CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75633

APPROVAL LETTER

ANDA 75-633

MAY 17 2000

Taro Pharmaceuticals U.S.A., Inc.
Attention: Lorraine Sachs
5 Skyline Drive
Hawthorne, NY 10532

Dear Madam:

This is in reference to your abbreviated new drug application dated May 7, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Clobetasol Propionate Cream USP, 0.05% (Emollient).

Reference is also made to your amendments dated December 15, 1999; and May 10, 2000.

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 Clobetasol Propionate Cream USP, 0.05%, (Emollient) to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Temovate E® Cream, 0.05%, of Glaxo Wellcome, Inc).

Under section 506A of the Act, 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 that 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/

Gary Buehler 5/17/00
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75633

DRAFT FINAL PRINTED LABELING

PK 3030-0
XX

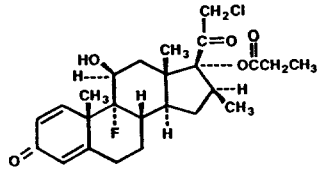
Clobetasol Propionate Cream (Emollient) USP, 0.05%

Rx only

FOR TOPICAL DERMATOLOGIC USE ONLY - NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE

DESCRIPTION

Clobetasol propionate cream (emollient) contains the active compound clobetasol propionate, a synthetic corticosteroid, for topical dermatologic use. Clobetasol, an analog of prednisolone, has a high degree of glucocorticoid activity and a slight degree of mineralocorticoid activity.
Chemically, clobetasol propionate is (11β,16β)-21-chloro-9-fluoro-11-hydroxy-16-methyl -17- (1-oxopropoxy)-pregna-1,4-diene-3,20-dione.
Clobetasol propionate has the molecular formula $C_{25}H_{32}ClFO_5$ and a molecular weight of 466.98. It is a white to cream-colored crystalline powder insoluble in water.
Clobetasol propionate cream (emollient) contains clobetasol propionate 0.5 mg/g in an emollient base of cetomacrogol 1000, cetostearyl alcohol, citric acid, dimethicone 350, imidurea, isopropyl myristate, propylene glycol, purified water, and sodium citrate.



CLINICAL PHARMACOLOGY

Like other topical corticosteroids, clobetasol propionate has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2.
Pharmacokinetics: The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle and the integrity of the epidermal barrier. Occlusive dressing with hydrocortisone for up to 24 hours has not been demonstrated to increase penetration; however, occlusion of hydrocortisone for 96 hours markedly enhances penetration. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin may increase percutaneous absorption.
Studies performed with clobetasol propionate cream (emollient) indicate that it is in the super-high range of potency as compared with other topical corticosteroids.

INDICATIONS AND USAGE

Clobetasol propionate cream (emollient) is a super-high potency corticosteroid formulation indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Treatment beyond 2 consecutive weeks is not recommended, and the total dosage should not exceed 50 g/week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. Use in children under 12 years of age is not recommended.
In the treatment of moderate to severe plaque-type psoriasis, clobetasol propionate cream (emollient) applied to 5% to 10% of body surface area can be used up to 4 consecutive weeks. The total dosage should not exceed 50 g/week. When dosing for more than 2 weeks, any additional benefits of extending treatment should be weighed against the risk of HPA suppression. Treatment beyond 4 consecutive weeks is not recommended. Patients should be instructed to use clobetasol propionate cream (emollient) for the minimum amount of time necessary to achieve the desired results (see PRECAUTIONS and INDICATIONS AND USAGE). Use in pediatric patients under 16 years of age has not been studied.

CONTRAINDICATIONS

Clobetasol propionate cream (emollient) is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

PRECAUTIONS

General: Clobetasol propionate is a highly potent topical corticosteroid that has been shown to suppress the HPA axis at doses as low as 2 g/day.
Systemic absorption of topical corticosteroids can produce reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal from treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on therapy.
Patients applying a dose to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA axis suppression. This may be done by using the ACTH stimulation, A.M. plasma cortisol, and urinary free cortisol tests. Patients receiving super-potent corticosteroids should not be treated for more than 2 weeks at a time, and only small areas should be treated at any one time due to the increased risk of HPA suppression.
In a controlled clinical trial involving patients with moderate to severe plaque-type psoriasis, clobetasol propionate cream (emollient) applied to 5% to 10% of body surface area resulted in additional benefits in the treatment of patients for 4 consecutive weeks. In this trial, there were no clobetasol-treated patients with clinically significant decreases in morning cortisol levels after 4 weeks of treatment; however, morning cortisol levels may not identify patients with adrenal dysfunction. Therefore, the additional benefits of extending treatment beyond 2 weeks should be weighed against the potential for HPA suppression. Therapy should be discontinued when control has been achieved. Treatment beyond 4 consecutive weeks is not recommended.
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 corticosteroid. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur that require supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products.
Pediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios (see PRECAUTIONS: Pediatric Use). The use of clobetasol propionate cream (emollient) for 4 consecutive weeks has not been studied in pediatric patients under 16 years of age.
If irritation develops, clobetasol propionate cream (emollient) should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing a *failure to heal* rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.
If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of clobetasol propionate cream (emollient) should be discontinued until the infection has been adequately controlled.
Clobetasol propionate cream (emollient) should not be used in the treatment of rosacea or

perioral dermatitis, and should not be used on the face, groin, or axillae.

Information for Patients: 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. This medication should not be used for any disorder other than that for which it was prescribed.
3. The treated skin area should not be bandaged, otherwise covered, or wrapped so as to be occlusive unless directed by the physician.
4. Patients should report any signs of local adverse reactions to the physician.
5. Patients should inform their physicians that they are using clobetasol propionate cream (emollient) if surgery is contemplated.
6. This medication should not be used on the face, underarms, or groin areas.
7. As with another corticosteroids, therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, contact the physician.

Laboratory Tests: The following tests may be helpful in evaluating patients for HPA axis suppression:
ACTH stimulation test
A.M. plasma cortisol test
Urinary free cortisol test

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential of clobetasol propionate.
Studies in the rat following oral administration at dosage levels up to 50 mg/kg per day revealed no significant effect on the males. The females exhibited an increase in the number of resorbed embryos and a decrease in the number of living fetuses at the highest dose.
Clobetasol propionate was nonmutagenic in three different test systems: the Ames test, the *Saccharomyces cerevisiae* gene conversion assay, and the *E. coli* B WP2 fluctuation test.

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application to laboratory animals.
Clobetasol propionate has not been tested for teratogenicity by this route; however, it is absorbed percutaneously, and when administered subcutaneously it was a significant teratogen in both the rabbit and mouse. Clobetasol propionate has greater teratogenic potential than steroids that are less potent.
Teratogenicity studies in mice using the subcutaneous route resulted in fetotoxicity at the highest dose tested (1 mg/kg) and teratogenicity at all dose levels tested down to 0.03 mg/kg. These doses are approximately 0.33 and 0.01 times, respectively, the human topical dose of clobetasol propionate cream (emollient). Abnormalities seen included cleft palate and skeletal abnormalities.
In rabbits, clobetasol propionate was teratogenic at doses of 3 and 10 mcg/kg. These doses are approximately 0.001 and 0.003 times, respectively, the human topical dose of clobetasol propionate cream (emollient). Abnormalities seen included cleft palate, cranioschisis, and other skeletal abnormalities.
There are no adequate and well-controlled studies of the teratogenic potential of clobetasol propionate in pregnant women. Clobetasol propionate cream (emollient) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when clobetasol propionate cream (emollient) is administered to nursing woman.

Pediatric Use: Safety and effectiveness of clobetasol propionate cream (emollient) in pediatric patients have not been established, and its use in pediatric patients under 12 years of age is not recommended. For continued use beyond 2 consecutive weeks, the safety of clobetasol propionate cream (emollient) has not been studied. Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of glucocorticosteroid insufficiency during or after withdrawal of treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in infants and children.
HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

ADVERSE REACTIONS

In controlled trials with all clobetasol propionate formulations, the following adverse reactions have been reported: burning/stinging, pruritus, irritation, erythema, folliculitis, cracking and fissuring of the skin, numbness of the fingers, tenderness in the elbow, skin atrophy, and telangiectasia. The incidence of local adverse reactions reported in the trials with clobetasol propionate cream (emollient) was <2% of patients treated with the exception of burning/stinging, which occurred in 5% of treated patients.
Cushing's syndrome has been reported in infants and adults as a result of prolonged use of topical clobetasol propionate formulations.
The following additional local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with super-high potency corticosteroids such as clobetasol propionate cream (emollient). These reactions are listed in an approximately decreasing order of occurrence: dryness, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, striae, and miliaria.

OVERDOSAGE

Topically applied clobetasol propionate cream (emollient) can be absorbed in sufficient amounts to produce systemic effects.

DOSAGE AND ADMINISTRATION

Apply a thin layer of clobetasol propionate cream (emollient) to the affected skin areas twice daily and rub in gently and completely (see INDICATIONS AND USAGE).
Clobetasol propionate cream (emollient) is a super-high potency topical corticosteroid; therefore, **treatment should be limited to 2 consecutive weeks and amounts greater than 50 g/week should not be used.** Use in children under 12 years of age is not recommended.
In moderate to severe plaque-type psoriasis, clobetasol propionate cream (emollient) applied to 5% to 10% of body surface area can be used up to 4 weeks. The total dosage should not exceed 50 g/week. When dosing for more than 2 weeks, any additional benefits of extending treatment should be weighed against the risk of HPA suppression. Therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary. Treatment beyond 4 consecutive weeks is not recommended. Use in pediatric patients under 16 years of age has not been studied.
Clobetasol propionate cream (emollient) should not be used with occlusive dressings.

HOW SUPPLIED

Clobetasol propionate cream (emollient) USP, 0.05% is supplied in 15-g, 30-g, 45-g and 60-g tubes.
Store between 15° and 30°C (59° and 86°F). Clobetasol propionate cream (emollient) should not be refrigerated.

Mfd. by: Taro Pharmaceuticals Inc., Bramalea, Ontario, Canada L6T 1C3
Issued: Dec. 1999

Each gram contains: Clobetasol propionate 0.5 mg in an emollient base composed of cetomacrogol 1000, cetostearyl alcohol, citric acid, dimethicone 350, imidurea, isopropyl myristate, propylene glycol, purified water, and sodium citrate.
Usual Dosage: Apply a thin layer of clobetasol propionate cream (emollient) to the affected skin areas twice daily and rub in gently and completely.
See package insert for full prescribing information.
Store between 15° and 30°C (59° and 86°F). Do not refrigerate.
Important: Do not use if seal has been punctured or is not visible.
To Open: Use cap to puncture seal.

60 g

NDC 51672-1297-3

Clobetasol Propionate Cream (Emollient) USP, 0.05%

For dermatologic use only - Not for ophthalmic use.

Rx only

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.

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60 g

NDC 51672-1297-3

Clobetasol Propionate Cream (Emollient) USP, 0.05%

For dermatologic use only - Not for ophthalmic use.

