CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 074286/S-006

Name: Desoximetasone Ointment USP 0.25%

Sponsor: Taro Pharmaceuticals, Inc.

Approval Date: December 19, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 074286/S-006

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 074286/S-006

APPROVAL LETTER

DIV

ANDA 74-286/S-006

DEC 19 2003

Taro Pharmaceuticals Inc.
Attention: Kalpana Rao
5 Skyline Drive
Hawthorne, NY 10532

Dear Madam:

This is in reference to your supplemental new drug application dated June 17, 2003, submitted pursuant to 21 CFR 314.70 regarding your abbreviated new drug application for Desoximetasone Ointment USP, 0.25%.

Reference is also made to your amendments submitted August 22, 2003 and September 17, 2003.

This supplemental application provides for the use of the proprietary name "Topicort" on your labels and labeling.

We have completed the review of this supplemental application and it is approved as of September 17, 2003 submission.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The materials submitted are being retained in our files.

Sincerely yours,

John J. Smith for 12-11-2003

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 73-193/S-006 (0.25%)
HFD-92
Field Copy
Division File
V:\FIRMSNZ/TARO\\LTRS&REV\74193/S006.apl

APPROVAL LETTER - SINGLE SUPPLEMENT

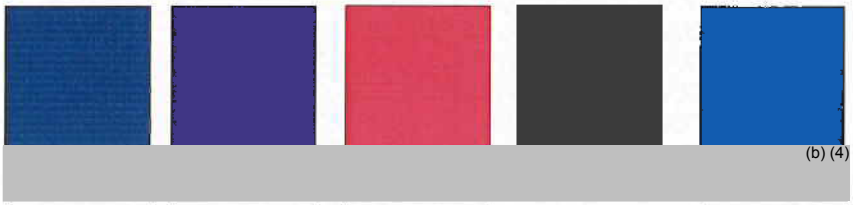
Endorsement:
HFD-613/Beverly Weitzman DAW 12/11/2003

CENTER FOR DRUG EVALUATION AND RESEARCH

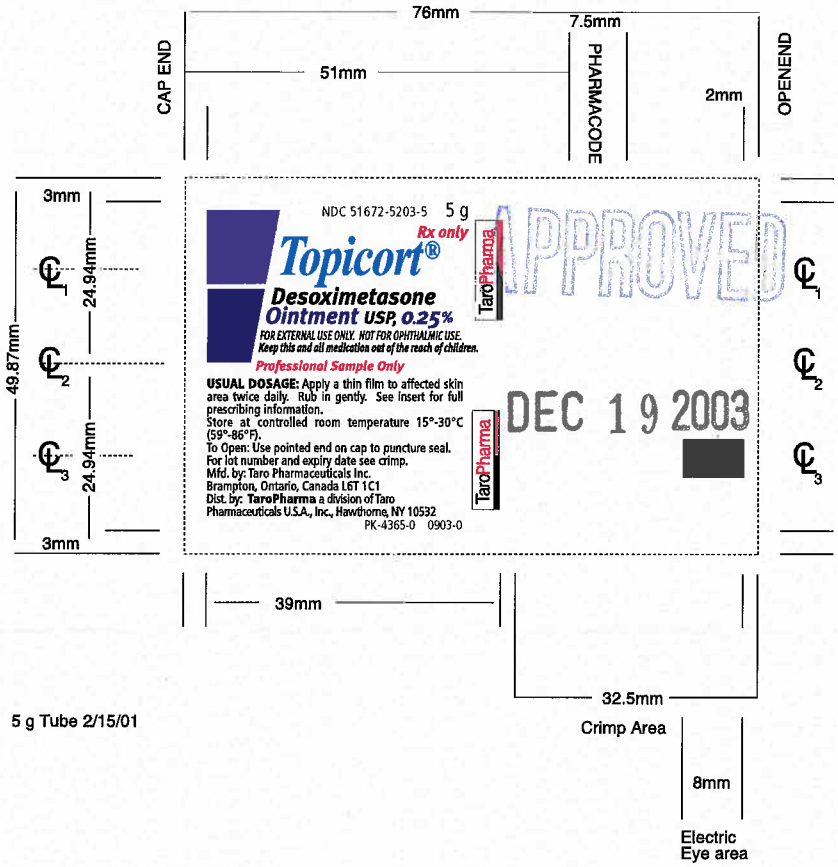
APPLICATION NUMBER:

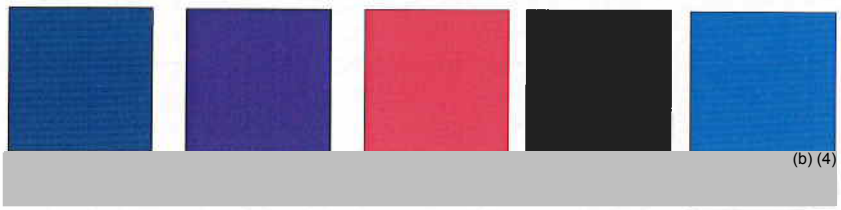
ANDA 074286/S-006

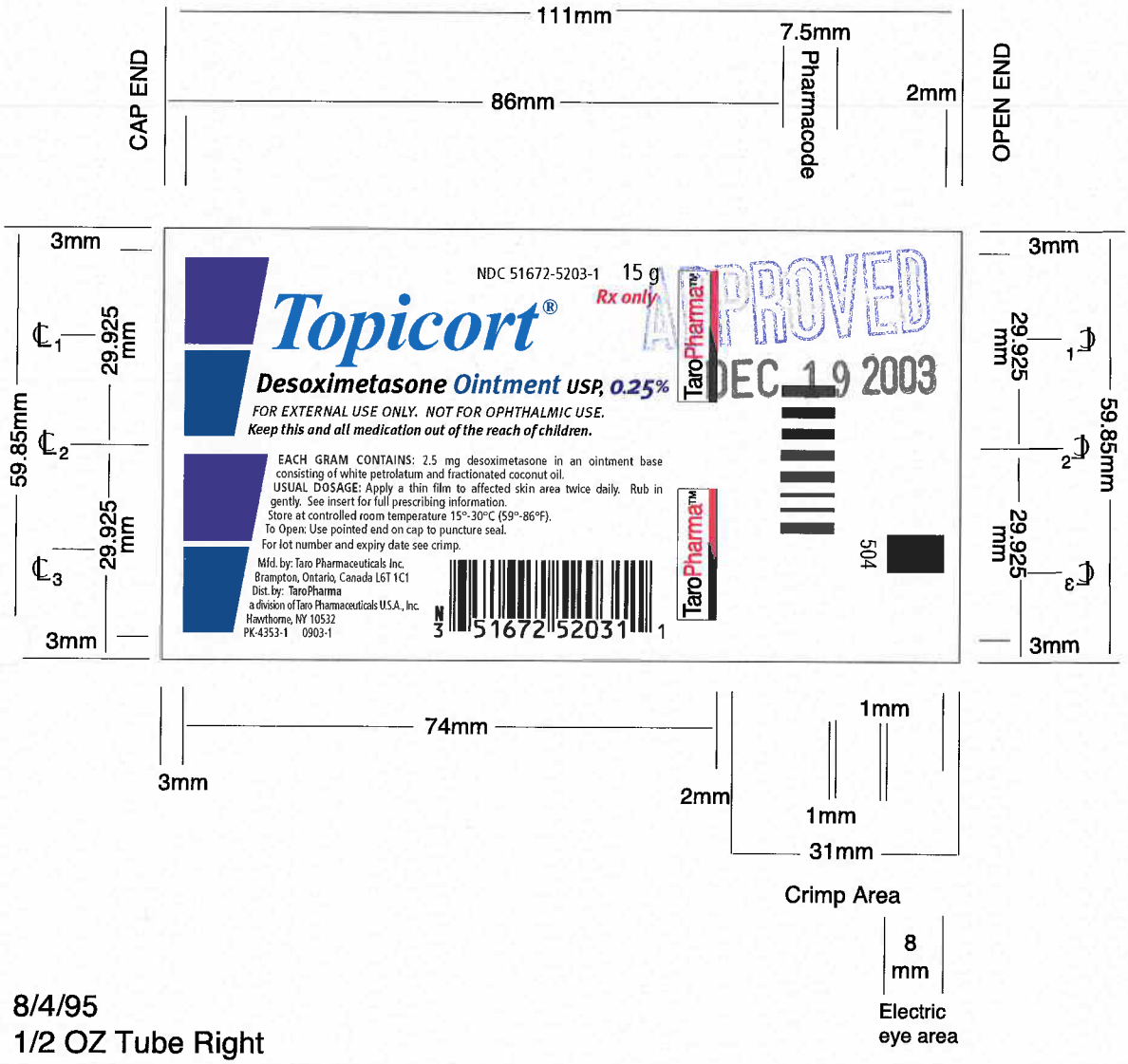
LABELING



(b) (4)


