

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-570

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-570 APPLICANT: Clay-Park Labs, Inc.

DRUG PRODUCT: Ammonium Lactate Lotion, 12%

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. An equivalence comparison is only valid if the reference treatment is effective against placebo in the trial. The test drug must also be effective against placebo in the trial. You did not analyze the reference drug against placebo and conducted a pooled analysis of the actives versus placebo. A separate analysis of the efficacy of test versus placebo and reference versus placebo should be conducted.
2. You changed the efficacy criteria for the efficacy analysis of Test versus Reference when the original analysis failed and did not change the equivalence criteria. Such a post-hoc change is not desirable. The criteria for evaluating efficacy and equivalence should be the same.
3. When these analyses were done, neither the Clay-Park test product nor the Lac-Hydrin reference product was superior to the placebo treatment.
4. The efficacy test should be carried out at $\alpha = 0.05$ for a two-sided test or $\alpha = 0.025$ for a one-sided test, not at an alpha level of 0.05 for a one-sided test.
5. The sample size calculation was not done correctly in that the previous points were not considered. In addition, the sample size was calculated for testing the difference between 2 treatments of the means of a variable with a 10-point scale while the statistical comparison was to be done on the difference in success rates of two treatments.

6. The sample size requirements were re-calculated for the efficacy testing for 15% difference using chi-square test and for equivalence testing of 15% limit using two one-sided tests (Farrington and Manning's asymptotic test procedure). The required sample size would be the maximum of the two sizes. The sample size required for the placebo group is between 100 and 170 depending on the assumed true response proportion of the placebo group. The sample size of each of the active treatment groups is between 112 and 159 depending on the true response proportion of the reference treatment group assuming that the response proportion of the reference treatment group ranges from 60% to 75%. It shows that the study was not designed with appropriate sample sizes to demonstrate the efficacy of test and reference over placebo or the equivalence of the test and reference treatments of dichotomized outcome.
7. The Per Protocol Population is used to evaluate equivalence. This population should exclude subjects who had protocol violations as well as those who were out of the visit window for the bioequivalence primary endpoint.
8. Using Wald's Test with Continuity Correction or the Farrington and Manning approach, the test and reference product do not meet bioequivalence criteria regardless of how the Per Protocol Population was defined.

Sincerely yours,



Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-570
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Final with Dates)
HFD-600/M. Fanning *MF 1/28/00*
HFD-650/Dale Conner *MF 1/28/00*

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BIOEQUIVALENCY - DEFICIENCIES Submission Date: March 26, 1999

- | | | |
|----|-------------------------------------|-----------------------|
| 1. | OTHER OPTIONS (less common): | Strengths: <u>12%</u> |
| | Bio study (STU) | Outcome: UN |
| 2. | Study Amendment (STA) | Strengths: <u>12%</u> |
| | September 16, 1999 | Outcome: UN |

Outcome Decisions:
UN - Unacceptable

WinBio Comments

**APPEARS THIS WAY
ON ORIGINAL**

REVIEW OF A BIOEQUIVALENCE STUDY WITH CLINICAL ENDPOINTS

ANDA 75-570
Drug Product: Ammonium Lactate Lotion, 12%
Sponsor: Clay Park Labs. Inc.
Reference Listed Drug: Lac-Hydrin[®] Lotion, 12%, Westwood-Squibb, NDA# 19155
Submission dates: March 29, 1999, July 14, 2003, and October 15, 2003
Date of Review: June 9, 2004
Reviewer: Carol. Y. Kim, Pharm.D.

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I. Introduction

Ammonium Lactate is a topical humectant and is indicated for the treatment of ichthyosis vulgaris and xerosis. The approved labeling recommends twice daily application to the affected area. Erythema, burning or stinging have each been reported in 9% to 12% of patients with ichthyosis vulgaris treated with topical ammonium lactate 12% lotion.

Ichthyosis Vulgaris

Hereditary ichthyosis vulgaris and acquired ichthyosis are both members of a group of cutaneous disorders of keratinization. Hereditary ichthyosis vulgaris is an autosomal dominant genetic disorder first evident in early childhood and is the most common form, accounting for more than 95% of ichthyosis. In the United States, the incidence of hereditary ichthyosis vulgaris is approximately 1:300. It is caused by altered profilaggrin expression leading to scaling and desquamation. Acquired ichthyosis is a nonhereditary condition associated with internal disease and is extremely rare.

Ichthyosis vulgaris is characterized by symmetrical scaling of the skin. Scales are small, fine, irregular, and polygonal in shape, often curling up at the edges to give the skin a rough feel. Scales vary in size from 1 mm to 1 cm in diameter, with color ranging from white to dirty gray to brown. The lower extremities generally are more affected than the upper extremities.

Hereditary ichthyosis vulgaris is a chronic disorder that may improve with age but requires continuous therapy for many patients. The main approach to treatment includes hydration of the skin. Topical ammonium lactate cream is effective for moisturizing the skin and reducing excessive epidermal keratinization.

II. Background

Previous submissions to ClayPark's ANDA

1. 1/19/98: Medical Officer's Review, IND 15-285 (ClayPark)

Since the original protocol review performed by the Division of Dermatologic and Dental Drug Products was not readily available, the OGD medical officer reviewed the protocol amendment (#951317) independently and issued several comments regarding appropriate primary and secondary analyses.

2. 3/29/99: Original Submission, ANDA 75-570

The OGD medical officer's review dated January 10, 2000 concluded that the sponsor's study failed to show the bioequivalence of the test and the reference products and issued various deficiencies regarding the appropriate statistical analyses. The OGD medical officer commented that the active treatment groups need to be superior over the vehicle/placebo to demonstrate that the study is sufficiently sensitive to discern a difference between products.

3. 7/14/03: The current submission, a new bioequivalence study (protocol #CPL-101), submitted for ANDA 75-570

Since the study design used for the treatment of Ichthyosis Vulgaris in Clay Park's ANDA 75-774 (Ammonium Lactate, 12% Cream) was accepted by the OGD, the sponsor used the same study design for the current submission. Ammonium Lactate, 12% Cream (ANDA 75-774) is currently available in the market.

4. 10/15/03: Study amendment

Based on this reviewer's request, the sponsor submitted additional information including samples of Case Report Form. The missing information for study sites #17-25 was also submitted for the review.

Generic applications submitted for ammonium lactate products for the same indication

1. IND _____ ANDA _____'s application failed to demonstrate the bioequivalency of their product.
2. ANDA 75-575: Paddock's application for ammonium lactate lotion was approved on June 11, 2002 and is currently available in the market.
3. ANDA 75-216: Taro's original study for ammonium lactate lotion was reviewed by the OGD medical officer. According to the medical officer's review dated 2/27/02, the sponsor conducted the study using an unacceptable study design. The OGD medical officer advised the sponsor to conduct the study using the appropriate study design as previously recommended by the OGD for their ANDA 75-883 (Ammonium Lactate Cream, 12%).
4. ANDA 75-774: Clay Park's application for ammonium lactate cream was approved on May 1, 2002.

