CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-501

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-501**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**5/16/05**
DRUG NAME:	**(b) (4) SPF 15 Water Resistance Sunscreen Lotion (avobenzone 2%, ecamsule 3%, octocrylene 10%)**
INDICATION:	**Prevention of sunburn (b) (4) due to sun exposure**
APPLICANT:	**L'ORÉAL USA**
DOCUMENTS REVIEWED:	**Vol. 1.1 - 1.55**
REVIEW DIVISION:	**Division of Dermatologic and Dental Drug Products (HFD-540)**
PHARM/TOX REVIEWER:	**Jiaqin Yao, Ph.D.**
PHARM/TOX SUPERVISOR:	**Paul C. Brown, Ph.D.**
DIVISION DIRECTOR:	**Stanka Kukich, M.D.**
PROJECT MANAGER:	**Elaine Abraham**

Date of review submission to Division File System (DFS): 2-2-2006

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability
The NDA is approvable from a pharm/tox perspective.

B. Recommendation for nonclinical studies
None

C. Recommendations on labeling
None, since it is an OTC drug.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

The nonclinical studies showed that the new active ingredient, ecamsule, had relatively low systemic absorption from the (b) (4) cream (a formulation similar to the drug product plus titanium dioxide). The toxicity studies showed that ecamsule and (b) (4) cream had low acute and repeat dose toxicity. Essentially no toxicity was observed after chronic oral dosing with ecamsule in rats or chronic topical dosing with the drug product in minipigs. Ecamsule appeared to be negative for genotoxic potential and was negative in a 2-year dermal carcinogenicity assay in mice.

Ecamsule or (b) (4) cream [or (b) (4) lotion (SPF 15), (b) (4) cream (SPF 20 –) did not increase UV induction of skin tumor formation in hairless mice. 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. No other 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.

b(4)

B. Pharmacologic activity

The active ingredients in the drug product act as sunscreens. Avobenzone, ecamsule and octocrylene absorb various UV wavelengths. The sponsor has developed the combination of active ingredients to attempt to provide a product that absorbs UV radiation across a relatively broad part of the spectrum.

C. Nonclinical safety issues relevant to clinical use
None

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

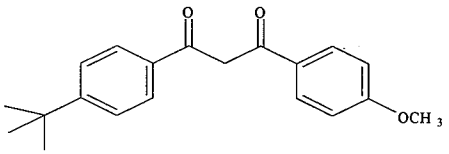
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-501
Review number: 1
Sequence number/date/type of submission: 000 / 16 May 2005 / original submission
Information to sponsor: Yes ( ) No (X)
Applicant and/or agent: L'ORÉAL USA
Manufacturer for drug substance:
Avobenzone: (b) (4)
Octocrylene: (b) (4)
Ecamsule: (b) (4)

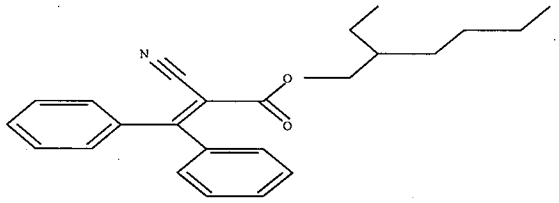
Reviewer name: Jiaqin Yao
Division name: Division of Dermatologic and Dental Drug Products
HFD #: 540
Review completion date: 2-2-2006

Drug:
Proposed trade name: (b) (4) SPF 15 water resistance (W/R) lotion (In previous submissions and study reports the product is referred to as (b) (4) cream)

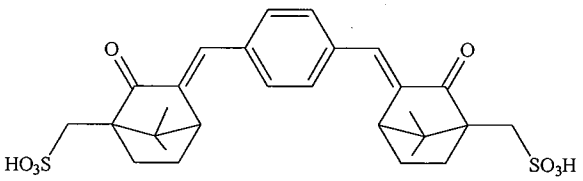
Generic name: Avobenzone
Chemical name: 1-[4-(1,1-dimethylethyl)phenyl]-3-(4-methoxyphenyl)-1,3-propanedione
CAS registry number: 70356-09-1
Molecular formula/molecular weight: $C_{20}H_{22}O_3$ / 310.40
Structure:



Generic name: Octocrylene
Chemical name: 2'-ethylhexyl-2-cyano-3,3-diphenylacrylate
CAS registry number: 6197-30-4
Molecular formula/molecular weight: $C_{24}H_{27}O_2$ / 361.49
Structure:



Generic name: Ecamsule (also referred to as Mexoryl SX)
Chemical name: 3,3'-(1,4-phenylenedimethylidyne)bis[7,7-dimethyl-2-oxo-bicyclo[2.2.1]hepatane-1-methanesulfonic acid]
CAS registry number: 92761-26-7
Molecular formula/molecular weight: $C_{28}H_{34}O_8S_2$ / 562.3
Structure:



Relevant INDs/NDAs/DMFs: [redacted] ((b) (4) Cream); IND 59,126 b(4)
((b) (4) Cream), (b) (4) [redacted]

Drug class: Sunscreen

Indication: Prevention of sunburn [redacted] due to sun exposure

Clinical formulation:

Ingredient	Formula (% w/w)	
	(b) (4) (b) (4)	(b) (4) SPF 15 W/R (NDA 21-501)
Ecamsule	3.0	3.0
Avobenzone	2.0	2.0
Octocrylene	10.0	10.0
Titanium dioxide		
Stearic acid		
Stearyl alcohol		
Dimethicone		
Glycerin		
Propylene glycol		
Carbomer 940		

b(4)

Hydroxypropyl methylcellulose
Isopropyl palmitate
Phenoxyethanol
Cyclomethicone
Purified water

b(4)

Route of administration: Topical to the skin

Drug history: Ecamsule was introduced for commercial use in Europe in 1993. Ecamsule was registered with the Canadian Health Protection Bureau in 1994 and the Australian Health Authorities in 1995. Avobenzone up to 3%, octocrylene up to 10%, and titanium dioxide up to 25% are listed as safe and effective for use as sunscreen active ingredients in the final OTC monograph for OTC sunscreen products which was finalized on May 21, 1999. The combination of avobenzone with titanium dioxide was not included as an acceptable combination of active ingredients in the monograph.

The sponsor opened IND 59,126 on 15 October 1999. The pharm/tox section of the original IND submission contained studies that had been reviewed under for (b) (4) which contained the new active filter, ecamsule, was submitted by L'Oreal . Additional nonclinical studies were reviewed in . All non-clinical studies within this submission were previously submitted to the Agency in (b) (4) The reader is referred to the pharmacology and toxicology review of (b) (4) for further details.

b(4)

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission: None

Studies not reviewed within this submission:

All non-clinical studies within this submission were previously included in (b) (4) The following review was duplicated or adapted from (b) (4)

2.6.2 PHARMACOLOGY

"The active ingredients in the drug product are intended to act as sunscreens. Avobenzone, ecamsule, and octocrylene absorb various UV wavelengths. The sponsor has developed the combination of active ingredients to attempt to provide a product that absorbs UV radiation across a relatively broad part of the spectrum. Avobenzone and octocrylene are included as active ingredients in the FDA Final Monograph for Sunscreen Drug Products for Over-The-Counter Human Use (FR Vol. 64, No. 98, May 21, 1999). Ecamsule has not been used in an approved drug product in the U.S. and is not included in the Monograph. The sponsor has provided absorption spectra of the drug product and of the individual active ingredients. Ecamsule absorbs from approximately 290 to 400 nm with a maximum absorption at 344 nm."

