CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-508/S005

MEDICAL REVIEW(S)

AUG 15 2000

Medical Officer's Review of NDA 20-508

Original

NDA #20-508
SE 5-008

Submission date: 8/24/99
CDER Stamp date: 8/26/99
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Sponsor: Bristol-Myers Squibb
Pharmaceutical Research Institute
Dermatology Clinical Research
100 Forest Avenue
Buffalo, NY 14213-1091

Generic name: Ammonium Lactate

Trade name: Lachydrin 12% Cream

Pharmacologic Category: Humectant

Proposed Indication(s): Ichthyosis Vulgaris, Xerosis

Dosage Form(s): Cream

Route (s) of Administration: Topical

NDA Drug Classification: 6S

Related Drugs: Lachydrin 12% Lotion – NDA 19-155

Related Reviews: Statistical Review dated: pending
Chemistry Review dated: pending

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3 Regulatory Background

3.1 Previous FDA Actions

This application is in response to a pediatric written request issued by the agency to study the safety of Lac-Hydrin 12% cream in pediatric patients ages 2 to 12 years old.

3.2 FDA/Applicant Meetings

There was a teleconference held in August and correspondence sent to the sponsor on August 24, 1999 to clarify the terms of the written request.

4 Material Reviewed

NDA 20-508 volumes 21.1 – 21.5
NDA 20-508 – SE8-005 BM

5 Clinical Background

5.1 Relevant Human Experience

Lac-Hydrin 12% Cream is a currently approved drug product in the United States for the indications of ichthyosis vulgaris and xerosis in adults. A related drug product, Lac-Hydrin 12% Lotion, approved for the same indications, is indicated in individuals as young as 2 years of age.

6 Proposed Labeling Change

6.1 Proposed Pediatric Use

Pediatric Use: The safety and effectiveness of Lac-Hydrin Cream have been established in pediatric patients as young as 2 years old.

7 Description of Clinical Data Sources

Protocol #DE109-035 – Double-blind, vehicle controlled study which is multicentered, involving 12 centers. The study initiation date was March 5, 1999 and study completion date was June 3, 1999.

8 Clinical Study

8.1 Reviewer's Trial # 1 Sponsor's protocol # DE109-035

Title: "A Double-Blind, Vehicle-Controlled, Parallel-Group Study of the Efficacy and Safety of Lac-Hydrin 12% Cream Versus Vehicle in Children with Ichthyosis Vulgaris"

8.1.1 Investigators

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11.	David Tashjian, M.D.	Fresno, CA
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8.1.1.1 Objective/Rationale

To evaluate the efficacy and safety of Lac-Hydrin 12% Cream versus its vehicle in the treatment of ichthyosis vulgaris in children, 2-16 years of age.

8.1.1.2 Design

This was a randomized, double-blind, vehicle-controlled, parallel-group study of Lac-Hydrin 12% Cream and its vehicle in the treatment of ichthyosis vulgaris in children.

8.1.1.3 Protocol

A total of 103 subjects were enrolled at 12 study sites. Fifty-two patients were randomized to the Lac-Hydrin 12% Cream treatment group and 51 subjects were randomized to the vehicle treatment group. Treatment was applied twice daily to all affected areas. There was a 2-week washout period prior to the 4-week treatment period. After the treatment period, there was a 2-week no treatment/observation period to examine the persistence of treatment effects.

Treatments began on visit 2 (week 0) twice daily for a 4-week period. A minimum of 8 hours separated the daily treatments. Liberal amounts of study medication were gently rubbed into the affected areas with a clean hand. The face was not treated during the study. Subjects

were instructed to refrain from bathing the treated areas for 6 hours after treatment application. Treatments were not to be given within 6 hours of a study visit.

Table 1 represents the schedule of events for the study.

Table 1
Schedule of Events

	Screening/ Randomization	Baseline	Treatment Period Weeks 1 - 4				Observation Period Weeks 5 and 6	
Event	Week -2	0	1	2	3	4	5	6
	Visit 1	2	3	4	5	6	7	8
Informed consent	■							
Inclusion/exclusion criteria	■							
Washout	■							
Urine pregnancy test	■	■				■		
Twice-daily treatment[1]		■	■	■	■	■		
No treatment							■	■
Clinical evaluation		■	■	■	■	■	■	■
Adverse event monitoring		■	■	■	■	■	■	■

[1]Subjects were randomized to Lac-Hydrin 12% Cream or vehicle cream in a 1:1 ratio.

An administrative change eliminating the need for subjects to participate in a formal 2-week washout phase under certain conditions was made to the protocol and approved on March 10, 1999. Specifically, the procedures for both Visit 1 (Week -2) and Visit 2 (Week 0) could be performed on the day the subject enrolled (Visit 1) if the subject:

- Fulfilled all requirements for enrollment
- Had not used moisturizers and/or emollients on the planned treatment sites for at least 2 days prior to the day they were enrolled (Visit 1).

Reviewer's Comment: *The sponsor does not state who specifically approved this change in the protocol. As stated here, it does not deviate from the intent of the 2-week wash out phase that was discussed with the sponsor in a teleconference. The division's viewpoint was that patients should not use topical therapy on the treatment sites but that "normally used cosmetics" were acceptable during the 2-week period prior to initiation of therapy in the trial.*

Inclusion and exclusion criteria were as follows:

Inclusion criteria:

Subject must have had a clinical diagnosis of ichthyosis vulgaris with a clinical score for overall disease severity of at least grade 4 (moderate)

A legally authorized representative signed the informed consent form for each subject. Subjects 12 years of age or older also signed the consent and subjects 2 to less than 12 years old also gave their assent if capable of understanding the implications of participating in the study

Subject was 2-16 years of age

Subject and caregiver were willing and able to comply with study procedures as directed and to commit to all study visits

Subject was in good health and free of any physical conditions that would impair evaluations of treatment areas (e.g., excess hair, scars, or conditions that would increase risks to the subject by study participation)

Female subjects of child-bearing potential had a negative urine pregnancy test (minimum sensitivity of 25 IU/L or equivalent units of human chorionic gonadotropin [HCG] hormone) within 72 hours prior to the start of study medication. Child-bearing potential was defined as any female who had experienced menarche and who had not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or was not postmenopausal (amenorrhea ≥ 12 consecutive months or women on hormone replacement therapy [HRT] with documented plasma follicle-stimulating hormone level > 35 mIU/mL). Additionally, females who were using oral, implanted, or injectable contraceptive hormones, mechanical products (intrauterine device), barrier methods (diaphragm, condoms, and spermicides) to prevent pregnancy, or practicing abstinence, or whose partner was sterile (e.g., vasectomy), were considered to be of childbearing potential.