5. ANDA 75-883: Taro's application for ammonium lactate cream was approved by the Agency on April 10, 2003.

III. New Study Summary (CPL-101)

Protocol Number: CPL-101

Title: A Double-Blind, Randomized, Parallel-Group, Placebo-Controlled, Multi-Center Study to Evaluate the Safety and Clinical Equivalence of a Generic Ammonium Lactate Lotion, 12% vs. Lac-Hydrin[®] 12% (Ammonium Lactate) Lotion in Subjects with Moderate to Severe Ichthyosis Vulgaris.

Objective: The objectives of the study were to demonstrate comparable safety and efficacy of Clay-Park Labs, Inc.'s Ammonium Lactate Lotion, 12% (Test Product) and Lac-Hydrin[®] 12% (ammonium lactate) Lotion (Westwood-Squibb Pharmaceuticals Inc.; Reference Product) in the treatment of subjects with moderate to severe Ichthyosis Vulgaris in order to establish bioequivalence, and to show the superiority of the active treatments over that of the Clay-Park Labs, Inc. vehicle (Vehicle).

Study Design: A randomized, double-blind, placebo (ClayPark vehicle) controlled parallel group study comparing ClayPark's Ammonium Lactate Lotion 12% to Westwood Squibb's Lac-Hydrin[®] Lotion.

Study Treatments: A total of 506 patients were enrolled and received the following treatments in 2:2:1 ratio (test, reference, and placebo):

1. Test Product: Ammonium Lactate Lotion, 12% (Clay-Park Labs, Inc.); Lot #: VA080
2. Reference Product: Lac-Hydrin[®] 12% (ammonium lactate) Lotion (Westwood-Squibb Pharmaceuticals Inc.); Lot #: 571M109
3. Vehicle: Ammonium Lactate Lotion, 12% - Placebo (Clay-Park Labs, Inc.); Lot #: RX053

Each patient applied the study medication to the designated test sites on both legs as well as all other affected areas of the body twice daily for 4 weeks.

Inclusion/Exclusion Criteria:

Inclusion Criteria

- Male or non-pregnant female;
- Age: 18 years or older;
- Diagnosis of moderate to severe Ichthyosis Vulgaris on both lower legs (test sites). Moderate to severe was defined as a rating of 6 or greater on the Overall Disease Severity Scale as described below;
- Considered healthy otherwise;

- Signed informed consent after the study has been fully explained.

Exclusion Criteria

- A dermal examination revealed the presence of psoriasis, contact dermatitis, infection, or other skin disease and/or condition located on or in close proximity to the test sites which, in the study physician's opinion, would confound the evaluation of the Ichthyosis Vulgaris condition;
- Known allergies to topical agents and/or known to be allergic, hypersensitive or otherwise intolerant to any component of the study medications;
- Has an unstable medical or psychological condition(s) evident in the 30 days prior to Pretreatment Screening visit or that could, in the investigator's opinion, be exacerbated during the course of the study;
- Use of systemic corticosteroids within 30 days or topical steroids within 2 weeks prior to the Pretreatment Screening visit. If the need for systemic steroid therapy arose during the course of the study, the patient was discontinued from the study. If the need for topical steroid therapy to treat an acute medical event arose during the course of the study, it could be applied to any affected area of the body except the lower legs;
- Has begun, stopped or changed the usage pattern of any chronic prescription drug(s), vitamin regimen(s), dietary intake, and/or non-prescription product(s) in the 30 days prior to the Pretreatment Screening visit. Any medication taken as needed permitted for an acute illness was at the discretion of the investigator;
- History of alcohol and/or drug abuse within the past 12 months;
- Has participated in any other clinical research study in the 30 days prior to the Pretreatment Screening visit;
- A pregnant patient (urine pregnancy test had to be negative at the Initial Dosing visit, Week 0) or lactating or any woman of childbearing potential who was not using or did not agree to use a medically acceptable form of contraception during the study who was not surgically sterilized or post-menopausal (at least 2 years) or who intended to become pregnant during the study. All females of childbearing potential must have had a urine pregnancy test performed at Initial Dosing visit (Week 0) and at Week 4 (End of Treatment) visit;
- A history of unresponsiveness to ammonium lactate therapy;
- Refused to sign the Informed Consent Form.

Study Procedures:

The study medication was applied to the lower legs (test sites) as well as all other affected areas twice daily for 4 weeks. The first dose was applied in the presence of a third-party dispenser prior to departing the study site. Patients applied an adequate amount of study medication to the test sites and rubbed it into the skin as much as possible, then applied study medication to other affected areas of the body. Patients applied the study medication twice per day, once in the morning and once in the evening, for a total of 28 days. Patients were instructed not to bathe for at least 6 hours after application of the study medication, and female patients were instructed not to apply study medication for at least 1 hour after shaving legs.

Visit 1: Pretreatment Screening (washout period up to 28 days if applicable)

After obtaining the signature on the Informed Consent Form, a complete medical history including current medications was completed. A brief physical examination was performed consisting of oral temperature, respiratory rate, pulse and blood pressure (sitting 5 minutes), heart, lung, and abdominal assessments.

Patients maintained a similar lifestyle during participation in the study relating to environmental factors (laundry detergent/aides, clothing such as pantyhose, socks, length of pants, etc.), change in environmental moisture (swimming, air conditioning, etc.), activities of daily living (job, housing, relaxation), diet, and hygiene (bath/shower, shaving, etc.).

Patients using skin lotions, creams, emollients and/or moisturizers that contained an active ingredient (e.g., keratolytic agents such as salicylate or α -hydroxy acids) on the lower legs entered into a minimum 14-day washout period (a skin lotion that did not contain an active ingredient could be used up to 48 hours immediately preceding the evaluation). Patients who were not using any skin lotions, creams, emollients and/or moisturizers on the lower legs were enrolled in the study without a washout period.

Visit 2: Initial Dosing (Week 0)

This visit was either combined with Visit 1 if no washout period was required, or performed after the appropriate washout period. The investigator rated the overall disease severity and ascertained changes in general health and medical history, lifestyle, and concomitant medications. A urine pregnancy test was performed on all females of childbearing potential prior to study entry. To meet the inclusion criteria, patients had to have an Overall Disease Severity Score of 6 or greater on both lower legs at this visit. Physician Global Assessment was not evaluated at this visit. Adverse events were assessed following application. Patients were instructed not to apply the randomized study medication within 6 hours prior to the next visit (Visit 3, Week 2).

