

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-009**

**SUMMARY REVIEW**

## Summary Basis for Regulatory Action

<b>Date</b>	March 28, 2008
<b>From</b>	Andrea Leonard-Segal, M.D., M.S.
<b>Subject</b>	Division Director Summary Review
<b>NDA/BLA #</b>	NDA 22-009
<b>Supp #</b>	
<b>Proprietary / Established (USAN) Names</b>	ANTHELIOS 40; UV EXPERT 40; CAPITAL SOLEIL 40 (Helioblock SX Cream SPF 40) L'Oreal, USA Products, Inc.
<b>Dosage Forms / Strength</b>	3% ecamsule/2% avobenzone/10% octocrylene/5% titanium dioxide cream
<b>Proposed Indication(s)</b>	1. Helps prevent sunburn 2. Higher SPF gives more sunburn protection 3. Helps provide protection from UVA rays (short and long wavelengths)
<b>Action:</b>	Approval

### 1. Introduction to Review

L'Oreal submitted this NDA for a sunscreen containing 4 active ingredients (3% ecamsule/2% avobenzone/10% octocrylene/5% titanium dioxide cream). This sunscreen is active against both UVA and UVB radiation. Per the OTC monograph (21 CFR 352.10, 21 CFR 352.20) and 64 FR 27666, avobenzone, octocrylene, and titanium dioxide are generally recognized as safe and effective in the concentrations present in this product. The OTC monograph provides that combinations of up to 3% avobenzone, 10% octocrylene, and 25% titanium dioxide are allowed provided that each contributes at least 2% SPF of protection. Ecamsule is a marketed OTC ingredient in sunscreens approved for adults and children  $\geq$  6 months old in 2006 in NDAs 21-471 (Avobenzone 2%; Ecamsule 2%; Octocrylene 10%; and Titanium Dioxide 2% Topical Cream), 21-501 (ecamsule (Mexoryl®) 3%; avobenzone 2%; octocrylene 10%), and 21-502 (ecamsule 2% (Mexoryl®); avobenzone 2%; octocrylene 10%). For further details, refer to the reviews for these three NDAs. Partial waivers were granted to the sponsor for children < 6 months of age for these three formulations.

The formulation under consideration in this NDA 22-009 was developed under IND 57,850 and subsequently the sponsor submitted it in \_\_\_\_\_ as \_\_\_\_\_

\_\_\_\_\_. On March 31, 2004, the Agency issued an approvable letter for \_\_\_\_\_ because the data \_\_\_\_\_

\_\_\_\_\_. There were also some unresolved chemistry issues. On March 1, 2006, the sponsor informed the Agency of their intention to submit data from IND 57,850 to support NDA 22-009 for a traditional sunscreen indication.

b(4)

b(4)



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.

#### 5. Clinical Pharmacology/Biopharmaceutics

There were no notable clinical pharmacology/biopharmaceutics issues. In addition to her review with Dr. Lydia Velazquez for NDA22-009 dated February 18, 2008, see the following two reviews by Dr. Abimbola Adebowale:

- o \_\_\_\_\_ dated February 4, 2004 b(4)
- o NDAs 21-501, 21-502, and 21-471 dated February 21, 2006

The applicant provided the previously submitted in vivo data for Helioblock SX \_\_\_\_\_ cream and the previously submitted in vitro permeation data to evaluate the impact of reformulation (triad products against the tetrad product) 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). b(4)

- 5.1. General clinical pharmacology/biopharmaceutics considerations, including metabolism, half-life, food effects, variability of bioavailability, and pharmacologic properties other than those related to therapeutic effect.

The pharmacokinetic data are based upon single and multiple topical applications of Helioblock SX \_\_\_\_\_ to the trunk, arms and legs demonstrated minimal systemic exposure. The ecamsule was tagged with C<sup>14</sup>. For 152 of 154 samples obtained in one 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 Helioblock SX cream for 8 days resulted in plasma concentrations < 2 ng/mL. Dr. Adebowale concluded this was also minimal systemic exposure compared to the highest plasma level (i.e., ~ 1000 ng/mL) at which no toxicity occurred in rats. The No Observable Effect Level was 50 mg/kg of orally administered ecamsule in a 28-day study in rats. The NOAEL for oral ecamsule in rats after 26 weeks was at least 1000 mg/kg/day. Because of the low systemic absorption of ecamsule, the sponsor did not find that it was feasible to study tissue distribution. b(4)

In vitro percutaneous absorption data following topical application of Helioblock SX cream and the three other ecamsule formulations (that were studied under IND 59,126 and subsequently approved) demonstrated minimal penetration of skin ( $\leq 1\%$ ) and are supportive of the in vivo data. There was no statistical penetration difference between the three other ecamsule containing sunscreen formulations and the Helioblock SX Cream formulation. This suggests that this formulation change does not impact the absorption of ecamsule and that systemic safety should not be different from the other previously approved formulations.

