

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75633

DRAFT FINAL PRINTED LABELING

MAY 17 2000

APPROVED



PK 3030-0
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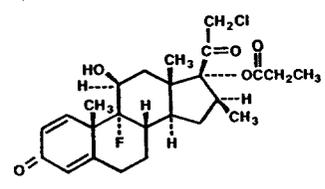
Clobetasol Propionate Cream (Emollient) USP, 0.05%

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 (11 β ,16 β)-21-chloro-9-fluoro-11-hydroxy-16-methyl-17-(1-oxopropoxy)-pregna-1,4-diene-3,20-dione. Clobetasol propionate has the molecular formula C₂₅H₃₂ClFO₅ 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 A₂ 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 A₂. 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

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DO NOT REMOVE

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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.

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

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Pharmaceuticals U.S.A., Inc.



60 g

NDC 51672-1297-3

Clobetasol Propionate Cream (Emollient) USP, 0.05%

For dermatologic use only - Not for ophthalmic use.

Rx only

Clobetasol Propionate Cream (Emollient) USP, 0.05%

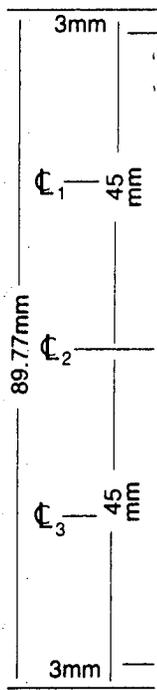
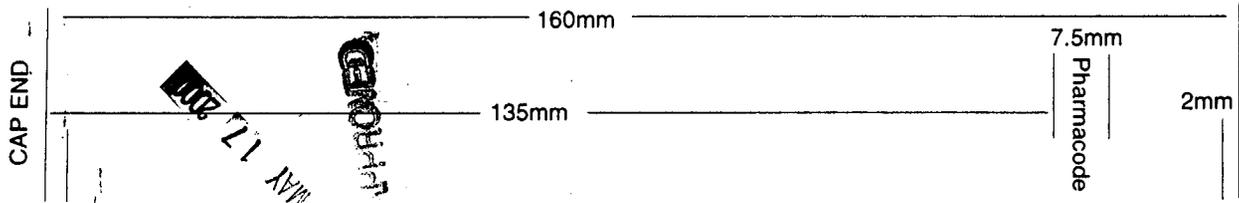
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PK-3029-0

185

Massp



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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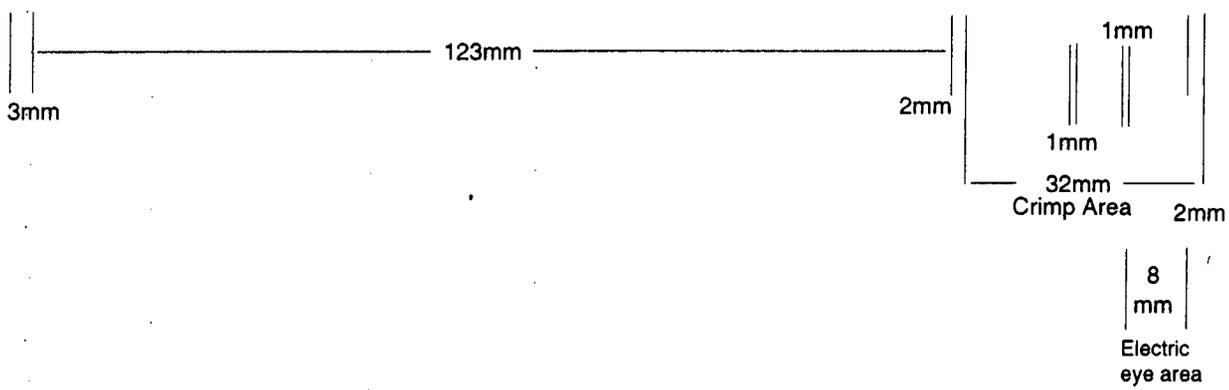
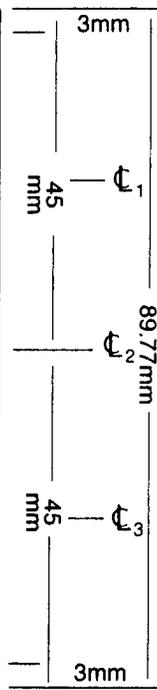
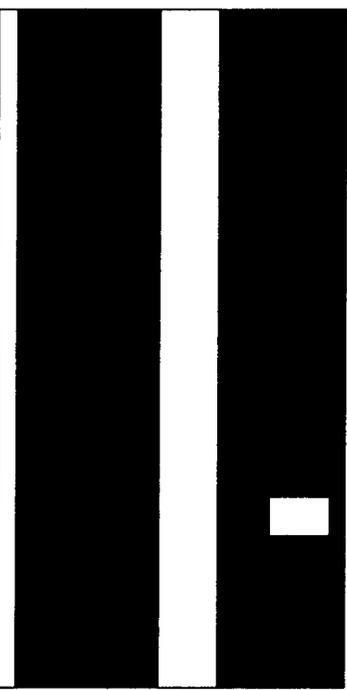
See package insert for full prescribing information.
Store between 15° and 30°C (59° and 86°F). Do not refrigerate.
See crimp for lot no. and expiration date.