Exclusion criteria:

The subject had a history of sensitivity to any of the ingredients in the formulations

The subject was involved in an investigational study concurrently or within the previous 30 days

The subject used any topical corticosteroid within 2 weeks prior to enrollment

The subject used systemic corticosteroids within 8 weeks prior to enrollment

Reasons for Withdrawal

Participation in this study may have been discontinued for any of the following:

Adverse reaction

Intercurrent illness

Administrative reasons

Subject's decision not to continue

Pregnancy

Investigator's opinion that it was in the subject's best interest

Additionally, if dry skin severity worsened during the no treatment/observation phase of this study to the degree that it required the administration of corrective therapy, the subject was to be withdrawn from the study.

8.1.1.3.1 Population

The population was comprised of healthy children, ages 2-16 years with ichthyosis vulgaris.

8.1.1.3.2 Endpoints

Primary Efficacy Variable:

Overall disease severity at the end of treatment (Visit 6, Week 4).

Efficacy Measures

At Study Visits 2-8 (Weeks 0-6), the subject was evaluated for the overall severity of the disease over the entire treatment area. Overall severity was an integrated judgement of the scaling, fissuring, and the erythema present and was graded as follows:

Overall Severity Scale

0	No evidence of disease
1*	
2	Mild
3*	
4	Moderate
5*	
6	Severe
7*	
8	Very Severe

*Intermediate intervals are midpoints between defined grades.

A clinically significant response was a 1-unit difference in the mean score for overall severity between Lac-Hydrin 12% Cream and its vehicle.

Secondary Efficacy Variables:

Degree of scaling of affected areas at the end of treatment (visit 6, week 4)

Degree of fissuring of affected areas at the end of treatment (visit 6, week 4)

Efficacy Measures

The following scales were used for measuring the secondary efficacy variables:

Scaling Scale

0 No evidence of scaling
1 Fine scaling with limited distribution
2 Fine scaling with wide distribution, and/or many larger specks of dry skin
3 Appearance of faint, but distinct polygonal scales with edges adherent to skin
4 Distinct polygonal scales with edges slightly lifted around circumference of scale plates
5 Moderate number of distinct polygonal scales with edges well lifted around circumference of scale plates
6 Large number of distinct polygonal scale plates with edges well lifted; may show signs of thickening and/or pigmentation
7 Majority of area covered with thick, pigmented scale plates
8 Involved areas completely covered with thick, hyperkeratotic, pigmented scale plates.

Fissuring Scale

0 No evidence of fissuring
1*
2 Fine, limited appearance of fissuring
3*
4 Moderate fissuring appearing between scale plates; light red may show in fissures
5*
6 Distinct areas of fissuring between scale plates; light red may show in fissures of approximately 1/16 to 1/4 inch in width
7*
8 Severe fissuring between scale plates; fissures may show light red to deep red appearance of approximately ≥1/4 inch width.

*Intermediate intervals are midpoints between defined grades.

Reviewer's Comment: *The objective of this study was to assess the safety of Lac-Hydrin 12% Cream. The efficacy analysis, therefore, is being reviewed as supportive. Efficacy of Lac-Hydrin 12% cream is being extrapolated from the adult trials.*

Safety Measures

Safety was assessed based on observed and reported adverse events (AEs). The primary safety outcome measure was the proportion of subjects experiencing skin-related AEs. The secondary safety outcome measure was the proportion of subjects experiencing AEs associated with other body systems.

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. The occurrence of AEs was monitored throughout the study. The collection of non-serious AE information began at initiation of use of the investigational product. Serious AEs (SAEs) were collected at any time following the subjects' written consent to participate in this study.

AEs were either spontaneously reported or elicited during questioning and evaluation of the subject. The subject and caregiver were queried about AEs that may have occurred since the last visit. All AEs were recorded and described on the appropriate non-serious AE page or the SAE page of the CRF. If known, the diagnosis of the underlying illness or disorder was recorded, rather than its individual symptoms. If a subject experienced an AE that caused an interruption or discontinuation of the study drug, or if the AE occurred at the end of the study, appropriate follow-up care was provided. When possible, the outcome of an AE that caused permanent discontinuation or that was present at the end of the study was reported, especially if the investigator considered it to be certainly, probably, or possibly related to the study drug.

8.1.1.3.3 Statistical considerations

Statistical and Analytical Plans

All Randomized Subjects (ARS) and the evaluable subjects (randomized subjects who were without a significant protocol deviation) were evaluated for baseline comparability. Unless otherwise noted, hypotheses were tested at a two-sided alpha level of 0.05. Efficacy analyses were based on both the ARS (primary dataset) and evaluable subjects population. Appendix C presents full documentation of statistical methods.

Baseline differences in overall severity, scaling, and fissuring were evaluated using the investigator-adjusted Wilcoxon rank-sum test. Baseline differences in age and weight between treatment groups were assessed using an analysis of variance (ANOVA) including terms for treatment and investigator. Differences in race and gender were evaluated by the investigator-adjusted Cochran Mantel-Haenszel test for general association. If baseline differences were detected, the baseline variable was used as a covariate in the on-treatment analysis.

Subjects who discontinued during the 2-week washout period were summarized using descriptive statistics.

