Public Assessment Report

Decentralised Procedure

CLOBAVATE 0.05% W/W OINTMENT

(Clobetasone butyrate)

Procedure No: UK/H/3212/001/DC

UK Licence No: PL 17507/0118

AUDEN MCKENZIE (PHARMA DIVISION) LTD
LAY SUMMARY

On 17 December 2012, Ireland and the UK agreed to grant a Marketing Authorisation to Auden Mckenzie (Pharma Division) Ltd for the medicinal product Clobavate 0.05% w/w Ointment (PL 17507/0118; UK/H/3212/001/DC). The licence was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, a Marketing Authorisation was granted in the UK on 18 January 2013. This is a prescription-only medicine (POM).

Clobavate 0.05% w/w Ointment contains the active ingredient clobetasone butyrate which belongs to a group of medicines called steroids. It helps to reduce swelling and irritation.

Clobavate 0.05% w/w Ointment is used to help reduce the redness and itchiness of certain skin problems. It is used for mild skin problems or to keep your skin problems under control. These skin problems include eczema, dermatitis or insect bites. It is also used to help reduce inflammation in the outer ear.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of using Clobavate 0.05% w/w Ointment outweigh the risks, hence a Marketing Authorisation has been granted.
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# Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Clobavate 0.05% w/w Ointment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Hybrid, Article 10.3</td>
</tr>
<tr>
<td><strong>Active Substances</strong></td>
<td>Clobetasone butyrate</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Ointment</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>0.05% w/w</td>
</tr>
</tbody>
</table>
| **MA Holder** | Auden Mckenzie (Pharma Division) Ltd  
McKenzie House  
Bury Street  
Ruislip  
Middlesex  
HA4 7TL  
UK |
| **Reference Member State (RMS)** | UK |
| **CMS** | Ireland |
| **Procedure Number** | UK/H/3212/001/DC |
| **Timetable** | Day 204 – 17 December 2012 |
Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3
Patient information Leaflet

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4
Labelling

CARTON:

TUBE:
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Clobavate 0.05% w/w Ointment (PL 17507/0118; UK/H/3212/001/DC) could be approved. This application was submitted by the decentralised procedure, with the UK as Reference Member State (RMS), and Ireland as Concerned Member State (CMS). This is a prescription-only medicine (POM).

Clobavate 0.05% w/w Ointment is indicated for the treatment of corticosteroid sensitive dermatoses, including atopic eczema, photodermatitis, otitis externa, primary irritant and allergic dermatitis (including napkin rash), intertrigo, prurigo nodularis, seborrhoeic dermatitis and insect bite reactions.

This application is made via the Decentralised Procedure (DCP), according to Article 10.3 of 2001/83/EC, as amended, as a hybrid application. The reference medicinal product for this application is Eumovate 0.05% Ointment which was first authorised in the UK to Glaxo Wellcome UK Ltd on 17 September 1975 (PL 10949/0037).

Clobetasone butyrate is a topically active corticosteroid of moderate potency (UK Class II - 2-25 times as potent as hydrocortisone). Clobetasone butyrate has little effect on hypothalamo-pituitary-adrenal function. This was so even when applied to adults in large amounts under whole body occlusion.

Clobetasone butyrate is less potent than other available corticosteroid preparations and has been shown not to suppress the hypothalamo-pituitary-adrenal axis in patients treated for psoriasis or eczema.

No new non-clinical studies were conducted, which is acceptable given that this is a hybrid application cross-referring to a product that has been licensed for over 10 years.