Rx only

60 g
Clobetasol Propionate Cream (Emollient) USP, 0.05%

TARO

TARO

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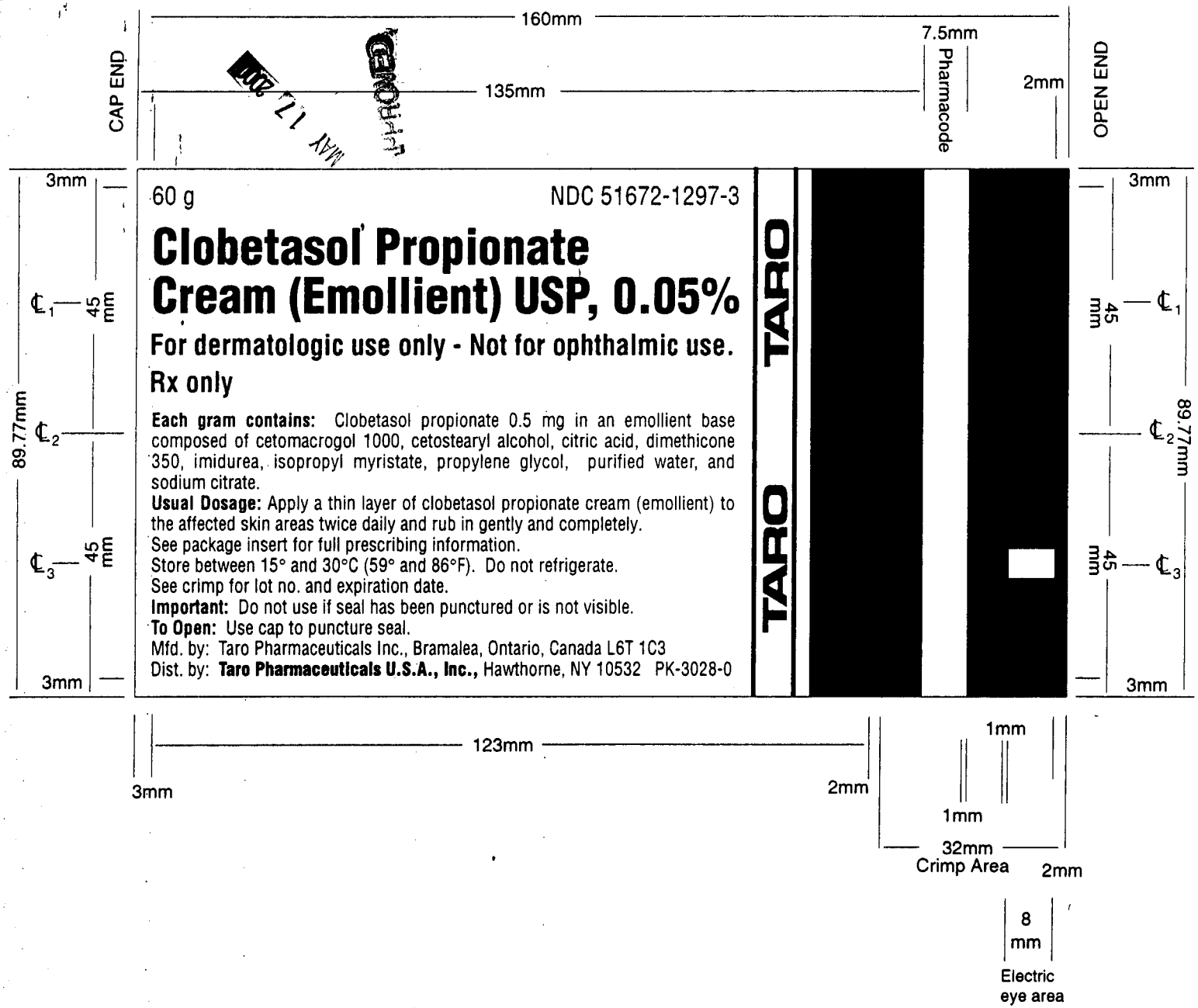
PMS 200

PK-3029-0

185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60 g
NDC 51672-1297-3
Clobetasol Propionate Cream (Emollient) USP, 0.05%
For dermatologic use only - Not for ophthalmic use.
Rx only
Each gram contains: Clobetasol propionate 0.5 mg in an emollient base composed of cetomacrogol 1000, cetostearyl alcohol, citric acid, dimethicone 350, imidurea, isopropyl myristate, propylene glycol, purified water, and sodium citrate.
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See crimp for lot no. and expiration date.
Important: Do not use if seal has been punctured or is not visible.
To Open: Use cap to puncture seal.
Mfd. by: Taro Pharmaceuticals Inc., Bramalea, Ontario, Canada L6T 1C3
Dist. by: Taro Pharmaceuticals U.S.A., Inc., Hawthorne, NY 10532 PK-3028-0
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Crimp Area
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8 mm
Electric eye area

173

Margo

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PMS 200

Each gram contains: Clobetasol propionate 0.5 mg in an emollient base composed of cetomacrogol 1000, cetostearyl alcohol, citric acid, dimethicone 350, imidurea, isopropyl myristate, propylene glycol, purified water, and sodium citrate.
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Important: Do not use if seal has been punctured or is not visible.
To Open: Use cap to puncture seal.

45 g

NDC 51672-1297-6

Clobetasol Propionate Cream (Emollient) USP, 0.05%

For dermatologic use only - Not for ophthalmic use.

Rx only

Mfd. by: Taro Pharmaceuticals Inc.
Bramalea, Ontario, Canada L6T 1C3
Dist. by: **Taro Pharmaceuticals U.S.A., Inc.**, Hawthorne, NY 10532

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N 3 51672 12976 7

TARO

PK-3027-0

45 g

NDC 51672-1297-6

Clobetasol Propionate Cream (Emollient) USP, 0.05%

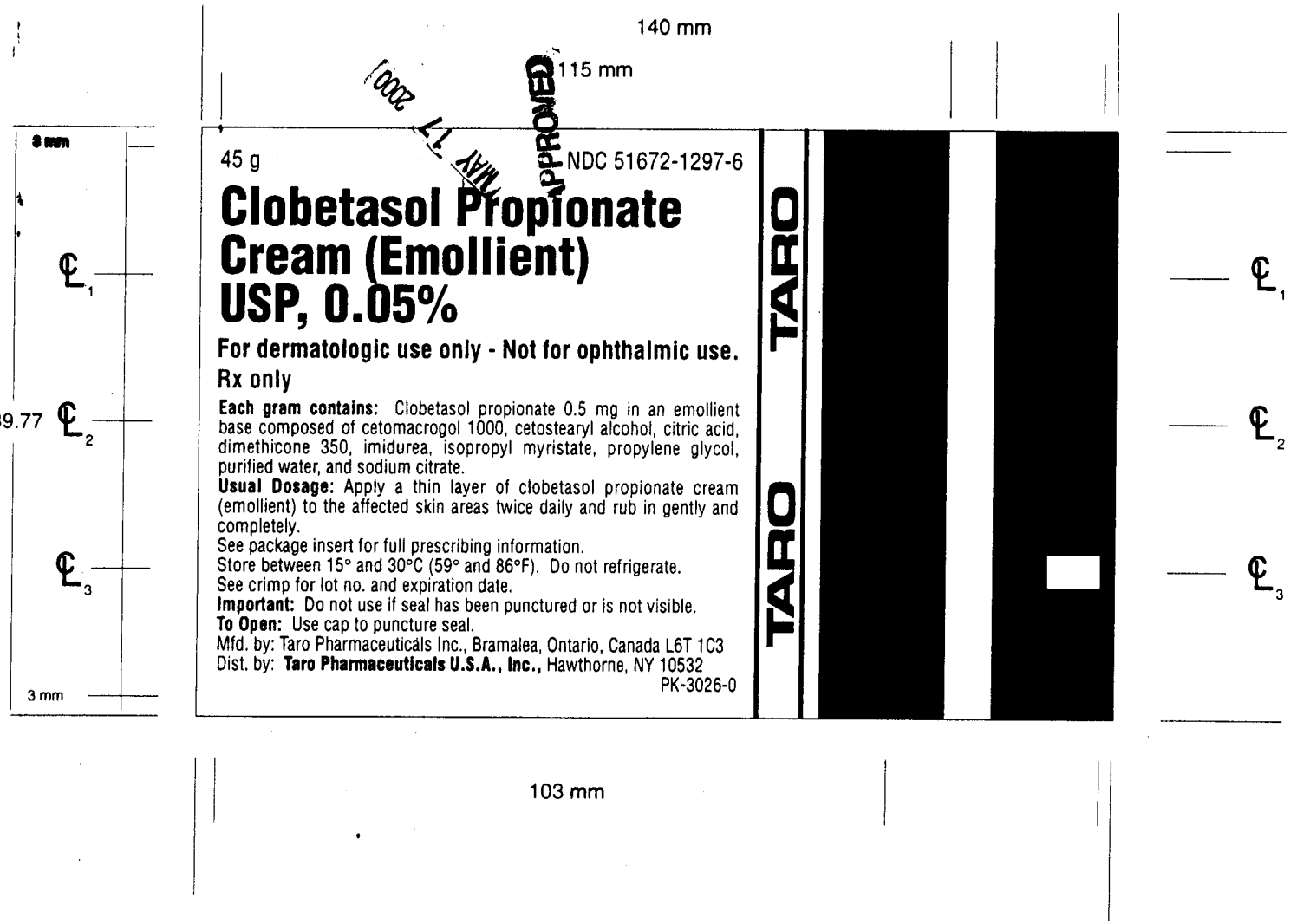
For dermatologic use only - Not for ophthalmic use.

