These records are from CDER's historical file of information previously disclosed under the Freedom of Information Act (FOIA) for this drug approval and are being posted as is. They have not been previously posted on Drugs@FDA because of the quality (e.g., readability) of some of the records. The documents were redacted before amendments to FOIA required that the volume of redacted information be identified and/or the FOIA exemption be cited. These are the best available copies.

NDA

019322

AL

DEC 27 1985

NDA 19-322

M. David MacFarlane, Ph.D.
Glaxo, Inc.
P.O. Box 13960
Research Triangle Park, North Carolina 27709

Dear Dr. MacFarlane:

Reference is made to your New Drug Application dated August 30, 1984, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Temovate (clobetasol propionate) Cream, 0.05%.

We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on December 6, 1985. Accordingly, the application is approved.

Please submit one market package of the drug when 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,

for J Bilstad 12/27/85

Elaine C. Esber, M.D.
Director
Office of Biologics Research and Review
Center for Drugs and Biologics

cc:
Orig NDA 19-323
(ATL-DO)
HFN-82
HFN-710
HFN-220
HFN-800
HFN-815
HFN-815/ETabor ET 12-27-85
HFN-815/Chem/RCasola
HFN-815/Pharm/JMDavitt
HFN-815/CCEvans
HFN-815/DCBostwick:bem:12/16/85:0545m MM 12-27-85

Rough Draft 12/16/85

FPL

APPROVED DEC 27 1985

PRODUCT INFORMATION
484281

TEMOVATE™

(clobetasol propionate)

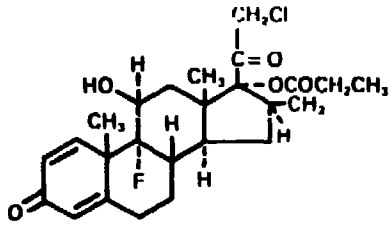
Cream, 0.05%
Ointment, 0.05%

(potency expressed as clobetasol propionate)

For Dermatologic Use Only—
Not for Ophthalmic Use.

DESCRIPTION: TEMOVATE™ (clobetasol propionate) Cream and Ointment contain the active compound clobetasol propionate, a synthetic corticosteroid, for topical dermatologic use. Clobetasol, an analog of prednisolone, has a high degree of glucocorticoid activity and a slight degree of mineralocorticoid activity.

Chemically, clobetasol propionate is 21-chloro-9-fluoro-11β, 17-dihydroxy-16β methylpregna-1,4-diene-3,20-dione, 17-propionate, with the empirical formula $C_{25}H_{32}Cl_2FO_5$, a molecular weight of 467, and the following structural formula:



Clobetasol propionate is a white to cream-colored crystalline powder insoluble in water.

TEMOVATE Cream contains clobetasol propionate 0.5 mg/g in a cream base of propylene glycol, glyceryl monostearate, cetostearyl alcohol, glyceryl stearate, PEG 100 stearate, white wax, chlorocresol, sodium citrate, citric acid monohydrate, and purified water.

TEMOVATE Ointment contains clobetasol propionate 0.5 mg/g in a base of propylene glycol, sorbitan sesquioleate, and white petrolatum.

CLINICAL PHARMACOLOGY: The corticosteroids are a class of compounds comprising steroid hormones secreted by the adrenal cortex, and their synthetic analogs. In pharmacologic doses, corticosteroids are used primarily for their anti-inflammatory and/or immunosuppressive effects. Topical corticosteroids, such as clobetasol propionate, are effective in the treatment of corticosteroid-responsive dermatoses primarily because of their anti-inflammatory, anti-pruritic, and vasoconstrictive actions. However, while the physiologic, pharmacologic, and clinical effects of the corticosteroids are well known, the exact mechanisms of their actions in each disease are uncertain.

Clobetasol propionate, a corticosteroid, has been shown to have topical (dermatologic) and systemic pharmacologic and metabolic effects characteristic of this class of drugs.

Pharmacokinetics: The extent of percutaneous absorption of topical corticosteroids, including clobetasol propionate, is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings (see **DOSAGE AND ADMINISTRATION**).

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

Once absorbed through the skin, topical corticosteroids enter 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, including clobetasol propionate and its metabolites, are also excreted into the bile.

TEMOVATE™ (clobetasol propionate) Cream and Ointment have been shown to depress the plasma levels of adrenal cortical hormones following repeated non-occlusive application to diseased skin in patients with psoriasis and eczematous dermatitis. These effects have been shown to be transient and reversible upon completion of a two-week course of treatment.

INDICATIONS AND USAGE: TEMOVATE™ Cream and Ointment are indicated for short-term treatment of inflammatory and pruritic manifestations of moderate to severe corticosteroid-responsive dermatoses. Treatment beyond two weeks is not recommended, and the total dosage should not exceed 50 grams per week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis.

These products are not recommended for use in children under 12 years of age.

CONTRAINDICATIONS: TEMOVATE™ Cream and Ointment are contraindicated in patients who are hypersensitive to clobetasol propionate, to other corticosteroids, or to any ingredient in these preparations.

PRECAUTIONS: General: TEMOVATE™ is a highly potent topical corticosteroid that has been shown to suppress the HPA axis at doses as low as 2 g per day. Systemic absorption of topical corticosteroids has resulted in reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Conditions which augment systemic absorption include the application of the more potent corticosteroids, 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 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 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 large 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.

Certain areas of the body, such as the face, groin, and axillae, are more prone to atrophic changes than other areas of the body following treatment with cortico-

steroids. Frequent observation of the patient is important if these areas are to be treated.

As with other potent topical corticosteroids, TEMOVATE™ (clobetasol propionate) Cream and Ointment should not be used in the treatment of rosacea and perioral dermatitis. Topical corticosteroids in general should not be used in the treatment of acne.

Information for Patients: Patients using TEMOVATE should receive the following information and instructions.

1. This medication is to be used as directed by the physician and should not be used longer than the prescribed time period. It is for external use only. Avoid contact with the eyes.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. The treated skin area should not be bandaged or otherwise covered or wrapped so as to be occlusive.
4. Any signs of local adverse reactions should be reported to your physician.

Laboratory Tests: The following tests may be useful in evaluating HPA axis suppression:

Urinary free cortisol test

ACTH stimulation test

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topically applied corticosteroids.

Studies to determine mutagenicity with prednisone have revealed negative results.

Pregnancy: *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 in animals after dermal application. Clobetasol propionate has not been tested for teratogenicity by this route; however, it appears to be fairly well absorbed percutaneously, and when administered subcutaneously it proved to be a relatively potent teratogen in both the rabbit and the mouse.

There are no adequate and well-controlled studies of the teratogenic effects of topically applied corticosteroids in pregnant women. 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 in 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, caution should be exercised when topical corticosteroids are prescribed for a nursing woman.

Pediatric Use: Use of TEMOVATE Cream and Ointment in children under 12 years of age is not recommended.

Pediatric patients may demonstrate greater average susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a large skin surface area to body weight ratio.

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.

ADVERSE REACTIONS: TEMOVATE™ (clobetasol propionate) Cream and Ointment are generally well-tolerated when used for two-week treatment periods.

The most frequent adverse reactions reported for TEMOVATE Cream have been local and have included burning sensation in 4 of 421 patients and stinging sensation in 3 of 421 patients. Less frequent adverse reactions were itching, skin atrophy, cracking and fissuring of the skin, which occurred in 1 of 421 patients.

The most frequent adverse events reported for TEMOVATE Ointment have been local and have included burning sensation, irritation, and itching. These occurred in 2 of 366 patients. Less frequent adverse reactions were stinging, cracking, erythema, folliculitis, numbness of fingers, skin atrophy, and telangiectasia, which occurred in 1 of 366 patients.

The following local adverse reactions are reported infrequently when topical corticosteroids are used as recommended. These reactions are listed in an approximately 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, and miliaria. Systemic absorption of topical corticosteroids has produced reversible HPA axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients. In rare instances, treatment (or withdrawal of treatment) of psoriasis with corticosteroids is thought to have provoked the pustular form of the disease.

OVERDOSAGE: Topically applied TEMOVATE™ can be absorbed in sufficient amounts to produce systemic effects (see **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION: A thin layer of TEMOVATE™ Cream or Ointment should be applied with gentle rubbing to the affected skin areas twice daily, once in the morning and once at night.

TEMOVATE Cream and Ointment are potent; therefore, treatment must be limited to 14 days, and amounts greater than 50 g per week should not be used.

TEMOVATE Cream and Ointment are not to be used with occlusive dressings.

HOW SUPPLIED: TEMOVATE™ Cream 0.05% is supplied in 15 g (NDC 0173-0375-73) and 30 g (NDC 0173-0375-72) tubes. TEMOVATE™ Ointment 0.05% is supplied in 15 g (NDC 0173-0376-73) and 30 g (NDC 0173-0376-72) tubes.

Store between 15° and 30°C (59° and 86°F). TEMOVATE Cream should not be refrigerated.

Glaxo

Glaxo Dermatology Products
Glaxo Inc.
Research Triangle Park, NC 27709

December 1985

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NDC 0173-0375-72 Tray of 12

Temovate™

(clobetasol propionate)

Cream, 0.05%

For dermatological use only—Not for ophthalmic use.

30 g

Caution: Federal law prohibits dispensing without prescription.

Glaxo

465301

Contains: Clobetasol propionate 0.05% in a cream base composed of propylene glycol, glyceryl monostearate, cetostearyl alcohol, glyceryl stearate, PEG 100 stearate, white wax, chlorocresol, sodium citrate, citric acid monohydrate, and purified water.

See package insert for full prescribing information.

Store between 15° and 30° C (59° and 86° F).

Do not refrigerate.

PN121452

Glaxo Dermatology Products
Glaxo Inc., Research Triangle Park, NC 27709

Glaxo

465301

NDC 0173-0375-72 Tray of 12

Temovate™
(clobetasol propionate)
Cream, 0.05%
For dermatological use only—Not for ophthalmic use.
30 g
Caution: Federal law prohibits dispensing without prescription.

NDC 0173-0375-73

Tray of 12

Temovate™

(clobetasol propionate)

Cream, 0.05%

For dermatological use only—Not for ophthalmic use.

15 g

Caution: Federal law prohibits dispensing without prescription.

465001

Glaxo

Contains: Clobetasol propionate 0.05% in a cream base composed of propylene glycol, glyceryl monostearate, cetostearyl alcohol, glyceryl stearate, PEG 100 stearate, white wax, chlorocresol, sodium citrate, citric acid monohydrate, and purified water.

See package insert for full prescribing information.

Store between 15° and 30° C (59° and 86° F).

Do not refrigerate.

PN121436

Glaxo Dermatology Products

Glaxo Inc., Research Triangle Park, NC 27709

Glaxo

465001

NDC 0173-0375-73

Temovate™

(clobetasol propionate)

Cream, 0.05%

For dermatological use only—Not for ophthalmic use.

15 g

Caution: Federal law prohibits dispensing without prescription.

Tray of 12

NDA No: 19-330 No. 12-19-95

12-23-95

Temovate™ Cream, 0.05%
(clobetasol propionate) PROFESSIONAL SAMPLE — NOT FOR SALE
Glaxo Dermatology Products
Glaxo Inc., Res. Tri. Pk., NC 27709

For dermatological use only. Not for ophthalmic use.
Store between 15° and 30°C (59° and 86°F).
Do not refrigerate

Contains Clobetasol propionate 0.05% in a cream base composed of propylene glycol, glyceryl monostearate, cetostearyl alcohol, glyceryl stearate, PEG 100 stearate, white wax, chlorocresol, sodium citrate, citric acid monohydrate, and purified water.
See package insert for full prescribing information.
Store between 15° and 30°C (59° and 86°F). Do not refrigerate.
See crimp for lot no. and expiration date.
Important: Do not use if seal has been punctured or is not visible.
To Open: Use cap to puncture seal.
Glaxo Dermatology Products
Glaxo Inc., Research Triangle Park, NC 27709 402802

NDC 0173-0376-73

Temovate™
(clobetasol propionate)
Cream, 0.05%
15 g
Glaxo

For dermatological use only—Not for ophthalmic use.

Caution: Federal law prohibits dispensing without prescription.

Contains Clobetasol propionate 0.05% in a cream base composed of propylene glycol, glyceryl monostearate, cetostearyl alcohol, glyceryl stearate, PEG 100 stearate, white wax, chlorocresol, sodium citrate, citric acid monohydrate, and purified water.
See package insert for full prescribing information.
Store between 15° and 30°C (59° and 86°F). Do not refrigerate.
See crimp for lot no. and expiration date.
Important: Do not use if seal has been punctured or is not visible.
To Open: Use cap to puncture seal.
Glaxo Dermatology Products
Glaxo Inc., Research Triangle Park, NC 27709 402802

NDC 0173-0376-72

Temovate™
(clobetasol propionate)
Cream, 0.05%
30 g
Glaxo

For dermatological use only—Not for ophthalmic use.

Caution: Federal law prohibits dispensing without prescription.

Clas
19-522 Date 10-19-95
Reviewed by: DMCoveland 12-27-95

NDC 0173-0375-73
Temovate
(clobetasol propionate)
Cream, 0.05%
15 g
Glaxo

NDC 0173-0375-73

Temovate®
(clobetasol propionate)
Cream, 0.05%

15 g

Glaxo

For dermatological use only—
Not for ophthalmic use.

Caution: Federal law prohibits dispensing without prescription.

Important: The opening of this product is covered by a metal tamper-resistant seal. If this seal has been punctured or is not visible, do not use and return product to place of purchase.

To Open: To puncture the seal, reverse the cap and place the puncture-top onto the tube. Push down firmly until seal is open. To close, screw the cap back onto the tube.

464901

NDC 0173-0375-73

Temovate®
(clobetasol propionate)
Cream, 0.05%

15 g

Glaxo

For dermatological use only—
Not for ophthalmic use.

Caution: Federal law prohibits dispensing without prescription.

Contains: Clobetasol propionate 0.05% in a cream base composed of propylene glycol, glyceryl monostearate, cetostearyl alcohol, glyceryl stearate, PEG 100 stearate, white wax, chlorocresol, sodium citrate, citric acid monohydrate, and purified water.

See package insert for full prescribing information.

Store between 15° and 30°C (59° and 86°F). Do not refrigerate.

PM121438

Glaxo Dermatology Products
Glaxo Inc., Research Triangle Park, NC 27709

464901

Carry
19 322 12-19-85
12-22-85

NDC 0173-0375-72
Temovate™
(clobetasol propionate)
Cream, 0.05%
30 g
Glaxo

NDC 0173-0375-72

Temovate™
(clobetasol propionate)
Cream, 0.05%

30 g
Glaxo

For dermatological use only—
Not for ophthalmic use.

Caution: Federal law prohibits dispensing without prescription.

m

Important: The opening of this product is covered by a metal tamper-resistant seal. If this seal has been punctured or is not visible, do not use and return product to place of purchase.

To Open: To puncture the seal, reverse the cap and place the puncture-top onto the tube. Push down firmly until seal is open. To close, screw the cap back onto the tube.

466201

NDC 0173-0375-72

Temovate™
(clobetasol propionate)
Cream, 0.05%

30 g
Glaxo

For dermatological use only—
Not for ophthalmic use.

Caution: Federal law prohibits dispensing without prescription.

Contains: Clobetasol propionate 0.05% in a cream base composed of propylene glycol, glyceryl monostearate, cetostearyl alcohol, glyceryl stearate, PEG 100 stearate, white wax, chlorocresol, sodium citrate, citric acid monohydrate, and purified water.

See package insert for full prescribing information.

Store between 15° and 30° C (59° and 86° F). Do not refrigerate.

PN121462

Glaxo Dermatology Products
Glaxo Inc., Research Triangle Park, NC 27709

466201

MED
REV

Medical Officer's Review of NDA 19-322

Applicant: Glaxo Inc.
5 Moore Drive
Research Triangle Park, N.C.

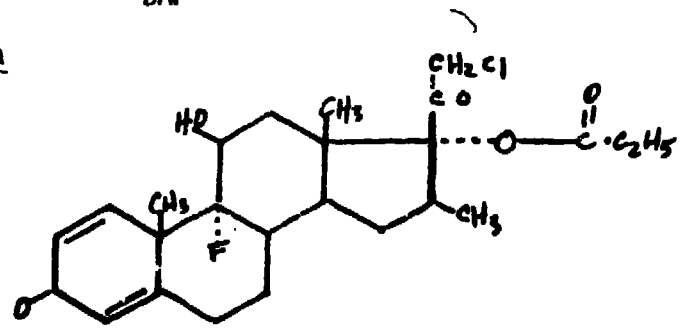
Drug: Removate[R] (clobetasol propionate) Cream 0.05%

Date of Receipt: 8-30-84

Related IND:

Code Names: Glaxo Chem. DMF
DMF

Structural Formula



Composition:

	% w/w
Clobetasol 17-propionate	
Cetostearyl alcohol BP	
Glyceryl monostearate	
White wax NF	
Propylene glycol USP	
Chlorocresol BP	
Sodium citrate BP	
Citric acid monohydrate BP	
Purified water USP	

I. Introductory Comment:

Clobetasol 17 propionate is the most potent steroid available to date, marketed in Europe, Japan and Canada under the name Dermovate, indicated for the topical treatment of psoriasis and other corticosteroid-responsive dermatoses. It is reported that repeated non-occlusive applications with doses of as low as 2.0 grams per day have been associated with depressed cortisol secretions as determined by a.m. plasma cortisol and/or urinary corticoid measurements.

II. Controls Review

In his review of 11/8/85, Mr. Ernest G. Pappas, chemist, noted deficiencies that were communicated to the sponsor via telecon on 11/16/84. In addition, a letter with a summary of the deficiencies was sent to the sponsor on 1/8/85.

III. Pharmacology - Toxicology Review: Under review.

IV. Review of Clinical Studies:

A. Special Studies

1. William Epstein, M.D., of San Francisco, California, conducted an open study to determine the sensitization potential using the maximization procedure developed by Kligman. This was achieved by pre-treating the area to be patch tested with an application of a 5% aqueous solution of sodium lauryl sulfate to the skin under occlusive dressing for 24 hours using 27 healthy subjects. Following this, the test preparation was applied to the site under an occlusive dressing for 48 hours. The entire procedure was repeated for a total of 5 times followed by a 14-day rest period, then a challenge by application under occlusion of the test material was read at 48 and 72 hours for signs of sensitization and irritation. It was concluded that none of the test preparations produced any significant irritant or allergic reactions.

2. Albert Cohen, M.D., of Miami, Florida, conducted an open study in seven patients with psoriasis and one patient with eczema to determine the effect of clobetasol cream on the pituitary-adrenal axis. This was achieved by applying 7 grams of the study medication to 30% of the body surface not using occlusive dressings each day for a total of 7 days. Baseline chemistries, urinalysis and pre-study ACTH stimulation tests were determined. During the in-patient phase of the study, 3 baseline and 2 post-treatment a.m. plasma cortisol determinations were made. It was determined that topical application of 7 grams of clobetasol cream has the potential of suppressing the cortisol secretion in patients exposed to the drug.

3. Roger C. Cornell, M.D., of La Jolla, California, conducted an open clinical study to determine the largest dose of clobetasol cream applied over a 7-day period that would not cause significant depression of cortisol secretion as determined by a.m. plasma cortisol levels and urinary corticoid concentrations. This was accomplished by evaluating 3 different dosage regimens of clobetasol cream 7.0 grmas/day, 3.5 grams/day and 2.0 grams per day in 12 patients with psoriasis and/or eczema using similar methods as discussed in the previously mentioned adrenal

suppression study. It was concluded that repeated topical application of clobetasol cream to patients with diseased skin can result in depression of cortisol secretion as determined by a.m. plasma cortisol and urinary corticoid measurements.

B. Clinical Studies for Efficacy:

1. The following investigators, all domestic, well-qualified dermatologists utilized a common clinical protocol to conduct a multicenter, double-blind, placebo-controlled study using clobetasol cream compared to its vehicle in the treatment of psoriasis.

Michael Fisher, M.D.
Bronx, New York

Thomas Nigra, M.D.
Washington, D.C.