Efficacy data were analyzed using the ARS and the evaluable subjects population. The last on-treatment observation was carried forward to the end-of-treatment visit (Visit 6, Week 4) to provide an endpoint evaluation in discontinued subjects. The primary efficacy endpoint, overall disease severity, was analyzed using the investigator-adjusted Wilcoxon rank-sum test to assess the null hypothesis of no treatment difference in means. Secondary endpoints, scaling and fissuring, were also analyzed by the Wilcoxon rank-sum test.

Poolability of data from different investigational sites was based on overall severity at the end of treatment. An ANOVA on ranked data was performed including terms for treatment,

investigator, and treatment-by-investigator interaction. Statistically significant interactions ($p \leq 0.1$) were examined to determine the type of interaction and the associated investigators. Treatment differences were examined within each investigational site and contrasts were performed comparing treatment differences within each site against the respective difference for the remaining sites considered as a totality.

Contrasts were performed at the 0.1 level of significance and were conditioned on the presence of a significant treatment-by-investigator interaction. Therefore, the overall type I error rate for all the contrasts was no greater than 0.1 under the complete null hypothesis.

Safety data were analyzed using the ARS population. AEs were summarized by causal relationship to treatment. AEs and SAEs that caused discontinuation were tabulated and described in detail.

Differences between treatments in the proportion of subjects with skin-related AEs were assessed by the investigator-adjusted Cochran Mantel-Haenszel test. Additionally, an analysis to determine the effect of age on skin-related AEs was performed using PROC LOGISTIC including terms for treatment, age, and interaction in the model. The interaction of treatment and age was included in the model to test the homogeneity of slope assumption. If this effect was not statistically significant, it was dropped from the model.

Subgroup analyses were performed for the effects of race, age, gender, and baseline overall severity. Qualitative variables (race and gender) were evaluated using a two-way ANOVA. Quantitative variables (age and baseline overall severity) were assessed by regressing the rank Week 4 overall severity on age or rank baseline overall severity. Additionally, treatment was included as an effect in the model. The interaction of treatment and age or baseline severity was included in the model to test the homogeneity of slope assumption. If the effect was not statistically significant (at the 0.1 level of significance), it was dropped from the model.

CRF tabulations were also produced.

8.1.1.4 Results

8.1.1.4.1 Populations enrolled/analyzed

Table 2 summarizes the subject demographics in the ITT (intent-to-treat) population. No statistically significant differences were observed between the treatment groups for any of the demographic parameters. The majority of subjects in the Lac-Hydrin 12% Cream and the vehicle cream treatment groups were male (65% and 75%, respectively) and White (73% and 75%, respectively). The average age was 10 years in the Lac-Hydrin 12% Cream treatment group and 9 years in the vehicle cream treatment group. All age subcategories were represented at similar levels for the two treatment groups.

There were no statistically significant differences at baseline in overall severity, scaling, fissuring, or treatment area between the two treatment groups. The mean overall severity, scaling, and fissuring scores at baseline were 5.6, 5.7, and 4.4 for the Lac-

Hydrin 12% Cream treatment group and 5.4, 5.5, and 4.4 for the vehicle cream treatment group, respectively. The mean treatment area (%) was 53.2% and 56.3% for the Lac-Hydrin 12% Cream and vehicle cream treatment groups, respectively.

Table 2
Baseline Demographic and Subject Characteristics (ITT Population)

Characteristic		Lac-Hydrin 12% Cream	Vehicle Cream	p-value*
Sex				
Male	n (%)	34 (65.4)	38 (74.5)	0.2677
Female	n (%)	18 (34.6)	13 (25.5)	
Race				
White	n (%)	38 (73.1)	38 (74.5)	0.7664
Black	n (%)	8 (15.4)	5 (9.8)	
Hispanic	n (%)	4 (7.7)	8 (15.7)	
Asian/Pacific Islander	n (%)	1 (1.9)	0 (0.0)	
Other	n (%)	1 (1.9)	0 (0.0)	
Age Group				N/A
2 – 6 years	n (%)	11 (21.2)	16 (31.4)	
7 – 11 years	n (%)	23 (44.2)	20 (39.2)	
12 – 16 years	n (%)	18 (34.8)	15 (29.4)	
Age (years)	n	52	51	0.1151
	Mean (SD)	10 (3.9)	8.9 (3.9)	
	Range	2.0 - 16.0	2.0 - 16.0	
Height (cm)**	n	52	51	0.3674
	Mean (SD)	141.2 (23.0)	137.1 (26.45)	
	Range	76.2 - 180.3	86.4 - 185.4	
Weight (kg)**	n	52	51	0.5406
	Mean (SD)	40.2 (18.0)	38.4 (18.9)	
	Range	11.3 - 90.7	13.2 - 79.8	
Area Treated (%)	n	52	51	0.2823
	Mean (SD)	53.2 (30.4)	56.3 (32.2)	
	Range	3.0 - 98.0	3.5 - 98.0	
Overall Severity	n	52	51	0.2756
	Mean	5.6	5.4	
Scaling	n	52	51	0.3893
	Mean	5.7	5.5	
Fissuring	n	52	51	0.9533
	Mean	4.4	4.4	

*Age, height, weight, and area treated were analyzed using ANOVA. Sex and race were analyzed using CMH test. Overall severity, scaling, and fissuring were analyzed using Wilcoxon rank-sum test.
**Height and weight for subjects # 0073, 0075, 0077, 0078, 0079, and 0080 were not obtained at baseline visit. The information was obtained further in the study during query resolution.