Rx only

45 g
Clobetasol Propionate Cream (Emollient) USP, 0.05%

TARO

161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3 mm
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NDC 51672-1297-6
Clobetasol Propionate Cream (Emollient) USP, 0.05%
For dermatologic use only - Not for ophthalmic use.
Rx only
Each gram contains: Clobetasol propionate 0.5 mg in an emollient base composed of cetomacrogol 1000, cetostearyl alcohol, citric acid, dimethicone 350, imidurea, isopropyl myristate, propylene glycol, purified water, and sodium citrate.
Usual Dosage: Apply a thin layer of clobetasol propionate cream (emollient) to the affected skin areas twice daily and rub in gently and completely.
See package insert for full prescribing information.
Store between 15° and 30°C (59° and 86°F). Do not refrigerate.
See crimp for lot no. and expiration date.
Important: Do not use if seal has been punctured or is not visible.
To Open: Use cap to puncture seal.
Mfd. by: Taro Pharmaceuticals Inc., Bramalea, Ontario, Canada L6T 1C3
Dist. by: Taro Pharmaceuticals U.S.A., Inc., Hawthorne, NY 10532
PK-3026-0
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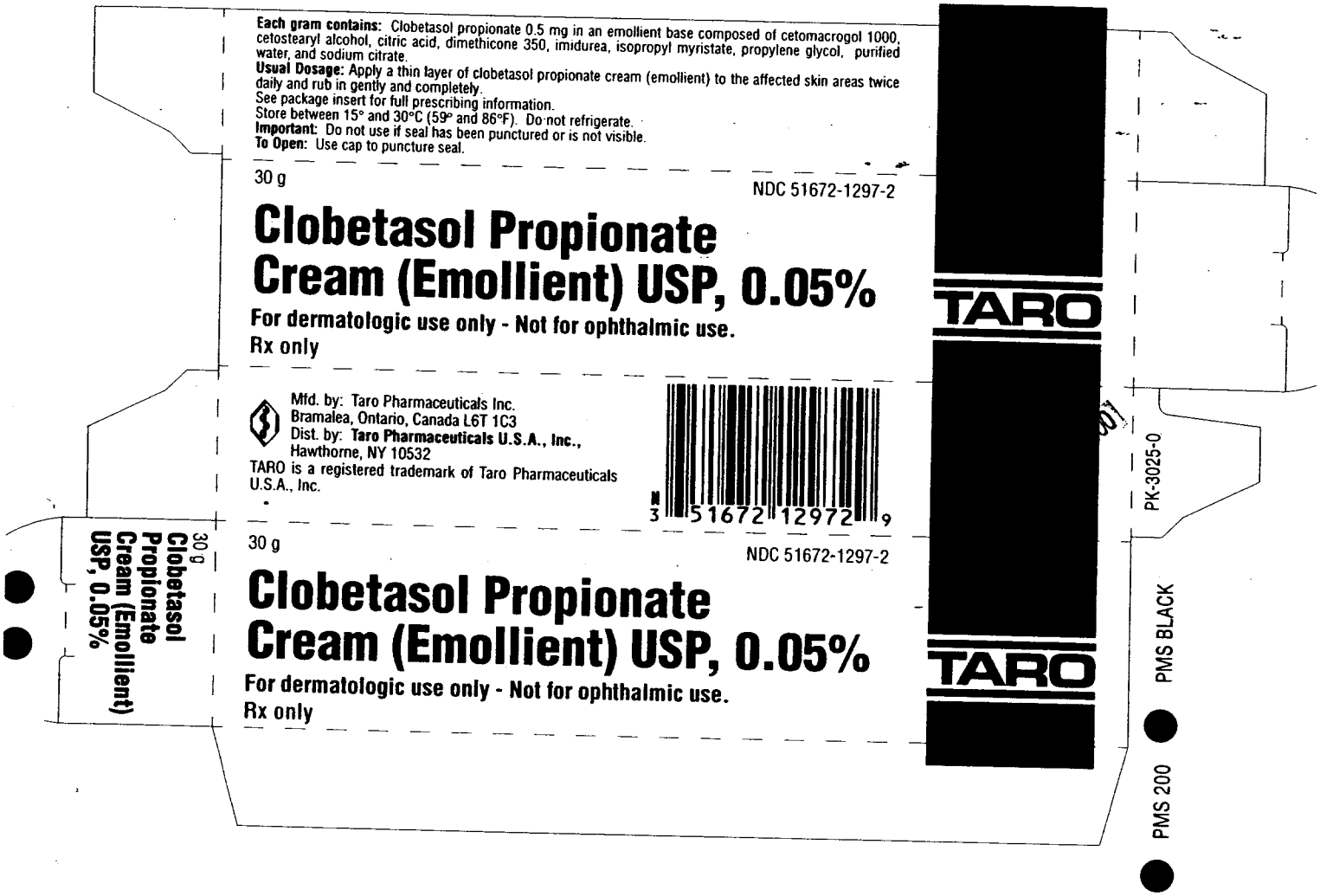
Mago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Store between 15° and 30°C (59° and 86°F). Do not refrigerate.
Important: Do not use if seal has been punctured or is not visible.
To Open: Use cap to puncture seal.
30 g
NDC 51672-1297-2
Clobetasol Propionate Cream (Emollient) USP, 0.05%
For dermatologic use only - Not for ophthalmic use.
Rx only
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.
3 51672 12972 9
TARO
30 g
Clobetasol Propionate Cream (Emollient) USP, 0.05%
30 g
NDC 51672-1297-2
Clobetasol Propionate Cream (Emollient) USP, 0.05%
For dermatologic use only - Not for ophthalmic use.
Rx only
TARO
PK-3025-0
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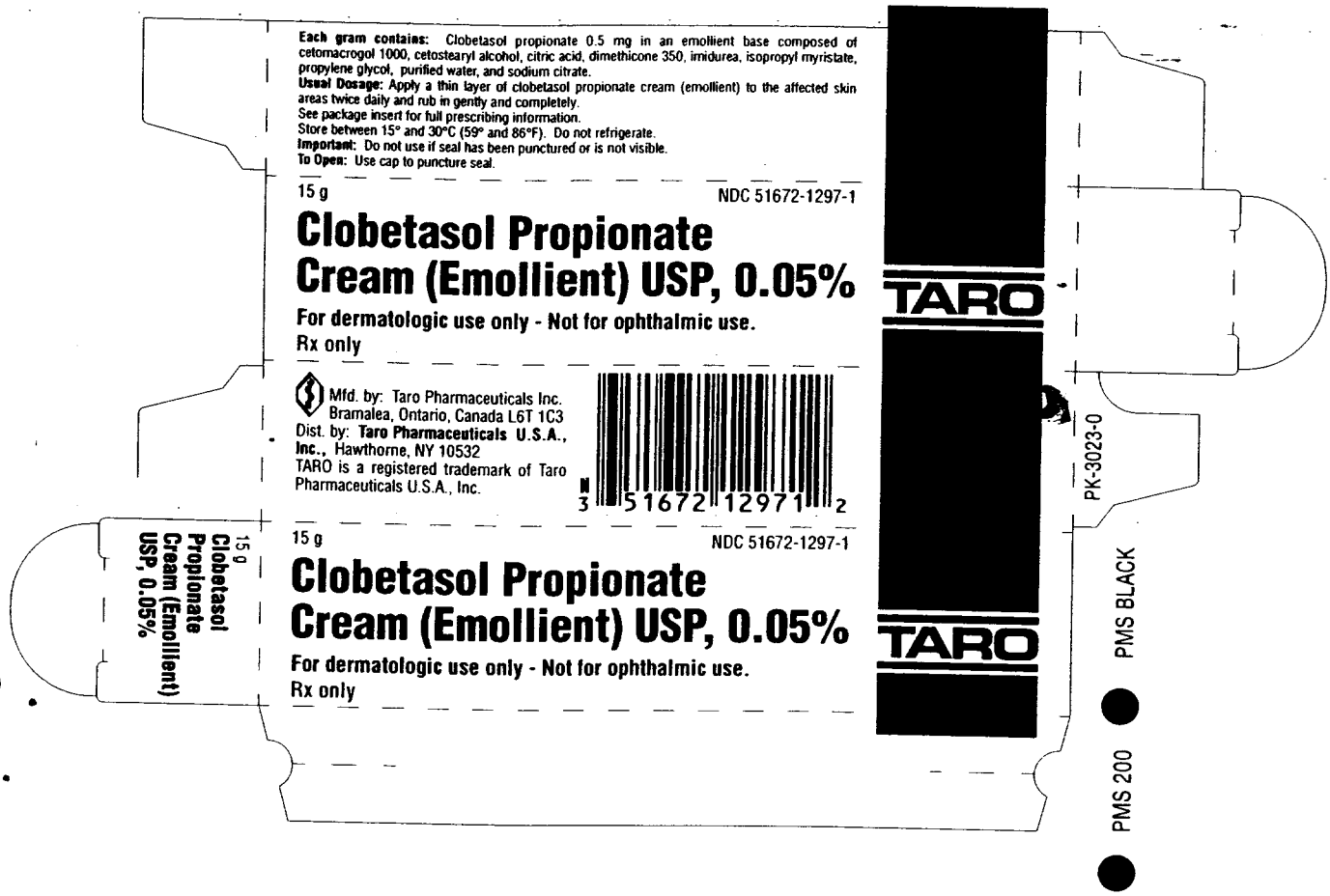
Each gram contains: Clobetasol propionate 0.5 mg in an emollient base composed of cetomacrogol 1000, cetostearyl alcohol, citric acid, dimethicone 350, imidurea, isopropyl myristate, propylene glycol, purified water, and sodium citrate.
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Important: Do not use if seal has been punctured or is not visible.
To Open: Use cap to puncture seal.
15 g
NDC 51672-1297-1
Clobetasol Propionate Cream (Emollient) USP, 0.05%
For dermatologic use only - Not for ophthalmic use.
Rx only
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.
3 51672 12971 2
15 g
NDC 51672-1297-1
Clobetasol Propionate Cream (Emollient) USP, 0.05%
For dermatologic use only - Not for ophthalmic use.
Rx only
TARO
TARO
15 g
Clobetasol Propionate Cream (Emollient) USP, 0.05%
PK-3023-0
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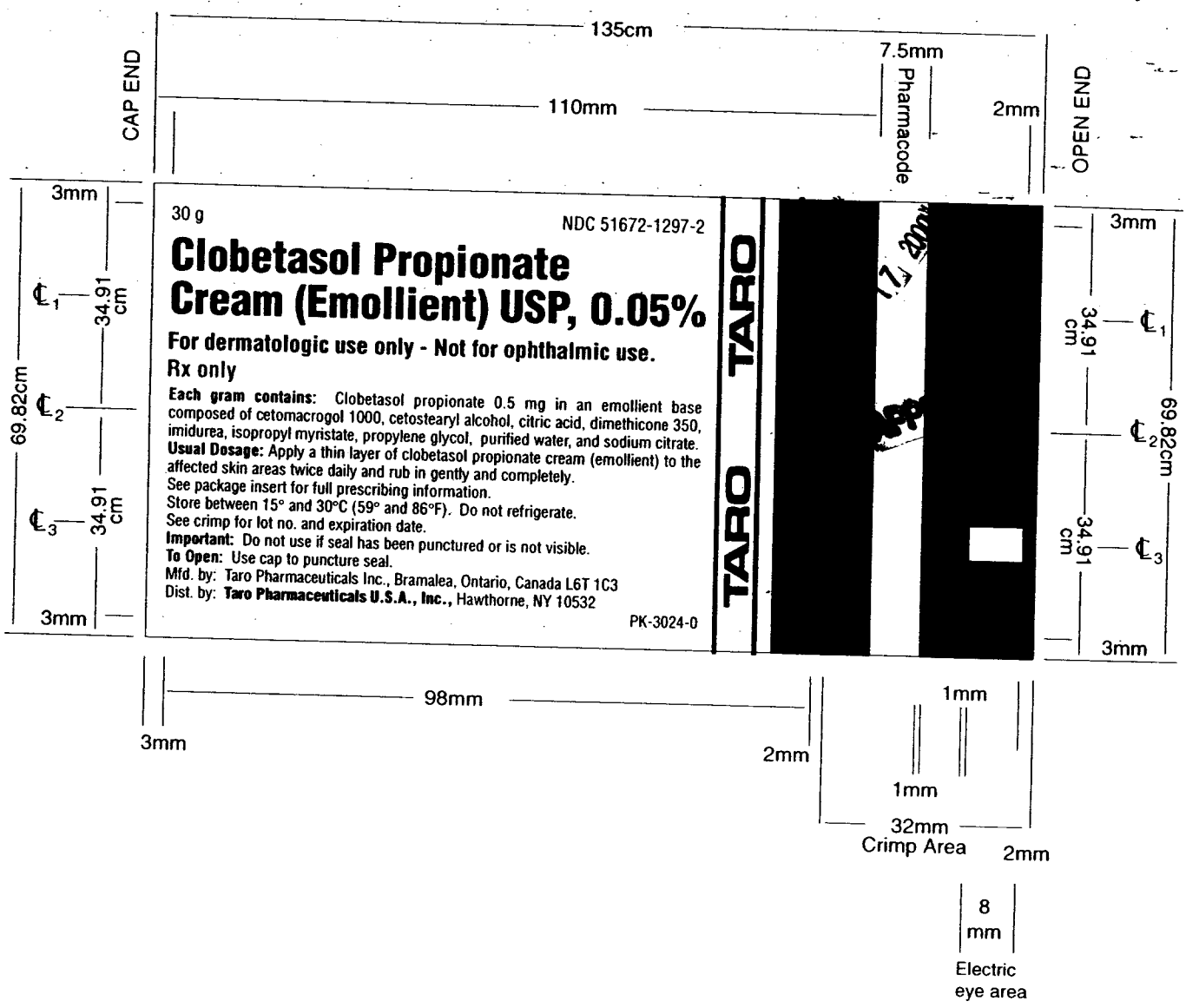
Margo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Pharmacode
2mm
OPEN END
3mm
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34.91 cm
34.91 cm
3mm
30 g
NDC 51672-1297-2
Clobetasol Propionate Cream (Emollient) USP, 0.05%
For dermatologic use only - Not for ophthalmic use.
Rx only
Each gram contains: Clobetasol propionate 0.5 mg in an emollient base composed of cetomacrogol 1000, cetostearyl alcohol, citric acid, dimethicone 350, imidurea, isopropyl myristate, propylene glycol, purified water, and sodium citrate.
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See crimp for lot no. and expiration date.
Important: Do not use if seal has been punctured or is not visible.
To Open: Use cap to puncture seal.
Mfd. by: Taro Pharmaceuticals Inc., Bramalea, Ontario, Canada L6T 1C3
Dist. by: Taro Pharmaceuticals U.S.A., Inc., Hawthorne, NY 10532
PK-3024-0
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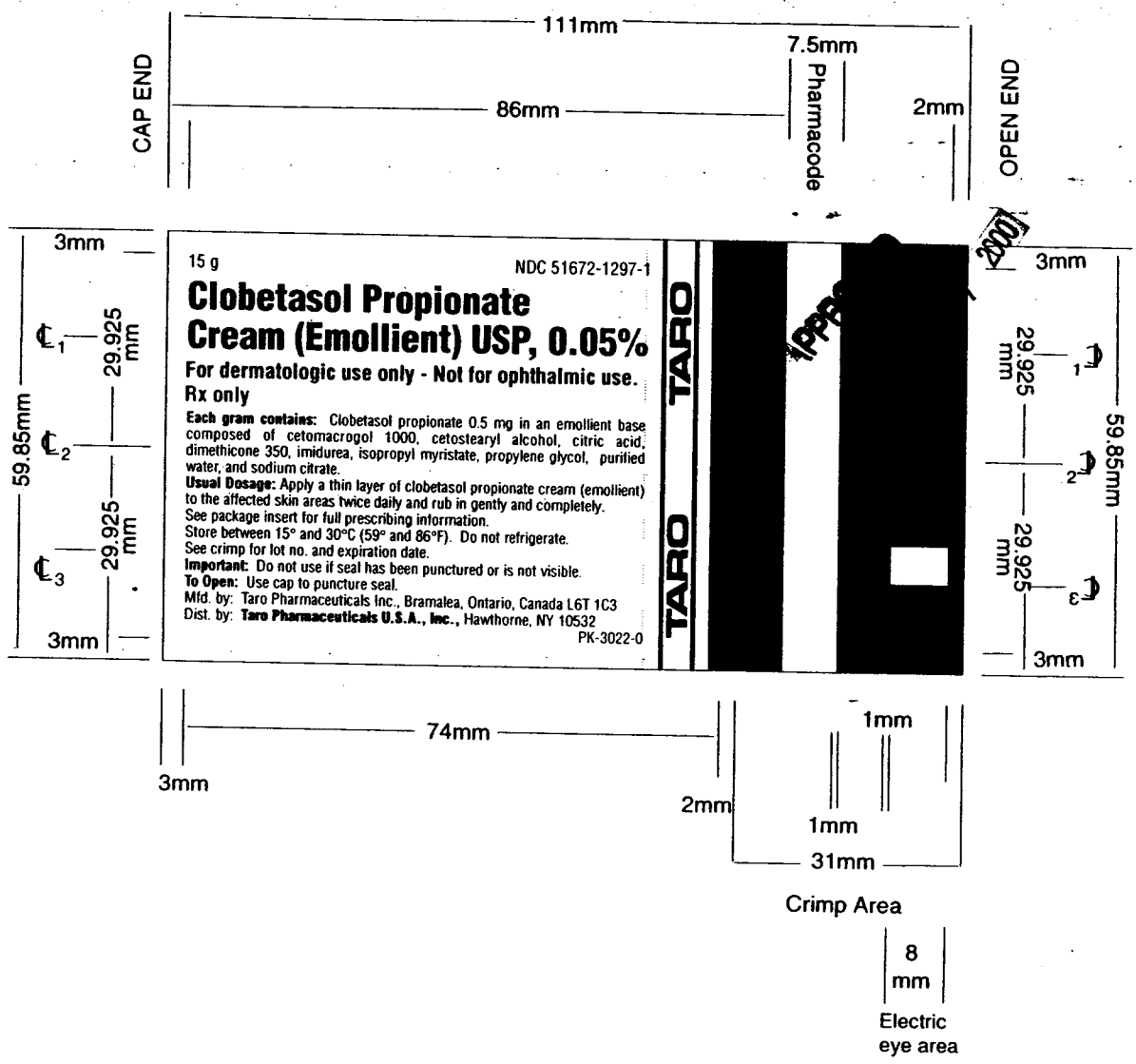
Crimp Area
2mm
8 mm
Electric eye area