Alan Shalita, M.D.
Brooklyn, New York

This was achieved by having patients apply the active medication to one side compared to vehicle applied to the opposite side in patients with symetrical lesions of psoriasis according to a predetermined randomization scheme. Treatment consisted of twice per day application for a period of two weeks. Global evaluation was made during, and after treatment using the following terms:

Cleared
Marked improvement
Slight improvement
No change
Worse

In addition, lesions were evaluated according to the following signs and symptoms:

Parameter	Severity
Erythema	0 = absent
Skin thickening	1 = mild
Scaling	2 = moderate
Pruritus	3 = severe

The following tables illustrate the overall response to therapy:

Investigator/Clinical Response		End of Therapy		One week follow-up	
Dr. Fisher		Clobetasol	Placebo	Clobetasol	Placebo
	Cleared	1(8.3%)	0	3(27%)	0
	Marked Improvement	6(50%)	0	5(45%)	0
	Slight Improvement	4(33%)	6(50%)	1(9%)	5(45%)
	Unchanged	1(8.3%)	5(42%)	1(9%)	4(36%)
	Worse	0	1(8.3%)	1(9%)	2(18%)
	Totals	12	12	11	11
Dr. Nigra		Clobetasol	Placebo	Clobetasol	Placebo
	Cleared	1(6%)	0	0	1(6%)
	Marked Improvement	7(46%)	2(13%)	10(66%)	1(6%)
	Slight Improvement	6 (40%)	10(66%)	2(13%)	7(46%)
	Unchanged	0	2(13%)	2(13%)	5(33%)
	Worse	1(6%)	1(6%)	1(6%)	1(6%)
	Totals	15	15	15	15
Dr. Shalita		Clobetasol	Placebo	Clobetasol	Placebo
	Cleared	3(17%)	0	3(17%)	0
	Marked Improvement	13(72%)	0	13(72%)	0
	Slight Improvement	2(11%)	4(22%)	1(6%)	2(11%)
	Unchanged	0	12(67%)	1(6%)	10(56%)
	Worse	0	2(11%)	0	6(33%)
	Totals	18	18	18	18

2. The following investigators, all domestic, well-qualified dermatologists, utilized a common clinical protocol to conduct a multicenter, double-blind, placebo-controlled study, using clobitasol cream compared to its vehicle in the treatment of psoriasis:

Coleman Jacobson, M.D.
Dallas, TX

Sheldon Pinnell, M.D.
Durham, N.C.

Richard Dobson, M.D.
Charleston, S.C.

This was accomplished by instructing patients to apply the active medication to one side compared to the vehicle applied to the opposite side in patients with symetrical lesions of psoriasis, according to a predetermined randomization scheme. Treatment consisted of application by the medications twice per day for two weeks. Global evaluation was made before, during, and after using the following terms:

Cleared
Marked improvement
Slight improvement
No change
Worse

In addition, lesions were evaluated according to the following signs and symptoms:

Parameter	Severity
Erythema	0 = absent
Skin thickening	1 = mild
Pruritus	2 = moderate
Scaling	3 = severe

The following tables illustrates the overall response to therapy:

Investigator/Clinical Response	End of Therapy		One week follow-up	
Dr. Jacobson	Clobetasol	Placebo	Clobetasol	Placebo
Cleared	2(10%)	0	6(30%)	0
Marked Improvement	13(65%)	1(5%)	9(45%)	2(10%)
Slight Improvement	2(10%)	6(30%)	3(15%)	4(20%)
Unchanged	3(15%)	12(60%)	1(5%)	13(65%)
Worse	0	1 (5%)	1(5%)	1(5%)
Totals	20	20	20	20
Dr. Pinnell	Clobetasol	Placebo	Clobetasol	Placebo
Cleared	2(10%)	0	7(35%)	1(5%)
Marked Improvement	17(85%)	4(20%)	12(60%)	1(5%)
Slight Improvement	1(5%)	12(60%)	1(5%)	12(60%)
Unchanged	0	3(15%)	0	6(30%)
Worse	0	1(5%)	0	0
Totals	20	20	20	20

Dr. Dobson	Clobetasol	Placebo	Clobetasol	Placebo
Cleared	0	0	1(4.7%)	1(4.7%)
Marked Improvement	18(90%)	4(20%)	16(76%)	3(14%)
Slight Improvement	2(10%)	7(35%)	3(14%)	9(43%)
Unchanged	0	9(45%)	1(4.7%)	8(38%)
Worse	0	0	0	0
Totals	20	20	21	21

3. The following investigators, all domestic, well-qualified dermatologists, utilized a multicenter, double-blind, active drug controlled study using clobetasol 0.05% cream compared to fluocinonide 0.05% cream in the treatment of psoriasis:

Phillip Frost, M.D.
Miami, Florida

David Cram, M.D.
San Francisco, California

Nicholas Lowe, M.D.
Los Angles, California

Roger Cornell, M.D.
La Jolla, California

Walter Gammon, M.D.
Chapel, Hill, North Carolina

Larry Becker, M.D.
Albuquerque, New Mexico

This was achieved by randomized assignment according to a predetermined scheme of investigational drug or known drug to patients with generalized psoriasis. Treatment consisted of application of the medications twice per day for two weeks. Global evaluation was made before, during, and after therapy, using the following terms:

Cleared
Marked improvement
Slight improvement
No change
Worse

In addition, lesions were evaluated according to the following signs and symptoms:

Parameter	Severity
Erythema	0 = absent
Skin thickening	1 = mild
Pruritus	2 = moderate
Scaling	3 = severe

The following charts illustrate the overall response to therapy:

Investigator/Clinical Response		End of Therapy		One week follow-up	
Dr. Frost		Clobetasol	Fluocinolone	Clobetasol	Fluocinolone
	No. of Pts				
	Cleared	0	0	1(12.5%)	0
	Marked Improvement	7(87.5%)	7(63.6%)	7(87.5%)	7(63.6%)
	Slight Improvement	1(12.5%)	4(36.3%)	0	3(27.2%)
	Unchanged	0	0	0	0
	Worse	0	0	0	1(9.0%)
	Totals	8	11	8	11
Dr. Cram		Clobetasol	Fluocinolone	Clobetasol	Fluocinolone
	No. of Pts				
	Cleared	3(30%)	0	1(10%)	0
	Marked Improvement	3(30%)	6(60%)	5(50%)	8(80%)
	Slight Improvement	2(20%)	3(30%)	3(30%)	2(20%)
	Unchanged	1(10%)	1(10%)	1(10%)	0
	Worse	1(10%)	0	0	0
	Totals	10	10	10	10
Dr. Lowe		Clobetasol	Fluocinolone	Clobetasol	Fluocinolone
	No. of Pts				
	Cleared	3(27%)	1(11%)	1(9%)	0
	Marked Improvement	4(36%)	1(11%)	7(63%)	2(22%)
	Slight Improvement	2(18%)	1(11%)	2(18%)	2(22%)
	Unchanged	1(9%)	5(55%)	1(9%)	4(44%)
	Worse	1(9%)	1(11%)	0	1(11%)
	Totals	11	9	11	9
Dr. Cornell		Clobetasol	Fluocinolone	Clobetasol	Fluocinolone
	No. of Pts				
	Cleared	1(5%)	0	3(14%)	0
	Marked Improvement	15(71%)	7(33%)	17(63%)	13(62%)
	Slight Improvement	5(24%)	13(62%)	1(5%)	8(38%)
	Unchanged	0	1(5%)	0	0
	Worse	0	0	0	0
	Totals	21	21	21	21
Dr. Gammon		Clobetasol	Fluocinolone	Clobetasol	Fluocinolone
	No. of Pts				
	Cleared	3(33%)	1(8%)	2(22%)	0
	Marked Improvement	4(44%)	2(16%)	5(55%)	2(16%)
	Slight Improvement	2(22%)	6(50%)	2(22%)	8(66%)
	Unchanged	0	2(16%)	0	2(16%)
	Worse	0	1(8%)	0	0
	Totals	9	12	9	12

Dr. Becker	Clobetasol	Fluocinolone	Clobetasol	Fluocinolone
No. of Pts				
Cleared	0	1(11%)	0	0
Marked Improvement	3(75%)	5(55%)	2(50%)	6(66%)
Slight Improvement	1(25%)	3(33%)	2(50%)	3(33%)
Unchanged	0	0	0	0
Worse	0	0	0	0
Totals	4	9	4	9

4. The following investigators, all domestic, well-qualified dermatologists, utilized a common clinical protocol to conduct a multicenter, double-blind, active drug controlled study, using clobetasol 0.05% cream compared to fluocinonide cream 0.05% in the treatment of psoriasis:

Brian Jegasothy, M.D.
Philadelphia, PA

Coleman Jacobson, M.D.
Dallas, Texas

Sheldon Pinnell, M.D.
Durham, N.C.

Lawrence Millikan, M.D.
New Orleans, Louisiana

Peter Lynch, M.D.
Tucson, Arizona

Marvin Porter, M.D.
Fort Myers, Florida

This was achieved according to a predetermined randomization scheme of investigational drug or known drug to patients with generalized psoriasis. Treatment consisted of the application twice per day for two weeks. Global evaluations were made before, during, and after therapy using the following terms:

Cleared
Marked Improvement
Slight Improvement
No change
Worse

In addition, lesions were evaluated according to the following signs and symptoms:

Parameter	Severity
Erythema	0 = absent
Skin thickening	1 = mild
Pruritus	2 = moderate
Scaling	3 = severe

The following charts illustrate the global response to the treatment regimens:

Investigator/Clinical Response	End of Therapy		One week follow-up	
Dr. Jegasothy	Clobetasol	Fluocinolone	Clobetasol	Fluocinolone
Cleared	1(20%)	0	2(40%)	0
Marked Improvement	2(40%)	1(20%)	2(40%)	3(60%)
Slight Improvement	2(40%)	4(80%)	1(20%)	1(20%)
Unchanged	0	0	0	0
Worse	0	0	0	1(20%)
Totals	5	5	5	5
Dr. Jacobson	Clobetasol	Fluocinolone	Clobetasol	Fluocinolone
Cleared	1(20%)	0	0	0
Marked Improvement	2(40%)	0	2(40%)	1(16%)
Slight Improvement	2(40%)	6(100%)	2(40%)	3(50%)
Unchanged	0	0	1(20%)	2(33%)
Worse	0	0	0	0
Totals	5	6	5	6
Dr. Pinnell	Clobetasol	Fluocinolone	Clobetasol	Fluocinolone
Cleared	3(30%)	1(10%)	1(10%)	1(10%)
Marked Improvement	5(50%)	1(10%)	8(80%)	1(10%)
Slight Improvement	1(10%)	6(100%)	0	7(70%)
Unchanged	0	1(10%)	0	0
Worse	1(10%)	1(10%)	1(10%)	1(10%)
Totals	10	10	10	10
Dr. Millikan	Clobetasol	Fluocinolone	Clobetasol	Fluocinolone
Cleared	5(41%)	1(8%)	4(33%)	2(16%)
Marked Improvement	4(33%)	5(41%)	6(50%)	6(50%)
Slight Improvement	3(25%)	6(50%)	2(16%)	4(33%)
No change	0	0	0	0
Worse	0	0	0	0
Totals	12	12	12	12

Dr. Lynch	Clobetasol	Fluocinolone	Clobetasol	Fluocinolone
No of Pts.	12	12	12	12
Cleared	1(8%)	0	1(8%)	0
Marked Improvement	9(75%)	5(41%)	8(66%)	4(33%)
Slight Improvement	2(16%)	7(58%)	3(25%)	8(66%)
No change	0	0	0	0
Worse	0	0	0	0
Totals	12	12	12	12

Dr. Porter	Clobetasol	Fluocinolone	Clobetasol	Fluocinolone
No of Pts.	12	12	12	12
Cleared	0	1(8%)	2(16%)	0
Marked Improvement	12(100%)	7(58%)	10(83%)	9(75%)
Slight Improvement	0	3(25%)	0	3(25%)
No change	0	1(8%)	0	0
Worse	0	0	0	0
Totals	12	12	12	12

5. The following investigators, all domestic, well-qualified dermatologists, utilized a common clinical protocol to conduct a multicenter, double-blind, placebo controlled, clinical study using clobetasol cream 0.05% compared to the cream vehicle in patients with eczematous dermatoses:

Brian Jegasothy, M.D.
Philadelphia, PA

Michael Fisher, M.D.
Bronx, N.Y.

Eugene Van Scott, M.D.
Philadelphia, PA

This was achieved by having the patients apply active medication to one side, compared to application of the vehicle to the opposite side in patients with symetrical lesions of eczema, according to a predetermined randomized scheme. Treatment consists of twice per day application of the medication for a period of two weeks. Overall or global evaluations were made before, and after treatment using the following terms:

Cleared
Marked improvement
Slight improvement
No change
Worse

In addition, lesions were evaluated according to the following signs and symptoms:

Parameter	Severity
Erythema	0 = absent
Skin thickening	1 = mild
Pruritus	2 = moderate
Scaling	3 = severe

The following charts illustrate the global responses to the treatment regimens:

Investigator/Clinical Response	End of Therapy		One week follow-up	
Dr. Jegaspthy	Clobetasol	Vehicle	Clobetasol	Vehicle
Cleared	7(50%)	0	8(57%)	0
Marked Improvement	7(50%)	9(64%)	5(35%)	9(64%)
Slight Improvement	0	4(28%)	0	3(21%)
Unchanged	0	0	1(7%)	1(7%)
Worse	0	1(7%)	0	1(7%)
Totals	14	14	14	14
Dr. Fisher	Clobetasol	Vehicle	Clobetasol	Vehicle
Cleared	0	0	0	0
Marked Improvement	5(71%)	2(29%)	6(86%)	3(43%)
Slight Improvement	2(29%)	2(29%)	1(14%)	1(14%)
Unchanged	0	3(42%)	0	2(28%)
Worse	0	0	0	1(14%)
Totals	7	7	7	7
Dr. Van Scott	Clobetasol	Vehicle	Clobetasol	Vehicle
Cleared	2(16%)	1(8%)	2(16%)	1(8%)
Marked Improvement	9(75%)	2(16%)	8(66%)	2(16%)
Slight Improvement	1(8%)	5(41%)	1(8%)	4(33%)
No change	0	4(33%)	1(8%)	5(41%)
Worse	0	0	0	0
Totals	12	12	12	12

6. The following investigators, all well-qualified domestic dermatologists, utilized a common clinical protocol to conduct a multicenter, double-blind placebo, drug controlled, study using clobetasol cream 0.05% compared to the vehicle cream in the treatment of eczematous dermatoses.

Coleman Jacobson, M.D.
Dallas, Texas.

Richard Dobson, M.D.
Charleston, S. C.

William Jordan, M.D.
Richmond, VA

This was achieved by having the patients apply active medication to one side compared to the placebo cream on the opposite side in patients with symetrical lesions of eczema according to a predetermined randomization scheme. Treatment consisted of twice per day application of the medication for a period of two weeks. Overall or global evaluations were made before, during, and after treatment using the following terms:

Cleared
Marked improvement
Slight improvement
No change
Worse

In addition, lesions were evaluated according to the following signs and symptoms:

Parameter	Severity
Erythema	0 = absent
Skin thickening	1 = mild
Pruritus	2 = moderate
Scaling	3 = severe

The following charts illustrate the overall responses to the treatment regimens:

Investigator/Clinical Response	End of Therapy		One week follow-up	
Dr. Jacobson	Clobetasol	Vehicle	Clobetasol	Vehicle
Cleared	5(25%)	3(15%)	8(40%)	3(15%)
Marked Improvement	13(65%)	6(30%)	10(50%)	6(30%)
Slight Improvement	2(5%)	8(40%)	2(10%)	7(35%)
Unchanged	0.	3(15%)	0	4(20%)
Worse	0	0	0	0
Totals	20	20	20	20

Dr. Dobson	Clobetasol	Vehicle	Clobetasol	Vehicle
Cleared	2(22%)	1(11%)	4(44%)	2(22%)
Marked Improvement	4(44%)	4(44%)	4(44%)	3(33%)
Slight Improvement	3(33%)	4(44%)	1(11%)	4(44%)
Unchanged	0	0	0	0
Worse	0	0	0	0
Totals	9	9	9	9

Dr. Jordan	Clobetasol	Vehicle	Clobetasol	Vehicle
No. of Patients	12	12	12	12
Cleared	6(50%)	0	5(42%)	1(8%)
Marked Improvement	5(42%)	0	4(33%)	1(8%)
Slight Improvement	1(8%)	5(42%)	2(16%)	2(16%)
Unchanged	0	6(50%)	1(8%)	7(58%)
Worse	0	1(8%)	0	1(8%)
Totals	12	12	12	12

7. The following investigators, all domestic well-qualified dermatologists, utilized a common clinical protocol to conduct a multicenter, parallel double-blind, active drug controlled study using clobetasol cream 0.05% compared to the fluocinonide cream 0.05% in the treatment of eczematous dermatoses.

Phillip Frost, M.D.
Miami Beach, FL

David Cram, M.D.
San Francisco, CA

Nicholas Lowe, M.D.
Los Angeles, CA

Roger Cornell, M.D.
La Jolla, CA

Walter Gammon, M.D.
Chapel Hill, N.C.

Peter Lynch, M.D.
Tucson, AZ

This was achieved by assignment according to a predetermined randomized distribution scheme, the investigational cream or the active cream. Treatment consisted of twice per day application of the medication for a period of two weeks. Overall or global evaluation was made before, during, and after treatment using the following terms:

Cleared
Marked improvement
Slight improvement
No change
Worse

In addition, lesions were evaluated according to the following signs and symptoms:

Parameter	Severity
Erythema	0 = absent
Skin thickening	1 = mild
Pruritus	2 = moderate
Scaling	3 = severe

The following charts illustrate the global response rate to the treatment regimen:

Investigator/Clinical Response	End of Therapy		One week follow-up	
Dr. Frost	Clobetasol	Fluocinolide	Clobetasol	Fluocinolide
Cleared	1(20%)	1(16%)	1(20%)	2(37%)
Marked Improvement	4(80%)	3(50%)	4(80%)	4(66%)
Slight Improvement	0	2(33%)	0	0
Unchanged	0	0	0	0
Worse	0	0	0	0
Totals	5	6	5	6
Dr. Cram	Clobetasol	Fluocinolide	Clobetasol	Fluocinolide
Cleared	3(50%)	5(100%)	5(83%)	4(80%)
Marked Improvement	2(33%)	0	1(17%)	1(20%)
Slight Improvement	0(17%)	0	0	0
No change	0	0	0	0
Worse	1	0	0	0
Totals	6	5	6	5

Dr. Lowe	Clobetasol	Fluocinolide	Clobetasol	Fluocinolide
Cleared	3(33%)	2(22%)	3(33%)	3(33%)
Marked Improvement	6(66%)	3(33%)	4(44%)	4(44%)
Slight Improvement	0	4(44%)	2(22%)	2(22%)
No change	0	0	0	0
Worse	0	0	0	0
Totals	9	9	9	9

Dr. Cornell	Clobetasol	Fluocinolide	Clobetasol	Fluocinolide
Cleared	0	0	1(8%)	1(10%)
Marked Improvement	7(58%)	5(50%)	8(66%)	5(50%)
Slight Improvement	4(33%)	4(40%)	3(25%)	3(30%)
No change	1(8%)	1(10%)	0	0
Worse	0	0	0	1(10%)
Totals	12	10	12	10

Dr. Gammon	Clobetasol	Fluocinolide	Clobetasol	Fluocinolide
Cleared	5(45%)	2(25%)	5(45%)	2(25%)
Marked Improvement	4(36%)	6(75%)	5(45%)	6(75%)
Slight Improvement	2(18%)	0	1(9%)	0
No change	0	0	0	0
Worse	1	0	0	0
Totals	11	8	12	8

Dr. Lynch	Clobetasol	Fluocinolide	Clobetasol	Fluocinolide
Cleared	2(20%)	1(10%)	0	1(10%)
Marked Improvement	5(50%)	6(60%)	7(70%)	6(60%)
Slight Improvement	3(30%)	3(30%)	3(30)	3(30%)
No change	0	0	0	0
Worse	1	0	0	0
Totals	10	10	10	10

8. The following investigators, all domestic well-qualified dermatologists, utilized a common clinical protocol to conduct a multicenter, parallel double-blind, active drug controlled study using clobetasol cream 0.05% compared to the fluocinonide cream 0.05% in the treatment of eczematous dermatoses.

