PRODUCT MONOGRAPH

LYDERM OINTMENT 0.05%
(Fluocinonide Ointment USP, 0.05%)

LYDERM GEL 0.05%
(Fluocinonide Gel USP, 0.05%)

LYDERM CREAM 0.05%
(Fluocinonide Cream USP, 0.05%)

Topical Corticosteroids

TaroPharma
A Division of Taro Pharmaceuticals Inc.
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Brampton, Ontario, Canada
L6T 1C1

Preparation Date: September 02, 2003

Control # 086260 (ointment, gel); 086263 (cream)
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LYDERM CREAM 0.05%
Fluocinonide Cream USP, 0.05%

Topical Corticosteroids

TaroPharma, Brampton, Ontario Canada.

ACTIONS AND CLINICAL PHARMACOLOGY
LYDERM 0.05% (fluocinonide) ointment, gel and cream are high potency, fluorinated corticosteroid preparations. Topical corticosteroids are synthetic derivatives of cortisone which are effective when applied locally to control many types of inflammatory, allergic and pruritic dermatoses. Modifications to the chemical structure such as fluorination, generally enhances both anti-inflammatory activity and increases the likelihood of adverse effects. The mechanism of anti-inflammatory activity of topical corticosteroids is generally unclear. However, corticosteroids are thought to induce phospholipase A2 inhibitor proteins, preventing arachidonic acid release and the biosynthesis of potent mediators of inflammation.

Topical corticosteroids are primarily effective because of their anti-inflammatory, anti-pruritic and vasoconstrictive actions.

Topical absorption of corticosteroids follow the same pharmacologic fate as systemically administered doses: Corticosteroids in the circulation are bound to plasma proteins, although the
fluorinated compounds are bound to a lesser degree, accounting for their increased potency compared to natural corticosteroids.

It is generally known that steroid hormones are metabolized predominantly in the liver and to a lesser extent in the kidney, intestines, spleen, muscles and other tissues and then excreted in the urine as conjugates.

**INDICATIONS AND CLINICAL USE**
LYDERM 0.05% (fluocinonide) ointment, gel and cream are indicated for topical therapy of corticosteroid responsive acute and chronic skin eruptions where an anti-inflammatory, anti-allergenic and anti-pruritic activity in the topical management is required.

**CONTRAINDICATIONS**
LYDERM 0.05% (fluocinonide) ointment, gel and cream should not be used in bacterial/fungal skin infections, tuberculosis of the skin, syphilitic skin infections, chicken pox, eruptions following vaccinations and viral diseases of the skin in general. LYDERM 0.05% (fluocinonide) ointment, gel and cream is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

LYDERM (fluocinonide) ointment, gel and cream are not recommended for ophthalmic use.

**WARNINGS**
When used under occlusive dressing, over extensive areas, or on the face, scalp, axillae and scrotum, sufficient absorption may occur giving rise to adrenal suppression and other systemic effects.

**PRECAUTIONS**

**General**
Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycaemia and glucosuria can also be
produced in some patients by systemic absorption of topical corticosteroids.

Conditions which augment systemic absorption include application of the more potent steroids, use over a large surface area, prolonged use, occlusive dressings. Patients receiving a large dose of potent topical steroids to a large surface area or under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression. This may be done by using the ACT stimulation test or other recognized/validated test. 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 topical corticosteroids. Infrequently, signs and symptoms of glucocorticoid insufficiency may occur requiring supplemental systemic corticosteroids. Occlusive dressings should not be applied if body temperature is elevated. To minimize systemic absorption when long-term therapy or large surface area for treatment is likely, periodic interruption of treatment or treatment of one area of the body at a time should be considered.

Children may be more susceptible to systemic toxicity from equivalent doses due to larger skin surface to body mass ratios (see Precautions - Pediatric Use).

Topical corticosteroids, particularly the more potent ones, should be used with caution on lesions close to the eye because systemic absorption may cause increased intraocular pressure, glaucoma or cataracts.

Prolonged use of topical corticosteroid preparations may produce striae or atrophy of the skin or sub-cutaneous tissue. Topical corticosteroids should be used with caution on lesions of the face, groin and axillae as these areas are more prone to atrophic changes than other areas of the body. Frequent observation is important if these areas are to be treated. If skin atrophy is observed, treatment should be discontinued.