#### 5.2. Drug-drug interactions

Data suggests that the effect of ecamsule on the systemic absorption of titanium dioxide, octocrylene, or avobenzone is minimal and unlikely to be clinically relevant. Review of literature suggests that application of sunscreen appears to enhance the absorption of Estrasorb<sup>TM</sup> (estradiol topical emulsion) and also of the insect repellent diethyltoluamide

(DEET). Dr. Adebowale recommended labeling the new sunscreen for these possible interactions. No nonprescription sunscreens currently carry such warnings.

With regard to Estrasorb™ it appears that a warning on the sunscreen label is not needed. The prescription label does state that Estrasorb™ should not be used at the same time as a sunscreen because estradiol absorption may be increased by 35%. Sunscreen application 25 minutes after application of Estrasorb™ increased exposure 15% (within the range of bioequivalence). Information included in the Patient Information for this prescription product states not to use at the same time as sunscreen. The directions for use for the Estrasorb™ are quite explicit (both in text and pictures) that the product should be applied once a day to clean, dry skin and that after the product is rubbed in, the area of application should be allowed to dry and covered with clothing. The directions state that the hands should be washed following application to remove any excess material. If consumers are following the directions for use of the product, the likelihood of applying with a sunscreen such that significant extra estradiol absorption would occur is remote.

Bioavailability can be increased when used concomitantly with sunscreens, but the products need to be used just about simultaneously for that to happen. Furthermore, the effect is not necessarily specific to sunscreens; it might happen with lotions and any product that might contain penetration enhancing ingredients. Importantly, in a worst case scenario, the foreseeable AEs resulting from increased bioavailability are not a serious concern and postmarketing data so far has not revealed serious safety concerns.

Apparently attempts are being made to obtain funding to produce studies that might shed light on what penetration enhancers could be important in relation to increased bioavailability. The consensus of clinical reviewers was that it would not seem appropriate at this time to select sunscreens in particular to add labeling regarding the potential increased bioavailability of topical estrogen from concomitant use, particularly in the absence of a significant clinical safety concern. (See e-mail reflecting communication between reviewers in the Division of Urological and Reproductive Products and the Division of Nonprescription Clinical Evaluation in Appendix 1.) This seems to be a reasonable approach to me, especially in light of the explicit instructions on how to use Estrasorb™ on that product label.

Regarding DEET, combination products of sunscreens and insect repellants (many of which are DEET insect repellants) are allowed and marketed. DEET is regulated by the Environmental Protection Agency; it is not a drug. The EPA has written that DEET is generally of low toxicity and that the normal use of DEET does not present a health concern to the general U.S. population. They have written that although DEET's use has been implicated in seizures in children, EPA believes that the incident data are insufficient to establish DEET as the cause of the reported effects.<sup>1,2</sup>

On February 22, 2007, the FDA and the EPA published companion documents in the Federal Register (see 72 CFR 35 at 7941 and 7979) requesting information and comments to formulate a regulatory position on insect repellant products that contain nonprescription sunscreen ingredients. The information received as a result of these publications would be used to generate benchmarks regarding product labeling as well as the development of performance

and safety standards. On August 8, 2007, following the closure of the comment period for these documents, the FDA and EPA met to discuss the comments and plan next steps.

b(5)

At this time it is unclear what the clinical consequence would be, if any, of increased absorption of DEET because of concurrent use with a sunscreen. Dr. Dennis Bashaw (Director, Division of Clinical Pharmacology III) and Dr. Matthew Holman (Team Leader, Division of Nonprescription Regulation Development) indicated to me that increased penetration of DEET may be related to the excipients in creams and lotions, and not to the sunscreens active ingredients themselves, so could involve broad ranges of topical products (drugs and cosmetics). Furthermore, the DEET penetration may relate to the specific insect repellent formulation. All of these variables suggest that the results of the study cited by Dr. Adebawale on increase absorption with DEET cannot be extrapolated to the NDA 22-009 formulation. It is not clear to us whether or not the ecamsule-containing sunscreens are being used with insect repellents, but there are no neurologic safety issues that emerged during the safety review conducted by Dr. Porres on the ecamsule-containing sunscreens.

We have no data to support a labeling warning about combined use with this new sunscreen product and DEET. At this point, it makes sense to see what emerges from the data under review, to watch for any adverse events, if any, that we may identify related to combined use of this and other sunscreens with DEET. It would make sense to consult the Office of Surveillance and Epidemiology to determine whether there is any clinical signal that they can identify with combined use of DEET with OTC topical products in adults or children.

### 5.3. Pathway of Elimination

Interspecies metabolism with hepatic microsomes and an in vivo oral rat study indicated that ecamsule is not metabolized, so no human metabolism studies were conducted. Ecamsule is recoverable in the urine. In data provided, none was detected in the feces.

### 5.4. Demographic interactions/special populations

The applicant stated that no clinical pharmacology and biopharmaceutics studies were conducted with children < 18 years of age, or otherwise compromised patients, or patients with a history of sun reactivity for the following reasons:

- Very low, mostly undetectable levels of ecamsule were reported even under maximized conditions of exposure in healthy volunteers despite low limits of quantitation
- There is no evidence that the skin exposed to the sun is clinically or histologically different from normal skin concerning the absorption profile of pharmaceutical products
- Permeability of the skin has been described as being relatively constant with respect to age, with no significant differences between the skin of children 6 months of age and older and adults regarding the penetration of topically applied substances.

