

**Public Assessment Report  
for paediatric studies submitted in accordance  
with Article 46 of Regulation (EC) No1901/2006, as  
amended**

**Clobetasone Butyrate 0.05% cream  
Clobetasone Butyrate**

**MT/W/011/pdWS/001**

**Marketing Authorisation Holder:  
GlaxoSmithKline**

|  |                           |
|--|---------------------------|
| <b>Rapporteur:</b>                       | Malta                     |
| <b>Finalisation procedure (day 120):</b> | 6 <sup>th</sup> July 2016 |

## ADMINISTRATIVE INFORMATION

|  |   |
|--|---|
| Invented name of the medicinal product:          | Eumovate cream 0.05% w/w  |
| INN (or common name) of the active substance(s): | Clobetasone Butyrate  |
| MAH:   | GlaxoSmithKline   |
| Currently approved Indication(s)                 | <p>Eumovate cream is a moderately potent topical corticosteroid indicated for adults, elderly, children and infants for the relief of the inflammatory and pruritic manifestations of steroid responsive dermatoses. These include the following:</p> <ul style="list-style-type: none"><li>- Atopic dermatitis</li><li>- Irritant or allergic contact dermatitis</li><li>- Seborrhoeic dermatitis</li><li>- Nappy rash</li><li>- Photodermatitis</li><li>- Otitis externa</li><li>- Prurigo nodularis</li><li>- Insect bite reactions</li></ul> <p>Eumovate may be used as maintenance therapy between courses of one of the more potent topical steroids.</p> |
| Pharmaco-therapeutic group (ATC Code):           | D07AB Corticosteroids, moderately potent (group II)   |
| Pharmaceutical form(s) and strength(s):          | Cream 0.05%w/w  |

## I. EXECUTIVE SUMMARY

SmPC changes are proposed in sections 4.2, 4.4 and the PL is to be updated accordingly

## II. RECOMMENDATION

A Type IB variation to update the SmPC as specified is to be submitted by the MAH within 30 days after the end of the procedure. The PL should also be updated accordingly.

## III. INTRODUCTION

On 31<sup>st</sup> July 2015, the MAH submitted a completed paediatric study for **clobetasone butyrate 0.05% cream**, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided. Clinical Expert statement and Expert CV Final Study Report 11187

The MAH stated that the results of the study report 11187 are in line with the approved product information in the EU and therefore no changes to the product information are considered necessary.

## IV. SCIENTIFIC DISCUSSION

### IV.1 Information on the pharmaceutical formulation used in the study(ies)

Clobetasone butyrate is a white cream for topical use containing clobetasone butyrate as the active ingredient. Clobetasone butyrate is a corticosteroid used topically for its glucocorticoid effects. Its chemical name is 21-chloro-9 $\alpha$ -fluoro-17 $\alpha$ -hydroxy-16 $\beta$ -methylpregna-1,4-diene-3,11,20-trione 17-butyrate.

The excipients are glycerol, glycerol monostearate, cetostearyl alcohol, beeswax substitute 6621, arlacel 165, dimethicone 20, chlorocresol, sodium citrate, citric acid monohydrate, water-purified.

### IV.2 Clinical aspects

#### 1. Introduction

Eczema or atopic dermatitis is a chronic, relapsing inflammatory dermatoses with exudation caused by several internal and external factors. Rash is pleomorphic, with strenuous itching and recurrent. It may be associated with other atopic disorders such as allergic rhinitis and/ or asthma. The clinical manifestations vary with age. In infancy the first eczematous lesions usually emerge on the cheeks and scalp. This is followed by scratching resulting in exudation of serum and crusted erosions. During childhood it tends to involve flexures and the dorsal aspects of the limbs. In adolescence and adulthood lichenified plaques affect the flexures, head and neck. .At each stage itching is present that continues throughout the day and worsens at night. There is a

disturbance of the epidermal barrier function that results in dry skin and IgE mediated sensitization to food and environmental allergens.

