PRODUCT MONOGRAPH

[Pr]pms -MOMETASONE

(Mometasone Furoate 0.1% Ointment USP)

Topical Corticosteroid

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THERAPEUTIC CLASSIFICATION

Topical Corticosteroid

ACTIONS AND CLINICAL PHARMACOLOGY

Mometasone furoate is a medium potency topical corticosteroid. 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.

Pharmacokinetics:

While the mechanism of the anti-inflammatory effect is unclear, it is recognized that there is a correlation between the therapeutic anti-inflammatory activity of corticosteroids and their vasoconstrictor potencies. Vasoconstrictor assays have therefore been used to compare and predict the relative therapeutic potencies of this class of compounds, which are applied topically and are not absorbed into the blood stream.

In a comparative bioequivalence study between pms-MOMETASONE 0.1% Ointment and the Canadian reference product, the relative potency of each product was measured using a ChromaMeter. This device measures the degree of local vasoconstrictor response by measuring the degree of skin blanching produced by each drug.

The following table reveals the results of the skin blanching measurements. Both products demonstrated comparable vasoconstrictor (therapeutic) activity.

Mean ChromaMeter Results comparing pms-MOMETASONE 0.1% Ointment (Test) with the Canadian Reference Product (Reference)

Evaluation	N	Test pms-MOMETASONE 0.1% Ointment (Pharmascience Inc.)	Reference: Elocom 0.1% Ointment (Schering Canada)	Ratio (%)[1]	90% Confidence Interval [2] Lower (%)	Upper (%)
ChromaMeter Reading (Skin blanching)	38	13	13.3	98	88	108.5

1: Ratio percent calculated as Test/Reference x 100

2: Confidence interval on the ratio

INDICATIONS AND CLINICAL USE

pms-MOMETASONE 0.1% Ointment (mometasone furoate) is indicated for relief of the inflammatory and pruritic manifestations of corticosteroid responsive dermatoses such as psoriasis and atopic dermatitis.

CONTRAINDICATIONS

pms-MOMETASONE (mometasone furoate) 0.1% Ointment is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation. pms-MOMETASONE 0.1% Ointment 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. pms-MOMETASONE 0.1% Ointment is not 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-pituitaryadrenal (HPA) axis suppression with the potential for glucorticosteroid 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 areas, prolonged use and 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 intra ocular 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, mometasone furoate 0.1% Ointment 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 favourable response does not occur promptly, use of mometasone furoate 0.1% Ointment 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. Mometasone furoate 0.1% Ointment 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 hydroadrenalism.

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 mometasone furoate 0.1% Ointment is administered to a nursing mother.

Pediatric Use:
Safely and effectiveness of mometasone furoate 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 effect 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.

Geriatrics:
Suitable precautions should be taken in using topical glucocorticoids in patients with impaired circulation suffering from stasis dermatitis and other skin diseases.

Carcinogenesis, Mutagenicity, Reproduction:
Long-term animals studies have been performed to evaluate carcinogenic potential of mometasone furoate (see TOXICOLOGY).

Mometasone furoate was nonmutagenic in the mouse lymphoma assay and the salmonella/mammalian microsome bioassay, and was classified as negative in the mouse bone marrow erythrocyte micronucleus assay. A test in Chinese hamster ovary cells was inconclusive whereas a similar test measuring chromosomal aberration frequencies using rat liver S9 fraction was negative (see TOXICOLOGY).

Mometasone furoate was tested for effects on reproduction. Dermal teratology studies demonstrated no unusual effects on the course of pregnancy or on embryo and fetal viability (see TOXICOLOGY).

ADVERSE REACTIONS

The following local adverse reactions have been reported with mometasone furoate ointment: During clinical studies in 812 patients: burning - 13, pruritus - 8, skin atrophy - 8, tingling/stinging - 7, and furunculosis -3.

The overall incidence of side effects was 4.9%, i.e., 40 of 812 subjects reported treatment-related adverse experiences.

Side effects were mild to moderate and were those typically associated with topical corticosteroid formulations after seven days of treatment.

No systemic treatment-related adverse experiences were seen.

The following additional local adverse reactions have been reported with topical corticosteroids and may occur 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 also been reported following topical corticosteroid therapy. Posterior subcapsular cataracts have been reported following systemic use of corticosteroids.

OVERDOSE: SYMPTOMS AND TREATMENT

Topically applied mometasone furoate 0.1% Ointment can be absorbed systemically. Percutaneous absorption is enhanced when large amounts of corticosteroids 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 mometasone furoate 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 intravenous fluids may be used. Should a convulsion persist despite oxygen therapy, small increments of ultra-short acting barbiturate (pentobarbital or secobarbital) may be given intravenously. Allergic reactions are characterized by cutaneous lesions, urticaria, edema or anaphylactoid reactions.

