no histories of allergy to product ingredients or active severe systemic cutaneous allergic conditions such as dermatitis, eczema, or psoriasis.

— sunscreen products should be applied only to healthy skin. However, sometimes it may be administered inadvertently to individuals with abnormal skin conditions. This situation is exemplified by one study, 1 — 750.03, where a 14-month-old boy with a history of eczema, was enrolled and developed a “flare-up” of eczema on the back of his neck while in the study. Upon application of the sunscreen product, the eczema worsened. The event was considered mild and possibly related to study medication. Following treatment with topical hydrocortisone, the event resolved. The sunscreen was not re-applied to the neck area but was used on other parts of his body. No further sequelae were observed.

— studies. — enrolled subjects with a demonstrated history of —. When not undergoing a flare-up, these subjects were considered to have “normal” skin. The adverse events reported by subjects in these studies did not indicate a new, emergent pattern of adverse events unique to individuals with —. The presence of — in the subject population did not change the safety profile of the study treatments in these predisposed subjects.

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

**Table 24. Treatment Related AEs in the Three — Long-Term Studies by Predisposing Conditions**

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

*Comment:*

*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. Labeling should also carry a warning to use caution when applying the sunscreen on damaged skin.*

#### 7.4.2.5 Explorations for drug-drug interactions

No formal drug-drug interaction studies have been conducted with — formulations. 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. None of the clinical studies conducted to support the two combination sunscreen drug products had a control group.

### 8 ADDITIONAL CLINICAL ISSUES

#### 8.1 Dosing Regimen and Administration



The proposed dosing directions for — 15 lotion are:

- apply evenly — before sun exposure —
- children under 6 months of age: ask a doctor

Both of the proposed dosing directions are consistent with the TFM for Sunscreen Drug Products for OTC Human Use.

#### 8.2 Drug-Drug Interactions

No formal drug-drug interaction studies have been conducted with — formulations. 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

These products are 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. As discussed in section 7.4.2.4 of this review, the labeling for the products should carry a warning to use caution when applying the sunscreen on damaged skin.

## 8.4 Pediatrics

The sponsor is requesting to market both of the combination sunscreen products in the OTC setting for daily use in children six months of age and older and in adults.

During the end-of-phase 2 meeting, FDA asked the sponsor to include children six months and older in the study — 750.02, and recommended that at least 50% of the subjects be below 12 years of age. In addition, FDA recommended including children ages 6 months to 12 years in both studies — 750.01. As an alternative to the pediatric — Only 64 children were included in the safety population in — 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 — 750.02.

Safety of the — sunscreen lotions in pediatric populations has been discussed in section 7.4.2.3 of this review. A total of 243 children 6 months to 12 years old participated in the — long term use clinical trials. There were no children under 12 years old included in the daily use study. — 750.01. Of 79 subjects in intermittent use study. — 750.03, 64 children 6 months to 12 years of age (81% of all subjects, 55 pediatrics completed the study) were included in the safety population. Additionally, in intermittent use study, — 750.02, 179 children 6 months to 12 years of age (73% of all subjects) were enrolled and 69% (124/179) of these children completed the study. While — 750.02 was conducted on a different — formula — than the — formulations being reviewed (see section 4.1, Table 1), it contained a higher concentration of the new chemical entity, ecamsule, than did 539-009 used for — 750.03.

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.

It is unclear whether safety or efficacy data are needed for these new sunscreen products in children below 6 months of age. Clinical practice guidelines published by the American Academy of Pediatrics (AAP)<sup>2</sup> do not recommend using sunscreens in children less than 6 months of age for the following reasons:

1. Since children of this age are not mobile and cannot remove themselves from uncomfortable light and heat, they should be kept out of direct sunlight, in a shade.
2. Many infants have impaired functional sweating. Exposure to the heat of the sun may increase the risk of heatstroke.
3. Sunburn may occur readily because an infant's skin has less melanin than at any other time in life.
4. Concerns are raised that human skin under 6 months may have different absorptive characteristics; biologic system systems that metabolize and excrete drugs may not be fully developed.