If irritation develops, LYDERM (fluocinonide) should be discontinued and appropriate therapy instituted. Allergic contact dermatitis from corticosteroids is usually diagnosed by observing 'failure
to heal' rather than clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

Suitable precautions should be taken when using topical corticosteroids in patients with stasis dermatitis and other skin diseases with impaired circulation.

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 LYDERM ointment, gel or cream should be discontinued until the infection has been adequately controlled.

Patients should be advised to inform subsequent physicians of the prior use of corticosteroids.

**Use in Pregnancy**

Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage. Desoximethasone has been shown to be teratogenic after dermal/subcutaneous application of human therapeutic doses in laboratory animals. LYDERM (fluocinonide) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, particularly in the first trimester of pregnancy. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for hypoadrenalism.

**Lactation/Nursing Mothers**

Systemically administered corticosteroids are secreted into human milk and could suppress growth, interfere with endogenous corticosteroid production or cause untoward effects. Caution should be exercised when LYDERM ointment, gel or cream are administered to a nursing mother.

**Pediatric Use**

The safety and effectiveness of LYDERM 0.05% (fluocinonide) ointment, gel and cream in children
and infants have not been established. Because of the higher ratio of skin surface area to body mass, children are at a greater risk than adults for HPA axis suppression when treated with topical corticosteroids. They are also at greater risk of glucocorticosteroid insufficiency after withdrawal of treatment and of Cushing's syndrome while on treatment. Adverse effects including striae have been reported with use of topical corticosteroids in infants and children. 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 ACT 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.

Carcinogenesis, Mutagenicity, Reproduction
Long-term animal studies have not been performed to evaluate the effect on fertility of fluocinonide.

Studies to determine mutagenicity with prednisolone and hydrocortisone have revealed negative results. Fluocinonide was not mutagenic in the Ames microbial mutagen test, with or without metabolic activation.

ADVERSE REACTIONS
The following local adverse skin reactions have been reported with topical corticosteroids and may occur more frequently with use of occlusive dressings. These reactions are listed in 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 and miliaria. In addition, there are reports of the development of pustular psoriasis from chronic plaque psoriasis following reduction or discontinuation of potent topical corticosteroid products.
Adrenal suppression has been shown to occur with prolonged use of large doses of topical corticosteroids, particularly under occlusion due to increased percutaneous absorption.

Posterior subcapsular cataracts have been reported following systemic use of corticosteroids.

**OVERDOSE: SYMPTOMS AND TREATMENT**

Topically applied LYDERM (fluocinonide) ointment, gel and cream can be absorbed systemically. Percutaneous absorption is enhanced when large amounts of corticosteroid are applied, when used under occlusive dressing or when used chronically. Toxic effects of hypercorticism and adrenal suppression may appear. Should toxic effects occur, the dosage of LYDERM (fluocinonide) ointment, gel and cream should be discontinued slowly, consistent with accepted procedures for discontinuation of chronic steroid therapy. The restoration of hypothalamic-pituitary axis may be slow; during periods of pronounced physical stress (severe infections, trauma, surgery); a supplement with systemic steroids may need to be considered. Toxic effect may include ecchymosis of skin, peptic ulceration, hypertension, aggravation of infection, hirsutism, acne, edema and muscle weakness due to protein depletion. Treatment of a patient with systemic toxic manifestations consists of assuring and maintaining a patent airway and supporting ventilation using oxygen and assisted or controlled respiration as required. This usually will be sufficient in the management of most reactions. Should circulatory depression occur, vasopressors and i.v. fluids may be used. Should a convulsion persist despite oxygen therapy, small increments of ultra-short acting barbiturate (pentobarbital or secobarbital) may be given i.v. Allergic reactions are characterized by cutaneous lesions, urticaria, edema or anaphylactoid reactions.
DOSAGE AND ADMINISTRATION

Gently, apply a thin film of LYDERM 0.05% (fluocinonide) ointment, gel or cream to the affected skin areas two to four times daily, depending on the severity of the condition. Rub in gently and completely.