Margo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15 g
NDC 51672-1297-1
Clobetasol Propionate Cream (Emollient) USP, 0.05%
For dermatologic use only - Not for ophthalmic use.
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To Open: Use cap to puncture seal.
Mfd. by: Taro Pharmaceuticals Inc., Bramalea, Ontario, Canada L6T 1C3
Dist. by: Taro Pharmaceuticals U.S.A., Inc., Hawthorne, NY 10532
PK-3022-0
TARO
TARO
3mm
29.925 mm
29.925 mm
59.85mm
3mm
74mm
3mm
2mm
1mm
1mm
31mm
Crimp Area
8 mm
Electric eye area

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75633

BIOEQUIVALENCY REVIEW(S)

1.1

Clobetasol propionate
Emollient Cream USP, 0.05%
ANDA #75-633
Reviewer: Sikta Pradhan
File #75633S2.599

Taro Pharmaceuticals Inc.
Bramalea, Ontario
Submission Dates:
May 7, 1999

Review of a pilot dose response study and a pharmacodynamic bioequivalence study

BACKGROUND

Clobetasol propionate 0.05% emollient cream (Temovate E^R 0.05%, Glaxo) is a high potency corticosteroid (potency I) indicated for the releif of inflammatory and puritic manifestations of corticosteroid-repsonsive dermatoses. The reference product is indicated for topical dermatologic use only.

This application contains two in vivo vasoconstrictor studies; a pilot dose response study and a pivotal bioequivalence study based on the June 2, 1995 guidance. This guidance was issued by the Office of Generic Drugs (OGD) for documentation of in vivo bioequivalence of topical dermatological corticosteroids, and it recommended the use of dose duration method to study pharmacodynamic effects of topical corticosteroids. The pharmacodynamic effect is manifested as blanching of treated skin. In this method, vasoconstrictor (skin blanching) responses of increasing durations of treatment with the test formulation are measured as a function of time after treatment administration. Because different dose durations represent different times for skin exposure to the test product, it has been assumed that increasing dose durations would results in correspondingly increasing amount of the drug available to penetrate the skin.

OGD guidance is based on recommendations of the September 12-13, 1994, Generic Drugs Advisory Committee meeting with representation of Dermatologic Drugs Advisory Committee. The committee recommended that bioequivalence of dermatologic corticosteroids be documented using the vasoconstrictor assay and the dose duration method. The dose duration to be used in the bioequivalence study comparing the test and the reference product should be based on the population ED_{50} value obtained from a pilot dose response study on the reference listed drug (RLD). The pivotal bioequivalence study also requires two calibrator dose durations D_1 and D_2, in addition

to the ED_{50}, where D_1 is approximately half of the bioequivalence study dose (ED_{50}) and D_2 is approximately 2 times the bioequivalence study dose.

The methodology employed to determine bioequivalence of Taro's Clobetasol Propionate Emollient Cream USP, 0.05% is based on the above pilot-pivotal study concept. Both pilot and pivotal studies are reviewed hereafter.

PILOT DOSE RESPONSE STUDY

OBJECTIVE: To demonstrate dose response relationship of Clobetasol Propionate Topical Emollient Cream USP, 0.05% (Temovate E^R 0.05% Cream) manufactured by Glaxo, and determine the population ED_{50} for its vasoconstrictor response.

STUDY SITE, PERSONNEL AND DATES: The vasoconstrictor pilot study was performed by

Principal Investigator:

Dosing Dates: March 28, 1997

Study Protocol and Informed Consent: The protocol used for this study (#9615052D) and Informed Consent were approved by

SUBJECT SELECTION: Fifteen (15) healthy female volunteers in the age range of 19 to 49 years were screened for vasoconstrictor response to the RLD, Temovate E^R 0.05% Cream and enrolled for this study. Subjects were selected based on acceptable medical history and negative pregnancy test. Each subject signed informed consent. The exclusion criteria used for this study were the following:

- Significant history or current evidence of chronic or infectious skin disease.
- Strenuous exercise.
- Skin defects that may interfere with evaluation of test sites.
- Clinically significant history of alcohol or drug abuse.
- Alcohol consumption within 24 hours and throughout the study.
- Greater than 300 mg caffeine intake within 24 hours of study and during study.
- History of allergy to clobetasol, corticosteroids, gels, lotions, ointments or cosmetics.
- History or concurrent evidence of hypertension or other medical conditions requiring regular treatment with prescription drugs.

- Skin coloration, which would interfere with assessment of skin blanching.
- Use of prescription medicine within 7 days, over-the-counter medication within 48 hours.
- Use of topical steroids on flexor surface of forearm within 30 days of dosing.
- Use of lubricant creams within 24 hours of dosing.
- Use of tobacco products within 7 days.
- Use of dermatologic drug therapy on ventral forearms, icluding prior involevment in a topical corticosteoid pharmacodynamic/pharmacokinetic study within one month of the current study.
- Pregrancy or lactating females.

STUDY DESIGN: The pilot study was conducted as a single period study. Clobetasol propionate topical product, Temovate E^R 0.05% emollient cream (Glaxo Wellcome), lot #6J232 (expiry date: 9/98) was used for this study. One 10 µl amount of the RLD (Temovate E^R 0.05% Cream) was applied to 7 sites on the flexor surface of each subject's right forearm and left in place for 3 minutes to 1 hour. Skin blanching response was determined both by visual assessment and with a ChromaMeter at 0, 2, 4, 6, 8, 10, 12, 20 and 24 hours after treatment removal.

METHOD VALIDATION: The sponsor has documented precision of drug application and reproducubility of chromameter readings. was used in this study to measure the reflective colors from the skin surface, and six high-sensitivity silicon photocells are used by the meter's double-beam feedback system to measure both incident and reflected light.

Prior to the study, precision of the ChromaMeter operator was evaluated from replicate evaluations (5 readings, at least 3 minutes apart) at 4 untreated skin sites on each arm of at least 4 different subjects. The between-site CV was less than 13% and the within-site CV was less than 7% for this operator (pp 361, vol 1.2).

The ChromaMeter operator and visual evaluator assessed the degree of blanching response at each site prior to treatment application and at 0, 2, 4, 6, 8, 10, 12, 20 and 24 hours after removal. All sites were assessed under standard lighting and at room temperature. All assessments were made within 5 minutes of their scheduled time with the ChromaMeter assessment always preceding the visual evaluation.

The ChromaMeter operator and visual evaluator were blinded as to the duration of application at each site.

DATA ANALYSIS: The chromaMeter data were normalized for baseline values and changes in the color of the untreated skin as recommended in the guidance. The dose-response relationship was evaluated using the ChromaMeter results for all available subjects. SAS PROC NLIN was used to fit a two-parameter, Emax model, $E = [(Emax *D)/(ED_{50} +D)]$.

AUEC's were calculated for 0-24 hours after drug application using the trapezoidal rule. The pooled AUEC data as a function of the dose duration were fitted to the simple E_{max} model using at the Agency to determine the polulation ED_{50}.

RESULTS

Based on the nonlinear mixed effect modeling, values of pharmacodynamic parameters calculated by the firm and the reviewer are as follows:

Comparison of firm and reviewer values for pilot data fits

Method	Parameter	Firm (A)	Reviewer (B)	A/B
Chromameter	ED_{50} (min)	5.10 (48.8)[1]	6.06 (67.4)[1]	0.84
	E_{max} (a-scale units*min)	-27.50 (11.6)[1]	-29.52 (32.7)[1]	0.93

Data are tabulated as population mean (CV%)

For the analysis performed by the reviewer, the graphics illustrating the population fitting are given in appendix 1 (attachment). These data are indicative of an approximate population ED_{50} value of 6 minutes and that is the dose duration value used for the pivotal bioequivalence study. A lower duration for 3 minutes (D1) and a longer duration for 12 minutes (D2) would also be included to validate that a subject is a good detector.