<sup>2</sup> American Academy of Pediatrics. Ultraviolet Light: A Hazard to Children. *Pediatr* 1999;104(2): 328-333

AAP further states that, it may be reasonable to apply sunscreen to small areas, such as face and the back of the hands when infant's skin is not protected adequately by clothing.

In the opinion of this reviewer, the — sunscreen lotions should be labeled as requested by the sponsor for the use in children six months and older. The need for pediatric studies will be also addressed by the Division of Pediatric Development.

### 8.5 Advisory Committee Meeting

There is no advisory committee meeting planned for these — NDAs.

### 8.6 Literature Review

The sponsor conducted a scientific literature search on all three active sunscreen ingredients:

- for ecamsule, up to 2004
- for octocrylene, from 1999 (TFM publication) to 2004, and
- for avobenzone, from 1995 up to 2004

The following databases were used for the search: 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. Only articles, where safety of these three sunscreen ingredients is discussed, are summarized below.

#### Ecamsule

No major side effects associated with the use of ecamsule-containing sunscreens have been identified by the sponsor in the scientific literature. Two articles (References 1 & 2) reported studies evaluating photosensitivity of different drug and cosmetic products and other environmental allergens. Ecamsule-containing cosmetic sunscreens were tested and were found to be photosensitizing photoallergens.

#### Octocrylene

One article (Reference 3) reported two cases of photoallergic dermatitis associated with the use of products containing octocrylene.

#### Avobenzone

A total of seven articles (References 4 through 10) reported photoallergies and one article (Reference 11) reported allergic contact dermatitis associated with use of sunscreen products containing avobenzone.

#### *Comments:*

*Photoallergic reactions to sunscreens are well known and documented in medical literature. These reactions are rare and most often related to the individual sensitivity of the subject. Many individuals, who reported photoallergic reactions after sunscreen use, had contact or photo allergies to several other medications or cosmetic products. Potential for irritation, contact*

*sensitization, phototoxicity or photosensitization will be addressed by the reviewer in the Division of Dermatological and Dental Drug Products.*

### **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 ecamsule-containing sunscreen ingredient in combination with other three monograph sunscreen ingredients is acceptable for OTC marketing.

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

SPF 15 lotion (Avobenzone 2%+Octocrylene 10%+Ecamsule (Mexoryl®) 2%) have an acceptable safety profile, and therefore, are 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**

If these NDAs are approved, a controlled study in pregnant women should be conducted to evaluate the relationship between the sunscreen exposure during pregnancy and vascular skin abnormalities in babies.

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

None.

### 9.4 Labeling Review

The proposed labeling for \_\_\_\_\_ sunscreen products is presented below. 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.

The sponsor should incorporate a warning to use caution when applying the sunscreen on damaged skin.

In addition to standard warnings, it is recommended to \_\_\_\_\_

Based on the safety data review, labeling should not carry cosmetic claims. Studies conducted to support the \_\_\_\_\_ are being reviewed by the reviewers in DDDDP. Final recommendations on the acceptability of those \_\_\_\_\_ claims will be provided by the reviewers in DDDDP.

#### 9.4.1 Labeling

2 Page(s) Withheld

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

✓ § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

## 10 APPENDICES

### 10.1 Review of Individual Study Reports

Sections 10.1.1 through 10.1.3 will present design and methods of the three long-term safety studies. Combined results of these studies have been discussed already earlier in the review.

#### 10.1.1 750.01. Clinical Safety Trial of “Daily-Use” Sunscreen (539-009) in Long-term Conditions

This was a multicenter (six centers), open-label, uncontrolled safety trial of product usage. Two hundred forty-eight (248) healthy volunteers were enrolled in the study. All 248 subjects were treated at least once with the study drug and are included in these analyses (Safety Population). The total study duration was 12 months, during which the subjects experienced periods of sun exposure.