76mm
7.5mm
CAP END
51mm
PHARMACODE
2mm
OPENEND
3mm
24.94mm
49.87mm
24.94mm
3mm
NDC 51672-5203-5 5 g
Rx only
Topicort®
Desoximetasone
Ointment USP, 0.25%
FOR EXTERNAL USE ONLY. NOT FOR OPHTHALMIC USE.
Keep this and all medication out of the reach of children.
Professional Sample Only
USUAL DOSAGE: Apply a thin film to affected skin area twice daily. Rub in gently. See insert for full prescribing information.
Store at controlled room temperature 15°-30°C (59°-86°F).
To Open: Use pointed end on cap to puncture seal.
For lot number and expiry date see crimp.
Mfd. by: Taro Pharmaceuticals Inc.
Brampton, Ontario, Canada L6T 1C1
Dist. by: TaroPharma a division of Taro Pharmaceuticals U.S.A., Inc., Hawthorne, NY 10532
PK-4365-0 0903-0
TaroPharma
APPROVED
TaroPharma
DEC 19 2003
39mm
32.5mm
Crimp Area
8mm
Electric Eye area
5 g Tube 2/15/01





8/4/95
1/2 OZ 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.

EACH GRAM CONTAINS: 2.5 mg desoximetasone in an ointment base consisting of white petrolatum and fractionated coconut oil.

USUAL DOSAGE: Apply a thin film to affected skin area twice daily. Rub in gently. See insert for full prescribing information.
Store at controlled room temperature 15°-30°C (59°-86°F).
For lot number and expiry date see flap of carton or crimp of tube.

APPROVED
DEC 19 2003

0.25%
OINTMENT

Topicort®

NDC 51672-5203-1 15 g

Rx only

Desoximetasone Ointment USP, 0.25%

FOR EXTERNAL USE ONLY. NOT FOR OPHTHALMIC USE.

Keep this and all medication out of the reach of children.

TaroPharma™

Mfd. by: Taro Pharmaceuticals Inc.
Brampton, Ontario, Canada L6T 1C1
Dist. by: **TaroPharma** a division of Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532

Topicort® is a registered trademark of Medicis Pharmaceutical Corporation used under license by Taro Pharmaceuticals U.S.A., Inc.

N 3 51672 52031 1

PK-4352-1
0903-1
M162

T 69

Topicort® 0.25% OINTMENT 15 g

0.25%
OINTMENT

Topicort®

NDC 51672-5203-1 15 g

Rx only

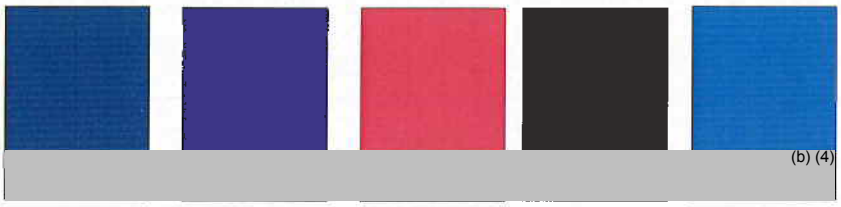
Desoximetasone Ointment USP, 0.25%

FOR EXTERNAL USE ONLY. NOT FOR OPHTHALMIC USE.

Keep this and all medication out of the reach of children.

TaroPharma™

(b) (4)



160mm
7.5mm
Pharmacode
135mm
2mm
CAP END
OPEN END
3mm
45 mm
89.7 mm
45 mm
45 mm
3mm
3mm
3mm

NDC 51672-5203-3 60 g

Topicort®

Rx only

APPROVED
DEC 19 2003

TaroPharma™

Desoximetasone Ointment USP, 0.25%

FOR EXTERNAL USE ONLY. NOT FOR OPHTHALMIC USE.

Keep this and all medication out of the reach of children.

EACH GRAM CONTAINS: 2.5 mg desoximetasone in an ointment base consisting of white petrolatum and fractionated coconut oil.