2.6.3 PHARMACOLOGY TABULATED SUMMARY

NA

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

"Ecamsule as the free acid or after neutralization with TEA is absorbed after oral administration in the rat. When given orally to the rat, most of the ecamsule was found unchanged in the feces. This could indicate that the material was not absorbed. After a single six hour occluded dermal application with Helioblock vehicle containing 3% ecamsule, it appears that approximately 10 to 14 % of the applied material was absorbed systemically and 3-4% was still in the skin at the application site. Slightly higher systemic absorption appeared to occur with repeated application (14 to 22%). Repeated application did not appear to lead to higher amounts of the drug in the skin. Absorption and penetration of ecamsule in rat skin from other formulations appears to be low (e.g. approximately 1% of total applied from a 4 hour application). The drug that penetrates was eliminated in the feces and urine. Some of the absorbed drug persisted in the skin for 96 hours after treatment. *In vitro* studies with a topical formulation different from (b) (4) showed that very little ecamsule (less than 0.016% of the applied amount) appeared to penetrate rat or human skin over a 24 hour period. Metabolism of ecamsule was not detected from *in vitro* studies using microsomes from man, minipig, rat or mouse. After oral or topical administration to the rat, ecamsule appeared to be essentially not metabolized. A study in mice showed that the absorption of ecamsule from (b) (4) Cream in mice appears to be similar to the absorption of ecamsule from a 5-10% aqueous solution."

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

NA

2.6.6 TOXICOLOGY

General toxicology:

"Ecamsule and (b) (4) cream appear to be relatively nontoxic when tested acutely. LD_{50} values in mice and rats for dermal and oral administration were greater then 2 ml/kg or 2000 mg/kg, respectively. LD_{50} values in mice and rats for intravenous administration were between 500 and 1000 mg/kg.

No toxic effect in rats was noted with 2 weeks of gavage treatment with ecamsule at up to 1050 mg acid/kg when administered as the acid, sodium salt or triethanolamine salt. Topical application of ecamsule acid or triethanolamine salt to rats daily for two weeks at a dose equivalent to 732 mg acid/kg appeared to be nontoxic. Oral doses of ecamsule of 500 mg/kg and higher given for 2 weeks were toxic in rabbits with some animals at these doses dying during the studies. The cause of death was not clear. In a 28 day study in rats of orally administered ecamsule, toxicologically significant changes were observed at 1000 mg/kg including body weight changes and kidney changes. Kidney changes were also observed at 250 mg/kg. The NOEL was 50 mg/kg. A 4 week study in rats of (b) (4) cream or ecamsule in solution (up to 2%) showed essentially no systemic toxicity and only limited dermal toxicity such as scabs in the ecamsule solution treated animals. Male rats treated for 90 days with 300 and 1000

mg/kg ecamsule had decreased mean thyroid weights compared to control although it was not clear if this was related to drug treatment since thyroid weights in control animals appeared to be higher than usual according to historical data. This possible thyroid effect was further explored in separate studies (see special toxicology below). Essentially no toxicity was noted in a 26 week oral (gavage) rat study with ecamsule. No thyroid effects were noted. Therefore, the NOAEL for oral ecamsule in rats after 26 weeks was at least 1000 mg/kg/day. Essentially no systemic or local toxicity was observed in 4 week and 9 month studies in minipigs conducted with the topical application of (b) (4) cream or ecamsule solutions (up to 24%). These studies also included (b) (4) cream without ecamsule. No toxicity was observed with or without ecamsule; therefore, these studies suggest that ecamsule did not increase the toxicity of the other active or inactive ingredients.