Topical corticosteroids are the most useful agents for the treatment and management of eczema and dermatitis, particularly acute flare-up of the disease. A wide and diverse range of corticosteroid products classified into categories ranging from mildly potent to very potent are available on prescription, the steroid class for treatment being selected according to the nature and severity of the skin disease.

The MAH submitted a final report for:

Protocol No.111187 - Multi-center, randomised, double-blind, paralalled, vehicle (cream base) controlled study of 0.05% Clobetasone Butyrate Cream in subjects with eczema to evaluate the efficacy and safety.

## **2. Clinical study**

### **Description.**

#### **➤ Protocol No: 111187**

Multi-centre, randomised, double-blind, parallel, vehicle (cream base) controlled study of 0.05% Clobetasone Butyrate Cream in

➤ subjects with eczema to evaluate the efficacy and safety

#### **➤ Methods**

- Objective(s) To investigate clinical efficacy and safety of 0.05% Clobetasone Butyrate Cream versus vehicle (cream base) applied to involved skin of subjects with moderate and above eczema for 14 days.

- Study design

This was a multi-center, randomised, double-blind, vehicle (cream base) -controlled, paralleled group study to evaluate the clinical efficacy and safety of 0.05% Clobetasone Butyrate Cream versus vehicle applied to involved skin

- Study population /Sample size

A total number of 240 subjects were enrolled, 120 subjects in clobetasone butyrate cream group and 120 subjects in cream base group.

- Treatments

Subjects were screened within 3 days prior to randomization. Subjects were assessed at baseline/randomization (Day 0). Eligible subjects were randomised to 0.05% Clobetasone Butyrate Cream group or vehicle (cream base) group at the rate of 1:1 and received application of the study drug. Subjects were instructed to apply a thin layer of cream to all areas of eczema, twice daily for 14 days. Subjects would also be instructed to apply to new areas of eczema arising during the treatment phase. Afterwards, further assessments including the scale of skin lesions, symptoms and signs of the disease were evaluated by investigators on Day 7 and Day 14. The total study duration was expected to be approximately 2 weeks for any subject

## Outcomes/endpoints

### Primary efficacy parameters

#### 1. Reduction percentage of EASI:

At the end of treatment (Day 14), the average reduction percentage of EASI was 65.34% and 38.83% in clobetasone butyrate cream and cream base group respectively. The test group is statistically significantly superior to that of control group ( $F=24.01$ ,  $p<0.0001$ ).

#### 2. Change of EASI:

The average EASI value of clobetasone butyrate cream and cream base group reduced with respect to baseline ( $p<0.0001$ ) on Day 7 and Day 14. The average reduction for clobetasone butyrate cream group was  $-1.64 \pm 1.57$  and  $-2.65 \pm 2.39$  on Day 7 and Day 14 respectively, the reduction was  $-1.11 \pm 1.90$  and  $-1.78 \pm 2.36$  for the cream base group. On comparing the two groups it can be seen that the differences are statistically significant ( $t = -2.38$ ,  $P = 0.018$  and  $t = -2.83$ ,  $P = 0.005$ ;  $F = 7.48$ ,  $P = 0.0067$  and  $F = 12.70$ ,  $P = 0.0004$ ) showing that the test group was superior.

N.B.: An EASI score is a tool used to measure the extent (area) and severity of atopic eczema (Eczema Area and Severity Index).

### Secondary efficacy parameters:

#### 1. IGA

The average IGA scores in both the clobetasone butyrate cream and base cream group were significantly reduced with respect to the baseline (both  $<0.0001$ ) at Day 7 and Day 14. The treatment success rates based on IGA score in the clobetasone butyrate cream group were 17.65% and 56.30% at Day 7 and Day 14 respectively and 3.36% and 21.58% in the cream base. These results showed that the results in the test group were superior ( $P < 0.0001$ ).

- Statistical Methods

Statistical analysis used the software of SAS 9.1.3 to calculate. Other statistical tests used two-sided test, except efficacy analysis. The analysis of efficacy parameters used one-sided test at a significance level of 0.05 with P value. The quantitative indexes included the calculation of number, mean, standard deviation, median, minimum and maximum. Categorical index include the percentage and number.