DOSAGE AND ADMINISTRATION

Apply a thin film of pms-MOMETASONE (mometasone furoate) 0.1% Ointment to affected areas of skin once daily. Rub in gently and completely. Therapy should be limited to 1 -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. Safely and effectiveness of mometasone furoate in children and infants have not been established.

pms-MOMETASONE 0.1% Ointment should not be used with occlusive dressing unless directed by a physician.

pms-MOMETASONE 0.1% Ointment is not recommended for children under 2 years of age.

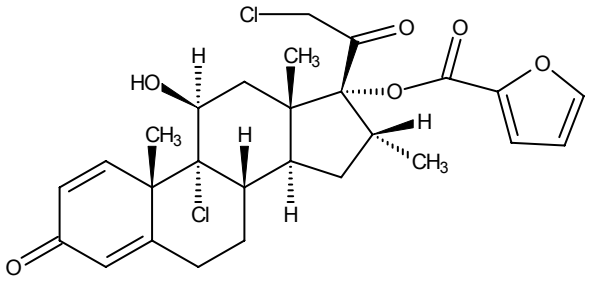
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: mometasone furoate

Chemical name: 9,21-dichloro-llβ,17-dihydroxy-16α-methyl-pregna -1,4-diene-3,20-dione 17-(2-furoate)

Structural formula:



Molecular formula: $C_{27}H_{30}Cl_20_6$

Molecular Weight: 521.43

Description: Mometasone furoate is a white to off-white powder practically insoluble in water, slightly soluble in octanol, and moderately soluble in ethyl alcohol.

Composition: pms-MOMETASONE (mometasone furoate) 0.1% Ointment**,** each gram contains 1 mg of mometasone furoate in a base of white wax and white petrolatum. Other constituents are hexylene glycol and propylene glycol monostearate.

AVAILABILITY AND DOSAGE FORMS

pms-MOMETASONE (mometasone furoate) 0.1% Ointment is supplied in 15 g and 50 g tubes, boxes of one.

Stability and Storage Recommendations: pms-MOMETASONE 0.1% Ointment is stored at room temperature, between 15 to 30°C.

PATIENT INFORMATION

Information for the Patient

Please read this leaflet before you start using pms-MOMETASONE (mometasone furoate) 0.1% Ointment. Each time you renew your prescription, re-read the leaflet that comes with your medicine, just in case any information has changed. Remember, this leaflet does not take the place of talking to your health care provider (such as your doctor, nurse, or pharmacist). You and your heath care provider should discuss pms-MOMETASONE 0.1% Ointment while you are using it.

What is pms-MOMETASONE?

pms-MOMETASONE 0.1% Ointment is a proprietary name of Pharmascience inc. for mometasone furoate. It is a topical corticosteroid. It belongs to the general family of medicines called steroids. pms-MOMETASONE 0.1% Ointment is indicated for relief of swelling and itching from skin conditions such as psoriasis and eczema.

pms-MOMETASONE is a white ointment. Each gram of pms-MOMETASONE 0.1% Ointment contains: 1mg mometasone furoarate, USP in an ointment base of hexylene glycol; phosphoric acid; propylene glycol stearate (55% monoester); white wax; white petrolatum; and purified water.

Before using pms-MOMETASONE:

Tell your doctor if you are currently using or have previously used corticosteroids for the treatment of skin disorders, allergic reactions, arthritis or asthma and if you have ever had any unusual or allergic reaction to corticosteroids. Also tell your doctor if you are allergic to any other substances, such as food, preservatives, or dyes.

Tell your doctor if you are pregnant, intend to become pregnant or are breast-feeding or intend to breast-feed before using pms-MOMETASONE 0.1% Ointment.

How to use pms-MOMETASONE:

This medication is to be used only as directed by your doctor. Do not use more of it, do not use it more often, and do not use it for a longer period of time than your doctor has specified.

Rub a small amount of pms-MOMETASONE 0.1% Ointment into the affected area once daily. Don't put on too much; a thin layer works best.

Contact your doctor if there is no improvement in your condition within one (1) week.

Do not use pms-MOMETASONE for any other skin condition without asking your doctor first.

pms-MOMETASON**E** is for external use only.

Be careful not to get this medication in your eyes. Wash your hands after using the medication.

Do not bandage or otherwise cover or wrap the treated skin area unless your doctor has told you to do so.

While you are using pms-MOMETASONE:

Do not get any vaccinations while you are using this medication without your doctor's approval.

Tell your doctor if you experience side effects to pms-MOMETASONE (e.g. burning or stinging).