PIVOTAL BIOEQUIVALENCE STUDY

OBJECTIVE: To determine in vivo bioequivalence of the test and reference Clobetasol propionate emollient creams. The test product was Taro's Clobetasol propionate 0.05%

Emollient Cream and the reference product was Temovate E^R manufactured by Glaxo.

STUDY SITE & PERSONNEL: Same as that mentioned for the pilot study.

INFORMATION ON PRODUCTS TESTED: The test and the reference products used in this study are the following:

Test Drug: Clobetasol Propionate E Cream, 0.05% (Taro Pharmaceuticals, Inc.), Lot #S114-51531; Manufacture date 08/20/98

Reference Drug: Temovate E^R Emollient 0.05%, Glaxo , Lot #7J384, Expiration date October, 1999.

STUDY PROTOCOL AND INFORMED CONSENT: The study protocol (#9915003) and subject's informed consent were approved by the

SUBJECT SELECTION: Potential subjects were screened for vasoconstrictor response to the reference listed drug Temovate E^R 0.05% as mentioned for the pilot study. All subjects were selected based on a demonstrated skin blanching response (pp 102-107).

DOSING GROUPS AND DATES: The subjects were entered into the study as 3 dosing groups. Subjects 01-20 were dosed in the first group mon 02/13/99; Subjects 21-40 were dosed in the second group on 02/20/99 and Subjects 41-60 were dosed in the third group on 02/27/99.

BIOEQUIVALENCE STUDY: A one-period, ramdomized, study was performed with sixty (59 completing) pre-screened, healthy female subjects. A 10 µl amount of each emollient cream was applied in triplicate to the flexor surface of each subject's forearms and left in place for 6 minutes. This duration time is based on ED_{50} estimates from a previous dose response (pilot) study conducted at

The Temovate E^R was also applied to two additional sites on each forearm for durations of 3 minutes (D1) and 12 minutes (D2), respectively. There were two untreated control sites on each arm.

The degree of vasoconstriction was determined by both visual assessment and with a ChromaMeter at pre-dose and at 0, 2, 4, 6, 8, 10, 12, 20 and 24 hours after treatment removal.

DATA ANALYSIS AND RESULTS:

The average of the duplicate pre-dose ChromaMeter readings at each site and the average reading for the untreated ChromaMeter reference sites on each arm were used to normalize all the ChromaMeter readings. The firm has also reported the visual readings normalized in the same fashion. Area under the response curve ($AUEC_{0-24}$) was determined for each treated site using both the visual and ChromaMeter data. The ratio of the mean area of the 12 minute Temovate^R duration (D2) to that of the 3 minute Temovate^R duration (D1) was determined for each subject.

The firm has stated that a subject was included in the ChromaMeter analyses if she met the qualification criteria, D2/D1 $\geq$ 1.25. If a subject showed no vasoconstrictor response for the D1 (where, D1 is equal to or less than 0) duration, but the response ratio for the D2 duration to the ED_{50} duration was at least 1.25, then the subject also qualified for inclusion in the data analysis. Thirty-two of 59 subjects met these qualifying criteria (29 subjects met the first criterion and 3 subjects met the second criterion) and their data were included in the statistical analysis.

The ratio of the ChromaMeter readings for the mean area of the 12 minute Temovate^R duration (D2) to that of the 3 minute Temovate^R duration (D1) was determined for each subject meeting D2/D1 $\geq$ 1.25 criterion (see Table 1).

Table 1

Subject #	Test (A)	Ref (B)	**AUC (0-24)** A/B	Ax(-1)	Bx(-1)
5	22.823	11.222	2.03	-22.82	-11.22
6	4.902	8.05	0.61	-4.90	-8.05
8	7.912	13.645	0.58	-7.91	-13.65
9	23.472	16.858	1.39	-23.47	-16.86
10	14.278	21.28	0.67	-14.28	-21.28
11	11.073	9.373	1.18	-11.07	-9.37
12	17.252	21.578	0.8	-17.25	-21.58
15	3.57	14.905	0.24	-3.57	-14.91
16	13.752	17.792	0.77	-13.75	-17.79
17	21.863	12.682	1.72	-21.86	-12.68
20	9.248	0.41	22.56	-9.25	-0.41
21	20.577	14.362	1.43	-20.58	-14.36
22	7.797	17.51	0.44	-7.80	-17.51
23	25.14	21.808	1.15	-25.14	-21.81

26	8.372	9.995	0.84	-8.37	-10.00
28	12.268	7.817	1.57	-12.27	-7.82
29	15.063	14.385	1.05	-15.06	-14.39
30	22.828	26.987	0.85	-22.83	-26.99
31	33.312	33.148	1	-33.31	-33.15
34	16.183	9.242	1.75	-16.18	-9.24
35	34.467	38.223	0.9	-34.47	-38.22
36	22.833	19.668	I.16	-22.83	-19.67
39	4.758	3.3	1.44	-4.76	-3.30
41	25.24	30.97	0.81	-25.24	-30.97
42	39.063	31.737	1.23	-39.06	-31.74
45	18.667	18.838	0.99	-18.67	-18.84
47	23.917	22.702	1.05	-23.92	-22.70
48	26.242	22.268	1.18	-26.24	-22.27
52	17.488	23.025	0.76	-17.49	-23.03
55	7.368	9.522	0.77	-7.37	-9.52
56	23.515	33.895	0.69	-23.52	-33.90
58	43.075	37.038	1.16	-43.08	-37.04

Locke's Method was applied for calculating confidence intervals and the results obtained by the firm were presented below:

CONFIDENCE INTERVALS EVALUATION

Evaluation Method	N	$AUEC_{0-24}$ (Mean)		Test/Ref	90% CI
		Test	Ref		
ChromaMeter	32	-18.70	-18.57	1.007	91.2-111.1
Visual Scoring	34	-16.16	-19.88	0.811	74.1-88.5

The Division of Bioequivalence has calculated the 90% confidence intervals using $AUEC_{0-24}$ data of all 32 subjects and also using $AUEC_{0-24}$ data of 29 subjects whose D_2/D_1 ratios were $\geq$ 1.25. The results are presented below and in Tables 2 and 3 (attached).

(attached). These results show the 90% confidence intervals meet the acceptable limits in both cases.

Evaluation Method	N	$AUEC_{0-24}$ (Mean)		Test/Ref	90% CI
		Test	Ref		
ChromaMeter	32	-18.70	-18.57	1.007	91.2-111.1
ChromaMeter	29	-19.18	-19.18	1.000	90.1-110.8

Therefore, based on ChromaMeter results, Taro's test emollient cream meets the 90% CI criteria (80 - 125%) for bioequivalence.

PRODUCT COMPOSITION:

Composition of Taro's Clobetasol propionate 0.05% Emollient Cream is presented in Table 4 below:

Table 4

Ingredient	TEST % (w/w)
Isopropyl Myristate	
Cetostearyl Alcohol	
Dimethicone (350 cst)	
Cetomacrogol 1000	
Purified Water	
Propylene Glycol	
Imidurea	
Citric Acid	
Sodium Citrate	

COMMENTS:

1. The sponsor performed a pilot dose response study on RLD (Temovate E^R 0.05% Cream) based on the OGD guidance. Based on the nonlinear mixed effect modeling of the chromameter dose response data, an ED_{50} of approximately 5.1 minutes was calculated. ED_{50} value based on visual scoring was 3.67 minutes. For the pivotal bioequivalence study the sponsor used D_1, ED_{50} and D_2 values of 3, 6 and 12 minutes, respectively. Based on reviewer's analyses the selection of these values is appropriate.

2. Sixty (60) subjects were dosed for pivotal bioequivalence study. Fifty-nine (59) subjects completed the study. For bioequivalence evaluation there were 32 "evaluable subjects".

3. Based on the chromameter evaluation of skin blanching, test product's $AUEC_{0-24}$ was 0.7% higher than that of the reference product. The 90% confidence intervals comparing these products were within the acceptable limit of 80-125%.

RECOMMENDATIONS

1. The in vivo bioequivalence study conducted by Taro comparing its Clobetasol propionate 0.05% Emollient Cream (lot #S114-51531) to the reference product, Temovate E^R 0.05% Cream (lot #7J384) has been found to be acceptable to the Division of Bioequivalence. The results of this vasoconstrictor study demonstrate that Taro's Clobetasol propionate 0.05% Emollient Cream is bioequivalent to the reference product, Temovate E^R 0.05% Cream, manufactured by Glaxo.

2. From the bioequivalence stand point the sponsor has met the requirements of in vivo bioequivalence on its Clobetasol propionate 0.05% Emollient Cream.

/S/

Sikta Pradhan, Ph. D.
Division of Bioequivalence
Review Branch I

/S/ 8/5/99

RD INITIALED YCHUANG
FT INITIALED YCHUANG

Concur: /S/ Date: 8/11/99

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 75-633S2.599 (original, duplicate), HFD-652 (Huang, Pradhan), HFD-650 (Director), Drug File, Division File
Attachment - 8 pages

Appendix I (P.1-6)
(Pilot Study)

ate : 07-01-1999

Individual parameters

Subject	C50	EMAX
Sbj 1		
Sbj 2		
Sbj 3		
Sbj 4		
Sbj 5		
Sbj 6		
Sbj 7		
Sbj 8		
Sbj 9		
Sbj 10		
Sbj 11		
Sbj 12		
Sbj 13		
Sbj 14		
Sbj 15		
N	15.	15.
Mean	8.45025	-29.52575
Min		
Max		
S.D.	6.97692	7.37121
Var.	48.67746	54.3347
C.V.	82.56474	-24.96535

ate : 07-01-1999

EM Algorithm: NO COVARIABLES (07-01-1999 - 10:24:26)

Model : Emax model
Measurement error variance : Homoscedastic
EM termination criteria (Relative parameter change) : .1
Marquardt precision on parameters : .001
Relative parameter change for gradient calculation : .001

Initial population parameter estimates :

	Mean	Std. Dev.	C.V.%	Distrib.
C50	1.79176E+0	7.728195E-1	4.313187E+1	Log.Normal
	(6.000003E+0)		(9.03944E+1	)
EMAX	-2.596664E+1	8.829488E+0	3.40032E+1	Normal