To support the application, the Marketing Authorisation Holder submitted four clinical studies. Three clinical studies (two pilot and one pivotal study) were submitted to establish equivalence of the vasoconstriction response between the proposed product Clobavate 0.05% w/w Ointment (by Auden Mckenzie [Pharma Division] Ltd) and the reference product Eumovate 0.05% Ointment (GlaxoSmithkline UK). In addition, the pivotal study also compared topical bioequivalence of the test and reference product through surrogate efficacy and safety measures. A fourth clinical study (cumulative skin irritation study) was submitted to determine and compare the mean cumulative irritation score of the proposed product Clobavate 0.05% w/w Ointment (by Auden Mckenzie [Pharma Division] Ltd) and the reference product Eumovate 0.05% Ointment (GlaxoSmithkline UK). The studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

The RMS and CMS considered that the application could be approved with the end of procedure (Day 204) on 17 December 2012. After a subsequent national phase, the licence was granted in the UK on 18 January 2013.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Clobavate 0.05% w/w Ointment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Clobetasone butyrate</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Corticosteroid, moderately potent (group II) (D07 AB01)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Ointment, 0.05% w/w.</td>
</tr>
<tr>
<td>Reference numbers for the Mutual Recognition Procedure</td>
<td>UK/H/3212/001DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Ireland</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 17507/0118</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Auden Mckenzie (Pharma Division) Ltd</td>
</tr>
<tr>
<td></td>
<td>McKenzie House</td>
</tr>
<tr>
<td></td>
<td>Bury Street</td>
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<td>Ruislip</td>
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<td>Middlesex</td>
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<td></td>
<td>HA4 7TL</td>
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<tr>
<td></td>
<td>UK</td>
</tr>
</tbody>
</table>
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

S.  Active substance

INN:  Clobetasone butyrate.
Chemical name:  1R, 2S, 10S, 11S, 13S, 14R, 15S)-14-(2-chloroacetyl)-1-fluoro-14-hydroxy-2,13,15-trimethyltetracyclo[8.7.0.0^{2,7}.0^{11,13}]heptadeca-3,6-diene-5,17-dione.

Structure:

Molecular formula:  C_{26}H_{32}ClFO_{4}
Molecular weight:  479.0 g/mol
Appearance:  Clobetasone butyrate is a white or almost white powder.
Solubility:  Clobetasone butyrate is practically insoluble in water, freely soluble in acetone and methylene chloride and slightly soluble in ethanol (90%).

Clobetasone butyrate is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

P.  Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients liquid paraffin and white soft paraffin.
All excipients comply with their respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

**Pharmaceutical Development**
The objective of the development programme was to formulate a stable topical preparation (ointment) that is comparable in performance to the reference product Eumovate 0.05% Ointment.

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in-vitro* diffusion and impurity profiles have been provided for the proposed and originator products.

**Manufacturing Process**
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at pilot scale and has shown satisfactory results.

**Finished Product Specification**
The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

**Container-Closure System**
The finished product is packaged in collapsible aluminium tubes internally coated with an epoxy resin based lacquer and closed with a polypropylene cap and is available in pack sizes of 30g and 100g tubes.

It has been stated that not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with foodstuff.

**Stability of the product**
Stability studies were performed in accordance with current guidelines on batches of the finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years (unopened tube) which reduces to 3 months once opened. The storage conditions are ‘Store in the original package in order to protect from light.’
Therapeutic Equivalence
Bioequivalence studies are not necessary to support this application. For products for local application intended to act without systemic absorption, the approach to determine equivalence on systemic measurements is not applicable and pharmacodynamic or comparative clinical studies are required. The applicant has submitted three studies (pilot and pivotal) to establish therapeutic equivalence of the vasoconstriction response between the proposed product and the reference product, and a fourth cumulative irritation study to demonstrate comparable safety between the test and reference products. The studies are discussed in Section III.3, Clinical Aspects.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labels are acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA forms
The MAA form is satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
There are no objections to the approval of this product from a pharmaceutical viewpoint.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of clobetasone butyrate are well-known, no new non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products’ pharmacology and toxicology.

As this product is intended for substitution with a product that is already marketed, no increase in environmental burden is anticipated and no Environmental Risk Assessment is necessary.

There are no objections to the approval of this product from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS
Clinical Pharmacology
The clinical pharmacology of clobetasone butyrate is well-known. With the exception of the clinical studies detailed below, no new pharmacodynamic or pharmacokinetic data are provided or required for this application.
**Efficacy**

For a locally applied, locally acting product clinical equivalence to the reference product needs to be demonstrated. For this purpose the *Note for Guidance on the Clinical Requirements for Locally Applied Locally Acting Products Containing Known Constituents*, allows for a pharmacodynamic model, e.g. the vasoconstrictor assay (VCA) to be used providing that the generic medicinal product possesses the same or similar quantitative and qualitative composition to that of the reference product.

