CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-729

APPROVAL LETTER

5 20

JUN 13 1988

NDA 19-729

James H. Conover, Ph.D.
Lederle Laboratories
Middletown Road
Pearl River, NY 10965

Dear Dr. Conover:

Reference is made to your New Drug Application (NDA) dated June 5, 1987, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cyclocort (amcinonide) Lotion, 0.1%.

Reference is also made to your communications dated March 23 and March 30, 1988, which included revised draft labeling.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted draft labeling. Accordingly, the application is approved, effective as of the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling.

Please submit twelve copies of the final printed labeling (FPL) to the Food and Drug Administration (FDA) as soon as available. For administrative purposes, this submission should be designated as an "FPL Supplement" to the approved NDA. Approval of this supplement by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of this drug product become available prior to our receipt of the final printed labeling, revision of that labeling may be required.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

Lillian Gavrilovich, M.D.
Acting Director
Division of Anti-Infective
Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: NYK-DO
ORIG. NDA 19-729
HFD-82
HFD-710
HFD-220
HFD-520
HFD-520/CHEM/DCBostwick/sdj/4/17/88/6/8/88
HFD-520/MO/CCEvans/4/25/88 (51) 6/10/88
HFD-520/PHARM/JMDavitt/4/21/88 (51) 6-9-88 - Supervisors Signatures on attached copy.
HFD-520/CHEM/ARCasola/4/25/88
F/T: 6/8/88

APPROVAL 1351u

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-729

FINAL PRINTED LABELING

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CYCLOCORT®
Amcinonide
Lotion
with AQUATAIN™ hydrophilic base

SEP 30 1983

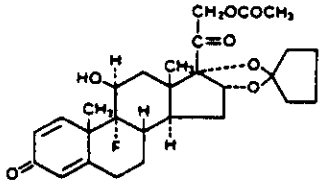
APPROVED

DESCRIPTION
Topical Lotion 0.1%

Each gram of CYCLOCORT amcinonide Lotion contains 1 mg of the active steroid amcinonide in AQUATAIN, a white, smooth, homogeneous, opaque emulsion composed of Benzyl Alcohol 1% (wt/wt) as preservative, Emulsifying Wax, Glycerin, Isopropyl Palmitate, Lactic Acid, Purified Water, and Sorbitol Solution. In addition, contains Polyethylene Glycol 400.

Sodium hydroxide may be used to adjust pH to approximately 4.4 during manufacture.

Amcinonide



$C_{28}H_{35}FO_7$ 502.58

Pregna-1,4-diene-3,20-dione, 21-(acetyloxy)-16,17-[cyclopentylidenebis(oxy)]-9-fluoro-11-hydroxy-, (11β, 16α).

CLINICAL PHARMACOLOGY
Topical corticosteroids have anti-inflammatory, antipruritic and vasoconstrictive actions.

The mechanism of anti-inflammatory activity of the topical corticosteroids is unclear. Various laboratory methods, including vasoconstrictor assays, are used to compare and predict potencies and/or clinical efficacies of the topical corticosteroids. There is some evidence to suggest that a recognizable correlation exists between vasoconstrictor potency and therapeutic efficacy in man.

Pharmacokinetics
The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings.

Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. (see *DOSAGE AND ADMINISTRATION*).

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees.

Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

INDICATIONS AND USAGE
Topical corticosteroids are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS
Topical corticosteroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

PRECAUTIONS

General

Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Conditions that augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings.

Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area or under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute with a less potent steroid.

Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity (see *PRECAUTIONS* - Pediatric Use).

If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted.

In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

The product is not for ophthalmic use.

Information for the Patient

Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
2. Patients should be advised not to use this medication for any disorder other than for which it was prescribed.
3. The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive unless directed by the physician.
4. Patients should report any signs of local adverse reactions, especially these that occur under occlusive dressings.
5. Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressings.

Laboratory Tests

The following tests may be helpful in evaluating the HPA axis suppression:

Urinary free cortisol test
ACTH stimulation test

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of topical corticosteroids or their effect on fertility.

Studies to determine mutagenicity with prednisolone and hydrocortisone have revealed negative results.

Pregnancy Category C

Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Nursing Mothers

It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant. Nevertheless, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced

HPA axis suppression and Cushing's syndrome than mature patients because of a higher ratio of skin surface area to body weight.

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

ADVERSE REACTIONS

In the clinical trials with CYCLOCORT Lotion, the investigators reported a 4.7% incidence of side effects. In a weekly acceptability evaluation, approximately 20% of the patients treated with CYCLOCORT Lotion or placebo reported itching, stinging, soreness or burning at one or more of the visits.

The following local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximate decreasing order of occurrence:

- Burning
- Itching
- Irritation
- Dryness
- Folliculitis
- Hypertrichosis
- Acneiform eruptions
- Hypopigmentation
- Perioral dermatitis
- Allergic contact dermatitis
- Maceration of the skin
- Secondary infection
- Skin atrophy
- Striae
- Miliaria

OVERDOSAGE

Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects (see *PRECAUTIONS*).

DOSAGE AND ADMINISTRATION

The lotion may be applied topically to the specified lesions, particularly to those in hairy areas, two times per day. The lotion should be rubbed into the affected area completely, and the area should be protected from washing, clothing, rubbing, etc. until the lotion has dried.

Occlusive dressings may be a valuable therapeutic adjunct for the management of psoriasis or recalcitrant conditions.

If an infection develops, the use of occlusive dressings should be discontinued and appropriate antimicrobial therapy instituted.

HOW SUPPLIED

CYCLOCORT® amcinonide Lotion 0.1% (1 mg/g) with AQUATAIN™ hydrophilic base is available as follows:

20 mL (19.6 g) Bottle - NDC 0005-9363-37
60 mL (58.8 g) Bottle - NDC 0005-9363-41

Store at Controlled Room Temperature 15-30°C (59-86°F).
DO NOT FREEZE.

LEDERLE LABORATORIES DIVISION
American Cyanamid Company, Pearl River, NY 10965

24514
REV. 8/88

2 Page(s) Redacted

Draft

Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-729

MEDICAL REVIEW(S)

April 7, 1988

MEDICAL OFFICER'S REVIEW OF NDA 19-729

Sponsor: Lederle Laboratories
Wayne, NJ 07970

Product: Cyclocort (amcinonide) Lotion, 0.1%

Date of Submission: March 23, 1988 and March 30, 1988.

Background: This NDA was found "approvable" on March 7, 1988. The March 23, 1988 submission includes a safety update and revised draft labeling. The March 30, 1988 provides a revised "Nursing Mothers" statement for the labeling.

Material Reviewed: The safety update reports that no new or unusual adverse reactions have been seen with the drug since the NDA was submitted.

Five labeling revisions were recommended in the approvable letter. The sponsor has agreed to the first four in the revised draft.

The last request was to include the following paragraph in the "ADVERSE REACTIONS" section:

The sponsor has proposed that this information be presented as follows:

> In the clinical trials with CYCLOCORT Lotion, the investigators reported a 4.7% incidence of side-effects. In a weekly acceptability evaluation, approximately 20% of the patients treated with CYCLOCORT Lotion or placebo reported itching, stinging, soreness or burning at one or more of the visits.

We have no objection to this revision. The incidence of adverse reactions included in other topical steroid labeling is a result of investigator reporting. The 4.7% incidence is about average for topical steroids. As noted in our earlier review, the sponsor's policy of presenting the patients with a written questionnaire which specifically solicited the above reactions is unusual and undoubtedly caused a greater number of reports than is usually seen.

Conclusions and Recommendation: This NDA may be approved. FPL identical to the March 30, 1988 draft should be requested.