Sigma = 1

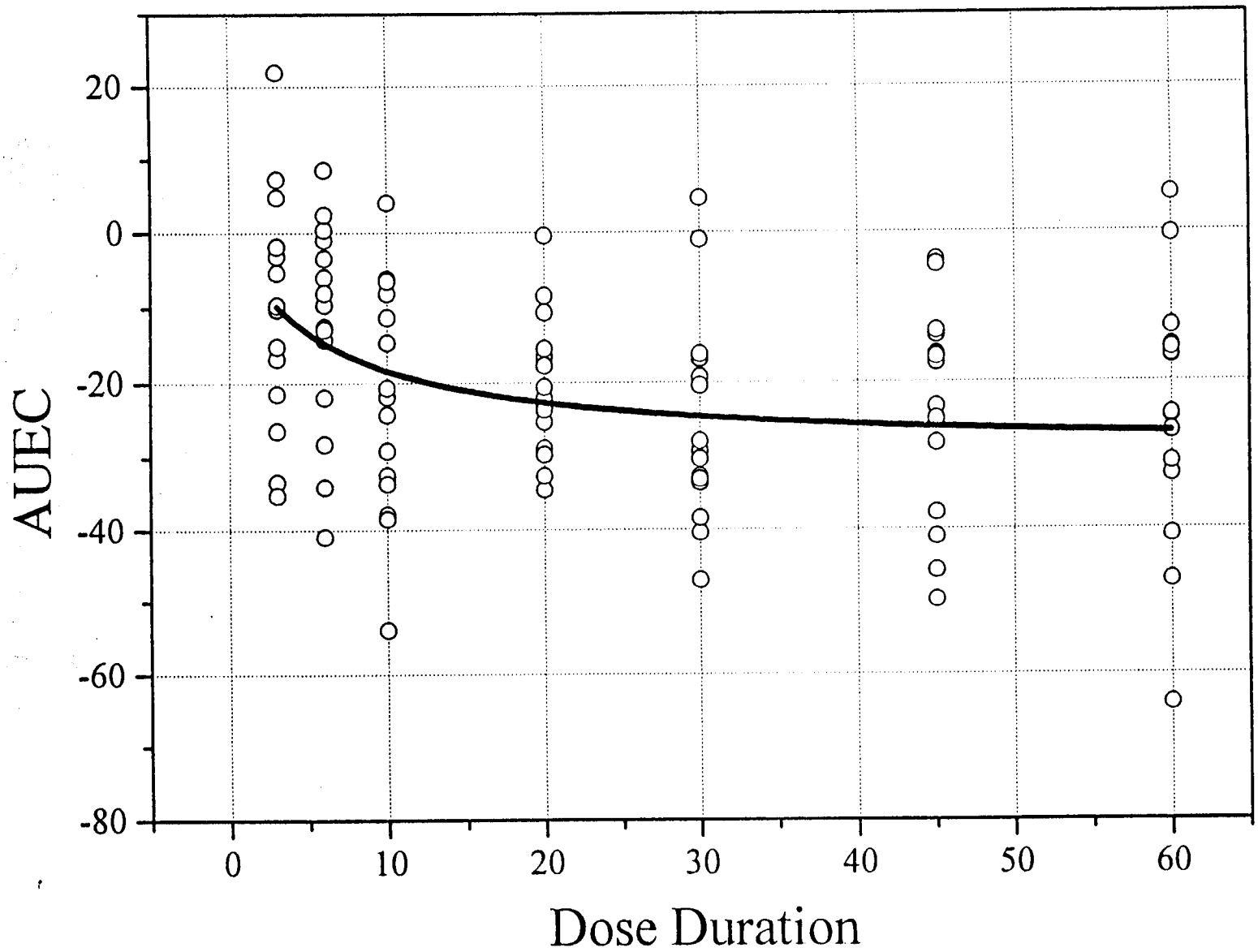
Nb of EM iterations : 5

Final population parameter estimates :

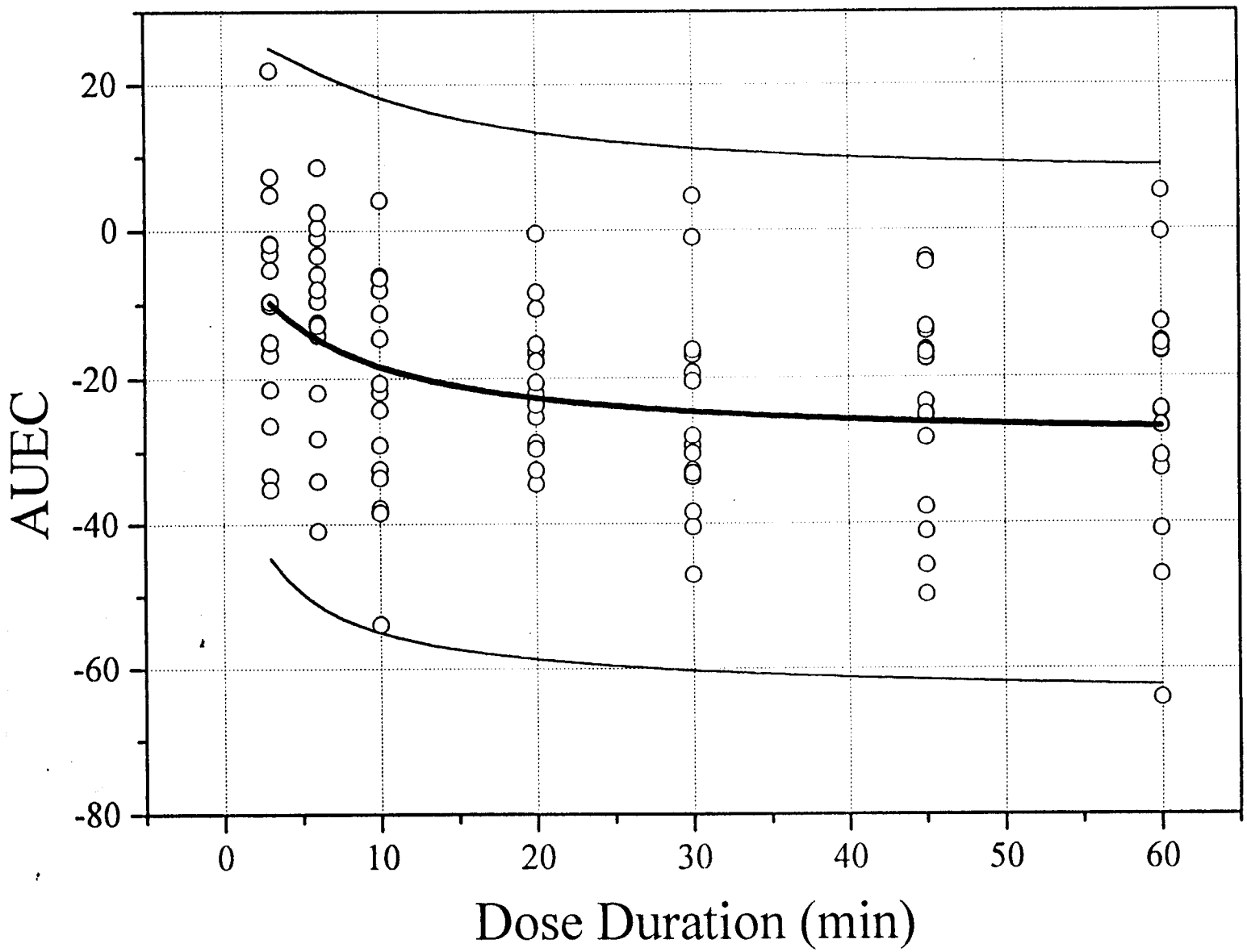
	Mean	Std. Dev.	C.V.%	Distrib.
C50	1.801738E+0	1.213593E+0	6.735677E+1	Log.Normal
	(6.060173E+0)		(1.833429E+2	)
EMAX	-2.952575E+1	9.656117E+0	3.270405E+1	Normal

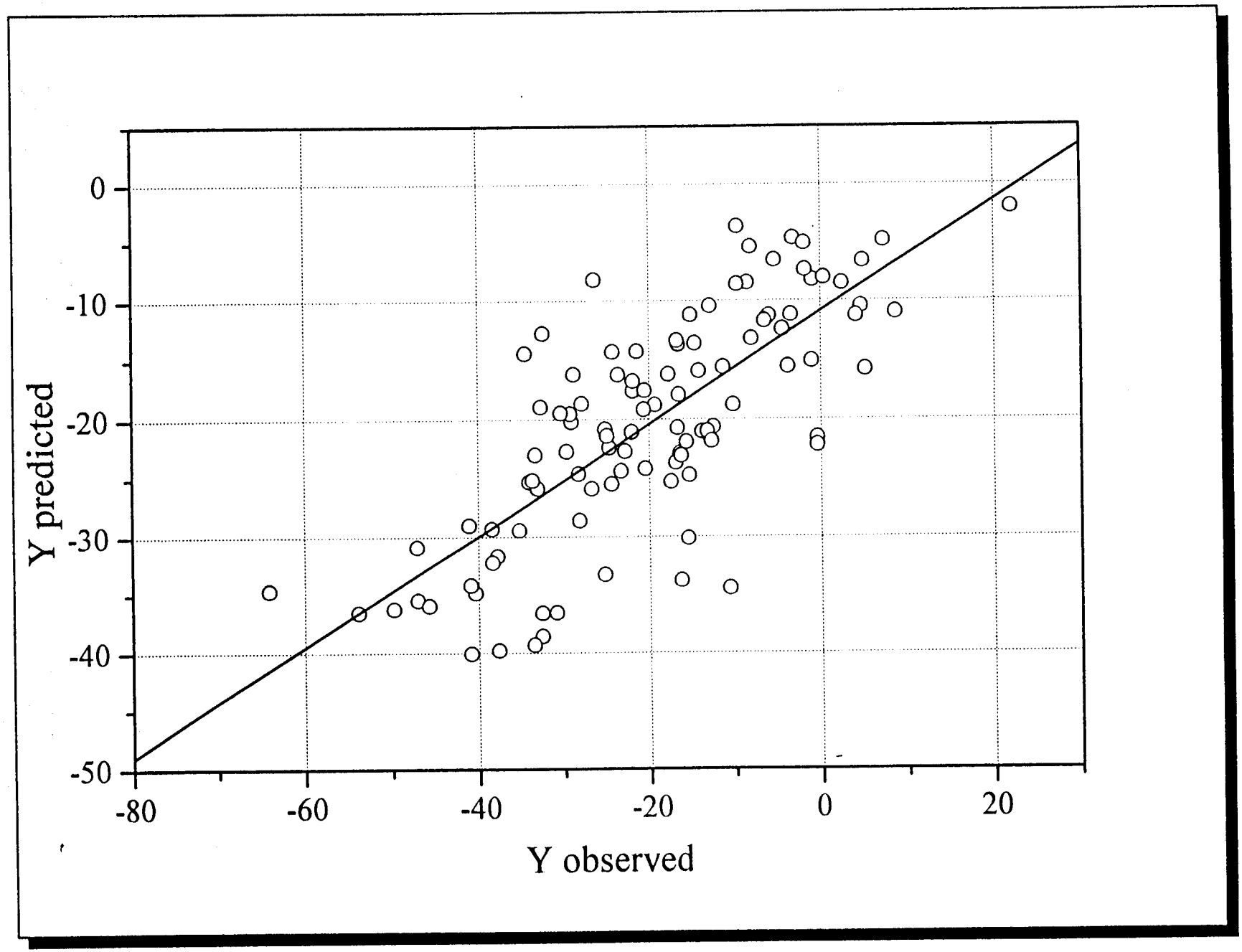
Sigma = 121.4684
Maximum Likelihood = -415.7412
AIC = 3.997535