Visit 3: Safety/Application (Week 2): Days 12-16

Patients returned two weeks after the initial dosing visit primarily for assessing safety. The overall disease severity was rated, occurrence of adverse events was solicited, changes in concomitant medications and lifestyle were recorded, and compliance was checked. The third-party dispenser reviewed the study medication application procedures, retrieved any empty bottles of study medication, and dispensed the third bottle at this visit. The patient was instructed not to apply the study medication within 6 hours prior to the next visit (Visit 4, Week 4).

Visit 4: End of Treatment (Week 4): Days 26-30, Primary Endpoint Evaluation

Four weeks after the initial dosing visit, patients returned for primary endpoint evaluation. The investigator rated the overall disease severity on the lower legs and provided a Physician's

Global Assessment.

The Physician's Global Assessment was graded on a scale of 0 to 6 as follows:

Physician's Global Assessment Scale

0=**Completely clear.**

1=**Almost clear.** Very significant clearing (about 90%); however, a slight degree of scaling and/or fissuring may be present.

2=**Marked improvement.** Significant improvement (about 75%); however, some evidence of disease remains.

3=**Moderate improvement.** Intermediate between slight and marked improvement; representing about 50% improvement.

4=**Slight improvement.** Some improvement (up to 25%); however, significant amount of disease is still present.

5=**No change.**

6=**Worse.**

The severity of disease on the lower legs was rated at each visit according to the Overall Disease Severity Scale. To assure consistency, the Overall Disease Severity was rated at the initial visit and at all following visits by the same investigator if possible.

The overall disease severity was graded on a scale of 0 to 9 as follows:

Overall Disease Severity Scale

0=Normal skin, no evidence of dryness.

1=Barely perceptible scales.

2=Perceptible scales with or without reticulation present.

3=**Mild.** Fine, white adherent scales reticulation present, skin slightly rough to touch.

4=Shallow furrows with fine scales, skin rough to touch.

5=Furrows more evident, more fine and larger scales.

6=**Moderate.** Shallow furrows very evident, larger adherent scales plus occasional plaques.

7=Fissures and furrows present, large scales plus plaques less than 0.5 mm in thickness.

8=Predominant fissures and deep furrows, plaques 0.5 to 1.0 mm thick.

9=**Severe.** Extremely deep fissures with pain, deep furrowed skin, inflammation and pigmented plaques greater than 1.0 mm.

Occurrence of adverse events was solicited, changes in concomitant medications and lifestyle were recorded, and compliance was checked. A brief physical examination was performed consisting of oral temperature, respiratory rate, pulse and blood pressure (sitting 5 minutes), heart, lung, and abdominal assessments. A urine pregnancy test was performed on all females of childbearing potential. All bottles of used and unused study medication were retrieved at this visit if they were not returned at the previous visit. Patients were instructed to abstain from using any skin products and to maintain similar lifestyle habits until the final study visit.

Visit 5: After Treatment Follow-up (Week 6): Days 40-44

Patients returned for a follow-up visit two weeks following the four weeks of treatment. The investigator rated the Overall Disease Severity and performed the Physician's Global Assessment. Occurrence of adverse events was solicited and compliance was checked. Changes in concomitant medications and lifestyle were recorded.

Safety:

Safety was assessed by recording the adverse events. If a sensitivity or irritation reaction occurred with the use of the study medication, the patient was to consult the study investigator for further instructions. All adverse events/concomitant illnesses reported by patients or observed by the investigator were characterized by severity, date of onset, duration, need for treatment, and investigator's assessment of relationship to use of study drug.

Compliance:

Patients applied the medication twice daily for 28 consecutive days. The history of applications was recorded in a diary, which became part of the source documentation for the study. A patient must not have missed more than 2 days of application of study medication in any 7-day period to be evaluated as a per-protocol (PP) patient.

Statistical Assessment of Endpoints:

1) Primary Endpoints:

Clinical success: The mean Overall Disease Severity Scale score of no more than 2 on a scale of 0 to 9 at the end of Week 4.

For the primary clinical equivalence analysis, a 90% confidence interval was constructed for the difference in the clinical success rates between the Test Product and Reference Product at the Week 4 visit. The interval was calculated using Wald's method with Yate's continuity correction. Bioequivalence was established if this 90% confidence interval was contained within the interval -0.20 to $+0.20$ (-20% to $+20\%$). The analysis in the per-protocol (PP) population was considered primary and that in the intent-to-treat (ITT) population as supportive.

2) The test for sensitivity of the study to show a difference between products:

Based on the clinical success rates at the end of treatment (week 4) and at the follow-up visit (week 6), tests for the clinical success proportions of each active treatment over that of the Vehicle were conducted using two-sided Z-tests at the 0.05 level of significance and included Yate's continuity correction.

A Last Observation Carried Forward (LOCF) approach was used for missing data in all

ITT analyses.

The mean Overall Disease Severity scores for each visit by treatment as well as the Physician's Global Assessment at the End of Treatment (Week 4) and at After Treatment Follow-up (Week 6) were also tabulated. Physician's Global Assessment was not performed at baseline visit.

No secondary efficacy variables were proposed.

Reviewer's comments:

- 1. The sponsor's evaluated primary endpoint, Clinical Success based on Overall Disease Severity (ODS) score at Week 4 (end of treatment) in the PP population, is acceptable. A patient is considered a clinical success if the mean ODS score (calculated by the mean of left and right leg score) is 2 or less on a scale of 0 to 9 at Week 4. This same dichotomized success/failure endpoint was the accepted primary endpoint in the previously approved application for Clay Park's Ammonium Lactate Cream, 12% (ANDA 75-774).*
- 2. To demonstrate that the study is sufficiently sensitive to discern a difference between products, Clinical Success rates for both the test and reference products should be superior over the vehicle group at Week 4 in the ITT population.*
- 3. For treatment of Ichthyosis Vulgaris, the OGD has previously recommended that both generic and reference products should be superior to placebo at both weeks 4 and 6 (in the ITT population) to demonstrate that the study is sufficiently sensitive to discern a difference between products. However, bioequivalence is evaluated only at week 4. Therefore, the week 6 data do not contribute to the evaluation of bioequivalence. By regulation, generic sponsors are required only to demonstrate bioequivalence of their product to the RLD, and bioequivalent products are assumed to have the same effectiveness. Therefore, the additional endpoint at week 6 is unnecessary. For this and future studies of ammonium lactate products for treatment of Ichthyosis Vulgaris, the OGD will consider the endpoint at week 4 only.*
- 4. Physicians Global Assessment (PGA) was considered as a secondary endpoint in ANDA 75-774 and ANDA 75-575 and was used as supportive information. Therefore, this sponsor's PGA at the end of treatment and at follow-up visit was considered as a secondary endpoint.*

Definition of variables

Per-Protocol Population (PP): Included all eligible patients who followed the protocol.