USUAL DOSAGE: Apply a thin film to affected skin area twice daily. Rub in gently. See insert for full prescribing information.

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

To Open: Use pointed end on cap to puncture seal.

For lot number and expiry date see crimp.

Mfd. by: Taro Pharmaceuticals Inc.
Brampton, Ontario, Canada L6T 1C1
Dist. by: **TaroPharma**
a division of Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532 PK-4355-1 0903-1

TaroPharma™

505

3 51672 52033 5

123mm
3mm
2mm
1mm
1mm
32mm
Crimp Area
2mm
8 mm
Electric eye area

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.

EACH GRAM CONTAINS: [illegible] g desoximetasone in an ointment base consisting of white petrolatum and fractionated coconut oil.

USUAL DOSAGE: Apply a thin film to affected skin area twice daily. Rub in gently. See insert for full prescribing information.
Store at controlled room temperature 15°-30°C (59°-86°F).
For lot number and expiry date see flap of carton or crimp of tube.

T 21

0.25%

OINTMENT

Topicort®

NDC 51672-5203-3 60 g

Rx only

Desoximetasone Ointment USP, 0.25%

FOR EXTERNAL USE ONLY. NOT FOR OPHTHALMIC USE.

Keep this and all medication out of the reach of children.

TaroPharma™

Mfd. by: Taro Pharmaceuticals Inc.
Brampton, Ontario, Canada L6T 1C1
Dist. by: **TaroPharma** a division of Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532

Topicort® is a registered trademark of Medicis Pharmaceutical Corporation used under license by Taro Pharmaceuticals U.S.A., Inc.

DEC 19 2008

APPROVED

N 3 51672 52033 5

PK-4354-1
0903-1
M105

Topicort®
0.25%
OINTMENT
60 g

0.25 %

OINTMENT

Topicort®

NDC 51672-5203-3 60 g

Rx only

Desoximetasone Ointment USP, 0.25%

FOR EXTERNAL USE ONLY. NOT FOR OPHTHALMIC USE.

Keep this and all medication out of the reach of children.

TaroPharma™

(b) (4)

FRONT

Topicort® (Desoximetasone)

PK-4360-1
171

For topical use only. Not for ophthalmic use.

Rx only

DESCRIPTION

Topicort® LP (desoximetasone) Cream 0.05%; Topicort® (desoximetasone) Cream 0.25%; Topicort® (desoximetasone) Gel 0.05%; and Topicort® (desoximetasone) Ointment 0.25% contain the active synthetic corticosteroid desoximetasone. The topical corticosteroids constitute a class of primarily synthetic steroids used as anti-inflammatory and antipruritic agents.

Each gram of TOPICORT LP Cream 0.05% contains 0.5 mg of desoximetasone in an emollient cream base consisting of white petrolatum, purified water, isopropyl myristate, lanolin alcohols, mineral oil, cetostearyl alcohol, and edetate disodium.

Each gram of TOPICORT Cream 0.25% contains 2.5 mg of desoximetasone in an emollient cream base consisting of white petrolatum, purified water, isopropyl myristate, lanolin alcohols, mineral oil, and cetostearyl alcohol.

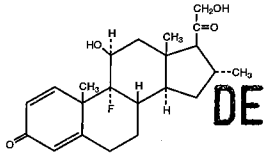
Each gram of TOPICORT Gel 0.05% contains 0.5 mg of desoximetasone in a gel base consisting of purified water, docusate sodium, edetate disodium, isopropyl myristate, carbomer 940, trolamine, and SDAG-1B 95% alcohol.

Each gram of TOPICORT Ointment 0.25% contains 2.5 mg of desoximetasone in an ointment base consisting of white petrolatum and fractionated coconut oil.

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 structural formula is:



DEC 19 2003

CLINICAL PHARMACOLOGY

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

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

Pharmacokinetics

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

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

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.

Pharmacokinetic studies in men with Topicort® (desoximetasone) Cream 0.25% with tagged desoximetasone showed a total of 5.2% ± 2.9% excretion in urine (4.1% ± 2.3%) and feces (1.1% ± 0.6%) and no detectable level (limit of sensitivity: 0.005 μg/mL) in the blood when it was applied topically on the back followed by occlusion for 24 hours. Seven days after application, no further radioactivity was detected in urine or feces. The half-life of the material was 15 ± 2 hours (for urine) and 17 ± 2 hours (for feces) between the third and fifth trial day.