/S/
David C. Bostwick

/S/
C. C. Evans, M.D.

cc:
ORIG. NDA 19-729
HFD-320
HFD-520 /S/
HFD-520/CHEM/DCBostwick/sdj/4/19/88
HFD-520/MO/CCEvans
HFD-520/PHARM
1351u

APPEARS THIS WAY
ON ORIGINAL

October 20, 1987

Medical Officer Review of NDA 19-729
Original Submission, dated June 5, 1987

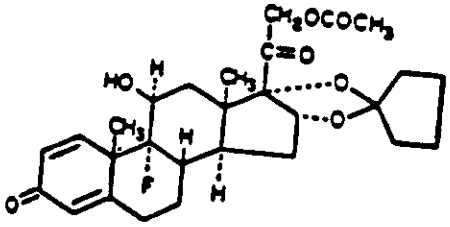
Sponsor: Lederle Laboratories
Wayne, New Jersey 07970

Product: Cyclocort (amcinonide) Lotion, 0.1%

Composition:

Ingredient	% (w/w)
Amcinonide	0.1
Benzyl Alcohol	1.0
Glycerin	
Isopropyl Palmitate	
Lactic Acid	
Polyethylene Glycol 400	
Emulsifying Wax	
Sorbitol Solution	
Purified Water	
Sodium Hydroxide [to adjust pH to 4.4]	

The active ingredient is a flourinated derivative of triamcinolone acetonide intended for topical use with the following chemical structure:



Indication: This product is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

Dosage: The lotion is to be applied to the affected areas of the skin twice daily.

Background: This is the third application to be submitted by Lederle for products which contain amcinonide. The other applications, both of which have been approved, are for Cyclocort Cream, 0.1% and 0.025% (NDA 18-116) and Cyclocort Ointment, 0.1% (NDA 18-498).

Chemistry: This review is not yet available.

Pharmacology: In his review dated June 22, 1987, Dr. Joshi, the pharmacologist, had no objection to approval of this application.

Statistics: In his review dated September 17, 1987, Dr. Harkins, the statistician, concluded that the active product had been shown to be superior to the placebo in the two submitted pivotal clinical studies.

Clinical Studies: Amcinonide has generally been considered to be one of the more potent topical corticosteroids, although not "superpotent", such as clobetasol propionate. An adrenal suppression study was performed in support of NDA 18-116, under exaggerated conditions. Briefly, Cyclocort Cream 0.1% was applied every 12 hours for five consecutive days to 50% of the total body surface of five healthy adult subjects. The area of application was occluded with Saran Wrap. Under these conditions plasma cortisol levels decreased to about 20% of baseline in all test subjects. Levels returned to baseline post-study.

A. Special Studies

1. Irritation and sensitization skin testing.

Investigator: William L. Epstein, M.D.
San Francisco, California 94143

Method: This was a double-blind bilateral study to determine the skin sensitizing and irritating ability of Cyclocort Lotion and its vehicle. The test products were applied to normal skin sites in 31 volunteers for 48 hours with occlusion. No irritation was observed, so the subjects were then treated with 7.5% sodium lauryl sulfate (SLS) solution for 24 hours under occlusion. Following a 14-day test period, challenge patches of the two test materials were applied, with occlusion, to different test sites for 48 hours. These challenge applications were preceded by 30-minute applications of 5% SLS, with occlusion, on one side and without SLS on the other. The presence or absence of a sensitization reaction was determined by examination of the sites at 48 and 72 hours after application of the patches.

Results: No reactions were produced by either the active product or its vehicle which were considered irritant or allergic in nature by the investigator.

2. Vasoconstriction Studies

Investigator: Richard Stoughton, M.D.
La Jolla, California 92093

Method: This was a double-blind study in which 30 volunteers were enrolled. Eight topical steroid preparations were to be tested; these consisted of six alternate lotion formulations, Cyclocort Cream, 0.1% and Lidex (flucinonide) Lotion, 0.05%. 0.01 g of each preparation was applied to a 3 cm in diameter test site on the volar surface of the arm of each volunteer -- 4 to each arm. The order of application was determined by randomization schedule. The application areas were washed with soap and water sixteen hours later

and assessed for vasoconstriction activity (amount of skin blanching) two hours later.

Vasoconstriction was graded on a 0 to 3+ basis, with 0 being no vasoconstriction; 3+ being maximum vasoconstriction; 1+ being minimal vasoconstriction; and 2+ being moderate vasoconstriction.

Results: A summary of the mean vasoconstriction scores is given below. Each value is the mean of 30 estimations (one from each volunteer). The "53" formulations are the alternate lotion formulations.

Study Drug	Vasoconstriction Score* (Mean ± SD)
53P	1.33 ± 0.99
53M	1.17 ± 1.02
53L	1.77 ± 0.77
LIDEX(R) Solution	2.17 ± 1.02
CYCLOCORT(R) Cream	1.47 ± 0.78
53O	1.53 ± 0.90
53Q	1.60 ± 0.93
53K	1.80 ± 0.96

Based on these results, formulations 53L and 53K were then tested separately vs. Lidex Lotion and Cyclocort cream, using the same protocol. The results were as follows:

Study Drug	Mean Score
53L	1.70 ± 0.79
53K	1.37 ± 0.85
LIDEX(R) Solution	2.07 ± 0.98
CYCLOCORT(R) Cream	1.50 ± 0.78

Based on these results, formulation 53L was chosen for controlled clinical testing.

Comments: It is noted that the proposed lotion product has not been tested for photo-toxicity or photo-allergenicity. It is felt that these tests are not necessary, given the results of the irritation and sensitization testing.

The results of the vasoconstriction studies are interesting. While the results for the Lidex Solution, Cyclocort Cream and formulation 53L products are consistent between the two tests, the mean vasoconstriction score for formulation 53K in the second study was only 76% of that obtained in the first study. This is of some concern in that this error is much larger than the margin of error we normally assign to testing of this type (±10%). Further, Dr. Stoughton is recognized as one of the most expert investigators in the vasoconstriction testing field.

It is felt that an adrenal suppression study should not be required for Cyclocort Lotion. The reasons for this are as follows:

1. The vasoconstriction assay indicates that the lotion formulation will be only marginally more potent than the already approved cream.

2. The adrenal suppression study already submitted for the cream, is more severe in some ways than the FDA guideline.

B. Controlled Effectiveness Studies

1. Double-Blind Cooperative Effectiveness Study in Psoriasis comparing Cyclocort Lotion 0.1% and its Vehicle.

Investigators: Charles Ellis, M.D.
Ann Arbor, Michigan

Stephen Horwitz, M.D.
Miami Beach, Florida

Alan Menter, M.D.
Dallas, Texas

Method: This was a cooperative, double-blind study comparing twice daily applications of Cyclocort Lotion and its placebo in the treatment of psoriasis of the scalp and/or other hairy areas. The study took place in parallel groups of patients (males and females, aged 19-82 years), who were each provided with five 60 ml bottles of either the active or placebo product along with instructions to apply the product twice daily (8 a.m. and 8 p.m.). Response to treatment was evaluated at 7, 14 and 21 days of treatment. Five disease signs and symptoms (erythema, scaling, excoriation, induration and pruritis) were rated on a seven-point scale ranging from 0.0 = absent to 3.0 = severe. Overall efficacy was rated on a seven point scale by the investigator, as follows:

1 = CLEARED - complete clearing obtained;

2 = EXCELLENT - clinical signs and symptoms significantly decreased (75% improvement);

3 = GOOD - clinical signs and symptoms persisted but to a considerably milder degree than before treatment (50% improvement);

4 = FAIR - clinical signs and symptoms were decreased slightly during treatment (25% improvement);

5 = POOR - clinical signs and symptoms decreased very slightly during treatment (25% improvement);

6 = NO EFFECT - clinical signs and symptoms unchanged;

7 = EXACERBATION - clinical signs and symptoms worse than at baseline.