Subjects who qualified for the study by meeting all of the inclusion/exclusion criteria were enrolled in the study and given Sunscreen (539-009) during the baseline visit. Also during this visit, concomitant therapy and medical history monitoring were conducted, as was a thorough dermatological examination of the face, neck, and hands. The subjects applied Sunscreen (539-009) to their face, neck, and hands at least once each morning after washing or cleansing. Subjects could use the sunscreen more than once daily on their face, neck, and hands, at their discretion, for periods of sun exposure. Subjects were encouraged to re-apply when needed. Other sunscreens could also have been used on other body areas during periods of sun exposure if needed. Subjects were given a diary in which they recorded daily product usage and sun exposure. All subjects were required to attend follow-up visits at the study site at Months 1, 2, 4, 6, 8, 10 and 12 for dermatological examinations, questioning about adverse events and concomitant medications, and to complete a questionnaire on UV exposure, any changes in the esthetics of the product, and where it had been stored.

#### Inclusion Criteria

- Male or female subjects of any race or skin type, 12 years of age or older, willing to use the product on a daily basis for 12 months.
- Subjects (and/or guardians) who signed an informed consent.
- Subjects (and/or guardians) who were 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

- Subjects with a condition, or in a situation, which in the investigator’s or sub-investigator’s opinion, may have suggested a significant hazard for the subject, may have

confounded the study results, or may have interfered with the subject's participation in the study.

- Subjects with known sensitivities to any of the study preparations.
- Subjects who participated in a clinical research study, including consumer product studies, within the last 30 days prior to enrollment.

Each subject received both verbal and written instructions as to the proper dosing and study drug application techniques. The subjects were directed to apply the study drug to the whole face, neck and hands each morning. This was the minimum surface area that needed to be covered by the sunscreen at least once each day.

Application of the study drug to other parts of the body was possible. The application to other exposed skin areas, in particular the forearms and upper chest, was encouraged, particularly during summer months. The study drug could be used occasionally for sun protection during longer periods of sun exposure; however, other sunscreens (possibly with higher SPFs) could have been utilized for this purpose. The subject was to tell the investigator where the other sunscreens were applied and to record this information in the diary. The subject was to record all products that were used on the face, hands, and neck, including cosmetics or topical drugs.

Subjects received a 2-month supply of the study drug treatment (4 tubes) at each visit except the Month 1 visit. The investigator could dispense more tubes, on an individual basis, if deemed necessary. At each follow-up visit, the subjects returned all containers of the study drug in their possession and were then assessed by the site personnel for compliance with study drug application. The site personnel assessed the tubes as empty, partially used or unused. At follow-up visits, any unused tubes were returned to the subjects and any used or only partially used tubes were replaced with new, sequentially numbered tubes.

Study drug containers were collected and examined by designated site personnel at the 2-, 4-, 6-, 8-, 10- and 12-month study visits to document usage. Subjects were also questioned regarding study drug application technique and frequency of application. Subjects reported the study drug usage on a daily basis in the subject diary. All used tubes were returned following the 6- and 12-month visit and a weight was taken and recorded by the labeler,

**Study — 750.01: Flow Chart of Study Procedures**

Procedures	Month							
	Baseline Visit 1	1 Visit 2	2 Visit 3	4 Visit 4	6 Visit 5	8 Visit 6	10 Visit 7	12 Visit 8
Informed Consent	X							
Demographics	X							
Inclusion/Exclusion Criteria	X							
Medical History	X							
Dermatological Examination	X	X	X	X	X	X	X	X
Subject's Diary Dispensed	X	X	X	X	X	X	X	
Subject's Diary Collected		X	X	X	X	X	X	X
Questionnaire Completed	X		X	X	X	X	X	X
Medication Dispensed	X		X	X	X	X	X	
Medication Returned			X	X	X	X	X	X
Concomitant Therapy	X	X	X	X	X	X	X	X
Urine Pregnancy Test								X
Exit case Report Form								X
Adverse Events		X	X	X	X	X	X	X

If a subject discontinued prematurely, all Month 12 (Visit 8) procedures were to be performed at the subject's final visit.

