# RECLASSIFICATION SUBMISSION

# EUMOVATE™
# Eczema and Dermatitis Cream

## (Clobetasone butyrate 0.05%)

## From Prescription Only Medicine

## To Pharmacist Only Medicine

## NOVEMBER 2000 MEETING

# PART A

**1. International non-proprietary name (INN) and British approved name (BAN) of the medicine.**

Clobetasone butyrate

**2. Trade name.**

EUMOVATE™ Eczema & Dermatitis Cream

**3. Company requesting reclassification.**

GlaxoWellcome (NZ) Ltd
Eighth Floor, Quay Tower
cnr Customs & Albert Streets
P B 106600
Downtown, Auckland
NEW ZEALAND

**4. Dose form and strength.**

Eczema & Dermatitis Cream
0.05%w/w.

**5. Pack size and other qualifications.**

EUMOVATE™ Cream is a smooth, white to off-white cream containing 0.05% w/w of clobetasone butyrate BP.

EUMOVATE ™ Cream is currently registered as a Prescription Only Medicine, however this application relates to a smaller pack size for use as Pharmacist Only Medicine available in 15g collapsible aluminium tube, packaged into a carton with an accompanying consumer information leaflet.

**6. Indication for which change sought.**

EUMOVATE ™ Cream is indicated for adults and children aged 10 years and over (use in children under 10 years - only on the advice of a doctor), for short-term treatment and control of patches of eczema and dermatitis including atopic and seborrhoeic eczema and primary irritant and allergic dermatitis.

**7. Present classification of medicine.**

Prescription Only Medicine

## 8. Classification sought.

Pharmacist Only Medicine

## 9. Classification in other countries where marketed.

Clobetasone butyrate 0.05%w/w cream has been available as a prescription product in over 80 countries.for more than 20 years.
There have been no previous approvals for OTC use, though applications for Eumovate Cream as a non-prescription medicine will be filed world-wide over the next few months. The current International regulatory status for OTC applications is contained in Appendix 1.

## 10. Extent and duration of usage.

Clobetasone butyrate 0.05%w/w cream was first registered in New Zealand in April 1976. It has been available on prescription in New Zealand under the tradename EUMOVATE™ Cream since 1978.

Between 1997 and 1999, 40400 units of 30g dose pack and 24400 units of 100g dose pack of EUMOVATE™ Cream and 20000 units of 30g and 14500 units of 100g dose pack of EUMOVATE™ Ointment were sold in New Zealand on a Prescription Medicine basis.

## 11. Proposed labelling.

- Draft primary and secondary container labelling for the reclassified presentation of EUMOVATE™ Eczema & Dermatitis Cream is contained in Appendix 2.

## 12. Proposed warning statements.

It is proposed to include a pack insert {Consumer Medicine Information} with the following statements:

***1. People who shouldn't use it***

*Don't use this cream*

- *If you've ever had a reaction to this cream or its ingredients*
- *On children under 10, unless a doctor told you to*
- *If you are pregnant, may be pregnant, or breast feeding.*
- *Talk to a doctor or pharmacist.*

***2. Don't use this cream on the wrong skin problems***

*It could make them worse.*

*Don't use this cream (or any other corticosteroid) on :*

- *Broken or infected skin: like cold sores, herpes, chicken pox, impetigo, ringworm, athlete's foot or thrush*
- *Psoriasis: this needs to be managed by your doctor*
- *Acne (spots or pimples)*

➢ *If you have any of these,ask a pharmacist or doctor for advice.*

***3. Don't use other skin medication with steroids in.***

*Don't use other steroids (like hydrocortisone) on the skin while you're using this cream.You would be doubling the dose.*

***4. Don't use it on certain areas of the body***

- *On your face*
- *On groins and private parts*
- *Between your toes.*

In addition, the following statements will appear on the outside of the carton

***Don't use Eumovate Eczema & Dermatitis Cream:***

- If you have ever had a reaction to Eumovate Eczema & Dermatitis Cream or any of its ingredients.
- If you are pregnant, may be pregnant or breastfeeding.
- If you are using any other topical corticosteroids.
- On children under 10.
- On broken or infected skin e.g. cold sores, athletes foot impetigo or thrush.
- To treat psoriasis
- To treat acne

In these cases ask a pharmacist or doctor for advice.

