CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 74904

Trade Name Desoximetasone Gel USP 0.05%

Generic Name Desoximetasone Gel USP 0.05%

Sponsor Taro Pharmaceuticals USA, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 74904

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)	X			
Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74904

APPROVAL LETTER

ANDA 74-904

Taro Pharmaceuticals USA, Inc.
Attention: Lorraine W. Sachs
U.S. Agent for: Taro Pharmaceuticals Inc.
5 Skyline Drive
Hawthorne, NY 10532

JUL 14 1998

Dear Madam:

This is in reference to your abbreviated new drug application dated May 17, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Desoximetasone Gel USP, 0.05%.

Reference is also made to your amendments dated October 3, 1996; and February 27 and June 11, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Desoximetasone Gel USP, 0.05% to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Topicort® Gel, 0.05% of Hoechst Marion Roussel Inc.).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ [redacted] 7/14/98

Douglas L. Spoon
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 74-904
Division File
FIELD COPY
HFD-610/JPhillips
HFD-92
HFD-210/B.Poole
HFD-330/
HFD-205/

/S/ [redacted] 98.

CMC

Endorsements:
HFD-629/N.Takiar/
HFD-629/P.Schwart
HFD-617/J.Buccine
HFD-613/L.Golson
HFD-613/J.Grace/
HFD-600/M.Fanning

/S/ [redacted] 98 98 7/9/98

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F/T by: gp/6/30/98

/S/ [redacted] 7/9/98

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74904

FINAL PRINTED LABELING

FPO

Desoximetasone Gel USP, 0.05%

PK-2091-0
000

For topical use only.
Not for ophthalmic use.

DESCRIPTION

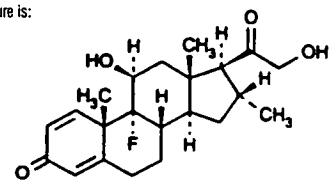
Desoximetasone Gel USP, 0.05 % contains the active synthetic corticosteroid desoximetasone. The topical corticosteroids constitute a class of primarily synthetic steroids used as anti-inflammatory and anti-pruritic agents.

Each gram of Desoximetasone Gel USP, 0.05%, for topical use, contains 0.5 mg desoximetasone in a gel consisting of purified water USP, docusate sodium USP, edetate disodium USP, isopropyl myristate NF, carbomer 940 NF, trolamine NF, and SDAG-1B 95 % alcohol.

The chemical name of desoximetasone is Pregna-1,4-diene-3, 20-dione, 9-fluoro-11, 21-dihydroxy-16-methyl-, (11β, 16α)-.

Desoximetasone has the molecular formula $C_{22}H_{29}FO_4$, and a molecular weight of 376.47. The CAS Registry Number is 382-67-2.

The chemical structure is:



CLINICAL PHARMACOLOGY

Topical corticosteroids share anti-inflammatory, anti-pruritic and vasoconstrictive actions.

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

Pharmacokinetics

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

Topical corticosteroids can be absorbed from normal, intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. Thus, occlusive dressings may be a valuable therapeutic adjunct for treatment of resistant dermatoses.(See **DOSAGE AND ADMINISTRATION**).

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

Studies with other similarly structured steroids have shown that predominant metabolite reaction occurs through conjugation to form the glucuronide, and sulfate ester.

INDICATIONS AND USAGE

Desoximetasone Gel USP, 0.05 % is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS

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

PRECAUTIONS

General

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

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

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

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

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

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

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

Information for the Patient

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

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

Laboratory Tests

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

- Urinary free cortisol test
- ACTH stimulation test

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

Pregnancy. Teratogenic Effects. Pregnancy Category C

Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

Desoximetasone has been shown to be teratogenic and embryotoxic in mice, rats, and rabbits when given by subcutaneous or dermal routes of administration in doses 15 to 150 times the human dose of desoximetasone gel 0.05 %. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. Therefore, Desoximetasone Gel USP, 0.05 % should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Nursing Mothers

It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities *not* likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are administered to a nursing woman.

Pediatric Use

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

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema. Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

ADVERSE REACTIONS

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

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

Apply a thin film of Desoximetasone Gel USP, 0.05 % to the affected skin areas twice daily. Rub in gently.

HOW SUPPLIED

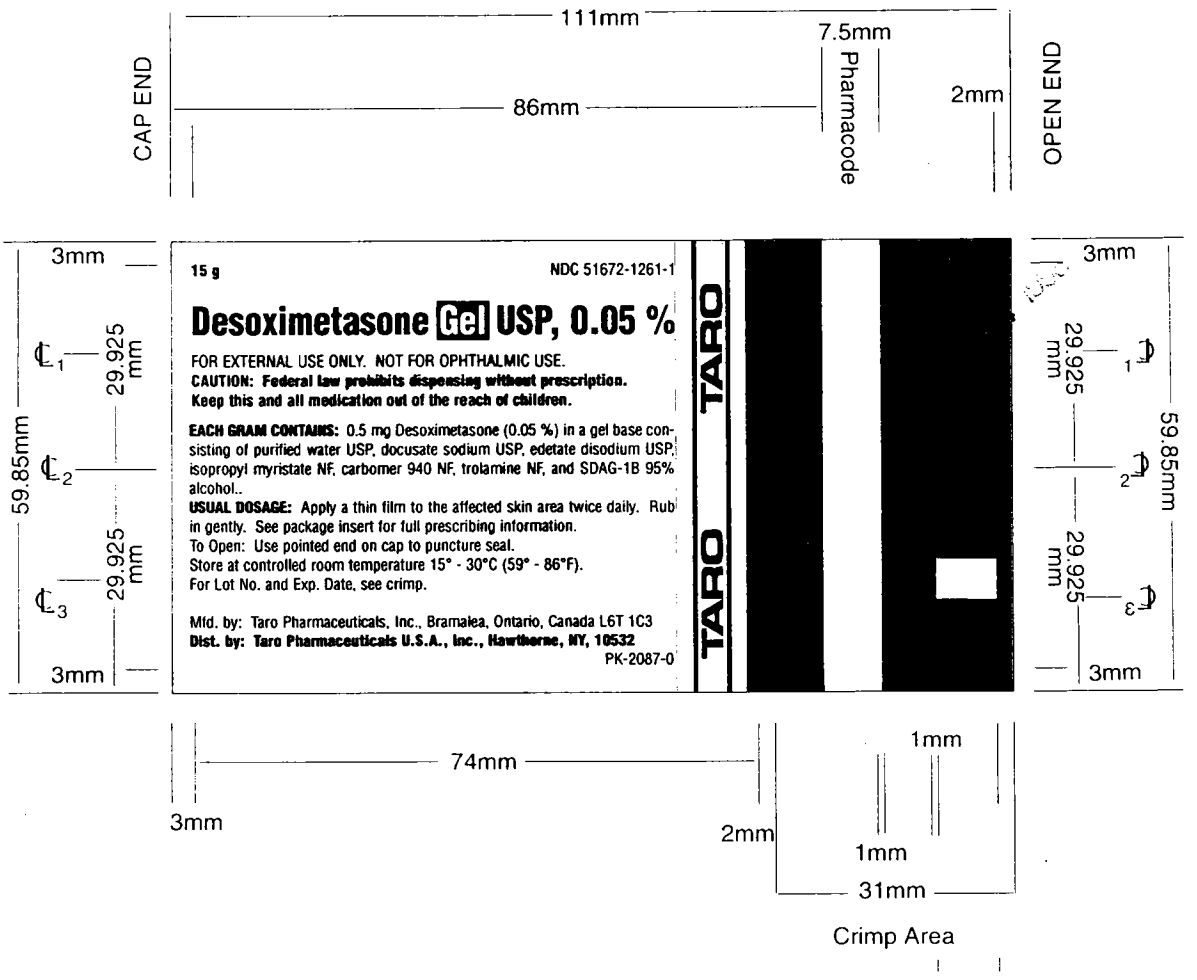
Desoximetasone Gel USP, 0.05 % is supplied in 15 gram and 60 gram tubes.

Store at controlled room temperature, 15° - 30°C (59° - 86°F).

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

Mfd By: Taro Pharmaceuticals Inc., Bramalea, Ontario, Canada L6T 1C3
Mfd For: Taro Pharmaceuticals U.S.A., Inc., Hawthorne, NY 10532

Issued: March 1997


111mm
7.5mm
Pharmacode
86mm
2mm
CAP END
OPEN END
3mm
59.85mm
29.925 mm
29.925 mm
3mm
15 g
NDC 51672-1261-1
Desoximetasone Gel USP, 0.05 %
FOR EXTERNAL USE ONLY. NOT FOR OPHTHALMIC USE.
CAUTION: Federal law prohibits dispensing without prescription.
Keep this and all medication out of the reach of children.
EACH GRAM CONTAINS: 0.5 mg Desoximetasone (0.05 %) in a gel base consisting of purified water USP, docusate sodium USP, edetate disodium USP, isopropyl myristate NF, carbomer 940 NF, trolamine NF, and SDAG-1B 95% alcohol..
USUAL DOSAGE: Apply a thin film to the affected skin area twice daily. Rub in gently. See package insert for full prescribing information.
To Open: Use pointed end on cap to puncture seal.
Store at controlled room temperature 15° - 30°C (59° - 86°F).
For Lot No. and Exp. Date, see crimp.
Mfd. by: Taro Pharmaceuticals, Inc., Bramalea, Ontario, Canada L6T 1C3
Dist. by: Taro Pharmaceuticals U.S.A., Inc., Hawthorne, NY, 10532
PK-2087-0
TARO
TARO
3mm
29.925 mm
29.925 mm
59.85mm
3mm
74mm
3mm
2mm
1mm
1mm
31mm
Crimp Area

Directions for puncturing tube seal: Remove cap. Turn cap upside down and place puncture tip onto tube. Push cap until tube end is punctured. Screw cap back on to reseal tube.

Mfd. by: Taro Pharmaceuticals Inc.
Bramalea, Ontario, Canada L6T 1C3
Dist. by: **Taro Pharmaceuticals U.S.A., Inc.**, Hawthorne, NY 10532
TARO is a registered trademark of Taro Pharmaceuticals U.S.A., Inc.

N 3 51672-1261-3 1

60 g NDC 51672-1261-3

Desoximetasone Gel USP, 0.05 %

FOR EXTERNAL USE ONLY. NOT FOR OPHTHALMIC USE.
CAUTION: Federal law prohibits dispensing without prescription.
Keep this and all medication out of the reach of children.

EACH GRAM CONTAINS: 0.5 mg Desoximetasone (0.05 %) in a gel base consisting of purified water USP, docusate sodium USP, edetate disodium USP, isopropyl myristate NF, carbomer 940 NF, trolamine NF, and SDAG-1B 95% alcohol..
USUAL DOSAGE: Apply a thin film to the affected skin area twice daily. Rub in gently.
See package insert for full prescribing information.
Store at controlled room temperature 15° - 30°C (59° - 86°F).
For Lot No. and Exp. Date, see end flap.

60 g NDC 51672-1261-3

Desoximetasone Gel USP, 0.05 %

FOR EXTERNAL USE ONLY. NOT FOR OPHTHALMIC USE.
CAUTION: Federal law prohibits dispensing without prescription.
Keep this and all medication out of the reach of children.