How to store pms-MOMETASONE:

pms-MOMETASONE 0.1% Ointment should be stored at controlled room temperature 15-30°C.

Avoid freezing.

ANIMAL PHARMACOLOGY

Pharmacodynamics:

One study of the topical activity of mometasone furoate involved the croton oil ear edema assay. In the mouse, following a single application, mometasone furoate, was equipotent to the standard betamethasone valerate. Following five daily applications, it was 7.7 times more potent than betamethasone valerate. Data indicate that the side effect potential does not parallel the anti-inflammatory potency, i.e., mometasone furoate was 0.6 times as potent as betamethasone valerate in suppressing the mouse hypothalamic-pituitary adrenal axis.

In estrogen-primed immature rabbits, changes indicative of mometasone furoate- induced progestational activity were evident. This type of activity is characteristic of corticosteroids.

Pharmacokinetics:

Studies (ADME) of the disposition of ^{3}H-mometasone furoate ointment in rats, rabbits and dogs have shown that the drug was poorly absorbed and did not accumulate in any tissues. Approximately 2.5% of a topically applied dose was absorbed by rats, 6% by rabbits and 2% by dogs.

The percutaneous absorption of ^{3}H-mometasone furoate cream was studied in the rabbit. Plasma radioactivity was low, corresponding to less than 1 mL equivalent/mL. An average of approximately 85% of the applied radioactivity was recovered from the protective devices and an average of 6.12% was recovered from treated skin. Thus, the average total recovery from these three sources (treated skin, wipes, protective devices) was 92.7% suggesting low systemic absorption (no more than 7% of the dose).

HUMAN PHARMACOLOGY

Pharmacodynamics:

Mometasone furoate, 0.1% cream or ointment, when applied twice daily, 15 g per application, for one week demonstrated no evidence of affecting HPA axis function, as measured by plasma cortisol levels.

Mometasone furoate, tested under maximized and exaggerated conditions of subject exposure, demonstrated minimal potential to effect irritation and exhibited no evidence of inducing photo-allergenicity, photo toxicity, or contact sensitization reactions.

Pharmacokinetics:

In man, ^{3}H-mometasone furoate 0.1% ointment applied to 6 male volunteers revealed 0.7% of the administered dose was absorbed into the systemic circulation: 0.2% being excreted into the urine and 0.5% into the faeces. Characterization of the metabolic profile was not feasible due to low concentrations in the serum.

TOXICOLOGY

Acute toxicity:

Single dose oral and/or subcutaneous toxicity studies of mometasone furoate were conducted in mice, rats and dogs.

LD_{50}'s mice and rats:	>2000 mg/kg by the oral route
LD_{50}'s, mice:	>200 mg/kg, subcutaneously
LD_{50}'s rats:	>2000 mg/kg subcutaneously

Long-Term Toxicity:

The observed local and systemic changes were typical of corticosteroids in long-term, multiple dose toxicity studies in:

Animal	**Route**	**Dosage Regimen**
Rats	Subcutaneous	0.3, 1 and 10 mg/kg/day
Dogs	Subcutaneous	0.06, 0.6 and 3 mg/kg/day
Rabbits	Dermal	0.1% with intact or abraded skin at 0.05 1.0 g/kg/day
Dogs	Dermal	0.5, 1 and 3 g/kg/day

The well-known systemic changes attributable to corticosteroid therapy were observed, such as liver and kidney enlargement; atrophy of the spleen, adrenals, skeletal muscle, thymus and lymph nodes; reduced body weight; abdominal distension; decrease in lymphocytes and increase in serum triglycerides.

The dermal changes were skin thinning, hyperkeratosis, slight erythema, reduced hair growth, desquamation, papules and/or pustules and some discrete areas of discoloration.

Dermal:

In guinea pigs, it was demonstrated that mometasone furoate has a weak potential for topical sensitization. The preparation was not significantly irritating to the eyes of rabbits during an acute ocular irritation study.

Mometasone cream 0.1% applied topically once daily to rabbits for 21 to 24 days at 1 to 3 times the estimated human daily therapeutic dose produced local and systemic effects typical of corticosteroids.

Reproduction:

Dermal teratology studies demonstrated no unusual effects on the course of pregnancy or on embryo and fetal viability.

Mutagenicity:

Mometasone furoate was nonmutagenic in the mouse lymphoma assay and the salmonella/mammalian microsome bioassay, and was classified as negative in the mouse bone marrow erythrocyte micronucleus assay. A test in Chinese hamster ovary cells was inconclusive whereas a similar test measuring chromosomal aberration frequencies using rat liver S9 fraction was negative.

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