Brian Jegasothy,M.D.
Philadelphia, PA

Colemen Jacobson, M.D.
Dallas, TX

Sheldon Pinnell, M.D.
Durham, N.C.

Gerald Weinstein, M.D.
Gary Cole, M.D.
Long Beach, CA

Marvin Porter, M.D.
Fort Myers, FL

This was accomplished by assignment according to a pretermined randomized distribution scheme, the investigational cream or the active cream. Treatment consisted of twice per day application of the medication for a period of two weeks. Overall or global evaluation was made before during, and after treatment using the following terms:

Cleared
Marked improvement
Slight improvement
No change
Worse

In addition, lesions were evaluated according to the following signs and symptoms:

Parameter	Severity
Erythema	0 = absent
Skin thickening	1 = mild
Pruritus	2 = moderate
Scaling	3 = severe

The following charts illustrates the global response rate to the treatment regimens:

Investigator/Clinical Response	End of Therapy		One week follow-up	
Dr. Jacobson	Clobetasol	Fluocinonide	Clobetasol	Fluocinonide
Cleared	2(25%)	2(20%)	1(12%)	3(30%)
Marked Improvement	4(50%)	5(50%)	6(75%)	6(60%)
Slight Improvement	2(25%)	3(30%)	1(12%)	1(10%)
No change	0	0	0	0
Worse	0	0	0	0
Totals	8	10	8	10

Dr. Pirnell	Clobetasol	Fluocinonide	Clobetasol	Fluocinonide
Cleared	3(25%)	0	1(12%)	1(8%)
Marked Improvement	8(66%)	6(50%)	10(83%)	7(58%)
Slight Improvement	1(8%)	4(33%)	1(12%)	3(25%)
No change	0	1(8%)	0	0
Worse	0	1(8%)	0	1(8%)
Totals	12	12	12	12

Dr. Millikan	Clobetasol	Fluocinonide	Clobetasol	Fluocinonide
Cleared	1(9%)	4(44%)	4(36%)	2(25%)
Marked Improvement	6(54%)	3(33%)	3(27%)	5(62%)
Slight Improvement	2(18%)	1(11%)	3(27%)	1(12%)
No change	0	0	1(9%)	0
Worse	2(18%)	1(11%)		0
Totals	11	9	11	8

Drs. Weinstein and Cole	Clobetasol	Fluocinonide	Clobetasol	Fluocinonide
Cleared	4(40%)	0	2(20%)	1(9%)
Marked Improvement	4(40%)	2(18%)	8(80%)	4(36%)
Slight Improvement	1(10%)	5(45%)	0	4(36%)
Unchanged	1(10%)	2(18%)	0	0
Worse	0	2(18%)	0	2(18%)
Totals	10	11	10	11

Dr. Porter	Clobetasol	Fluocinonide	Clobetasol	Fluocinonide
Cleared	2(42%)	1(10%)	3(30%)	1(10%)
Marked Improvement	7(70%)	5(50%)	7(70%)	5(50%)
Slight Improvement	0	4(40%)	0	4(40%)
Unchanged	1(10%)	0	0	0
Worse	0	0	0	0
Totals	10	10	10	10

V. Review by Biometrics: Under review

VI. Adverse Reactions:

In a total of 422 patients who received the drug in controlled clinical studies including patients with psoriasis and eczema, there were 10(2.4%) reported to have experienced adverse events as follows; burning 4(1.0%), stinging 3(0.7%), itching 1(0.2%), skin atrophy 1(0.2%), cracking 1(0.2%), and fissures 1(0.2%). These are what one might expect with potent fluorinated corticosteroid drugs.

NDA 19-322

VII. Package Insert Labeling:

The section under the heading "Clinical Trials," should be omitted. The chart titled "Clinical Improvement of Paired Psoriatic Lesions," should be ommitted. Under the "Indications and Usage" section, a statement should be included as follows:

"Because of the potential demonstrated in clinical studies to suppress the hypothalmic-pituitary adrenal axis (HPA) after topical applications without occlussive dressings, Removate Cream and Ointment are indicated only as short course treatments (two weeks) for relief of the inflammatory and pruritic manifestations of moderate to severe corticosteroid-responsive dermatoses." The products are not recommended for use in children under 12 years of age.

VIII. Evaluation and Comment:

When compared to the presently available potent topical corticosteroid products, clobetasol propionate, appears to be much more potent as evidenced by its demonstrated ability to depress the HPA axis when used without occlussive dressings. For this reason, the indication section should make mention of this fact and indicate use no longer than two weeks. In addition, a class statement should be made that the product is not indicated for pediatric use.

IX. Recommendation:

The product should be approved with revisions made in the labeling.

JBSanders
John B. Sanders, M.D.

cc:
Orig NDA
HFN-815
HFN-815/CSO
HFN-340
HFN-815/JBSanders:bam:2/8/85
3045b

JT 3/4/85

e.c.e. 4/21/85

Addendum to Medical Officer's Review of NDA 19-322

Applicant: Glaxo, Inc.
5 Moore Drive
Research Traingle Park, N. C.

Drug: Removate[R] (clobetasol propionate) Cream 0.05%

Introductory Comment: This NDA was reviewed on February 8, 1985 with a recommendation that the product should be approved and revisions made in the labeling. When reviewed by James Bilstad, M.D., (HFN-801), on August 30, 1985 was agreed that the NDA should be approved, however, he commented that the recommended indications be revised because of "an unduly negative tone for an indication" and also that the Cohen and Cornell studies in regard to the drug's potential for suppressing the HPA-Axis be reviewed more completely "i.e., the data should be presented".

Review of Clinical Studies: Albert N. Cohen, M.D.
, Miami, Florida, conducted an open study to determine the effect of clobetasol cream on the pituitary-adrenal axis in patients with severe psoriasis or eczema involving approximately thirty percent of the body surface area. Patients underwent a thorough screening including history, physical examination and laboratory studies prior to admission to the research facility for 10 days. During the in-patient phase of the study, three baseline and two post-treatment A.M. plasma cortisol determinations were made. Plasma cortisol results were corroborated by two baselinne and two post-treatment 24-hour urine collections for the determination of 17-hydroxycorticoid and 17-Ketosteroid concentrations. A pre-treatment ACTH stimulation test was performed. The study medication was applied twice daily for seven consecutive days, without occlusive dressings, at an initial dose of 7 grams per day. Selected blood chemistries, urinalysis and hematology were performed before and after treatment. The following charts depict the results.

HPA-AXIS EFFECTS
7.0 GRAMS PER DAY CREAM/DAY

Drug: Clobetasol Cream

	Study Day	Pt #1 (psoriasis)	Pt #2 (psoriasis)
8:00 a.m.	1		
Plasma Cortisol	2		
Normal Range	3		
5-25 mcg/dl	9		
	10		
	17		
	24		
ACTH Stimulation	1		
mcg cortisol	17		
dl plasma	24		
Urine	1		
17 Ketosteroids	2		
Normal Range	8		
Male 7-23 mg/24hrs	9		
Urinary Creatinine	1		
Normal Range	2		
Male 100-2000 mg/24hrs	8		
	9		

HPA-AXIS EFFECTS
3.5 GRAMS PER DAY CREAM/DAY

	Day	Pt #3	Pt #4	Pt #5	Pt #6	Pt #7	Pt #8
8:00 a.m.	1						
Cortisol	2						
	3						
	9						
	10						
	17						
ACTH Stimulation	1						
	17						

HPA-AXIS EFFECTS
3.5 GRAMS PER DAY CREAM/DAY (Cont'd)

	Day	Pt #3	Pt #4	Pt #5	Pt #6	Pt #7	Pt #8
Urine 17-hydroxi Steroids	1						
	2						
	8						
	9						
Urine 17-Keto Steroids	1						
	2						
	8						
	9						
Urinary Creatinine	1						
	2						
	8						
	9						

The following conclusion can be drawn from the above results:

1. 7.0 grams per day of topically applied clobetasol cream has the potential for depressing cortisol secretion in the psoriatic patient.

2. 3.5 grams per day of topically applied clobetasol cream appears to have less potential for suppressing cortisol secretion than the 7.0 grams per day dose.

3. The HPA-axis effects produced from topically applied clobetasol cream are transient and reversible upon discontinuing treatment.

Roger C. Cornell, M.D., of La Jolla, California conducted an open study to determine the effects of topical application of clobetasol cream on the pituitary-adrenal axis in patients with severe psoriasis or atopic dermatitis. This was achieved by selecting patients with at least 30% involvement of the body surface area. All patients underwent a screening visit where qualifying diagnostic information, medical history and laboratory tests were performed. Upon completion patients were admitted to the test facility for ten days. The first three days of the in-patient period involved baseline assessments of the HPA-axis as determined by a.m. plasma cortisol levels and 24 hour urinary, 17-hydroxycorticoids. Treatment consisted of seven consecutive days of twice daily non-occlusive applications of clobetasol cream to as much diseased skin as feasible.

Plasma cortisol and urinary corticoid measurements were made after 2,4,6 and 7 days of dosing. Plasma samples were stored for measurement of clobetasol levels via radioimmunoassay. Metyrapone tests were performed two weeks after plasma cortisol levels returned to normal in those cases where a.m. plasma cortisol levels were below 5 Mcg/dl after 6 and/or 7 days of treatment. Selected blood chemistries were performed before and after treatment. The following charts depict the results:

HPA-AXIS EFFECTS
7.0 GRAMS PER DAY CREAM/DAY

	Study Day	Pt #1 (male eczema)	Pt #2 (female eczema)
8:00 a.m. Plasma Cortisol	1		
	2		
	3		
	5		
	7		
	9		
	10		
	Follow-up		
Urine 17-hydroxysteroids	2		
	3		
	5		
	7		
	9		
	10		
Urine Free Cortisol	2		
	3		
	5		
	7		
	9		
	10		
Urinary Creatinine	2		
	3		
	5		
	7		
	9		
	10		
Metyrapone plasma Cortisol Mcg/dll plasma 5 Mcg/dl			

HPA-AXIS EFFECTS
3.5 GRAMS PER DAY CREAM/DAY

	Study Day	Pt #3 (female eczema)	Pt #4 (female eczema)	Pt #5 (female eczema)	Pt. #6 (male psoriasis)
8:00 a.m. Plasma Cortisol	1				
	2				
	3				
	5				
	7				
	9				
	10				
	Follow-up				
Urine 17-hydroxysteroids	2				
	3				
	5				
	7				
	9				
	10				
Urine Free Cortisol	2				
	3				
	5				
	7				
	9				
	10				
Urinary Creatinine	2				
	3				
	5				
	7				
	9				
	10				
Metyrapone plasma Cortisol Mcg/dll plasma 5 Mcg/dl	-				

(Dr. Cornell also tested 6 patients at a level of 2 grams of cream per day. One patient, a female with eczema, had a plasma cortisol reading of mcg/dl on study day 5. All other readings were in the normal range).

Evaluation and Comment:

It should be noted that in some patients an application as little as 3.5 gram (almost one tenth of one ounce) of clobetasol cream reduced plasma cortisol levels to ≤ 2.0 mcg/dl. Because of the potential to lower plasma cortisol

levels with such a small amount of this extremely potent topical corticostroid, I feel that the prescribing physician should be alerted and therefore if an unduly negative tone "cannot be used in the indication section, then a highlighted precaution statement should be made as follows:

> "Because application of amounts of clobetasol of as little as 3.5 to 2.0 gram per day have been shown to reduce plasma cortisol levels to < 2.0 Mcg/ml in some patients, precaution should be taken with its use."

Recommendation: The product should be approved and the labeling changed as stated above.

John B. Sanders, M.D.

cc:
Orig NDA
HFN-340
HFN-815 ET 9/23/85
HFN-815/CSO
HFN-815/JBSanders:bam:9/12/85
0211m

C.C.E.
9/20/85

NDA 19-322
NDA 19-323

December 11, 1985

Review of Final Printed Labeling and Safety Update

Name of Drug: NDA 19-322: Temovate (clobetasol propionate) Cream, 0.05%

NDA 19-323: Temovate (clobetasol propionate) Ointment, 0.05%

Sponsor: Glaxo, Inc.
Research Triangle Park, N.C.

Date of Submission: Safety update - November 27, 1985
Final printed labeling - December 6, 1985

Labeling Review: The sponsor has complied with the requests made in our November 18, 1985 Approvable letters. The trade name of the products is to be "Temovate." We requested that the second sentence of the "Pregnancy" subsection of the PRECAUTIONS section read,

> The more potent corticosteroids, including clobetasol 17-propionate, have been shown to be teratogenic after dermal applications in laboratory animals.

* The sponsor has proposed an alternative. This section is now to read,

> The more potent corticosteroids have been shown to be teratogenic in animals after dermal application. Clobetasol propionate has not been tested for teratogenicity by this route; however, it appears to be fairly well-absorbed percutaneously, and when administered subcutaneously, it proved to be a relatively potent teratogen in both the rabbit and the mouse.

The second version is factually accurate and is acceptable.

Safety Update: Information has been provided concerning the period from December 1, 1983 (the NDA cut-off point) to June 25, 1985 for NDA 19-322 and to October 15, 1985 for NDA 19-323.

1. NDA 19-322: 148 patients have been treated in domestic studies since the cut-off point. One case each of itching, dermatitis, folliculitis, tingling sensation, and headache have been reported. Three cases of a burning sensation have been reported.

   Overseas reports from countries in which Temovate is already marketed list 10 reactions as follows: contact dermatitis, (2); pain, erythema and bullae (one patient); contact allergy, (2); burning skin; impotence; and skin atrophy (3), connected with burning and pruritus in two patients and reduced cortisol in one.

2. NDA 19-323: 438 patients have been treated in domestic studies since the cut-off point. Three reports of burning; four of itching; and one each of stinging; rosaceaform eruption; secondary skin infection; increased blood pressure; impotence; and (in one patient) euphoria, nausea, diarrhea and sleepiness have been reported.

No unusual reactions were reported in foreign studies.

Conclusions: These reports confirm the impression that Temovate is a very potent steroid which can cause serious reactions. The data submitted do not change the conclusion that this drug is sufficiently safe when used as directed.

David C. Bostwick

C. Carnot Evans, M.D.

cc:
Orig NDA 19-322
NDA 19-323

HFN-340
HFN-815
HFN-815/CSO
HFN-815/DCBostwick:bam:12/16/85:0545m

Pharm
Rev

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

NDA 19-322 (Original Submission, dated 8/30/84)

Date Review Completed: 2/8/85

Applicant: Glaxo, Inc., Research Triangle Park, NC

Drug Names:

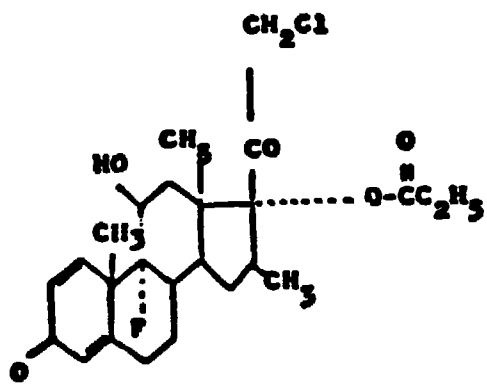
Generic (USAN): Clobetasol 17-propionate (C-P)

Proprietory: Removate (USA), Dermovate (UK, Japan), Dermoxin (Germany)

Code: 2925, SN 201, GR 2/925

Chemical: 21-chloro-21-desoxybetamethasone 17-propionate

Chemical Structure:



Dosage Form: 0.05% Cream

Indications: Topical treatment of moderate to severe corticosteroid-responsive dermatoses

Composition: % w/w

Clobetasol 17-propionate
Cetostearyl alcohol BP
Glyceryl monostearate

White wax NF
Propylene glycol USP
Chlorocresol BP
Sodium citrate BP
Citric acid monohydrate BP
Purified Water, USP

Related Submissions: NDA 19-323 (ointment); INDs

PRECLINIAL STUDIES

PHARMACOLOGY

The following studies had previously been submitted in connection with IND and have been reviewed (see pharm. rev. dated 4/29/82).

1. Effect of SC & oral admin. on thymolytic activity in the mouse
2. Effect on anti-granuloma activity in the mouse
3. Effect of SC & oral admin. on thymolytic activity in the rat
4. Effect on anti-granuloma activity in the rat
5. Effect of SC inject. on mineralocorticoid activity in the rat
6. Effect of SC inject. on androgenic-anabolic activity in the mouse
7. Effect of SC inject. on androgenic-anabolic activity in the rat
8. Effect of SC inject. on estrogenic & anti-estrogenic activity in the mouse
9. Effect of SC inject. on estrogenic activity in the rat
10. Effect of SC inject. on anti-estrogenic activity in the rat
11. Effect of SC & oral admin. on progestational activity in the rabbit
12. Effect of SC inject. on anti-gonadotropic activity in the rat
13. Acute pharmacodynamic effects in cats
14. Metabolism of steroid esters by rat, mouse or human skin (NDA metabolism study #s 1, 2, 3) in vitro
15. Stability of C-P "in vitro" with rat liver, plasma, stomach & intestinal preparations
16. Pharmacokinetics of C-P after topical admin. to rats
17. Bioavailability studies with C-P in the rat

Two new ADME studies, submitted in this NDA, are reviewed below.

1. Percutaneous absorption of C-P from Cream & Ointment Formulations in the Rat: [Report WBP 84/018]

   Lab Perf. Study: Glaxo Group Research Ltd., Ware, England

   Material Tested: [16, 16 alpha-^{3}H] C-P cream & ointment (0.05%)

Species, Sex & No. Animals: AH/A albino rats; M & F; 4/sex/group

Dose Levels & Groups: Groups 1-4 received 150 ug [^{3}H]-C-P/kg (0.3g formulation/kg) as follows: Gp 1 - cream, occluded; Gp 2 - cream, unoccluded; Gp 3 - ointment, occluded; Gp 4 - ointment, unoccluded. Group 5 was an undosed control group

Methods: The test materials were applied on the clipped backs of the rats (4x5 cm) and rubbed in. In gps 1 & 3, the site of application was occluded with aluminum foil. The animals were restrained in Bollman cages for the first 24 hrs, after which the occlusion & restraint were removed. Urine & feces were collected at 24-hr intervals for 168 hrs and blood samples were collected at various time intervals. At 168 hrs after dosing, the rats were sacrificed and skin from the site of application was excised. Radioactivity (RA) was determined in urine & blood, on the application sites, bandages & cages.

Results: The proportion of the applied dose that entered the skin (applied dose minus amount recovered in the application site washes) was significantly greater when the skin was occluded (54.75-60.41% of the applied dose) than when the skin was unoccluded (41.08-48.18% of the applied dose).

Peak plasma conc'ns of RA were not attained until 48 hrs after dosing. The avg. conc'ns of RA (calculated from AUC) in the plasma in the occluded gps (mean = 2.55 ng equiv./ml) were significantly higher than the avg. conc'ns in the non-occluded gps (mean = 1.45 ng equiv./ml). There was no sig. difference between avg. conc'n of RA in plasma in the cream (mean = 1.80 ng equiv./ml) and ointment (mean = 2.06 ng equiv./ml) treated gps. The observed peak plasma conc'ns of RA in the occluded gps (mean = 3.97 ng equiv./ml) were significantly higher than those in the non-occluded gps (2.25 ng equiv./ml). There was no sig. difference between peak conc'ns from the cream (2.80 ng equiv./ml) and ointment (3.19 mg equiv./ml) treated gps.

Relatively small amounts of RA (mean = 3.31-5.34% of the dose) were recovered in the urine in 0-168 hrs; excretion of RA in the feces was approx. 5x greater than that in the urine. The total recovery of RA was between 77.42 & 81.14% of the applied dose.

Urinary & fecal excretion of RA is shown in the table below.