The drug product contains an excipient that has not been used previously in an approved drug product: polyvinylpyrrolidone (PVP)/eicosene copolymer. This excipient was present in the nonclinical and clinical studies conducted with (b) (4) cream. These studies included acute and repeat dose studies in mouse and rat and a chronic study in minipigs. It was also studied in photocarcinogenicity studies, primary skin and eye irritation studies, sensitization and photosensitization studies. These studies, combined with the clinical data, appear adequate to qualify the use of this excipient in the drug product." b(4)

Genetic toxicology:

"Ecamsule was mostly negative for genotoxicity in a variety of assays although some positive results were obtained. Ames assays of ecamsule were negative. A mutation assay in *E.* coli was also negative in the presence of UVA and UVB light. Six assays for chromosomal aberrations were conducted in Chinese hamster ovary (CHO) cells with ecamsule. In two assays for chromosomal aberrations in CHO cells positive results were obtained in the presence of S9 activation (Study No. 109/381A and 413/52). The first study was considered invalid by the sponsor since the laboratory conducting the study notified the sponsor that the S9 mix itself was toxic and clastogenic. In another CHO study, ecamsule was positive at inducing chromosomal aberrations in CHO cells in the absence but not in the presence of S9 (Study No. 12174 MIC) and in another CHO study no chromosomal aberrations were induced either with or without S9. A study conducted with and without UV radiation in CHO cells also found no increase in chromosomal aberrations. Another study in CHO cells was also conducted examining the potential to cause mutation in the HPRT locus. Ecamsule did not demonstrate mutagenic potential in this assay in the presence or absence of S9. Other tests for clastogenicity were negative including *in vivo* rat and mouse micronucleus studies and an *in vivo* study in rats for chromosomal aberrations in bone marrow. A brief tabular summary of the genotoxicity results are presented below.

Study type	Study No.	Outcome
Ames	801205	Negative
Ames	G185-109/314	Negative
E coli photo	EU1REBRP.031	Negative
CHO HPRT	LRL 170/921 503	Negative

CHO chrom ab	G220-109/381	Negative
CHO chrom ab	G220-109/381A	Positive with S9 (sponsor called study invalid for several reasons including S9 toxicity)
CHO chrom ab	June 13, 1988	Negative (study not considered valid since concentration of ecamsule was not clear)
CHO chrom ab	12174 MIC	Positive without S9 at toxic doses (56% or more reduction in MI)
CHO chrom ab	413/52-D6172	Positive with S9 at toxic doses (49% or more cytotoxicity)
CHO chrom ab w/ and w/o UV	ICHUREBRP.031	Negative
In vivo chrom ab in rat bone marrow	12640 MOR	Negative
In vivo micronucleus in mice	8809 MAS	Negative
In vivo micronucleus in rats	12639 MAR	Negative

It is not clear that the positive results in the CHO chromosomal aberration studies listed above are evidence that ecamsule is clastogenic. The positive results appear to only occur with relatively high (approximately 50% or more) toxicity. In addition, in the two valid positive CHO studies, the aberrations did not occur under the same conditions. In one case they occurred with S9 and in the other without S9. In the study that produced positive results with S9 the replicate cultures did not always give the same results and separate experiments within this study gave different dose responses. Further, there were negative results in other *in vitro* and *in vivo* assays that should detect clastogenicity.

Overall, the results of the genetic toxicology studies suggest that ecamsule is not genotoxic. The active ingredient, ecamsule, did not induce gene mutations in bacterial or mammalian cells *in vitro*. No significant clastogenic effects were noted with ecamsule in mammalian cells *in vitro* or in micronucleus assays in mice and rats or in a bone marrow chromosomal aberration assay in rats."

Carcinogenicity:

"A study of the carcinogenicity of ecamsule neutralized with TEA in aqueous solution was conducted for 104 weeks in CD-1 mice. No statistically or biologically significant increase in tumor incidence was observed in this study. This study appears to be adequate for the assessment of ecamsule in (b) (4) Cream since the high concentration in the study was 26% ecamsule and a pharmacokinetic study in mice showed that exposure to ecamsule from this concentration exceeds that from the ecamsule in (b) (4) Cream." The Executive CAC committee concurred that this was an adequate study and that there were no drug-related tumor findings.