Important: Do not use if seal has been punctured or is not visible.

To Open: Use cap to puncture seal.

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TARO TARO



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APPROVED
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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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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



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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

TARO

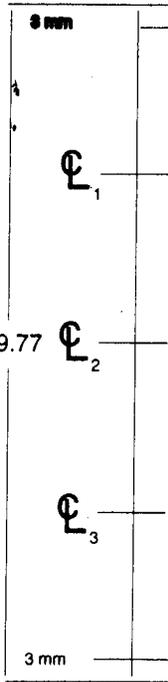
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115 mm

APPROVED MAY 17 2002



45 g

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.

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See package insert for full prescribing information.
Store between 15° and 30°C (59° and 86°F). Do not refrigerate.

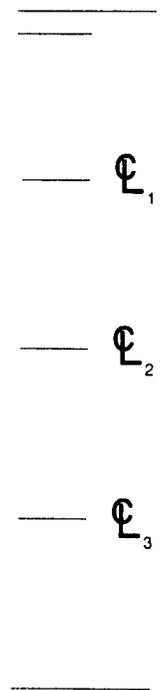
See crimp for lot no. and expiration date.
Important: Do not use if seal has been punctured or is not visible.

To Open: Use cap to puncture seal.

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PK-3026-0

TARO TARO



103 mm

Marg

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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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

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Dist. by: Taro Pharmaceuticals U.S.A., Inc.,
Hawthorne, NY 10532
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01

PK-3025-0

30 g

NDC 51672-1297-2

Clobetasol Propionate Cream (Emollient) USP, 0.05%

For dermatologic use only - Not for ophthalmic use.
Rx only

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



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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, iridurea, isopropyl myristate, propylene glycol, purified water, and sodium citrate.
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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.
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15 g
Clobetasol Propionate Cream (Emollient) USP, 0.05%

