CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-508/S005

PHARMACOLOGY REVIEW(S)

AUG 8 2000

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

Reviewer Name: Paul C. Brown
Division Name: Division of Dermatologic and Dental Drug Products
HFD#540
Review Completion Date: August 2, 2000
NDA number: 20-508
Serial number/date/type of submission: 005 / 24 August 1999 / efficacy supplement
Information to sponsor: Yes
Sponsor (or agent): Bristol-Myers Squibb Pharmaceutical Research Institute
Drug: Lac-Hydrin 12% (ammonium lactate cream) Cream
Indication: ichthyosis vulgaris and xerosis.

Introduction:
This submission proposes updated labeling for the approved product Lac-Hydrin 12% Cream. The new labeling incorporates information on the safety and efficacy of Lac-Hydrin 12% Cream in pediatric patients down to 2 years of age.

Labeling Review:
The sponsor has not proposed any changes in the Carcinogenesis, Mutagenesis, Impairment of Fertility: or the Teratogenicity: Pregnancy category sections of the label. However, these sections should be updated since the sponsor has conducted additional nonclinical studies that would be appropriate to describe in these sections.

The sponsor conducted a dermal carcinogenicity study with ammonium lactate. This study was previously submitted to the agency and reviewed. A description of the results of this study should be included in the label. In this study CD-1 mice were treated with 100 µl/day of 12, 20 or 30% formulations and so received approximately 480, 840, or 1200 mg/kg/day of the ammonium lactate. These are equivalent to approximately 0.3, 0.5 and 0.7 fold the maximum possible human dose on a mg/m^2 basis (maximum human dose = 130 mg/kg or 4810 mg/m^2). No increase in local or systemic neoplasms was observed in this study.

The sponsor has conducted two genotoxicity studies with ammonium lactate. Ammonium lactate was evaluated in an Ames assay and no increase in mutation was observed. An *in vivo* micronucleus assay was conducted using dermal application in mice and no genotoxicity was observed.

The sponsor conducted Segment I, II and III reproductive toxicity studies in rats and Segment II studies in rabbits using dermal application. The Segment I and III studies in rats used does of 60, 120 and 300 mg/kg. The segment II studies used doses of 60, 210 and 600 mg/kg in rats and 120, 300 and 600 mg/kg in rabbits. No reproductive toxicity was observed in these studies.

The previous label for Lac-Hydrin 12% Cream has a Pregnancy Category of C. This is because no animal or human data on the reproductive toxicity of ammonium lactate was

available when the label was first written. The sponsor now has animal data that shows no reproductive toxicity of ammonium lactate. According to 21 CFR 201.57, a drug should be labeled Pregnancy Category B if animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well controlled studies in pregnant women. Therefore, the Pregnancy Category for Lac-Hydrin 12% cream should be B.

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The wording below for the Carcinogenesis, Mutagenesis, Impairment of Fertility: and Teratogenic effects: Pregnancy category sections of the label is adapted from the wording proposed ———— The animal to human dose ratio calculations are provided as an appendix to this review. The sponsor's proposed labeling is shown for comparison.

Sponsor's proposed labeling	Revised labeling
Carcinogenesis, mutagenesis, Impairment of Fertility: ***Carcinogenesis:*** [	**Carcinogenesis, Mutagenesis, Impairment of Fertility:** The topical treatment of CD-1 mice with 12%, 20% or 30% ammonium lactate formulations for two-years did not produce a significant increase in dermal or systemic tumors in the absence of increased exposure to ultraviolet radiation. The maximum systemic exposure of the mice in this study was 0.7 times the maximum possible systemic exposure in humans. However, a long-term photocarcinogenicity study in hairless albino mice suggested that topically applied 12% ammonium lactate cream enhanced the rate of ultraviolet light-induced skin tumor formation.] The mutagenic potential of ammonium lactate cream was evaluated in the Ames assay and in the mouse *in vivo* micronucleus assay, both of which were negative. In dermal Segment I and III studies with ammonium lactate cream there were no effects observed in fertility or pre- or post-natal development parameters in rats at dose levels of 300 mg/kg/day (1800 mg/m^2/day), approximately 0.4 times the human topical dose

Sponsor's proposed labeling	Revised labeling
[redacted]	**Teratogenic effects: Pregnancy Category B:** Animal reproduction studies have been performed in rats and rabbits at doses up to 0.7 and 1.5 times the human dose, respectively (600 mg/kg/day, corresponding to 3600 mg/m^2/day in the rat and 7200 mg/m^2/day in the rabbit) and have revealed no evidence of impaired fertility or harm to the fetus due to ammonium lactate cream. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Lac-Hydrin Cream should be used during pregnancy only if clearly needed.

Conclusions:
The labeling supplement for Lac-Hydrin 12% is approvable from a pharm/tox perspective with the suggested label changes.

/S/ 8/8/00

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cc:
NDA 20-508
HFD-340
HFD-540
HFD-540/Pharm/Brown
HFD-540/TL/Jacobs
HFD-540/MO/Cook
HFD-540/Chem/Turujman
HFD-540/PM/White

Concurrence Only:
HFD-540/DD/Wilkin /S/ 8/17/00 DFS
HFD-540/TL/Jacobs /S/ 8/8/00

Draft date (# of drafts): August 2, 2000 (1st draft)
Appendices: Animal to human dose ratio calculations

Animal to human dose ratio calculations:

body surface area for 60 kg individual = 16200 cm^2
topical dose = 2.0 $\mu l/cm^2$
daily dose = 2.0 $\mu l/cm^2$ x 16200 cm^2 x 2/day
= 64800 μl
= 64.8 ml
daily dose of ammonium lactate = 0.12 x 64.8 ml
= 7.8 ml
≈ 7800 mg
dose for 60 kg individual = 7800 mg/60 kg
= 130 mg/kg
dose for 60 kg individual in mg/m^2
= 130 mg/kg x km
= 130 mg/kg x 37 kg/m^2
= 4810 mg/m^2

Species	mg/kg	Km	mg/m^2	animal/human ratio
Mouse	480	3	1440	0.3
	840	3	2520	0.5
	1200	3	3600	0.7
Rat	300	6	1800	0.4
	600	6	3600	0.7
Rabbit	600	12	7200	1.5

APPEARS THIS WAY
ON ORIGINAL