DESCRIPTION OF THE PRODUCT

The Elocom® Cream, Ointment and Lotion formulations contain mometasone furoate (SCH 32088; Figure 1.1), a synthetic 17-heterocyclic corticosteroid with anti-inflammatory, antipruritic and vasoconstrictive properties, which is presently being therapeutically used for the treatment of corticosteroid responsive dermatoses, such as psoriasis and atopic dermatitis.

1.1 PHARMACEUTICAL PARTICULARS

1.1.1 Drug Substance

Mometasone furoate (see Figure 1.1), 9,21-dichloro-11β,17-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione 17-(2)-furoate, is a synthetic, anti-inflammatory corticosteroid whose steroid nucleus is the 16α-methyl analog of beclomethasone, but with a 21-chloro group and a novel (2)-furoate 17-ester function. The empirical formula is C\textsubscript{27}H\textsubscript{30}Cl\textsubscript{2}O\textsubscript{6} and Molecular Weight (MW) is 521.44.
1.1.2 Drug Product

1.1.2.1 Cream
Each gram of Mometasone furoate cream 0.1% contains: 1 mg mometasone furoate in a cream base of white soft paraffin, hexylene glycol, aluminium starch octenylsuccinate, white wax, purified water, hydrogenated soybean lecithin, titanium dioxide, phosphoric acid.

1.1.2.2 Ointment
Each gram of Mometasone furoate ointment 0.1% contains: 1 mg mometasone furoate in an ointment base of hexylene glycol, propylene glycol stearate, white wax, white petrolatum, purified water and phosphoric acid to adjust the pH.

1.1.2.3 Lotion
Each gram of Elocom Lotion 0.1% contains: 1 mg of mometasone furoate in a lotion base of isopropyl alcohol, propylene glycol, hydroxypropylcellulose, sodium dihydrogen phosphate dehydrate and purified water. May also contain phosphoric acid to adjust the pH.
2 PRECLINICAL INFORMATION

2.1 PHARMACODYNAMIC PROPERTIES

The pharmacodynamic activity of mometasone furoate cream, ointment and lotion is directly related to its active component, mometasone furoate, and the vehicles.

Like other topical corticosteroids, mometasone furoate has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear. Corticosteroids, however, 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.

Mometasone furoate is a potent inhibitor of the in vitro production of three inflammatory cytokines that are involved in initiating and maintaining the inflammatory state: interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor α (TNF-α).

2.2 PRECLINICAL PHARMACOKINETICS AND METABOLISM

Several studies were conducted to investigate for mometasone furoate the absorption, distribution, metabolism and excretion following various routes of administration and in different species. Mometasone furoate and/or its metabolites are rapidly and extensively distributed in the rat. Mometasone furoate undergoes extensive first-pass metabolism and is excreted as metabolites mostly via the bile, and to a limited extent into the urine.
2.3 PRECLINICAL SAFETY DATA

No toxicological effects unique to mometasone furoate exposure were demonstrated during the course of preclinical testing. All observed effects are typical of this class of compounds and are related to exaggerated pharmacologic effects of glucocorticoids.

Preclinical studies demonstrate that mometasone furoate is devoid of androgenic, anti-androgenic, estrogenic or anti-estrogenic activity but, like other glucocorticoids, it exhibits some anti-uterotrophic activity and delays vaginal opening in animal models at high oral doses of 56 mg/kg/day and 280 mg/kg/day.

Mometasone furoate was non-mutagenic in the mouse-lymphoma assay and the Salmonella/E. coli/mammalian microsome mutagenicity bioassay. At cytotoxic doses only, mometasone furoate produced an increase in chromosome aberrations in vitro in Chinese hamster ovary cell (CHO) cultures in the non-activation phase, but not in the presence of rat liver S9 fraction. However, mometasone furoate did not induce chromosomal aberrations in vitro in a Chinese hamster lung cell (CHL) chromosomal-aberrations assay or in vivo in the mouse bone-marrow erythrocyte-micronucleus assay, in the rat bone-marrow clastogenicity assay, and the mouse male germ-cell clastogenicity assay. Mometasone furoate also did not induce unscheduled DNA synthesis in vivo in rat hepatocytes. The finding of simple chromosomal aberrations in the non-activation phase of the CHO assay is considered to be related to cytotoxicity and is not considered to be of significance in the risk assessment of mometasone furoate because of the negative results in the S9 phase of this assay, the negative results in a second in vitro chromal aberrations assay (CHL assay), and the negative results in three in vivo chromosomal aberrations assays.

In studies of reproductive function, subcutaneous mometasone furoate was well tolerated at doses up to 7.5 µg/kg. At 15 µg/kg, mometasone furoate caused prolonged gestation and prolonged and difficult labor
occurred with a reduction in offspring survival and body weight or body weight gain. There was no effect on fertility.