Reviewer's Comment: *There were 6 patients in the study who had less than 8% of their body surface area treated. Although ichthyosis vulgaris is inherited as an autosomal dominant disorder with incomplete penetrance, it is a symmetrical genodermatosis. The lower legs are usually the most involved and thus it would be expected that at a minimum patients would have at least 8% of the BSA involved. There was one patient with 3% involvement, 4 patients with 4% involvement, one patient with 5% involvement, and one patient with 7% involvement. Unfortunately, the CRFs submitted did not have the sheet that is included in the sample CRF which would have provided the investigator a way to document the exact location of treatment. Given this premise, and after discussing it with the statistician, a modified intent-to-treat analysis will be done that will exclude these six patients, patient 105 (Lac-Hydrin), 121(Lac-Hydrin), 122 (Lac-Hydrin), 123 (vehicle), 126 (Lac-Hydrin), and 127 (vehicle). This will be compared with the sponsor's ITT analysis which includes all patients randomized into the trial. It is of interest that 5 of these 6 patients, all but patient 105, are from the same center. The other two patients from that center had higher body surface area involvement, 12% and 80%, were on vehicle, and failed therapy.*

Of the 103 subjects enrolled, 52 (50.5%) were randomized to Lac-Hydrin 12% Cream and 51 (49.5%) were randomized to the vehicle cream. Most of the subjects (91%) completed the study (49 subjects [94%] and 45 subjects [88%] in the Lac-Hydrin 12% Cream and vehicle cream treatment groups, respectively). Table 3 summarizes the reasons for discontinuation after randomization.

Table 3
Summary of Subject Disposition (All Randomized Subjects)

Subject Disposition	Lac-Hydrin 12% Cream		Vehicle Cream	
	n	%	n	%
Study Completion	49	94.2	45	88.2
Lost to Follow-up	1	1.9	1	2.0
Non-compliance	1	1.9	0	0.0
Treatment Failure/Lack of Efficacy	0	0.0	1	2.0
Adverse Event	0	0.0	1	2.0
Other	1	1.9	3	5.9
Total	52	100.0	51	100.0

Only one subject (#0069, vehicle) discontinued due to an adverse event (moderate eczema with secondary infection). The event was considered unrelated to treatment. The disposition of subjects by visit is presented in Table 4.

Table 4
Disposition of Subjects by Visit (All Randomized Subjects)

Subject Disposition	Treatment	Visit						
		Baseline	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
		n	n	n	n	n	n	n
Evaluated	Lac-Hydrin 12% Cream	52	52	49	48	48	46	50
	Vehicle Cream	51	48	47	44	46	44	45
Missed Visit	Lac-Hydrin 12% Cream	0	0	2	2	2	4	0
	Vehicle Cream	0	2	2	2	0	1	0
Discontinued – Other[1]	Lac-Hydrin 12% Cream	0	0	1	2	2	2	2[2]
	Vehicle Cream	0	1	2	4	5	5	5
Discontinued – AE	Lac-Hydrin 12% Cream	0	0	0	0	0	0	0
	Vehicle Cream	0	0	0	0	0	1	1
Visit Total	Lac-Hydrin 12% Cream	52	52	52	52	52	52	52
	Vehicle Cream	51	51	51	50[3]	51	51	51

[1]Includes discontinuations due to "lost to follow-up," "non-compliance," "treatment failure/lack of efficacy" and "other"
[2]Subject # 00120 had an evaluation at Visit 8, but was recorded as a discontinuation due to non-compliance. For the purpose of this table, subject was counted as evaluated.
[3] Subject # 00118 had an evaluation at Visit 5, but the efficacy data were collected after database lock.

Similar numbers of protocol deviations were reported in the Lac-Hydrin 12% Cream and vehicle cream treatment groups (39 subjects [75%] and 32 subjects [63%], respectively). The most common deviation in both treatment groups was the use of treatment for greater than 4 weeks (35 subjects [67%] and 28 subjects [55%] in the Lac-Hydrin 12% Cream and vehicle cream treatment group, respectively), with the majority of subjects using treatment for an additional 1 to 2 days. Subject #00120 was discontinued from the study due to non-compliance (missed visits).

8.1.1.4.2 Efficacy endpoint outcomes

Mean overall severity scores for the ITT population evaluated at baseline (visit 2, week 0) and all subsequent visits are summarized in table 5. In the ITT population, there was no clinically or statistically significant difference in overall disease severity at baseline between the treatment groups. Overall severity scores for the Lac-Hydrin 12% Cream treatment group were lower than vehicle cream treatment group at weeks 2, 3, 4, and 5. The mean overall severity score at the end of treatment, week 4, for subjects using Lac-Hydrin 12% Cream was 1.9 compared with 3.0 for subjects using vehicle cream. Mean overall severity score with Lac-Hydrin 12% Cream was clinically (greater than one unit difference) as well as statistically ($p=0.0004$) significantly lower than vehicle cream at week 4.

The mean overall severity score with Lac-Hydrin 12% Cream was also statistically significantly lower ($p=0.0141$) than vehicle cream at Visit 5 (Week 3). A week after treatment was stopped (Visit 7, week 5), overall severity was still significantly lower ($p=0.0225$) in the

Lac-Hydrin 12% Cream treatment group. At Visit 8, two weeks after treatment was stopped, no significant differences in overall severity were observed between the two treatment groups.

Table 5
Overall Disease Severity
ITT Population

Visit		Lac-Hydrin 12% Cream (N=52)	Vehicle Cream (N=51)	p-value*
Baseline	n	52	51	0.2756
	mean overall severity	5.6	5.4	
Visit 3	n	52	51	0.8038
	mean overall severity	4.0	4.0	
Visit 4	n	52	51	0.1665
	mean overall severity	3.1	3.6	
Visit 5	n	52	51	0.0141
	mean overall severity	2.3	3.2	
Visit 6	n	52	51	0.0004
	mean overall severity	1.9	3.0	
Visit 7	n	46	44	0.0225
	mean overall severity	2.7	3.5	
Visit 8	n	50	45	0.8921
	mean overall severity	3.9	4.0	

*p-value based on the Wilcoxon rank-sum test.

Table 6 shows the results of the modified ITT population for overall disease severity, where 6 patients were excluded from the efficacy analysis because the diagnosis is in doubt.