## ➤ Results

- Recruitment/ Number analysed

A total number of 240 subjects were enrolled, 120 subjects in clobetasone butyrate cream group and 120 subjects in cream base group. It was decided after data review that there were 119, 119, 104 subjects for SS, FAS, PPS in both groups respectively. 18 subjects withdrew during the treatment course, the dropout rate was 7.50%, 7 (5.83%) in the clobetasone butyrate cream group and 11 (9.17%) in the cream base group. The difference between the

two groups was not statistically significantly ( $p>0.05$ ). Disposition of FAS and PPS population between the clobetasone butyrate cream and cream base groups was same (99.17%, 86.67% respectively).

- **Baseline data**

There were 46 male and 74 female subjects in the clobetasone butyrate cream group; 53 male and 66 female subjects in the cream base group. No statistically significant difference in gender decompositions between the two groups ( $\chi^2=0.85$ ,  $p=0.3573$ ). The average age of clobetasone butyrate cream group was  $41.90\pm12.93$  years (minimum 16.00 and maximum 65.00) and  $41.89\pm12.65$  years (minimum 14.00 and maximum 64.00) for cream base group. There was no statistically significant difference ( $t=0.01$ ,  $p=0.9960$ ). The subjects' other baseline demographic information and vital signs including weight, pulse and blood pressure showed no statistical significance between two groups ( $p>0.05$ ).

- **Efficacy results**

- **Safety results**

The incidence of AE in clobetasone butyrate cream group (9.24%) was slightly higher than that of cream base group (5.88%). However, the difference between the two groups were not statistically significant ( $p > 0.05$ ). Local adverse events where topical treatment was applied were moderate and resolved spontaneously. There were no serious adverse events and no deaths reported.

The safety analysis showed that 0.05% clobetasone butyrate cream is well tolerated, the incidence of investigational product related adverse reaction was 1.68%, which is the same as the cream base group, manifested as mild local reactions.

### **3. Discussion on clinical aspects**

The benefit risk balance for the population studied is favourable, however, because of the greater likelihood of increased absorption in infants and children with greater possibility of adverse effects including adrenal and growth suppression special consideration should be given to ensure that appropriate warnings should be made in the SmPC for the paediatric population.

## **V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION**

### **➤ Overall conclusion**

Clobetasone butyrate 0.05% w/w cream has a well established effective and safety profile and it is recommended that the statements for Sections 4.2, 4.4 should be in the SmPCs of all the member states. This information should be reflected in the patient leaflet.

It is recommended that a specific sub-section 'Paediatric population' should be included in Sections 4.2 and 4.4 of the SmPC to appropriately highlight that special care is needed in children as follows:

## **Section 4.2 Posology and Method of Administration**

### **Paediatric population**

Use in children under 12 years should be on the advice of a doctor.

When clobetasone is used in the treatment of dermatoses in children, extreme caution is required and treatment should not normally exceed seven days.

If the condition worsens or does not improve within seven days, treatment should be reviewed.

Once the condition has been controlled, the frequency of application should be reduced to the lowest effective dose for the shortest time possible.

Continuous daily treatment for longer than four weeks is not recommended in children.

## **Section 4.4 Special Warnings and Precautions for Use**

### **Paediatric Population**

Children are more likely to develop local and systemic adverse reactions due to the use of local corticosteroids because of their higher surface area to body mass ratio and, in general, require a shorter treatment.

Particularly, in infants and toddlers the diaper can be considered as an occlusive dressing and therefore can enhance absorption .

In infants and children under 12 years of age, long-term continuous topical corticosteroid therapy should be avoided where possible, as adrenal and growth suppression is more likely to occur.

The PL should also be updated accordingly

### **➤ Recommendation**

**Type IB variation to be submitted by the MAH within 30 days after the end of the procedure. The PL should also be updated accordingly.**