Intent-to-Treat Population (ITT): included all eligible patients who were treated with at least one dose of study medication.

Clinical Success: A success was defined as the mean Overall Disease Severity score of no more than 2 on a scale of 0 to 9.

Sample Size

The sponsor proposed to enroll at least 350 evaluable patients, 140 per active treatment arm and 70 on placebo arm, based on the assumed efficacy rate of 0.74 at Week 4 for both the test and reference products and a success rate of 0.51 for the vehicle.

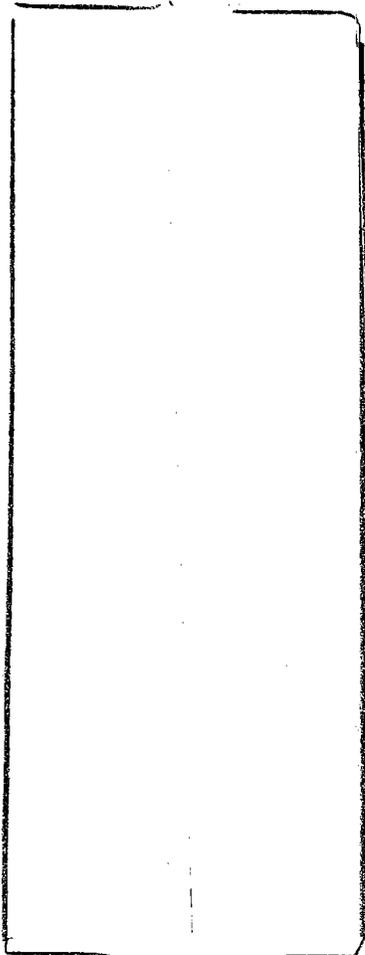
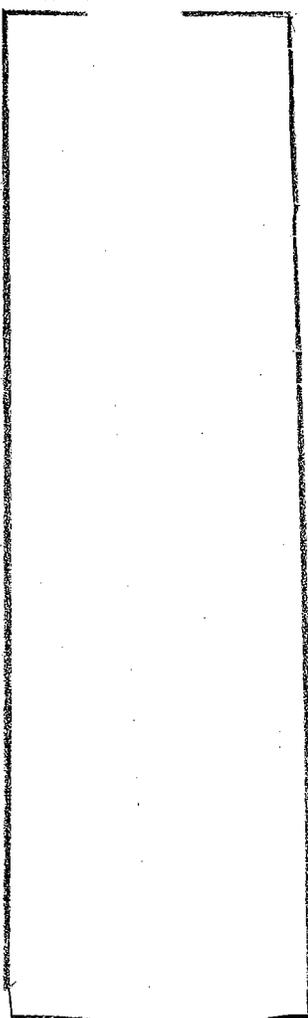
IV. Results:

Study Period: February 1, 2001 to September 28, 2001

Contract Research Organization (CRO): _____

Study Site(s): 25 sites

List of Investigators:

Center	Principal Investigator and Address	Center	Principal Investigator and Address
01		14	
02			
03			
04			
05			
06			
	15		
	16		
	17		
	18		
	19		

Center	Principal Investigator and Address	Center	Principal Investigator and Address
07		20	
08		21	
09		22	
10		23	
11		24	
12		25	
13			

Patient Enrollment

A total of five hundred six (506) patients were enrolled in the study; 205 in the test, 199 in the reference, and 102 patients in the vehicle/placebo group. All 506 patients were included in the ITT population analysis.

The distribution of patients per treatment group and the reasons for the exclusion from the evaluable population are listed for each treatment group in Table I. See Table IA for the list of patient numbers in details.

Table I – Distribution of patients by analysis population (per reviewer)

Population	Test (T)	Reference (R)	Vehicle (V)	Total
Safety	205	199	102	506
Intent-to-Treat (ITT)	205	199	102	506
^Non-compliance	-6	-4	-3	
^^Out of accepted visit window (days 26-30)	-26	-20	-20	
*No visit 4 data/lost to follow-up	-3	-2	0	
Assessed by non-board certified dermatologist (Dr. _____)	-5	-5	-3	
Discontinued due to ADE	-5	0	-1	
Prohibited Medication Use	-2	-3	-2	
**Violated inclusion/exclusion criteria	-1	-3	-3	
Evaluable Population (EP)	157	162	70	389

^ A patient must not have missed more than 2 days of application of study medication in any 7-day period to be evaluated as a per-protocol (PP) patient.

^^Week 4 visit window ranged from Days 17 to 49.

*lost to follow-up: 547 (17), 379 (24) in the reference group

**1) 212 (10)-T, 384 (25)-R: not appropriate washout period prior to entry

2) 577 (13)-R: topical steroid use within 2 weeks prior to visit

3) 529 (11)-V: study medication not applied to whole targeted area due to papules formed at the bilateral calves

4) 414 (25)-R, 205 (10)-V, 257 (14)-V: did not apply medication at least 6 hours prior to visit

Table IA. List of patients excluded by the reviewer from the Evaluable Population analysis

	Test [patient # (site #)]	Reference [patient # (site #)]	Vehicle [patient # (site #)]
OVW (day 26-30)	443 (2), 31 (4), 564 (6), 44 (8), 50 (8), 63 (9), 175 (7), 66 (9), 73 (9), 512 (11), 528 (11), 403 (12), 576 (13), 255 (14), 225 (17), 236 (17), 544 (17), 545 (17), 549 (17), 556 (17), 425 (20), 313 (21), 476 (22), 369 (24), 370 (24), 376 (24)	507 (3), 510 (3), 32 (4), ^328 (6), 190 (7), 49 (8), 65 (9), 210 (10), 217 (10), 220 (10), 107 (16), 115 (16), 238 (17), 285 (20), 467 (21), 468 (21), 362 (24), 366 (24), 367 (24), 382 (25)	506 (3), 200 (7), 45 (8), 48 (8), 52 (8), 271 (8), 213 (10), 511 (11), 521 (11), 253 (14), 92 (15), 113 (16), 229 (17), 542 (17), 548 (17), 483 (19), 487 (19), 284 (20), 302 (21), 471 (22),
Non-compliance	447 (2), 562 (6), 209 (10), 235 (17), 270 (18), 307 (21)	444 (2), 563 (6), 251 (14), 485 (19)	56 (8), 348 (22), 148 (23)
No visit 4 data	28 (4), 530 (11), 361 (24)	547 (17), 379 (24)	-
Dr. _____ non-board certified dermatologist)	388 (25), 389 (25), 395 (25), 396 (25), 412 (25)	387 (25), 390 (25), 397 (25), 400 (25), 411 (25)	394 (25), 415 (25), 416 (25)
Discontinued due to Adverse events	171 (7), 214 (10), 408 (12), 126 (19), 363 (24)	-	423 (20)
Prohibited med use (corticosteroid related product use)	8 (272), 21 (466)	6 (566), 11 (454), 15 (81)	13 (583), 15 (96)
Violate ex. Criteria	212 (10)-not appropriate washout pd prior to entry	577 (13)- topical steroid use w/in 2 weeks prior to initial visit, 384 (25)-not appropriate washout pd prior to entry	
Didn't apply to whole targeted area	-	-	529 (11)
Patient did not apply medication at least 6 hours prior to visit	-	414 (25)	205 (10), 257 (14)