At the request of the Agency, Protocol — 750.01 was extended to 12 months in duration. It was also designed to recruit approximately half of the subjects from sites in geographical locations with high sunlight exposure, such as Scottsdale, Arizona and Modesto and Santa Monica, California. As per the Agency's recommendation, this protocol was designed to incorporate the return and weighing of used product tubes at the conclusion of the study. In addition, a questionnaire was added to the Case Report Form to collect data from the subjects at 2-month intervals regarding product consistency/integrity (texture, color change, and odor) as well as storage conditions and additional questions on sun exposure. This study did not include children from 6 months to 12 years of age since it is unlikely that the product would be used by children under 12 years of age, due to the positioning of the product as a daily-use facial moisturizer cosmetic containing sunscreen.

Safety was measured by the occurrence of adverse events. At each visit, the investigator asked the subject an open question regarding their health and medical status since the last visit. The investigator reviewed the subject's diary for any information that may have indicated a change in status from baseline or any adverse events. Any time a subject experienced a severe adverse drug experience they were encouraged to come to the site, regardless of whether it was between regularly scheduled visits.

All demographic data, evaluations and other observations were recorded directly, promptly and legibly in black ink on the CRF. Completed CRFs were signed by the investigator. Data from the CRFs were captured in a software package that was customized for data entry and that maintained an electronic audit trail. All data was double entered except for comments.

All study statistics for the primary endpoints were to be descriptive. Approximately 250 subjects were to be enrolled in the study in order to obtain approximately 200 subjects with 12 months of product usage.

10.1.2 — 750.02. Clinical safety trial of long-term intermittent use of — sunscreen —

The objective of this study was to determine the long-term safety of — Sunscreen — in intermittent long-term use conditions in normal subjects, including children 6 months of age and older.

This was a multicenter, open-label, uncontrolled safety trial of product usage in normal subjects, including children 6 months of age and older.

No particular inclusion or exclusion criteria were applied to subjects to identify them as having sensitive skin. However, it was recorded in the CRF if the subject had self-assessed sensitive skin (i.e., in the subject's opinion), or if he/she had an atopic background (atopic dermatitis, allergic rhinitis or asthma in personal history) or previous intolerance problems to topical products, including cosmetics. The phototype (based on the Fitzpatrick scale — described in the monograph“) and the type of skin (oily, normal, dry and combination skin) was recorded at the baseline visit as well.

Inclusion Criteria:

- Male or female subjects of any race or skin type, 6 months of age or older, willing to use the product for 12 months. During the 12-month period, 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.
- Subjects (and/or guardians) who signed an informed consent.
- Subjects (and/or guardians) who were 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:

- Subjects with a condition, or in a situation, which in the investigator's or sub-investigator's opinion, may have suggested a significant hazard for the subject, may have confounded the study results, or may have interfered with the subject's participation in the study.
- Subjects with known sensitivities to any of the study preparations.

- Subjects who participated in a clinical research study, including consumer product studies, within the last 30 days prior to enrollment.

A subject could withdraw from the study at any time and for any reason. The reasons stated for withdrawal were documented in detail on the subject's CRF and on the Adverse Event form if need be. Participation in the study could have been discontinued:

- either at the investigator's request, for safety reasons (e.g., severe adverse reactions, or conditions that may have jeopardized the subject's health if they were to continue in the trial), or at the subject's request;
- for deviations or non-compliance with the requirements of the protocol;
- when a subject was lost to follow-up. The investigator was to attempt to reach the subject with two telephone calls and a certified or registered letter before considering the subject lost to follow-up. These actions were to be reported in the comment section of the Exit Form, and a copy of the follow-up letter was to be maintained in the investigator's file.