The vasoconstriction response produced from exposure to topical corticosteroids has been proven to be an effective indicator of steroid delivery through the epidermal barrier of the skin. Although the vasoconstriction response to steroids is not known to be directly related to their biochemical activity in skin diseases, it is well known that the vasoconstriction response is an indicator of steroid delivery and will, to some extent, predict comparative efficacy to a skin disease.

With the exception of the data provided in the studies detailed below, no new efficacy data have been submitted and none are required.

In support of the application, the Marketing Authorisation Holder has submitted the following studies:

**Pilot Studies**

**Pilot Study 1**

*A single-exposure study to evaluate the vasoconstriction activity of topically delivered clobetasone butyrate 0.05% ointment in normal skin in healthy adult subjects; a dose ranging study.*

Objectives
The objectives of the study:
Part A: To validate the vasoconstrictor assay precision.
Part B: To evaluate the dose response vasoconstriction profile of Eumovate 0.05% Ointment at different dose durations over a short period of time (10 minutes – 300 minutes).
Values for Maximum effect ($E_{\text{max}}$), Effective Dose – 50% ($ED_{50}$) and $D_1$ (half $ED_{50}$) and $D_2$ (twice $ED_{50}$) were calculated.

Methodology
In Part A of the study, subjects had four 4-cm$^2$ untreated sites on one forearm measured by chromameter (no dose) to assess reproducibility and precision of the test facility’s technique and instrumentation. These six subjects continued into the next phase of the study.

In Part B of the study, subjects had eight 4-cm$^2$ sites on both forearms evaluated for vasoconstriction response to a single lot of Eumovate 0.05% Ointment following different durations of dose application ranging from 15 minutes to 300 minutes, in duplicate. Two sites on each forearm remained untreated to serve as control sites. All sites remained un-occluded throughout the dose exposure period. Vasoconstriction response was evaluated by chromameter measurement at pre-dose, and after dose removal at 11 time points up to 24 hours.

Skin blanching quantification was determined by chromameter assessment.

Subjects were observed and queried for the occurrence of adverse events throughout the study.
Statistical Methods
Vasoconstriction data analyses were conducted as described in the FDA Guidance utilising the chromameter L*a*b*-a values for each time point of assessment.

Chromameter L*a*b*-a values, for each assessment time point, were corrected for baseline reading and by the untreated site reading. Negative Area Under the Effect Curve (AUEC) values, for the duration of 0 to 24 hours post dose removal were calculated from the final corrected (a) values according to the trapezoidal rule, using SAS for Windows. Maximum Effect (E_{max}) and Effective Dose – 50% (ED_{50}) were determined using Kinetica software containing features specifically designed for population E_{max} modelling.

Results
Summary of the Results of the Analysis Performed on the Negative AUEC Values for Eumovate 0.05% Ointment (0 – 24 hour) Using Normal Model

<table>
<thead>
<tr>
<th>E_{max}</th>
<th>ED_{50} (Minutes)</th>
<th>AIC</th>
<th>BIC</th>
<th>OBJ</th>
<th>Log Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.57</td>
<td>201.41</td>
<td>52.23</td>
<td>52.25</td>
<td>19699.71</td>
<td>-10026.29</td>
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</tbody>
</table>

Summary of the Results of the Analysis Performed on the Negative AUEC Values for Eumovate 0.05% Ointment (0 – 24 hour) Using Log-Normal Model

<table>
<thead>
<tr>
<th>E_{max}</th>
<th>ED_{50} (Minutes)</th>
<th>AIC</th>
<th>BIC</th>
<th>OBJ</th>
<th>Log Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.58</td>
<td>139.67</td>
<td>54.99</td>
<td>55.01</td>
<td>20759.87</td>
<td>-10556.37</td>
</tr>
</tbody>
</table>

The use of the Akaike criteria (AIC), Schwartz criteria (BIC), objective function (OBJ), and negative log likelihood goodness of fit parameters provides an objective evaluation of the model curve fit. In general, suitable and applicable model results have AIC values in the range of 3.7 – 4.2, BIC values in the range of 3.8-3.9, OBJ values in the range of 965 – 1150, and Log Likelihood values in the range of 637 – 750 (based on historical data on file). The AIC, BIC, OBJ and Log Likelihood values observed for this study indicate an inability of the E_{max} model to define an appropriate approximation of the data.