Group		Percentage of dose recovered Urine	Feces
Cream	- occluded	4.78	24.78
	unoccluded	3.31	15.69
Ointment	- occluded	5.34	28.95
	unoccluded	3.54	19.04

2. A Study on the Absorption, Distribution & Excretion of SN 201:

I. Experiments Conducted on Rats: [Report by ___

Lab Perf. Study:

Material Tested: SN 201 (C-P) ^{3}H-labeled 0.15% cream & ointment and 0.05% solution

Species, Sex & No. Animals: Wistar rats (M); 3-6/gp

Routes of Admin.: SC (sol'n) & percutaneous (cream, oint. or sol'n) under occlusion

Results: After SC admin., the peak plasma RA was seen at 4 hrs after treatment, followed by a gradual decrease ($t_{1/2}$ = 9 hrs).

After percutaneous application, the peak plasma conc'n of RA was reached at 8 hrs after drug treatment and stayed almost at a constant level for about 96 hrs in all cases (cream, oint. or sol'n). The peak levels in blood expressed as SN 201 equivalents were: 0.011, 0.0025 & 0.011 mg equiv. SN 201/ml for cream, oint. & sol'n, respectively.

Tissue distribution of RA, determined only after SC admin., showed high levels in the liver, GI tract, kidneys, adrenals, pituitary, thyroid, prostate & fat. The RA in these organs (or tissues) in many cases, showed a trend of change with time similar to that found with plasma RA.

In 72 hrs after SC admin., 16.2 & 70.8% of the RA of the administered dose had been excreted via urine & feces, respectively. The amount remaining in the body was 4.62% of the administered dose. 54% of the dose was excreted into the bile by the 45th hr after admin., and there was very little enterohepatic circulation. Exhalation of RA was less than 1% of the dose in 48 hrs after dosing.

The primary excretion route after percutaneous dosing was also via feces. The totals excreted via feces & urine up to the 96th hr after admin. were 9.20, 1.22 & 8.86% of the administered RA for cream, oint. & sol'n, respectively. The remaining amounts in the body (excluding site of application) were 0.92, 0.42 & 2.85% of the administered amount, respectively. These results indicated that when applied percutaneously, the absorption was satisfactory in the cases of cream & sol'n but not with the oint. It was also revealed that when the drug was administered in the form of cream or sol'n (percutaneously), a reasonable plasma conc'n of the drug could be maintained for a long period of time, even after a single administration.

TOXICOLOGY

A. The following acute, SC & chronic toxicities were submitted in connection with IND and have already been reviewed.

- Acute toxicity in mice (SC & oral)
- Acute toxicity in rats (SC & oral)
- Acute toxicity in guinea pigs (SC)
- Acute toxicity in rabbits (IM)

- Acute toxicity in cats (IM)
- Acute toxicity in dogs (IM)
- 3-mo. SC toxicity study in rats (done in 1971)
- 3-mo. SC toxicity study in dogs (done in 1971)

The sponsor has submitted in this NDA, English translation of 3 Japanese published papers on the toxicity studies of C-P. These are briefly reviewed here.

1. Study on the toxicity of clobetasol propionate: [Masaki Kuramoto et al. Shikoku Ishi 31(6): 377-398, 1975]

"Acute toxicity by oral, subcutaneous & intraperitoneal administration and subacute & chronic toxicities by subcutaneous successive administration in rats."

Material Tested: Clobetasol propionate (C-P) in 0.04% Tween-80 suspension

a) Acute Toxicity (LD_{50})

Species	# Rats/Gp	Route	Sex	LD_{50} (C.I.) mg/kg
Mouse	10	SC	M	81.7 (63.9-104.4)
			F	81.7 (64.4-103.5)
		IP	M	156.4 (125.3-195.0)
			F	117.8 (93.1-149.1)
Rat	10	SC	M	397.3 (317.8-496.6)
			F	365.8 (294.5-454.4)
		IP	M	413.7 (340.5-502.6)
			F	351.3 (291.3-423.7)
Rat & Mouse	10	PO	M & F	>3000

Period of Observation: 21 days

Signs of Toxicity:

PO: Initially, lack of activity, raising of hair etc.; by the end of the 2nd wk, these symptoms disappeared. No death was recorded. Autopsy revealed a yellowish-brown kidney and slight adrenal & splenic atrophy in the mice, and slight atrophy & whitening of the adrenals, pale liver & hyperemia in the jejunum in the rats.

SC: In the mice, dose-related increases in symptoms such as raised hair, closed eyes, crouching, emaciation & hair loss were reported. Autopsy revealed changes similar to those seen in the orally dosed mice & rats. Rats also showed occasional hemorrhage in the cecum in addition to the other symptoms seen in the orally dosed animals. Additionally in the HD gp, slight degree of atrophy of the testicles, epididymus, uterus & ovaries were seen.

IP: In both rats & mice, symptoms & progressions similar to those seen in the case of SC admin. were reported.

b) Subacute Toxicity

Methods: Wistar rats were divided into gps of 10/sex each. SC admin. of C-P was continued for 3 mos. with daily doses of 6.25, 12.5, 25.0, 50 or 100mg/kg, respectively. Control animals received vehicle only. Admin. was discontinued at the end of the 10th wk in the 100mg/kg gp because of high mortality.

Results: Emaciation, hair loss & decreased activity were noted at 25mg/kg & over. An extremely high mortality (16/20) was seen at 100mg/kg (all F died). At 25 & 50mg/kg, only 1 F in each gp died during the treatment period. Considerable wt losses were noted in the treated animals.

Regarding the hemogram, the major changes noted were an increase in neutrophils and a decrease in lymphocytes in the LD gps and slight increase in the HD gps. No conspicuous change was noted in the no. of blood platelets. Both SGOT & SGPT values showed sig. decrease with increasing dose levels of C-P, with no conspicuous changes in blood electrolytes.

Necropsy showed abscesses in the lungs which suggested the existence of a secondary infection. With respect to organ wts, sig. reduction in abs. & rel. wts were seen for the thymus & adrenals glands.

Histologically, necrosis & infiltration of neutrophils in the lungs of the treated animals were noted. In the adrenals, most of the C-P-treated gps showed atrophy of the bundled layer of the cortex. The extent of this atrophy was almost in proportion to dosage. In the thymus, cortical atrophy and a reduction in lymphocytes were noted.

c) Chronic Toxicity

Methods: Groups of rats (20/gp: 10/sex) were administered C-P SC on the back for 6 mos. at doses of 2.5, 5, 10, 20 & 40mg/kg, respectively. A control gp received solvent only.

Results:

Clinical Signs: Loss of hair, emaciation & occasional diarrhea were reported at 20mg/kg & higher.

Mortality: None

Body Wt: A Dose-related decrease in body wt gain was seen in all treated gps. At 40mg/kg, wt gain was about 75% that of controls.

Food & Water Intake: Food intake was slightly suppressed in all gps to about the same extent. Water intake was increased significantly at 40mg/kg.

Hematology: At 40mg/kg, sig. decrease in the RBC counts (no change in Hb or Hct) and an increase in neutrophils, accompanied by a decrease in lymphocytes, were reported. A sig. decrease in WBC cts was noted in the M gps at 10mg/kg & higher, and the F gps at 5mg/kg & higher.

Clinical Chemistry: The F at 10mg/kg showed a decrease in activity in both SGOT & SGPT. A decrease in albumin was noted at 40mg/kg. However, no sig. difference was present in terms of the A/G ratio.

Urinalysis: Changes noted did not show any dose effect. 7/10 M at 10mg/kg showed positive urinary protein. M at 40mg/kg showed an increase in Na and a decrease in K excretion; however, F of this group did not show any such changes.

Organ Wt: A sig. decrease in rel. thymus wt was reported in F at 5mg/kg & higher and in the 40mg/kg M. A decrease in both abs. & rel. wts of spleen was noted at HD (40mg/kg).

Gross Pathology: At 10 & 20mg/kg, thymus size was reduced to 1/2 to 1/4 that of controls and atrophy was more pronounced at higher doses. Adrenals showed almost no atrophy. Hemorrhage & hyperemia of the lungs were seen in all gps.

Histopathology: At 40mg/kg, occasional decrease in thymus cortex lymphocytes, atrophy of the bundled layer of the adrenal cortex in all animals, and vacuolation of the adrenocortical cells in about 1/2 of the animals, focal hepatic necrosis in 1 M & 1 F, hyaline casts in the renal tubules of 2 M and enlargement of the red pulp of the spleen in some F animals were described. No degeneration or regeneration of the renal tubules or cell infiltration of the stroma was observed. One M at 20mg/kg showed a reduction in the formation of sperm and testicular atrophy.

2. Study on the Toxicity of Clobetasol Propionate by Percutaneous Successive 1- & 3-Month Applications in Rats: [M. Kuramoto et al. Shikoku Acta Medica 31(6): 399, 1975.]

Methods: Groups of rats (10/sex/gp) were given C-P oint. & cream percutaneously at conc'ns of 0.05% (clinical conc'ns) & 0.25% (0.3gm/rat/day, except Sundays) for 1 or 3 mos. The following results were reported.

a) 1-Month Study

Clinical Observations: Emaciation, decreased activity, upright hair & occasional diarrhea were noted in both cream & ointment gps at LD & HD levels.

Body Wts: In the F of both dose gps, there was loss of body wt with both cream & oint. admin. In the M, body wts remained essentially unchanged with 0.05% oint., but decreased in the 0.25% oint. and 0.05% & 0.25% cream gps.

Mortality: In the oint. gps, 1 M & 1 F at 0.25% died. With the cream, 8/10 F at 0.25% died (no death among the M). Autopsies revealed abscesses in the lungs.

Food & Water Intake: Decreased food intake in the M oint. gps and a sharply reduced intake in the F of 0.25% cream gp were reported. Similar trends in water intake was also seen.

Hematology: Slight decrease in RBC cts, Hb & Hct values were noted in the F 0.25% oint. gp. A decrease in WBC cts was noted in all gps except the F 0.25% cream gp. Dose-related increases in neutrophils with corresponding decreases in lymphocytes were seen for both cream & oint. in both sexes.

Clinical Chemistry: The C-P treated gps showed a trend of increase in SGOT & SGPT activity, particularly in the 0.25% cream gps. A similar trend was shown for Alk-P.

Urinalysis: Unremarkable, except some positive tests in some animals from all gps.

Organ Wt: Decreased rel. wts were seen for the thymus, spleen & adrenal glands in the C-P treated gps (0.25% cream & oint.). Thymus atrophy was seen in all C-P-treated gps in a dose-related manner.

Gross Pathology: No pathological changes were noted in the 0.05% & control gps. The 0.25% gps (cream & oint.) showed changes mainly in the lungs & liver. In the oint. gp, 4 cases each of M & F showed hemorrhage spots over the entire area of the liver. Abscesses were seen in 4 M & 2 F over the entire area of the lungs. Similar conditions were seen in the cream gps. Atrophic changes were seen in the thymus & adrenal glands of the C-P-treated gps.

Histopathology: With both cream & oint., the adrenal glands, thymus, lungs & liver showed evidence of histological changes.

Atrophy of the bundled layer of the adrenal cortex was observed in all C-P-treated gps (0.05% & 0.25% gps) and in both sexes. In some cases, vacuolation was noted sporadically in the cells of the cortex.

Cortical atrophy and decrease in lymphocytes were observed in the thymus.

In the liver, the majority of the 0.25% oint. & cream gp rats showed localized necrosis. In the lungs, mild to severe pneumonia with necrosis covering large areas were seen.

in the kidney, one rat of the 0.25% cream gp showed nodes consisting of neutrocytes in part of the medulla with urinary casts at the lower part of the nodes.

b) 3-Month Study: In this study, only 0.05% conc'n was used for both cream & oint.

Clinical Observations: Slight emaciation, upright hair, thinning of the skin & insufficient hair growth at the application sites were reported.

Mortality: 3 F in the oint. gp & 1 F in the cream gp died after the 11th wk of treatment.

Food & Water Intake: No sig. treatment-related effects were seen.

Hematology: Slight decrease in no. of erythrocytes in M of the C-P cream gps, a sig. increase in Hct value in the C-P oint. gps, and a decrease in Hb in F of the C-P cream gps were noted. M of the C-P cream gps showed a sig. decrease in WBC cts. All treated animals showed an increase in neutrophil and a decrease in lymphocytes.

Clinical Chemistry: No clinically sig. changes were noted.

Urinalysis: Unremarkable

Organ Wt: The rel. thymus wt decreased in the oint. gps. In the F, rel. & abs. adrenal wts decreased as compared to controls. In some F of the C-P-treated gps, abs. & rel. lung wts increased.

Gross Pathology: The thymus in both sexes was about 1/2 the size of those found in controls. Although no hemorrhage or necrosis was observed in the thymus, small abscesses were noted in both the cream & oint. gps with 4 cases of adhesion. Slightly smaller spleen (compared to controls) were seen in the C-P oint. & cream gps.

Histopathology: In the cream gps, slight thymic atrophy (no marked changes), slight vacuolation of the adrenal cortical cells and follical atrophy in the spleen (2 F) were noted. In half the animals of both cream & oint. gps, pneumonia was reported. There was widespread necrosis of the lungs in these animals, with cell infiltration in the periphery of these focal necroses and a proliferation of granulocytes observed.

3. Comparative Toxicity Test of Dexamethasone Valerate (DV-17) & Other Steroid Ointments in Rats: [Y. Shimo et al. J. Toxicol. Sci. 7(1): 15-33, 1982]

The comparative toxicity test was performed on M rats, which were percutaneously treated with a volume of 0.25g/kg of 0.12% dexamethasone valerate (DV-17) oint. as a test drug, and 0.1% dexamethasone (DEX), 0.05% fluocinonide (FAA), 0.025 beclomethasone dipropionate (BMD), 0.1%

hydrocortisone butyrate (HB), 0.05% clobetasol propionate (CP) & 0.12% betamethasone valerate (BMV) ointments as active control drugs for 30 consec. days to evaluate the effects on the following toxicity parameters: body wt change, adrenal function (organ wt, histological changes, serum corticosterone contents), pathological changes of the hypophysis & lymphatic systems (thymus, mesenteric lymph nodes, spleen) and skin changes. A recovery gp was also included in the test. The drug was applied on shaved skin without occlusion.

All gps consisted of 20 rats. About 9-10 were subjected to autopsy at the end of the drug admin. period, and about 7-10 were subjected to necropsy at the end of recovery. The dosage of each drug was as follows: DV-17, 0.3mg/kg; DEX, 0.25mg/kg; BMV, 0.3mg/kg; HB, 0.25mg/kg; FAA, 0.125mg/kg; CP, 0.125mg/kg; BMD, 0.0625mg/kg.

Results: The 4 deaths noted during treatment all occurred in the FAA-treated gp.

The overall results of the present study suggest that admin. of the above drugs was accompanied by suppression of body wt increase, lowering of serum corticosterone conc'n, decrease in the demarcation ratio of the lymphocyte fraction, and atrophy of the adrenals, thymus, spleen & mesenteric lymph nodes. All animals in the FAA gp showed moderate atrophy of the anterior lobe of the hypophysis, while the DEX gp demonstrated slight atrophy in half of the animals. In these gps, a hyaline change was observed in the basophilic cells that was considered to be a secondary change caused by adrenocortical atrophy. In the CP gp, several animals showed slight atrophy of the hypophysis.

Thymus: In the DV-17 & BMV gps, slight to moderate atrophy was noted in many cases in the cortex & medulla. In the HP gp, slight atrophy was noted in a few cases. In the CP gp, moderate to strong atrophy was seen in all cases, while the FAA & DEX gps demonstrated strong atrophy in all cases. There was a correlation between the degree of these changes in the thymus and the extent of suppression of increase in body wt.

Spleen: There was slight atrophy of the lymph follicles in some cases of the DV-17 & HB gps, in half the animals of the BMV gp, and in all of the CP gp. All cases of the FAA & DEX gps showed strong atrophy accompanied by a decrease in the no. of lymphocytes.

Adrenals: Changes in adrenal glands included slight to moderate atrophy in the zona fasciculata of the cortex in the majority of CP gp animals, and in about half of the DV-17 & BMV gp animals. The change in the FAA & DEX gps was much stronger than in the DV-17 gp. The HB gp showed a weaker change than the DV-17 gp. The FAA & DEX gps presented conspicuous atrophy in the deeper part of the zona fasciculata, particularly in the cell encasements.

Liver: Focal necrosis was noted in the FAA, DEX, BMV, HB & BMD gps, but not with DV-17 & CP.

About half of the cases of the DV-17 & BMV gps showed slight atrophy in the cortex & paracortex of the mesenteric lymph nodes. The changes that occurred in the CP gp were nearly the same in degree as those of the DV-17 gp, but the frequency of occurrence was higher in the CP gp. All FAA & DEX gp animals showed strong atrophy of the cortex, paracortex & medulla.

Concerning local effects, suppression of hair growth and thinning of skin were observed at the skin site of drug admin. in the DV-17, BMV, HB, CP, FAA & DEX gps. Histological exams revealed atrophy in the epidermis, dermis & appendages of the skin at the site of admin. These changes were mild in the DV-17 gp, moderate to strong in the FAA, DEX & CP gps and slightly milder in the BMV gp than those in the DV-17 gp. Changes in the BMV gp were somewhat more severe than in the DV-17 gp, and no marked changes were seen in the BMD gp.

From the above results, it was concluded that all the drugs used in this study manifested local effects almost parellel with systemic effects. On the basis of the results obtained, it was estimated that the order of the strength of toxicity of these drugs was FAA > DEX > CP > BMV > DV-17 > HB > BMD.

B. Reproduction & Teratology Studies

The following studies had been submitted in connection with the original IND , and have been reviewed (pharm. rev. dated 4/29/82). Both studies were performed in 1970.

1. SC Teratogenicity Study in Mice

2. SC Teratogenicity Study in Rabbits

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1. Study of Teratogenicity of SN-201 in Rabbits during Organogenesis: (Segment II reproduction study)

Lab Perf. Study:

Material Tested: SN-201 suspended in saline-containing 0.04% Tween-80

Species & No. Animals: Japanese white rabbits; 10/dose group

Dose Levels & Route of Admin.: 0 (C), 2 (LD), 4 (MD), 8 (MHD) or 16 (HD) ug/kg/day; SC

Treatment Period: Day 7 to day 18 of pregnancy (day of copulation = day 0 of pregnancy)

Results:

Body Wts of Dams: Slight but not sig. decrease was noted in wt gain at the MHD & HD as compared to C & lower dose gps.

Mortality: Dams: None

Reproduction Data

Table I

Parameter	Control	2ug/kg	4ug/kg	8ug/kg	16ug/kg
Abortions	0	0	0	0	0
# corpora lutea/dam	NA*	NA	NA	NA	NA
# delivered by C-section	10	10	10	10	10
Total # implants	80	83	75	86	89
% resorption	NA	NA	NA	NA	NA
Mean # implants/dam	8.0	8.3	7.5	8.6	8.9
Dead embryos (total)	0	7	9	6	17
Fetal mortality (%)	0.0	8.4	12.0	7.0	19.1
Avg. # live fetuses/dam	8.0	7.6	6.6	8.0	7.2**
Sex ratio (F/M)	1.50	1.45	1.13	1.00	1.25
Avg. fetal body wt (g)	40.3	41.7	42.6	48.5	27.6
Avg. fetal body length (cm)	10.1	10.4	10.0	10.0	9.3**

*Not available
**Significantly different from control values

Malformations

External: Other than 1 case of short tail in the LD gp, there were no external abnormalities in the MHD or lower gps (including C). In the HD gp, 5 dams had a total of 11 fetuses with malformations. There were 3 cases of open eyelid (2 accompanied by keratolysis of the head and 1 by microtia), 7 cases of keratolysis of the head (1 accompanied by microtia) and 1 instance of talipes varus.

Internal: All living fetuses were normal in macroscopic exam of the internal organs.

Skeletal: No skeletal abnormalities of live fetuses were seen in the C & LD gps. At the MD, there was 1 case of incomplete 2nd cervical vertebra. At the MHD, there was 1 case of cranioschisis. At the HD, 6/11 cases of cranioschisis occurred with the finding of keratolysis of the head.

Occurrence of 13th rib: The rates of occurrence were 36.3, 25.0, 31.8, 23.8 & 4.2% in the C, LD, MD, MHD & HD gps, respectively.