Total weekly dose should not exceed 45 g in adults. Therapy should be limited to 2 weeks. If a symptomatic response is not noted within a few days to a week, the local applications of corticosteroid should be discontinued and the patient re-evaluated. Therapy should be discontinued as soon as lesions heal.

It is recommended that LYDERM 0.05% ointment, gel and cream not be used under occlusive conditions.

PATIENT INFORMATION

LYDERM is a proprietary name of TaroPharma for fluocinonide ointment, gel and cream USP.

LYDERM is a highly potent topical corticosteroid. It possesses anti-inflammatory, antipruritic and vasoconstrictive actions. The mechanism of anti-inflammatory activity of topical corticosteroids is unclear. There is some evidence to suggest that therapeutic efficacy in man is related to vasoconstrictor activity of the topical corticosteroid. Hence, vasoconstrictor assays are used to compare and predict potencies and/or clinical efficacies of topical corticosteroids.

LYDERM is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

This medication is to be used as directed by the physician. It is only for external use. Avoid contact with the eyes.

The medication should not be used for any disorder other than that for which it is prescribed.
Do not use occlusive wrapping/bandages on treated sites unless directed by a physician.

If you are pregnant, intend to become pregnant or are breast feeding or intend to breast feed, inform you physician.

Inform your physician of prior or current use of corticosteroids for treatment of skin disorders, allergic reactions, arthritis or asthma. In particular, tell your physician if you have developed an allergy or intolerance to such medicine. Also inform your physician of allergies to other substances such as foods, dyes etc.

Do not exceed prescribed dose.

Contact your physician if there is no improvement in your condition within 1 week.

Report any signs of local adverse reactions to your physician.

Do not have any immunizations without your doctor's approval if you are using this medication.
PHARMACEUTICAL INFORMATION

Chemical Name
Pregna-1,4-diene-3,20-dione, 21-(acetyloxy)-6,9-difluoro-11-hydroxy-16,17-[(1-methylethylidene)bis(oxy)]-(6α,11β,16α)-

6α,9-Difluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione, cyclic 16,17-acetal with acetone, 21-acetate
[356-12-7]

Structural Formula

![Structural Formula Image]

Molecular Formula
C_{26}H_{32}F_2O_7

Molecular Weight
494.53

Description
Fluocinonide is a white to creamy white, practically odorless, crystalline powder which melts at about 300°C with decomposition. It is sparingly soluble in acetone and chloroform, slightly soluble in ethanol and methanol, very slightly soluble in ether and practically insoluble in water.
**Composition**
LYDERM 0.05% ointment contains 0.5 mg/g fluocinonide in an ointment base consisting of glycercyl monostearate, propylene carbonate, propylene glycol, white petrolatum and white wax.

LYDERM 0.05% gel contains 0.5 mg/g fluocinonide in a gel base consisting of carbomer, edetate disodium, propylene glycol, propyl gallate, purified water and sodium hydroxide.

LYDERM 0.05% cream contains 0.5 mg/g fluocinonide in a cream base consisting of citric acid, glycerin, 1,2,6-hexanetriol, PEG-3350, PEG-8000, propylene glycol and stearyl alcohol.

**Stability and Storage Recommendation**
LYDERM 0.05% Ointment, Gel and Cream should be stored at room temperature (15°C - 30°C).

**Availability of Dosage Forms**
LYDERM 0.05% Ointment, Gel and Cream are available in 15 gram and 60 gram collapsible tubes. LYDERM 0.05% Cream is also available in 400 gram plastic jars.
**PHARMACOLOGY**

Fluocinonide demonstrated 310 and 160 times the subcutaneous and oral thymolytic activity of cortisol respectively. Its anti-granuloma activity in relation to cortisol was of the same magnitude as its thymolytic activity. The composite results of seven assays demonstrates that fluocinonide has 350 times the topical anti-inflammatory activity of cortisol when tested utilizing the croton oil-inflamed ear. The glucocorticoid activity of fluocinonide to cortisol was determine in adrenalectomized male rats. The results demonstrate that fluocinonide had approximately 50 times the glucocorticoid activity of cortisol.

Fluocinonide has approximately 400 times the adrenal suppressive activity of cortisol when given subcutaneously to female rats. In adrenalectomized mice, fluocinonide had approximately 100 times the activity of cortisol with regard to the effect on the white blood count and depletion of eosinophils.