The applicant also stated that even considering higher penetration on compromised skin or higher systemic exposure in children due to a larger body surface/body weight ratio, the overall safety margin for such populations is large, considering that ecamsule was found to be devoid of any toxic potential at the highest dose tested in animals. Considering the body surface to weight ratio to be considerably larger for children, the safety margin of adults should be divided by a factor of 1.3 – 1.4 to estimate the safety margin in children from the percutaneous data. An adult safety margin of 1000 determined for the ANTHELIOS 40 sunscreen is estimated to be > 700 in children which remains a very high safety margin. Dr. Adebowale notes that the clinical pharmacology data was found to be adequate when combined with the clinical safety data for the 3 previously approved sunscreen ecamsule-containing formulations.

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 indicates that the systemic exposure of ecamsule following the topical application of Helioblock SX sunscreen 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. She recommends that the applicant has met the requirements outlined in 21 CFR 320 and their application is acceptable.

**6. Clinical Microbiology** (*where relevant*)

6.1. Not relevant.

**7. Clinical/Statistical**

**7.1. General Discussion**

**Efficacy**

Refer to the review by Drs. Michael Koenig and Matthew Holman.

The formulation meets the criteria for UVB radiation protection in 21 CFR 352.20(a) and the data from 3 studies support that this cream is protective at a SPF of 40. The formulation also meets the criteria outlined in the 1993 tentative final monograph for OTC sunscreen drug products making claims of UVA protection. Two clinical studies demonstrated that the product effectively protects against UVA radiation in both men and women. The data supported that the protective factor for UVA (PFA) in this formulation greatly exceeds two times the number of active ingredients. The sponsor provided one in vitro study SOL-DP1-97-021 using human synthetic skin. In that study, the to-be-marketed Anthelios 40 formulation containing USP grade titanium dioxide and another Anthelios 40 formulation containing \_\_\_\_\_ titanium dioxide each exhibited the ability to absorb light at 380 nm. Thus, each formulation exhibited the ability to meet the criterion of protecting against UVA radiation, absorbing at  $\geq 360$  nm. The products to be marketed under NDA 22-009 may bear UVA protection claims, such as “broad spectrum” or “Protects against UVA rays or radiation” (58 FR 28194 at 28233) but they may not make claims as to the degree of UVA protection. In summary, one in vitro and five clinical studies that include ANTHELIOS 40 supported the conclusion of the reviewers that this product provides UVB and UVA protection and could be approved based upon the efficacy data.

b(4)

It is expected that Anthelios 40 will also be effective on children > 6 months of age. The topical product would be expected to demonstrate UVA and UVB protection in this population since, as Dr. Kettl explains in his February 19, 2008 Division of Dermatology and Dental Products consultative review, histologically, infant skin is similar to adult skin by the age of six months for infants born at term.

The skin is not mature prior to 6 months of age, but, although absorption might be different, the UVA and UVB blocking characteristics of the sunscreen would not be expected to change. For example, if there is slightly higher absorption, the sunscreen still has the same UVA and UVB absorption properties. The degree of protection may or may not be different, but, then again, there is variability in the testing even in adults with different skin characteristics.

#### 7.2.5 Pediatric use/PREA waivers/deferrals

The sponsor has requested a partial waiver for studies in children < 6 months of age for NDA 22-009.

Whether studies should be performed in the pediatric population < 6 months of age was addressed during the approval process of the 3 ecamsule-containing sunscreen formulations approved down to the age of 6 months in 2006. Initially, the Pediatric and Maternal Health Staff (PMHS) recommended that the sponsor should study the pharmacokinetics and safety in use of these products in infants < 6 months of age because infants in this age category could benefit from availability of a nonprescription sunscreen. The sponsor was told for NDA 21-471 that the studies were deferred in that age group.

Subsequently, the sponsor provided partial waiver requests for their three sunscreens. The sponsor provided the following reasons for the basis of their partial waiver request:

- It is inappropriate to use the sunscreens in infants < 6 months of age due to safety concerns:
  - As per the recommendations of the American Academy of Pediatrics (1999)<sup>3</sup>, infants < 6 months of age should not be exposed to the sun. The sponsor referenced the AAP statement “In situations where the infant’s skin is not protected adequately by clothing, it may be reasonable to apply sunscreen to small areas, such as the face and the back of the hands” as “tentative in its language reflecting the uncertain safety of sunscreen use in young infants.”
  - Infants are very sensitive to UV damage and the adverse effects of solar exposure. Also they may be at increased risk from overexposure to sunlight than older children or adults because they cannot remove themselves from uncomfortable light and heat.
  - Sunscreen use in these infants may increase their exposure to sunlight due to a parental false sense of security that their infant is protected.
  - Infants may be exposed to higher and potentially inappropriate systemic levels of sunscreen ingredients, potentially leading to adverse effects due to increased absorption from their higher body surface area to body mass ratio, the immaturity of their skin barrier, and developmentally immature metabolism and drug clearance pathways. The sponsor quoted from Meurer (2006)<sup>4</sup> that

- research is lacking for this age group and the risk of harm is real and thus it would be reasonably prudent to use sunscreen when physical protection from the sun is impossible, and to avoid ingredients that caused a previous reaction.
- Many infants have impaired functional sweating that may be further impaired by application of sunscreen.
  - The conduct of studies in babies < 6 months of age would be impractical and pose ethical concerns. The sponsor commented that performance of efficacy studies would require exposure of treated and control skin to UV radiation sufficient to induce burning and that conduct of PK studies would require blood sampling from infants and exposure to radioactive labels. These issues would pose difficulty in obtaining IRB approval and parental consent.