Table 6
Overall Disease Severity
Modified ITT Population

Visit		Lac-Hydrin 12% Cream (N=48)	Vehicle Cream (N=49)	p-value*
Baseline	n	48	49	0.3054
	mean overall severity	5.6	5.4	
Visit 3	n	48	49	0.9648
	mean overall severity	4.1	4.1	
Visit 4	n	48	49	0.2360
	mean overall severity	3.1	3.6	
Visit 5	n	48	49	0.0194
	mean overall severity	2.3	3.2	
Visit 6	n	48	49	0.0012
	mean overall severity	1.9	3.1	
Visit 7	n	43	42	0.0307
	mean overall severity	2.7	3.6	
Visit 8	n	46	43	0.9867
	mean overall severity	4.0	4.1	

*p-value based on the Wilcoxon rank-sum test.

The degree of scaling of affected areas was evaluated at baseline (Visit 2, Week 0) and all subsequent visits (Visits # 3-8). In the ITT population, mean scaling scores for the Lac-Hydrin 12% Cream treatment group were lower than vehicle cream treatment group at Visits 3, 4, 5, 6, and 7. At Visit 6 (Week 4, end of treatment), the mean scaling scores were 1.7 for the Lac-Hydrin 12% Cream treatment group and 3.1 for the vehicle cream treatment group. There was statistically significantly less (p=0.0001) scaling in the Lac-Hydrin 12% Cream treatment group at Visit 6 (Week 4). A week after treatment was stopped (Visit 7, week 5), mean scaling scores were still significantly lower (p=0.0116) in the Lac-Hydrin 12% Cream treatment group. At Visit 8, two weeks after treatment was stopped, no significant differences in mean scaling scores were observed between the two treatment groups (see table 7).

Table 7
Summary of Scaling
ITT Population

Visit		Lac-Hydrin 12% Cream (N=52)	Vehicle Cream (N=51)	*p-value
Baseline	n	52	51	0.3893
	mean scaling	5.7	5.5	
Visit 3	n	52	51	0.7873
	mean scaling	3.9	4.0	
Visit 4	n	52	51	0.5151
	mean scaling	3.1	3.4	
Visit 5	n	52	51	0.0790
	mean scaling	2.3	2.9	
Visit 6	n	52	51	0.0001
	mean scaling	1.7	3.1	
Visit 7	n	46	44	0.0116
	mean scaling	2.5	3.5	
Visit 8	n	50	45	0.7323
	mean scaling	3.9	4.0	

*p-value based on the Wilcoxon rank-sum test.

Table 8 shows the results of the modified ITT population for scaling, where 6 patients were excluded from the efficacy analysis because the diagnosis is in doubt.

Table 8
Summary of Scaling
Modified ITT Population

Visit		Lac-Hydrin 12% Cream (N=48)	Vehicle Cream (N=49)	p-value*
Baseline	n	48	49	0.4247
	mean scaling	5.7	5.5	
Visit 3	n	48	49	0.8484
	mean scaling	4.0	4.0	
Visit 4	n	48	49	0.4580
	mean scaling	3.1	3.4	
Visit 5	n	48	49	0.0516
	mean scaling	2.2	2.9	
Visit 6	n	48	49	0.0001
	mean scaling	1.7	3.1	
Visit 7	n	43	42	0.0110
	mean scaling	2.5	3.6	
Visit 8	n	46	43	0.7898
	mean scaling	4.0	4.1	

*p-value based on the Wilcoxon rank-sum test.

Similar results were observed for the evaluation of fissuring which occurred at baseline (week 0) and all subsequent weeks. Mean fissuring scores at Visits 3, 4, 5, 6, and 7 were lower for the Lac-Hydrin 12% Cream treatment group than for the vehicle cream treatment group. At Visit 6 (Week 4, end of treatment), mean fissuring scores were 1.3 for the Lac-Hydrin 12% Cream treatment group and 2.2 for the vehicle cream treatment group. There was statistically significantly less fissuring at the end of treatment (Visit 6) with Lac-Hydrin 12% Cream treatment (p=0.0008). There was also statistically significantly less fissuring with Lac-Hydrin 12% Cream treatment at Visit 5 (Week 3, p=0.0112). A week after treatment was stopped (Visit 7, Week 5), mean fissuring scores were still significantly lower in the Lac-Hydrin 12% Cream treatment group (p=0.0156). At Visit 8, two weeks after treatment was stopped, no significant differences in mean fissuring scores were observed between the two treatment groups (see table 9).

Table 9
Summary of Fissuring
ITT Population

Visit		Lac-Hydrin 12% Cream (N=52)	Vehicle Cream (N=51)	p-value*
Baseline	n	52	51	0.9533
	mean fissuring	4.4	4.4	
Visit 3	n	52	51	0.6112
	mean fissuring	2.6	2.8	
Visit 4	n	52	51	0.2587
	mean fissuring	2.1	2.4	
Visit 5	n	52	51	0.0112
	mean fissuring	1.3	2.0	
Visit 6	n	52	51	0.0008
	mean fissuring	1.3	2.2	
Visit 7	n	46	44	0.0156
	mean fissuring	1.7	2.6	
Visit 8	n	50	45	0.4965
	mean fissuring	3.0	2.9	

*p-value based on the Wilcoxon rank-sum test.

Table 10 shows the summary of fissuring for the modified ITT population.

Table 10
Summary of Fissuring
Modified ITT Population

Visit		Lac-Hydrin 12% Cream (N=48)	Vehicle Cream (N=49)	p-value*
Baseline	n	48	49	0.9912
	mean fissuring	4.4	4.4	
Visit 3	n	48	49	0.7259
	mean fissuring	2.7	2.8	
Visit 4	n	48	49	0.3279
	mean fissuring	2.1	2.4	
Visit 5	n	48	49	0.0124
	mean fissuring	1.3	2.0	
Visit 6	n	48	49	0.0024
	mean fissuring	1.3	2.2	
Visit 7	n	43	42	0.0453
	mean fissuring	1.7	2.6	
Visit 8	n	46	43	0.4809
	mean fissuring	3.2	2.0	

*p-value based on the Wilcoxon rank-sum test.