Conclusions
The E_{max} population modelling using Kinetica was unable to fit the data well nor could it determine good estimates for E_{max} or ED_{50} based on the AIC, BIC, and negative log likelihood scores observed from the fitting attempts. Therefore, it is not recommended to conduct a pivotal study for this formulation using these model results.

Overall, Eumovate 0.05% Ointment was well tolerated as a single topical dose of 5.0 μL/cm² (20 μL total/4 cm² site) when administered to healthy adult subjects.

Pilot Study 2
A single exposure study to evaluate the vasoconstriction activity of topically delivered clobetasone butyrate 0.05% ointment in normal skin in healthy adult subjects; a dose ranging study.

The design, objectives and patient population in this study were identical to that of pilot study 1 (see above), with the exception that the dose of Eumovate 0.05% Ointment was doubled.

Test Product: Eumovate Ointment clobetasone butyrate 0.05% w/w
Dose: 10.0 μL/cm² (40 0 μL total/4-cm² site)

Results
Summary of the Results of the Analysis Performed on the Negative AUEC Values for Eumovate 0.05% Ointment (0 – 24 hour) Using Normal Model
Conclusion
Based on the ED50 estimate of 156.33 minutes for the normal model, a dose duration for evaluating bioequivalence using the FDA Guidance study design for a pivotal bioequivalence study is nominally indicated as 160 minutes (ED50) with D1=80 minutes and D2=320 minutes.

Pilot studies 1 and 2 were conducted in accordance with the FDA guidance and the methodology is accepted.

In the first pilot study with a lower dose of Eumovate ointment the goodness of fit parameters indicated an inability of the Emax model to define an appropriate approximation of the data. Therefore the study was repeated with a higher dose and the appropriate dose and time of exposure could be estimated for use in the pivotal study.

There were no deaths or Serious Adverse Events (SAEs) in either study and no clinically serious adverse events. The Eumovate Ointment was well tolerated in these single dose studies.

Pivotal Study
A single-blind, single-exposure study in healthy adult male and female subjects to evaluate the vasoconstriction activity of topically delivered clobetasone butyrate ointment 0.05% in normal skin.

Objectives
The objective of the study was to compare the vasoconstriction response profile and bioequivalence between Eumovate 0.05% Ointment (GlaxoSmithKline UK) and a test ointment formulation containing clobetasone butyrate 0.05% (Auden Mckenzie [Pharma Division] Ltd.).

Methodology
This study followed the pivotal vasoconstriction study design as recommended in the FDA Guidance.

Enrolled subjects had a total of ten 4-cm² sites, as pairs, demarcated on each forearm, of which eight 4-cm² sites on each forearm were dosed with 2 formulations which contained clobetasone butyrate 0.05% ointment. Two (2) sites on each forearm remained untreated to serve as control sites. Dose durations of D1 (80 minutes), D2 (320 minutes), and ED50 (160 minutes) were based on values for the Reference Product, Eumovate 0.05% Ointment, as determined in the dose ranging pilot study 2. The Reference Product Eumovate 0.05% Ointment was dosed on 2 sites per arm for the D1, ED50, and D2 durations. The Test Product, clobetasone butyrate 0.05% ointment was dosed on 2 sites per arm using the same ED50 dose duration.

All applied doses were 10.0 μL/cm² of formulation to a 4-cm² site. Application was made using an Eppendorf repeat dose pipette set to deliver 40 μL. The applied dose was evenly spread and gently rubbed into the test site with a glass rod. All sites remained un-occluded after application.

The “staggered application with synchronized removal” method was utilised. The test products were applied to skin sites at different times and all removed at the same time. The
dose durations evaluated were $D_1 = 80$ minutes, $ED_{50} = 160$ minutes, $D_2 = 320$ minutes.