After reviewing the request for partial waivers, the PMHS recommended that the partial waivers be granted. (See the review by Dr. Jean Temeck and Dr. Lisa Mathis 11/17/06 for NDA 21-501.) They agreed with the sponsor that use of sunscreen products in infants < 6 months of age may lead to inappropriately high systemic levels of the ingredients in these products and pose safety concerns. They recommended that the labeling pertaining to use of sunscreens indicate that for infants less than 6 months of age that sunscreens be avoided and that sun exposure be avoided and that children be protected from sunlight with proper clothing, hats, and by being shaded. Based upon this reasoning on February 23, 2007 the sponsor was granted partial waivers for their sunscreen NDAs.

Consideration of the partial waiver request for NDA 22-009:

Upon receiving the partial waiver request for NDA 22-009, the Division of Nonprescription Clinical Evaluation consulted the Pediatric and Maternal Health Staff. As part of this January 23, 2008 review, Dr. Hari Sachs and Dr. Lisa Mathis commented that for children  $\geq$  6 months of age, the DNCE should determine whether the safety data are sufficient. They noted that a rationale for extrapolating efficacy should be provided, and that consideration should be given to obtaining pharmacokinetic data in this population. However, they noted that the extent of absorption of ecamsule has not been tested directly for any age pediatric patient, including in infants less than 6 months of age. Dr. Sachs and Dr. Mathis state that since sunscreen products are marketed and used in infants, consideration should be given to requesting "actual use" safety studies and PK studies in children < 6 months of age. They, and the Pediatric Review Committee (PeRC) on which they both sit, acknowledged that these studies might be challenging to perform but could be done in children following existing guidelines about sun exposure and using a product with directions that state to apply to face and hands without mandating exposure to other skin surfaces.

When the PeRC met to discuss this application (although the minutes of that meeting are not ready at the time of this memorandum) it is my understanding that they did not recommend that any studies were needed in children  $\geq$  6 months of age when they recognized the extensive safety data that we have in that age population. I agree with this.

However, the PeRC did recommend PK data collected as part of actual use studies in children < 6 months of age. The PeRC says parents use sunscreens in young infants and expects that parents use the product much more liberally than the American Academy of Pediatrics

recommends. They think that the study is ethical because it is not encouraging use but taking advantage of natural variation. They suggest that the data would provide adequate information for labeling.

In an e-mail from Rosemary Addy March 17, 2008 she conveyed more of the thinking from the PeRC. *"If there is not sufficient pharm tox data to determine a NOAEL, then this data would be needed to make any use of pk data if it was obtained. If one assumes 100% absorption for maximal applications of the product to a child under 6 months of age (and I would think that would not exceed 30 grams/day), if the possible exposure is still multiples below any NOAEL, we cannot see any utility in obtaining PK samples."*

(See Appendix 2)

Thirty grams/day is an ounce of sunscreen applied to a newborn (for the sake of discussion, a 3 kg infant). (If it all were absorbed, it would far exceed the NOAEL discussed under the Clinical Pharmacology Section above.) This 30 g/day suggested maximum exposure for an infant far exceeds (based upon both weight and body surface area) what was considered maximal use for the purposes of the clinical pharmacology studies in adults and seems unrealistic to me. In the PK studies, adults applied up to 15 grams (depending on the study) per application to the trunk, legs, and arms up to twice daily.

In an e-mail communication March 18, 2008 with Dr. Paul Brown, the pharmacology/toxicology reviewer who reviewed the data for Helioblock SX for \_\_\_\_\_ he stated, *"If pediatric studies in children under 6 months are required and the question is do juvenile animal studies need to be conducted before doing pediatric studies in these children, then I think the answer is probably not. The NOAELs in animal studies exceed the likely maximum dose. True, none of these are juvenile animal studies although there was a peri/postnatal study in rats that went from day 6 of gestation through weaning with no signs of toxicity. Based on these results it seems that there is little concern for any short term safety problems. The issues of concern if the sunscreen were used chronically in infants would presumably be possible effects on growth and development. There is no signal to suggest such an effect although this has not been fully assessed in animals."*

b(4)

(See Appendix 3)

Since chronic use in young infants would be 6 months of use and it is extremely unlikely that infants up to six months of age would use the product daily from birth, use chronicity could not be established in this young infant population. Ecamsule essentially does not get absorbed through mature skin (age 6 months and older).