At the baseline visit, for demonstration purposes, the investigator or designee applied the first dose of study drug. The investigator or designee showed the subject how to use the product and directed the subject to apply wherever the sun could reach the skin during the anticipated sun exposure. Subjects also had written instructions that they could refer to. The study drug was to be applied as homogeneously as possible to all sun-exposed areas. In the case of small children, the parents/guardians applied the study drug. Make-up products such as lipsticks or foundations containing sunscreens were permitted as daily cosmetic products. During the study, the subjects recorded all topically used products that were applied to the area where the study drug was applied. Use of any product that contained sunscreen (make-up, foundation, cream, moisturizer, aftershave, etc.) was to be documented in the concomitant therapy form.

The study drug was to be reapplied, at the discretion of the subject, as needed during extended outdoor usage. The subjects were instructed to re-apply frequently, as needed.

Subjects received a 2-month supply of the study drug treatment (4 tubes) at each visit except the Month 1 visit. The investigator could dispense more tubes, on an individual basis, if deemed necessary. At each follow-up visit, the subjects returned all containers of the study drug in their possession. At the same time, subjects were also assessed for compliance by the site personnel. The site personnel assessed if the tubes were empty, partially used or unused. At follow-up visits, any unused tubes were returned to the subjects and any used or only partially used tubes were replaced with new, sequentially numbered tubes.

Study drug containers were collected and examined by designated site personnel at the 2-, 4-, 6-, 8-, 10-, 12-month study visits to document usage. All remaining materials were collected at the 12-month visit. Subjects were also questioned regarding test-material application technique and frequency of application. Subjects reported the product usage on a daily basis in the subject diary.

The following procedures were performed by designated, trained personnel on the corresponding visit day:

**Study — 750.02: Flow Chart of Study Procedures**

Procedures	Month							
	Baseline Visit 1	1 Visit 2	2 Visit 3	4 Visit 4	6 Visit 5	8 Visit 6	10 Visit 7	12 Visit 8
Informed Consent	X							
Demographics	X							
Inclusion/Exclusion Criteria	X							
Medical History	X							
Dermatological Examination	X	X	X	X	X	X	X	X
Subject's Diary Dispensed	X	X	X	X	X	X	X	
Subject's Diary Collected		X	X	X	X	X	X	X
Questionnaire Completed	X		X	X	X	X	X	X
Medication Dispensed	X		X	X	X	X	X	
Medication Returned			X	X	X	X	X	X
Concomitant Therapy	X	X	X	X	X	X	X	X
Urine Pregnancy Test								X
Exit case Report Form								X
Adverse Events		X	X	X	X	X	X	X

If a subject discontinued prematurely, all Month 12 (Visit 8) procedures were to be performed at the subject's final visit.

At Visit 1 (baseline), the investigator thoroughly examined the skin of each participant to collect information on interfering conditions, signs and symptoms, or skin abnormalities, especially on the areas where the study drug was to be applied. This information was recorded on the appropriate CRF. At each follow-up visit, the investigator examined all areas of the skin to which the subject had applied the study drug, specifically to look for cutaneous signs of irritation, sensitization, or photosensitivity.

Safety was measured by the occurrence of adverse events. At each visit, the investigator asked the subject an open question regarding their health and medical status since the last visit. The investigator reviewed the subject's diaries for any information that may have indicated a change in status from baseline or any adverse events. Any time subjects experienced a severe adverse drug experience, they were encouraged to come to the site, regardless of whether it was between regularly scheduled visits.

Adverse event was defined as any unfavorable and unintended sign, symptom, or disease temporary associated with the use of a drug.

