

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75043

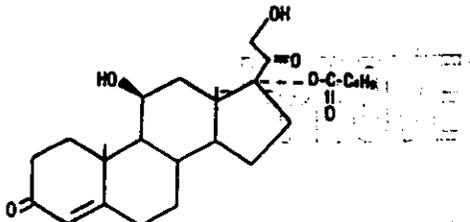
FINAL PRINTED LABELING

Hydrocortisone Valerate Ointment 0.2%

For External Use Only. Not for Ophthalmic Use.

DESCRIPTION

HYDROCORTISONE VALERATE OINTMENT 0.2% is a topical formulation containing hydrocortisone valerate, a non-fluorinated steroid. It has the chemical name Pregn-4-ene-3,20-dione, 11, 21-dihydroxy-17-[(1-oxopentyl) oxy]-, (16 β); the molecular formula is: $C_{26}H_{38}O_6$; the molecular weight is 446.59, and the CAS registry number is: 57524-89-7. The structural formula is:



Each gram of HYDROCORTISONE VALERATE OINTMENT 0.2% contains 2 mg hydrocortisone valerate in a hydrophilic base composed of carbomer 834P, dibasic sodium phosphate, methylparaben, mineral oil, propylene glycol, purified water, sodium lauryl sulfate, stearath-2, stearath-100, stearyl alcohol and white petrolatum.

CLINICAL PHARMACOLOGY

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

The mechanism of anti-inflammatory activity of the topical corticosteroids is unclear.¹ Various laboratory methods, including vasoconstrictor assays, are used to compare and predict potencies and/or clinical efficacies of the topical corticosteroids.² There is some evidence to suggest that a recognizable correlation exists between vasoconstrictor potency and therapeutic efficacy in man.³

Pharmacokinetics

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings.^{4,5,6}

Topical corticosteroids can be absorbed from normal intact skin.^{5,6,7} Inflammation and/or other disease processes in the skin increase percutaneous absorption.⁸ Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids.^{6,7} Thus, occlusive dressings may be a valuable therapeutic adjunct for treatment of resistant dermatoses (see DOSAGE AND ADMINISTRATION).

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

INDICATIONS AND USAGE

Hydrocortisone Valerate Ointment is indicated for the relief of the inflammatory and pruritic manifestations of the corticosteroid-responsive dermatoses.

CONTRAINDICATIONS

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

PRECAUTIONS

General

Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.⁹

Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings.¹⁰

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

Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug.¹⁰ Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.^{11,12}

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity.^{13,14} (See PRECAUTIONS - Pediatric Use.)

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

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

Information for the Patient

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

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

Laboratory Tests

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

- Urinary free cortisol test
- ACTH stimulation test

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Studies to determine mutagenicity with prednisolone and hydrocortisone have revealed negative results.^{15,16}

Pregnancy, Teratogenic Effects, Pregnancy Category C

Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Nursing Mothers

It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant.^{17,18} Nevertheless, caution should be exercised when topical corticosteroids are administered to a nursing woman.

Pediatric Use

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

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilloedema.

Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

ADVERSE REACTIONS

The following local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximate decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, milium.

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

HYDROCORTISONE VALERATE OINTMENT 0.2% SHOULD BE APPLIED TO THE AFFECTED AREA AS A THIN FILM TWO OR THREE TIMES DAILY DEPENDING ON THE SEVERITY OF THE CONDITION.

Occlusive dressings may be used for the management of psoriasis or recalcitrant conditions.

If an infection develops, the use of occlusive dressings should be discontinued and appropriate antimicrobial therapy instituted.

HOW SUPPLIED

HYDROCORTISONE VALERATE OINTMENT 0.2% is supplied in 15 g, 45 g and 60 g tube sizes.

STORAGE

Store below 26°C (78°F).

CAUTION: Federal law prohibits dispensing without prescription.

Mfd. by: TARO Pharmaceuticals Inc., Bramalea, Ontario, Canada L6T 1C3

Date issued: October 1, 1997

PK-2343-0

REFERENCES

1. Maibach HI, Stoughton RB: *Med Clin N Am* 57: 1253-64, 1973.
2. Engel JC, et al: *Arch Dermatol* 109: 863-5, 1974.
3. Barry BW: *Dermatologica* 152 (Supplement 1): 47-65, 1976.
4. McKenzie AW, Stoughton RB: *Arch Dermatol* 86: 608-10, 1962.
5. Feldmann RJ, Maibach HI: *J Invest Dermatol* 52: 89-94, 1969.
6. Feldmann RJ, Maibach HI: *J Invest Dermatol* 48: 181-3, 1967.
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11. Nathan AW, Rose GL: *Lancet* 1: 207, 1979.
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15. Seino Y, et al: *Cancer Res* 38: 2148-56, 1978.
16. Hemmerly J, Demaree M: *Cancer Res* 15 (Supplement 3): 69-75, 1955.
17. McKenzie SA, Selley JA, Agnew JE: *Arch Dis Child* 60: 694-6, 1975.
18. Katz FH, Duncan BR: *N Eng J Med* 293: 1154, 1975.

160mm

135mm

7.5mm

2mm

CAP END

OPEN END

60 g

NDC 51672-1292-3

Hydrocortisone Valerate Ointment 0.2%

FOR EXTERNAL USE ONLY. NOT FOR OPHTHALMIC USE.

CAUTION: Federal law prohibits dispensing without prescription.
Keep this and all medication out of the reach of children.

EACH GRAM CONTAINS: 2 mg of hydrocortisone valerate in a hydrophilic base composed of carbomer 934P, dibasic sodium phosphate, methylparaben, mineral oil, propylene glycol, purified water, sodium lauryl sulfate, steareth-2, steareth-100, stearyl alcohol and white petrolatum.