Regarding collecting efficacy data in children:

In my opinion, it would be unethical to test efficacy of sunscreens in the pediatric population. This testing is performed in a laboratory, with a grid placed on the skin and different light exposures provided over time. Further, the infants and children would need to lay flat for up to several hours to test this sunscreen, a non water resistant sunscreen with an SPF of 40. These would be healthy children and therefore, children without an underlying condition that would enable them to directly benefit from the testing. Further, young infants may not have much melanin and the risk of being exposed to UV light in the "control skin area" which has no sunscreen placed, is not acceptable. Considering these factors and based upon what we know about these products and human skin, and knowing that the first recommendation

regarding sun is to stay out of it and wear protective clothing (for all ages, adults and children) I think that it is reasonable to extrapolate efficacy to the pediatric population.

Regarding the PMHS (Dr. Sachs) recommendation to conduct pharmacokinetic data in children and infants  $\geq 6$  months of age and  $< 6$  months of age:

Children and infants  $\geq 6$  months of age:

I do not think these data are needed and thus it would not be ethical to request PK studies. We have substantial and comforting safety data in this population from clinical trials, time and extent of use of all sunscreen ingredients in this product, and now, 1 ½ years of postmarketing of ecamsule-containing sunscreens in the United States. Further, we have evidence that there is minimal absorption of sunscreen ingredients through mature human skin ( $\geq 6$  months of age) and the safety of the small amounts of ecamsule absorbed through the skin is well supported by the preclinical data as well as the clinical data. With this information in place, I think it would be unethical and impractical for the sponsor to enroll children of this age to perform PK studies that involve multiple needle sticks and the possible need to use radioactively tagged ecamsule.

Infants  $< 6$  months of age:

Current AAP guidelines discourage the use of sunscreens in children less than 6 months of age for the following reasons:

- 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.
- Many infants have impaired functional sweating. Exposure to the heat of the sun may increase the risk of heatstroke.
- Sunburn may occur readily because an infant's skin has less melanin than at any other time in life.
- Concerns are raised that human skin under 6 months may have different absorptive characteristics; biologic systems that metabolize and excrete drugs may not be fully developed.

However, the 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.

Importantly, several guidelines specify that pediatric participants in clinical studies are expected to benefit from the clinical study.<sup>5</sup> Studies should not be performed in healthy children who cannot derive a benefit from being in those studies.

The following ethical reasons argue against the conduct of a standard PK study in children  $< 6$  months of age: exposure to excessive levels of the topical product (maximum possible exposure) without a benefit, potential for adverse events, the need to expose children  $< 6$  months to sun for the purposes of the clinical evaluation of the product, and subjecting these young infants to phlebotomy required by PK studies. It is difficult to come up with the circumstances where young infants would not be able to be placed in a shaded area (or covered with appropriate garments, including a hat) instead of requiring sunscreen application. There is

a realistic possibility that parents would enroll children in such a trial purely for financial gain since it is difficult to postulate another reason.

Furthermore, I doubt that PK studies in children of any age could be done in a standardized manner in a controlled clinical setting (which would be the usual approach) because this would mean enrolling healthy children in this study who would not be having the condition (sun exposure) at the time of the trial such that they could derive some benefit from participating. It is my understanding that the PeRC agrees with this. However, if the study were to be conducted with sparse PK draws after sun exposure during a trip to the beach (as some have suggested), the lack of standardization of the methodology (e.g., unpredictable time lags to blood draws, lack of standardization of sunscreen quantity applied, inability to observe how the sunscreen was applied) would likely lead to uninterpretable data. If the PK data showed a higher concentration of ecamsule than in adults, this would not change labeling to promote use in children < 6 months. If data showed the same absorption as adults or less, it is not clear that labeling would change, because it would not be clear whether the moving target methodology of the study was responsible or if the lack of measurable levels was real.

Regardless of the ability to interpret PK results, I have concerns about the behavioral consequences of labeling a sunscreen down to neonate because they are unknown; the unintended consequence might be to encourage more use of the sunscreen in infants and more sun exposure. I do not think that the PK study data would be apt change current recommendations about sun avoidance. I agree with Dr. Porres that these PK studies should not be performed.

*Regarding the actual use study in infants < 6 months old that was suggested by the PMHS and the PeRC:*

The actual use study is motivated by the notion that parents ignore physician advice and expose their young infants to the sun and, when outdoors, do not cover them up properly. This may be the case and good actual use data might help to clarify what parents do. Parents may, as some on the PeRC have argued, bring their young infants to beaches and swimming pools and do not keep them shaded or covered. However, it is clear that they certainly do not have to do this and should not do this.

I appreciate the reasons why the PeRC and the PMHS would recommend asking for actual use data for the very young babies. The PMHS did this before for the other ecamsule-containing NDAs and at that time I went along with the recommendation and signed the letter deferring studies. Then the PMHS changed their opinion about asking for these studies in 2006 and I thought about their reasons for this and agreed and granted the partial waiver. Now the PMHS and PeRC have reversed their thinking, again. Dr. Porres recommends that an actual use study should not be performed. After once again carefully considering the issues, I think that this actual use study is impracticable and feel that it may not even be ethical.