Observations on Ossification: There was retarded ossification of the OS occipital in 6 cases (8.3%) in the HD gp only. The rate of retardation of the sternebrae was 22.5, 19.7, 15.2, 45.0 & 43.1% in the C, LD, MD, MHD & HD gps, respectively. The rates of retarded ossification of the first phalanx of the forepaw & handpaw were 40.3 & 27.8%, respectively at the HD, being significantly different from C. There was a slight but sig. decrease in the no. of canda vertebrae ossification (14.4) in the HD gp as compared to C (15.7).

The table showing occurrence of spontaneous malformation in this colony of rabbits is appended to this review.

2. Rate of Spontaneous Occurrence of Abnormalities in JCL-Wistar Rats: [K. Ezaki et al.

This study was done in 26 pregnant JCL-Wistar rats (day vaginal plug noted = day 0 of pregnancy). Results are shown in the following tables:

Table II
Number of Implantations, Deaths during Fetal Period, Fetal Weight & External Abnormalities

No. of animals used	No. of Implantations (Average)	Deaths during fetal per.		Living fetuses			Fetus wt. (X±S.D.)		External abnormalities
		Placenta remain.	mac. fetus	♂	♀	total	♂	♀	
26	443 (17.0)	19	3 (5.0%)	224	197 (16.2)	421	3.3g ±0.3	3.3g ±0.3	3* (0.7%)

One case of subcutaneous hemorrhage at right ear auricle*, two cases of slightly kinky tail.

Table III
Skeletal Abnormalities & Progress of Ossification in JCL-Wistar Rats

No. examined	Skeletal abnormalities	Characteristics indicating ossification progress							
		No. of caudal vertebrae	No. of metacarpus**				No. of metatarsus**		
			2/2	3/3	3/4	4/4	2/3	3/4	4/4
305	2*	3.6 ±0.6	1	107	15	182 59.7%	3	2	300 98.4%

*1 case cervical vertebral-thoracic vertebrae fissure, 1 case of stunted 13th rib.
**left metacarpus (metatarsus)/right metacarpus (metatarsus)

Table IV
Number of Ribs in JCL-Wistar Rats

No. examined	Number of ribs *			
	13/13	13/14	14/13	14/14
305	299	1	4 (2.0%)	1

Internal abnormalities have not been reported because the study was still ongoing.

3. Study Concerning Effect of C-P on Reproduction and Effects on Rats of Admin. before Pregnancy & at the Early Stage of Pregnancy: [Kuramoto et al. The Clinical Report, 10(9): 20, 1976]

Lab Perf. Study: Tokushima Univ. School of Medicine, Japan

Material Tested: C-P in saline (0.04% Tween-80)

Species & No. Animals: Wistar rat; 20/group

Dose Levels: 0 (C), 6.25 (LD), 12.5 (MD), 25 (MHD) or 50 (HD) mg/kg

Route & Duration: SC; 60 consecutive days prior to mating for M; F were treated for 14 days before and 7 days after mating was confirmed.

Animal Groups: The following combinations of C-P-treated & nontreated animals were used:

Group A - M treated, F treated
Group B - M treated, F untreated
Group C - M untreated, F treated
Group D - Both M & F treated with solvent (control)

Note: Within each gp, the M & F were mated.

Results:

General Observations: No sig. changes in the F were noted. In the M, mild emaciation, decreased activity, etc. were noted at the HD and to some extent, at the MHD.

Body Wt: In gp A males, suppression of growth rates were observed at the MHD & HD. In the F, there was a similar trend, but no sig. difference from C was seen. Gp B males showed growth curves similar to those of gp A. The pregnant F (gp B) showed normal growth curves. Gp C females did show growth suppression, but after cessation of drug admin. (pregnancy day 8), quick recovery followed.

Mortality: None in any group

Food & Water Intake: Slight suppression was seen at the MHD & HD.

Table V
Effect of C-P Administration on Mating Results

Dosage (Mg/kg)	Grp.A (treated males, treated females)			Grp.B (treated males, nontreated females)			Grp.C (nontreated males, treated females)		
	#test anim.	#mating estab.	%preg. estab.	#test anim.	#mating estab.	%preg. estab.	#test anim.	#mating estab.	#pregnancy estab.
Solvent	20	16 (80)	16 (100)	—	—	—	—	—	—
6.25	20	15 (75)	13 (86.7)	20	14 (70)	12 (85.7)	20	16 (80)	15 (93.7)
12.5	20	15 (75)	13 (86.7)	20	19 (95)	18 (94.7)	20	18 (90)	17[4] (94.4)
25.0	20	19 (95)	18 (94.7)	20	18 (90)	12 (66.7)	20	16 (80)	10 (62.5)
50.0	20	13 (65)	18[3] (100)	20	18 (90)	17 (94.4)	20	19 (95)	15 (78.9)

(Wistar rats, subcutaneous)

(1) % of test animals supplied;
(2) % of number of animals in which mating was established;
(3) five animals erroneously thought to be sterile and killed immediately after mating;
(4) one animal erroneously thought to be sterile and killed immediately after mating.

Slight decrease in pregnancy rates was seen at 25mg/kg in gps B & C, but at the HD, the rat was higher.

Table VI
Organ Wts in Male Rats after 60 Days C-P Administration
(Group A)

Dosage (μg/kg)		(Control) Solvent	6.25	12.5	25.0	50.0
No. dissected		20	20	20	20	20
Body weight	g	362.1±44.0	363.5±32.9	349.3±32.2	316.3±22.1	299.3±34.8
Brain	g	1.98±0.12	1.99±0.10	2.00±0.08	1.93±0.10	1.96±0.09
	g%	0.56±0.07	0.55±0.04	0.58±0.06	0.62±0.04**	0.66±0.06**
Pituitary	mg	10.2±1.2	10.8±1.5	9.9±1.0	9.5±2.2	9.6±0.8
	mg%	2.8±0.4	3.0±0.4	2.9±0.3	3.0±0.7	3.2±0.3
Thyroid	mg	20.2±2.9	20.6±3.5	20.0±3.5	19.1±3.8	19.5±3.2
	mg%	5.7±1.0	5.7±0.9	5.8±0.9	6.0±1.2	6.6±1.23*
Thymus	g	0.34±0.06	0.27±0.05**	0.22±0.04**	0.19±0.04**	0.11±0.04**
	g%	0.10±0.03	0.07±0.01*	0.07±0.01*	0.06±0.01**	0.04±0.02**
Heart	g	1.09±0.07	1.15±0.12	1.09±0.13	1.06±0.12	1.00±0.10**
	g%	0.31±0.05	0.32±0.02	0.31±0.03	0.34±0.03	0.34±0.03
Lung	g	1.46±0.15	1.50±0.24	1.42±0.15	1.36±0.24	1.24±0.12**
	g%	0.41±0.08	0.42±0.06	0.41±0.04	0.43±0.06	0.42±0.04
Liver	g	13.82±1.59	13.86±1.73	13.54±1.77	12.90±1.63*	11.35±1.69**
	g%	3.76±0.30	3.81±0.31	3.87±0.31	3.95±0.36	3.79±0.34
Spleen	g	0.78±0.08	0.74±0.08	0.70±0.11*	0.60±0.08**	0.53±0.09**
	g%	0.22±0.05	0.20±0.02	0.20±0.03	0.21±0.10	0.18±0.03**
Kidneys	g	2.53±0.22	2.67±0.28	2.58±0.30	2.40±0.22	2.34±0.29
	g%	0.59±0.07	0.74±0.06*	0.74±0.07*	0.76±0.05**	0.78±0.06**
Adrenals	mg	54.6±7.8	54.7±12.7	50.2±8.8	42.0±6.7**	38.2±7.4**
	mg%	14.9±1.9	15.0±3.1	14.4±2.2	13.6±1.8*	13.2±2.7*
Prostate	g	0.38±0.08	0.43±0.10	0.47±0.11	0.44±0.11	0.36±0.11
	g%	0.11±0.03	0.12±0.03	0.13±0.03	0.14±0.02	0.12±0.04
Seminal ves.	g	0.67±0.12	0.73±0.08	0.74±0.23	0.70±0.08	0.71±0.08
	g%	0.19±0.04	0.20±0.02	0.21±0.06	0.22±0.02*	0.24±0.04**
Testis	g	3.21±0.24	3.34±0.23	3.28±0.28	3.21±0.20	3.16±0.35
	g%	0.88±0.11	0.93±0.10	0.94±0.12	1.02±0.09**	1.07±0.12**
Epididymis	g	1.05±0.06	1.08±0.08	1.07±0.10	0.99±0.07	1.03±0.08
	g%	0.29±0.03	0.30±0.03	0.31±0.04*	0.31±0.03*	0.35±0.04**

(Mean ± S.D.)

g, mg = absolute wt
% = relative wt

*significant difference from control, $p < 0.05$
** " " " " $p < 0.01$

Table VII
Organ Wts in Dams at End of Pregnancy with C-P Admin.
Before & at Beginning of Pregnancy
(Group A)

		(Control)				
Dosage (μg/kg)		Solvent	6.25	12.5	25.0	50.0
No. dissected		16	15	16	10	15
Body weight	g	344.0±27.4	352.7±23.7	350.0±29.3	337.1±26.4	339.9±18.4
Brain	g	1.87±0.07	1.89±0.08	1.94±0.08*	1.90±0.08	1.95±0.06**
Pituitary	mg	11.7±1.4	12.3±1.6	11.8±1.8	12.1±1.0	12.7±1.2
Thyroid	mg	17.9±3.0	18.2±2.0	18.4±2.5	18.3±2.5	19.9±3.8
Thymus	g	0.24±0.04	0.26±0.05	0.23±0.05	0.23±0.10	0.24±0.05
Heart	g	0.84±0.07	0.89±0.09	0.88±0.09	0.91±0.10*	0.96±0.12**
Lung	g	1.19±0.11	1.19±0.10	1.15±0.13	1.16±0.11	1.18±0.11
Liver	g	14.34±1.41	14.71±0.79	14.36±1.57	13.32±1.39	13.82±1.54
Spleen	g	0.63±0.10	0.61±0.07	0.57±0.08	0.61±0.09	0.62±0.10
Kidneys	g	1.79±0.18	1.88±0.06	1.77±0.17	1.75±0.12	1.54±0.19
Adrenals	mg	61.9±8.7	68.3±6.5	59.3±7.6	63.2±9.8	59.5±9.4
Ovaries	g	0.13±0.03	0.12±0.01	0.12±0.01	0.13±0.02	0.13±0.03

(Mean ± S.D.)

g, mg = absolute wt
% = relative wt

*significant difference from control, $p < 0.05$
** " " " " $p < 0.01$

Table VIII
Organ Wts in Male Rats after 60 Day C-P Admin.
(Group B)

Dosage (µg/kg)		(Control) Solvent	6.25	12.5	25.0	50.0
No. dissected		20	20	20	20	20
Body weight	g	362.1±44.0	363.0±24.2	343.1±32.3	315.4±37.8	282.0±31.3
Brain	g	1.98±0.12	2.05±0.05	2.03±0.10	1.93±0.13	1.98±0.09
	g%	0.56±0.07	0.57±0.0[illegible]	0.60±0.05*	0.62±0.06**	0.71±0.07**
Pituitary	mg	10.2±1.2	10.9±0.9	10.0±1.0	9.3±1.0	9.4±1.8
	mg%	2.8±0.4	3.0±0.3	3.0±0.3	3.0±0.3	3.3±0.4*
Thyroid	mg	20.2±2.9	21.1±3.9	18.9±2.5	18.5±2.6	17.7±3.2*
	mg%	5.7±1.0	5.8±1.0	5.7±0.9	5.9±0.6	5.9±1.7
Thymus	g	0.34±0.08	0.30±0.05	0.25±0.06**	0.17±0.04**	0.11±0.03**
	g%	0.10±0.03	0.09±0.01	0.08±0.02*	0.06±0.01**	0.04±0.01**
Heart	g	1.09±0.07	1.16±0.10*	1.10±0.11	1.05±0.12	1.00±0.12**
	g%	0.31±0.05	0.32±0.03	0.33±0.02	0.34±0.03	0.35±0.03
Lung	g	1.46±0.15	1.45±0.09	1.32±0.11**	1.25±0.17**	1.16±0.13**
	g%	0.41±0.06	0.40±0.02	0.39±0.04	0.40±0.04	0.41±0.03 –
Liver	g	13.82±1.55	14.70±1.24	13.92±1.85	12.45±2.01*	11.83±1.90**
	g%	3.76±0.30	4.05±0.25*	4.09±0.33*	3.94±0.31	4.18±0.34**
Spleen	g	0.78±0.08	0.72±0.10*	0.73±0.09	0.64±0.17**	0.51±0.07
	g%	0.22±0.05	0.20±0.02	0.22±0.02	0.20±0.03	0.18±0.02**
Kidneys	g	2.53±0.22	2.77±0.25	2.61±0.25	2.51±0.32	2.42±0.33
	g%	0.69±0.07	0.76±0.05**	0.77±0.05**	0.81±0.08**	0.80±0.17**
Adrenals	mg	54.6±7.8	5[illegible].3±6.7	50.2±7.5	43.6±7.0**	33.9±8.1**
	mg%	14.9±1.9	14.4±1.7	14.9±2.5	13.9±2.4	12.4±2.6**
Prostate	g	0.38±0.08	0.42±0.11	0.40±0.07	0.40±0.09	0.39±0.08
	g%	0.11±0.03	0.12±0.03	0.12±0.01	0.13±0.02	0.14±0.03*
Seminal ves.	g	0.67±0.12	0.72±0.11	0.70±0.08	0.67±0.11	0.63±0.10
	g%	0.19±0.04	0.20±0.03	0.21±0.02	0.21±0.04	0.23±0.04**
Testis	g	3.21±0.24	3.09±0.31	3.32±0.21	3.14±0.27	3.27±0.32
	g%	0.88±0.11	0.85±0.09	0.96±0.09**	0.94±0.22	1.17±0.12**
Epididymis	g	1.06±0.06	1.08±0.07	1.07±0.07	1.02±0.11	0.99±0.07
	g%	0.29±0.03	0.30±0.03	0.32±0.04*	0.33±0.03*	0.35±0.04**

(Mean ± S.D.)

g, mg = absolute wt
% = relative wt

*significant difference from control, $p > 0.05$
** " " " " $p > 0.01$

Table IX
Organ Wts at End of Pregnancy of Dams Receiving C-P Admin.
Before & at Early Stage of Pregnancy
(Group C)

		(Control)				
Dosage (μg/kg)		Solvent	6.25	12.5	25.0	50.0
No. dissected		16	15	16	10	15
Body weight	g	344.0±27.4	348.2±32.8	353.3±20.1	349.5±25.9	336.5±18.1
Brain	g	1.87±0.07	1.92±0.07	1.87±0.06	1.91±0.10	1.89±0.10
Pituitary	mg	11.7±1.4	11.6±1.2	11.3±1.5	11.5±1.3	12.2±1.4
Thyroid	mg	17.9±3.0	18.4±3.7	18.8±4.4	20.5±2.4*	19.3±3.4
Thymus	g	0.24±0.04	0.25±0.05	0.25±0.06	0.23±0.04*	0.23±0.04
Heart	g	0.84±0.07	0.91±0.09*	0.90±0.07*	0.93±0.09*	0.95±0.09**
Lung	g	1.19±0.11	1.28±0.10*	1.28±0.07*	1.22±0.12	1.33±0.10**
Liver	g	14.34±1.41	14.65±1.82	14.95±1.41	15.32±1.10	15.23±1.20
Spleen	g	0.63±0.10	0.69±0.13	0.65±0.12	0.61±0.04	0.61±0.06
Kidneys	g	1.79±0.15	2.01±0.17*	1.96±0.20	1.91±0.15	1.92±0.15
Adrenals	mg	61.9±5.7	58.7±7.3	60.5±4.8	58.2±9.8	61.3±7.0
Ovaries	g	0.13±0.03	0.13±0.03	0.12±0.02	0.12±0.01	0.12±0.01

(Mean ± S.D.)

g, mg = absolute wt
% = relative wt

*significant difference from control, $p > 0.05$
** " " " " $p > 0.01$

In the treated M, a dose-related decrease was seen in thymus & adrenal wts (not seen in treated F). Commonly noted changes in all C-P-treated M rats were adrenal & thymic atrophy in the HD gps.

Reproduction & Fetal Data:

Table X
Effect on Fetuses of C-P Admin.
Before & at Early Stage of Pregnancy
(Group A)

Dosage (μg/kg)	Solvent	6.25	12.5	25.0	50.0
No. of mothers	16	13	13	18	12
No. of implants(avg)	197 (12.3)	171 (13.1)	184 (14.1)	246 (13.6)	177 (14.7)
No. of absorbed embryos (%)	11 (5.6)	3 (1.8)	12 (6.5)	20 (8.1)	39 (22.0)
No. of dead fetuses	0	0	0	0	1 (0.6)
No. of living fetuses: Total (%)	186 (94.4)	168 (98.2)	172 (93.5)	226 (91.9)	138 (78.0)
No. of living fetuses: Male/female	86/100	79/89	80/92	112/114	74/64
No. of living fetuses: Sex ratio (♂=1.00)	0.860	0.888	0.870	0.983	1.156
Wt. of living fetuses: Male	3.64±0.34	3.54±0.39	3.47±0.32	3.61±0.37	3.75±0.40
Wt. of living fetuses: Female	3.35±0.36	3.32±0.40	3.34±0.30	3.41±0.33	3.55±0.36
Wt. of living fetuses: g±S.D.(g)					
External abnormal.	0	*	**	0	0
Organ abnormal. (No. of fetuses examined)	0 (96)	0 (96)	0 (81)	0 (105)	0 (74)

*Brain hernia-1 (with spinal rupture)
**Thin tail-1

(Wistar rats, subcutaneous, males and females treate

Table XI
Effect on Fetuses of C-P Admin. to Males Only Before Mating
(Group B)

Dosage (μg/kg)	Solvent	6.25	12.5	25.0	50.0
No. of mothers	16	12	18	13	17
No. of implants(avg)	197 (12.3)	143 (11.9)	212 (11.7)	167 (12.8)	246 (14.4)
No. of absorbed embryos (%)	11 (5.6)	7 (4.9)	22 (10.4)	18 (10.8)	12 (4.9)
No. of dead fetuses	0	0	0	0	0
No. of living fetuses: Total (%)	186 (94.4)	136 (95.1)	190 (96.2)	149 (89.2)	231 (93.9)
No. of living fetuses: Male/female	86/100	61/75	110/80	75/74	112/119
No. of living fetuses: Sex ratio (♂=1.00)	0.860	0.813	1.375	1.014	0.941
Wt. of living fetuses: Male	3.64±0.34	3.53±0.37	3.68±0.41	3.57±0.31	3.57±0.28
Wt. of living fetuses: Female	3.35±0.36	3.36±0.37	3.41±0.48	3.34±0.35	3.36±0.32
Wt. of living fetuses: g±S.D.(g)					
External abnormal.	0	0	0	0	0
Organ abnormal. (No. of fetuses examined)	0 (96)	0 (73)	0 (91)	0 (73)	0 (101)

(Wistar rats, subcutaneous, males only treated)

Table XII
Effect on Fetuses of C-P Admin. to Females Only
Before & at Early Stage of Pregnancy
(Group C)

Dosage (mg/kg)	Solvent	6.25	12.5	25.0	50.0
No. of mothers	16	15	16	10	15
No. of implants (avg)	197 (12.3)	209 (13.9)	224 (14.0)	146 (14.6)	182 (13.2)
No. of absorbed embryos (%)	11 (5.6)	39 (18.7)	36 (16.1)	17 (11.6)	52 (28.6)
No. of dead fetuses	0	0	0	0	0
No. of living fetuses: Total (%)	186 (94.4)	170 (81.3)	188 (83.9)	128 (87.7)	144 (79.1)
Male/female	86/100	89/81	100/88	72/56	77/67
Sex ratio (♀=1.00)	0.860	1.099	1.171	1.286	1.149
Wt. of living fetuses x̄±S.D.(g): Male	3.64±0.34	3.73±0.31	3.64±0.48	3.40±0.30	3.42±0.41
Female	3.35±0.36	3.22±0.88	3.46±0.29	3.24±0.34	3.24±0.34
Extern. abnormal.	0	0	*	0	**
Organ abnormal. (No. of fetuses examined)	0 (98)	0 (91)	0 (103)	0 (63)	0 (71)

(Wistar rats, subcutaneous, females only treated)

*Thin tail- 1
Subcutaneous edema- 1

**Brain hernia- 1 (with spinal rupture
Thin tail- 1

An increase in resorption and a decrease in the no. of living fetuses were seen in the HD animals of gps A & C (F treated). In gp B, no sig. difference from control in any parameters observed were noted. In gp A, external fetal abnoralities consisted of 1 case of brain hernia accompanied by rachischisis in the LD gp and 1 case of thin tail in the MD gp. In gp C, 1 case of brain hernia in the 50mg/kg gp and 1 case each of short tail & subcutaneous hydrops were noted in the MD animals.