Inclusion criteria included a diagnosis of psoriasis of the scalp and/or other hairy areas of the body, as well as a minimum total baseline score of 6 for the signs erythema, excoriation, scaling and induration (see explanation of scale above). Exclusion criteria included pustular or other recalcitrant psoriasis, fungal and viral diseases of the skin, etc. However, psoriatic lesions in areas of the body not being evaluated could be treated with tar, anthralin, or emollients. In addition, concurrent UVB treatment could be continued provided the scalp was covered. While these concomitant treatments do not invalidate the study, they do somewhat complicate evaluation of the study since the patients were outpatients and could conceivably have mixed up treatments.

We have examined the randomization data submitted and conclude that this study was adequately randomized.

Results: Of the 165 patients who entered the study, seven failed to return for any evaluation after baseline, and no further data is available on them. The remaining 158 were evaluated for safety. One additional patient was not evaluated for efficacy because of a possibly drug-related episode of periorbital edema. This patient was on the active product. The remaining 157 patients were evaluated for efficacy.

It is felt that the reduction in total sign and symptom scores and the physician's overall evaluation are the most significant indicators of efficacy. Further, it is felt that the most useful evaluation point is the last valid patient visit. For most test subjects, this would be the 21-day evaluation (end of study). However, the last valid visit (also called "endpoint" evaluation) is more useful because it includes patients who may have left the study early for reasons of adverse reactions or lack of effectiveness.

i. For the total sign and symptom scores, the signs erythema, scaling, excoriation and induration have been included in the evaluation. The symptom pruritis has been omitted, since it is a more subjective variable than the other four. In this evaluation, the endpoint evaluation was compared to the before-treatment scores. The highest possible score would be 12.0 (4 signs averaging a severity of 3 for each patient).

Mean Total Sign and Symptom Scores and % Reduction

Investigator	Drug	Mean Before Treatment	Mean at Endpoint*	% Reduction	Number of Patients
Dr. Ellis	Vehicle	6.98	4.11	41	27
	Cyclocort	7.70	2.26	71	25
Dr. Horwitz	Vehicle	8.05	6.34	21	28
	Cyclocort	7.91	2.91	63	27
Dr. Menter	Vehicle	8.08	5.08	37	25
	Cyclocort	7.68	2.76	64	25
Totals	Vehicle	7.70	5.38	30	80
	Cyclocort	7.77	2.65	66	77

*Endpoint = Status of disease at least visit.

11. Global Evaluation of Change in Lesion Status at Endpoint - number of Patients (%)

Investigator	Drug	Number of Patients	Cleared	Excellent	Good	Fair	Poor	No Change	Exacerbation
Dr. Ellis	Vehicle	27	0	6(22%)	5(19%)	7(26%)	8(30%)	0	1(4%)
	Cyclocort	25	6(24%)	10(40%)	3(12%)	2(8%)	3(12%)	0	1(4%)
Dr. Horwitz	Vehicle	28	0	1(4%)	3(11%)	7(25%)	9(32%)	8(29%)	0
	Cyclocort	27	3(11%)	12(44%)	4(15%)	4(15%)	2(7%)	2(7%)	0
Dr. Menter	Vehicle	25	1(4%)	2(8%)	3(12%)	8(32%)	8(32%)	2(8%)	1(4%)
	Cyclocort	25	8(32%)	6(24%)	4(16%)	5(20%)	2(8%)	0	0
Totals	Vehicle	80	1(1%)	9(11%)	11(14%)	22(28%)	25(31%)	10(13%)	2(3%)
	Cyclocort	77	17(22%)	28(36%)	11(14%)	11(14%)	7(9%)	2(3%)	1(1%)

Safety Results:

Of 78 patients on the active medication evaluated for safety, one reported a case of periorbital edema of moderate severity (probably related to the drug) which caused discontinuation of therapy. Possibly drug-related hair color changes were seen in two other patients. Folliculitis of 10 days duration occurred in one patient. Other reactions noted included stinging (9), itching (11), burning (9) and soreness (2).

Two reactions were noted in the vehicle group which were not drug related. One patient suffered a heart attack during the study, and another misapplied the medication (placed it in his ear). Possibly drug-related hair color changes were seen in one other patient. Other reactions were stinging (9), itching (17), burning (8), and soreness (2).

Evaluation:

This study establishes that twice daily treatment with Cyclocort Lotion, 0.1% is superior in terms of effectiveness to twice daily treatment with lotion placebo in the therapy of psoriasis.

2. Double-Blind Cooperative Effectiveness Study in Seborrheic Dermatitis comparing Cyclocort Lotion, 0.1% and its Vehicle

Investigators:

Roger Cornell, M.D.
La Jolla, California

Yelva Lynfield, M.D.
Brooklyn, New York

Stephen Horwitz, M.D.
Miami Beach, Florida

Larry Milliken, M.D.
New Orleans, Louisiana

Arthur Huntley, M.D.
Sacramento, California

Alan Shalita, M.D.
Brooklyn, New York

Method:

This was a cooperative double-blind study comparing twice daily applications of Cyclocort Lotion and its placebo in the treatment of seborrheic dermatitis of the scalp and/or other hairy areas. The study took place in parallel groups of patients (males and females, aged 18-87 years). The protocol was otherwise very similar to that used in the psoriasis study above, except that the disease signs and symptoms evaluated were erythema, excoriation, crusting/scales and pruritis.

We have examined the randomization data submitted and conclude that this study was adequately randomized.

Results:

Of the 167 patients who entered the study, nine failed to return for any evaluation after baseline, and no further data is available on them.

The remaining 158 were evaluated for safety. One additional patient was not evaluated for efficacy because he was the only patient enrolled by the investigator (Dr. Shalita).

i. For the total sign and symptom scores, the signs erythema, excoriation and crusting/scales have been included in the evaluation. The subjective symptom pruritis has been omitted. In this evaluation, the endpoint evaluation was compared to the before-treatment scores. The highest possible score would be 9.0 (3 signs averaging a severity of 3 for each patient).

Mean Total Sign and Symptom Scores and % Reduction

Investigator	Drug	Mean Before Treatment	Mean at Endpoint	% Reduction	Number of Patients
Dr. Cornell	Vehicle	5.83	2.96	49	12
	Cyclocort	5.81	1.62	72	13
Dr. Horwitz	Vehicle	5.04	2.17	57	12
	Cyclocort	4.85	1.08	78	13
Dr. Huntley	Vehicle	4.72	2.17	54	9
	Cyclocort	4.96	0.54	89	14
Dr. Lynfield	Vehicle	5.24	2.54	52	27
	Cyclocort	4.93	0.57	88	27
Dr. Milliken	Vehicle	5.04	2.37	53	15
	Cyclocort	4.50	0.37	92	15
Totals	Vehicle	5.20	2.47	52	75
	Cyclocort	4.98	0.77	85	82

ii. Global Evaluation of Change in Lesion Status at Endpoint - number of Patients (%)

Investigator	Drug	Number of Patients	Cleared	Excellent	Good	Fair	Poor	No Change	Exacerbation
Dr. Cornell	Vehicle	12	0	1(8%)	5(42%)	5(42%)	1(8%)	0	0
	Cyclocort	13	1(8%)	4(31%)	8(62%)	0	0	0	0
Dr. Horwitz	Vehicle	12	4(33%)	2(17%)	0	1(8%)	4(33%)	1(8%)	0
	Cyclocort	13	4(31%)	4(31%)	4(31%)	0	1(8%)	0	0
Dr. Huntley	Vehicle	9	2(22%)	2(22%)	1(11%)	0	1(11%)	2(22%)	1(11%)
	Cyclocort	14	7(50%)	6(43%)	1(7%)	0	0	0	0
Dr. Layfield	Vehicle	27	2(7%)	4(15%)	9(33%)	4(15%)	3(11%)	4(15%)	1(4%)
	Cyclocort	27	9(33%)	7(26%)	9(33%)	2(7%)	0	0	0
Dr. Milliken	Vehicle	15	2(13%)	3(20%)	3(20%)	1(7%)	4(27%)	1(7%)	1(7%)
	Cyclocort	15	11(73%)	2(13%)	0	1(9%)	1(9%)	0	0
Totals	Vehicle	75	10(13%)	12(16%)	18(24%)	11(15%)	13(17%)	8(11%)	3(4%)
	Cyclocort	82	31(39%)	23(28%)	22(27%)	3(4%)	2(2%)	0	0

Safety Result:

There were four adverse experiences which caused the patients to be withdrawn from the study permanently. One patient on the active product suffered a fine papulopustular rash, and another patient on the active product experienced moderate burning. Both these reactions were probably drug related. In addition, one patient on the placebo had a severe acne outbreak and another on placebo had erythema, itching and scaling. Both these reactions were probably drug-related.