***The cream should not be used in the following areas:***

- On your face
- On private parts
- Between the toes

**Keep all medicines out of the reach of children.**

**Always read the enclosed leaflet.**

The proposed Data Sheet for EUMOVATE™ Eczema & Dermatitis Cream as a Pharmacist Only Medicine is attached as Appendix 3 and a Consumer Medicine Information as Appendix 4.

## 13. Other products containing the same active ingredient which may be affected by the proposed classification change.

Nil

## PART B

### 1. Benefits

Eczema is the most common form of inflammatory skin disease and accounts for a large proportion of dermatological consultations in general practice. The terms “eczema” and “dermatitis” tend to be used synonymously by health professionals, although there is a public perception that eczema is a distinct and more serious condition than dermatitis.

In the UK the majority of people with eczema, in its various forms, are managed in general practice with only the more severe cases being referred to dermatologists. Once the condition is recognised, those with endogenous eczema learn to manage their condition with the use of topical corticosteroids, during flare-ups, and emollients in between. Short courses (3-7days) of potent or moderately potent topical corticosteroids are commonly prescribed to bring the condition under control (National Prescribing Centre 1999). The long-term management is with emollients and the occasional use of the lowest potency topical steroid that is effective. In this situation topical hydrocortisone or Eumovate, as cream or ointment, are widely used.

When a small patch of eczema/dermatitis develops the first symptom the sufferer notices is the itch, which may be accompanied by erythema. The urge to scratch is irresistible. Scratching releases pro-inflammatory chemicals such as cytokines, IL-1$\alpha$, TGF$\alpha$, and other mediators of inflammation. These trigger the development of an enlarging area of dermatitis and an increase in itching. This results in further scratching, the release of pro-inflammatory cytokines and an expansion of the area of dermatitis. This is the vicious itch/scratch cycle. Itching and scratching damage the epidermal barrier, allowing irritants and allergens to penetrate the skin, which leads to further inflammation. In addition the skin of people with eczema is colonised by very large number of *Staphylococcus aureus*, which can release superantigenic exotoxins. Superantigens are potent immunostimulatory molecules. In addition to making the eczema worse the skin becomes an even better environment for the multiplication of the bacterium. The itch/scratch cycle and *Staph.aureus* superantigen vicious cycles combine to produce a rapid deterioration in the skin condition. As a result, an area of dermatitis left untreated can rapidly enlarge causing sleep disturbance, discomfort and an unsightly appearance. The most effective way to prevent a deterioration of an exacerbation of dermatitis/eczema is to start treatment as soon as possible, ideally as the itching and redness are developing. A delay in starting treatment, as may be necessary to obtain a prescription, can allow the itch/scratch cycle to become established. Furthermore, by the time the sufferer gains access to a medical

practitioner the condition may be much more difficult to treat and could require treatment with potent steroids with or without topical and /or oral antibiotics.

The availability of Eumovate™ OTC would enable the eczema or dermatitis sufferer rapidly to take control of an exacerbation of mild to moderate eczema or dermatitis before it quickly deteriorates and becomes much more difficult to control.

The safety and efficacy profile of Eumovate, has been derived from widespread clinical experience of its use, on prescription, in over 80 countries over more than 20 years. In the period from May 1990 until end of Feb 2000 alone, approximately 24 million tubes of Eumovate cream and approximatley 40 million tubes of Eumovate ointment have been sold worldwide.

Eumovate has also been used for the treatment of vulnerable areas of skin, such as the face, without reports of untoward effects.

In clinical practice Eumovate, as a moderately potent corticosteroid, is perceived to be more effective than hydrocortisone 1% and, like hydrocortisone, has not been associated with the well-publicised serious adverse effect seen with the misuse and abuse of potent and very potent steroids. With this background, Eumovate would now seem a suitable candidate, from the safety point of view, for switching from prescription use to self-medication with certain restrictions:

- It would be for use in a more limited range of skin conditions
- The age range would be more restricted
- Its use on certain areas of skin would be excluded to avoid confusion with other skin conditions
- Duration of treatment would be limited

Eumovate cream base formulation has emollient properties, which may have additional benefits to the consumer in the management of their conditions.

## 2. Ease of self-diagnosis

Recognition of eczema and dermatitis by the consumer is most likely to be based on experiencing a recurrence of a previously doctor-diagnosed condition. In the case of contact dermatitis the diagnosis is likely to be based on the individual, with or without the assistance of a pharmacist, recognising that they have developed a local reaction to an irritant or allergic substance. This may, or may not, have been previously diagnosed by a physician.