Reviewer's Comment: *Since more than half the patients (67.3% in the Lac-Hydrin Cream, 12% group and 54.9% in the vehicle group) continued to use the medication beyond 4 weeks, one*

cannot conclude that treatment effect was maintained without drug at any time period beyond the primary efficacy time point of week 4 (visit 6).

Subgroup analyses were performed for effects of gender, race, age, and baseline overall severity based on the last observation of overall severity carried forward to Visit 6 (week 4) as the dependent variable. Table 11 shows the results of these analyses. The results of the subgroup analysis shows that females had a lower mean score than males for both treatment groups. However, there was not a difference for race or age.

Table 11
Summary of Overall Severity of Ichthyosis Vulgaris by Gender, Race, and Age Group at Visit 6 (end of treatment)
ITT Population

Subgroups	Lac-Hydrin 12% Cream		Vehicle Cream		
	n	Mean	n	Mean	p-value
Gender*					0.0099
Male	34	2.1	38	3.2	
Female	18	1.5	13	2.7	
Race*					0.1280
White	38	1.9	38	3.1	
Non-White	14	1.9	13	2.9	
Age Group					N/A**
2 – 6 years	11	1.5	16	2.7	
7 – 11 years	23	1.9	20	3.0	
12 – 16 years	18	2.1	15	3.5	

*Analyzed using two-way ANOVA with the rank of Visit 6 overall severity as the dependent variable.
**p-value for age as a continuous variable was 0.1705

When the subgroup analysis is done with the modified intent-to-treat population (excluding patients that probably did not have ichthyosis vulgaris), a difference for gender is not supported.

Table 12
Summary of Overall Severity of Ichthyosis Vulgaris by Gender, Race, and Age Group at Visit 6 (end of treatment)
Modified ITT Population

Subgroups	Lac-Hydrin 12% Cream		Vehicle Cream		
	n	Mean	n	Mean	p-value
Gender*					0.1853
Male	33	2.1	37	3.2	
Female	15	1.4	12	2.8	
Race*					0.9854
White	35	1.9	36	3.1	
Non-White	13	1.9	13	2.9	
Age Group					0.3238
2 – 6 years	11	1.5	16	2.7	
7 – 11 years	21	1.9	18	3.1	
12 – 16 years	16	2.1	15	3.5	

*Analyzed using two-way ANOVA with the rank of Visit 6 overall severity as the dependent variable.
Reference: Tables 11.a, b, c and d.
**p-value for age as a continuous variable was 0.1705

8.1.1.4.3 Safety outcomes

All randomized subjects received double-blind study medication (Lac-Hydrin 12% Cream or vehicle cream) for 4 weeks. Treatments were administered topically twice daily in all subjects except subject # 00103 (Lac-Hydrin 12% Cream), in whom the dose was reduced due to mild irritation at the treatment site on the abdomen. There were several subjects in each treatment group who used study medication for longer than 4 weeks (67.0% and 55.0% in Lac-Hydrin 12% Cream and vehicle cream treatment groups, respectively). Extent of drug exposure in the ITT population is presented in table 13.

Of the subjects who completed 4 weeks of treatment and whose drug use information was recorded, mean drug use was calculated. Mean drug use for vehicle cream (386 g/subject) was slightly higher than in the Lac-Hydrin 12% Cream group (283 g/subject). There were 15 subjects for whom cumulative drug inventory forms were obtained after database lock. These subjects were excluded from the analysis of mean drug use.

Table 13
Extent of Drug Exposure
ITT Population

Length of Drug Exposure	Lac-Hydrin 12% Cream		Vehicle Cream		Exposure Total
	n	%	n	%	N
Exposure Duration Unknown	1	1.9	1	2.0	2
One Week or Less	0	0.0	0	0.0	0
> 1 Week to 2 Weeks	0	0.0	2	3.9	2
> 2 Weeks to 3 Weeks	1	1.9	1	2.0	2
> 3 Weeks to 4 Weeks	15	28.8	19	37.3	34
> 4 Weeks	35	67.3	28	54.9	63
Treatment Total	52	100.0	51	100.0	103

Table 14 presents a summary of the overall incidence of AEs in the ITT population. Eighteen subjects (35%) in each treatment group had at least one adverse event. There were no SAEs or deaths reported in this study. One subject (2%) discontinued from the study due to an AE. Subject #00069 experienced moderate eczema with secondary infection while on vehicle cream treatment. The AE was classified as unrelated to study drug.

Table 14
Overall Incidence of Adverse Events
ITT Population

	Lac-Hydrin 12% Cream (n = 52)		Vehicle Cream (n = 51)	
	n	%	n	%
Subjects with at least one AE	18	34.6	18	35.3
Subjects with at least one treatment-related AE	7	13.5	5	9.8
Subjects with at least one skin and appendages AE	12	23.1	7	13.7
Subjects with at least one SAE	0	0	0	0
Subjects discontinuing due to AEs	0	0	1	2.0

A total of 52 AEs were reported by 36 subjects. In the Lac-Hydrin 12% Cream treatment group, 18 subjects reported a total of 27 AEs. In the vehicle cream treatment group, 18 subjects reported a total of 25 adverse events. Table 15 summarizes AEs by body system and relationship to study drug.

Table 15
Incidence of Adverse Events by Body System and Relationship To Treatment
ITT Population

Body System	Lac-Hydrin 12% Cream		Vehicle Cream	
	Related to Treatment n (%)	Unrelated to Treatment n (%)	Related to Treatment n (%)	Unrelated to Treatment n (%)
Total All Systems	7(13.5)	11 (21.2)	5 (9.8)	13 (25.5)
Body as a Whole	0 (0.0)	6 (11.5)	0 (0.0)	8 (15.7)
Cardiovascular System	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)
Digestive System	0 (0.0)	1 (1.9)	0 (0.0)	1 (2.0)
Hemic/Lymphatic System	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Musculoskeletal System	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Respiratory System	0 (0.0)	2 (3.8)	0 (0.0)	3 (5.9)
Skin/Appendages	7 (13.5)	5 (9.6)	5 (9.8)	2 (3.9)
Special Senses	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)

Fourteen percent (7/52) of the subjects in the Lac-Hydrin 12% Cream group and 10% (5/51) in the vehicle cream treatment group had at least one treatment-related AE. All treatment-related AEs in both treatment groups involved the "skin/appendages" body system. Events under "body as a whole" was the most common reported adverse event not related to study treatment, with infection being the most common adverse event reported in both treatment groups.