Other reactions included a patient in the active group who reported itching of 30 minutes duration and a placebo patient who experienced moderate facial swelling. Both reactions were probably drug-related.

Minor reactions noted in the active drug group were stinging (3), itching (11), burning (7), and soreness (2). In the placebo group, there were stinging (8), itching (11), burning (6) and soreness (4).

Evaluation:

This study establishes that twice daily treatment with Cyclocort Lotion, 0.1% is superior in terms of effectiveness to twice daily treatment with lotion placebo in the therapy of seborrheic dermatitis.

Labeling Review:

The labeling for this drug follows the guideline labeling for topical steroids and is satisfactory except for the following points:

1. The last sentence of the DESCRIPTION section-(

   -is unnecessary and should be deleted.

2. The percentage of patients on active drug in the clinical studies who reported adverse reactions which were probably or possibly drug-related should be stated at the beginning of the ADVERSE REACTIONS section, as follows:

It should be noted that the overall incidence of adverse reactions is very high for topical steroids. However, it is felt that the sponsor's procedure of asking the patients to respond to a written questionnaire on a weekly basis which specifically asked whether stinging, itching, burning or soreness had been experienced resulted in a higher number of reports than does the usual procedure of oral inquiry by the investigator. The irritation and sensitization testing and infrequency of serious reactions in the clinical studies suggest that Cyclocort Lotion is not an unusually toxic product.

Evaluation and Comment:

1. There is substantial evidence in this application that Cyclocort Lotion, 0.1% is effective when properly used for the treatment of corticosteroid-responsive dermatoses. This evidence consists of a vasoconstrictor assay and one vehicle-controlled study each in psoriasis and seborrheic dermatitis. This testing is consistent with the data FDA has required for approval of an alternate formulation of a topical steroid manufactured by the drug company which holds the original NDA for the steroid.

2. The overall incidence of adverse reactions noted in the clinical studies should be added to the labeling.

Conclusions and Recommendations:

Pending submission of acceptable final printed labeling this application should be made approvable.

/S/
David Bostwick

/S/
C.C. Evans, M.D.

Orig. NDA /S/ 2/28/87
HFN-815
HFN-340
HFN-815/Bostwick
HFN-815/Evans
1195u/MBurns/12-2-87/12-16-87

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-729

CHEMISTRY REVIEW(S)

Division of Anti-Infective
Drug Products
Chemist's Review #1
Date Completed: 11/5/87

A.1. NDA 19-729

Sponsor: Lederle Laboratories, Div.
American Cyanamid Co.
Pearl River, NY 10955

2. Product Names:

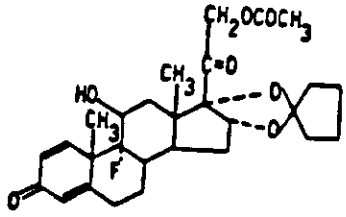
Proprietary: Cyclocort
Non-proprietary: amcinonide

3. Dosage Form & Route of Administration: Rx, topical lotion

4. Pharmacological Category and/or Principal Indication: treatment of psoriasis and seborrheic dermatitis

5. Structural Formula and Chemical Name(s):

(11β,16α-21-(Acetyloxy)16,17[cyclopentylidenebis(oxy)] - 9-fluoro -11-hydroxypregna-1,4-diene-3,20-dione.



B. 1. Initial Submission: 6/5/87

2. Amendments: 9-9-87

3. Related Documents: NDA 18-116

C. Remarks:
Manufacturer has presented controls information on a product closely resembling approved NDA 18-116 Cyclocort Cream . All pertinent information has been presented and is well organized. An amendment of 9-9-87 contains further stability data (up to 12 months). Linear regression analysis, plus data on the closely related approved cream, support a 24 month expiration date. The standard 3-point stability commitment has been made.

D. Conclusions:
The NDA may be approved from the standpoint of manufacturing and controls.

/S/
Lola G. Wayland

cc: Orig. NDA
HFN-815 HFN-815/CSO HFN-815/Wayland: gm 11/17/87
HFN-815/MO R/D initialed by: ARCasola 11/13/87 /S/ 11/24/87
HFN-815/Tabor
0846c

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-729

PHARMACOLOGY REVIEW(S)

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

NDA 19-729 (Original Submission, dated 6/11/87)

DATE REC'D: 6/15/87

DATE REVIEW COMPLETED: 6/22/87

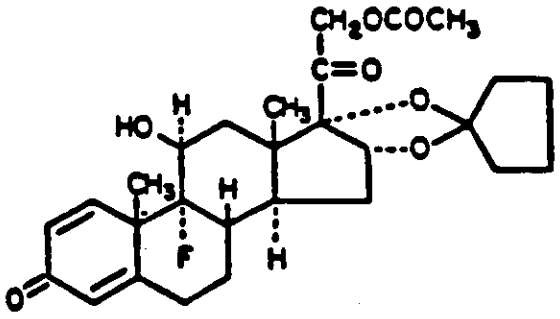
SPONSOR: Lederle Laboratories Division, American Cynamid Company
Pearl River, NY

DRUG: Cyclocort^{R} (amcinonide) Lotion, 0.1%

CATEGORY: Anti-inflammatory corticosteroid, topical (dermal)

INDICATION: Corticosteroid-responsive dermatoses

CHEMISTRY:



(11β16α)-21(acetyloxy)-16,17[cyclopentylidenebis(oxy)]
-9-fluoro-11-hydroxypregna-1,4-diene-3,20-dione

FORMULATION: (NDA Vol. 3, p. 2)

	Percent (w/w)
· Amcinonide	0.1
· Benzyl Alcohol	1.0
· Glycerin	
· Isopropyl Palmitate	
· Lactic Acid	approx.
· Polyethylene Glycol 400	
· Emulsifying Wax	
· Sorbitol Solution	
· Purified Water	
· Sodium Hydroxide [to adjust pH to 4.4]	

RELATED SUBMISSIONS: NDAs 18-116 (cream) & 18-498 (ointment)

PRECLINICAL DATA

1. Primary Dermal Irritation Study in Rabbits of Cyclocort[R] Lotion Formulation Compared with Cyclocort[R] Cream Formulation

Study No. 86062; T.E. 21: 1348-1396A; study dates, 3/13/86 to 3/20/86

Materials Tested

a) Amcinonide lotion 0.1% & the placebo (vehicle); formulation similar to that proposed for marketing

b) Amcinonide cream 0.1% & the placebo (vehicle)

Animals: Total of 12M + 12F NZ albino rabbits; 3/sex/gp

Methodology: [Followed OECD guidelines] The test articles were applied to the right (abraded) and left (unabraded) dorsal sides of each rabbit. A one inch square 2 layer thick piece of cotton gauze was inoculated with 0.5 ml of the formulation. The site was evaluated 24- and 72 hrs later. [Note: It is not clear whether or not the test site was occluded.]