15 g

NDC 51672-1297-1

Clobetasol Propionate Cream (Emollient) USP, 0.05%

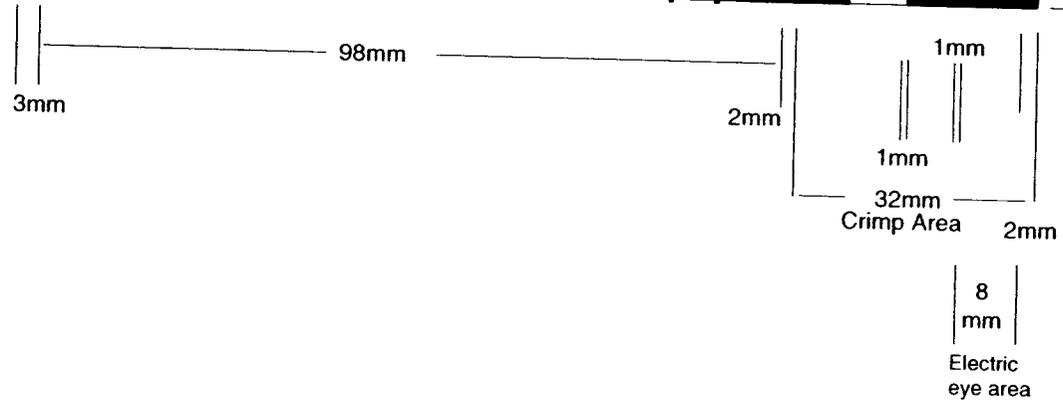
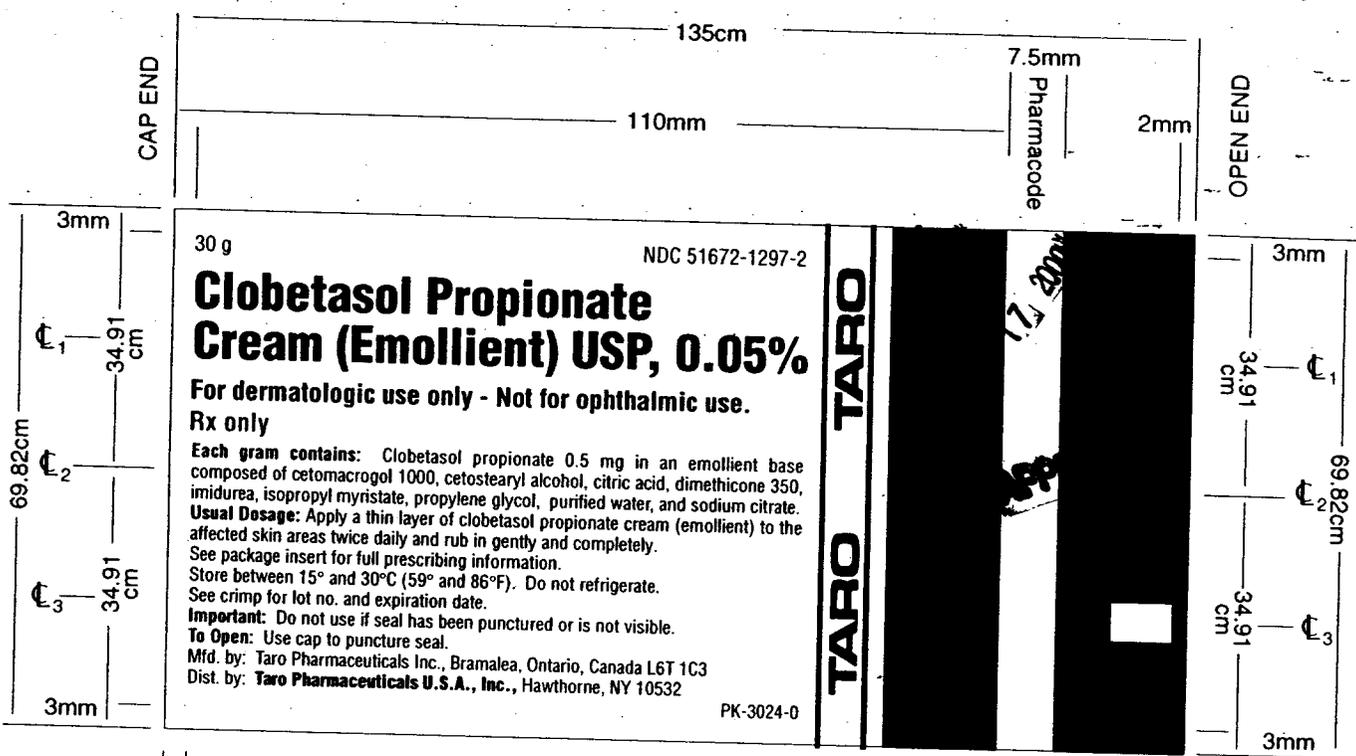
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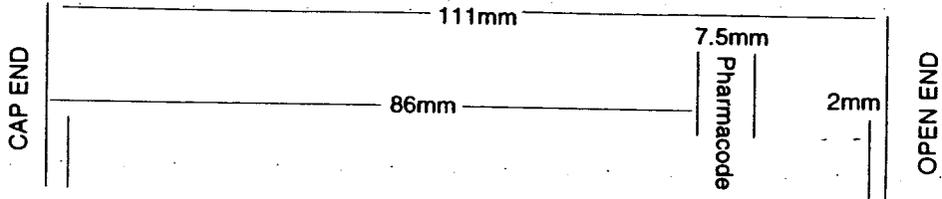
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Margo



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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.

Rx only

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Dist. by: Taro Pharmaceuticals U.S.A., Inc., Hawthorne, NY 10532
PK-3022-0

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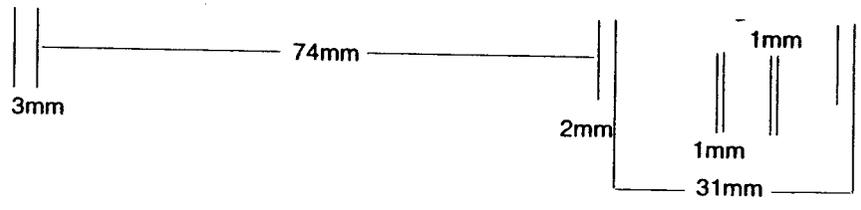
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2 59.85mm

3 29.925 mm

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Crimp Area