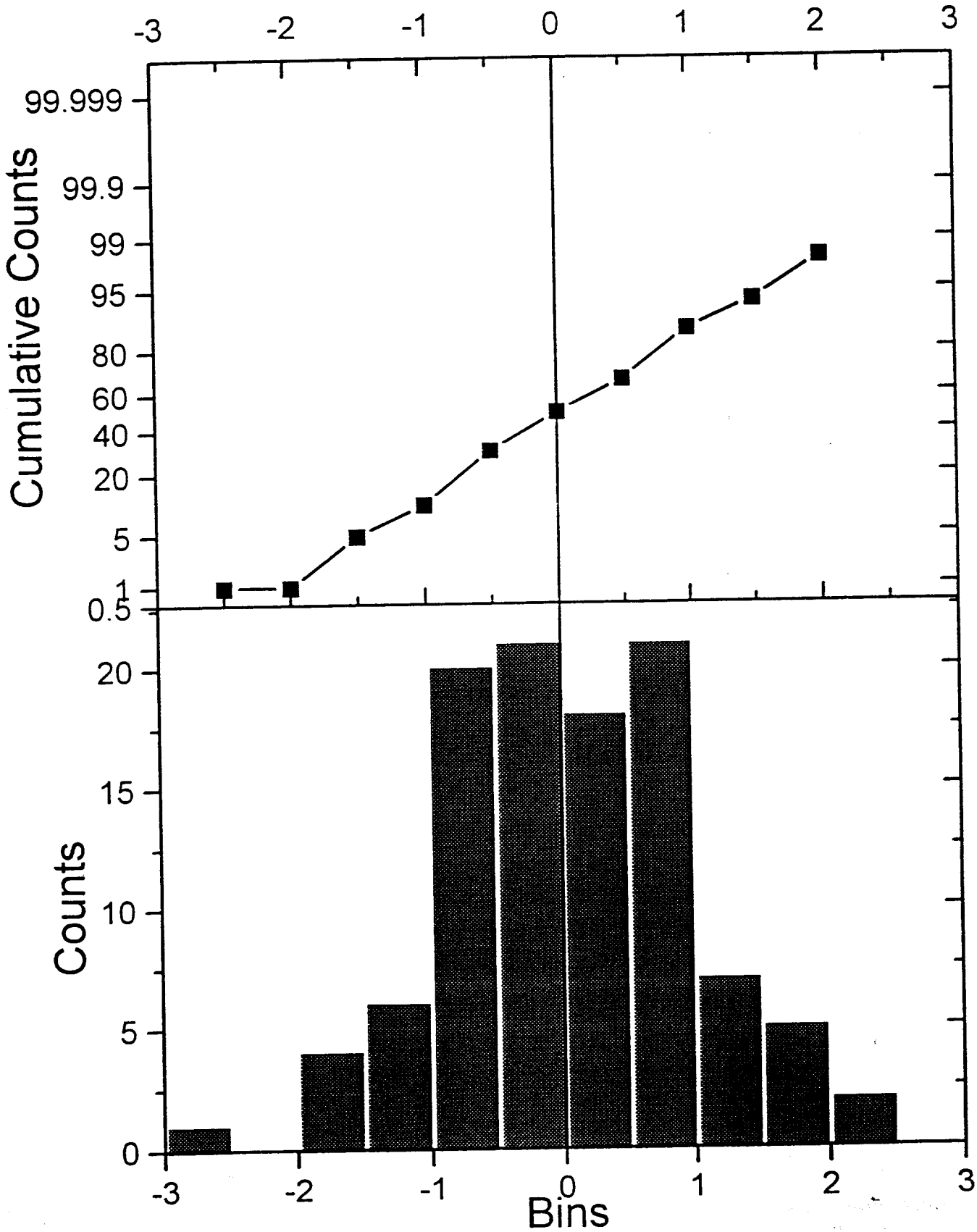
Population Fitting



Population Fitting




0
-10
-20
-30
-40
-50
Y predicted
-80
-60
-40
-20
0
20
Y observed



Residuals' Histogram

P. 6

Table 3:

Locke, CS (1984) An exact confidence interval from untransformed data for the ratio of two formulation means. *J. Pharmaco. Biopharm. 12:* 649-655 (N: 9)

AVETest	-19.18	
AVEREF	-19.18	
DTR	79.45	
DRR	95.94	
DTT	101.48	
Inta Sub Var (%)	23	
K	0.39	
SQRT(K)	0.63	
W	0.03	
n	29	
t	1.7011	
t^2	2.89	
Gr	0.03	
DRR*W	3.31	
SQRT(DRR*W)	1.82	
+CINT	0.9010	
-CINT	1.1084	
90% CI:	**90.10**	**110.84**

SUB	TEST	REF	(TEST)^2	(REF)^2	(TEST)*(REF)
5	-22.82	-11.22	520.89	125.93	256.12
6	-4.90	-8.05	24.03	64.80	39.46
8	-7.91	-13.65	62.60	186.19	107.96
10	-14.28	-21.28	203.86	452.84	303.84
11	-11.07	-9.37	122.61	87.85	103.79
12	-17.25	-21.58	297.63	465.61	372.26
15	-3.57	-14.91	12.74	222.16	53.21
17	-21.86	-12.68	477.99	160.83	277.27
20	-9.25	-0.41	85.53	0.17	3.79
21	-20.58	-14.36	423.41	206.27	295.53
22	-7.80	-17.51	60.79	306.60	136.53
23	-25.14	-21.81	632.02	475.59	548.25
26	-8.37	-10.00	70.09	99.90	83.68
28	-12.27	-7.82	150.50	61.11	95.90
29	-15.06	-14.39	226.89	206.93	216.68
30	-22.83	-26.99	521.12	728.30	616.06
31	-33.31	-33.15	1109.69	1098.79	1104.23
34	-16.18	-9.24	261.89	85.41	149.56
35	-34.47	-38.22	1187.97	1461.00	1317.43
36	-22.83	-19.67	521.35	386.83	449.08
41	-25.24	-30.97	637.06	959.14	781.68
42	-39.06	-31.74	1525.92	1007.24	1239.74

Table 2.

Locke, CS (1984) An exact confidence interval from untransformed data for the ratio of two formulation means. *J. Pharmaco. Biopharm. 12:* 649-655 (N: 9)

AVETest	-18.70
AVEREF	-18.57
DTR	78.76
DRR	94.64
DTT	99.67
Inta Sub Var (%)	23
K	0.38
SQRT(K)	0.62
W	0.03
n	32
t	1.6950
t^2	2.87
Gr	0.02
DRR*W	2.96
SQRT(DRR*W)	1.72
+CINT	0.9118
-CINT	1.1108
90% CI:	**91.18 111.08**

SUB	TEST	REF	(TEST)^2	(REF)^2
5	-22.82	-11.22	520.89	125.93
6	-4.90	-8.05	24.03	64.80
8	-7.91	-13.65	62.60	186.19
9	-23.47	-16.86	550.93	284.19
10	-14.28	-21.28	203.86	452.84
11	-11.07	-9.37	122.61	87.85
12	-17.25	-21.58	297.63	465.61
15	-3.57	-14.91	12.74	222.16
16	-13.75	-17.79	189.12	316.56
17	-21.86	-12.68	477.99	160.83
20	-9.25	-0.41	85.53	0.17
21	-20.58	-14.36	423.41	206.27
22	-7.80	-17.51	60.79	306.60
23	-25.14	-21.81	632.02	475.59
26	-8.37	-10.00	70.09	99.90
28	-12.27	-7.82	150.50	61.11
29	-15.06	-14.39	226.89	206.93
30	-22.83	-26.99	521.12	728.30
31	-33.31	-33.15	1109.69	1098.79
34	-16.18	-9.24	261.89	85.41
35	-34.47	-38.22	1187.97	1461.00
36	-22.83	-19.67	521.35	386.83

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-633 APPLICANT: Taro Pharmaceuticals Inc.

DRUG PRODUCT: Clobetasol Propionate Emollient Cream 0.05%

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

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75633

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NUMBER
2 (two)

2. ANDA NUMBER
75-633

3. NAME AND ADDRESS OF APPLICANT
Taro Pharmaceuticals USA Inc.
Attention: Lorraine Sachs
5 Skyline Drive
Hawthorne, NY 10532

4. LEGAL BASIS for ANDA SUBMISSION
The basis of Taro's proposed ANDA for Clobetasol Propionate Emollient Cream USP, 0.05%, is the reference listed drug, Temovate E® Emollient, 0.05% (NDA 20340) manufactured by Glaxo Wellcome. According to information published in the list of Approved Drug Products 18th Ed., Temovate E® Emollient, 0.05% is not covered by any patents and marketing exclusivities.

5. SUPPLEMENT(s)
None

6. NAME OF DRUG
Clobetasol Propionate Emollient Cream USP

7. NONPROPRIETARY NAME
Clobetasol Propionate Emollient Cream USP

8. SUPPLEMENT(s) PROVIDE(s) FOR
None

9. AMENDMENTS AND OTHER DATES

5/7/1999	Original submission
12/15/99	Major amendment
3/8/00	Correspondence (change of ownership)
4/18/00	Amendment
5/10/00	Telephone amendment

10. PHARMACOLOGICAL CATEGORY
Anti-inflammatory

11. HOW DISPENSED
Prescription

12. RELATED IND/NDA/DMF(s)

Product	Holder	DMF No.	LOA
			V1.3, p1117
			V1.4, p1321
			V1.4, p1352
			V1.4, p1355
			V1.4, p1359
			V1.4, p1362

13. DOSAGE FORM

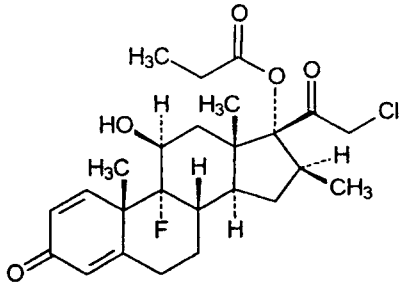
Cream

14. POTENCY

0.05%

15. CHEMICAL NAME AND STRUCTURE

Clobetasol Propionate. Pregna-1,4-diene-3,20-dione, 21-chloro-9-fluoro-11-hydroxy-16-methyl-17-(1-oxopropoxy)-, (11β,16β)-. $C_{25}H_{32}ClFO_5$. 466.99. 25122-46-7.



16. RECORDS AND REPORTS

None

17. COMMENTS

New owner: Taro Pharmaceuticals USA Inc.
The application is approvable.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER AND DATE COMPLETED

Liang-Lii Huang, Ph.D. / May 4, 2000
Endorsed by Paul Schwartz, Ph.D. / May 4, 2000

Redacted 15

pages of trade

secret and/or

confidential

commercial

information

Chem

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75633

CORRESPONDENCE

May 10, 2000

ORIG AMENDMENT

TARO

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

Reference: **ANDA 75-633**
Clobetasol Propionate Emollient Cream USP, 0.05%
Telephone Amendment

Dear Sir:

Please find enclosed Taro Pharmaceuticals' Telephone Amendment for the above-referenced application.

As required by 21 CFR 314.96(d)(5), Taro is forwarding a copy of the technical data (including 356h form). Taro Pharmaceuticals Inc. certifies that the technical sections contained in this copy are true copies of the same sections submitted to OGD. If there are any questions relating to the information submitted, please contact us at:

Taro Pharmaceuticals U.S.A., Inc.,
attention: 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.
V.P., Regulatory Affairs

Encl. : Field Copy

CENTER FOR DRUG
MAY 11 2000
OGD
EVALUATION AND RESEARCH

May 10, 2000

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

RE: **ANDA 75-633**
Clobetasol Propionate Emollient Cream USP, 0.05%
Telephone Amendment

Dear Sir,

Reference is made to our Abbreviated New Drug Application (ANDA) for the above referenced product, submitted on May 7, 1999 pursuant to 21 CFR 314.70. and our Major Amendment of December 15, 1999. Reference is also made to the telephone conversation of May 10, 2000 between Elaine Hu, Paul Schwartz and Liang-Li Huang of the Agency and Lorraine Sachs of Taro Pharmaceuticals, during which the Agency requested that the page 4 of our Major Amendment (page 1110 of the original ANDA) be corrected to indicate the composition of the intended commercial batch kg).

In **supplementary page 1**, submitted is the revised page 4 of our Major Amendment (page 1110 of the original ANDA) indicating the qualitative/quantitative composition for the intended commercial size batch kg).

This completes our Telephone Amendment of May 10, 2000. If there are any questions with regards to this amendment, please do not hesitate to contact us at:

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

April 18, 2000

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

NEW CORRESP
NC

RE: **ANDA 75-633**
Clobetasol Propionate Emollient Cream USP, 0.05%
Major Amendment

Dear Madam,

As per you telephone request of today, please find attached the first page of our Major Amendment Letter of December 15, 1999, missing from the original Major Amendment. We apologize for any inconvenience this may have caused.

If you need any further information, please do not hesitate to contact us.

Sincerely,

TARO PHARMACEUTICALS INC.

Derek Ganes, Ph.D.
V.P. Regulatory Affairs

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APR 20 2000
OGD

December 15, 1999

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

ORIG AMENDMENT
N/A C

ORIG AMENDMENT

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

Reference: **ANDA 75-633**
Clobetasol Propionate Emollient Cream USP, 0.05%
Major Amendment

Dear Sir:

Please find enclosed Taro Pharmaceuticals' response to a recent deficiency letter from the FDA, dated November 22, 1999, for the above-referenced application.