Results

Group	Dermal Scores [OECD guidelines] Responses (No. Reacting/No. Treated)		
	Erythema*	Eschar	Edema
I. Cyclocort Cream - placebo	4/6	0/6	0/6
II. " Lotion - placebo	0/6	0/6	0/6
III. " Cream	3/6	0/6	0/6
IV. " Lotion	5/6	0/6	0/6

*Numerical values (indicative of degree of erythema) were 1.

Based on these findings cyclocort lotion and cyclocort cream formulation were classified as "non-irritating" to "very mildly irritating" to rabbit skin.

2. Primary Ocular Irritation Study in Rabbits of Cyclocort[R] Lotion Formulation Compared with Cyclocort[R] Cream Formulation:

Study No. 86061; T.E. 21: 1044-1067; study dates, 3/31/86 to 4/14/86

Materials Tested: Same as # 1 above

Animals: Total of 12M + 12F NZ albino rabbits; 3/sex/gp

Methodology: Instilled 0.1 ml of the formulation into either left or the right eye (determined "healthy" prior to treatment by fluorescein dye test). The untreated contralateral eye served as control. Eyes were evaluated 24- and 72 hrs later; Draize scores and observation for damage to the cornea by fluorescein dye test.

Groups: Same as in # 1 above

Results: All Draize ocular irritation scores were zero (0) at 24 & 72 hrs following dosing, indicating that none of the formulations tested were eye irritants.

COMMENTS & RECOMMENDATION

1. The active ingredient, amcinonide, is an approved drug and is currently marketed in concentration up to 0.1% in cream (NDA 18-116) & ointment (NDA 18-498) forms. Amcinonide (0.1%) in a lotion vehicle is the subject of the present application.

2. Two animal toxicity studies employing the proposed formulation were submitted in this application. The remaining preclinical data was submitted (and reviewed) for Lederle's previous applications cited above.

3. I have no objection from the safety standpoint to the approval of this application, provided the labeling is similar to that for the marketed products.

/S/ 7/2/87

S.R. Joshi D.V.M., Ph.D.

cc: Orig. NDA
HFN-815 /S/ 7/31/87
HFN-815/MO
CSO
HFN-340
HFN-815/SRJoshi/smc/7/2/87
R/d init.by:JMDavitt
5437b

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-729

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

SEP 17 1987

NDA #: 19-729/Drug Class 3C

Applicant: Lederle Laboratories

Product Name: Cyclocort® Lotion, 0.1% (Amcinonide)

Documents Reviewed: Volumes 1 and 4 through 8 dated June 6, 1987.

Indication: Psoriasis and seborrheic dermatitis

Medical Input: John Sanders M.D. (HFN-815). I have discussed this review with Dr. Sanders. He is in agreement with my conclusions.

I. Introduction

Cyclocort® Amcinonide Lotion 0.1% is proposed for treatment of psoriasis and seborrheic dermatitis involving hairy areas of the body.

For study inclusion, patients could be either sex, at least 18 years old, must have psoriasis for one study or, for the other study, seborrheic dermatitis of the scalp or other hairy areas of the body and have a minimum baseline score of 6 for signs and symptoms for psoriasis, and 4 for the seborrhea. Subjective and objective signs and symptoms evaluated for efficacy determination were erythema, crusting/scales, excoriation, induration and pruritus. Each was ranked from 0.0 = absent to 3.0 = severe.

In addition, the investigators and patients completed a therapeutic efficacy evaluation compared to baseline, where 1 = Cleared (complete clearing), 2 = Excellent, (a greater than 75% clearing) to 6 = No Effect (clinical signs and symptoms unchanged) and 7 = Exacerbation (clinical signs and symptoms worse than baseline).

The lotion was applied twice daily for a period of three weeks, and patients were evaluated at baseline and days 7, 14 and 21. In addition, any adverse reactions reported were rated as to severity and probable relation to treatment.

II. Evaluation of Study

"Cyclocort® Lotion 0.1% vs. Placebo in the Treatment of Patients with Psoriasis Protocol DP 27-15".

A. The objective of this double-blind, parallel group, randomized, multicenter study was to compare efficacy and safety/side effects of Cyclocort® and its vehicle (placebo). Three centers enrolled

83 Cyclocort® and 82 placebo patients, with 65 and 67, respectively finishing the study. The 18 cyclocort® losses were as follows: (a) 5 failed to return after baseline evaluation, (b) 1 dropped out at day 4 due to adverse reaction (Periorbital edema), (c) 3 dropped out between day 7 and 14 due to missed visit time frame (d) 1 because medicine was too greasy, (e) 4 dropped out by day 21 because of improvement and (g) 4 because their return visit was after day 24. The placebo group lost 15 subject as follows: (a) 2 failed to return after baseline check-up, (b) 4 stopped medication by day 7, (c) 3 quit by day 14, (d) 5 were outside visit time frame and (e) 1 violated protocol.

Patients accepted to the study had baseline determinations for symptoms of erythema, excoriation, scaling, induration, and pruritus. Evaluations were repeated at days 7, 14 and 21. The efficacy measurement evaluated was improvement from baseline for each symptom. The primary efficacy parameters used are patient and investigator overall evaluations. However, all efficacy parameters were evaluated.

Any patient that was negative for any of the signs and symptoms at baseline was not evaluated for improvement on subsequent days.

End-point analyses was performed by carrying any lost subject forward as unchanged from their last status for each efficacy parameter. Similarly, those randomized to the study with no "on treatment" observations were carried forward with their corresponding baseline evaluation.

Statistical evaluations used were appropriate. These included SAS FREQ (Mantel-Haenszel) procedure to test for homogeneity of demographic parameters for the two treatment groups, tests for center by treatment response interaction using SAS Proc GLM, raw mean values and raw mean changes from baseline with associated standard errors for each of the five signs and symptoms of psoriasis, and Mantel-Haenszel test from SAS FREQ for investigator and patient global improvement evaluations.

No evidence of interaction was noted and the two groups were statistically homogeneous.

The sponsor concluded that Cyclocort® is statistically superior to placebo for each investigator and for all investigators combined.

B. Reviewer's Comments

I checked the sponsor's results and my calculations were in agreement with theirs. For example, at day 21 for the global evaluation of evaluable patients; the sponsor, using Mantel-Haenszel, obtained a p-value less than .001 showing Cyclocort® superior to placebo. Their end-point analysis yielded $p < .01$. A portion of the data is shown in Table 2 for day 21.

Table 2

Global Evaluation
Evaluable Patients

Number (%)

Category	Placebo(1)	Cyclocort R (2)
Cleared	1 (1)	17 (26)
Excellent	7 (10)	25 (38)
Good	10 (15)	9 (14)
Fair	19 (28)	9 (14)
Poor	20 (30)	4 (6)
No-Effect	9 (13)	1 (2)
Exacerbation	1 (1)	0 (0)

(1) Sample size = 67, (2) Sample size = 65.

My check value yielded chi square (6) > 36, $p < .001$ for these data. My end-point analysis yielded chi square (6) = 13.24, $p < .05$ which is in agreement with the sponsor's results.

My analyses agree with the sponsor's that Cyclocort^R is statistically more efficacious than placebo in the treatment of psoriasis.

There were insufficient subjects with adverse effects to warrant statistical evaluation.

III. Evaluation of "Double-Blind, Randomized, Parallel Group, Study Comparing The Efficacy and Safety of Cyclocort^R Amcinonide Lotion 0.1% with Placebo in the Treatment of Patients with Seborrheic Dermatitis of Scalp and/or Other Hairy Areas".

A. The protocol, patient evaluation, data handling and processing for this study were identical to that for the previous study.

There were six investigators signed up to conduct this clinical trial. However, one investigator was dropped because he signed up only two subjects and one of those failed to meet the inclusion criteria.

The sponsor calculated they needed at least 75 subjects per treatment group to obtain adequate power. They actually signed up 176 and used 168 (86 in the Cyclocort^R group and 82 in the placebo group). Six of the 8 lost failed to meet inclusion criteria and two in the placebo group failed to return after the baseline visit.