The investigator assessed the relationship (causality) of an AE to the study drug according to the following definitions:

- **Definitely Related.** No uncertainty about the relationship between the event and test drug administration. The event follows a definite reasonable temporal sequence from the time of test drug administration and improves upon stopping the dose of the study drug. A re-challenge is positive. The event cannot be reasonably explained by the known characteristics of the subject's clinical state or by other modes of therapy administered to the subject. The event follows a known response pattern to the study drug.
- **Probably related.** High degree of certainty about the relationship between the event and test drug administration. The event follows a reasonable temporal sequence from the time of test drug administration and improves upon stopping the dose of the study drug. The event cannot be reasonably explained by the known characteristics of the subject's clinical state or by other modes of therapy administered to the subject.
- **Possibly related.** Unlikely but cannot rule out with certainty the relationship between the event and test drug administration. The event may follow a reasonable temporal sequence from the time of test drug administration. The event may have been produced by the subject's clinical state or by other modes of therapy concomitantly administered to the subject.
- **Unlikely related.** Clinical event has an unlikely relationship with the test drug administration. There is no reasonable temporal association between the study drug and the suspected event and the event could have been reasonably produced by the subject's clinical state or other modes of therapy administered to the subject.
- **Unrelated.** Clinical event is clearly not due to test drug administration. There is no reasonable temporal relationship between the test drug administration and the suspected event (e.g., event occurs before test drug administration) or no reasonable causality, such as in accidents which cannot be remotely related to study participation (injuries sustained in a car accident).

All study statistics for the primary endpoints were descriptive. Adverse drug experiences were described and tabulated. As this trial was open and non-comparative, only descriptive data presentations were made, and no formal statistical hypothesis was tested.

The Safety Population was defined as all subjects enrolled and treated at least once with study drug. The Safety Population was the primary population used for the analyses.

Demographic and baseline characteristics were summarized by descriptive statistics. For the continuous variable, age, the following descriptive statistics were provided: sample size (N), mean, standard deviation, minimum, lower quartile, median, upper quartile, and maximum. For categorical variables, sex, race, and skin phototype, counts and percentages were provided. Subject disposition was tabulated and reasons for discontinuation were summarized by counts and percentages.

Adverse events were coded against a modified COSTART dictionary of terms prior to any analyses and therefore, body systems and preferred terms were available for all AEs. All information pertaining to AEs noted during the study were listed by subject, detailing verbatim given by the investigator, the preferred term, the body system, start/stop dates, severity, and drug relatedness. The AE onset was also shown relative (in number of days) to the day of initial dose of the study drug.

For this study, the planned number of subjects (250) for treatment for up to 12 months at dosage levels intended for clinical use was thought to be adequate to characterize the pattern of AEs over time. The sample size for this study was established from the ICH E1 Guideline on the Extent of Population Exposure to Assess Clinical Safety." To achieve this objective the cohort of exposed subjects was to be 300-600 subjects for 6 months treatment and 100 subjects for a year. Therefore, this study was designed to enroll 250 subjects, taking into account an anticipated drop out rate of 25%.

#### 10.1.3 — .750.03. Clinical safety trial of long-term intermittent use of — sunscreen ( —

The objective of this study was to determine the long-term safety of — Sunscreen — in intermittent use conditions for up to 12 months in healthy subjects, including children 6 months of age and older.

This was a two-center, open label, uncontrolled safety trial of product usage. Eighty healthy subjects including children 6 months of age and older were to be enrolled in the study.

The study population was defined according to the following inclusion/exclusion criteria.

##### Inclusion Criteria:

- Male or female subjects of any race or skin type, 6 months of age or older, who were willing to use the product for 12 months. During the 12-month period, 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.
- Subjects (and/or guardians) who signed an informed consent.
- Subjects (and/or guardians) who were willing and capable of cooperating to the extent and degree required by the protocol, especially regarding compliance with the long-term dosing requirements.

##### Exclusion Criteria:

- Subjects with a condition, or in a situation, which in the investigator's or sub-investigator's opinion, may have suggested a significant hazard for the subject, may have confounded the study results, or may have interfered with the subject's participation in the study.
- Subjects with known sensitivities to any of the ingredients in the study preparations.

- Subjects who participated in a clinical research study, including consumer product studies, within the last 30 days prior to enrollment.