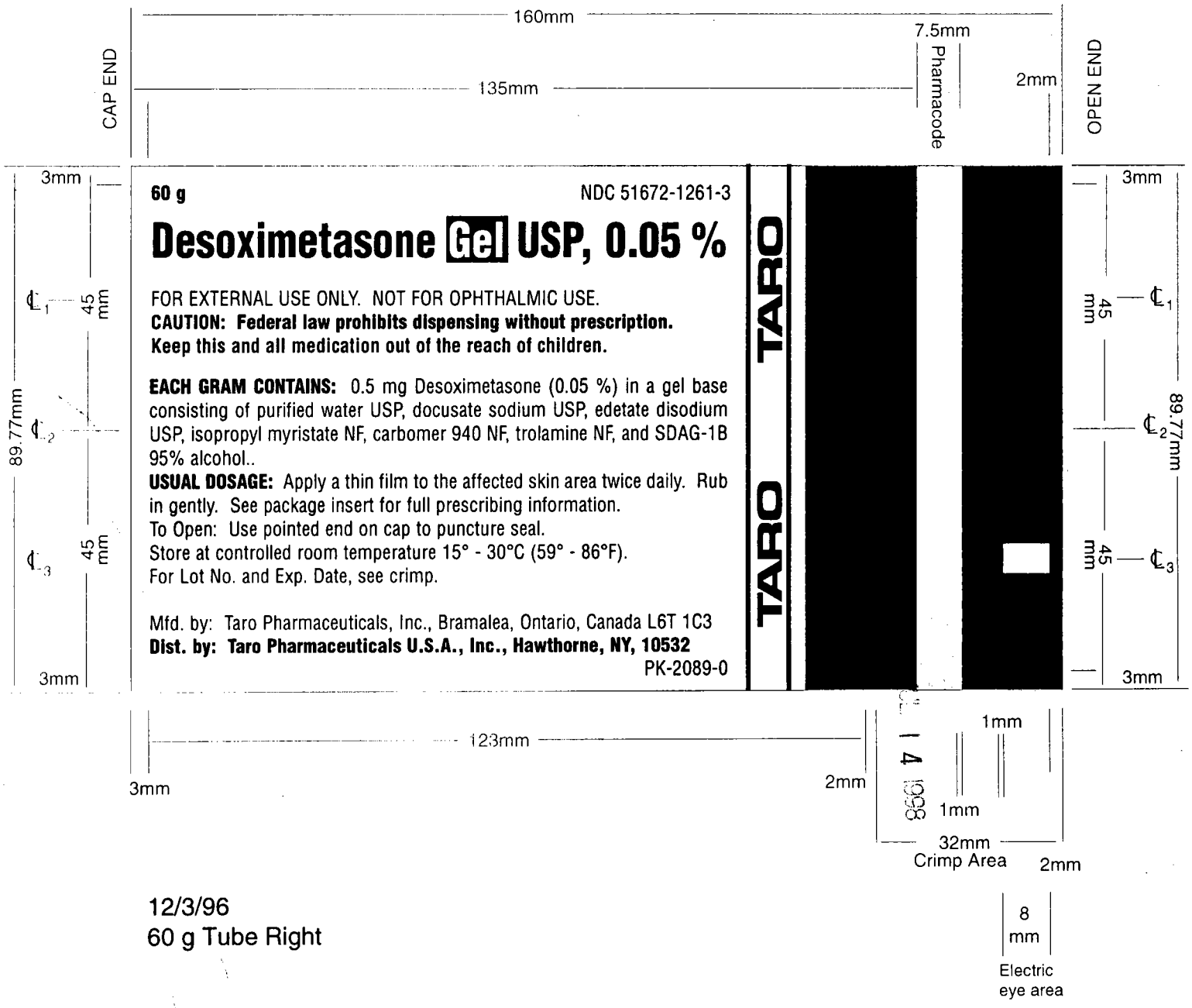
TARO

TARO

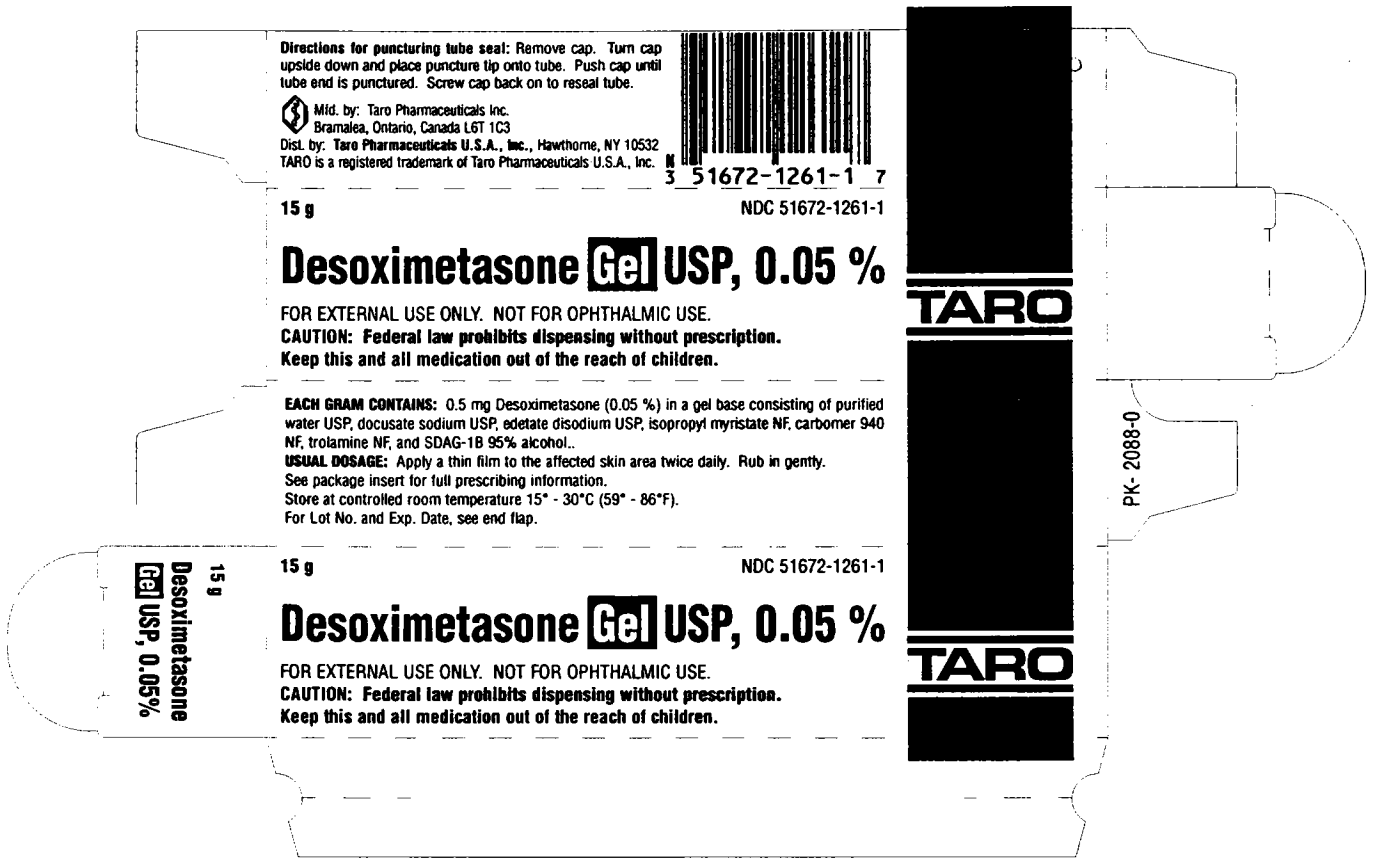
PK-2090-0

2.33

60 g Desoximetasone Gel USP, 0.05%



12/3/96
60 g Tube Right


Directions for puncturing tube seal: Remove cap. Turn cap upside down and place puncture tip onto tube. Push cap until tube end is punctured. Screw cap back on to reseal tube.
Mfd. by: Taro Pharmaceuticals Inc.
Bramalea, Ontario, Canada L6T 1C3
Dist. by: Taro Pharmaceuticals U.S.A., Inc., Hawthorne, NY 10532
TARO is a registered trademark of Taro Pharmaceuticals U.S.A., Inc.
N 3 51672-1261-1 7
15 g
NDC 51672-1261-1
Desoximetasone Gel USP, 0.05 %
FOR EXTERNAL USE ONLY. NOT FOR OPHTHALMIC USE.
CAUTION: Federal law prohibits dispensing without prescription.
Keep this and all medication out of the reach of children.
EACH GRAM CONTAINS: 0.5 mg Desoximetasone (0.05 %) in a gel base consisting of purified water USP, docusate sodium USP, edetate disodium USP, isopropyl myristate NF, carbomer 940 NF, trolamine NF, and SDAG-1B 95% alcohol..
USUAL DOSAGE: Apply a thin film to the affected skin area twice daily. Rub in gently.
See package insert for full prescribing information.
Store at controlled room temperature 15° - 30°C (59° - 86°F).
For Lot No. and Exp. Date, see end flap.
TARO
PK- 2088-0
15 g
Desoximetasone Gel USP, 0.05%
15 g
NDC 51672-1261-1
Desoximetasone Gel USP, 0.05 %
FOR EXTERNAL USE ONLY. NOT FOR OPHTHALMIC USE.
CAUTION: Federal law prohibits dispensing without prescription.
Keep this and all medication out of the reach of children.
TARO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74904

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **CHEMISTRY REVIEW NO.#** 3

2. **ANDA #** 74-904

3. **NAME AND ADDRESS OF APPLICANT:**

Taro Pharmaceuticals USA, Inc.
Attention: Lorraine Sachs
5 Skyline Drive
Hawthorne, NY 10532

4. **LEGAL BASIS FOR SUBMISSION:**

There is no unexpired patent or exclusivity. The RLD is TOPICORT® Gel 0.05%, NDA 18-586, Hoechst-Roussel Pharmaceuticals Inc. An ANDA suitability petition was not required.

5. **SUPPLEMENT(s):** N/A

6. **PROPRIETARY NAME:** None

7. **NONPROPRIETARY NAME:** **Desoximetasone Gel USP, 0.05%**

8. **SUPPLEMENT(s) PROVIDE(s) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**

05/17/96 ANDA was submitted.
06/13/96 "Refuse to File" letter.
07/10/96 Amendment in response to RTF.
07/11/96 Date acceptable for filing.
10/04/96 Bio amendment.
11/15/96 Bio telecon re syringe size.
03/28/97 Bio "no further questions" letter.
03/04/97 Major chemistry deficiencies were faxed to the firm.
04/22/97 Major amendment in response to 3/4/97.
01/27/98 Deficiency letter - Major amendment
02/27/98 **Amendment** - Response to deficiency letter of 01/27/98.
06/10/98 T-CON
06/11/98 Response to T-CON of 6/10/98

10. **PHARMACOLOGICAL CATEGORY**: Synthetic corticosteroid

11. **Rx or OTC**: Rx

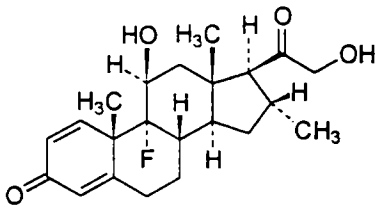
12. **RELATED IND/NDA/DMF(s)**: See DMF Checklist.

    Taro also holds approved ANDAs 73-193 and 73-210 for Desoximetasone Cream and 74-286 for Desoximetasone Ointment.

13. **DOSAGE FORM**: Gel

14. **POTENCY**: 0.05%

15. **CHEMICAL NAME AND STRUCTURE:**



$C_{22}H_{29}FO_4$ 376.47 *[382-67-2]*
Pregna-1,4-diene-3,20-dione, 9-fluoro-11,21-dihydroxy-16-methyl-, (11β, 16α)-.
Refer to USP 23, page 465.

16. **RECORDS AND REPORT:** N/A

17. **COMMENTS**:

18. **CONCLUSIONS AND RECOMMENDATIONS:**

    The application is approvable.

19. **REVIEWER**: Neeru B. Takiar
    Endorsed by P. Schwartz, Ph.D.

    DATE COMPLETED: 06/04/98
    Revised: 06/17/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74904

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA #74-904 **SPONSOR : Taro Pharamceuticals**
DRUG & DOSAGE FORM : Desoximetasone Gel, USP

STRENGTH (s) : 0.05%
TYPE OF STUDY: Skim Blanching Study-PD study
STUDY SITE: CLINICAL : (b)(4)(CC) **ANALYTICAL : N/A**

STUDY SUMMARY :

A. Pilot Study: Estimation of ED50

Parameter	Visual Area	Chromameter Area
ED_{50}	7.27	6.18
SE	3.92	3.33

Based on ED50 estimation, a pivotal bioequivalence study was conducted at a 7 minute duration. A lower duration of application (D1) was at 4 minutes and a higher duration (D2) was at 15 minutes.

B. Pivotal Study

Locke' Method: 90% Confidence Interval for Chromameter and Visual Data

	N	Means		Ratio	90% CI	
		Taro	Reference		Lower	Upper
Visual	28	23.21	21.35	1.09	100.88	117.89
Chromameter	22	21.60	21.28	1.02	89.64	116.22

Both pilot and pivotal studies are acceptable.