An informed consent form for this type of study would need to state that parents should not expose their young infants to direct sunlight and that, when outside, they should keep their infants out of the sun and shaded. It would need to state the reasons why they should keep their children out of the sun. Then it would need to state, somehow, that if parents cannot

comply with this proper sun avoidance way to take care of their children, that they can use the sunscreen on their babies' hands and faces. The informed consent would need to tell parents the purpose of the study, which would be to lead to new labeling for the sunscreen. The PeRC suggested that the study might lead to new labeling, but I have significant doubts about this. Actually, I think it would not lead to new labeling for reasons cited below and, therefore, disagree that the study should be performed.

The label already carries the skin "rashes and irritation" warning and this warning addresses anyone who uses the product. (Therefore, if neonates were to be exposed and developed rashes or skin irritation in the study the current labeling already covers what to do about this.) The labeling already has a Sun Alert, "Limiting sun exposure, wearing protective clothing and using sunscreens may reduce the risks of skin aging, skin cancer, and other harmful effects of the sun." Small exposures to this sunscreen (applied to an infant's hands and face), even under conditions of increased absorption would not be expected to cause systemic harm based upon the preclinical and clinical data that we already have.

Let's consider what might happen if sunscreens were to be labeled down to neonate. As I stated above, the behavioral consequences of labeling a sunscreen down to neonate are unknown; the unintended consequence might be to encourage more use of the sunscreen in infants and more sun exposure, and this makes me uncomfortable. The behavioral consequences of the label change would be extremely difficult, if not impossible, to test except possibly in the "hypothetical" (e.g., What would you do based upon this labeling?). However, data from "hypotheticals" generally are not reliable because respondents are known to try to please study interviewers and may not actually state what they are really thinking. If one tried to test the parental behavioral consequences of changed labeling in an actual use study, the study would need to consist of at least two arms (to compare the behavior based on each label), and be large. If it, for example, occurred at a beach, parents would need to remember to bring the diary and a writing implement to the beach with all of the other paraphernalia and distractions going to the beach with a baby entails. Alternatively, they would record what they did about applying sunscreen to the infant based upon recall later in time, a notably inaccurate way to collect data. Thus, it is highly unlikely that meaningful data on the consequences of a labeling change on parental behavior could be collected.

The bottom line is that I feel that the actual use study proposed by the PeRC is in essence enrolling parents to misbehave. If they do not, then no safety data is collected. If they do, then is this condoning or somehow promoting inappropriate parental behavior and is that ethical? It seems to me that parents who would sign on to such a study would only do it for money. It is difficult to think of another reason. Finally, it is difficult to conceive of this study leading to a labeling change that would clearly benefit these very young babies and it is possible a labeling change may, in fact, cause unintended harm by promoting more sunscreen use and more sun exposure. Collecting meaningful data on the consequences of the labeling change would be impracticable.

For these reasons, I think a partial waiver for pediatric studies in babies under 6 months of age should be granted.

## 7.2. Safety

Refer to the clinical review and the clinical safety update review by Dr. Porres. Much of the data for NDA 22-009 are identical to data submitted in the three other ecamsule-containing sunscreen NDAs (21-471, 21-501 and 21-502) from L'Oreal USA Products, Inc. As with the other 3 approved ecamsule containing combination product sunscreens, there were no safety signals of concern with this new 4-ingredient formulation. In clinical studies there were 1268 subjects exposed to this formulation plus an additional 135 subjects exposed to a formulation containing the same concentrations of each active ingredient, but with \_\_\_\_\_ form of titanium dioxide. Additionally, there were 1805 subjects exposed to other ecamsule-containing formulations. There were no deaths or serious adverse events attributed to the sunscreen. Drug related adverse events were limited to the skin and involved skin rashes and irritation none of which were severe and all of which resolved. In clinical studies of ecamsule-containing sunscreens, there have been occasional reports of conjunctivitis, one of which was thought to be drug-related.

b(4)

There were 6 people who dropped out of study PEN.750.04 (formulation the same as ANTHELIOS 40, except the titanium dioxide was \_\_\_\_\_, because of skin reactions, none of which were severe. The safety profile from clinical data on this 4-ingredient formulation is like that noted in clinical studies of the three other ecamsule-containing approved sunscreens.

b(4)

For the NDAs 21-501, 21-502 and 21-471 the sponsor had submitted acnegenicity/comedogenicity data that were not adequate to conclude that these formulations were not acnegenic or comedogenic. There are no new such data submitted with this application and there were a small number of reports of acne.

### Safety update

Safety update data did not present new safety concerns with regard to adverse event reports through January 31, 2008. L'Oreal conducted a literature search current up to 11/20/07 (to support the IND Annual Report for IND 59,126 submitted December 14, 2007 relative to ecamsule containing sunscreen formulations) and stated that they found no information relative to ecamsule that would impact the safety or safety labeling of ecamsule containing sunscreen products.

The above literature search was extended to 1/31/08 and again the sponsor stated that they found no new information that would impact the safety labeling of the subject NDA formulation. Dr. Porres performed his own Pub Med search and found nothing that would impact the safety labeling on ecamsule.