The advice given by the pharmacist will also be supported by the labelling for the product. This will be reinforced by written advice in the product information leaflet that, if the consumer has any doubts about the diagnosis, or they are aged under 10 they should consult a doctor. This written advice is based on leaflets that have been shown, by consumer testing, to be correctly understood by target populations.

## 3. Relevant data for like compounds.

The most widely used experimental model for screening new topical steroids is the vasoconstriction test. The degree of skin blanching (vasoconstriction) induced by a steroid is considered to reflect the anti-inflammatory properties of that agent. There are several methods for assaying corticosteroids using the blanching phenomenon.

It is clear, that the potency of a preparation is related, not only to the active molecule within it, but also to the vehicle used (Kaidby and Kligman 1974, Lee and Maibach 1998, Stoughton 1972, Poelman *et al* 1984). In general, ointments are more effective because of their occlusive effect (Stoughton 1972). Conversely, creams are not only associated with less absorption of the steroid, but are also cosmetically preferred by users.

Two reports have been identified in which Eumovate cream has been directly compared with hydrocortisone 1% cream in patients. The first report is a paper in the British Medical Journal in 1975. A dose ranging study comparing clobetasone butyrate 0.01%, 0.025% and 0.05% with hydrocortisone 1% showed that at the lowest concentration, clobetasone butyrate was similar to hydrocortisone 1% but at 0.05% (as in Eumovate) it was significantly more effective ($p<0.05$).

A second, unpublished Glaxo-sponsored study, conducted in 1982, involved 44 patients, of whom 17 had bilateral eczema or dermatitis. Eumovate was applied to lesions on one side of the body and hydrocortisone 1% cream to the other twice daily, without occlusion for two weeks. The response to treatment looked similar between the two groups at one week but at two weeks more Eumovate-treated patients were considered to have healed.

As might be expected of a mature product like Eumovate, the clinical trials in support of its efficacy and safety were conducted some years ago, before the introduction of Good Clinical Practice. Nevertheless, they were adequate at the time and for the purpose and provided evidence that Eumovate is effective in the treatment of eczema and

Not Applicable

## 8. Adverse events

**Glaxo Wellcome (NZ) Limited requested a report from CARM on adverse events associated with clobetasone butyrate and the response from CARM was that to the end of March 2000, CARM has had no reports of adverse events to clobetasone butyrate.**

Clobetasone butyrate cream and ointment have been available worldwide for over 20 years. The reporting rate of adverse events with the preparations is low. The rate of reporting of spontaneous adverse events cannot give an indication of the true incidence of adverse reactions. However, it would seem that in clinical practice, when used as recommended, most reactions are mild and confined to the skin.

Most of the concerns about the side effects of topical steroids arise from their potential to cause skin thinning.

One of the concerns about clobetasone butyrate is that, being a more potent steroid than hydrocortisone it may have a significantly greater potential to cause skin atrophy. The studies reviewed in the Expert Report use severe test conditions for prolonged periods of time and often with occlusion. None of these conditions are relevant to the proposed OTC use of Eumovate, except in the most extreme conditions of misuse or abuse.

To 29 February 2000, a total of 96 spontaneous adverse event reports have been received by Worldwide Product Safety and dermatitis. Its efficacy appears to be at least as good as that of hydrocortisone 1%, as well as that of other moderately potent steroids.

Recently, a Glaxo Wellcome sponsored study, based on the work by Seidanari et al (1997), was piloted in 18 volunteers using nickel allergy model of dermatitis. The primary endpoint was the physician's global assessment of healing at day 8. Transepidermal water loss, being an indicator of skin barrier function and therefore healing, was also measured from day 1 to 8. Eumovate was found to be statistically significantly more effective, than either hydrocortisone 1% or no treatment, at reducing transepidermal water loss. This effect on transepidermal water loss is evidence of long-lasting moisturising properties of Eumovate cream.

An account of clinical studies highlighting efficacy of Eumovate compared to other moderately potent steroids e.g. flurandrenolone cream (0.0125-0.25%), fluocinolone acetonide (0.01%), fluocortolone pivalate (0.1%) and fluocortolone hexanoate (0.1%) and more potent topical steroids e.g. fluticasone propionate (0.05%) and mometasone furaote

(0.1%) is documented in Section 3 of the Clinical Expert Report. The current efficacy and safety profile has been built on extensive clinical usage, which in some countries, extends over more than 20 years.

**4. Local data or special considerations relating to New Zealand.**

GlaxoWellcome (NZ) Ltd has identified no local data or special considerations with regard to EUMOVATE™ Cream which could be regarded as being specific to New Zealand.