PRIMARY REVIEWER : Jahnavi S. Kharidia **BRANCH : 3**
INITIAL : /S/ **DATE :** 6/11/97

Team Leader :Ramakant M. Mhatre **BRANCH : 3**
INITIAL : /S/ **DATE :** 6/11/97

DIRECTOR
DIVISION OF BIOEQUIVALENCE
INITIAL : /S/ **DATE :** 1/26/98

DIRECTOR
OFFICE OF GENERIC DRUGS
INITIAL : _____ **DATE :**

11

ANDA 74-904

MAR 28 1997

Taro Pharmaceuticals USA, Inc.
Attention: Michael Kohlbrenner
U.S. Agent for: Taro Pharmaceuticals, Inc.
6 Skyline Drive
Hawthorne, NY 10532

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Desoximetasone Gel USP, 0.05%

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. In the pivotal study submitted, only one untreated control site per arm for the baseline correction was used. The guidance recommends subtracting the average of two untreated sites from all active drug sites on each arm. Future studies should be conducted according to Office of Generic Drugs Policies.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/ [redacted]

for Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

MAR 24 1997

Desoximetasone Gel, USP
Topical Gel, 0.05%
ANDA # 74-904
Reviewer: Jahnavi S. Kharidia
x:\wpfile\Biofinal\74904s.596

Taro Pharmaceuticals, Inc.
130 East Drive
Bramalea, Ontario
Canada
Submission Date:
May 17, 1996
Oct 31, 1996

Review of a bioequivalence study based on the vasoconstrictor assay: pilot and pivotal studies

The firm submitted an application containing data from a pharmacodynamic bioequivalence study based on vasoconstriction assay on its desoximetasone topical gel, 0.05%. The application also contains *in-vitro* data comparing the test product and the reference product, Topicort® gel manufactured by Hoechst-Roussel Pharmaceuticals, Inc.

Introduction

Desoximetasone Gel USP, 0.05% contains the active synthetic corticosteroids desoximetasone. It demonstrates anti-inflammatory, anti-pruritic and vasoconstrictive actions. It is generally used to relieve the redness, swelling, itching and discomfort of many skin problems. While the mechanism of the anti-inflammatory effects is unclear, there appears to be a correlation between the therapeutic effects of corticosteroids and their vasoconstrictive properties.

Bioequivalence of topical corticosteroids has been evaluated based on the performance of the vasoconstrictor assay. The assay measures the ability of topically applied corticosteroids to produce blanching in normal skin. Vasoconstriction of topical corticosteroids can be measured as a function of dose or the length of the time for exposure to the skin. The Division of Bioequivalence historically has relied on the vasoconstriction assay (pharmacodynamic assay) to approve generic topical corticosteroids. The study design has gradually evolved from observations based on a single time-point assay (pre 1992), a multiple time point assay (the 1992 OGD interim guidance on topical corticosteroids), to an assay incorporating a pilot dose response study and a pivotal bioequivalence study (the 1995 OGD guidance for topical dermatological corticosteroids).

The 1995 OGD guidance for topical dermatological corticosteroids recommended performance of two *in vivo* studies: (1) a pilot dose duration - response study and (2) a pivotal in vivo bioequivalence study. The pilot study characterizes the dose duration-response relationship for the drug in terms of the E_{max} model and is conducted solely with the reference listed drug. The comparison of test and reference products in pivotal study is then based on three dose duration: ED_{50} (population estimation of ED_{50} from pilot study), D1

(approximately 0.5 times ED_{50}) and D2 (approximately 2 times ED_{50}). The bioequivalence studies presented in this application are based on a pilot study and a pivotal study.

A. Pilot Study: Dose Response of Topicort® Gel

1. OBJECTIVE:

The purpose of this study was to estimate the ED_{50} of the vasoconstrictive dose-response relationship for topical desoximetasone gel (Topicort® Gel, 0.05%).

2. STUDY SITE, INVESTIGATORS AND DATES:

Protocol Number:

9515038D-1: Dose-response of Topicort® gel
One-period vasoconstrictor pilot study
The (b)(4)(CC) Institutional Review Board approved this study prior to its commencement.

Study Site:

(b)(4)(CC)

Investigators:

Principal Investigator: (b)(4)(CC)

Sub Investigator:

Study Dates:

August 19,1995

3. SUBJECT SELECTION:

Subject selection for this study was carried out according to the procedure described in the OGD guidance. Fifteen subjects, who participated in this study were normal, healthy non-tobacco-using Caucasian females in the

age range of 20-37 years, and were within 15% of their ideal weight. Potential study participants were screened to determine blanching response to the test gel. 10 µl of Topicort® was applied to the upper arm above the forearm. These applications were left in place for approximately 2 hours, then evaluated visually approximately 6 hours after application. All subjects were selected based on a demonstrated blanching response and the absence of any clinically significant findings on the medical history or vital sign assessment.

Subjects were excluded from the study based on the following criteria:

- History of allergy or hypersensitivity to any corticosteroids or to any topical products.
- Presence of any skin condition or coloration which would interfere with the assessment of skin blanching
- Presence of a medical condition requiring regular treatment with prescription drugs.
- Use of pharmacological agents which may affect vasoconstrictor response within 28 days prior to dosing.
- Positive urine pregnancy test
- Use of any topical corticosteroid on the flexor surface of the forearms within 30 days of dosing.
- Drug or alcohol addiction requiring treatment in the past 12 months.
- Use of any tobacco products in the 30 days prior to screen

4. STUDY CONDUCT:

Drug Treatment:

Topicort® gel 0.05% (desoximetasone)
Hoechst-Roussel Pharmaceuticals, Inc.
Lot#0140074 Exp. Date: 10/96

Application and Removal:

Topicort® gel was applied to the left forearm of each subject. Nine (9) circular application sites measuring approximately 1.6 cm diameter were designated on the flexor surface of forearm between the wrist and the elbow. After baseline chromameter (in duplicate) and visual readings, an open washer was positioned over each site and taped to the forearm using hypo-allergenic scanpor paper tape on the sides of the washer so that the treated area was not occluded. Using a 250 µl glass Hamilton syringe, a 10 µl

application of Topicort® gel 0.05%, was applied to the 8 assigned sites on left arm at times according to the randomization schedule. An untreated site was not randomly assigned.

Topicort® gel was applied to the left arm 5, 10, 20, 30 and 45 minutes, and 1, 1.5 and 2 hours prior to removal. The applications were spread evenly over the skin surface at each site with the conical tip of a microcentrifuge tube. All applications were removed at the same time point (0.0 hour). The washers were detached and the residual surface treatment was removed by gently wiping several times with a cotton ball. The untreated site on each arm was similarly wiped with a clean cotton ball.

⇒ The purpose of pilot study in bioequivalence of topical products is to estimate population ED_{50} to guide pivotal studies. The OGD guidance recommends that the application of the reference listed drug in the pilot study should be equally divided between the two arms. In a pilot study presented in this application, Topicort® gel was applied only to the left arm. The reason for this deviation was that (b)(4)(CC) simultaneously conducted dose duration study for another topical product (Lidex® gel) using the right arm of the same subjects. The above mentioned deviation in the pilot study, however, should not significantly affect the estimation of population ED_{50}. Therefore, the study design of pilot study conducted by (b)(4)(CC) on Topicort® 0.05% gel has been found acceptable to the reviewer.

Housing and Meals:

The subjects were institutionalized in the clinic at least 12 hours before drug application. A meal was provided on check-in day. Meals were served at traditional times; caffeine and alcohol were restricted during the study. Water was permitted *ad lib* throughout the study.

Restrictions:

The subjects were instructed to avoid the following during the study:

- Contact with water on their arms.
- Extremes of temperature and strenuous physical exercise.
- Tight clothing on the forearms.
- Rest their heads on their arms within 1 hour of any assessment time.

Assessments:

The degree of skin blanching was assessed both by visual assessment and with a chromameter at each site prior to treatment application, immediately after removal (0) and at 2, 4, 6, 8, 10, 12, 20 and 24 hours after removal. All assessments were made within 5 minutes of their scheduled time. The chromameter operator and visual evaluator were blinded as to the duration of application at each site. Chromameter assessments were based on the a-scale response. Visual scoring used the following rating scale:

0 = No pallor; no change from surrounding area.
1 = Mild pallor; slight or indistinct outline of application site.
2 = Moderate pallor; discernable outline of application site.
3 = Intense pallor; clean, distinct outline of application site.

5. DATA ANALYSIS:

The chromameter raw data of each skin blanching response versus time profile (both active drug sites and untreated control sites) were corrected for the baseline value at that site. To compensate for skin tone changes that occur over time, the baseline-adjusted value for the untreated site was subtracted from the baseline-adjusted chromameter value for each active drug site at each assessment time. These "corrected" baseline-adjusted chromameter values were used in all subsequent analyses. Chromameter areas under the effect curve (AUEC) over 24 hours were calculated from the corrected, baseline-adjusted readings by the linear trapezoidal method. The AUEC was used for the pharmacodynamic modeling. As the chromameter a-scale reading lowers with increased blanching, the resulting areas would be negative. The chromameter areas were multiplied by -1 to conform to the conventional format for area under the curve. An E_{max} model was used to fit the pooled AUEC data from 15 subjects using PCNONLIN and the pharmacodynamic parameters (ED_{50} and E_{max}) for this population.

The sponsor has also analyzed the visual data using an E_{max} model.

6. RESULTS:

All of the fifteen subjects successfully completed the study.

Adverse Events:

None of the subjects reported any adverse events during this study.

Precision of Chromameter:

Prior to the study, the precision of the chromameter operators was evaluated from replicate (5 readings, $\geq$ 3 minutes apart) evaluations at 4 untreated skin sites on each arm of 4 different subjects. The between-site CV was 10% for both operators and the within-site CV was less than 7%.

Accuracy of AUEC Calculation:

The pharmacodynamic data are given in this application in the form of AUEC values. The reviewer has randomly calculated AUEC from the raw chromameter readings to verify the data submitted by the firm. As shown in Table 1, AUEC values reported by the firm were found to be accurate.

Table 1: Verification of the AUEC values reported by the firm

Subject	Duration (minute)	Sponsor (A)	Reviewer (B)	A/B
1	5	-1.09	-1.09	1
3	120	18.26	18.26	1
4	10	9.8	9.8	1
6	60	44.07	44.07	1
8	10	15.97	15.97	1
8	45	24.03	24.03	1
9	45	15.06	15.06	1
11	120	3.76	3.76	1
12	30	12.72	12.72	1

13	30	25.66	25.66	1
14	30	21.99	21.99	1

Pharmacodynamic Analysis:

The estimated pharmacodynamic parameters for desoximetasone are presented in Table 2. Figures 1 and 2 represent the plots of observed and predicted AUEC data for chromameter and visual data, respectively. The Topicort® chromameter and visual results were reasonably consistent with ED_{50} estimates of 6 minutes and 7 minutes, respectively.

Table 2: Estimation of Pharmacodynamic Parameters Using Naive Pool Method

Emax Model	Visual Area	Chromameter Area
Emax	24.63	24.62
Standard Error	2.74	2.55
CV%	11	10
ED_{50}	7.27	6.18
Standard Error	3.92	3.33
CV%	54	54

The reviewer has also analyzed the same data sets by naive pooled method using ADAPT II computer program. Based on reviewer's analysis, the ED_{50} values of Topicort® gel were found to be 7.279 minutes for visual data and 6.178 minutes for chromameter data.

In the Naive Pooled data (NPD) analysis, data from all individuals are considered as arising from one unique experimental unit. The limitation of NPD is that it tends to mask intersubject variability. NPD may perform well when variations between subjects are small. Therefore, caution is necessary when extrapolating mean outcomes on the basis of the parameter estimation by NPD. In this regard,

population pharmacodynamic parameters for Taro's desoximetasone gel using mixed effect modeling (P-Pharm program) were estimated in the Division. The results are as follows:

Table 3: Estimation of Pharmacodynamic Parameters Using Mixed Effect Modeling

Emax Model	Visual Area	Chromameter Area
Emax	32.31 (53)	28.38 (104)
ED_{50}	42.55 (146)	21.07 (158)

⇒ Given the enormous intersubject variability of pharmacodynamic response, estimation of ED_{50} from mixed effect modeling represent the true population parameter. The firm has performed pivotal bioequivalence study based on the ED_{50} (7 minute) estimation from NPD. This indicates that the firm conducted the study with a dose much smaller than the population ED_{50}, which is at a very sensitive region of the dose response curve. Therefore, the proposed pivotal study, which is based on the NPD analysis is acceptable.

7. CONCLUSION:

For a pivotal bioequivalence study, testing at a 7 minute duration of application would provide evaluation in the region of the dose-response curve which is not at saturation. A lower duration of application (D1) at 4 minutes and a higher duration (D2) at 15 minutes would be included to establish that a subject was a good detector.

B. Pivotal Study: Bioequivalence of Desoximetasone Topical Gel

1. OBJECTIVE:

The purpose of this study was to demonstrate *in vivo* bioequivalence between Taro Pharmaceuticals' desoximetasone gel, and the reference product, Hoechst-Roussel Pharmaceuticals' Topicort® gel.

2. STUDY SITE, INVESTIGATORS AND DATES:

Protocol Number:

9515042D : Bioequivalence of Desoximetasone Topical Gel
One-period, randomized, vasoconstrictor study
The (b)(4)(CC) Institutional Review Board approved this study prior to its commencement.