Pharmacokinetic studies in men with Topicort® (desoximetasone) Ointment 0.25% with tagged desoximetasone showed no detectable level (limit of sensitivity: 0.003 μg/mL) in 1 subject and 0.004 and 0.006 μg/mL in the remaining 2 subjects in the blood when it was applied topically on the back followed by occlusion for 24 hours. The extent of absorption for the ointment was 7% based on radioactivity recovered from urine and feces. Seven days after application, no further radioactivity was detected in urine or feces. 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

Topicort® LP (desoximetasone) Cream 0.05%; Topicort® (desoximetasone) Cream 0.25%; Topicort® (desoximetasone) Gel 0.05%; and Topicort® (desoximetasone) Ointment 0.25% are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS

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

WARNINGS

Topicort® LP (desoximetasone) Cream 0.05%; Topicort® (desoximetasone) Cream 0.25%; Topicort® (desoximetasone) Gel 0.05%; and Topicort® (desoximetasone) Ointment 0.25% are not for ophthalmic use.

Keep out of reach of children.

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 an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute 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.

Pediatric patients 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 dressings.
5. Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressings.

Laboratory Tests

The following tests may be helpful in evaluating the hypothalamic-pituitary-adrenal (HPA) axis suppression:

Urinary free cortisol test
ACTH stimulation test

Carcinogenesis, Mutagenesis, and Impairment of Fertility

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

Studies to determine mutagenicity with prednisolone and hydrocortisone have revealed negative results. Desoximetasone did not show potential for mutagenic activity *in vitro* in the Ames microbial mutagen test with or without metabolic activation.

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 3 to 30 times the human dose of Topicort® (desoximetasone) Cream 0.25% or Topicort® (desoximetasone) Ointment 0.25% and 15 to 150 times the human dose of Topicort® LP (desoximetasone) Cream 0.05% or Topicort® (desoximetasone) Gel 0.05%. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. Therefore, TOPICORT LP Cream 0.05%, TOPICORT Cream 0.25%, TOPICORT Gel 0.05%, and TOPICORT Ointment 0.25% 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.

HPA axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in pediatric patients receiving topical corticosteroids. Manifestations of adrenal suppression in pediatric patients 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 pediatric patients should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of pediatric patients. Safety and effectiveness of TOPICORT Ointment in pediatric patients below the age of 10 have not been established.

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

In controlled clinical studies the incidence of adverse reactions was low (0.8%) for Topicort® (desoximetasone) Cream 0.25% and included burning, folliculitis, and folliculo-pustular lesions. The incidence of adverse reactions was also 0.8% for Topicort® LP (desoximetasone) Cream 0.05% and included pruritus, erythema, vesiculation, and burning sensation. The incidence of adverse reactions was low (0.3%) for Topicort® (desoximetasone) Ointment 0.25% and consisted of development of comedones at the site of application.

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

Apply a thin film of Topicort® LP (desoximetasone) Cream 0.05%, Topicort® (desoximetasone) Cream 0.25%, Topicort® (desoximetasone) Gel 0.05%, and Topicort® (desoximetasone) Ointment 0.25% to the affected skin areas twice daily. Rub in gently.

HOW SUPPLIED

Topicort® LP (desoximetasone) Cream 0.05% is supplied in 5 gram tubes for physician samples, 15 gram and 60 gram tubes.

Topicort® (desoximetasone) Cream 0.25% is supplied in 5 gram tubes for physician samples, 15 gram and 60 gram tubes.

Topicort® (desoximetasone) Gel 0.05% is supplied in 5 gram tubes for physician samples, 15 gram and 60 gram tubes.

Topicort® (desoximetasone) Ointment 0.25% is supplied in 5 gram tubes for physician samples, 15 gram and 60 gram tubes.

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

Mfd. by: Taro Pharmaceuticals Inc., Brampton, Ontario, Canada L6T 1C1
Dist. by: **TaroPharma** a division of Taro Pharmaceuticals U.S.A., Inc., Hawthorne, NY 10532

Revised: September, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 074286/S-006

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Taro Pharmaceuticals U.S.A., Inc.