**Results**

Only the data of ‘detectors’, i.e., individual subjects whose negative AUEC values at $D_1$ and $D_2$ were both positive and that met the dose duration-response criterion below, were included in the final analysis. The dose duration-response criterion was:

$$\frac{\text{AUEC} \text{ at } D_2}{\text{AUEC} \text{ at } D_1} \geq 1.25$$

The following table summarises the means of negative AUEC (0 – 24 hr), ratio of means, and 90% CI of clobetasone butyrate 0.05% ointment:

<table>
<thead>
<tr>
<th>Mean Negative AUEC (0 – 24 hr)</th>
<th>% Ratio</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clobetasone butyrate 0.05% ointment</td>
<td>19.86</td>
<td>20.89</td>
</tr>
<tr>
<td>Eumovate Ointment 0.05%</td>
<td>95.06</td>
<td>(86.45, 104.79)</td>
</tr>
</tbody>
</table>

**Conclusion of the pivotal study**

The 90% confidence intervals of the test/reference ratio for the means of negative AUEC(0-24hr) lie within the equivalence interval of 80.00-125.00%. Thus the data support the claim that the test product Clobavate 0.05% w/w Ointment (Auden Mckenzie [Pharma Division] Ltd.) is therapeutically equivalent to the reference product Eumovate 0.05% Ointment (GlaxoSmithKline UK).

**Safety**

In further support of the application, the Marketing Authorisation Holder submitted a skin irritation study to demonstrate that the proposed product was therapeutically equivalent to the reference product, Eumovate 0.05% Ointment (GlaxoSmithKline UK).

**Skin Irritation Study**

A single-centre, within-subject randomised, multiple application, double-blind, study to evaluate the 21-day cumulative irritation potential of clobetasone butyrate 0.05% ointment in normal skin in healthy adult subjects.

The design and conduct of the study was in line with the FDA Guidance for Industry on skin irritation and sensitisation testing of generic transdermal drug products, which has been accepted in Europe for generic topical dermatological products.

**Methodology**

The 21-day, cumulative skin irritation study, utilising standard methodology was used to detect the skin sensitisation properties of the test product Clobavate 0.05% w/w Ointment (Auden Mckenzie [Pharma Division] Ltd.) in comparison with the reference innovator Eumovate 0.05% Ointment (GlaxoSmithKline UK), placebo (sterile Water for Injection) as a negative control and the irritant sodium lauryl sulphate 0.1% w/v solution as a positive control.

Each subject received twenty-one consecutive daily applications of each test article to the test sites on the outside of the upper arms under occluded conditions. The test articles were applied to the same sites every 24 hours (± 1 hour) for a total of 21 applications. Scoring of skin reactions was performed between 20 and 40 minutes following patch removal on Days 2 through 22.
Skin reactions were scored using pre-defined scales. The primary objective was to determine and compare the mean cumulative irritation score (as the sum of all combined “Dermal Response” and “Other Effects” scores) from 21 consecutive daily applications of the reference product to the cumulative irritation produced by test product and thereby determine whether the test product was non-inferior to Eumovate 0.05% Ointment in terms of cumulative irritation.

The secondary objective of this cumulative irritation study was to assess safety by monitoring adverse events (AEs).

The relevant hypotheses were:

$$H_0: \text{median}_T - 1.25 \cdot \text{median}_R > 0 \quad \text{(not non-inferior)}$$

$$H_1: \text{median}_T - 1.25 \cdot \text{median}_R \leq 0 \quad \text{(non-inferior)}$$

To demonstrate non-inferiority of the Test formulation compared to the Reference formulation with regard to the cumulative irritation scores, the upper bound of the one-sided 95% confidence interval (CI) of the median cumulative irritation score for the Test formulation (median\(_T\)) minus the median of 1.25 times the cumulative irritation score for the reference product (median\(_R\)) must be less than or equal to 0.

A 95% bootstrap CI of the median difference between Test and Reference was used for evaluating non-inferiority. In addition, the comparison of the Positive Irritant Control and the Negative Irritant Control was performed in an identical manner.