### Pediatric Safety Data

The sponsor provided the following data in children:

- Long-term safety data in children > 12 years of age with PMLE using the formulation in NDA 22-009
- Long-term safety data in health children 6 months to 12 years of age with a formulation identical to that in NDA 22-009 except that it used \_\_\_\_\_

b(4)

- Several long-term safety trials in pediatric populations down to 6 months of age with different ecamsule-containing sunscreens
- Fourteen long-term European cosmetic use studies in children < 12 years of age with formulations containing up to 6% ecamsule
- Extensive worldwide marketing history since 1993 and since 2006 in the United States of ecamsule-containing sunscreen formulations.

These data do not suggest safety concerns in children  $\geq$  6 months of age. During his review of the safety data, Dr. Porres did not find any reports of adverse events in infants < 6 months of age.

#### 7.2.1. Special safety concerns

##### Dermal Safety Studies:

Dr. Kettl from the Division of Dermatologic and Dental Products reviewed the dermal safety studies for NDA 22-009. Three studies (previously reviewed as part of \_\_\_\_\_ assessed Helioblock SX cream:

b(4)

- Irritation and contact sensitization
- Phototoxicity
- Photoallergy

Three studies (reviewed previously as part of NDA 21-502) were supportive but did not use the Helioblock SX cream, instead using three \_\_\_\_\_ products.

b(4)

- Cumulative irritation and sensitization
- Photosensitization
- Phototoxicity

Dr. Kettl concluded that the results from these studies are adequate to conclude that significant irritation, contact sensitization, phototoxicity, or photosensitization did not occur. Dr. Kettl did not recommend additional dermal safety studies.

##### Pregnancy Warning:

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

Eleven study participants in the clinical studies became pregnant. Four infants of mothers using Helioblock SX developed birthmarks: two with hemangiomas, one with a nevus flammeus and one with a café au lait spot. This information was considered in detail during the review of the 3 already approved ecamsule-containing formulations. The animal teratogenicity and reproductive function studies were negative, there is minimal human systemic absorption of ecamsule under maximized conditions of exposure, and there is a high background incidence of vascular skin abnormalities in babies.

Drs. Phyllis Huene and Jonathan Wilkin in their reviews of the Helioblock SX ? \_\_\_\_\_ for the \_\_\_\_\_ indication commented on the vascular lesions seen in infants born to women in the long term safety study. Dr. Wilkin noted that vascular formations are fairly common in neonates and that estrogen has been theorized to play a role. He stated that although some

b(4)

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 recommended 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 recommended 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 Helioblock SX 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 three \_\_\_\_\_ sunscreen formulations and Dr. Shetty, in her review of NDAs 21-501, 21-502 and 21-471 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. b(4)

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 Pregnancy and Lactation Team (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 (RD.06.SRE.18047) which was reviewed for the Helioblock SX \_\_\_\_\_ 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. b(4)

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 Helioblock SX 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:

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

Considering the totality of the available data, I supported this recommendation.

There were no new safety signals identified in the safety review regarding neonate vascular lesions in this NDA 22-009 submission. There is no need to add a pregnancy warning to this sunscreen.

#### **8. Advisory Committee Meeting**

No advisory committee meeting was convened to discuss this NDA. This product does not raise new issues (OTC indication, new consumer use issues, etc.) that would generate the need for input from the committee.

#### **9. Other Regulatory Issues**

None applicable.

#### **10. Labeling**

Refer to the reviews by Dr. Michael Koenig. There are no outstanding labeling issues.

#### **11. DSI Audits**

One study center (Consumer Product Testing, Co.) for this NDA was inspected in support of NDA 21-471 and found to be satisfactory.

#### **12. Conclusions and Recommendations**

Regulatory action:

In accordance with the recommendations of all the reviewers, this NDA 22-009 should be approved. The data suggests that it is safe and effective in adults and children  $\geq$  6 months of age.

I do not recommend any additional studies.

I recommend that a partial waiver be granted for children < 6 months of age; studies would be impracticable.

Regarding combined sunscreen use and DEET:

While the Office of Nonprescription Products continues its work with the EPA, it would make sense to further explore the safety of the concomitant use of OTC topical drugs and DEET, by consulting the Office of Surveillance and Epidemiology to look for any clinical safety signals that they can identify in adults and/or children.

#### REFERENCES:

1. EPA-738-F-95-010 DEET, EPA R.E.D. Facts, United States Environmental Protection Agency; Prevention, Pesticides and Toxic Substances (7508W); April 1998.
2. EPA Reregistration Eligibility Decision DEET. Prevention, Pesticides and Toxic Substances (7508W). EPA738-R-98-010, September, 1998.
3. American Academy of Pediatrics, Committee on Environmental Health. Ultraviolet light; a hazard to children. *Pediatrics* 1999;104:328-333.
4. Muerer L, Jamieson B. What is the appropriate use of sunscreen for infants and children? *J Fam Pract* 2006;55(5):437, 440, 444.
5. 45 CFR §46 and ICH guidelines E11 and E6.

Appendix 1

**From:** Porres, Joseph  
**Sent:** Thursday, March 20, 2008 10:59 AM  
**To:** Leonard Segal, Andrea  
**Cc:** Shetty, Daiva; Schiffenbauer, Joel; Van Der Vlugt, Theresa H  
**Subject:** RE: Helioblock

I had an informal, pleasant, and informative discussion with Theresa Van Der Vlugt and this my summary of what I understood.