^ withdrew consent

Reviewer's comments:

1. *The sponsor excluded patient #54 (8) in the test group due to initiation of a new medication during the 6 week study. Since the patient used Lactic acid lotion for the treatment of Ichthyosis Vulgaris, this patient should be included in the evaluable population as a treatment failure.*
2. *The sponsor excluded 25 patients from the evaluable population analysis due to initiation of a new medication during the 6 week study. Since these concurrent medication uses are not likely to alter the outcome of the study, it is not necessary to exclude them from the evaluable population. They were used mainly for the treatment of pain, seasonal allergy, high blood pressure, and infection not caused by Ichthyosis Vulgaris.*
3. *The sponsor also excluded 26 patients from the evaluable population because they were not assessed by the same investigator. The study protocol was designed to have the same investigator perform the dermatological assessments throughout the study. However, in this case, the score that was used for a clinical success does not depend on change from baseline. Therefore, it is not necessary to exclude them from the evaluable population due to protocol deviations that are considered minimal. The dermatological assessments made by other dermatologist in the absence of the principal investigator are not likely to interfere with the outcome of the study.*
4. *Patient #433 (20) was excluded by the sponsor due to lost to follow-up and initiation of new medication for muscle pain, which is not known to interfere with the study. Patient #572 (13) was excluded by the sponsor due to missing visit 3 data. Since visit 4 data are available for these two patients, they should be included in the evaluable population.*
5. *Therefore, the following patients as mentioned above should be included in the evaluable population at week 4.*

	Test [patient # (site #)]	Reference [patient # (site #)]	Vehicle [patient # (site #)]
Excluded by the sponsor due to use of Lactic Acid should be analyzed as treatment failure	54 (8)	-	-
Excluded due to new medication use during 6 week study but they are not known to affect the outcome of the study (pain killers, antibiotics, seasonal allergy drug products, blood pressure control medications)	445 (2), 323 (6), 330 (6), 276 (8), 79 (9), 580 (13), 256 (14), 114 (16), 232 (17), 131 (19), 283 (20), 433 (20), 392 (25)	27 (4), 43 (8), 47 (8), 55 (8), 104 (16), ^^153 (23), 365 (24)-allergic rhinitis, ex.criteria per sponsor, 377 (24)	451 (11), 86 (15), 133 (19), 345 (22)
Assessment by different investigator (dermatologist) should not affect the outcome of the study.	196 (7), 223 (17), 227 (17), 230 (17), 550 (17), 373 (24), 378 (24)	174 (7), 197 (7), 275 (8), 224 (17), 226 (17), 231 (17), 234 (17), 541 (17), 551 (17), 554 (17), 128 (19), 310 (21)	176 (7), 233 (17), 237 (17), 553 (17), 308 (21), 311 (21), 372 (24)
Data at visit 4 available and not known to have other protocol violation	-	572 (13)	-

^^The sponsor claimed that patient #153 (site #23) used systemic corticosteroid during six week study. According to the case report form, this patient was not on systemic corticosteroid and received Avapro for the treatment of hypertension.

Baseline Demographics

Of the total 506 patients enrolled, 178 were male and 328 were female patients. Eighty percent (406) of the study patients were White, 14% (69) Black and 2% (12) Hispanic, 2% (9) Asian, and 2% (10) were described as Others. The mean age of all enrolled patients was 52, and the mean age was comparable in all treatment groups. See Table II for the sponsor's reported demographic characteristics.

TABLE II – DEMOGRAPHIC CHARACTERISTICS FOR INTENT-TO-TREAT SUBJECTS

Parameter	Ammonium Lactate Lotion, 12% (N=205)	Lac-Hydrin® 12% Lotion (N=199)	Vehicle (N=102)	p-value
Gender(n,%)				
Male	70 (34%)	72 (36%)	36 (35%)	0.900 ¹
Female	135 (66%)	127 (64%)	66 (65%)	
Race(n,%)				
White	170 (83%)	158 (79%)	78 (76%)	0.339 ¹
Black	25 (12%)	29 (15%)	15 (15%)	
Hispanic	4 (2%)	4 (2%)	4 (4%)	
Asian	2 (1%)	5 (3%)	2 (2%)	
Other	4 (2%)	3 (2%)	3 (3%)	
Age(years)				
Mean ± SD	52.22 ± 14.45	52.20 ± 15.64	51.07 ± 13.57	0.740 ²
Min - Max	18.0 - 84.8	18.3 - 90.2	20.5 - 79.3	

¹P-values for treatment comparisons from Cochran-Mantel-Haenszel test for general association, adjusted for site. For the variable race, the p-value was calculated after combining the following categories: Black, Hispanic, Asian, and Other.

²P-values for treatment comparisons from a two-way analysis of variance with factors of treatment and site.

Baseline Evaluation Comparison

At baseline, the Overall Disease Severity scores were assessed by the investigator. The mean overall disease severity scores at Week 0 were comparable for all three treatment groups in the ITT population as shown in Table III.

**APPEARS THIS WAY
ON ORIGINAL**

TABLE III – OVERALL DISEASE SEVERITY SCORES AT WEEK 0 FOR INTENT-TO-TREAT SUBJECTS

Parameter	Ammonium Lactate Lotion, 12% (N=205)	Lac-Hydrin® 12% Lotion (N=199)	Vehicle (N=102)	p-value
Week 0 Overall Disease Severity Score¹				
Mean ± SD	6.60 ± 0.78	6.58 ± 0.73	6.73 ± 0.89	0.514 ²
Median	6.0	6.0	6.3	
Min - Max	6.0 - 9.0	6.0 - 9.0	6.0 - 9.0	

¹Scores are the average of the right leg and the left leg.

²P-value for treatment comparison from Friedman's Chi-Square Test adjusting for site.