Like other glucocorticoids, mometasone furoate is a teratogen in rodents and rabbits. Teratology studies were conducted in rats, mice and rabbits by the oral, topical and/or subcutaneous routes. Effects noted were umbilical hernia in rats, cleft palate in mice, and gall bladder agenesis, umbilical hernia, and flexed front paws in rabbits. There were also reductions in maternal body weight gains, effects on fetal growth (lower fetal body weight and/or delayed ossification) in rats, rabbits and mice, and reduced offspring survival in mice.

In an oral teratology study in rabbits, at 700 µg/kg, increased incidences of resorption and malformations, including cleft palate and/or head malformations (hydrocephaly or domed head) were observed. Pregnancy failure was observed in most rabbits at 2800 µg/kg.

The carcinogenicity and toxicological potential of inhaled Mometasone Furoate (aerosol with CFC propellant and surfactant) at concentrations of 0.25 to 2.0 ug/l was investigated in studies in mice and rats of up to 24 months. Typical glucocorticoid-related effects, including several non-neoplastic lesions, were observed. No statistically significant dose-response relationship was detected for any of the tumor types.

3 CLINICAL PHARMACOLOGY

3.1 PHARMACOKINETIC PROPERTIES

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle and the integrity of the epidermal barrier and the use of occlusive dressings. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous
absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids.

3.1.1 Absorption

The percutaneous absorption of $^3$H-mometasone furoate was studied in man following topical application of cream (0.1%) and ointment (0.1%) formulations. Results showed that only about 0.4% and 0.7% of the steroid, respectively, were systemically absorbed following 8 hours of contact, without occlusion, through intact skin of normal volunteers. The percutaneous absorption of $^3$H-mometasone furoate also was studied in psoriasis patients following a single dose topical application of the ointment 0.1% formulation over a 100cm$^2$ area. Results showed that only 1.3% of mometasone was absorbed systemically following 12 hours of application through unoccluded skin. Minimal absorption would be anticipated with the lotion formulation.

In studies of the effects of mometasone furoate cream and ointment on the hypothalamic-pituitary-adrenal axis (HPA), 15 grams were applied twice daily for 7 days to 6 patients with psoriasis or atopic dermatitis. The cream or ointment was applied without occlusion to at least 30% of the body surface. The results suggest that the drug caused a slight lowering of adrenal corticosteroid secretion, although in no case did plasma cortisol levels go below the lower limit of the normal range.

Mometasone furoate lotion was applied at 15 ml twice daily (30 ml per day) to diseased skin (patients with scalp and body psoriasis) of four patients for seven days, to study its effects on the hypothalamic-pituitary-adrenal (HPA) axis. Plasma cortisol levels for each of the four patients remained well within the normal range and changed little from baseline.
In a study involving 24 children (6 months to 13 years of age) with moderate to severe atopic eczema, mometasone furoate cream was applied once daily for three to six weeks. Occlusive dressings were not used. The plasma cortisol levels for all patients remained within or above the normal range during the course of treatment. Clinical laboratory values of the children generally remained within the normal range. There were some laboratory values that were outside the normal range during the course of treatment; however, the investigator did not consider these values to be of clinical significance or indicative of specific organ system toxicity.

Mometasone furoate ointment, 15 grams, was applied daily under occlusion for three weeks in 24 psoriasis patients. Plasma cortisol levels remained within normal limits for all patients.

### 3.1.2 Distribution
Due to the negligible absorption of mometasone furoate following topical administration, the pharmacokinetics of the drug was evaluated following intravenous administration of mometasone furoate. The apparent volume of distribution was 917 liters, indicating that any absorbed mometasone furoate would be extensively distributed in human plasma, mometasone furoate is over 99% bound.

### 3.1.3 Metabolism
Absorbed mometasone furoate undergoes rapid and extensive metabolism to multiple metabolites. The multiple metabolites are more polar than mometasone furoate, and because of their polarity, are not considered to have pharmacological activity. No major metabolite is formed. After intravenous administration, the total body clearance of mometasone furoate was 976 ml/min, confirming extensive metabolism.
3.1.4 Excretion

Following intravenous administration and based on compartmental modeling, the effective plasma elimination half-life is 5.8 hours. Any absorbed drug is excreted as metabolites mostly via the bile, and to a limited extent, into the urine.

4 INDICATIONS AND USAGE

4.1 THERAPEUTIC INDICATIONS

Mometasone furoate cream, ointment and lotion are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses, such as psoriasis, atopic dermatitis.

5 SAFETY INFORMATION

5.1 CONTRAINDICATIONS

Elocom is contraindicated in facial rosacea, acne vulgaris, skin atrophy, perioral dermatitis, perianal and genital pruritus, napkin eruptions, bacterial (e.g. impetigo, pyodermas), viral (e.g. herpes simplex, herpes zoster and chickenpox verrucae vulgares, condylomata acuminata, molluscum contagiosum), parasitical and fungal (e.g. candida or dermatophyte) infections, varicella, tuberculosis, syphilis or post-vaccine reactions. Elocom should not be used on wounds or on skin which is ulcerated. Elocom should not be used in patients who are sensitive to mometasone furoate or to other corticosteroids or to any of the ingredients in this medicine.
5.2 WARNINGS/PRECAUTIONS

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

In the presence of a dermatological infection, 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 is adequately controlled.