I am cc'ing her as well so she can correct me:

1. Women who use estrogen creams usually apply it to one thigh or one arm, typically for a few days.
2. Once estrogen is absorbed, blood levels are not significant after 24 hours.
3. Bioavailability can be increased when used concomitantly with sunscreens, but they need to be used just about at the same time for that to happen. If there is even one hour of difference between applications, the effect is none or minimal.
4. The effect is not necessarily specific to sunscreens. It might happen with lotions and any product that might contain penetration enhancing ingredients.
5. In a worst case scenario, the foreseeable AEs resulting from increased bioavailability are not a serious concern.
6. Postmarketing data so far has not revealed serious concerns
7. An attempt is being made to obtain funding to produce studies that might shed light on what penetration enhancers could be important in relation to increased bioavailability.
8. It would not seem appropriate at this time to select sunscreens in particular to add labeling regarding the potential increased bioavailability of estrogen from the concomitant use of estrogen topical products

Joseph Porres, MD  
Medical Officer  
Office of Nonprescription Products  
Food and Drug Administration  
10903 New Hampshire Ave.  
Bldg. 22, Rm. 5435  
Silver Spring, MD 20993-0002

## Appendix 2

**From:** Addy, Rosemary  
**Sent:** Monday, March 17, 2008 12:08 PM  
**To:** Leonard Segal, Andrea  
**Cc:** Schiffenbauer, Joel; Mathis, Lisa  
**Subject:** RE: Follow-up to PeRC discussion of sunscreen products - PeRC Member Action Required

Andrea,

Sorry for taking so long to get back to you. After polling the PeRC members with your question, we have come up with the following:

The use study should include population PK data to determine the extent of absorption, given that an infant's skin is not fully developed. We recommend that the sponsor do an actual use study for which parents record a diary of daily use. They could be informed about the AAP recommendations, but may or may not follow them. When the diary is returned to the investigator (or representative), it can be screened quickly to see if the actual use exceeded a predefined threshold for performing a blood level (i.e., a population PK approach) based, for example, on a body surface area per day of exposure calculation. The parent could then be asked to participate in such a study (i.e., allow a single blood test) with a second consent document. Given the likelihood that many parents will use the sunscreen outside of the AAP recommendations (as was discussed at PeRC), we believe such a study would be feasible (and ethical in that you are not encouraging such use but simply taking advantage of the natural variation). If the data from studies provided adequate information for labeling (which is what we are supposed to be requesting), then indeed the product would be labeled.

If there is not sufficient pharm tox data to determine a NOAEL, then this data would be needed to make any use of PK data if it was obtained. If one assumes 100% absorption for maximal applications of the product to a child under 6 months of age (and I would think that would not exceed 30 grams/day), if the possible exposure is still multiples below any NOAEL, we cannot see any utility in obtaining PK samples.

Please let me know if you have any questions.

*Rosemary Addy, M.H.S.  
Regulatory Health Project Manager  
Pediatric and Maternal Health Staff  
Office of New Drugs  
FDA/CDER  
10903 New Hampshire Ave.  
Bldg #21, Room 1653  
Silver Spring, MD 20993-0002  
301-796-1640  
Please note new email address: [rosemary.addy@fda.hhs.gov](mailto:rosemary.addy@fda.hhs.gov)*

### Appendix 3

**From:** Brown, Paul C  
**Sent:** Tuesday, March 18, 2008 11:01 AM  
**To:** Harrouk, Wafa; Leonard Segal, Andrea  
**Cc:** Schiffenbauer, Joel  
**Subject:** RE: Follow-up to PeRC discussion of sunscreen products - PeRC Member Action Required

I am not familiar enough with the current situation to know exactly what the questions are.

Is the sponsor requesting a waiver from doing clinical studies in children under 6 months of age? Is the sunscreen likely to be used chronically in infants?

What is the design and intent of the pediatric study?

If pediatric studies in children under 6 months are required and the question is do juvenile animal studies need to be conducted before doing pediatric studies in these children, then I think the answer is probably not. The NOAELs in animal studies exceed the likely maximum dose. True, none of these are juvenile animal studies although there was a peri/postnatal study in rats that went from day 6 of gestation through weaning with no signs of toxicity. Based on these results it seems that there is little concern for any short term safety problems. The issues of concern if the sunscreen were used chronically in infants would presumably be possible effects on growth and development. There is no signal to suggest such an effect although this has not been fully assessed in animals.

If the pediatric study will examine long term safety then an animal study to look at this is probably not necessary since the human data would likely be most informative.

If the human study is to look at PK then the question of whether there is any concern about effects on growth and development can be addressed once it is known whether any drug is absorbed. Obviously, if none is absorbed then there is no concern.

Perhaps a tiered approach is needed. If the study shows there is use long term use in infants and that there is absorption of the drug, then maybe additional studies will be needed to address what the effects are on growth and development.

Paul

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

/s/

-----  
Andrea Segal  
3/28/2008 03:51:50 PM  
MEDICAL OFFICER