Study Site:

(b)(4)(CC)

Investigators:

Principal Investigator: (b)(4)(CC)

Biostatistician:

Study Dates:

Sixty subjects were enrolled into the study. For the confinement of the study, the subjects were divided into three groups.

Group 1:	January 14, 1996
Group 2:	January 27, 1996
Group 3:	February 24, 1996

3. SUBJECT SELECTION:

Sixty subjects were enrolled into the study. Subject screening, inclusion and exclusion criteria were the same as in the pilot study (page no 2-3 of this review).

4. STUDY CONDUCT:

Dosing Groups:

The subjects were entered into the study as three dosing groups. Subjects 01-20 were dosed in the first group on 1/14/96; Subjects 21-40 were dosed in the second group on 1/27/96 and Subjects 41-60 were dosed in the third group on 2/24/96.

Treatments:

Test: 10 µl applications of desoximetasone 0.05% gel
Lot#S128-5455

Ref-1: 10 µl applications of Topicort® gel 0.05% (USA)
Lot# 0140074 Exp Date: 10/96

Ref-2: 10 µl applications of Topicort® gel 0.05% (Canada)
Lot # 1266A Exp Date: 7/97

Dosing:

- The arm of each subject was washed with a mild soap and gently dried 2 hours prior to dosing.
- An open washer (inside diameter of approximately 1.6 cm) was placed on the designated nine sites on each forearm. A washer was taped to the forearm using hypo-allergenic scanpor paper tape
- Nine sites (drug application on 8 sites and 1 untreated site) were randomly designated on the flexor surface of each forearm. Application patterns on the left forearms were complementary to those on the right arm. (Appendix 5)
- Using a 250 µl glass Hamilton syringe, a 10 µl application of test and reference products was applied to the 8 assigned sites on each arm. The test and reference (USA and Canada) products were applied to 2 sites on each forearm for 7 minutes duration (based on the estimation of ED_{50} from the pilot study). The USA reference was also applied to one site for 4 minutes duration (D1) and to one site for 15 minutes duration (D2) on each arm.

⇒ The 1995 Guidance suggests total eight testing sites per arm.

T: the test product (two sites)
R: the reference listed drug-RLD (two sites)
D1: the shorter dose duration RLD calibrator (one site)
D2: the longer dose duration RLD calibrator (one site)
UNT: the untreated control (two sites)

The guidance recommends subtracting the average of two untreated sites from all active drug sites on each arm. The sponsor used only one untreated control site per arm, which may introduce more variability into data. However, this should not affect the final outcome of the study since both (test and reference) drug sites were treated in the same way. The deviation from the OGD guidance is therefore acceptable.

Assessments:

The degree of skin blanching was assessed both by visual assessment and with a chromameter at each site prior to treatment application, immediately after removal (0) and at 2, 4, 6, 8, 10, 12, 20 and 24 hours after removal.

Housing and Meals:

Same as in the pilot study

Restriction:

Same as in the pilot study

5. DATA ANALYSIS:

- As discussed in the pilot study section, the areas under the effect curve (AUEC) over 24 hours were calculated from the corrected, baseline-adjusted readings for both visual and chromameter readings.

- The ratio of the mean area under the response curve for the reference 15-minute duration (D2) to that of the 4-minute duration (D1) was calculated for each subject.

- Subjects whose D2/D1 ratio was at least 1.25 were considered qualified for inclusion in the statistical analysis of the bioequivalence of the test and reference products.

- Locke's Method for calculating confidence intervals was applied to the visual scoring and chromameter results from qualifying detectors in this study.

6. RESULTS:

A total of 60 subjects were entered into the study and all subjects completed the study.

Adverse Events:

No serious or unexpected adverse events were reported. All events (Nausea, emesis and headache) were mild to moderate in nature. Most of the events were resolved spontaneously.

***Pharmacodynamic Analysis*:**

- In the pivotal study, the sensitivity is established through dosing of the RLD calibrators at D1 and D2 duration. Each subject becomes a 'detector' in the study. Therefore, the OGD guidance recommends only the data of 'detectors,' i.e., individual subjects whose D2/D1 ratio was at least 1.25 , should be included in the data analysis. Based on this criteria, 28 subjects qualified for the visual results and 22 subjects qualified for the chromameter results.

- D1/D2 ratios of average AUEC based on chromameter and visual data for all subjects are shown in Appendix 1 and 2, respectively.

- The sponsor has also qualified the subject as a detector if she did not show a vasoconstrictor response for the D1 duration, but the ratios for the average areas for her D2 duration to USA reference 7-minute duration were greater than 2. According to this criteria, subjects 27 and 54 were qualified for the inclusion in the bioequivalence evaluations of chromameter and visual data, respectively. <u>The current OGD guidance does not include the above mentioned criteria (ratio of D2/USA reference), therefore, the reviewer has excluded these subjects from the statistical analysis.</u>

- Thus, a total of 28 of the 60 subjects met the qualifying criteria for the visual results and 22 met the criteria for the chromameter results. Only these subjects were included in the statistical analyses for the evaluation of the bioequivalence of the test and reference products. Average AUEC values for test and reference products based on chromameter and visual data are summarized in Appendix 3 and 4, respectively.

- The mean visual and chromameter reading up to 24 hours after drug removal for the test and reference products are comparable and shown in Figures 3 and 4.

- The statistical analysis requires the use of untransformed data because calculated AUEC values of treatments (test and reference), although generally negative, are sometimes positive. Locke's method was used for the assessment of bioequivalence of test and reference products since this method provides an exact confidence interval from untransformed data. The results of these analysis are summarized below in terms of mean response and 90% confidence intervals for visual and chromameter evaluation of Taro' desoximetasone gel vs. reference Topicort® gel.

Table 4: 90% Confidence Interval for Chromameter and Visual Data

	N	Means		Ratio	90% Confidence Interval	
		Taro	Reference		Lower (%)	Upper (%)
Visual	28	23.21	21.35	1.09	100.88	117.89
Chromameter	22	21.60	21.28	1.02	89.64	116.22

- In the present study, the confidence intervals for both visual and chromameter data fell within the conventional bioequivalence limits of 80% to 125%.

C. Comparative *In Vitro* Performance:

The Division of Bioequivalence 1995 Guidance for Topical Corticosteroids has not specified about *in vitro* testing of test and reference products. At present, no recognized quality control test is available for assessing batch-to-batch uniformity of topical products in terms of drug release. A commercially available diffusion cell and synthetic membrane has been suggested to determine drug release rate, which in turn would reflect the quality of a product, its stability and the effects of numerous manufacturing and processing variables.

The sponsor has submitted *in vitro* testing data on its desoximetasone gel compared to the reference product, Topicort® gel using (b)(4)(CC) cell and synthetic membrane. The method and results are presented in Table 5 .

Table 5

Drug:	**Desoximetasone Gel, 0.05%**	
ANDA No.:	**74-904**	
Firm:	**Taro Pharmaceuticals, Inc.**	
Submission Date: 5-17-96		
I. Conditions for measuring In Vitro Release Rate: Taro's Method (No USP method available at this time)		
(b)(4)(CC)		
Mean	37.28	36.48
RSD	12.77%	11.02%

The amount of desoximetasone was determined using a validated (b)(4)(CC) method. This method employed a reverse phase (b)(4)(CC) (b)(4)(CC) The calibration standards used were in the range of (b)(4)(CC) The inter-run accuracy and precision were within acceptable range.

D. Comparative Formulation (Not to be released under FOI):

Ingredient	Test Product Taro's Desoximetasone Gel (% w/w)	Reference Product Topicort® Gel (% w/w)
Desoximetasone USP	0.05	0.05
Purified Water	(b)(4)(TS)	
Carbomer 940 NF		
(b)(4)(CC)		
Docusate Sodium USP		
EDTA		
Isopropyl Myristate		
Trolamine NF		
SDAG 1-B 95% Alcohol		
(b)(4)(CC)		

- Not present in the formulation

*(b)(4)(CC)

- The dosage form, strength, ingredients and route of administration of test product are qualitatively identical to those used in reference product.

Comments:

1. The sponsor has conducted a pilot and a pivotal dose response studies as per the OGD 1995 Guidance on topical corticosteroids.

2. In the pivotal study, the sponsor used only one untreated control site per arm for the baseline correction. The guidance recommends subtracting the average of two untreated sites from all active drug sites on each arm. The study is acceptable, however, the firm should be advised to conduct future studies according to the OGD guidance.

3. A total of 60 subjects participated in the pivotal study. Data from the 28 subjects were used in statistical analysis of visual results and 22 subjects qualified for the chromameter results.

4. There was no severe medical event reported during a pilot study and a pivotal study.

5. The mean vasoconstrictor profiles based on visual and chromameter readings up to 24 hours after drug removal for the test and reference products are comparable.

6. Locke's method was applied for calculating confidence intervals. The 90% confidence intervals for both chromameter and visual results are all within 80-125% range. The study is acceptable.

7. The firm has also compared its desoximetasone gel against the Canadian reference and the confidence intervals were 95.0% to 108.2% for visual data and 81.7% to 103.8% chromameter data.

8. There is no USP method available for determination of *in vitro* release rate. The firm has submitted *in vitro* release data using (b)(4)(CC) cell and synthetic membrane. The data is acceptable.

Recommendation:

1. The *in vivo* bioequivalence study conducted by Taro Pharmaceuticals, on its desoximetasone 0.05% gel, lot #S128-5455 comparing it to Hoechst-Roussel Pharmaceuticals' Topicort® gel, lot # 0140074, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Taro's desoximetasone 0.05% gel, is bioequivalent to the reference product, Topicort® gel.

The firm should be informed of comment # 2 and of the recommendation.

/S/

Jahnavi S. Kharidia, Ph.D.
Review Branch III
The Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE /S/ Date 2/10/97

Concur: /S/ Date 3/24/97
Rabindra Patnaik, Ph.D.
for ~~Acting~~ Director
Division of Bioequivalence

have reviewed this analysis & concur with the findings & conclusions.