Reviewer's comments: Per sponsor's analysis, there was no statistically significant difference in the baseline mean Overall Disease Severity scores in all treatment groups. According to the sponsor's provided data in Table III, all patients appear to meet the minimum entry criteria of a moderate to severe Ichthyosis Vulgaris defined as an Overall Disease Severity score of 6 or higher at baseline. However, the FDA statistician discovered 34 patients (16 in the test, 14 in the reference, and 4 in the placebo) with the baseline Overall Disease Severity score lower than 6 that were included in the sponsor's ITT population analysis. Due to protocol violation, these 34 patients that did not meet the inclusion criteria were excluded from both the ITT and PP populations by the FDA statistician. See summary of statistical review for details.

Evaluation of Bioequivalence (PP population)

The sponsor compared the clinical success rates of the test and reference groups for the Per Protocol population at week 4. The clinical success rates of the active treatments over the vehicle group in the Intent-to-Treat Population at weeks 4 and 6 were also tabulated in Table IV. The sponsor's summary of physician's global assessment for the ITT population at weeks 4 and 6 is shown in Table V.

**APPEARS THIS WAY
ON ORIGINAL**

Table IV. Bioequivalence Comparisons (per sponsor)

	Ammonium Lactate Lotion, 12%	Lac-Hydrin® 12% Lotion	Vehicle	90% C.I. for Bioequivalence of Ammonium Lactate Lotion, 12% to Lac-Hydrin® 12% Lotion	p-values	
					Ammonium Lactate Lotion, 12% vs Vehicle	Lac-Hydrin® 12% Lotion vs Vehicle
Per-Protocol Subjects (n,%)						
Week 4	(N=136)	(N=141)	(N=59)			
Success	98 (72%)	101 (72%)	27 (46%)	-9.19% to 10.04% ¹		
Failure	38 (28%)	40 (28%)	32 (54%)			
Intent-to-Treat Subjects (n,%)						
Week 4	(N=205)	(N=199)	(N=102)			
Success	141 (69%)	136 (68%)	39 (38%)		<0.001 ²	<0.001 ²
Failure	64 (31%)	63 (32%)	63 (62%)			
Week 6	(N=205)	(N=199)	(N=102)			
Success	82 (40%)	85 (43%)	15 (15%)		<0.001 ²	<0.001 ²
Failure	123 (60%)	114 (57%)	87 (85%)			

¹Confidence intervals calculated using Wald's method with Yate's continuity correction.

²P-values from Z-test with Yate's continuity correction.

Table V. Summary of Physician's Global Assessment at Week 4 and Week 6 for Intent-to-Treat Subjects (per sponsor)

Parameter	Ammonium Lactate Lotion, 12% (N=205)	Lac-Hydrin® 12% Lotion (N=199)	Vehicle (N=102)
Week 4 Physician's Global Assessment ¹			
Mean ± SD	1.44 ± 1.22	1.51 ± 1.26	2.47 ± 1.57
Median	1.0	1.0	3.0
Min - Max	0.0 - 5.0	0.0 - 5.0	0.0 - 6.0
Week 4 Frequency Distribution (n,%) ¹			
0.0	46 (22.4%)	48 (24.1%)	12 (11.8%)
Week 6 Physician's Global Assessment ¹			
Mean ± SD	2.29 ± 1.34	2.35 ± 1.36	3.42 ± 1.54
Median	2.0	2.0	4.0
Min - Max	0.0 - 6.0	0.0 - 6.0	0.0 - 6.0
Week 6 Frequency Distribution (n,%) ¹			
0.0	12 (5.9%)	11 (5.5%)	2 (2.0%)

¹Scores are the average of the right leg and the left leg.

Reviewer's comments:

- *The primary endpoint (clinical success rate at Week 4) of the sponsor's analysis met 90% CI criteria (within -.20, +.20) and demonstrated superiority of the test and reference products to vehicle at Week 4 and at Week 6.*

- Based on this reviewer's comments as mentioned above, the FDA statistician was consulted for reanalysis and verification of the sponsor's analysis.

Summary of Adverse Events

No death was reported during the study. Five patients experienced serious adverse events during the study but they were not considered treatment related as shown in Table VI. The sponsor's summary analyses for the skin related adverse events were tabulated in Table VII and VIII. Of these events, ninety-three adverse events (67 patients) were reported at the application site and their relationship to the study drug is summarized by this reviewer in Table IX.

Table VI. Serious Adverse Events

Patient # (site #)	Treatment	Adverse event	Severity	Relationship to study drug	Comments	Included in PP week 4
235 (17)	Test	Fractured wrist Pneumonia	Moderate Moderate	Not related Not related	Non-compliant	no
261 (18)	Test	Abdominal aortic aneurysm	Moderate	Not related	Completed visit 4 but not visit 5	Yes
323 (6)	Test	Angioplasty	Severe	Not related	Completed visits 4 and 5	Yes
400 (25)	Reference	Worsening hypertension	Severe	Not related	Assessed by non-board certified MD	No
261 (18)	Test	Abdominal aortic aneurysm	Moderate	Not related	Completed visit 4 only	Yes

TABLE VII. SUMMARY OF ADVERSE EVENTS BY COSTART TERM FOR SKIN RELATED EVENTS (PER SPONSOR)

	Ammonium Lactate Lotion, 12% (N=205)	Lac-Hydrin® 12% Lotion (N=199)	Vehicle (N=102)
SKIN AND APPENDAGES ¹	38 (18.5%)	22 (11.1%)	21 (20.6%)
APPLICATION SITE REACTION	25 (12.2%)	15 (7.5%)	11 (10.8%)
CONTACT DERMATITIS	1 (0.5%)	0 (0.0%)	1 (1.0%)
DRY SKIN	0 (0.0%)	2 (1.0%)	1 (1.0%)
ECZEMA	0 (0.0%)	0 (0.0%)	1 (1.0%)
EXFOLIATIVE DERMATITIS	2 (1.0%)	1 (0.5%)	1 (1.0%)
HERPES SIMPLEX	1 (0.5%)	0 (0.0%)	0 (0.0%)
PARESTHESIA	0 (0.0%)	1 (0.5%)	0 (0.0%)
PRURITUS	2 (1.0%)	0 (0.0%)	1 (1.0%)
PSORIASIS	1 (0.5%)	0 (0.0%)	0 (0.0%)
RASH	8 (3.9%)	3 (1.5%)	2 (2.0%)
SKIN BENIGN NEOPLASM	0 (0.0%)	1 (0.5%)	0 (0.0%)
SKIN CARCINOMA	1 (0.5%)	1 (0.5%)	0 (0.0%)
SKIN DISORDER	0 (0.0%)	2 (1.0%)	1 (1.0%)
SKIN HYPERTROPHY	0 (0.0%)	1 (0.5%)	0 (0.0%)
SKIN ULCER	0 (0.0%)	0 (0.0%)	1 (1.0%)
SUBCUTANEOUS NODULE	1 (0.5%)	0 (0.0%)	1 (1.0%)
SWEATING	0 (0.0%)	1 (0.5%)	0 (0.0%)
URTICARIA	1 (0.5%)	0 (0.0%)	0 (0.0%)

¹Counts reflect numbers of subjects in each treatment group reporting one or more adverse events that map to the COSTART 5th edition body system. At each level of summarization (body system or event) subjects are only counted once. Percentages of subjects in each treatment group are also given.