End-point analysis was performed by carrying all subjects lost forward with no change from their last visit.

The sponsor states a 50%, or better improvement from baseline is considered clinically significant. Cyclocort® showed a 50% improvement by day 7 and better than 90% improvement by day 21. The placebo group showed a 50% improvement by day 21.

The statistical evaluation procedures used were appropriate for this type data.

B. Reviewers Comments

I verified the sponsors evaluation of demographic data. The two groups were not statistically different relative to weight, age, etc. nor for any of the baseline measurements, overall nor by investigator.

The sponsor's statistical evaluation was very thorough and exhaustive. I could find no problems, and my check calculations were in agreement with their results.

I confirmed their conclusions that Cyclocort® Lotion 0.1% is statistically superior to its vehicle (placebo) in treatment of seborrheic dermatitis. Cyclocort® is also statistically better than the 50% clinical improvement stated in the protocol, i.e. Cyclocort® achieved 90% improvement from baseline. For example, for the efficacy parameter "Scaling" the baseline value was 2.32 and at day 21 the mean improvement value was 2.11 for Cyclocort®; i.e. a 91% improvement. The 95% C.I. for this mean improvement value is (1.91, 2.306). For placebo, baseline value was 2.43 and day 21 mean improvement from baseline was 1.34, which yields a 55% improvement rate. The 95% C.I. is (1.14, 1.54).

These two 95% confidence intervals show that (a) Cyclocort(®) is statistically superior to placebo, (b) with this C.I., Cyclocort's percent mean improvement could be as low as $(1.91 \times 100)/2.32 = 82\%$ and (c) similarly placebo percent mean improvement could be as high as $(1.54 \times 100)/2.43 = 63\%$.

There was insufficient side effects data to do any statistical evaluation.

IV. Conclusions (Which May be Conveyed to the Sponsor)

1. The first study shows statistically that Cyclocort® Lotion 0.1% is superior to placebo in the treatment of psoriasis.

2. The second study shows statistically that Cyclocort® Lotion 0.1% is superior to placebo in the treatment of seborrheic dermatitis.

3. There was insufficient adverse reactions in either study to do a statistical evaluation that could be related to safety/side effects.

/S/

Ralph Harkins, Ph.D.
Mathematical Statistician

cc:
Orig. NDA #19-729 ✓
HFN-815
HFN-815/Mr.Bostwick
HFN-815/Dr. Sanders
HFN-815/Dr. Evans
HFN-713/Dr. Dubey [File: DRU 1.3.2]
HFN-713/Dr. Harkins
HFN-344/Dr. Lisook
Chron.
R.Harkins:x34594:SERB:skj:9-10-87:#0978n

Concur: Dr. Nevius /S/ 9/11/87

Dr. Dubey /S/ 9-15-87

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-729

ADMINISTRATIVE DOCUMENTS

NDA SUPPLEMENT REVIEW

CHEMIST'S REVIEW

1. ORGANIZATION: DAIDP

2. NDA NUMBER: 19-729

3. NAME AND ADDRESS OF APPLICANT (CITY AND STATE)
Lederle Laboratories
Pearl River, NY 10965

4. AF NUMBER

5. SUPPLEMENT(s)

NUMBER(s)	DATE(s)
S-002	8/16/88

6. NAME OF DRUG: Cyclocort

7. NONPROPRIETARY NAME: amcinonide

8. SUPPLEMENT(s) PROVIDES FOR:
minor additions to the Title, Description, and "How Supplied" sections of the labeling, specifically 'Aquatain™ hydrophilic base'

9. AMENDMENTS AND OTHER (REPORTS, etc) DATES

10. PHARMACOLOGICAL CATEGORY
Anti-inflammatory

11. HOW DISPENSED
X Rx OTC

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM(s)
Topical lotion

14. POTENCY(ies)
0.1%

15. CHEMICAL NAME AND STRUCTURE

16. RECORDS AND REPORTS

CURRENT	
Yes	No
REVIEWED	
Yes	No

17. COMMENTS

The revisions to the labeling are made to accomodate the trademark "Aquatain" for the hydrophilic base of this lotion. This labeling was permitted for the Cyclocort Cream NDA 18-116. On the package insert, since this is a lotion, after listing the Aquatain ingredients, the statement "In addition, also contains Polyethylene Glycol 400" has been added. The trademark also appears under the Title, and in the How Supplied section after the drug name and strength.

In all other particulars, the labeling is unchanged from that originally approved.

18. CONCLUSIONS AND RECOMMENDATIONS:
From the manufacturing and controls standpoint the supplement may be approved.

cc: ORIG NDA
HFD-520 HFD-520/CSO
HFD-520/MO HFD-520/Wayland:gm 9/27/88
R/D initialed by: ARCasola 9/27/88 (1.51) 9/28/88

19. REVIEWER			
NAME	SIGNATURE		DATE COMPLETED
Lola G. Wayland	(1.51)		9-26-88
DISTRIBUTION	ORIGINAL JACKET	REVIEWER	DIVISION FILE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-729

CORRESPONDENCE

NDA 19-729

James H. Conover, Ph.D.
Lederle Laboratories
Middletown Road
Pearl River, NY 10965

Dear Dr. Conover:

Reference is made to your New Drug Application (NDA) dated June 5, 1987, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cyclocort (amcinonide) Lotion, 0.1%.

Reference is also made to your additional communications dated August 12, September 1 and November 24, 1987.

We have completed our review of this application and it is approvable. Before the application may be approved, however, we request that you submit the following:

1. Safety update reports in accordance with section 314.50(d)(5)(vi)(b) of Title 21 of the Code of Federal Regulations.

2. Twelve copies of the final printed labeling for the drug that are identical to the draft copy, with the following exceptions:

   a. The last sentence of the DESCRIPTION section is unnecessary and should be deleted.

   b. In the first sentence of the CLINICAL PHARMACOLOGY section, the word "share" should be changed to "have".

   c. The last sentence of the first paragraph of the "Pharmacokinetics" subsection should be deleted.

   d. The last sentence of the "Nursing Mothers" subsection of the PRECAUTIONS section should read as follows:

      Nevertheless, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

   e. The percentage of patients on active drug in the clinical studies who reported adverse reactions which were probably or possibly drug-related should be stated at the beginning of the ADVERSE REACTIONS section, as follows:

Please submit, in duplicate, the advertising copy that you intend to use in your proposed introductory promotional and/or advertising campaign. One copy should be submitted to the Division of Anti-Infective Drug Products, and the second copy to the Division of Drug Advertising and Labeling, HFN-240, Room 10B-04, 5600 Fishers Lane, Rockville, Maryland 20857. All proposed materials should be submitted in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission; this form is for routine use, not proposed materials.

Within 10 days after the date of this letter, you are required to amend the application, or notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.110. In the absence of such action the Food and Drug Administration may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Sincerely yours,

Edward Tabor, M.D.
Director
Division of Anti-Infective
Drug Products
Office of Biologics Research and Review
Center for Drugs and Biologics

APPROVABLE

Orig. NDA
HFN-80
HFN-710
HFN-220
HFN-800
HFN-815
HFN-815/ETabor,MD
HFN-815/MO/CCEvans,MD/I:2-2-88
HFN-815/Pharm/SRJoshi,DVM
HFN-815/Chem/LGWayland/I:1-27-88
HFN-815/CSO/DCBostwick/RD:1-13-88
HFN-815/JMDavitt/I:1-27-88
HFN-815/ARCasola,PhD/I:1-28-88
3865m/MBurns/1-13-88/1-14-88/2-11-88

(51) 3/7/88
(51) 2-10-88
(51) 2/12/88
(51) 2/12/88

APPEARS THIS WAY
ON ORIGINAL

LEDERLE LABORATORIES

Lederle

A Division of AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK 10965
AREA CODE 914 735-5000

March 23, 1988

Edward Tabor, M.D., Director
Division of Anti-Infective
Drug Products
HFN 815 - Room 12B/45
Office of Biologic Research and Review
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA ORIG AMENDMENT
(SU)

NDA 19-729
CYCLOCORT R Amcinonide
Lotion 0.1%
Serial #002

Dear Doctor Tabor:

Reference is made to your approvable letter for the subject Notice NDA, dated March 7, 1988.