In addition to these criteria, it was recorded in the CRF if the subject had self-assessed sensitive skin (i.e., in the subject's opinion), and if he/she had an atopic background (atopic dermatitis, allergic rhinitis or asthma in personal history) or previous intolerance to topical products, including cosmetics. The skin phototype (based on the Fitzpatrick scale — ) and the type of skin (oily, normal, dry or combination skin) were recorded at the baseline visit as well.

Each subject received both verbal and written instructions as to the proper dosing and study drug application techniques. The subjects were directed to apply the study drug wherever the sun could reach the skin during the anticipated exposure. The study drug was to be applied as homogeneously as possible to all sun-exposed areas. In the case of small children, the parents/guardians applied the study drug. Make-up products such as lipsticks or foundations containing sunscreens were permitted as daily cosmetic products. During the study, the subjects recorded all topically used products that were applied to the area where the study drug was applied. Use of any product that contained sunscreen (make-up, creams, foundation, moisturizer, aftershave, etc.) was documented in the concomitant therapy form.

The study drug was to be reapplied, at the discretion of the subject, as needed during extended outdoor exposure. The subjects were instructed to re-apply as frequently as needed.

During the 12 months of the study, subjects were to plan for a significant sun-exposure period, such as a beach vacation or weekend outdoor activities with at least 14 sun-exposure days minimum, where the use of a sunscreen was required. Subjects were allowed to use the study drug on a daily basis on areas such as the face, neck, hands and forearms. Subjects were given a diary in which they recorded daily product usage and sun exposure.

Subjects received a 2-month supply of the study drug treatment (4 tubes) at each visit except the Month 1 visit. The investigator could dispense more tubes, on an individual basis, if deemed necessary. At each follow-up visit, the subjects returned all containers of the study drug in their possession and were assessed by the site personnel for compliance with the study drug application. The site personnel assessed if the tubes were empty, partially used or unused. At follow-up visits, any unused tubes were returned to the subjects and any used or only partially used tubes were replaced with new, sequentially numbered tubes.

All subjects received \_\_\_\_\_ Sunscreen \_\_\_\_\_

Neither the investigator nor subject was blinded in this study.

During the baseline visit, a medical history was obtained on each subject and included any pertinent previous and concomitant medications. These were recorded on the CRF. Any therapy used by the subject was considered concomitant therapy (e.g., aspirin, birth control pills, vitamins, moisturizers, etc.). Use of any sunscreen, including sunscreen in cosmetic products such as foundations or moisturizers, aside from the study drug, was recorded as a concomitant therapy. The use of these products was discouraged but was not considered a protocol deviation.

Non-medicated shampoos and soaps were not recorded in the CRF. Subjects were instructed to notify the investigator if there were any changes in the dosage of any concomitant therapy.

Study drug containers were collected and examined by designated site personnel at the 2, 4, 6, 8, 10, and 12-month study visits to document usage. Subjects were also questioned regarding study drug application technique and frequency of application. Additionally, subjects reported the product usage on a daily basis in the subject diary.

Upon receipt of the clinical supplies, the investigator (or other designated study personnel) conducted a complete inventory of all study drug materials and assumed responsibility for their storage and dispensing. In accordance with regulations, study drug materials were kept in a secure, locked location with restricted access.

The following procedures were performed during the course of the study:

**Study — 750.03: Flow Chart of Study Procedures**

Procedures	Month							
	Baseline Visit 1	1 Visit 2	2 Visit 3	4 Visit 4	6 Visit 5	8 Visit 6	10 Visit 7	12 Visit 8
Informed Consent	X							
Demographics	X							
Inclusion/Exclusion Criteria	X							
Medical History	X							
Dermatological Examination	X	X	X	X	X	X	X	X
Subject's Diary Dispensed	X	X	X	X	X	X	X	
Subject's Diary Collected		X	X	X	X	X	X	X
Questionnaire Completed	X		X	X	X	X	X	X
Medication Dispensed	X		X	X	X	X	X	
Medication Returned			X	X	X	X	X	X
Concomitant Therapy	X	X	X	X	X	X	X	X
Urine Pregnancy Test								X
Exit case Report Form								X
Adverse Events		X	X	X	X	X	X	X

If a subject discontinued prematurely, all Month 12 (Visit 8) procedures were to be performed at the subject's final visit.