Table 16 presents a summary of AEs in the "skin and appendages" body system by treatment and relationship to the study drug in the ITT population. There were no statistically significant differences (p=0.3555) in the number of skin-related AEs reported between the two treatment groups. Twenty-three percent (12/52) of the subjects in the Lac-Hydrin 12% Cream treatment group experienced at least one skin-related AE. The vehicle group had 14% (7/51) of the subjects reporting at least one skin-related AE.

Table 16
Incidence of Skin and Appendages Adverse Events
ITT Population

Skin/Appendages Preferred Term	Lac-Hydrin 12% Cream		Vehicle Cream	
	Related to Treatment n (%)	Unrelated to Treatment n (%)	Related to Treatment n (%)	Unrelated to Treatment n (%)
Burning Skin	5 (9.6)	0 (0.0)	3 (5.9)	0 (0.0)
Dermatitis	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)
Desquamation	0 (0.0)	2 (3.8)	0 (0.0)	0 (0.0)
Dry Skin	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Eczema	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.9)
Furunculosis	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)
Irritation Skin	1 (1.9)	0 (0.0)	1 (2.0)	0 (0.0)
Neoplasm Skin Benign	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)
Stinging Skin	1 (1.9)	0 (0.0)	1 (2.0)	0 (0.0)
Redness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Itching	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
Oozing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Crusting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vesiculation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urticaria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Papules	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)

The most common skin-related AE was "burning skin," which was reported in 10% of subjects exposed to Lac-Hydrin 12% Cream and 6% of subjects using the vehicle cream treatment.

The proportion of subjects who experienced skin-related AEs in the ITT population was summarized by age group and analyzed by age (see table 17). The analysis of incidence of skin-related AEs by age (as a continuous variable) was not statistically significant (p=0.755).

Table 17
Proportion of Subjects Reporting Skin and Appendages Adverse Events by Age Group
ITT Population

Age Group	Lac-Hydrin 12% Cream (N=52)				Vehicle Cream (N=51)			
	Skin and Appendages AE? Yes		No		Skin and Appendages AE? Yes		No	
	N*	%**	N*	%**	N*	%**	N*	%**
2-6 Years	1	9.1	10	90.9	3	18.8	13	81.3
7-11 Years	5	21.7	18	78.3	3	15.0	17	85.0
12-16 Years	4	22.2	14	77.8	1	6.7	14	93.3

*Includes all subjects who reported at least one skin and appendages adverse event. Subjects reporting more than one event are counted only once.
**Denominator includes all randomized subjects within each treatment group and age category.

Table 18 summarizes AEs by drug relationship and intensity for the ITT population. All treatment-related AEs in both treatment groups were of mild/Grade I intensity. Most of the AEs classified as unrelated to treatment in the Lac-Hydrin 12% Cream treatment group were of mild/Grade I intensity (9 subjects, 18%). Three subjects (6%) reported moderate/Grade II intensity AEs. There was only one severe/Grade III AE reported. Subject #00136 reported severe/Grade III intensity migraine headache that was classified as unrelated to treatment. In the vehicle cream treatment group, an equal number of mild/Grade I and moderate/Grade II intensity AEs unrelated to treatment was reported (8 subjects, 16%).

Table 18
Incidence of Adverse Events by Drug Relationship and Intensity
ITT Population

Intensity	Related to Treatment		Unrelated to Treatment	
	Lac-Hydrin 12% Cream	Vehicle Cream	Lac-Hydrin 12% Cream	Vehicle Cream
	n (%)	n (%)	n (%)	n (%)
Mild/Grade I	7 (13.5)	5 (9.8)	9 (17.6)	8 (15.7)
Moderate/Grade II	0 (0.0)	0 (0.0)	3 (5.8)	8 (15.7)
Severe/ Grade III	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)
Very severe/ Grade IV	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	7 (13.5)	5 (9.8)	13 (25.5)	16 (31.4)

There were no serious adverse events reported and no deaths reported in this study.

8.1.1.5 Conclusions Regarding Efficacy

This double-blind placebo controlled study did demonstrate efficacy of Lac-Hydrin 12% Cream in pediatric patients ages 2-16 years of age over its placebo when used twice daily for four weeks. Mean overall severity was statistically significantly reduced in the Lac-Hydrin group as compared to placebo [(p=0.0012) using the modified ITT population]. The secondary efficacy variables of fissuring and scaling supported the overall severity analysis.

8.1.1.6 Conclusions Regarding Safety

All the adverse events that were considered related to treatment were observed and/or reported in the skin and appendages category. The most frequently reported adverse event was that of burning, which occurred in 10% of children. Pruritus was the second most frequently reported adverse event with 4% of patients reporting this event. The other adverse events reported that occurred in 2% of patients each were stinging and rash (includes erythema and irritation). There were no statistically significant differences in adverse events between Lac-Hydrin 12% Cream and its vehicle. However, no one in the vehicle group complained of pruritus. No patient discontinued due to a treatment related adverse event.

9 Overall Conclusions

Although this study was a double-blind placebo controlled study, the primary objective was to collect safety data in the pediatric population as young as 2 years of age with ichthyosis vulgaris and xerosis, which was not done in the original NDA. In the adult data, the higher incidence of adverse events occurred in the ichthyosis vulgaris patients, therefore a study of patients with this genodermatosis was sufficient for both indications. Given that the natural history of ichthyosis vulgaris is the same in both the adult and pediatric populations, adult efficacy data was extrapolated to the pediatric population at the outset. This study did, however, demonstrate on its own that Lac-Hydrin 12% Cream is efficacious in treating this disorder in the pediatric population (p=0.0012) for mean reduction in overall severity.