cc: ANDA # 74904 (original, duplicate), Kharidia, HFD-658HFD-630, Division File

/S/ 4/9/98

Figure 1. Topicort Gel Chromameter Area Results

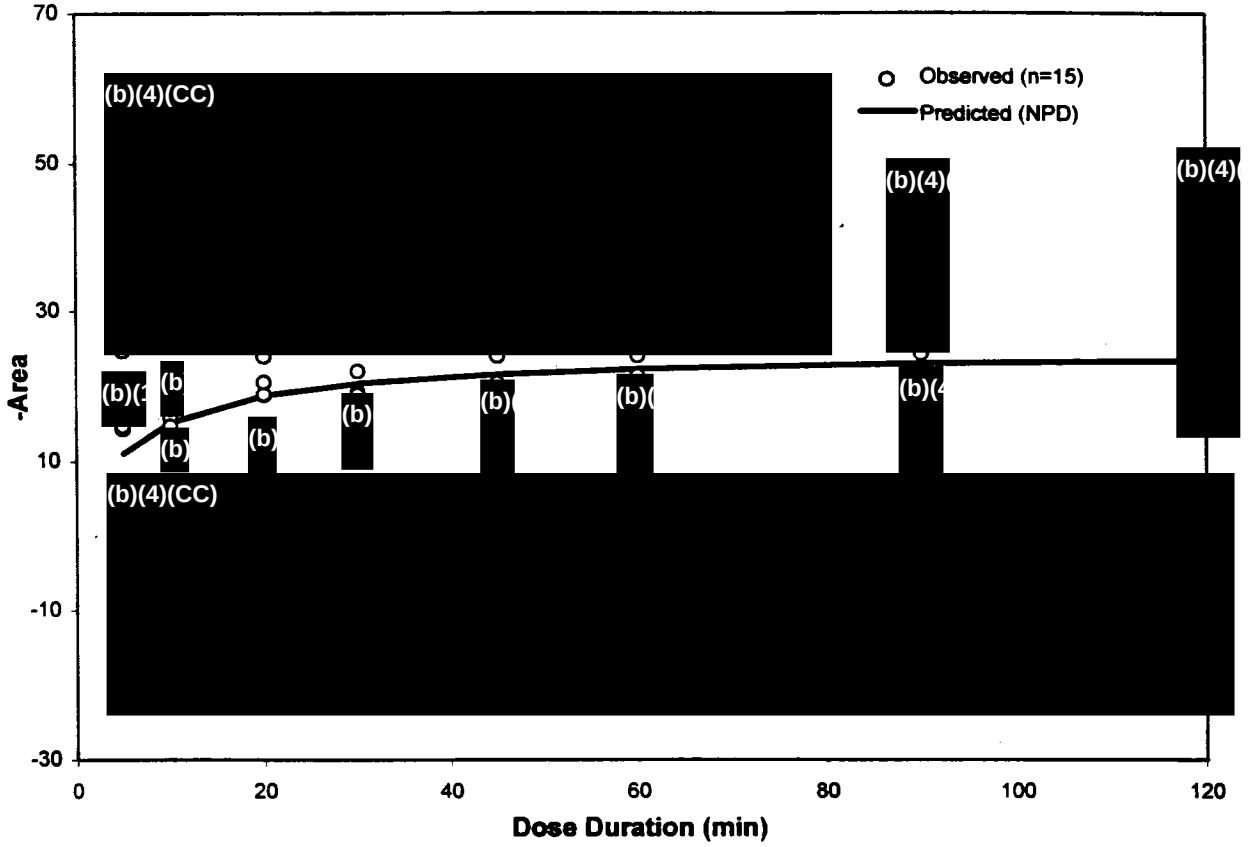


Figure 2. Topicort Gel Visual Area Results

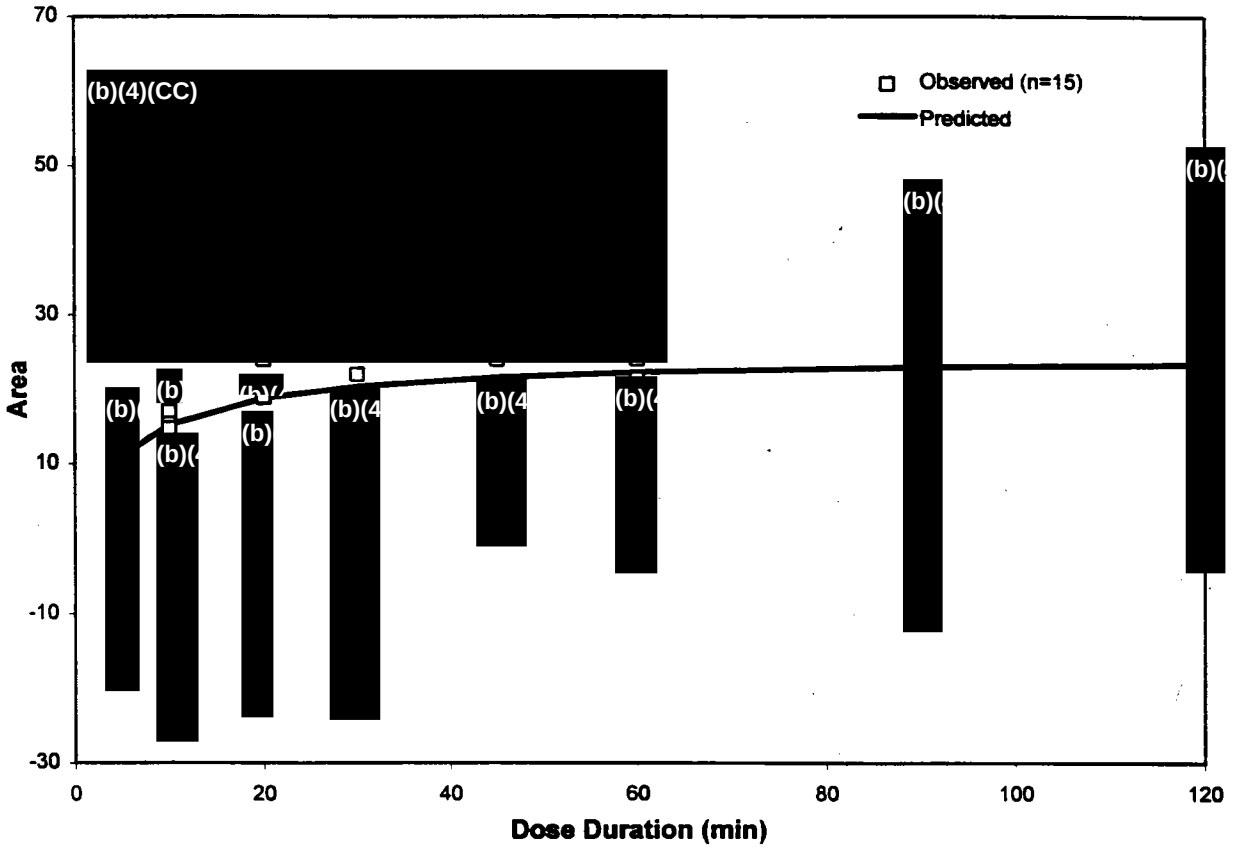


Figure 3. Mean Corrected Baseline- Adjusted Values (n=29), Visual Data

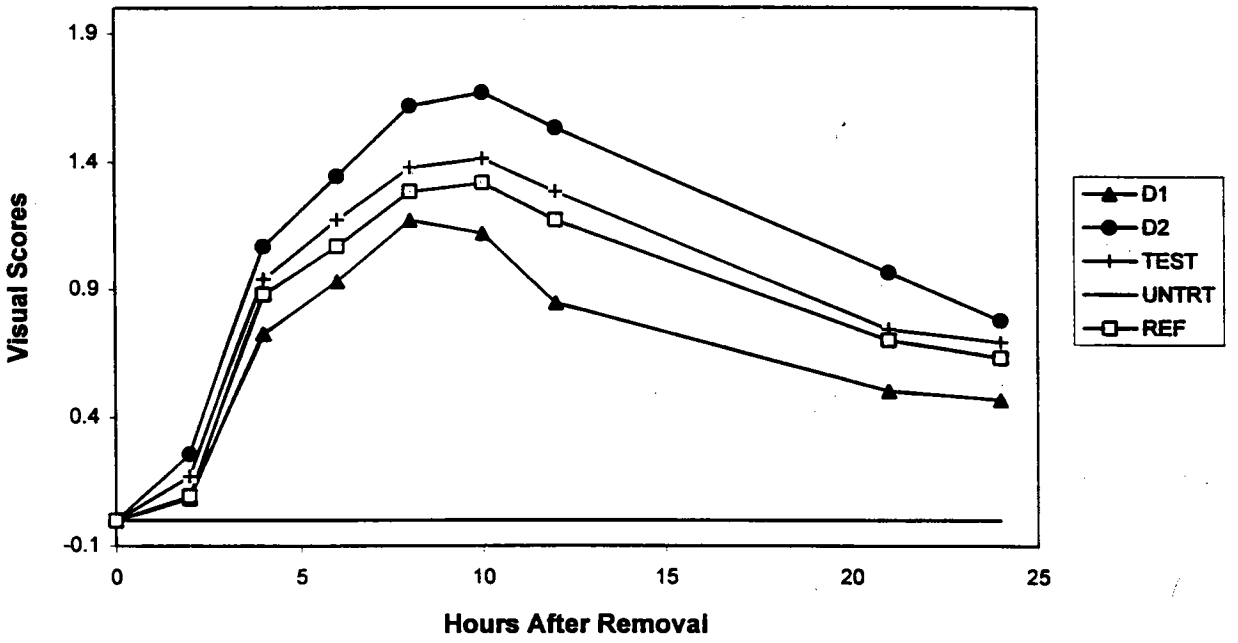
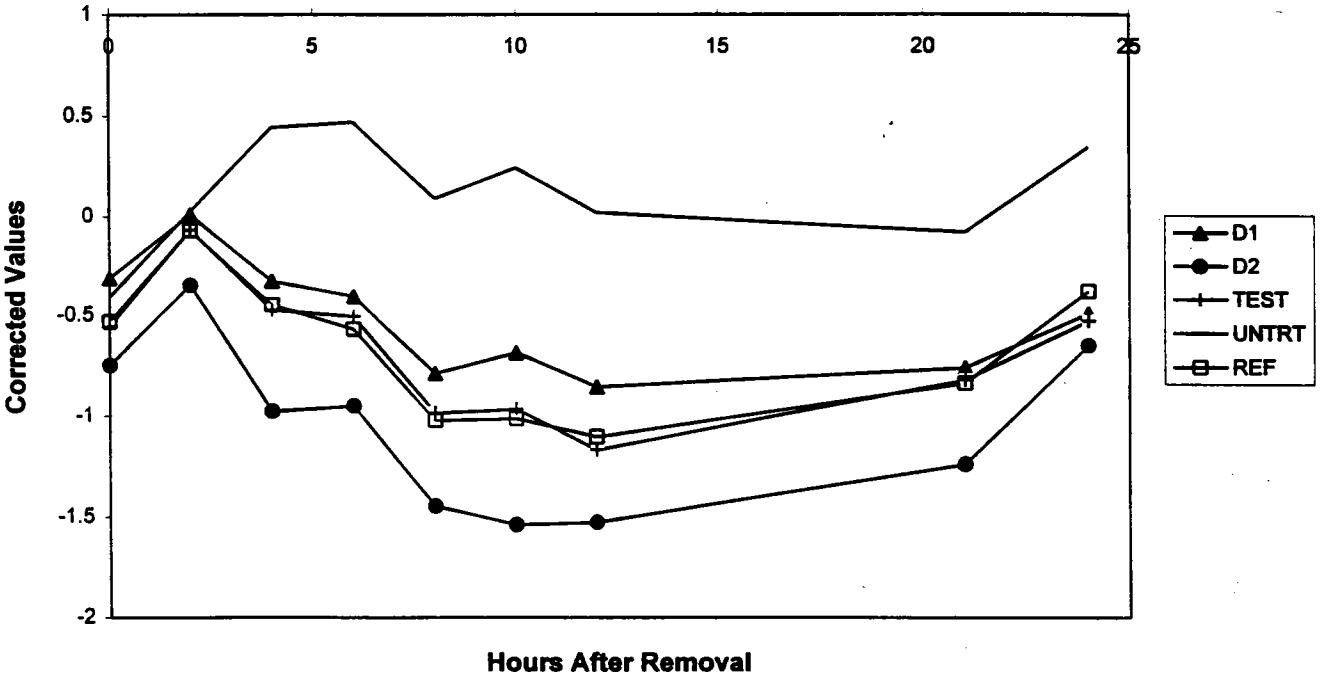


Figure 4. Mean Corrected Baseline-Adjusted Values (n=23), Chromameter Data



Pivotal In Vivo Bioequivalence Study

Appendix 1: D1/D2 Ratios of Average AUEC Based on Chromameter Data

Subject	D1	D2	D2/D1*	Subject	D1	D2	D2/D1*
1	(b)(4)(CC)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							
21							
22							
23							
24							
25							
26							
27							
28							
29							
30							

	D1	D2	D2/D1
Mean	25.30	30.27	1.06
Std Dev	17.41	17.38	2.30
CV%	68.82	57.42	217.09

* Highlighted cells indicates AUEC ratio $\geq$ 1.25

Pivotal In Vivo Bioequivalence Study

Appendix 2: Average AUEC for Test and Reference Products Based on Chromameter Data

All subjects

D1/D2≥	Subject	Test	Ref	Test/Ref	D1/D2 ≥ 1.25	Subject	Test	Ref	Test/Ref
[redacted] (b)(4)(CC)									

Detectors (D2/D1 > 1.25) *

Subject	Test	Ref	Test/Ref
2	[redacted] (b)(4)(CC)		
4			
5			
7			
8			
12			
14			
15			
16			
17			
23			
25			
29			
32			
33			
35			
36			
40			
43			
44			
47			
55			
Mean	21.60	21.28	1.41
Std	11.09	12.43	3.44
CV%	51.32	58.39	243.92

n=22

Pivotal In Vivo Bioequivalence Study

Appendix 3: D1/D2 Ratios of Average AUEC Based on Visual Data

Subject	D1	D2	D2/D1*	Subject	D1	D2	D2/D1*
1	(b)(4)(CC)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							
21							
22							
23							
24							
25							
26							
27							
28							
29							
30							

	D1	D2	D2/D1
Mean	23.22	28.31	1.84
Std Dev	11.40	12.11	4.20
CV%	49.08	42.76	228.02

* Highlighted cells indicates AUEC ratio $\geq$ 1.25

Pivotal In Vivo Bioequivalence Study

Appendix 4: Average AUEC for Test and Reference Products Based on Visual Data

All subjects

D1/D2 ≥ 1.25	Subject	Test	Ref	Test/Ref	D1/D2 ≥ 1.25	Subject	Test	Ref	Test/Ref
[redacted]									

(b)(4)(CC)

Detectors (D2/D1 > 1.25) *

Subject	Test	Ref	Test/Ref
[redacted]			
Mean	23.21	21.35	1.19
Std	10.38	10.94	0.43
CV%	44.73	51.24	36.07

(b)(4)(CC)

n=28

APPENDIX 5

EXAMPLE OF COMPLIMENTARY TREATMENT APPLICATIONS

If the Right Arm were randomized as follows, the Left Arm applications would be "complimentary", as in the following example:

ANTECUBITAL FOSSA

Right Arm		Left Arm	
Site	Treatment	Site	Treatment
9	D2	18	D1
8	Reference (USA)	17	Test
7	Reference (Can)	16	Reference (Can)
6	Test	15	Reference (USA)
5	Untreated	14	Untreated
4	Reference (USA)	13	Test
3	D1	12	D2
2	Reference (Can)	11	Reference (Can)
1	Test	10	Reference (USA)

WRIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74904

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 74-904 Date of Submission: May 17, 1996

Applicant's Name: Taro Pharmaceuticals, Inc.