Internal Abnormalities: Compared to C, adrenal atrophy in all gp C fetuses and in about half the gp A fetuses were seen at the HD. Histological changes consisting of thinning of cellular layers and small-sized cells in the inner layers were seen in these adrenals.

Ossification & Skeletal Abnormalities: No remarkable differences from C gps were seen in gps A, B or C at any dose level.

4. Study Concerning the Effect of C-P on Reproduction and Effect on Rat Fetus of Admin. during Organogenesis Period: [M. Kuramoto et al. The Clinical Report 9(13), December 20, 1975]

Lab Perf. Study: Pharmacology & Anatomy Depts., Tokushima Univ. School of Medicine, Japan

Material Tested: C-P in 0.04% Tween-80-saline

Species & No. Animals: Wistar rats; 31 dams

Dose Levels: 0 (C), 0.03 (LD), 0.1 (MD) or 0.4 (HD) mg/kg

Route & Duration: SC; day 8 to day 17 of pregnancy

Methods: On day 20 of pregnancy, 20 dams from each gp were delivered by C-section, and the reproductive parameters were ascertained. The fetuses were examined for abnormalities or anomalies. 11 dams were allowed to deliver naturally and rear the pups for 4 wks. The newborns of 5 mothers were killed and examined for abnormalities. The mothers (F_0) were killed for determination of reproductive parameters. The newborns of 5 mothers (F_1 generation) were examined for reproductive performance by allowing to mate to obtain F_2 generation.

Results:

Body Wt & General Observations: Slight piloerection & sedation, and loss of body wt were seen in the HD gp.

Water Intake: No gp difference was observed.

Organ Wt: There was a dose-related decrease in abs. wts of thymus, liver, spleen & adrenals.

Necropsy: Splenic & adrenal atrophy were reported in the MD & HD dams.

Reproductive Parameters (F_0 dams) & Observations on F_1 Fetuses Delivered by C-section:

Table XIII
Effect on F_1 Fetuses of C-P Admin. during Organogenesis Period

Group (F_0 dosage level mg/kg)		P_1 (solvent)	S_1 (0.03)	M_1 (0.10)	L_1 (0.40)
No. of DAMS		20	20	20	20
No. of Implants (average)		264 (13.2)	253 (12.7)	252 (12.6)	239 (12.6)
No. of dead fetuses	resorbed embryos (%)	19 (7.2)	11 (4.3)	19 (7.5)	17 (7.1)
	No. of dead fetuses (%)	0	0	0	5 (2.1)
No. of living fetuses	total (%)	245 (92.8)	242 (95.7)	233 (92.1)	217 (90.8)
	male/female	130/115	115/127	108/125	94/123
	sex ratio (♀ = 1.00)	1.13	0.91	0.86	0.76
living fetus weight	male	3.76±0.33	3.77±0.40	3.43±0.30	2.64±0.41
	female	3.50±0.33	3.32±0.35	3.22±0.40	2.53±0.35
external abnormalities		1 rear limb strephenopodia	2 rear limb strephenopodia	1 rear limb strephenopodia	5 rear limb strep. 1 cleft palate 2 brain hernia 1 (w. anophthalmia)

X±S.D.

Table XIV
Effect of C-P Admin. during Organogenesis Period
on Skeletal Variations & Internal Abnormalities in F_1 Fetuses
(Wistar rats, SC)

Group (F_0 dosage level mg/kg)		F_1 (solvent)	S_1 (0.03)	M_1 (0.10)	L_1 (0.40)
No. of DAMS		10	10	10	10
Skeletal VARIATIONS	No. of fetuses examined	123	120	122	111
	14th rib	0	0	0	0
	14th rib trace	7 (5.7)	7 (5.4)	3 (2.5)	0
	irregular sternebrae	48 (39.0)	60 (52.2)	54 (44.3)	81 (73.0)
	absence of 1st thor. vt.	0	0	1 (0.8)	2 (1.8)
	separated 10th thoracic vertebra	0	0	0	1 (0.9)
	separated 11th t.v.	0	0	0	4 (3.6)
	separated 12th t.v.	0	0	1 (0.8)	0
	separated lumbar v.	0	0	0	1 (0.9)
	other abnormalities	0	0	0	0
No. of mothers		10	10	10	10
Internal abnor.	No. of fetuses examined	122	112	111	103
		None	None	None	None

Reproductive Paramaters (F_0 dams) & Observations on F_1 Fetuses Delivered Normally:

Table XV
Effect of C-P Admin. during Organogenesis Period on Development of F_1 Newborns
(Wistar rats, SC)

Group (F_0 dosage level mg/kg)		P_1 (solvent)		S_1 (0.03)		M_1 (0.10)		L_1 (0.40)	
No. of Dams		11		11		11		11	
Pregnancy per'd (days)		22.4± 0.0		22.4± 0.9		22.4± 0.0		22.7± 0.3	
No. of implants (avg.)		134 (12.2)		152 (13.8)		169 (15.4)		155 (14.1)	
No. of offspring delivered (avg.)		124 (11.3)		142 (12.9)		157 (14.3)		118 (25)** (10.7)	
Delivery rate (%)		92		93.4		92.9		76.1*	
Avg. wt. of living fetuses		no	wt. (g)	no.	wt. (g)	no.	wt. (g)	no	weight (g)
male	at birth	66	6.2± 0.4	80	5.7± 0.4	80	5.0± 0.5	40	4.4± 0.5
	1week old	65	14.5± 1.4	79	12.5± 1.5	80	11.5± 1.7	14	8.8± 1.8
	2weeks old	64	26.5± 3.2	78	25.8± 2.8	79	22.4± 3.4	14	19.1± 3.3
	3weeks old	64	43.5± 6.4	78	38.1± 4.0	78	33.7± 6.0	14	30.4± 4.7
	4weeks old	64	77.1± 9.4	78	70.6± 6.1	78	60.5±10.1	14	55.7±11.0
female	at birth	58	5.6± 0.4	62	5.3± 0.5	77	4.9± 0.5	33	4.2± 0.4
	1week old	56	14.2± 1.3	62	13.4± 2.2	73	11.5± 1.7	12	8.5± 1.6
	2weeks old	57	26.9± 3.3	60	25.4± 4.2	72	22.6± 3.2	11	19.3± 3.3
	3weeks old	57	40.9± 6.0	60	36.1± 6.1	72	34.5± 6.2	11	30.6± 4.6
	4weeks old	57	71.5± 9.0	60	68.5±10.4	72	62.3± 8.7	11	56.4±11.0
sex ratio (M/F)		1.12 (64/57)		1.30 (78/60)		1.08 (78/72)		1.27 (14/11)	
survival rate (%)		97.6		97.2		95.5		95.9*	
No. of offspring w. extern. or organ abnor.		0		0		0		RETARDATION OF HAIR GROWTH	
abnormality in behavior or senses		none		none		none		none	

*Compared to P (solvent) group. Significant when P 0.05.
X ± S.D.

Delivery rate: no. of offspring delivered/no. of implants

Survival rate: no. of offspring nursed/no. of offspring delivered

Decrease in nursing rate due to (1) death immediately after birth, (2) eaten by mother.

Necropsy of 4-Week-Old F_1 Pups: Only LD & MD F_1 pups were examined. No dose effects were seen on organ wts. Gross & histopathology were unremarkable.

Reproductive Parameters of F_1 Generation:

Table XVI
Pregnancy Rate of 10-week-old F_1 Newborns

Group F_0 dosage level (mg/kg)	No. of animals	% [1]	No. of animals	% [2]
P_0 solvent	20/25	80.0	20/22	90.9
S_0 (0.03)	21/25	84.0	21/24	88.4
M_0 (0.10)	18/25	72.0	18/22	81.8
L_0 (0.40)	9/11	81.6	9/10	90.0

1) $\frac{\text{Number of pregnant animals}}{\text{Number of animals used}}$

2) $\frac{\text{Number of pregnant animals}}{\text{Number in which mating was confirmed}}$

Table XVII
State of Sexual Maturity of F_1 Newborns with Admin. of C-P during Organogenesis Period

		10 weeks old					14 weeks old				
	Group F_0 dosage lev. (mg/kg)	No. of animals	State of sperm in epididymis (%) norm.	head abn.	trunk abn.	tail abnorm.	No. of anim.	State of sperm inside epididymis (%) normal	head abnor	trunk abnor.	tail abnorm.
male	P_0 (solvent)	3	84.7	8.0	3.6	2.7	14	88.8	5.4	1.0	4.8
	S_0 (0.03)	4	88.7	6.6	1.2	3.5	18	86.5	5.9	3.8	3.8
	M_0 (0.10)	7	88.8	7.2	0.5	3.5	16	86.7	4.3	4.2	4.8
	L_0 (0.40)	2	88.5	6.8	0.5	3.5	9	87.8	7.9	1.1	3.2
	Group F_0 dosage lev. (mg/kg)	No. of anim.	State of sexual cycles (no. of animals) normal	irreg.	none	No. of anim.	State of sexual cycles (no. of animals) normal	irreg.	none		
female	P_0 (solvent)	3	1	1	1	3	3	—	—		
	S_0 (0.03)	4	—	1	3	4	3	1	—		
	M_0 (0.10)	7	—	2	5	7	7	—	—		
	L_0 (0.40)	2	—	—	2	2	2	—	—		

(Examination of animals in which pregnancy was not established during mating at 10 wks, but as for the 14-wk-old M, exams were performed on the animals which had induced pregnancy.)

Table XVIII

Effect on F_2 Fetuses of C-P Admin. during Organogenesis Period

Group (F_0 dosage level (mg/kg)		F_2(solvent)	S_2 (0.03)	M_2 (0.10)	L_2 (0.40)
No. of DAMS (F_1)		13	12	12	6
No. of implants (average)		177 (13.6)	178 (14.8)	166 (13.8)	84 (14.0)
No. of dead fetuses	No. of RESORBED embryos (%)	11 (6.2)	14 (7.9)	15 (9.0)	6 (7.1)
	No. of dead fetuses	0 (0)	0 (0)	0 (0)	0 (0)
No. of living offspring	Total (average) (%)	166 (13.8) (93.8)	164 (13.7) (92.1)	151 (12.6) (91.0)	78 (13.0) (92.9)
	M/F	91/75	89/75	77/74	39/39
	sex ratio (f = 1.00)	1.21	0.73	1.04	1.00
weight of living offspring (g)	MALE	3.54±0.31	3.69±0.27	3.62±0.32	3.62±0.30
	FEMALE	3.41±0.31	3.50±0.26	3.52±0.45	3.50±0.39
external abnormalities		none	none	none	none

$\bar{X} \pm S.D.$

No internal or external abnormalities or dose-dependent skeletal variations were reported in F_2 fetuses delivered by C-section.

Development of F_2 Pups: (F_1 dams with normal delivery)

Table XIX

Group (F_0 dosage level mg/kg)		F_2 (solvent)		S_2 (0.03)		M_2 (0.10)		L_2 (0.40)	
No. of DAMS (F_1)		6		6		6		3	
Pregnancy period (days)		23.4± 0.0		23.4± 0.3		23.3± 0.3		23.3± 0.1	
No. of implants (average)		88 (14.7)		97 (16.2)		94 (15.7)		30 (10.0)	
No. of offspring delivered (average)		83 (13.8)		88 (14.7)		89 (14.8)		27 (9.0)	
Delivery rate (%)		94.3		90.7		94.7		90.0	
Average weight of living fetuses (F_2)		no.	wt. (g)	no.	wt. (g)	no.	wt. (g)	no.	wt. (g)
male	at birth	38	5.8± 0.6	40	5.6± 0.6	35	5.8± 0.7	18	6.2± 0.4
	1week old	36	14.4± 2.1	38	13.3± 2.6	33	13.7± 2.2	18	15.4± 1.5
	2weeks old	36	28.5± 3.3	34	25.6± 4.5	32	26.2± 3.1	18	28.5± 2.9
	3weeks old	36	42.8± 5.7	31	41.1± 4.7	32	41.3± 5.9	18	45.2± 6.2
	4weeks old	36	78.3±10.3	31	74.6± 6.1	30	77.6± 8.0	18	82.7± 8.3
female	at birth	45	5.5± 0.5	46	5.4± 0.5	34	5.6 ±0.4	9	6.3± 0.4
	1week old	44	13.8± 1.9	46	12.7± 1.7	33	12.8± 1.8	9	15.8± 1.6
	2weeks old	42	26.4± 3.0	45	26.3± 2.5	31	24.0± 2.8	9	31.0± 3.1
	3weeks old	41	38.8± 3.7	45	40.2± 3.9	31	38.4± 4.7	9	50.3± 5.9
	4weeks old	41	68.9± 3.6	45	71.6± 4.3	31	68.9± 6.7	9	86.3± 7.6
Sex ratio (M/F)		0.98 (36/41)		0.89 (31/45)		1.02 (32/31)		2.00 (18/9)	
Survival rate (%)		92.8		88.4		92.3		100.0	
No. of offspring w. external or organ ab.		0		0		0		0	
Abnormalities in behavior or reflexes		none		none		none		none	

$\bar{X} \pm S.D.$

Necropsy of 4-week-old F_2 Pups: In the HD gp, a sig. decrease in rel. adrenal & spleen wts was noted. No abnormal histopathology or skeletal malformations (checked by X-ray) were reported.

C. Miscellaneous Studies

1. Skin Irritancy Tests: The following studies submitted in this NDA were previously submitted in connection with the original IND and have been reviewed.

   - 14-Day Irritancy Test in Guinea Pigs with 0.05% & 0.1% Cream
   - 14-Day Irritancy Test in Rabbits with 0.05% & 0.1% Cream

2. Eye Irritancy Tests: The following studies submitted in this NDA were previously submitted in connection with the original IND and have been reviewed.

   - 14-Day Eye Irritancy Test in Guinea Pigs with 0.05% & 0.1% Cream
   - 14-Day Eye Irritancy Test in Rabbits with 0.05% & 0.1% Cream

3. Mutagenicity Studies

Lab Perf. Studies: Glaxo Research Ltd., Harefield, U.K.

Material Tested: C-P (GR 2/925)

Test Systems:

a) Ames Test: TA 98, 100, 1535, 1536 & 1538 were used.

b) Fluctuation Tests: E. coli B WP2 trp E was used to detect both DNA cross-linking agents and base change mutagens. WP2 trp E uvrA (R 46) was used to detect base change mutagens. E. coli K-12 343/113 lys 60 (R 46) was used to detect both base change & frameshift activities.

c) Gene Conversion Assay: Saccharomyces cerivisiae JD 1 was used in this assay. Gene conversion was monitored at the his 4 and trp 5 loci.

Results: C-P was negative in the Ames test at conc'ns up to 400 ug/plate in both the presence & absence of rat liver microsomal enzymes. There was evidence of mild toxicity at the highest conc'n tested (400 ug/plate) resulting in a mean reduction in colony counts of approx. 25% for the 5 strains.

The drug was negative in both macroscale & microscale fluctuation tests. Toxicity limited the effective test conc'n to 50 ug/ml in microtitre tests & 100 ug/ml in macroscale tests.

Comprehensive gene conversion tests using Saccharomyces cerevisiae JD 1 at two heteroallelic loci were negative in both the presence & absence of rat liver microsomes.

EVALUATION

Clobetasol 17-propionate (C-P) is a highly potent topically active fluorinated corticosteroid. Structurally, it resembles betamethasone dipropionate, but has an unusual feature, namely, substitution of a chlorine atom for OH at the 21-position. C-P has been marketed in the U.K. since 1974 by Glaxo Labs under the trade name "Dermovate". In Germamy, the drug has been registered under the name "Dermoxin". It has also been marketed in Japan & Canada. It is available in these countries as a 0.05% cream or ointment for treatment of corticosteroid-responsive dermatoses, including severe psoriasis & eczema. Clinical Studies in this country have been carried out by the sponsor under INDs The present NDA (19-322) is for the 0.05% cream formulation.

All preclinical studies were performed by the sponsor in England, except for an ADME study and some reproduction studies which were done in Japan, presumably for marketing in that country. A percutaneous absorption study, the mutagenicity studies and the Japanese studies are new submissions. All others contained in this NDA have been previously submitted in connection with the corresponding INDs and have been reviewed.

The potency of C-P was clearly demonstrated by vasoconstriction assay, in which it was 18.7x more active than fluocinolone acetonide. Predictably, increased toxicity was also observed. Pharmacodynamic studies showed that in the mouse, C-P was considerably more thymolytic than betamethasone alcohol, irrespective of route or vehicle.

In thymolytic activity, C-P showed interspecies differences. In mice, when given SC in saline, it was 11x more potent in thymolytic activity than betamethasone alcohol, but the two drugs are equipotent in the rat. A similar species difference was also observed in antigranuloma activity of the drug. The steroid showed no androgen-anabolic or antigonadotrophic activity and had only weak mineralocorticoid & estrogenic activities. It did, however, show marked anti-estrogenic effect (87x that of progesterone) and progestational activity (37x that of progesterone), when both drugs were given SC.

IV infusion of the steroid at up to 4mg/kg to cats produced no remarkable hemodynamic effects. Above this dose level, respiratory embarrassment & increased BP were seen; at 65mg/kg, death was reported due to respiratory depression attributed to the effects of particulate nature of the infusion material.

ADME studies with C-P (submitted in IND revealed several unusual characteristics, some of which were rather confusing. Thus, neither in vitro incubation with rat liver homogenate nor in vivo metabolism resulted in the hydrolysis of the C-P ester linkage. On dermal application, more radioactivity was found in the excreta from unoccluded animals when compared to the results from occluded animals. Unchanged drug was detected in the urine & feces of unoccluded animals, but not in the excreta of occluded animals. Furthermore, when the drug was administered PO or SC, no unchanged drug could be detected in the excreta. The investigator has tried to explain the absence of unchanged drug in the feces after an oral dose by suggesting

that unabsorbed C-P was metabolized by the flora of the lower gut. Such metabolism, however, cannot account for the observed SC results or the appearance of unchanged drug in excreta after unoccluded dermal application, but not after occluded application. The sponsor was, therefore, urged to repeat the dermal absorption study with the cream & ointment formulation.

The sponsor has submitted results of such a repeat study. Additionally, a second percutaneous absorption study (Japanese) has also been submitted. As one would expect, these studies showed clearly that there was significantly more percutaneous absorption of C-P from occluded animals (rats) compared to that from unoccluded animals. Absorption was slow with the cream and even slower with the ointment formulation. The absorbed drug was distributed throughout the body tissue examined and cleared in a similar manner to that observed after SC injection. The drug is metabolized by the liver and is excreted primarily via the bile into the feces. There was considerable enterohepatic circulation. The terminal half-life of the drug after SC administration to rats has been reported to be 31 hrs.

Acute, subacute & chronic toxicity studies have been performed in several species.

Acute toxicity (LD_{50}) has been determined in several species using oral, SC & IP routes. The SC route proved to be the most toxic. Based on the oral LD_{50} in rats, the substance may be classified as slightly toxic.