**Results**

**The results of the study are presented below:**

**Summary of the cumulative irritation scores:**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference Formulation</td>
<td>14.17</td>
<td>4.44</td>
<td>15</td>
</tr>
<tr>
<td>Test Formulation</td>
<td>13.03</td>
<td>5.35</td>
<td>14</td>
</tr>
<tr>
<td>Positive Control</td>
<td>57.61</td>
<td>13.28</td>
<td>60</td>
</tr>
<tr>
<td>Negative Control</td>
<td>15.08</td>
<td>4.05</td>
<td>16</td>
</tr>
</tbody>
</table>

**Summary of 95% Bootstrapping Confidence Intervals based on the cumulative irritation scores (Test -1.25* Reference):**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Median Difference</th>
<th>Upper Bound of 95% Bootstrap Confidence Limit of the Median Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Formulation vs. Reference Formulation</td>
<td>-4.875</td>
<td>-3.75</td>
</tr>
<tr>
<td>Positive Control vs. Negative Control</td>
<td>39.5</td>
<td>44</td>
</tr>
</tbody>
</table>

The results of this study indicate that Clobavate 0.05% w/w Ointment was non-inferior to Eumovate 0.05% Ointment in terms of irritation. In addition, the Positive Irritant Control was not non-inferior (i.e. superior) to the Negative Irritant Control in terms of cumulative irritation supporting the validity of the study methodology.

**Adverse Events (AEs)**

Reports of adverse events were collected during the vasoconstrictor assay studies (pilots and main) and during the skin irritation study. During the course of these studies few adverse events were reported and other than one report of application site pruritus associated with the
application of Eumovate ointment, none of the adverse events was considered to be related to the drug application.

In the main study and the skin irritation study all subjects were exposed to both test and reference product simultaneously so the adverse events could not be attributed to one particular treatment. None of the adverse events were serious and all were considered unlikely to be related to the treatments.

No serious adverse events or deaths were reported during the pivotal vasoconstriction assay study or the cumulative skin irritation study.

**Overall conclusion on safety**

With the exception of the data from the above pilot and pivotal vasoconstriction assay studies and the skin irritation study, no new clinical data were submitted and none were required. The safety data collected during the studies showed that the test and reference product had a comparable tolerability. No new safety issues arose during the studies and the proposed product has shown equivalence to the reference product such that the safety can be expected to be equivalent to the marketed Eumovate 0.05% Ointment (GlaxoSmithKline UK).

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**

The SmPC, PIL and labels are acceptable from a clinical perspective. The SmPC is consistent with that for the reference product. The PIL is consistent with the details in the SmPC and in-line with the current guidelines. The labelling is in-line with the current guidelines.

**Clinical Overview**

The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Pharmacovigilance System and Risk Management Plan**

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a Risk Management Plan for this product.

**Conclusion**

The grant of a Marketing Authorisation is recommended.
IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Clobavate 0.05% w/w Ointment are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of clobetasone butyrate are well-known, no additional data were required.

EFFICACY
With the exception of the data submitted in the pilot and pivotal vasoconstriction assay studies and the skin irritation study, no new clinical data were submitted and none are required for this type of application.

Therapeutic equivalence has been demonstrated between the proposed product Clobavate 0.05% w/w Ointment and the reference product Eumovate 0.05% Ointment (Glaxo Wellcome UK Ltd).

SAFETY
The safety profile of clobetasone butyrate is well-known. With the exception of the safety data generated during the pilot and pivotal vasoconstriction assay studies and the skin irritation study, no new safety data were submitted and none are required for this type of application. No new or unexpected safety issues arose during the pilot and pivotal vasoconstriction assay studies or the skin irritation study. The proposed product has shown equivalence to the reference product such that the safety can be expected to be equivalent to the already licensed and marketed Eumovate 0.05% Ointment (GlaxoSmithkline UK).

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product, where appropriate, and consistent with current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with clobetasone butyrate is considered to have demonstrated the therapeutic value of the product. The benefit/risk balance is, therefore, considered to be positive.
## Module 6

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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