The sodium and potassium retaining activity of fluocinonide using desoxycorticosterone as a positive control was determined by subcutaneous injection in adrenalectomized male rats with a dosage range of 1 to 16 mcg/rat. When no sodium load is given, there was a significant (P<0.01) increase in potassium excretion with the 16 mcg dose only. Significant (P<0.05) increase in potassium excretion was observed at all doses studied. When fluocinonide is given along with a sodium load, it produces only a slight elevation of urinary sodium, whereas a dose as low as 1 mcg/kg significantly (P<0.01) increases potassium excretion.

**Vasoconstrictor Tests**

Vasoconstrictor assay has proved to be a reliable human bioassay for the screening of compounds with topical corticosteroid activity, and for the comparative evaluation of biologic effects relative to existing standards.

Although the results of this standardized assay method cannot be directly equated with topical efficacy in dermatologic therapy, they appear to have definite predictive value, and to correlate well with clinical activity and potency. According to McKenzie, "the most powerful vasoconstrictors are
those substances which clinical studies have shown to be the most effective topical anti-inflammatory agents”.

Vasoconstrictor tests were performed comparing fluocinonide creams and ointments to betamethasone 17-valerate, and hydrocortisone. Results of the alcoholic vasoconstrictor assay, demonstrate the relative activity of fluocinonide to be of the order of 400 times the activity of hydrocortisone and 4 times the activity of betamethasone 17-valerate.

Stoughton reports fluocinonide to be five times as potent as betamethasone 17-valerate in inducing vasoconstriction. The in vitro penetration* of fluocinonide and betamethasone is shown in the following table:

<table>
<thead>
<tr>
<th></th>
<th>Human* Skin</th>
<th>Hairless* Mouse Skin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betamethasone 17-valerate</td>
<td>1.7</td>
<td>2.1</td>
</tr>
<tr>
<td>Fluocinonide</td>
<td>9.1</td>
<td>13.0</td>
</tr>
</tbody>
</table>

*Agent showing least in vitro penetration (fluocinolone alcohol) and least activity in vasoconstrictor bioassay (betamethasone alcohol and fluocinolone alcohol) listed as one (1.0). All other agents listed in the numerical ratio of their abilities to penetrate skin in vitro or induce vasoconstriction, respectively.

These data demonstrated that fluocinonide penetrates both human skin and hairless mouse skin better than betamethasone 17-valerate in this test system.

Place, V.A. et al., with a recent modification of the Stoughton-McKenzie Assay, demonstrated fluocinonide to have approximately five times the potency of betamethasone 17-valerate as determined by vasoconstriction in normal skin.
A one-period, randomized, vasoconstrictor study was performed on 40 pre-screened, asymptomatic, female subjects to compare the bioavailability of LYDERM Ointment 0.05% manufactured by TaroPharma with the currently marketed Lidex® Ointment manufactured by Syntex, Canada. The degree of vasoconstriction was determined both by visual assessment and with a chromameter. Based on both the visual and chromameter results, LYDERM Ointment is bioequivalent to the Lidex® Ointment.

Table 1: Mean Results for Visual and Chromameter Evaluation of LYDERM Ointment vs. Lidex® Ointment using Locke's Method for calculating confidence intervals:

<table>
<thead>
<tr>
<th>LYDERM vs. Lidex® Ointment</th>
<th>N</th>
<th>Means</th>
<th>Ratio (%)</th>
<th>90% Confidence Interval²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TaroPharma</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Visual</td>
<td>35</td>
<td>17.20</td>
<td>17.81</td>
<td>96.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>88.5</td>
<td>105.7</td>
<td></td>
</tr>
<tr>
<td>Chromameter</td>
<td>29</td>
<td>15.28</td>
<td>13.60</td>
<td>112.4</td>
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<tr>
<td></td>
<td></td>
<td>88.6</td>
<td>136.8</td>
<td></td>
</tr>
</tbody>
</table>

1 Ratio percent calculated as: (Taro/Reference) x 100%.
2 Confidence interval on the ratio.

A one-period, randomized, vasoconstrictor study was performed on 40 pre-screened, asymptomatic, female subjects to compare the bioavailability of LYDERM Gel 0.05% manufactured by TaroPharma, with the currently marketed Topsyn® Gel manufactured by Syntex, Canada. The degree of vasoconstriction was determined both by visual assessment and with a chromameter. Based on both the visual and chromameter results, LYDERM Gel is bioequivalent to the Topsyn® Gel.