"Several photocarcinogenicity studies with ecamsule or (b) (4) *(or* (b) (4) *lotion,* (b) (4) *cream)* have been conducted. These studies have been of varying design and have yielded different results although there is no evidence that ecamsule or (b) (4) Cream enhance skin tumor formation induced by UV exposure. Interestingly, in one study, while (b) (4) Cream and other topical formulations containing ecamsule did not increase skin tumor formation, they also did not offer protection from the UV-induced skin tumors, as might be expected. This lack

of protection may be due to the design of the study. For example, the topical formulations were applied before irradiation three days per week and after irradiation two days per week."

Reproductive toxicology:

"Oral doses of ecamsule of up to 1000 mg/kg did not have any effect on fertility parameters in the rat. 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 at the 1000 mg/kg dose but no effect was seen at 100 and 300 mg/kg.

Oral doses of ecamsule of 30, 100, and 300 mg/kg were not embryotoxic or teratogenic in the rat. None of the tested doses exhibited any toxicity in the dams.

Oral doses of ecamsule of 40, 120, and 360 mg/kg were essentially nontoxic to the rabbit dams in a study of embryofetal development. In a dose range finding study preceding this study, 450 mg/kg was found to have pronounced maternal toxicity. No drug related change in reproductive parameters was noted. No increase in fetal abnormalities was noted at any dose of ecamsule. While the results of this study appear acceptable, the validity of this study is somewhat in question since results from the laboratory that conducted the study have been found to be unreliable during the timeframe under which the study was conducted.

Ecamsule in aqueous solution was tested by topical application in an embryofetal development study in rabbits at doses of 100, 300, and 600 mg/kg/day. The dose of 100 mg/kg did not produce toxicity in the dams; however, 300 mg/kg induced decreased weight gain and 600 mg/kg induced decreased weight gain and food consumption as well as local skin reactions. No treatment related malformations were observed.

A study on pre- and post-natal development was conducted in rats with ecamsule by the oral route. No toxicity or effects on the reproductive parameters were observed in F0 female rats when they were administered up to 1000 mg ecamsule/kg/day from gestation day 6 to day 21 post-partum. No effects were observed on the physical or behavioral development of the F1 generation. The F1 generation also had normal reproductive function after reaching sexual maturity. The NOAEL for ecamsule was 1000 mg/kg for this study.

The rat embryofetal development study was conducted with a high oral dose (300 mg/kg) that did not produce significant toxicity in the dams. The sponsor was advised that this dose appeared to be low and that they should use adequate doses in further developmental toxicity studies. The sponsor used a higher dose (1000 mg/kg) in the subsequent peri-/postnatal study in rats. Even this dose appeared to be relatively nontoxic. However, the evaluation of the reproductive and developmental toxicity of ecamsule may be sufficient for several reasons. First, no evidence of embryotoxic or teratogenic effects was observed in the rat studies. While the peri-/postnatal study did not include necropsy of the F_1 pups, gross malformations and other physical and

developmental parameters were assessed and these offspring would have been exposed during the period of organogenesis since the dosing of the F_0 females began on day 6 of gestation. Second, the rabbit studies appear to have used adequate doses and no embryotoxic or teratogenic effects were noted. Third, the high doses used in the rat and rabbit studies exceed the maximum estimated human dose even when the comparisons are made on a mg/m^2 basis. The systemic exposure to ecamsule in humans appears to be very low, so a comparison of the animal to human doses using systemic exposure would probably provide an even greater margin of safety, although adequate data to make these comparisons is not available."