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, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment. Patients applying a topical steroid to a large surface area or areas under occlusion should be evaluated periodically for evidence of HPA axis suppression.

Any of the side effects that are reported following systemic use of corticosteroids, including adrenal suppression, may also occur with topical corticosteroids, especially in infants and children.

Pediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios.

As the safety and efficacy of Elocom in pediatric patients below 2 years of age have not been established, its use in this age group is not recommended.
Local and systemic toxicity is common especially following long continued use on large areas of damaged skin, in flexures and with polythene occlusion. If used in childhood, or on the face, occlusion should not be used. If used on the face, courses should be limited to 5 days and occlusion should not be used. Long term continuous therapy should be avoided in all patients irrespective of age.

Topical steroids may be hazardous in psoriasis for a number of reasons including rebound relapses following development of tolerance, risk of centralised pustular psoriasis and development of local or systemic toxicity due to impaired barrier function of the skin. If used in psoriasis careful patient supervision is important.

As with all potent topical glucocorticoids, avoid sudden discontinuation of treatment. When long term topical treatment with potent glucocorticoids is stopped, a rebound phenomenon can develop which takes the form of a dermatitis with intense redness, stinging and burning. This can be prevented by slow reduction of the treatment, for instance continue treatment on an intermittent basis before discontinuing treatment.

Glucocorticoids can change the appearance of some lesions and make it difficult to establish an adequate diagnosis and can also delay the healing. Elocom ointment and lotion contains propylene glycol which may cause skin irritation.

Elocom topical preparations are not for ophthalmic use, including the eyelids, because of the very rare risk of glaucoma simplex or subcapsular cataract.

Pregnancy and lactation:
During pregnancy and lactation treatment with Elocom should be performed only on the physician’s order. Then however, the application on large body surface areas or over a prolonged period should be avoided. There is inadequate evidence of safety in human pregnancy. Topical
administration of corticosteroids to pregnant animals can cause abnormalities of fetal development including cleft palate and intra-uterine growth retardation. There are no adequate and well-controlled studies with Elocom in pregnant women and therefore the risk of such effects to the human fetus is unknown. However as with all topically applied glucocorticoids, the possibility that fetal growth may be affected by glucocorticoid passage through the placental barrier should be considered. There may therefore be a very small risk of such effects in the human fetus. Like other topically applied glucocorticoids, Elocom should be used in pregnant women only if the potential benefit justifies the potential risk to the mother or the fetus.

It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Elocom should be administered to nursing mothers only after careful consideration of the benefit/risk relationship. If treatment with higher doses or long term application is indicated, breast-feeding should be discontinued.

5.3 ADVERSE REACTIONS

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<thead>
<tr>
<th>Table 1: Treatment-related adverse reactions reported with Elocom by body system and frequency</th>
</tr>
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<tbody>
<tr>
<td>Very common (≥1/10); common (≥1/100, &lt;1/10); uncommon (≥1/1,000, &lt;1/100); rare (≥1/10,000, &lt;1/1,000); very rare (&lt;1/10 000,); not known (cannot be estimated from available data)</td>
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<table>
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<tr>
<th>Infections and infestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not known</td>
</tr>
<tr>
<td>Infection, furuncle</td>
</tr>
<tr>
<td>Very rare</td>
</tr>
<tr>
<td>Folliculitis</td>
</tr>
<tr>
<td>Nervous system disorders</td>
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<td>--------------------------</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
</tr>
</tbody>
</table>

Local adverse reactions reported infrequently with topical dermatologic corticosteroids include: skin dryness, irritation, dermatitis, perioral dermatitis, maceration of the skin, miliaria and telangiectasiae.

Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced hypothalamic-pituitary-adrenal axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio. Chronic corticosteroids therapy may interfere with the growth and development of children.
5.4 DRUG ABUSE AND DEPENDENCE
None known.

5.5 OVERDOSAGE
Excessive, prolonged use of topical corticosteroids can suppress hypothalamic-pituitary-adrenal function, resulting in secondary adrenal insufficiency which is usually reversible.

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.

The steroid content of each container is so low as to have little or no toxic effect in the unlikely event of accidental oral ingestion.

5.6 DRUG INTERACTIONS
None known

5.7 INTERFERENCE WITH LABORATORY TESTS
None identified

6 DOSAGE AND ADMINISTRATION
Apply a thin film of mometasone furoate cream of ointment or a few drops of mometasone furoate lotion to the affected skin areas once daily.

7 STORAGE
Store below 25°C.
Elocom ointment: after first opening, use within 1 month.
Elocom lotion and cream: after first opening, use within 3 months.
8 MANUFACTURER

Elocom ointment and cream: Schering-Plough Labo N.V., Heist-op-den-Berg, Belgium.

Elocom lotion: Merck Sharp & Dohme Corp., New-Jersey, USA.

9 REGISTRATION HOLDER


The format of this leaflet was determined by the Ministry of Health and its content was checked and approved in December 2014.