The adverse effects reported in the subacute and chronic (6-month) toxicity studies (dermal & SC) were of the type usually associated with long-term potent steroid therapy. These included emaciation, thinning of the skin & retardation of hair growth at the application site, increases in serum SGOT & SGPT values, decreased plasma cortisol levels, involution of the thymus, adrenal atrophy, localized hepatic necrosis, hyperglycemia and lymphopenia. The incidence and severity of these effects were significantly greater when the drug was administered SC than when administered topically. The steroid is probably a potent immunosuppresant, since bronchial and lung infections were rather rampant among the treated animals, resulting in considerable number of deaths, particularly in the high-dose groups. By the SC route, a maximum tolerated dose of the drug substance in the rat appears to be 20 ug/kg/day. When the drug substance was applied topically, a "no-effect" dose was 7.5 ug/kg/day, and 1 gm/kg/day of 0.05% P-C cream appears to have no significant toxic effects in this species. This is about 14x the proposed maximum clinical dose per day.

A comparative study done by Shino et al. demonstrated that while clobetasol propionate is a very active anti-inflammatory steroid that can produce both local & systemic effects following percutaneous application, the changes that occur are reversible, less marked than dexamethasone & fluocinonide and indicate minimal local irritation.

Reproduction & teratology studies were performed in rats, mice & rabbits. Teratogenicity studies done by the sponsor in mice & rabbits using the SC route showed that the drug was fetotoxic at the highest dose tested (1mg/kg) and teratogenic at all dose levels employed (lowest dose, 0.03mg/kg) in mice. In rabbits, a dose of 1 ug/kg had no adverse effect on fetuses, but the drug was teratogenic at 3 & 10 ug/kg dose levels. These studies indicated that C-P, as a teratogen, was at least 10x as active as betamethasone.

Teratogenicity studies performed in rabbits by the Japanese indicated that doses of 8 ug/kg or less were probably not teratogenic. One case of short tail in the 2 ug/kg group fetuses was reported. In the rat, SC administration of C-P during pregnancy days 8-17 showed that at the highest dose level (0.4mg/kg), the drug was teratogenic (cleft palate, brain hernia). Maternal toxicity (decreased body wts) & fetotoxicity were also seen in the mid- (0.1mg/kg) & high-dose levels. Newborn rats at the high-dose did not thrive, and those that survived were generally underweight & immature. The reproductive capacity of the F_1 rats seemed unaffected by treatment. No treatment-related effects were seen in the F_2 generation. A "no-effect" dose in this study was found to be 0.03mg/kg. However, the drug treatment was started in these animals on day 8 of pregnancy instead of day 6, as recommended by FDA. Thus, some early effects on pregnancy parameters might have been missed.

In the segment I reproduction study in rats done in Japan, growth suppression and adrenal and thymic atrophy were reported at doses of 25 & 50 ug/kg/day. Results showed no significant effect on mating or on fetuses when males were treated with C-P. Effects of C-P administration to females were limited to an increase in the number of resorbed embryos and a decrease in the number of living fetuses only at the maximum dose (50 ug/kg/day).

Single cases of fatal abnormalities seen at some dose levels were well within the range normally seen in rats. At any rate, there was no dose-related increase in the incidence of these abnormalities.

C-P was nonmutagenic in 3 different test systems, one of which was the Ames test.

Cream containing 0.05% or 0.1% C-P was nonirritating when applied to the intact skin or eyes of guinea pigs & rabbits for 14 days.

None of the original Japanese articles have been submitted. The English translation provided in the NDA contains seveal mistakes. For example, on page 20-285 (vol. 20), the report states that there were 2 deaths in the ointment group, but on page 20-286 (vol. 20) 3 deaths were described in the ointment group. Tables 9 & 10 (pp. 20-293 & 20-294, vol. 20) giving the organ weights should be for 3-month studies, not for 1-month study as shown. The most serious mistake has been made in giving the dose levels as mg/kg instead of ug/kg (page 21-094, vol. 21) for the segment I reproduction study in rats. I confirmed this with the sponsor over the telephone, who promised to send the necessary correction as an amendment to this NDA.

Although other potent corticosteroids have been shown to be teratogenic in animals, C-P is particularly potent in this respect, showing teratogenic activity at least 10x greater than betamethasone. The labeling should be changed to contain in the "Pregnancy Category" the following statement: "The more potent corticosteroids, including clobetasol 17-propionate, have been shown to be teratogenic after dermal application in laboratory animals."

Clinical experience reports indicate that there has been at least one case of fatal iatrogenic Cushing's syndrome on prolonged topical use of this medication (vol. 15, page 15-095).

The "Indications and Usage" section should be modified to include the statement "not to exceed 50 gm/week". Otherwise, the labeling appears to be satisfactory.

RECOMMENDATION

With the changes in the labeling detailed above, I find this NDA approvable.

Syed N. Alam, Ph.D.

cc: Orig. NDA
HFN-815 3/8/85
HFN-815/MO
CSO
HFN-340
HFN-815/SNAlam/smc/3/5/85
R/d init.by:JMDavitt
3175b

Appendix table—1 Occurrence of spontaneous malformation in japanese white rabbits (hybrid)

exp. No.	route	No. of fetuses used	mean body weight of dams in gestation (kg)			total No. of implants (mean ±SD)	total dead implants (%)	viable fetuses										No. of anomalies		
			0 day	28 th day	body weight gain			total (mean±SD)	male	female	proportion (P/M)	body weight (g)		body length (cm)		tail length (cm)		external (%)	internal (%)	skeletal (%)
												male	female	male	female	male	female			
1	P.O.	10	2.74 ±0.25	3.45 ±0.43	0.71 ±0.18	84 (8.4±1.8)	5 (6.0)	79 (7.9±1.9)	37	42	1.14	38.8 ± 5.7	37.8 ±5.5	10.4 ±0.6	10.4 ±0.7	12.2 ±1.1	12.1 ±0.8	0	0	0
2	P.O.	10	2.50 ±0.52	4.18 ±0.56	0.68 ±0.24	67 (6.7±2.9)	0	67 (6.7±2.9)	29	38	1.31	36.4 ±10.5	39.7 ±9.9	10.3 ±1.2	10.5 ±1.4	11.4 ±2.5	12.4 ±2.6	0	0	0
3	P.O.	10	3.49 ±0.24	4.14 ±0.23	0.65 ±0.23	99 (9.9±2.3)	6 (6.1)	93 (9.3±2.3)	43	50	1.16	39.7 ± 7.7	38.2 ±4.2	11.0 ±0.4	10.5 ±0.3	12.7 ±1.0	13.1 ±0.8	0	0	0
4	I.V.	10	3.39 ±0.26	4.30 ±0.31	0.91 ±0.18	94 (9.4±2.0)	6 (6.5)	86 (8.6±2.1)	45	41	0.91	41.6 ± 6.4	41.1 ±6.9	10.7 ±0.8	10.6 ±0.8	13.6 ±1.4	13.6 ±1.5	0	0	1 (1.2)

Appendix table—2 Skeletal malformation in live fetuses of japanese white rabbits (hybrid)

exp. No.	route	No. of fetuses used	Axial Skeleton											Forepaw	Hindpaw
			Skull	Rib			Sternebra			Change of pre-cost-transverse	Vertebra			non-ossified middle phalange	non-ossified middle phalange
			incomplete formation of supraoccipital	12	12—13	13	delayed ossification	extra sternebra	asymmetry		precaudal vertebrae		sacral caudal		
											26	27			
			fk (%)	fk (%)	fk (%)	fk (%)	fk (%)	fk (%)	fk (%)	fk (%)	fk (%)	fk (%)	mean ±S.D.	fk (%)	fk (%)
1	P.O.	79	0	56	8	15	19 (24.1)	0	0	0	69	10 (12.7)	15.3 ±1.4	12 (15.2)	1 (1.3)
2	P.O.	67	0	49	5	13	10 (14.9)	0	0	0	64	3 (4.5)	15.3 ±1.2	19 (28.4)	2 (3.0)
3	P.O.	93	0	42	13	38	35 (37.6)	1	1	31 (33.3)	83	10 (10.8)	15.3 ±1.0	13 (14.0)	2 (2.2)
4	I.V.	86	0	61 (70.9)	10 (11.6)	15 (17.4)	18 (20.9)	1 (1.2)	3 (3.5)	31 (36.0)	83	3 (3.5)	15.3 ±1.0	9 (10.5)	0

CHEM

REV

Division of Anti-Infective
Drug Products
Chemist's Review 1
Date Completed: 11/8/84

A.1. NDA 19-322

Sponsor: Glaxo, Inc.
Research Triangle Park, NC

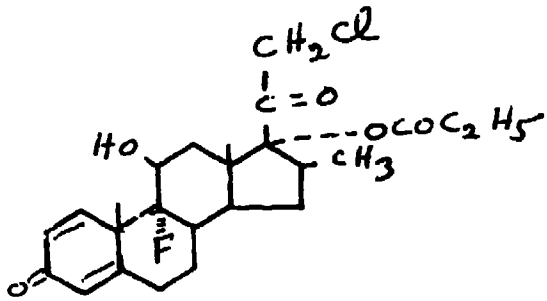
2. Product Names:

Proprietary: Removate
Non-proprietary: clobetasol 17-propionate
USAN: Same

3. Dosage Form & Route of Administration: 0.05% Cream

4. Pharmacological Category and/or Principal Indication: anti-inflammatory agent

5. Structural Formula and Chemical Name(s):



21-chloro-21-desoxybetamethasone 17-propionate

B. 1. Original Submission: 8/30/84; (rec'd BD 8/30/84; assigned 9/12/84)

2. Amendments: 9/20/94 (refers to DMF

3. Supporting Documents: IND DMF's

C. Remarks:
The NDA contains a 3C classification. Manufacturing and controls were found deficient in several areas which needs correcting before granting an approval for the controls (refer to chemist review notes). The labeling was found acceptable from a technical standpoint. Methods Validation pending; EIR pending.

Conclusions and/or Recommendations:
Manufacturing and control deficiencies have been observed in the NDA and were communicated by telephone (telecon 11/16/84). These deficiencies should also be sent to the applicant as an information letter requesting corrections within 30 days. Refer to the Draft of Chemist Letter to Applicant.

Ernest G. Pappas 11/29/84

Ernest G. Pappas

cc: Orig. NDA 8/85
~~HFN-815~~ ~~CI~~ HFN-815/CSO HFN-815/Pappas: gm 11/27/84
HFN-616 R/D Init. by: ARCasola 11/18/84 ARC 12/7/84
2341b

Division of Anti-Infective
Drug Products
Chemist's Review #1
Date Completed: 3/21/85

A.1. NDA 19-322 & 19-323

Sponsor: Glaxo, Inc.
Research Triangle, Park, NC

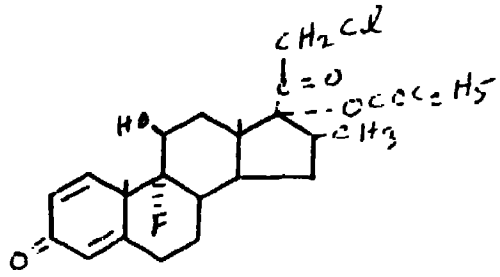
2. Product Names:

Proprietary: Removate
Non-proprietary: clobetasol 17-propionate

3. Dosage Form & Route of Administration: 0.05% Cream (NDA 19-322)
0.05% Ointment (NDA 19-323)

4. Pharmacological Category and/or Principal Indication:
Anti-inflammatory agent.

5. Structural Formula and Chemical Name(s):



21-chloro-21-desoxybetamethasone 17-propionate

B. 1. Initial Submission: 8/30/84; Rec'd in Bureau: 8/30/84
Rec'd by Chemist: 9/12/84

2. Amendments: 9/20/84 (refers to DMF 1/30/85

C. Remarks:
The firm responded on 1/30/85 to the control deficiencies of the original application (see chem. Rev. 11/8/84). This amendment was reviewed and found acceptable (see chem. notes). Draft Labeling was also reviewed and found acceptable from a technical standpoint.

D. Conclusions and/or Recommendations:
From a manufacturing and controls standpoint, the application is approvable. FPL should be requested.

Ernest G. Pappas 3/22/85

Ernest G. Pappas

cc: Orig. NDA 3/25/85
HFN-815 HFN-815/CSO HFN-815/Pappas: gm 3/22/85
R/D Init. by: ARCasola 3/22/85 ARC 3/25/85
HFN-815/MO
3482b

NDA 19322

Analytical Method

Section 8(n)

2. Specifications for the finished dosage form

2.1 Specification for purpose of batch release

The bulk cream complies with the specification given in Section 8(h) 4, namely:-

Appearance	White cream
Identity of clobetasol 17-propionate	Complies with test
pH	
Chlorocresol content	
Clobetasol 17-propionate content	

The filled tubes and sachets comply with the following specification:-

Appearance of contents	White cream
Minimum fill	Complies with USPXX (Fill weights are determined during in-process control as described in Section 8(h) 4).

Additionally, the identity of clobetasol 17-propionate test will be performed by Glaxo Inc., on filled tubes and sachets prior to release for distribution.

Section 8(n)

2.2 Specification to be met throughout life

Appearance of contents	White to off-white cream
Identity of clobetasol 17-propionate	Complies with test
pH	
Chlorocresol	
Clobetasol 17-propionate content	
Minimum fill	Complies with USP XX

2.3 Specification for Glaxo Inc.

Each batch of REMOVATE CREAM shipped to the United States for marketing by Glaxo Inc. will be accompanied by a Certificate of Analysis certifying that the batch meets the specification for the finished dosage form (for the purpose of batch release - see section 8(n)2.1). Upon receipt by Glaxo Inc. each batch will be visually inspected and tested for identity.

Each batch of BULK REMOVATE CREAM shipped to the United States for filling into sachets will be accompanied by a certificate of analysis certifying that the batch meets the specification for bulk cream. Upon receipt by Glaxo Inc. each batch will be visually inspected and tested for identity.

Section 8(n)

2.4 Justification of standards applied to filled tubes and sachets

The tests and standards given in the specification to be met throughout the shelf life are similar to those found in pharmacopoeial monographs for creams containing steroids.

Clobetasol 17-propionate is identified either from the retention time of the steroid peak in the reverse-phase HPLC assay or by TLC using a normal-phase system.

The aqueous phase of the cream is buffered with a mixture of sodium citrate and citric acid. The pH of the cream is approximately and the specified range satisfactorily accommodates the variations that occur during manufacture and storage.

Chlorocresol is determined by HPLC and the proposed standards satisfactorily accommodate the normal variation in the manufacturing process and the variability of the analytical method.

Clobetasol 17-propionate is determined by a specific HPLC assay that separates clobetasol 17-propionate from potential degradation products and the likely impurities from the synthesis. The proposed standards of per cent of the labelled content are skewed to accommodate the per cent overage. When testing tubes, three portions of the cream are assayed and the standards apply to the mean of the three assay results. This is the procedure adopted during the stability testing programme and takes account of the variation in steroid content that may occur in some tubes on storage. This is discussed further in Section 8(p)2.9, page 17 089.

The test for minimum fill is applied to ensure compliance with the requirements of the USP.

In-process control is effected by testing the bulk cream for appearance, identity of clobetasol 17-propionate, pH, chlorocresol content and clobetasol 17-propionate content. The standards proposed for clobetasol 17-propionate content are per cent of the labelled content and these are symmetrical with respect to the steroid input. Clobetasol 17-propionate is identified from the retention time of the peak in the reverse-phase HPLC assay. This distinguishes clobetasol 17-propionate from the other topical steroids that may be used on the manufacturing site as shown by the following table of typical retention times. The table also lists typical Rf values for the steroids in the TLC identity test.

Section 8(n)

Compound	HPLC		TLC
	Retention time (minutes)	Relative retention time	Rf value
Hydrocortisone			
Hydrocortisone acetate			
Clobetasol 17-propionate			
Betamethasone 17-valerate			
Clobetasone 17-butyrate			
Beclomethasone dipropionate			

The bulk is appropriately labelled. It is checked onto the filling/packaging line by the Packaging Department line supervisor and subsequently by a Quality Control inspector as part of routine in-process monitoring checks that ensure that the correct bulk is released for filling and packaging. Filled tubes and sachets are tested for fill weight and appearance of contents at regular intervals during the filling process.

The steroid content of three lots of tubes and three lots of sachets filled from different batches of cream was determined during the preparation of samples for stability testing. Replicate portions of cream were assayed from the mixed contents of each of 10 tubes taken systematically throughout each run. The steroid content of each of 10 sachets taken systematically throughout each run was determined. The results obtained are summarised in the following table.

Bulk batch number	Number of filled containers examined	Number of assays	Clobetasol 17-propionate	
			Mean %w/w	Coefficient of variation %
PHDO 11/6	10 tubes	25	0.0537	1.4
PHDO 11/7	10 tubes	20	0.0521	1.0
PHDO 11/8	10 tubes	21	0.0527	1.0
EPPG 2/6	10 sachets	10	0.0513	1.5
EPPG 1/54	10 sachets	10	0.0531	0.5
EPPG 1/55	10 sachets	10	0.0521	1.2

Section 8(n)

Compound	HPLC		TLC
	Retention time (minutes)	Relative retention time	Rf value
Hydrocortisone			
Hydrocortisone acetate			
Clobetasol 17-propionate			
Betamethasone 17-valerate			
Clobetasone 17-butyrate			
Beclomethasone dipropionate			

The bulk is appropriately labelled. It is checked onto the filling/packaging line by the Packaging Department line supervisor and subsequently by a Quality Control inspector as part of routine in-process monitoring checks that ensure that the correct bulk is released for filling and packaging. Filled tubes and sachets are tested for fill weight and appearance of contents at regular intervals during the filling process.

The steroid content of three lots of tubes and three lots of sachets filled from different batches of cream was determined during the preparation of samples for stability testing. Replicate portions of cream were assayed from the mixed contents of each of 10 tubes taken systematically throughout each run. The steroid content of each of 10 sachets taken systematically throughout each run was determined. The results obtained are summarised in the following table.

Bulk batch number	Number of filled containers examined	Number of assays	Clobetasol 17-propionate	
			Mean %w/w	Coefficient of variation %
PHDO 11/6	10 tubes	25	0.0537	1.4
PHDO 11/7	10 tubes	20	0.0521	1.0
PHDO 11/8	10 tubes	21	0.0527	1.0
EPPG 2/6	10 sachets	10	0.0513	1.5
EPPG 1/54	10 sachets	10	0.0531	0.5
EPPG 1/55	10 sachets	10	0.0521	1.2

Section 8(n)

Forty six recovery experiments gave a mean recovery of clobetasol 17-propionate of 100.1% with a coefficient of variation of 0.6%. The assay error thus accounts for a proportion of the variation observed when assaying individual tubes and sachets for steroid content.

In these circumstances it is considered that satisfactory control is achieved by the proposed test procedures and that it is not necessary to determine the steroid content of tubes or sachets before release. This conclusion will be confirmed by the determination of the steroid content of filled tubes and sachets during the process validation of full scale production batches and thereafter the determination of the steroid content of the filled tubes and sachets will be reduced to a monitoring level.

The microbiological attributes of six lots of filled tubes and three lots of filled sachets were determined during the preparation of stability samples. For all samples the Total Aerobic Microbial Count was less than 10 microorganisms per gram. No Staphylococcus aureus, Pseudomonas aeruginosa, Salmonella species or Escherichia coli were isolated. It is therefore considered that the microbiological attributes of production batches are likely to be acceptable. This conclusion will be confirmed by the determination of microbiological attributes during process validation of full scale production batches and thereafter the determination of microbiological attributes will be reduced to a monitoring level.

Section 8(n)

3. Analytical procedures

3.1 Bulk cream

3.1.1 Appearance

Note the appearance of the cream.

3.1.2 Identity of clobetasol 17-propionate

In the determination of clobetasol 17-propionate and chlorocresol content the chromatogram obtained with the sample solution for chromatography contains a peak with the same retention time as the clobetasol 17-propionate peak in the chromatogram obtained with the standard solution for chromatography.

3.1.3 Clobetasol 17-propionate and chlorocresol content

Equipment

Pipettes and volumetric glassware.

Stoppered tubes. Tubes approximately 15cm in length and 2cm in diameter with a volume of approximately 15ml are suitable.

Water bath maintained at 60°C.