Established Name: Desoximetasone Gel USP, 0.05%

Labeling Deficiencies:

1. CONTAINER (15 g and 60 g tubes)

   Revise "EACH GRAM CONTAINS" statement to include listing of inactive ingredients. You are referred to 21 CFR 201.100(b)(5) for further guidance.

2. CARTON (15 g and 60 g)

   See CONTAINER comment.

3. INSERT

   a. DESCRIPTION

      i. Revise the second paragraph to read, "Each gram of Desoximetasone Gel USP, 0.05%, for topical use,..."

      ii. Revise the inactive ingredient "Carbomer 980" to read "carbomer 940 NF".

      iii. Revise the fourth paragraph to read "molecular formula" rather than "empirical formula".

   b. CLINICAL PHARMACOLOGY (Pharmacokinetics)

      i. Revise the second paragraph to read, "...resistant dermatoses. (See **DOSAGE AND ADMINISTRATION**)".

      ii. Delete the first three sentences of the ultimate paragraph.

   c. PRECAUTIONS

      i. General

Revise the fourth paragraph so that the sentence "If irritation develops..." begins a new paragraph.

ii. Information for the Patient

Revise to number each information and instruction listing rather than use bullets.

iii. Carcinogenesis, Mutagenesis, and Impairment of Fertility

a) Delete "and" in the subsection heading.

b) Revise to delete the ultimate sentence of this subsection.

iv. Pregnancy Category C

Revise subsection heading to read:

Pregnancy. Teratogenic Effects. Pregnancy Category C

v. Nursing Mothers

Revise the second sentence to italicize "*not*"

d. Revise the CAUTION statement to read, "...WITHOUT PRESCRIPTION". (delete "A")

Please revise your labels and labeling, as instructed above, and submit in final print, or draft if you prefer.

Please note that the Agency reserves the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/ [redacted] for

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74904

CORRESPONDENCE

MAJOR AMENDMENT

MAR 4 1997

ANDA/AADA: 74-904

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 [redacted]

TO: APPLICANT TARO PHONE 914 345 9001 x 347
ATTN: Timothy Anderson FAX 914 345 8728

FROM: Joseph Buccine PROJECT MANAGER (301-594-1841)

Dear Sir/Madam:

This facsimile is in reference to your abbreviated new drug/antibiotic application dated MAY 17, 1996, submitted pursuant to Section 505(j)/507 of the Federal Food, Drug, and Cosmetic Act for Desoximetasone Gel

Reference is also made to your amendments dated July 10, 1996.

The application is deficient and, therefore not approvable under Section 505/507 of the Act for the reasons provided in the attachments (8 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

SPECIAL INSTRUCTIONS:

x:\new\ogdadmin\faxtrak\faxcov.mjr

June 11, 1998

TARO

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

1C

RE: ANDA 74-904
Desoximetasone Gel USP, 0.05%
Telephone Amendment

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application (ANDA) for the above referenced product, submitted on May 17, 1996 pursuant to 21 CFR 314.70.

Reference is also made to a phone call from Mr. Joe Buccine on June 10, 1998 in which the following was requested:

Comment: The proposed stability specification for individual degradants of NMT [redacted]

Response: The Agency's observation is correct that the highest individual degradant we see is at [redacted] over either 24 months at room temperature or over 3 months at accelerated conditions. However, the regression analyses, which come from our previously submitted stability summaries, (see **Attachment 1** chart) show that we could receive results of up to [redacted] The calculated upper confidence intervals at [redacted] We are concerned that based on these results, a limit of [redacted] will not allow any room for analytical variability. Therefore, we propose that the Agency would reconsider their request and would permit a stability limit of NMT [redacted]

This concludes our response to the Agency's phone call of June 10, 1998. If you should have any further questions, please feel free to contact me at (914) 345-9001.

Sincerely,

Lorraine W. Sachs, RAC
Associate Director, Regulatory Affairs

cc: Acting Director, FDA, Office of International Programs

RECEIVED
JUN 12 1998
GENERIC DRUGS

Taro Pharmaceuticals U.S.A., Inc. Five Skyline Drive, Hawthorne, NY 10532 Tel: 914-345-9001 Fax: 914-345-8728 http://www.taropharma.com

RECORD OF TELEPHONE CONVERSATION

Reference was made to the p 63 of the submission dated 2/27/98.

At the request of N. Takiar, I called the firm and requested a change in specifications for individual degradation products from (b)(4)(CC to (b)(4)(CC) This change is supported by data contain in their application.

Sue said she would refer the issue to Lorraine and Terry Feldman, and respond.

cc:

ANDA
Division File
T-con Binder

DATE
6/10/98

ANDA NUMBER
74-904

IND NUMBER

TELECON

INITIATED BY FDA

PRODUCT NAME
Desoximetasone Gel 0.05%

FIRM NAME
Taro

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Sue for Lorraine Sachs, DRA

TELEPHONE NUMBER
914-345-9001

SIGNATURE
/S/ [redacted]
6/10/98

February 27, 1998

TARO PHARMACEUTICALS INC.
130 EAST DRIVE
BRAMALEA, ONTARIO
L6T 1C3

Center for Drug Evaluation and Research
Central Document Room
12420 Parklawn Drive
Room 2-14
Rockville, Maryland
USA 20852

Attention: Associate Director, FDA, Office of International Programs

RE: **ANDA 74-904 Major Amendment**
Desoximetasone Gel USP, 0.05%

Dear Sir/Madam:

Taro Pharmaceuticals Inc. hereby submits and certifies that the enclosed field copy is a true copy of the technical information provided in the above referenced amendment.

If there are any questions in regards to this documentation, please do not hesitate to contact the undersigned or our U.S. agent,

Taro Pharmaceuticals U.S.A., Inc.
Attn.: Lorraine Sachs, RAC
Associate Director, Regulatory Affairs
5 Skyline Drive
Hawthorne, New York 10532
(914) 345-9001

Regards,

Derek Ganes, Ph.D.
Vice President, Regulatory Affairs

TELEPHONE
905-791-8276
1-800-268-1975
VOICE MAIL
905-791-5181
TELEFAX NO.
905-791-5008

ARCHIVE

February 27, 1998

TARO PHARMACEUTICALS INC.
130 EAST DRIVE
BRAMALEA, ONTARIO
L6T 1C3

Office of Generic Drugs
Center for Drug Evaluation and Research
Food And Drug Administration
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20857
USA

FDA DRUG ... MENT

N/AC

RE: **ANDA 74-904, Desoximetasone Gel USP, 0.05%**
Major Amendment

Dear Sir,

Reference is made to our Abbreviated New Drug Application (ANDA) for the above referenced product, submitted on May 17, 1996, pursuant to 21 CFR 314.70.

Reference is also made Taro's amendment submitted April 22, 1997 and to The Agency's letter of January 27, 1998, in which it is stated that the application is deficient and, therefore, not approvable.

We now wish to respond to the comments presented in the Agency's correspondence. For ease of review, the comments are restated in bold and are immediately followed by Taro's response and any necessary supportive documentation.

We trust the information is complete. If you have any further comments, please contact the undersigned or our US agent:

Taro Pharmaceuticals U.S.A. Inc.
Attn.: Lorraine Sachs, RAC
Associate Director, Regulatory Affairs
5 Skyline Drive
Hawthorne, New York 10532
(914) 345-9001

Sincerely yours,

TARO PHARMACEUTICALS INC.

Derek Ganes, Ph.D.
Vice President, Regulatory Affairs

/ J. Hobbs
cc. Acting Director, FDA, Office of International Programs

RECEIVED
APR 2 1998
GENERIC DRUGS

TELEPHONE
905-791-8276
1-800-268-1975
VOICE MAIL
905-791-5181
TELEFAX NO.
905-791-5008

JAN 27 1998

38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-904 APPLICANT: Taro Pharmaceuticals Inc.

DRUG PRODUCT: Desoximetasone Gel USP, 0.05%

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

(b)(4)(TS)

[redacted]

2. (b)(4)(TS) [redacted]

3. [redacted]

4. [redacted]

5. [redacted]

6. [redacted]

7. (b)(4)(TS)

8.

9.

B. (b)(4)(TS) [redacted]

Sincerely yours,

/S/ [redacted]

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

MAJOR AMENDMENT

JAN 27 1998

ANDA: 74-904

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT TARO PHONE 914 345 9001
ATTN: LORRAINE SACHS FAX 914 ~~827~~ 8728
345

FROM: Joseph Buccine, Project Manager (Tel: 301-827-5848) (Fax: 301-594-0180)

Dear Sir/Madam:

This facsimile refers to your abbreviated new drug application(s) dated
submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act
for DESOXIMETASONE GEL USP, 0.05%

Reference is also made to your amendment(s) dated

The application is deficient and, therefore not approvable under Section 505 of the Act for the reasons provided in the attachments (4 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

SPECIAL INSTRUCTIONS:

CHEMISTRY COMMENTS ARE PROVIDED. THIS IS THE SECOND OCCASION MAJOR DEFICIENCIES HAVE BEEN IDENTIFIED.

x:\new\ogdadmin\faxtrak\faxcovjb.mjr

April 22, 1997

TARO PHARMACEUTICALS INC.
130 EAST DRIVE
BRAMALEA, ONTARIO
L6T 1C3

Center for Drug Evaluation and Research
Central Document Room
12420 Parklawn Drive
Room 2-14
Rockville, Maryland
U.S.A. 20852

Attention: Associate Director, FDA, Office of International Programs

RE: **ANDA 74-904 Major Amendment**
Desoximetasone Gel USP, 0.05%

Dear Sir/Madam:

TARO Pharmaceuticals Inc. hereby submits and certifies that the enclosed field copy is a true copy of the technical information provided in the above referenced amendment.

If there are any questions in regards to this documentation, please do not hesitate to contact the undersigned or our U.S. agent,

Taro Pharmaceuticals U.S.A., Inc.
Attn: Lorraine H. Sachs
Senior Regulatory Affairs Specialist
5 Skyline Drive
Hawthorne, New York 10532
(914) 345-9001

Regards,

Derek Ganes, Ph.D.
Director, Regulatory Affairs

TELEPHONE
905-791-8276
1-800-268-1975
VOICE MAIL
905-791-5181
TELEFAX NO.
905-791-5008

ARCHIVE

April 22, 1997

TARO PHARMACEUTICALS INC.
130 EAST DRIVE
BRAMALEA, ONTARIO
L6T 1C3

Office of Generic Drugs
Center for Drug Evaluation and Research
Food And Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20857
USA

NDA ORIG AMENDMENT
N/AC

RE: **ANDA 74-904**
Desoximetasone Gel USP, 0.05%
Major Amendment

Dear Sir,

Reference is made to our Abbreviated New Drug Application (ANDA) for the above referenced product, submitted on May 17, 1996, pursuant to 21 CFR 314.70.

Reference is also made to your letter of March 4, 1997, in which it is stated that the applications are deficient and, therefore, not approvable.

We now wish to respond to the comments presented in the aforementioned correspondence. For ease of review, the Agency's comments are restated in bold and are immediately followed by TARO's response and any necessary supportive documentation.

We trust the information is complete. If you have any further comments, please contact the undersigned or our US agent:

Taro Pharmaceuticals U.S.A. Inc.
Attn: Lorraine H. Sachs
Senior Regulatory Affairs Specialist
5 Skyline Drive,
Hawthorne, New York 10532
(914) 345-9001

Sincerely yours,

TARO PHARMACEUTICALS INC.

Derek Ganes, Ph.D.
Director, Regulatory Affairs

/ J. Hobbs
cc. Acting Director, FDA, Office of International Programs

RECEIVED
APR 2 8 1997
GENERIC DRUGS

TELEPHONE
905-791-8276
1-800-268-1975
VOICE MAIL
905-791-5181
TELEFAX NO.
905-791-5008

MAR 4 1997

38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-904 APPLICANT: Taro Pharmaceuticals Inc.