TABLE VIII – FREQUENCY DISTRIBUTIONS FOR THE NUMBER OF ADVERSE EVENTS REPORTED PER SUBJECT FOR SKIN RELATED EVENTS (PER SPONSOR)

Number of Adverse Events	Number (%) of Subjects			p-value Ammonium Lactate Lotion, 12% vs Lac- Hydrin® 12% Lotion
	Ammonium Lactate Lotion, 12% (N=205)	Lac-Hydrin® .12% Lotion (N=199)	Vehicle (N=102)	
Adverse Events Regardless of Relationship to Study Medication				
0	167 (81%)	177 (89%)	81 (79%)	0.222 ¹
1	32 (16%)	12 (6%)	15 (15%)	
2	4 (2%)	7 (4%)	5 (5%)	
3	0 (0%)	3 (2%)	1 (1%)	
4	1 (0%)	0 (0%)	0 (0%)	
7	1 (0%)	0 (0%)	0 (0%)	
Adverse Events Related or Probably Related to Study Medication				
0	177 (86%)	182 (91%)	90 (88%)	0.279 ¹
1	23 (11%)	9 (5%)	9 (9%)	
2	3 (1%)	6 (3%)	2 (2%)	
3	0 (0%)	2 (1%)	1 (1%)	
4	1 (0%)	0 (0%)	0 (0%)	
7	1 (0%)	0 (0%)	0 (0%)	

¹P-values from Cochran-Mantel-Haenszel test for row mean scores, adjusted for site.

Table IX. Number of adverse events reported at the application site (per reviewer)

Adverse Events	Test	Reference	Vehicle
Stinging/burning/tingling	15	17	12
Red spots/allergic reaction/redness/erythema/contact dermatitis/rash	13	6	2
Peeling skin	3	1	1
Irritation	1	0	0
Sunburn/photosensitive	2	0	1
Itching	5	2	6
Edema/hypertrophy	1	3	0
Dry skin	0	1	0
White spot	0	0	1
Total number of events (# of patients)	40 (29)	30 (22)	23 (16)

Reviewer's Comments: A total of 67 patients (14%: T, 11%: R, 17%: V) reported skin-related adverse events at the application site. The percentage of patients reported with skin-related adverse events at the application site in the test, reference and vehicle groups were similar except for a higher number of reports of redness/rash in the test group. However, the number of these adverse events in the vehicle group was lower than in the reference group. The total number of patients with incidence of rash/erythema and burning/stinging are reported as 13

(6%) and 15 (7%) in the test and 6 (3%) and 17 (8.5%) in the reference group, respectively. They are comparable to the reported incidence in the reference labeling, Lac-Hydrin[®] Lotion [erythema (10%), burning (9%) and stinging (12%)].

Four out of the five patients in the test group and none from the reference group that discontinued the study due to adverse events had reaction at application site (rash, edema) that were thought to be treatment related. One patient discontinued the study due to the presence of petechia that was judged not to be related to the study drugs.

V. Formulation

The OGD chemistry reviewer identified all components and composition in the test product as satisfactory and is shown below (see review dated 5/29/03, vol. 1.1).

Ingredient	Quantity (mg/g)	% w/w
Ammonium lactate		
Cetyl alcohol		
Fragrance		
Glycerin		
Laureth-4		
Light mineral Oil		
Magnesium Aluminum Silicate		
Methylcellulose		
Methylparaben		
Polyoxyl-40 Stearate		
Propylene Glycol		
Propylparaben		
Water		

**APPEARS THIS WAY
ON ORIGINAL**

The RLD formulation is listed below per COMIS database.

Ingredient	Quantity
Ammonium Lactate	EQ 12% base

Reviewer's Comments: *The test and reference products are qualitatively and quantitatively not the same. Clay-Park's formulation contains a small amount of Fragrance _____ mg/gm) and the RLD formulation contains Fragrance _____ mg/gm) instead.*

VI. Review of Division of Scientific Investigation (DSI) report: 2/17/04

Of three sites (#8, 17, and 25) inspected, the DSI issued a Form FDA 483 at two sites (#17 and 25). Among several objectionable findings related to minor protocol deviations, a significant violation of regulatory requirement common to all three sites was regarding retention of bioequivalence testing samples (21 CFR Parts 320.38 and 320.63). The DSI concluded that the inspected sites failed to comply with the final rule for retention of bioavailability (BA) and bioequivalence (BE) testing samples and stated that the test and reference products for each shipment used in the study were not retained at the site.

Reviewer's Comments: *Besides the retention sample issues, no major flaw in the study was addressed in the DSI report. The DSI noted several protocol deviations in each site but concluded that those violations were not likely to have any significant impact on the study outcome. Given that these sites were not aware of their responsibilities to retain reserve samples for each shipment and the DSI categorized this deficiency as VAI (voluntary action indicated), the data from this study need not be discarded due to this deficiency. However, it is the sponsor's responsibility to assure that the clinical sites for all future BE studies comply with the requirements for retention of study drugs for each shipment as per 21 CFR 320.38 and 320.63. If the sponsor fails to comply with the Agency's regulation in any subsequent study, the study may be found unacceptable and a new bioequivalence study may be requested.*

VII. Review of the FDA Statistical Report (5/20/04)

The conclusion of the FDA statistical analysis supports the bioequivalence of the test and the reference products. The 90% CI of the proportional difference in clinical success (mean Overall Disease Severity scale score of 2 or less on a scale of 0 to 9) for the evaluable population at the primary endpoint (end of treatment, Week 4) is within $-.20$ and $+.20$. The test and the reference products are also shown to be significantly superior to the placebo/vehicle at Week 4 in the ITT population.

- The FDA statistician discovered 34 patients (16 in the test, 14 in the reference, and 4 in the placebo) that did not meet the minimum Overall Disease Severity (ODS) score of 6 at baseline and excluded them from the final statistical analysis.
- Prior to these findings, patient #54 (8) in the test group was asked to be included in the PP population as treatment failure by this reviewer because this patient used Lactic acid lotion for the treatment of Ichthyosis Vulgaris. Since this patient's baseline ODS was below a score of 6, the FDA statistician excluded this patient from both ITT and PP populations.
- Patient 197 (7) in the reference product was initially asked to be included in the PP population because assessment by different investigator (dermatologist) was not considered to affect the outcome of the study. However, for the same reason as mentioned above, this patient was also excluded from the ITT and PP population analyses by the FDA statistician.