Pursuant to our notification to the Agency of our intent to file an amendment under 21 CFR 314.110(a) we hereby provide the following information that you requested we submit.

1. Safety update reports in accordance with section 314.50 (d)(5)(vi)(b) of Title 21 CFR. Our subject Notice NDA dated June 5, 1987 contained all our clinical data from studies that were completed prior to submission to FDA. Beyond the NDA, we filed two randomized, blinded comparative protocols to the CYCLOCORT

   (a) Protocol 27-20 (filed July 20, 1987), Cyclocort Lotion vs. Valisone in seborrheic dermatitis.

   (b) Protocol 27-21 (filed July 24, 1987), Cyclocort Lotion vs. Lidex in psoriasis.

   To date efficacy and safety results from both of these clinical studies appear no different than that which was reported for CYCLOCORT Lotion in the subject Notice NDA. No patients died nor were any discontinued from treatment because of an adverse experience.

2. We are not submitting final printed labeling, because we have made revisions in the draft labeling that require your approval as follows:

   (a) We have deleted the last sentence of the DESCRIPTION section, as you suggested.

(b) We have changed the word "share" to "have" in the first sentence of the CLINICAL PHARMACOLOGY section, as you suggested.

(c) We have deleted the last sentence of the first paragraph of the "Pharmacokinetics" subsection (pg. 3), as you suggested, but have modified a sentence with the same content as that deleted under the DOSAGE ADMINISTRATION section (pg. 11).

(d) We have incorporated your suggested wording of the last sentence of the "Nursing Mothers" subsection of the PRECAUTIONS section.

(e) We have modified your suggested sentences relevant to the adverse experience incidence reporting. This was done in an effort to distinguish the clinical investigator's reported adverse experience incidence from the patient's weekly acceptability evaluation. Our suggested statements have been inserted at the beginning of the ADVERSE REACTIONS section.

As yet, no advertising copy is available for our introductory promotional and/or advertising campaign.

Sincerely yours,

J. Conover

James H. Conover, Ph.D.
Assistant Director
Regulatory Liaison

JHC:ps
enclosure

cc: Mr. David Bostwick
Dr. John Sanders

LEDERLE LABORATORIES

Lederle

A Division of AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK 10965
AREA CODE 914 735-5000

March 30, 1988

Edward Tabor, M.D., Director
Division of Anti-Infective Drug Products
HFN 815 - Room 12B/45
Office of Biologic Research and Review
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA 18-728
CYCLOCORT® Amcinonide
Lotion 0.1%
Serial #008

Dear Doctor Tabor:

Reference is made to your approvable letter for the subject Notice NDA dated March 7, 1988, and to our response to the former dated March 28, 1988.

In our response, we included a revised package circular draft but inadvertantly omitted four words from the phraseolgy you suggested under "Nursing Mothers." We now resubmit pg. 3 of the above-mentioned circular, which contains the complete statement that you recommended. Please substitute this page for the pg. 3 found in our revised draft circular sent on March 28.

I've informed Mr. D. Bostwick of this change by phone on March 29.

Sincerely,

James H. Conover, Ph.D.
Assistant Director
Regulatory Liaison

JHC:ps
enclosure

Desk Copies: Mr. D. Bostwick
Dr. J. Sanders

LEDERLE LABORATORIES

Lederle

A Division of AMERICAN CYANAMID COMPANY

PEARL RIVER, NEW YORK 10965

AREA CODE 914 735-5000

ORIG NEW CORRES

BEST POSSIBLE COPY

November 24, 1987

/S/

Dr. E. Tabor, M.D., Director
Division of Anti-Infective Drug Products
HFN 815 - Room 12B/45
Office of Biologic Research and Review
Center for Drugs and Biologics
Food and Drug Adminstration
5600 Fishers Lane
Rockville, Maryland 20857

NDA 19-729
CYCLOCORT® Lotion
General Correspondence

Dear Doctor Tabor:

We hereby submit to the subject Notice two groups of four tables each of psoriasis and seborrheic dermatitis data that was requested by Mr. David Bostwick for the review of our NDA submission. These tables contain no additional data, nor does it represent any re-analysis of information that was otherwise contained in the initial NDA submissions.

Sincerely yours,

J. Conover

James H. Conover, Ph.D.
Assistant Director
Regulatory Liaison

JHC:ps
enclosure

APPEARS THIS WAY
ON ORIGINAL

LEDERLE LABORATORIES

A Division of AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK 10965
AREA CODE 914 735-5000

March 11, 1988

Edward Tabor, M.D., Director
Division of Anti-Infective
Drug Products
HFN 815 - Room 12B/45
Office of Biologic Research and Review
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

ORIG NEW COR...

CYCLOCORT ® (Amcinonide)
Lotion 0.1%
NDA 19-729
Serial #001

Dear Doctor Tabor:

We are in receipt of your approvable letter for the subject Notice NDA.

Pursuant to 21 CFR 314.110(a), we hereby notify the Agency of our intent to file an amendment that will satisfy the issues raised in the approvable letter.

Sincerely yours,

J. Conover

James H. Conover, Ph.D.
Assistant Director
Regulatory Liaison

JHC:ps

CC: Dr. J. Sanders
Mr. D. Bostwick

1-1

LEDERLE LABORATORIES

A Division of AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK 10965
AREA CODE 914 735-5000

BEST POSSIBLE COPY

September 1, 1987

Edward Tabor, M.D., Acting Director
Div. of Anti-Infective Drug Products
National Center for Drugs & Biologics
HFN 815
Document Control Room 12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

CYCLOCORT® amcinonide
Lotion, 0.1%
NDA 19-729

Dear Doctor Tabor:

We hereby amend the referenced NDA dated June 5, 1987, to update the stability section 3B.VII(3), filed in Volume 2 of the original submission.

The report contains satisfactory data on three lots stored for 12 months at 23°C, 6 months at 37°C, and 2 months at 42°C.

Sincerely yours,

Gordon R. Personeus
Director, Technical Services
Regulatory Affairs

GRP:drm
Enc.
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SEP 09

APPEARS THIS WAY ON ORIGINAL

LEDERLE LABORATORIES

Lederle

A Division of AMERICAN CYANAMID COMPANY

PEARL RIVER, NEW YORK 10965

AREA CODE 914 735-5000

August 12, 1987

Edward Tabor, M.D., Director
Division of Anti-Infective Drug Products
HFN 815 - Room 12B/45
Office of Biologic Research and Review
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Amcinonide
CYCLOCORT ® 0.1% Lotion
NDA 19-729
(Lederle #87-1)

Dear Tabor:

We hereby amend the subject Notice with a reformatted NDA Section 10.b., Methods Validation Package, at the request of the reviewing Chemist. This is only a reformatting of information already provided in the initial submission, and does not represent the addition of any new data or analysis.

Section 10.b, Methods Validation Package, of the subject NDA received June 11, 1987 by FDA provided no data per se but instead refered to Section 3 of the same application. On request we are also submitting under separate cover to Ms. Lola Wayland three copies of Section 10.b., each of which has all of the elements of Section 3 attached for the convenience of the reviewer.