As required by 21 CFR 314.96(d)(5), Taro is forwarding a copy of the technical data (including 356h form). Taro Pharmaceuticals Inc. certifies that the technical sections contained in this copy are true copies of the same sections submitted to OGD. If there are any questions relating to the information submitted, please contact our US Agent:

Taro Pharmaceuticals U.S.A., Inc.,
attention: 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.
V.P., Regulatory Affairs

Encl. : Field Copy

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RECD
DEC 16 1999
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905-791-5008

2. **Please change the title of certificate of analysis for Dimethicone (350 cst) from to Dimethicone (350 cst) NF.**

Response

The specifications for Dimethicone (350 cst) have been revised to change the title from to Dimethicone (350 cst), NF, and are submitted in **supplementary page 30**.

3. **Please provide the batch record, release testing results, and available stability data of the scale-up batch, S114-51723, which was manufactured**

Response

The scale-up batch (L) S114-51723 was manufactured as an experimental scale-up batch in order to serve as a basis for the scale-up master manufacturing document as well as to be used in comparative in-vitro release testing with the biostudy batch. This batch was not packaged or put on stability, therefore no stability data on this batch are available.

Taro has manufactured another kg exhibit batch (L) S114-51806 using the proposed manufacturing procedure This batch was fully packaged, tested and monitored in both accelerated and room temperature stability study. The batch record, packaging work orders, release testing results and 3 months accelerated and room temperature stability data on the batch S114-51806 are provided in **supplementary pages 31 - 72**.

4. **The mixer attached to the mixing vessel two agitators, primary and secondary as described on page 1225. The agitator speed changed at different steps in the exhibit batch, S114-51531, but the batch record did not specify which agitator at each step. Please clarify.**

Response

Since primary and secondary agitators in the mixing vessel are attached to each other, the speed of one cannot be changed without changing the speed of the other. Therefore the agitator speed and the changes in the agitator speed in the batch record for the exhibit batch (L) S114-51531 were recorded as one numerical value, which represents the speed of the secondary agitator.

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5. **on page 1398 is not acceptable. Please refer to the Guidance for Industry on Container Closure Systems. We recommend that you withdraw the protocol at this time.**

Response

Taro hereby withdraws the submitted on page 1398 of the original ANDA.

6. **Please revise the in-process control specification to establish the limit for**

Response

The limits for in-process specifications have been established as follows:

Separation:	NMT slight
Particulates (waxy lumps)/10 fields of view:	None
Crystals (µm):	None

Revised in-process/bulk product specifications are submitted in **supplementary page 73.**

7. **Please revise the in-process control, finished product, and stability specifications to establish the limits for viscosity.**

Response

The in-process, release and stability limits for viscosity have been established as follows:

Lower limit: NLT cps

Upper limit: Upper limits for in-process and release testing will be established based on the data obtained on the three process validation batches. Upper stability limits for viscosity will be set based on a minimum of 12 months RT stability data obtained on the process validation batches. CBE supplements proposing the above limits will be submitted to the Agency.

Revised in-process/bulk, packaged product and stability specifications are provided in **supplementary pages 73 - 75.**

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8. **Please provide a sampling plan for the blend uniformity test in a production batch. We recommend the blend uniformity test acceptance criteria as % (mean of individual test results) with a maximum relative standard deviation (RSD) of %.**

Response

The in-process/bulk product specifications indicate that the sampling for the blend uniformity test will be performed from the beginning, middle and end of the bulk transfer from the mixing vessel to the holding container. The acceptance criteria for this test have been revised to be % LC (mean of individual test results). The allowable RSD has been set to NMT % due to the small number of samples (3).

In-process/bulk product specifications indicating the above changes are submitted in **supplementary page 73**.

9. **Please provide an antimicrobial preservative effectiveness test data at the 70% level of label claim of imidurea to justify the limits in the in-process, finished product, and stability specifications.**

Response

The Antimicrobial Preservative Efficacy Test Report for Clobetasol Propionate Emollient Cream, justifying the lower specification limit of % LC for Imidurea, is provided in **supplementary pages 76 - 77**.

10. **Please revise the finished product and stability specifications to establish limits for individual and total impurities.**

Response

Based on the stability data compiled to date, the following limits for degradation products have been established:

Degradation Products	Packaged Product Specifications	Stability Specifications
Individual	NMT %	NMT %
Total	NMT %	NMT %

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The packaged product and stability specifications indicating the above limits are submitted in **supplementary pages 74 - 75**.

11. Please revise the stability protocol to commit that assay testing on accelerated stability samples will be performed from the top, middle, and bottom of the tube for all package sizes at all stability stations.

Response

Taro' Stability Protocol for Clobetasol Propionate Emollient Cream USP, 0.05%, submitted in **supplementary pages 78 - 79**, has been revised to indicate that the samples in both accelerated and room temperature stability testing will be tested from the top, middle and bottom of the tube for all package sizes at all stability time points.

12. Please revise the post-approval stability protocols to commit that expiration dates may be extended as three production batches, stability data, which justify the extension, are provided.

Response

The Postapproval Stability Commitment, presented in **supplementary page 80**, is now revised to state the following:

"As additional room temperature data, beyond 24 months, become available, the expiration date will be extended as warranted. The extension will be filed in annual reports in accordance with CFR 314.70 (d)(5), supported by the stability data obtained on three production size batches."

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

1. A satisfactory compliance evaluation of the facilities listed for drug substance and drug product manufacturing and quality control in the application is necessary at the time of the approval of the application.

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Response

We acknowledge that the facilities referenced in our ANDA relative to the drug substance and drug product manufacturing and testing must be in compliance with CGMP at the time of the application approval.

2. **Your analytical methodology is not identical to the US Pharmacopeial methods for the final drug product. Please be advised that the USP methods are the regulatory methods and will prevail in the event of any dispute.**

Response

We acknowledge that the USP methods are regulatory methods and will prevail in the event of any dispute.

3. **Please provide the up-to-date long term stability data for all package sizes.**

Response

Twelve months room temperature stability data for the exhibit batch (L) S114-51531 in all package sizes are provided in **supplementary pages 81 - 92.**

Bioequivalency Comments

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

Response

Acknowledged.

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Labeling Deficiencies

1. GENERAL COMMENTS

a) The established name of this drug product is clobetasol propionate cream. The modifier "emollient" should appear separate from the established name (i.e. clobetasol propionate cream (emollient)).

b) Please note that USAN name are common nouns and should be treated as such in the text of labeling (i.e. lower case). Upper case may be used when the USAN name stands alone as on labels or the title of the package insert.

2. CONTAINER (15 g, 30 g, 45 and 60 g)

a) Change the "contains" statement to : Each gram contains: clobetasol propionate 0.5 mg in an ...

b) Include "Usual Dosage" before the "See package insert" statement.

3. CARTON (15 g, 30 g, 45 and 60 g)

a) See GENERAL COMMENTS

b) See CONTAINER comments.

4. INSERT

a) see GENERAL COMMENTS

b) DESCRIPTION

Change the molecular weight to "466.98" to be in accord with USP 23.

c) PRECAUTIONS (General)

Revise the 2nd sentence of the 7th paragraph to .....observing the failure....(including 'a")

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d) ADVERSE REACTIONS

"Formulations in the first sentence of the first paragraph should be plural.

e) HOW SUPLLIED

Relocate "Rx only" to appear directly beneath the insert title.

Please revise your labels and labeling, as instructed above, and submit in final print.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference-listed drug. We suggest that you routinely monitor the following web site for any approval changes-

htpp://www.fda.gov/cder/ogd/rid/labeling_review_branch.htlm

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.

Response

The labels and labeling have been revised as instructed above. The following has been provided:

Twelve (12) final printed labels:

- 15 g tube labels (**supplementary pages 93 - 104**)
- 15 g carton labels (**supplementary pages 105 - 116**)
- 30 g tube labels (**supplementary pages 117 - 128**)
- 30 g carton labels (**supplementary pages 129 - 140**)
- 45 g tube labels (**supplementary pages 141 - 152**)
- 45 g carton labels (**supplementary pages 153 - 164**)
- 60 g tube labels (**supplementary pages 165 - 176**)
- 60 g carton labels (**supplementary pages 177 - 188**)
- package insert (plastic pouch with the **supplementary page 189**)

Side-by-side comparison of the proposed labeling with the last submission with all differences annotated and explained is provided in **supplementary pages 190 - 205.**

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This completes our response to the Agency's deficiency letter dated November 22, 1999. If there are any questions with regards to this amendment, 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

This Major Amendment is being submitted in two copies. In addition a third (Field copy) is enclosed.

Sincerely yours,
TARO PHARMACEUTICALS INC.

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

/ V.Lucic
cc. Acting Director, FDA, Office of International Programs

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May 7, 1999

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

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

Re: **ANDA for Clobetasol Propionate Emollient Cream USP, 0.05 %**

Dear Mr. Sporn:

Taro Pharmaceuticals Inc. submits today an original Abbreviated New Drug Application (ANDA) seeking approval to market Clobetasol Propionate Emollient Cream USP, 0.05% that is bioequivalent to the listed drug, TEMOVATE E®, manufactured by Glaxo Wellcome Inc. pursuant to NDA 20-340.

This ANDA consists of four volumes. Taro Pharmaceuticals Inc. is filing an archival copy (in blue folders) of the ANDA that contains all the information required in the ANDA and a technical review copy (in red folders) which contains all the information in the archival copy with the exception of the Bioequivalence section (VI). A separate copy of the Bioequivalence section is provided in orange folders. The diskette with the biostudy data is included in the archival copy, section VI "Bioavailability and Bioequivalence".

Taro Pharmaceuticals Inc. hereby certifies that, the field copy of this ANDA submission contained in burgundy folders is a true copy of the technical sections of the ANDA. The field copy also contains a copy of the signed 356h form and a certification that the contents are a true copy of the technical sections of the ANDA.

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

Taro Pharmaceuticals USA, Inc.,
Attn: Kalpana Rao
5 Skyline Drive
Hawthorne, NY 10532
Tel: (914) 345-9001

Sincerely,
Taro Pharmaceuticals Inc.

Derek Ganes, Ph.D.
V.P. , Regulatory Affairs

/Vesna Lucic

Enclosures:

Archival Copy (1 set):
All Sections (I - XX), 4 volumes (Blue)
Review Copies:
CMC (Sections I-V and VII-XX), 2 volumes (Red)
Bioequivalence (Sections I-VII): 3 volumes (Orange)
Field Copy (1 set)
CMC (Sections I-V and VII-XX), 2 volumes (Burgundy)

TARO PHARMACEUTICALS INC.
TELEPHONE
905-791-8276
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March 8. 2000

TARO

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room, MPN II
7500 Standish Place, Room 150
Rockville. MD 20855-2773

Re: ANDA #
ANDA #75-508 - Diflorasone Diacetate Cream, 0.05%
ANDA #75-633 - Clobetasol Propionate Emollient Cream, 0.05%
ANDA
ANDA #75-673 - Clotrimazole/Betamethasone Dipropionate Cream USP, 1%/0.05%

General Correspondence – Change in Ownership

Dear Sir/Madam:

Reference is made to our previous general correspondence dated December 21, 1999 concerning the change in ownership of the above referenced ANDA's, and to phone conversations with Ms. Nadine Warren of the Office of Generic Drugs on March 1 and March 8. 2000.

As requested by Ms.Warren, enclosed please find signed copies of form FDA 356h for each of these five ANDA's from the previous owner, Taro Pharmaceuticals Inc. in Bramalea. Ontario. Canada.

Sincerely,

Lorraine W. Sachs, RAC
Associate Director, Regulatory Affairs

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