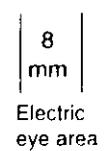
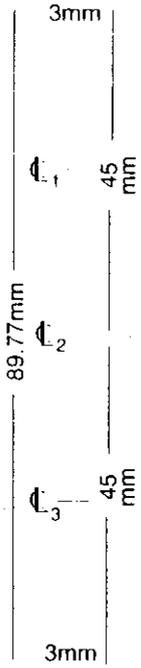
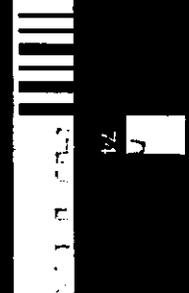
USUAL DOSAGE: Apply a small amount to affected areas 2 or 3 times daily. Read accompanying literature carefully.
Store below 26°C (78°F).

To Open: Use pointed end on cap to puncture seal.
For Lot No. and Exp. Date see crimp of tube.

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

PK-2340-0

TARO TARO



12/3/96
60 g Tube Right

214

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

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Bramalea, Ontario, Canada L6T 1C3
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3 51672 1292 3 1

60 g

NDC 51672-1292-3

Hydrocortisone Valerate Ointment 0.2%

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EACH GRAM CONTAINS: 2 mg of hydrocortisone valerate in a hydrophilic base composed of carbomer 934P, dibasic sodium phosphate, methylparaben, mineral oil, propylene glycol, purified water, sodium lauryl sulfate, steareth-2, steareth-100, stearyl alcohol and white petrolatum.

USUAL DOSAGE: Apply a small amount to affected areas 2 or 3 times daily. Read accompanying literature carefully.

Store below 26°C (78°F).

Lot No. & Expiry Date, see flap of carton or crimp of tube.

60 g

NDC 51672-1292-3

Hydrocortisone Valerate Ointment 0.2%

FOR EXTERNAL USE ONLY. NOT FOR OPHTHALMIC USE.

CAUTION: Federal law prohibits dispensing without prescription.
Keep this and all medication out of the reach of children.

TARO

TARO

PK-2341-0
M886

203

60 g
Hydrocortisone
Valerate
Ointment 0.2%

140 mm

115 mm

45 g

NDC 51672-1292-6

Hydrocortisone Valerate Ointment 0.2%

FOR EXTERNAL USE ONLY. NOT FOR OPHTHALMIC USE.

**CAUTION: Federal law prohibits dispensing without prescription.
Keep this and all medication out of the reach of children.**

EACH GRAM CONTAINS: 2 mg of hydrocortisone valerate in a hydrophilic base composed of carbomer 934P, dibasic sodium phosphate, methylparaben, mineral oil, propylene glycol, purified water, sodium lauryl sulfate, steareth-2, steareth-100, stearyl alcohol and white petrolatum.

USUAL DOSAGE: Apply a small amount to affected areas 2 or 3 times daily. Read accompanying literature carefully.
Store below 26°C (78°F).

To Open: Use pointed end on cap to puncture seal.
For Lot No. and Exp. Date see crimp of tube.

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PK-2338-0

TARO TARO

73

3 mm

ℓ₁

89.77 ℓ₂

ℓ₃

3 mm

190

103 mm

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

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3 51672 1292 6 2

45 g

NDC 51672-1292-6

Hydrocortisone Valerate Ointment 0.2%

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Lot No. & Expiry Date, see flap of carton or crimp of tube.

45 g

NDC 51672-1292-6

Hydrocortisone Valerate Ointment 0.2%

FOR EXTERNAL USE ONLY. NOT FOR OPHTHALMIC USE.

**CAUTION: Federal law prohibits dispensing without prescription.
Keep this and all medication out of the reach of children.**



TARO



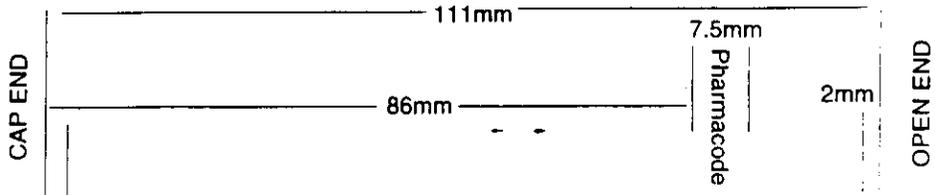
TARO



PK-2339-0
M885

178

45 g
Hydrocortisone
Valerate
Ointment 0.2%



3mm

1

29.925 mm

59.85mm

2

29.925 mm

3

29.925 mm

3mm

15 g NDC 51672-1292-1

Hydrocortisone Valerate Ointment 0.2%

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CAUTION: Federal law prohibits dispensing without prescription.
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USUAL DOSAGE: Apply a small amount to affected areas 2 or 3 times daily. Read accompanying literature carefully.

Store below 26°C (78°F).

To Open: Use pointed end on cap to puncture seal.
 For Lot No. and Exp. Date see crimp of tube.

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PK-2336-0

3mm

1

29.925 mm

59.85mm

2

29.925 mm

3

29.925 mm

3mm

TARO

TARO

74mm
2mm
31mm
1mm

Crimp Area

8 mm

Electric eye area

8/4/95
1/2 OZ Tube Right

Mango

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

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51672 1292 17

15 g

NDC 51672-1292-1

Hydrocortisone Valerate Ointment 0.2%

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USUAL DOSAGE: Apply a small amount to affected areas 2 or 3 times daily. Read accompanying literature carefully.
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Lot No. & Expiry Date, see flap of carton or crimp of tube.

15 g

NDC 51672-1292-1

Hydrocortisone Valerate Ointment 0.2%

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



PK-2337-0
M99

15 g
Hydrocortisone
Valerate
Ointment 0.2%