Sincerely yours,

James H. Conover, Ph.D.
Assistant Director
Regulatory Liaison

JHC:ps

NDA 19-729

AUG 1 8 1987

James H. Conover, Ph.D.
Lederle Laboratories Division
American Cyanamid Company
Middletown Road
Pearl River, New York 10965

Dear Dr. Conover:

On the basis of our initial review of your New Drug Application (NDA) for Cyclocort (amicinonide) Lotion, 0.1% which was received by us on June 17, 1987, we find the application to be sufficiently complete to permit a substantive review. We have therefore filed the application on August 17, 1987.

Sincerely yours,

Edward Tabor, M.D.
Director
Division of Anti-Infective
Drug Products
Office of Biologics Research and Review
Center for Drugs and Biologics

cc:
NYK
Orig NDA
HFN-80
HFN-815
HFN-815/MO
HFN-815/DBostwick:js/8/7/87
2811m

APPEARS THIS WAY
ON ORIGINAL

NDA 19-729

JUN 17 [illegible]

James H. Conover, Ph.D.
Lederle Laboratories
Middle Road
Pearl River, NY 10965

Dear Dr. Conover:

We are pleased to acknowledge your New Drug Application submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug: Cyclocort Lotion

Date of Application: June 5, 1987

Date of Receipt: June 11, 1987

Our Reference Number: NDA 19-729

We will correspond with you further after we have had the opportunity to study the application. Should you have any questions prior to our contacting you, please call:

David Bostwick
301-443-4290

Sincerely yours,

Donald A. Fowler
Supervisory Consumer Safety Officer
Division of Anti-Infective
Drug Products
Office of Biologics Research and Review
Center for Drugs and Biologics

cc: NYK-DO
ORIG. NDA 19-729
HFN-82
HFN-815
HFN-815/CSO//sdj/6/16/87
HFN-815/MO
HFN-815/CHEM
0009u

ACKNOWLEDGEMENT LETTER

LEDERLE LABORATORIES

A Division of AMERICAN CYANAMID COMPANY
1 CYANAMID PLAZA, WAYNE, NEW JERSEY 07470

June 5, 1987

Edward Tabor, M.D., Acting Director
Division of Anti-Infective Drug
Products HFN 815/Room 12B-45
Office of Biologic Research and Review
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA
CYCLOCORT® Amcinonide Lotion 0.1%

Dear Doctor Tabor:

We hereby submit a New Drug Application which provides for CYCLOCORT® Amcinonide Lotion 0.1% and all clinical, statistical, toxicological as well as chemistry, manufacturing and controls data needed for the review of this product. Also provided are case report forms for all subjects enrolled in clinical trials, and patent certification information.

CYCLOCORT® Lotion, 0.1% is a new formulation for use in the treatment of psoriasis and seborrheic dermatitis. This same strength (0.1%) of CYCLOCORT® has been the subject of two prior submissions, NDA 18-116 CYCLOCORT® Cream and NDA 18-498 CYCLOCORT® Ointment, both of which have been approved.

This submission consists of an archival copy containing a total of 17 volumes, and review copies of each technical section as detailed in the series of FDA Guidelines published in association with the New Drug and Antibiotic Regulations of February 22, 1985.

Please refer to the attached Form FDA 356H and accompanying NDA Index which details the complete contents of this NDA.

Sincerely yours,

James H. Conover, Ph.D.
Assistant Director
Regulatory Liaison

JHC:af
Attachments

ORIG

NDA NO. 19729 REF. NO. SLF.OE

NDA SUPPL FOR Labeling "FPL"

LEDERLE LABORATORIES

A Division of AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK 10965
AREA CODE 914 732-5000

August 16, 1988

Lillian Gavrilovich, M.D., Acting Director
Division of Anti-infective Drug Products
HFD 520/Room 12B-45
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 19-729
CYCLOCORT® Lotion 0.1%
(amcinonide)

Dear Dr. Gavrilovich:

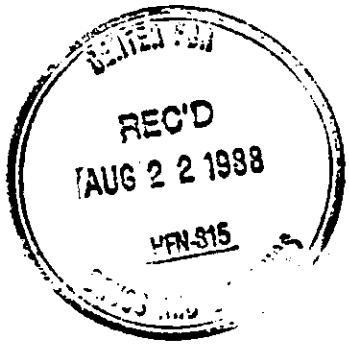
Pursuant to Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act and with reference to 21 CFR 314.70(b)(3), we herewith submit a supplement to the above subject approved New Drug Application.

This supplement provides for a minor addition in the TITLE, DESCRIPTION and HOW SUPPLIED sections of the labeling.

Specifically, the phrase, "with AQUATAIN™ hydrophilic base" has been added to the TITLE, immediately below the title CYCLOCORT® amcinonide lotion. In the DESCRIPTION section, the name AQUATAIN™ has been added in the second line just prior to the listing of the ingredients of AQUATAIN. A second sentence has been added which states, "In addition, contains Polyethylene Glycol 400". Finally, in the HOW SUPPLIED section, the phrase, "....with AQUATAIN™ hydrophilic base..." has been inserted in the first sentence.

As noted above the change for which approval is requested is the addition of the 'AQUATAIN™ hydrophilic base" in the appropriate sections of the labeling. No other changes have been made in the labeling.

Please find enclosed for your timely review and approval twelve (12) copies of the final printed labeling (Code 24514 D2).



Sincerely,

Allan Hitchcock
Assistant Director
Global Regulatory Compliance

Attachment
AH/mh

SEP 30 1988

NDA 19-729/S-002

Mr. Allan Hitchcock
Assistant Director
Global Regulatory Compliance
Lederle Laboratories
Pearl River, NY 10965

Dear Mr. Hitchcock:

We acknowledge receipt on August 22, 1988 of your supplemental New Drug Application dated August 16, 1988 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cyclocort^{R} (amcinonide) Lotion 0.1%.

We also acknowledge receipt of an additional communication dated September 21, 1988.

The supplemental application provides for adding the term "Aquatain^{TM}" to the Title, Description, and How Supplied sections of the labeling.

We have completed the review of this supplemental application and it is approved. Our letter of June 13, 1988 detailed the conditions relating to the approval of this application.

Sincerely yours,

/S/

Armand R. Casola, Ph.D.
Supervisory Chemist
Division of Anti-Infective
Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Orig NDA
HFD-520
HFD-520/CSO/Bostwick
HFD-520/ARCasola
HFD-520/Gavrilovich
HFD-520/Wayland:gm 9/27/88
R/D init. by: ARCasola 9/27/88
Approved

/S/ 9/30/88
/S/ 9/30/88

1164c

LEDERLE LABORATORIES

Lederle

A Division of AMERICAN CYANAMID COMPANY

PEARL RIVER, NEW YORK 10965

AREA CODE 914 732-5000

NDA SUPPL AMENDMENT

September 21, 1988

/S/

Lillian Gavrilovich, M.D., Acting Director
Division of Anti-Infective Drug Products
HFD 520/Room 12B-45
Office of Drug Evaluation/Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 19-729 S-002
CYCLOCORT® Lotion 0.1%
(amcinonide)

Dear Dr. Gavrilovich:

This submission should be considered as an addendum to the subject submission (S-002) that was dated 8/16/88 and received at FDA 8/22/88.

We submit herewith the bottle labels and boxes for CYCLOCORT® Lotion 0.1% with AQUATAIN™ hydrophilic base.

Please find enclosed twelve copies of each of the following:

For the 20mL bottle	
Bottle Label (front)	Code D1 23554
Bottle Label (back)	Code D1 23572
Box	Code D1 23555

For the 60mL bottle	
Bottle Label (front)	Code D1 23557
Bottle Label (back)	Code D1 23570
Box	Code D1 23558

For your convenience, we are also attaching a copy of our August 16, 1988 letter and attached package insert (Code No. 24514 D2).

Your timely review and approval will be appreciated.

CENTER FOR
REC'D
SEP 26 1988

Sincerely,

Allan Hitchcock
Assistant Director
Global Regulatory Compliance

AH/mf
Attachment

Desk Copy: Mr. David Bostwick
HFN-815/12B45