At Visit 1 (baseline), the investigator thoroughly examined the skin of each subject to collect information on interfering conditions, signs and symptoms, or skin abnormalities, especially on the areas where the study drug was to be applied. This information was recorded on the

appropriate CRF page. At each follow-up visit, the investigator examined all areas of the skin to which the subject had applied the study drug, to specifically look for signs of cutaneous irritation, sensitization, or photosensitivity.

Safety was measured by the occurrence of adverse events. At each visit, the investigator asked the subject an open question regarding their health and medical status since the last visit. The investigator reviewed the subject's diaries for any information that may have indicated a change in status from baseline or any adverse events. If a subject experienced a severe adverse drug experience, he or she was encouraged to come to the site, regardless of whether it was between regularly scheduled visits.

All demographic data, evaluations and other observations were recorded directly, promptly and legibly in black ink on the CRF. The investigator signed the completed CRFs. Any changes in entries were made so as not to obscure the original entry and all changes were dated and signed at the time of the change.

The study was conducted under the sponsorship of L'OREAL USA Products, Inc. in compliance with all appropriate local regulations as well as the International Conference on Harmonization (ICH) Guidelines. At the end of the study, [redacted] conducted an audit of the data, documentation and text portions of this report.

All study statistics for the primary endpoints were descriptive. Adverse events were described and tabulated. As this trial was open and non-comparative, only descriptive data presentations were made, and no formal statistical hypothesis was tested.

Two independent study centers each were to enroll 40 subjects. Subjects were stratified into the following age groups: 6 months to < 2 years, > 2 years to < 6 years, > 6 years to < 12 years, >12 years to < 18 years, and > 18 years to < 65 years. In accordance with the pediatric rule, subpopulations of ages were selected so that approximately 70% of the subjects would be 12 years of age or younger, and results analyzed for the different age groups.

The safety population was defined as all subjects enrolled and treated at least once with the study drug. The Safety Population was the primary population used for the analyses.

Demographic and baseline characteristics were summarized by descriptive statistics. For the continuous variable, age, the following descriptive statistics were provided: sample size (N), mean, standard deviation, minimum, lower quartile, median, upper quartile, and maximum. For categorical variables, sex, race, and skin phototype, counts and percentages were provided. Patient disposition was tabulated and reasons for discontinuation were summarized by counts and percentages.

Adverse events were coded against a modified COSTART dictionary of terms prior to any analyses and therefore, body systems and preferred terms were available for all AEs. All information pertaining to AEs noted during the study was listed by patient, detailing verbatim given by the investigator, the preferred term, the body system, start/stop dates, severity, action

taken, and drug relatedness. The AE onset was also shown relative (in number of days) to the day of initial dose of the study drug. A subset of subjects was identified from medical histories, baseline examinations and certain nonrelated adverse events who are considered predisposed to dermatologic conditions.

Eighty subjects were enrolled in the study for treatment up to 12 months. This study was designed to enroll 60 subjects with an anticipated drop-out rate of 25%. About 45 subjects were anticipated to complete the study including 15 in the age group of 6 months to 2 years of age and 15 in the age group of 2 to 6 years of age. It was thought that the number expected to complete the study would be adequate to characterize the pattern of AEs over time in these particular age

## 10.2 Line-by-Line Labeling Review

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

**Appears This Way  
On Original**

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Daiva Shetty  
1/6/2006 10:00:42 AM  
MEDICAL OFFICER

Karen Feibus  
1/6/2006 02:48:55 PM  
MEDICAL OFFICER