The safety data did not reveal any new adverse events specific to the pediatric population. The incidence of burning and pruritus was about the same. The incidence of stinging and rash was much higher in the adult population (see table 19).

Table 19
Skin Related Adverse Events In Adults* and Children
With Exposure to Lac-Hydrin 12% Cream

	Lac-Hydrin 12% Cream	
Event	Children (2-16 years)	Adults (>12 years)
Burning	10%	10-15%
Stinging	2%	10-15%
Rash (includes erythema and irritation)	2%	10-15%
Itching	4%	5%

*as per current labeling

Reviewer's Comment: The following label is the proposed package insert as submitted by the sponsor on August 26, 2000. The only section with proposed changes is the pediatric use section. Recommended additions are noted by shadowing and deletions by ~~strikeout~~.

10 Labeling Review

Rx only

LAC-HYDRIN 12%* (ammonium lactate cream) Cream

For Dermatologic use only. Not for ophthalmic, oral or intravaginal use.

10.1 Description

DESCRIPTION: *LAC-HYDRIN is a formulation of 12% lactic acid neutralized with ammonium hydroxide, as ammonium lactate with a pH of 4.4 - 5.4. LAC-HYDRIN Cream also contains water, light mineral oil, glyceryl stearate, polyoxyl 100 stearate, propylene glycol, polyoxyl 40 stearate, glycerin, cetyl alcohol, magnesium aluminum silicate, laureth-4, methyl and propylparabens, and methylcellulose. Lactic acid is a racemic mixture of 2-hydroxypropanoic acid and has the following structural formula:

10.2 Clinical Pharmacology

CLINICAL PHARMACOLOGY: Lactic acid is an alpha-hydroxy acid. It is a normal constituent of tissues and blood. The alpha-hydroxy acids (and their salts) are felt to act as humectants when applied to the skin. This property may influence hydration of the stratum corneum. In addition, lactic acid, when applied to the skin, may act to decrease corneocyte cohesion. The mechanism(s) by which this is accomplished is not yet known.

An *in vitro* study of percutaneous absorption of Lac-Hydrin Cream using human cadaver skin indicates that approximately 6.1% of the material was absorbed after 68 hours.

10.3 Indications and Usage

Indications and Usage: LAC-HYDRIN Cream is indicated for the treatment of ichthyosis vulgaris and xerosis.

10.4 Contraindications

CONTRAINDICATIONS: None known.

10.5 Warnings

WARNING:
Use of this product should be discontinued if hypersensitivity to any of the ingredients is noted. Sun exposure to areas of the skin treated with Lac-Hydrin Cream should be minimized or avoided (See Precautions section).

10.6 Precautions

10.6.1 General

PRECAUTIONS:
General:
For external use only. Stinging or burning may occur when applied to skin with fissures, erosions, or that is otherwise abraded (for example, after shaving the legs). Caution is advised when used on the face because of the potential for irritation. The potential for post-inflammatory hypo- or hyperpigmentation has not been studied.

10.6.2 Information for patients

Information for patients:
Patients using LAC-HYDRIN Cream should receive the following information and instructions:

1. This medication is to be used as directed by the physician, and should not be used for any disorder other than for which it was prescribed. It is for external use only. Avoid contact with eyes, lips, or mucous membranes.

2. Patients should minimize or avoid use of this product on areas of the skin that may be exposed to natural or artificial sunlight, including the face. If sun exposure is unavoidable, clothing should be worn to protect the skin.

3. This medication may cause stinging or burning when applied to skin with fissures, erosions, or abrasions (for example, after shaving the legs).

4. If the skin condition worsens with treatment, the medication should be promptly discontinued.

10.6.3 Carcinogenesis, mutagenesis, impairment of fertility

[ ]

[

]

10.6.4 Pregnancy

[

]

10.6.5 Nursing mothers

Nursing mothers:
Although lactic acid is a normal constituent of blood and tissues, it is not known to what extent this drug affects normal lactic acid levels in human milk. Because many drugs are excreted in human milk, caution should be exercised when LAC-HYDRIN is administered to a nursing woman.

10.6.6 Pediatric use

Pediatric use: The safety and effectiveness of Lac-Hydrin Cream have been established in pediatric patients as young as 2 years old.

10.7 Adverse Reactions

ADVERSE REACTIONS:
In controlled clinical trials of patients with ichthyosis vulgaris, the most frequent adverse reactions in patients treated with Lac-Hydrin Cream were rash (including erythema and irritation) and burning/stinging. Each was reported in approximately 10 - 15% of patients. In addition, itching was reported in approximately 5% of patients.

In controlled clinical trials of patients with xerosis, the most frequent adverse reactions in patients treated with Lac-Hydrin Cream were transient burning, in about 3% of patients, stinging, dry skin and rash, each reported in approximately 2% of patients.

10.8 Dosage and Administration

DOSAGE AND ADMINISTRATION: Apply to the affected areas and rub in thoroughly. Use twice daily or as directed by a physician.

10.9 How Supplied

HOW SUPPLIED: LAC-HYDRIN Cream is available in cartons of 280 g (2 -140 g plastic tubes) and 385 g plastic bottle. Store at controlled room temperature, 15° to 30°C (59° to 86°F).

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11 Recommendations

It is recommended that Lac-Hydrin 12% Cream be approved for use in the treatment of xerosis and ichthyosis vulgaris in patients as young as 2 years of age.

/S/

Denise Cook, M.D.
Medical Officer, Dermatology

7/18/00

cc: HFD-540
HFD-340
HFD-540/CSO/WhiteK
HFD-540/CHEM/
HFD-540/PHARM/BrownP
HFD-540/MO/CookD
HFD-725/Stats/ThomsonS
✓ Not in DFS

For Concurrence Only:
HFD-540/Clinical TL/WalkerS /S/ 7/14/00
HFD-540/DivDir/WilkinJ /S/ 8/15/00