Table 2: Mean Results for Visual and Chromameter Evaluation of LYDERM Gel vs. Topsyn® Gel Using Locke’s Method for Calculating Confidence Intervals:

<table>
<thead>
<tr>
<th>LYDERM vs. Topsyn® Gel</th>
<th>N</th>
<th>Means</th>
<th>Ratio (%)</th>
<th>90% Confidence Interval²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TaroPharma</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Visual</td>
<td>22</td>
<td>35.74</td>
<td>37.63</td>
<td>95.0</td>
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<tr>
<td></td>
<td></td>
<td>91.1</td>
<td>99.1</td>
<td></td>
</tr>
<tr>
<td>Chromameter</td>
<td>26</td>
<td>30.52</td>
<td>30.47</td>
<td>100.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90.2</td>
<td>111.2</td>
<td></td>
</tr>
</tbody>
</table>

1 Ratio percent calculated as: (TaroPharma/Reference) x 100%.
The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle and the integrity of the epidermal barrier.

Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. 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. They 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.

Absorption studies utilizing fluocinonide cream and ointment 0.05% in quantities of 30 to 60g/day (15 to 30 mg/day of active material) were done in 13 patients during 10 days. Transient suppression of adrenal activity has been noted in 3 out of 4 patients receiving 30 g/day of the cream under occlusion and in 2 out of 6 patients without occlusion. Transient adrenal suppression was noted with the application of 60 g/day of the cream in 2 patients out of 3 without occlusive therapy. Adrenal suppression can be expected in a number of patients with such large quantities since it is known that it depends on several factors such as the percentage of body surface treated, the concentration of the corticosteroid in the topical preparation, and most important, the integrity of the skin barrier. The adrenals apparently revert to normal function within 48 hours after cessation of therapy.

Laboratory results for fasting blood sugar, SGPT or SGOT, blood urea nitrogen, serum potassium and serum sodium were determined in the patients entered in the above absorption studies. Examination of the data shows values to be in normal range.

A Draize test was performed on 213 healthy adult volunteers, one of whom had previous exposure to fluocinonide, the cream base or the ointment. There was no evidence of contact hypersensitivity to the cream or ointment formulation. However, in a few volunteers, a slight degree of erythema was noted which rapidly disappeared after removing the patch and it represented a very mild degree.
of irritation.

**TOXICOLOGY**

Fluocinonide is an active synthetic corticosteroid. As judged by animal tests, the compound can be absorbed through the skin to produce systemic effects similar to those observed following oral, parenteral or aerosol administration.

In some cases, the LD₅₀ of fluocinonide, when administered as a single intraperitoneal dose to rats, is of the same order of magnitude as that seen with other synthetic corticosteroids. In other cases, the LD₅₀ value of this compound is lower. As with previously studied corticoids, the toxic effects include reduction in adrenal weight, liver changes, lung consolidation, septicemia, and gastrointestinal effects. When deaths occurred, time after dosing with fluocinonide was about the same as that reported for other corticosteroids.

Subacute and chronic administration of fluocinonide to various species of laboratory animals produced typical corticosteroid effects, which included hyperglycemia, lymphopenia and changes in liver structure. These effects were generally not severe and were reversible with cessation of treatment.

No cleft palates or other skeletal anomalies were observed in pups from rabbits dosed with the compound during organogenesis.

**CLINICAL STUDIES**

Forty-seven investigators completed a large-scale double-blind, paired comparison clinical trial utilizing a common protocol. Seven hundred and seventeen patients were studied on the cream formulation, and 731 patients on the ointment formulation.

The results of these studies were analyzed statistically utilizing both the truncated sequential method and the student t-tests. Fluocinonide in the cream and ointment formulation, when tested in steroid-responsive dermatoses, gave significant therapeutic results. The low incidence and mild
severity of adverse reactions noted by the patients and the investigators indicate that the drug is safe and effective when used as directed.

**BIBLIOGRAPHY**