DRUG PRODUCT: Desoximetasone Gel USP, 0.05%

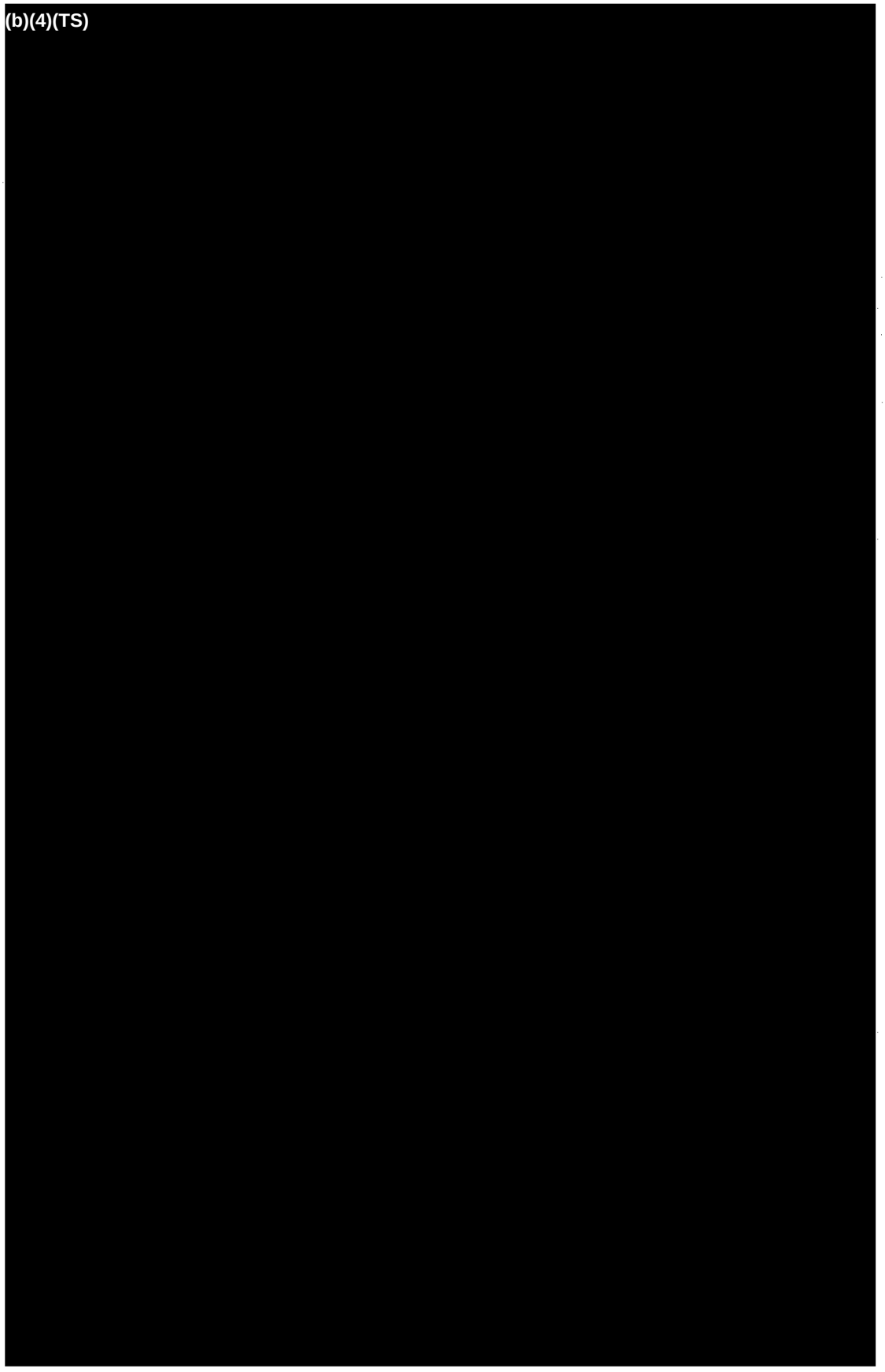
The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

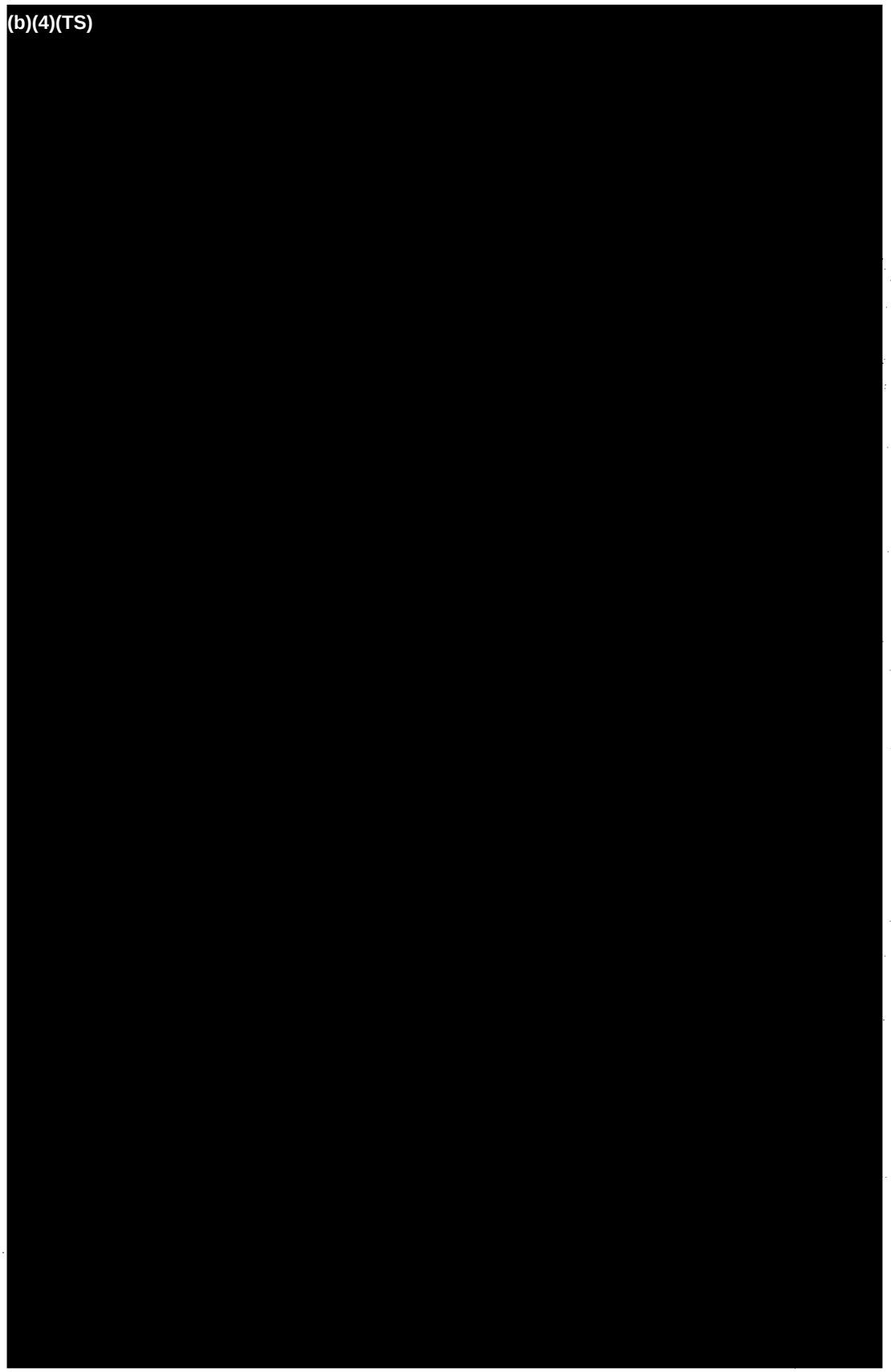
(b)(4)(TS)

[redacted]

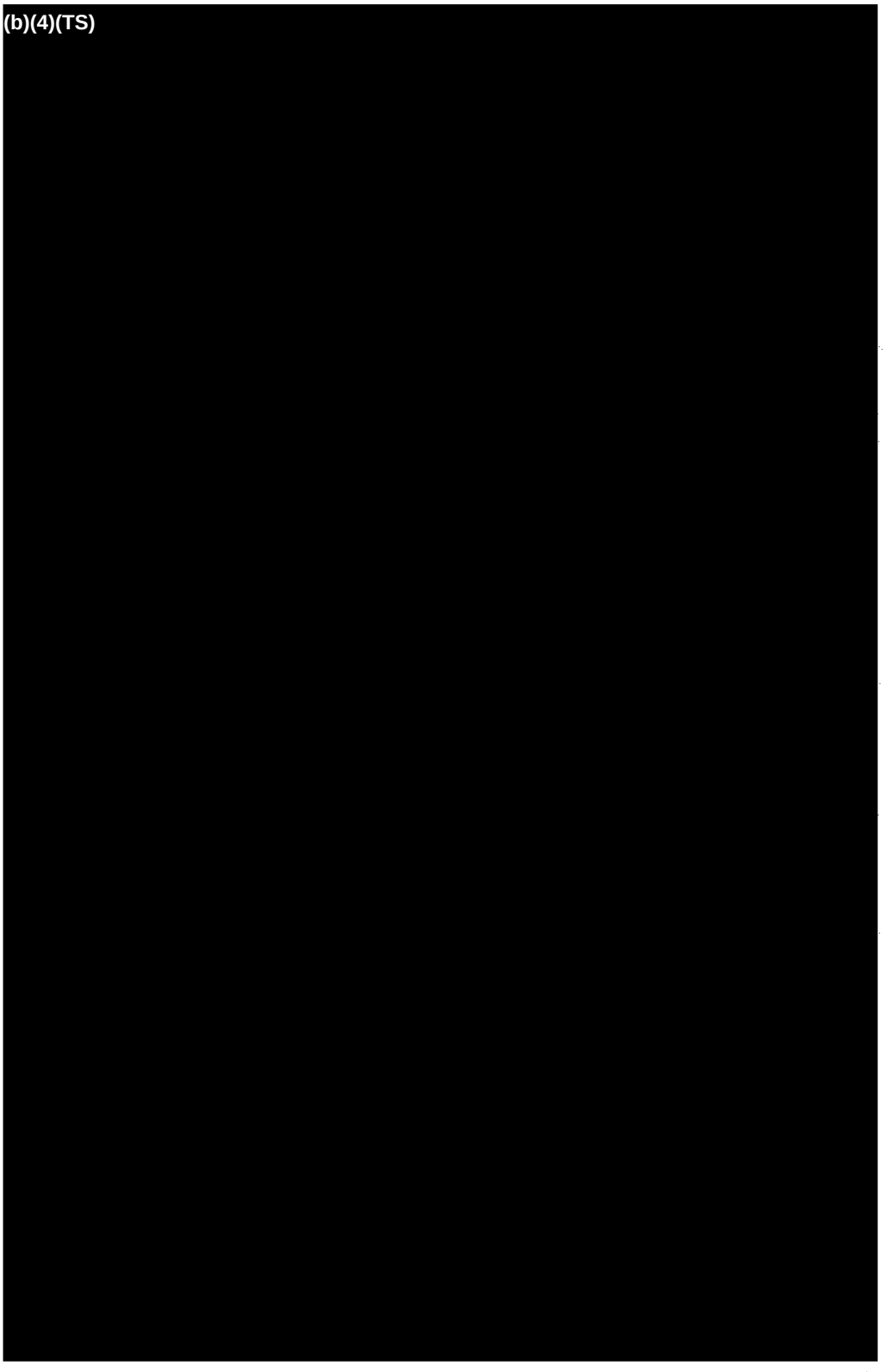
(b)(4)(TS)