Special toxicology:

"A number of special toxicology studies were conducted with ecamsule or (b) (4) Cream. (b) (4) Cream caused transient slight to well defined erythema on scarified or nonscarified rabbit skin after 24 hour occlusive application. The product was considered to be practically nonirritating. (b) (4) Cream was considered slightly irritating to the eyes in rabbits. (b) (4) Cream did not produce a cutaneous sensitization reaction when applied at full concentration in guinea pigs. Similarly, no sensitization was detected in guinea pigs with ecamsule in solution at a concentration of up to 36.7%. No dermal photoirritation was noted in guinea pigs with (b) (4) and (b) (4) . In two studies of photoallergy in guinea pigs, no photoallergic potential was identified with (b) (4) Cream or (b) (4) vehicle. Three repeat dose studies were conducted in the rat to assess the effect of ecamsule on thyroid function. Although these studies found no effect on the thyroid, the validity of the studies is questionable since an audit of the studies found incomplete raw data and uncertainty about the administered dose."

2.6.7 TOXICOLOGY TABULATED SUMMARY

NA

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The formulation of this drug product is similar to (b) (4) Cream in the ——— (b) (4) except that the latter contains titanium dioxide —, (see Clinical formulation). The nonclinical studies of ecamsule, (b) (4) Cream, and other formulations, together with the established use of avobenzone and octocrylene in OTC sunscreen drug products are sufficient to assess the pharmacology and toxicology of this drug product for the intended use to prevent sunburn and skin damage due to sun exposure.

b(4)

The CMC reviewer noted that some impurities/degradants in the drug product appeared to exceed the ICH Q3B qualification thresholds. The maximum daily use of the drug product was assumed to be approximately 50 gm per day. The concentration of the active ingredients in this drug product is 3.0% for ecamsule, 2.0% for avobenzone, and 10.0% for octocrylene. Therefore, the maximum daily dose is 1.5 gm for ecamsule, 1 gm for avobenzone, and 5 gm for octocrylene. Based on ICH Q3B, the qualification threshold for the ecamsule or avobenzone impurities would be 0.2% or 3 mg total daily

dose, whichever is lower. For the octocrylene impurities, the qualification threshold would be 0.15%. The following impurities/degradants have been identified: [redacted] for ecamsule; [redacted] for avobenzone; [redacted] for octocrylene. The acceptance criteria for ecamsule impurities are now tightened to comply with Q3B requirements (0.2% and 3 mg total daily dose). Although the acceptance criteria, [redacted] for avobenzone impurities and [redacted] for octocrylene impurities, do not follow Q3B requirements, they are set according to USP monograph limits for these two drug substances. Avobenzone up to 3% and octocrylene up to 10% are listed as safe and effective for use as sunscreen active ingredients in the final OTC monograph for OTC sunscreen products. From the Pharmacology/Toxicology perspective, avobenzone and octocrylene use at monograph levels within the USP monograph impurity limits is reasonably safe. In addition, a requirement has also been included for total avobenzone impurities and total octocrylene impurities consistent with the USP. b(4)

The sponsor commits to monitor and track the known and the unknown degradation products, using the newly developed and validated method, [redacted] The sponsor also commits to attempt to identify, qualify, and establish appropriate specifications for any unknown impurity routinely observed above ICH Q3B threshold. From the Pharmacology/Toxicology perspective, it may be reasonable to set the limit for individual unknown at [redacted] at this moment, due to the unavailability of actual data. Safe and reliable specification limits must be established based on actual data developed. b(4)

This NDA is approvable from a pharmacology/toxicology perspective.

Unresolved toxicology issues (if any): None

Recommendations: None

Suggested labeling: None for an OTC drug.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

cc: list:
HFD-560/PM/AbrahamE
HFD-540/Pharm. Sup./BrownP
OPS/ONDQA/DPAMS/Chemist/LinS
HFD-540/MO/HueneP
FD-540/TL/LukeM
FD-540/ADDD/LindstromJ
HFD-540/ADD/KukichS

APPENDIX/ATTACHMENTS

None

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

/s/

Jiaqin Yao
2/2/2006 10:18:18 AM
PHARMACOLOGIST

Paul Brown
2/2/2006 11:59:43 AM
PHARMACOLOGIST