Reviewer's comments: *Excluding above mentioned patients that did not meet the minimum entry criteria at baseline from the ITT and PP analyses is acceptable.*

Based on this reviewer's comments above, the FDA statistician provided the summary of the equivalence test for the evaluable population as shown below. As commented above, only Week 4 was considered for determination of bioequivalence of this product. Physician's Global Assessment was considered as supportive information.

**APPEARS THIS WAY
ON ORIGINAL**

Primary endpoint: Clinical Success at Week 4 (end of treatment)

Summary of the efficacy and clinical equivalence analysis (Evaluation at Week 4)

Population	% of success (No. of success / Total No)			p-value ²		90% CI for Test vs. Ref. (%)	Is the 90% CI within (-20%, 20%)?
	Test	Reference	Vehicle	Test vs. Vehicle	Reference vs. Vehicle		
PP Clinical Success *	70% (100/143)	66% (98/148)	48% (31/65)			(-6.0,13.4)	YES
PGA	63% (90/143)	60% (88/148)	46% (30/65)			(-6.6,13.6)	YES
MITT Clinical Success	65% (122/189)	62% (115/185)	38% (37/98)	< 0.001	< 0.001		
PGA	58% (109/189)	54% (100/185)	36% (35/98)	< 0.001	0.0040		

2: The p-values were derived from the 2-sided Fisher's exact test. *: Primary endpoint for efficacy and equivalence tests.

The secondary endpoint (clinical success rate based on mean ODS score at week 6 and PGA assessment at week 6) analyses also demonstrate that the 90% CI of both the clinical success rates and PGA assessment for the test and the reference products are within -0.20 and +0.20. Both active drug products were superior to the placebo/vehicle for a clinical success rates and PGA assessment at week 6.

VIII. Conclusion

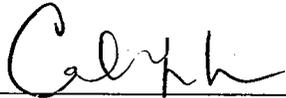
The data presented in this ANDA 75-570 demonstrate that Clay Park Labs. Inc.'s Ammonium Lactate Lotion, 12%, is bioequivalent to the reference listed drug, Lac-Hydrin® Lotion, 12%. The FDA statistical review confirms that the 90% CI of the proportional difference in clinical success (mean Overall Disease Severity score of 2 or less on a scale of 0 to 9) between the test and reference products at week 4 (end of treatment) is within (-.20, +.20).

**APPEARS THIS WAY
ON ORIGINAL**

IX. Comments to be conveyed to Sponsor

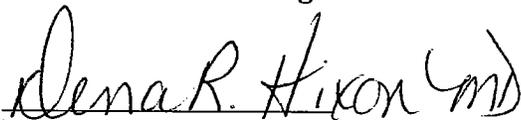
The data submitted to ANDA 75-570, using the primary endpoint of clinical success (mean Overall Disease Severity score of 2 or less on a scale of 0 to 9) rate at the end of treatment (Week 4), are adequate to demonstrate bioequivalence of Clay Park Labs. Inc.'s Ammonium Lactate Lotion, 12%, with the reference listed drug, Westwood-Squibb's Lac-Hydrin[®] Lotion, 12%. Both active treatments demonstrated superiority over the placebo arm at Week 4.

1. For bioequivalence studies with clinical endpoints involving treatment of ichthyosis vulgaris, the OGD has previously recommended that both generic and reference products should be superior to placebo at both weeks 4 and 6 (in the ITT population) to demonstrate that the study is sufficiently sensitive to discern a difference between products. However, bioequivalence is evaluated only at week 4. The week 6 endpoint does not contribute to the evaluation of bioequivalence. Therefore, for this and future studies of ammonium lactate products for treatment of ichthyosis vulgaris, the OGD will consider the endpoint at week 4 only.
2. It is your responsibility to assure that the clinical sites for all future BE studies comply with the requirements for retention of study drugs for each shipment as per 21 CFR 320.38 and 320.63. If you fail to comply with the Agency's regulation in any subsequent study, the study may be found unacceptable and a new bioequivalence study may be requested. Please refer to "Handling and Retention of BA and BE Testing Samples", posted 8/20/02 for details.



Carol Y. Kim, Pharm.D.
Clinical Reviewer
Office of Generic Drugs

6/9/04
Date



Dena R. Hixon, M.D.
Associate Director for Medical Affairs
Office of Generic Drugs

6/9/04
Date



Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs

6/9/04
Date

CC: ANDA 75570
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-600/ C.Kim
HGD-600/ D. Hixon

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Endorsements: (Final with Dates)

HFD-655/C. Kim *ck 6/9/04*
HFD-600/D. Hixon *DEH 6/9/04*
HFD-650/D. Conner *MC 6/9/04*

BIOEQUIVALENCY - ACCEPTABLE

submission dates:

March 19, 1999 (failed study)
July 14, 2003

1. Bioequivalence Study (STU); July 14, 2003 Strengths: 12%
Outcome: AC
2. Study Amendment (STA); October 15, 2003 Strengths: 12%
Outcome: AC

Please note: This review should close the BCE and BST assignments.

Outcome Decisions: AC - Acceptable
WC - Without charge
IC - Incomplete
UC - Unacceptable

**APPEARS THIS WAY
ON ORIGINAL**

6.1

**OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE**

ANDA # : 75-570

SPONSOR : Clay Park Labs. Inc.

DRUG AND DOSAGE FORM : Ammonium Lactate Lotion, 12%

STRENGTH(S) : 12%

TYPES OF STUDIES : Clinical Endpoint

CLINICAL STUDY SITE(S) : multiple sites

ANALYTICAL SITE(S) : N/A

STUDY SUMMARY: Study is acceptable

DISSOLUTION : N/A

DSI INSPECTION STATUS

Inspection needed: <input checked="" type="checkbox"/> YES / NO	Inspection status: complete (2/17/04)	Inspection results: acceptable (VAI)
First Generic _____	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
other _____		

PRIMARY REVIEWER : Carol Y. Kim, Pharm. D.

INITIAL : CEL / h DATE : 6/9/04

ASSOCIATE DIRECTOR FOR MEDICAL AFFAIRS: Dena R. Hixon, M.D.

INITIAL : DRH DATE : 6/9/04

DIRECTOR, DIVISION OF BIOEQUIVALENCE : Dale P. Conner, Pharm. D.

INITIAL : DP DATE : 6/9/04