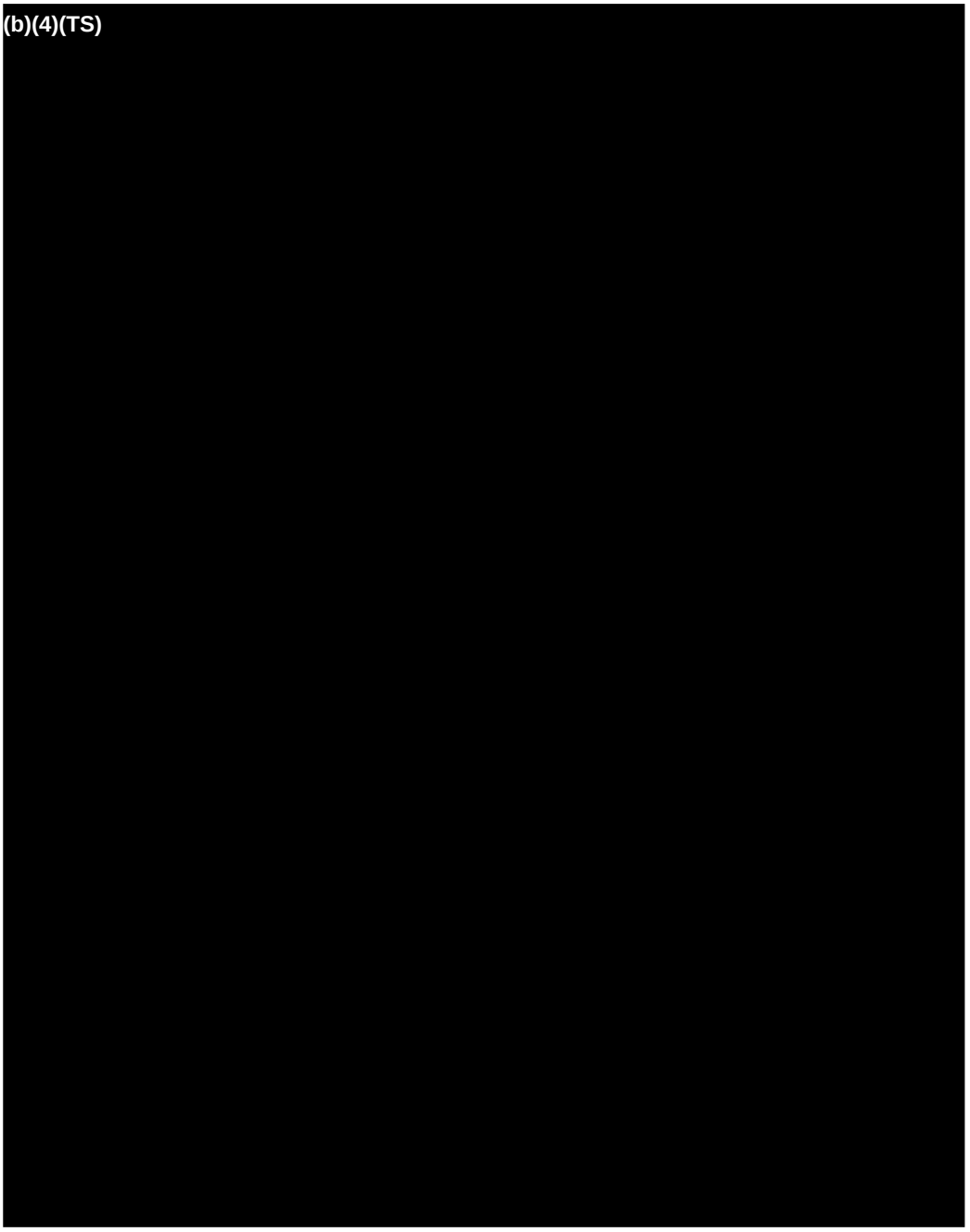
(b)(4)(TS)



(b)(4)(TS)



(b)(4)(TS)



20. Please update the stability specifications (pages 1445 and 1446) by setting limits for pH and degradation products (individual and total).

21. The second footnote on pages 1445 and 1446, regarding tests not to be performed at (b)(4)(CC) months, is not linked to any of the tests in the table.

22. (b)(4)(TS) [redacted]

23. [redacted]

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. DMF (b)(4)(C[redacted] has not been updated within the past two years. Therefore, there is no assurance that the DMF information is current, and the DMF review cannot be concluded. The DMF holder is being notified.

2. Please acknowledge that the USP assay methods will be the regulatory methods and will prevail in case of a dispute, and the methods described in your (b)(4)(TS) [redacted]

Sincerely yours,

/S/ [redacted]

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Archival Copy

TARO PHARMACEUTICALS INC.
130 EAST DRIVE
BRAMALEA, ONTARIO
L6T 1C3

July 10, 1996.

Office of Generic Drugs
Document Control Room
Metro Park North II
Food and Drug Administration
7500 Standish Place, Room 150
Rockville, Maryland
USA 20855-2773

RECEIVED
JUL 11 1996
GENERIC DRUGS

AC

Reference: **ANDA 74-904**
Desoximetasone Gel USP, 0.05%
Response to FDA Refusal To File Letter of 13 June 1996

Dear Sir:

Reference is made to our abbreviated new drug application dated 17 May 1996, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Desoximetasone Gel USP, 0.05%. Reference is also made to the FDA Refusal To File Letter dated 13 June 1996. At this time, we wish to amend our application to include additional supporting information relating to Carbomer 940 NF and SDAG 1B 95 % Alcohol.

In the letter from FDA, the following reasons are cited for the refusal to file:

"...your proposed formulation contains inactive ingredients that have not been approved in a drug product for human use by the same route of administration [21CFR 314.127(a)(8)(11)] According to the regulation, there is reasonable basis to conclude that two of the inactive ingredients of your proposed product (i.e. Carbomer 980 and SD AG 1B 95% alcohol), may raise questions of safety, the Office of Generic Drugs (OGD) will not file this application as an ANDA. New inactive ingredients must be the subject of a new drug application."

Response:
In the opinion of Taro Pharmaceuticals, neither Carbopol® 980, nor SDAG 1B 95% alcohol is a new inactive ingredient. Additional supporting information for each ingredient follows.

Carbopol® 980
In the ANDA, Carbomer 940 NF is incorrectly referred to as (b)(4)(TS) The item should be referred to as (b)(4)(TS) (Carbomer 940 NF) wherever it appears in the ANDA.

TELEPHONE
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905-791-5181
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905-791-5008

Carbomer is the generic, CTFA designation for this group of products. Carbopol® is a registered trademark of (b)(4)(CC) or their brand of carbomer resins. (b)(4)(CC) supplies several grades of carbomer, including Carbomer 940 NF, which is available as (b)(4)(CC)

Taro's formulation utilizes a (b)(4)(TS) (b)(4)(TS) are the same resin; however, the (b)(4)(CC) is different. Both (b)(4)(TS) comply with the monograph for Carbomer 940 NF (page 1).

For further information on (b)(4)(CC) Carbomer 940 NF, please refer to (b)(4)(CC) A letter from the manufacturer, authorizing FDA to refer to the information in support of Taro's application, has been included with this amendment (page 2).

SDAG 1B 95% Alcohol

In the USA, regulations exist which govern the formulas and uses of a series of specially denatured (SD) alcohols (27 CFR, Section 21.74 -77). In Canada, Taro's intended site of manufacture for Desoximetasone Gel USP, Revenue Canada Customs and Excise also issues regulations which govern the allowable denaturants available in Canada. As can be expected, the exact formulas for most of the SD alcohols differ between the two jurisdictions.

Taro has selected the 1B grade (Canadian designation) to be the closest to that used by Topicort® as declared on their labeling - SD alcohol 40 (US designation). Below is a comparison of several US grades and the Canadian grade of SD alcohols.

Comparison of US and Canadian Grades of Denatured Alcohol

(b)(4)(TS)

TARO PHARMACEUTICALS INC.
TELEPHONE
905-791-8276
1-800-268-1975
TELEFAX NO.
905-791-5008

July 10, 1996.
ANDA 74-904
Desoximetasone Gel USP, 0.05 %
Response to FDA Refusal to File Letter of 13 June 1996

The Canadian grade 1B contains two denaturants (b)(4)(CC) (b)(4)(CC), which are individually represented in various SD grades in the USA. Furthermore, the Inactive Ingredient Guide lists only 'Alcohol, Denatured' (with no specific formula designation), for use in topical gels up to 96.9 %. The following additional information has been included with this amendment:

1. Revenue Canada Customs and Excise Specifications for the Composition and Authority for Use of Specially Denatured Alcohol, as published in Canada Gazette (page 3).
2. MSDS for SDAG 1B 95 % Alcohol from Commercial Alcohols Inc.(pages 4 to 9)
3. Copy of IIG reference to 'Alcohol Denatured' (page 10)
4. Copy of 27 CFR reference on denatured alcohol (pages 11 to 14)

Based on this information, Taro asserts that Carbopol® 980 and SDAG 1B 95% Alcohol are not new inactive ingredients, and as such may be the subject of an abbreviated application.

Finally, we wish to amend the application to certify that the Field Copy is a true copy of the technical sections of the ANDA, and that it was sent to the OGD at the time of submission of our original application. Separate certification has been provided (page 15).

This concludes our amendment to the application. If there are any questions or if additional information is required, please contact our U.S. Agent:

Dr. Avi Yacobi
Taro Pharmaceuticals U.S.A., Inc.,
Five Skyline Drive
Hawthorne, New York 10532
(914) 345-9001

Sincerely,

Livia Maduri
Regulatory Affairs Associate

cc. Office of International Programs

This amendment includes 15 supplementary pages.

TARO PHARMACEUTICALS INC.
TELEPHONE
905-791-8276
1-800-268-1975
TELEFAX NO.
905-791-5008

ANDA 74-904

Taro Pharmaceuticals USA, Inc.
Attention: Michael Kohlbrenner
U.S. Agent for: Taro Pharmaceuticals, Inc.
6 Skyline Drive
Hawthorne, NY 10532

JUN 13 1996

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated May 17, 1996, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Desoximetasone Gel USP, 0.05%.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

The application is not acceptable for filing under Section 505(j) of the Act because your proposed formulation contains inactive ingredients that have not been approved in a drug product for human use by the same route of administration [21 CFR 314.127(a)(8)(ii)]. According to the regulation, there is reasonable basis to conclude that two of the inactive ingredients of your proposed product (ie, Carbomer (b)(4) and SD AG 1B 95% alcohol), may raise questions of safety, the Office of Generic Drugs (OGD) will not file this application as an ANDA. New inactive ingredients must be the subject of a new drug application.

Furthermore, you must demonstrate that if any qualitative or quantitative differences do exist between your proposed drug product and the reference listed drug, these differences do not affect the safety of the proposed drug product [21 CFR 314.94(a)(9)(iii)]. The information to demonstrate safety should include, but is not limited to: (a) examples of approved drug products administered by the same route of administration which contain the same inactive ingredients and that are within the same concentration range, (b) a description of the purpose of the inactive ingredients when different inactive ingredients are included in the proposed drug product, and (c) information to show that the inactive ingredients do not adversely affect safety or efficacy of the proposed drug product.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Also, while we note you have certified that the field copy is a "true" copy of the technical sections of the application, you have failed to certify that this field copy has been sent to the Office of Generic Drugs (OGD). Please provide a revised field copy certification with an original signature.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3)If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

William Russell
Project Manager
(301) 594-0315

Sincerely yours,

/S/ [redacted] 6/13/96

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-904
cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-600/Reading File
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Chief, RSB /S/ [redacted] 6/13/96 date
HFD-615/WRussell, CSO /S/ [redacted] 6/13/96 date
HFD-629/PSchwartz, Sup.Chem._____date
WP File\x:\new\firmsnz\Taro\ltrs&rev\74904rtf.f
F/T File hrw 6-12-96
ANDA Refuse to File!

Return to file
5/31/96

TARO PHARMACEUTICALS INC.
130 EAST DRIVE
BRAMALEA, ONTARIO
L6T 1C3

May 17, 1996

Office of Generic Drugs
Document Control Room
CDER, FDA
MPN II,
7500 Standish Place, Room 150
Rockville, MD 20855

Dear Sir/Madam:

RE: **ANDA for Desoximetasone Gel USP, 0.05 %**

Taro Pharmaceuticals Inc. submits today an original Abbreviated New Drug Application seeking approval to market Desoximetasone Gel USP, 0.05 % that is bioequivalent to the listed drug, TOPICORT, manufactured by Hoechst-Roussel.

Taro hereby certifies that the field copy is a true copy of the technical sections of the ANDA (also included is a copy of the field copy cover letter, the 356 h form, and a certification that the contents are a true copy of those filed with the Office of Generic Drugs.) This field copy is contained in a burgundy folder.

Please note that Taro Pharmaceuticals Inc. has recently relocated the corporate headquarters to "130 East Drive, Bramalea, Ontario, Canada, L6T 1C3". However, some documentation may indicate the former corporate address of "305 Supertest Road, Downsview, Ontario, Canada, M3J 2M4.

If there are any questions regarding this application, or if additional information is required, please contact our US agent:

Mr. Michael Kohlbrenner
Taro Pharmaceuticals U.S.A., Inc.,
6 Skyline Drive, Hawthorne, New York 10532
Tel: (914) 345-9001

Sincerely,

Livia Maduri
Regulatory Affairs Associate

TELEPHONE
905-791-8276
1-800-268-1975
TELEFAX NO.
905-791-5008