A suitable high performance liquid chromatograph equipped with the following:

A suitable low dead volume cell, typically in the range 8 to 12 microlitres;

A suitable light path length typically of 10 millimetres;

A suitable ultraviolet variable wavelength detection system operating at an appropriate wavelength near 240nm;

Section 8(n)

A 10cm analytical column having an inside diameter of about 4.5 millimetres and packed with a reverse phase packing, such as 5 micrometre Spherisorb ODS 1 or equivalent:

A suitable oven capable of maintaining the analytical column at a temperature of 60°C:

A suitable recorder of at least 20-centimetre deflection:

A digital integrator or equivalent

Reagents

The preparation of specific volumes of reagents is described below. Alternative volumes of reagents may be prepared by appropriate modification to the weights and dilutions.

Mobile phase : Transfer 400ml of ethanol (AR grade absolute alcohol from to a 1000ml volumetric flask, dilute to 1000ml with water and mix. Degas the mobile phase by a suitable procedure before use eg by boiling under reflux for 2-3 minutes.

Internal standard solution: Transfer 100mg ± 10mg of beclomethasone dipropionate to a 50ml volumetric flask, add about 40ml ethanol and shake till dissolved. Dilute to volume with ethanol and mix.

Chlorocresol standard solution

Transfer 150mg ± 10mg of chlorocresol standard, accurately weighed, to a 100ml volumetric flask. Add about 80ml of ethanol and shake till dissolved. Dilute to volume with ethanol and mix.

Clobetasol 17-propionate standard solution

Transfer 100mg ± 10mg of clobetasol 17-propionate working stardard, accurately weighed, to a 100ml volumetric flask. Add about 80ml of ethanol and shake till dissolved. Dilute to volume with ethanol and mix.

Standard solution for chromatography

Transfer 10.0ml of the clobetasol 17-propionate standard solution to a 100ml volumetric flask, add 10.0ml of the internal standard solution and 10.0ml of the chlorocresol

Section 8(n)

A 10cm analytical column having an inside diameter of about 4.6 millimetres and packed with a reverse phase packing, such as 5 micrometre Spherisorb ODS 1 or equivalent:

A suitable oven capable of maintaining the analytical column at a temperature of 60°C:

A suitable recorder of at least 20-centimetre deflection:

A digital integrator or equivalent

Reagents

The preparation of specific volumes of reagents is described below. Alternative volumes of reagents may be prepared by appropriate modification to the weights and dilutions.

Mobile phase : Transfer 400ml of ethanol (AR grade absolute alcohol from to a 1000ml volumetric flask, dilute to 1000ml with water and mix. Degas the mobile phase by a suitable procedure before use eg by boiling under reflux for 2-3 minutes.

Internal standard solution: Transfer 100mg ± 10mg of beclomethasone dipropionate to a 50ml volumetric flask, add about 40ml ethanol and shake till dissolved. Dilute to volume with ethanol and mix.

Chlorocresol standard solution

Transfer 150mg ± 10mg of chlorocresol standard, accurately weighed, to a 100ml volumetric flask. Add about 80ml of ethanol and shake till dissolved. Dilute to volume with ethanol and mix.

Clobetasol 17-propionate standard solution

Transfer 100mg ± 10mg of clobetasol 17-propionate working standard, accurately weighed, to a 100ml volumetric flask. Add about 80ml of ethanol and shake till dissolved. Dilute to volume with ethanol and mix.

Standard solution for chromatography

Transfer 10.0ml of the clobetasol 17-propionate standard solution to a 100ml volumetric flask, add 10.0ml of the internal standard solution and 10.0ml of the chlorocresol

standard solution to the flask. Dilute to volume with ethanol and mix. Mix 10.0ml of the resulting solution with 5.0ml of water.

Compound GR2/443 solution

Transfer 2mg ± 0.2mg of compound GR2/443 to a 20ml volumetric flask. Add about 15ml of ethanol and shake till dissolved. Dilute to volume with ethanol and mix.

Test solution for chromatography

Transfer 10.0ml of the clobetasol 17-propionate standard solution to a 100ml volumetric flask. Add 10.0ml of the internal standard solution, 10.0ml of the chlorocresol standard solution plus 2.0ml of the compound GR2/443 solution to the flask. Dilute to volume with ethanol and mix. Mix 10.0ml of the resulting solution with 5.0ml of water.

Preparation of sample solution for the high performance liquid chromatograpic assays

Transfer 2g ± 0.2g of the sample, accurately weighed, to a 15ml stoppered tube. This can be conveniently carried out by transferring about 2.5 grams of cream to a 2ml plastic disposable syringe and using this to transfer the sample to the stoppered tube without getting cream onto the neck of the tube.

Add 10.0ml of the internal standard solution to the tube. Stopper the tube firmly with a plastic stopper.

CAUTION: IT IS ESSENTIAL THAT THE FOLLOWING OPERATION IS CARRIED OUT IN A FUME CUPBOARD, BEHIND A GLASS SCREEN FOR COMPLETE FACIAL PROTECTION AND THAT A FACE MASK AND HEAT RESISTANT GLOVES ARE WORN.

Place the tube in a water bath maintained at 60°C and heat for 4 minutes. Remove the tube from the water bath and shake vigorously for 1 minute.

Replace the tube in the water bath for 4 minutes, remove from the bath and again shake vigorously for 1 minute.

Allow the tube to cool to room temperature, add 3.0ml of water and mix.

standard solution to the flask. Dilute to volume with ethanol and mix. Mix 10.0ml of the resulting solution with 5.0ml of water.

Compound GR2/443 solution

Transfer 2mg ± 0.2mg of compound GR2/443 to a 20ml volumetric flask. Add about 15ml of ethanol and shake till dissolved. Dilute to volume with ethanol and mix.

Test solution for chromatography

Transfer 10.0ml of the clobetasol 17-propionate standard solution to a 100ml volumetric flask. Add 10.0ml of the internal standard solution, 10.0ml of the chlorocresol standard solution plus 2.0ml of the compound GR2/443 solution to the flask. Dilute to volume with ethanol and mix. Mix 10.0ml of the resulting solution with 5.0ml of water.

Preparation of sample solution for the high performance liquid chromatograpic assays

Transfer 2g ± 0.2g of the sample, accurately weighed, to a 15ml stoppered tube. This can be conveniently carried out by transferring about 2.5 grams of cream to a 2ml plastic disposable syringe and using this to transfer the sample to the stoppered tube without getting cream onto the neck of the tube.

Add 10.0ml of the internal standard solution to the tube. Stopper the tube firmly with a plastic stopper.

CAUTION: IT IS ESSENTIAL THAT THE FOLLOWING OPERATION IS CARRIED OUT IN A FUME CUPBOARD, BEHIND A GLASS SCREEN FOR COMPLETE FACIAL PROTECTION AND THAT A FACE MASK AND HEAT RESISTANT GLOVES ARE WORN.

Place the tube in a water bath maintained at 60°C and heat for 4 minutes. Remove the tube from the water bath and shake vigorously for 1 minute.

Replace the tube in the water bath for 4 minutes, remove from the bath and again shake vigorously for 1 minute.

Allow the tube to cool to room temperature, add 3.0ml of water and mix.

Section 8(n)

Transfer the solution to a centrifuge tube and place it in ice cold water for 5 minutes. Centrifuge at 3500 rpm for 10 minutes. Carefully insert the tip of a Pasteur pipette through the layer of fat on top of the solution in the centrifuge tube and withdraw 2-3ml of the clear supernatant. Transfer the supernatant to a suitable container: this is the sample solution for chromatography.

High performance liquid chromatograpic assay of clobetasol 17-propionate and chlorocresol

Section 8(n)4, page 16197, describes the development of the method and gives details of the selectivity, accuracy and precision of the procedure.

Operating conditions

Perform the assay at a temperature of 60°C with a typical flow rate of 2ml per minute and a column pressure of approximately 1500 to 2000 pounds per square inch. Maintain the column at a constant temperature by using a suitable air oven. Use a detector sensitivity setting or attenuate the signal from the detector such that when 10 microlitres (or other suitable volume) of the standard solution for chromatography is injected the peak height for the clobetasol 17-propionate on the recorded chromatogram is at least fifty per cent of full scale deflection.

Use an elution time and mobile phase composition that gives satisfactory separation of chlorocresol, compound GR2/443, clobetasol 17-propionate and the internal standard when 10 microlitres (or any other suitable volume) of the test solution for chromatography is injected into the chromatograph. The elution order is chlorocresol, compound GR2/443, clobetasol 17-propionate and the internal standard. The run takes approximately 10 minutes. Ordinarily the minimum between the peaks due to compound GR2/443 and clobetasol 17-propionate should be no more than 2 millimetres above the baseline. The test solution is chromatographed whenever a new column is taken into use. It is also used as appropriate to monitor the change in performance of a column with time but it is not chromatographed on every occasion that a given column is used. If the required separations cannot be obtained with a given column the ethanol concentration of the mobile phase may be varied. Ordinarily the required separations can be obtained with an ethanol concentration of 40 per cent v/v. A typical chromatogram is given in Figure 8(n)1, page 16205.

Transfer the solution to a centrifuge tube and place it in ice cold water for 5 minutes. Centrifuge at 3500 rpm for 10 minutes. Carefully insert the tip of a Pasteur pipette through the layer of fat on top of the solution in the centrifuge tube and withdraw 2-3ml of the clear supernatant. Transfer the supernatant to a suitable container: this is the sample solution for chromatography.

High performance liquid chromatograpic assay of clobetasol 17-propionate and chlorocresol

Section 8(n)4, page 16197, describes the development of the method and gives details of the selectivity, accuracy and precision of the procedure.

Operating conditions

Perform the assay at a temperature of 60°C with a typical flow rate of 2ml per minute and a column pressure of approximately 1500 to 2000 pounds per square inch. Maintain the column at a constant temperature by using a suitable air oven. Use a detector sensitivity setting or attenuate the signal from the detector such that when 10 microlitres (or other suitable volume) of the standard solution for chromatography is injected the peak height for the clobetasol 17-propionate on the recorded chromatogram is at least fifty per cent of full scale deflection.

Use an elution time and mobile phase composition that gives satisfactory separation of chlorocresol, compound GR2/443, clobetasol 17-propionate and the internal standard when 10 microlitres (or any other suitable volume) of the test solution for chromatography is injected into the chromatograph. The elution order is chlorocresol, compound GR2/443, clobetasol 17-propionate and the internal standard. The run takes approximately 10 minutes. Ordinarily the minimum between the peaks due to compound GR2/443 and clobetasol 17-propionate should be no more than 2 millimetres above the baseline. The test solution is chromatographed whenever a new column is taken into use. It is also used as appropriate to monitor the change in performance of a column with time but it is not chromatographed on every occasion that a given column is used. If the required separations cannot be obtained with a given column the ethanol concentration of the mobile phase may be varied. Ordinarily the required separations can be obtained with an ethanol concentration of 40 per cent v/v. A typical chromatogram is given in Figure 8(n)1, page 16205.

Section 8(n)

Procedure

Inject duplicate 10 microlitre volumes of the standard and sample solutions for chromatography using the specified conditions and materials. Measure the areas of the chlorocresol, clobetasol 17-propionate and internal standard peaks in each chromatogram and calculate the peak area ratios as follows:

Peak area ratio =

$$\frac{\text{chlorocresol or clobetasol 17-propionate peak area}}{\text{internal standard peak area}}$$

Calculate the mean peak area ratios for the duplicate standard and sample chromatograms. Calculate the chlorocresol and clobetasol 17-propionate contents of the cream. Specimen calculations are given below based on the typical conditions described for the preparation of sample and standard solutions.

Chlorocresol %w/w

$$\frac{R_a \times W_s \times 10 \times 10 \times 100}{R_b \times 100 \times 100 \times W} = \frac{R_a \times W_s}{R_b \times W}$$

Clobetasol 17-propionate %w/w

$$\frac{R_c \times W_{s1} \times 10 \times 10 \times P}{R_d \times 100 \times 100 \times W} = \frac{R_c \times W_{s1} \times P}{R_d \times W \times 100}$$

where:

R_a = mean peak area ratio of chlorocresol for the sample chromatogram

R_b = mean peak area ratio of chlorocresol for the standard chromatogram

R_c = mean peak area ratio of clobetasol 17-propionate for the sample chromatogram

R_d = mean peak area ratio of clobetasol 17-propionate for the standard chromatogram

W_s = weight of chlorocresol working standard in grams

Section 8(n)

Procedure

Inject duplicate 10 microlitre volumes of the standard and sample solutions for chromatography using the specified conditions and materials. Measure the areas of the chlorocresol, clobetasol 17-propionate and internal standard peaks in each chromatogram and calculate the peak area ratios as follows:

Peak area ratio =

$$\frac{\text{chlorocresol or clobetasol 17-propionate peak area}}{\text{internal standard peak area}}$$

Calculate the mean peak area ratios for the duplicate standard and sample chromatograms. Calculate the chlorocresol and clobetasol 17-propionate contents of the cream. Specimen calculations are given below based on the typical conditions described for the preparation of sample and standard solutions.

Chlorocresol %w/w

$$\frac{R_a \times W_s \times 10 \times 10 \times 100}{R_b \times 100 \times 100 \times W} = \frac{R_a \times W_s}{R_b \times W}$$

Clobetasol 17-propionate %w/w

$$\frac{R_c \times W_{s1} \times 10 \times 10 \times P}{R_d \times 100 \times 100 \times W} = \frac{R_c \times W_{s1} \times P}{R_d \times W \times 100}$$

where:

R_a = mean peak area ratio of chlorocresol for the sample chromatogram

R_b = mean peak area ratio of chlorocresol for the standard chromatogram

R_c = mean peak area ratio of clobetasol 17-propionate for the sample chromatogram

R_d = mean peak area ratio of clobetasol 17-propionate for the standard chromatogram

W_s = weight of chlorocresol working standard in grams

Ws1 = weight of clobetasol 17-propionate working standard in grams

W = weight og sample in grams

P = % purity of clobetasol 17-propionate working standard

3.2 Filled tubes during their shelf life

3.2.1 Appearance of contents

Note the appearance of the cream.

3.2.2 Identity of clobetasol 17-propionate

Examine the cream for the presence of clobetasol 17-propionate by using one of the following two identity tests:

HPLC test

In the determination of clobetasol 17-propionate and chlorocresol content the chromatogram obtained with the sample solution for chromatography contains a peak with the same retention time as the clobetasol 17-propionate peak in the chromatogram obtained with the standard solution for chromatography.

TLC test

Reagent

The preparation of a specific volume of the solvent system is described below. Alternative quantities may be prepared by appropriate modifications to the volumes of solvents taken.

Solvent system: Mix together 100ml of chloroform, 10ml of acetone and 5ml of ethanol. Transfer the mixture to a TLC tank.

Clobetasol 17-propionate standard solution

Transfer 5mg of clobetasol 17-propionate, accurately weighed, to a 10ml volumetric flask, dissolve in and dilute to volume with chloroform and mix.

Ws1 = weight of clobetasol 17-propionate working standard in grams

W = weight og sample in grams

P = % purity of clobetasol 17-propionate working standard

3.2 Filled tubes during their shelf life

3.2.1 Appearance of contents

Note the appearance of the cream.

3.2.2 Identity of clobetasol 17-propionate

Examine the cream for the presence of clobetasol 17-propionate by using one of the following two identity tests:

HPLC test

In the determination of clobetasol 17-propionate and chlorocresol content the chromatogram obtained with the sample solution for chromatography contains a peak with the same retention time as the clobetasol 17-propionate peak in the chromatogram obtained with the standard solution for chromatography.

TLC test

Reagent

The preparation of a specific volume of the solvent system is described below. Alternative quantities may be prepared by appropriate modifications to the volumes of solvents taken.

Solvent system: Mix together 100ml of chloroform, 10ml of acetone and 5ml of ethanol. Transfer the mixture to a TLC tank.

Clobetasol 17-propionate standard solution

Transfer 5mg of clobetasol 17-propionate, accurately weighed, to a 10ml volumetric flask, dissolve in and dilute to volume with chloroform and mix.

Ws1 = weight of clobetasol 17-propionate working standard in grams

W = weight og sample in grams

P = % purity of clobetasol 17-propionate working standard

3.2 Filled tubes during their shelf life

3.2.1 Appearance of contents

Note the appearance of the cream.

3.2.2 Identity of clobetasol 17-propionate

Examine the cream for the presence of clobetasol 17-propionate by using one of the following two identity tests:

HPLC test

In the determination of clobetasol 17-propionate and chlorocresol content the chromatogram obtained with the sample solution for chromatography contains a peak with the same retention time as the clobetasol 17-propionate peak in the chromatogram obtained with the standard solution for chromatography.

TLC test

Reagent

The preparation of a specific volume of the solvent system is described below. Alternative quantities may be prepared by appropriate modifications to the volumes of solvents taken.

Solvent system: Mix together 100ml of chloroform, 10ml of acetone and 5ml of ethanol. Transfer the mixture to a TLC tank.

Clobetasol 17-propionate standard solution

Transfer 5mg of clobetasol 17-propionate, accurately weighed, to a 10ml volumetric flask, dissolve in and dilute to volume with chloroform and mix.

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Preparation of sample solution

Transfer about 1.5g of the cream, accurately weighed, to a 15ml stoppered tube. Add 10.0ml of methanol and stopper the tube firmly with a plastic stopper.

CAUTION: IT IS ESSENTIAL THAT THE FOLLOWING OPERATION IS CARRIED OUT IN A FUME CUPBOARD, BEHIND A GLASS SCREEN FOR COMPLETE FACIAL PROTECTION AND THAT A FACE MASK AND HEAT RESISTANT GLOVES ARE WORN.

Place the tube in a water bath maintained at about 60°C for 4 minutes, remove the tube from the bath and shake vigorously for 1 minute. Repeat the heating and shaking operation once more. Cool to room temperature, add 3.5ml of water and mix. Transfer the mixture to a centrifuge tube and centrifuge at 3500 rpm for 10 minutes.

Transfer 5.0ml of the supernatant to a 100ml separator. Add 1g of sodium chloride and 10ml of water to the separator and mix. Add 5ml of chloroform to the separator and shake the separator for 1 minute. Allow the two layers to separate. Transfer the lower chloroform layer via a plug of cotton wool, previously washed with chloroform, into a 15ml tube. Remove the solvent in a stream of nitrogen. Dissolve the residue in 0.5ml of chloroform.

Procedure

Using a micro-syringe transfer to separate points on a pre-coated glass backed 20cm x 20cm Merck silica gel 60 F254 TLC plate 10µl aliquots of the clobetasol 17-propionate standard solution and the sample solution. Develop the chromatogram by placing it in a saturated tank containing the solvent system until the solvent has travelled about 15cm. Remove the plate from the TLC tank and allow it to dry in air.

Examine the plate under UV light of wavelength 254nm.

The principal spot in the sample chromatogram should have the same Rf value as the principal spot in the chromatogram obtained from the clobetasol 17-propionate standard solution. The Rf value of clobetasol 17-propionate is about 0.5.

3.2.3 Clobetasol 17-propionate and chlorocresol content

Carry out the procedure described in Section 3.1.3, page 16 189. Squeeze the cream from the tube via the nozzle and assay the clobetasol 17-propionate and chlorocresol contents of three sample weights taken from approximately the beginning, middle and end of the tube. Calculate the mean clobetasol 17-propionate and chlorocresol contents of the cream.

Note

The sample may be conveniently transferred to a stoppered tube by squeezing out about 2.5g of cream into a 2ml plastic disposable syringe and using this to transfer the sample to the stoppered tube without getting cream onto the neck of the tube.

3.2.4 Minimum fill

Determine the minimum fill as described in the USP XX.

3.3 Filled sachets during their shelf life

3.3.1 Appearance of contents

Note the appearance of the cream.

3.3.2 Identity of clobetasol 17-propionate

Carry out one of the two tests described in Section 3.2.2, page 16 194.

3.3.3 Clobetasol 17-propionate and chlorocresol content

Accurately weigh two sachets. Cut off the ends of the two sachets avoiding loss of cream and carefully extrude their contents as completely as possible into a stoppered tube. A tube approximately 15cm in length and 3cm in diameter with a volume of approximately 50ml is suitable. Reweigh the two sachets together with the cut off ends to determine the weight of sample taken for the assay. Carry out the procedure described in Section 3.1.3, page 16 189.

3.3.4 Minimum fill

Determine the minimum fill as described in the USP XX.