17 June, 2003

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 NO. 74-286 REF. NO. SL-006
NDA SUPPL FOR Labeling Rev-AT

FPL

RE: ANDA #74-286
Desoximetasone Ointment USP, 0.25%
Changes Being Effected Supplement – Use of Topicort® as the Trade Mark Name

Dear Sir/Madam,

Reference is made to the above-referenced Abbreviated New Drug Application for **Desoximetasone Ointment USP, 0.25%** approved on June 7, 1996. Taro Pharmaceuticals Inc. wishes to supplement this application to use Topicort® as the Trade Mark Name when marketing the above referenced product.

Taro Pharmaceuticals Inc., has received licensing permission from Medicis Pharmaceutical Corporation located at 8125 North Hayden Road, Scottsdale, AZ 85258-2463, to use the Topicort® trade mark to market its desoximetasone products in the United States. Please note that Topicort® trade name was already approved for Medicis Desoximetasone products (NDA # 018763, 018586, 018309, 017856). A copy of the letter granting this permission from Medicis Pharmaceuticals Corp is herewith enclosed. We are also enclosing the final printed labeling containing the trade name of Topicort® for both container closure and the carton. The package insert with appropriate changes is also herewith enclosed.

Sincerely,

6/17/03

Kalpana Rao (U.S.Agent)
Vice president, Regulatory Affairs

RECEIVED
JUN 18 2003
OGD / CDER

August 22, 2003

Taro Pharmaceuticals U.S.A., Inc.

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

Re: **ANDA #74-286**
Desoximetasone Ointment USP, 0.25% SUPPLEMENT AMENDMENT
CBE-Labeling Amendment SL006/AL

Dear Sir/Madam:

Reference is made to Taro Pharmaceuticals Inc.'s (Taro) Abbreviated New Drug Application (ANDA), approved on June 7, 1996, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Desoximetasone Ointment USP, 0.25%. Reference is also made to our CBE Supplement dated June 17, 2003 in which we requested the use of the tradename "Topicort" and to the telephone call from Ms. Beverly Weitzman of the Agency in which she indicated the following:

The labeling for your 5 gm physician sample tube in unacceptable as the name "Topicort" is mis-spelled.

Response
Attached please find 12 Final Printed Labels of the 5 gm physician sample tube in which the spelling of Topicort has been corrected from the previously submitted ((b) (4)).

This concludes our response to the Agency's telephone call of August 21, 2003. Please feel free to contact the undersigned should you have any questions.

Sincerely,

8/22/03

Kalpana Rao (U.S. Agent)
Vice President, Regulatory Affairs

RECEIVED
AUG 2 5 2003
OGD/CDER

September 17, 2003

Taro Pharmaceuticals U.S.A., Inc.

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

SUPPLEMENT AMENDMENT
5/2006/AL

Re: **ANDA #74-286**
Desoximetasone Ointment USP, 0.25%
Telephone Amendment to CBE Supplement

Dear Sir/Madam:

Reference is made to Taro Pharmaceuticals Inc.'s (Taro) Abbreviated New Drug Application (ANDA), approved on June 7, 1996, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Desoximetasone Ointment USP, 0.25%. In addition, reference is made to our CBE Supplement dated June 17, 2003 in which we requested the use of the tradename "Topicort" and to the telephone calls from Ms. Beverly Weitzman on September 11 and 12, 2003 in which she indicated and requested:

Comment
Please provide Final Printed labeling for all package sizes. In addition, the package insert provided in the supplement is incorrect as it refers to a different drug product on the back side. As such, your CBE supplement is denied. Please correct your package insert and provide in final print.

Response
We have corrected the package insert and we apologize for the error. We have included in this amendment:

- **12 - Final Printed 5 g physician sample tubes**
- **12 - Final Printed 15 g Tubes and Cartons**
- **12 - Final Printed 60 g Tubes and Cartons**
- **12 - Final Printed Package Inserts**

Comment
Please provide a side-by-side labeling comparison with your proposed labels and your previously approved labels.

Response
Please find, in Attachment 1, a photocopy of each of our previously approved labeling components. In addition, we have provided in Attachment 2, a side-by-side comparison of our package insert and all labeling components with our previously approved package insert and labeling components with all differences annotated and explained.

This concludes our response to the Agency's calls of September 11 and 12, 2003. Please feel free to contact the undersigned should you have any questions.

Sincerely,

9/17/03

Kalpana Rao (U.S. Agent)
Vice President, Regulatory Affairs