**5. Interactions with other medicines.**

Not Applicable

**6. Contraindications.**

It will be clearly stated on the labelling that the cream must not be used to treat psoriasis, acne vulgaris or on the face, on broken or infected skin, on the skin around the groins or genitals or between the toes.

The age range will be 10 years or over, with the advice that it is not to be used on children under 10 except on medical advice.

People who know they are allergic to Eumovate cream or any of its ingredients will be told not to use it.

Women who are pregnant or breast-feeding will be advised not to use Eumovate cream without the advice of their doctor.

**7. Potential for development of drug resistance.**Pharmacovigilance (WPSP) of Glaxo Wellcome Research and Development (GWRD) in association with topical clobetasone butyrate (Eumovate). Breakdown by formulation is as follows:

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|---|---|---|
| Cream | - | 48 reports |
| Ointment | - | 27 reports |
| Unknown formulations | - | 21 reports |

Clobetasone butyrate is also available as a scalp application, eye drops and in combination preparations with antibacterial agents. Spontaneous reports occurring with these preparations have been excluded from this review.

Clobetasone butyrate and Eumovate cream appear to have no greater propensity to cause sensitivity reactions than other steroid preparations. Indeed, there is some evidence to suggest that allergic reactions may

occur less often with Eumovate cream than with some other topical steroid preparations.

The serious adverse effects recognised with the overuse of potent and very potent topical steroids, namely irreversible skin thinning and systemic absorption, have not been reported with the use of Eumovate in clinical practice. Its profile, in this respect, more closely resembles that of hydrocortisone 1% then that of more potent topical steroids. Details are given in Section 4.3 in the Clinical Expert Report.

## 9. Abuse or misuse.

The use of topical steroids needs to be more carefully monitored in children whose skin is more vulnerable to the adverse effects of misuse. Children develop rashes associated with childhood infections that may be misdiagnosed by adults and treated inappropriately. Therefore, the medical view, that the management of childhood eczema should remain under the supervision of a physician, is supported by limiting the age range, for self-medication with Eumovate, without a doctor's advice, to 10 and older. This is in line with the age limitations on the use of OTC hydrocortisone in a number of countries.

There is no evidence to suggest that, when used in the same quantities and for the same length of time as OTC hydrocortisone 1%, it is associated with any greater adverse effects. Nor is the potential for misuse or abuse any different from that associated with the OTC availability of hydrocortisone 1%.

Incorrect use of topical steroids has led to much concern about their potential to cause side effects. Much of this concern has arisen from the misuse of potent and very potent topical steroids especially on the face or in children.

There is evidence that, currently, the commonest misuse of topical steroids is using too little rather than excessive amounts. The commonest concern related to a perceived risk of skin thinning (34.5%).

Eumovate has been widely used in children and also used on the face without reports of untoward effects. However, in order to allay concerns about use in these areas, the labelling for Eumovate in the OTC setting will clearly exclude use on the face, in the groins and between the toes and in children under 10 years of age.

## 10. Summary

In dermatological practice, hydrocortisone 1% remains the treatment of choice for eczema on the face but it is often not effective for eczema elsewhere on the body. Adding Eumovate cream to the list of products available without prescription, should offer benefits to people with these conditions.

Its efficacy and safety profiles are well established from its widespread prescription use, which in most countries covers a period of more than 20 years.

By making it available without prescription, the consumer will have access to an effective treatment, early in an exacerbation of mild to moderate eczema or dermatitis. These are skin conditions that are readily self-diagnosable with or without the advice of a pharmacist or doctor.

Early treatment can prevent damage that is produced by scratching. Furthermore, by the time the sufferer gains access to a medical practitioner the condition may be much more difficult to treat and could require treatment with potent steroids with or without topical and/or oral antibiotics. Eumovate cream would therefore provide consumers with another safe and effective treatment for the self management of eczematous skin conditions.

APPENDICES

1. International Regulatory Status for Eumovate™ Cream as a Pharmacist Only Medicine.

2. Proposed primary and secondary container labelling for Eumovate™ Eczema & Dermatitis Cream as a Pharmacist Only Medicine (Pack design still to be confirmed).

3. Proposed Data Sheet for Eumovate™ Eczema & Dermatitis Cream as a Pharmacist Only Medicine.

4. Proposed Consumer Information Leaflet for Eumovate™ Eczema & Dermatitis Cream as a Pharmacist Only Medicine.