Public Assessment Report

Decentralised Procedure

Audavate RD 0.025% w/w Ointment

Betamethasone valerate

Procedure No: UK/H/5037/001/DC

UK licence no: PL 17507/0116

Auden Mckenzie (Pharma Division) Ltd
Audavate RD 0.025% w/w Ointment

PL 17507/0116

LAY SUMMARY

On 18th September 2012, the Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation to Auden Mckenzie (Pharma Division) Ltd for the medicinal product Audavate RD 0.025% w/w Ointment (PL 17507/0116; UK/H/5037/001/DC). This is a Prescription-only medicine (POM).

Audavate RD contains an active ingredient called betamethasone valerate. It belongs to a group of medicines called steroids. It helps to reduce swelling and irritation.

Audavate RD is used to help reduce the redness and itchiness of certain skin problems. These skin problems include eczema, psoriasis and dermatitis.

RD stands for ‘Ready Diluted’. It contains less active ingredient than Audavate 0.1% preparations. It is used:
• For milder skin problem, or
• To keep your skin under control after Audavate 0.1% has improved it.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Audavate RD 0.025% w/w Ointment outweigh the risks, hence a Marketing Authorisation has been granted.
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# Module 1

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<th><strong>Product Name</strong></th>
<th>Audavate RD 0.025% w/w Ointment</th>
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<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Article 10.3, Hybrid Application</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>betamethasone valerate</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Ointment</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>0.025% w/w</td>
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<tr>
<td><strong>MA Holder</strong></td>
<td>Auden Mckenzie (Pharma Division) Ltd</td>
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<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>HA4 7TL</td>
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<td>UK</td>
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<tr>
<td><strong>RMS</strong></td>
<td>UK</td>
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<tr>
<td><strong>CMSs</strong></td>
<td>Republic of Ireland</td>
</tr>
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<td><strong>Procedure Number</strong></td>
<td>UK/H/5037/001/DC</td>
</tr>
<tr>
<td><strong>Timetable</strong></td>
<td>Day 210: 13th September 2012</td>
</tr>
</tbody>
</table>
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

Each 1 g contains 0.25 mg of betamethasone (0.025% w/w) as betamethasone valerate. Also contains liquid paraffin and white soft paraffin.

Please read the enclosed leaflet before use.

For external use only.

Do not store above 30°C. Once opened, do not use this medicine for more than 6 months. Medicinal product subject to medical prescription.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

POM

Statement to the Image Authority: The Authorised Person with Responsibility for Image Authority is shown in the signature block of this document.
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member State (CMS) consider that the application for Audavate RD 0.025% w/w Ointment (PL 17507/0116; UK/H/5037/001/DC could be approved.

This Prescription only medicine (POM) is indicated for the treatment of eczema in children and adults; including atopic and discoid eczemas, prurigo nodularis; psoriasis (excluding widespread plaque psoriasis); neurodermatoses, including lichen simplex, lichen planus; seborrhoeic dermatitis; contact sensitivity reactions; discoid lupus erythematosus and they may be used as an adjunct to systemic steroid therapy in generalised erythroderma.

Audavate RD 0.025% preparations are indicated for maintenance treatment when control has been achieved with Audavate 0.1%.

In general, ointment preparations are particularly appropriate for dry, lichenified or scaly skin conditions whereas a cream preparation may be more suitable in the case of moist or weeping lesions.

This application was submitted under Article 10.3 of 2001/83 EC, as amended, as a hybrid application. The reference medicinal product for this application is Betnovate RD ointment 0.025%w/w (PL 10949/0022), which was first licensed in the UK to Glaxo Wellcome UK Limited, on 14th January 1993.

With UK as the RMS in this Decentralised Procedure (UK/H/5037/001/DC), Auden Mckenzie (Pharma Division) Ltd applied for the Marketing Authorisation for Audavate RD 0.025% w/w Ointment in Republic of Ireland.

Betamethasone valerate is an active corticosteroid with topical anti-inflammatory activity. The extent of percutaneous absorption of topical corticosteroid is determined by many factors including the vehicle, 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.

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systematically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolised primarily by the liver and are then excreted by the kidneys.

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of the originator product that has been licensed for over 10 years.

To support the application the, the Marketing Authorisation Holder submitted three clinical studies. These studies included a pilot study to validate the vasoconstriction assay precision,
a pivotal study to demonstrate equivalence of the vasoconstriction response between the test and the reference products and a comparative dermal irritation study to compare the safety profile of the test and the reference products. The studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that 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. A suitable justification has been provided for non-submission of a Risk Management Plan.

All member states agreed to grant a respective Marketing Authorisation for the above product at the end of procedure (Day 210 – 13th September 2012). After a subsequent national phase, the UK granted a Marketing Authorisation for this product on 18th September 2012 (PL 17507/0116).
II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Audavate RD 0.025% w/w Ointment</th>
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<tr>
<td>Name(s) of the active substance(s) (USAN)</td>
<td>betamethasone valerate</td>
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<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Bethamethasone valerate is an active corticosteroid with topical anti-inflammatory activity. ATC code: D07 AC01 (Corticosteroid, potent)</td>
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<td>Pharmaceutical form and strength(s)</td>
<td>Ointment and 0.025% w/w</td>
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<td>Reference Member State</td>
<td>United Kingdom</td>
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<td>Concerned Member States</td>
<td>Republic of Ireland</td>
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<td>Marketing Authorisation Number(s)</td>
<td>PL 17507/0116</td>
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<tr>
<td>Name and address of the authorisation holder</td>
<td>Auden Mckenzie (Pharma Division) Ltd McKenzie House Bury Street Ruislip Middlesex HA4 7TL UK</td>
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III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

DRUG SUBSTANCE

INN: Betamethasone valerate

Structure:

\[
\text{Molecular formula: } C_{27}H_{37}FO_6 \\
\text{Molecular weight: } 476.6 \\
\text{Physical form: White or almost white, crystalline powder.} \\
\text{Solubility: Practically insoluble in water, freely soluble in acetone and in ethanol.}
\]

Betamethasone valerate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance betamethasone valerate are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients white soft paraffin and liquid paraffin.

All excipients comply with the European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for these excipients.

The above excipients do not contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

There were no novel excipients used.

Pharmaceutical Development

The objective of the pharmaceutical development programme was to obtain stable topical preparation that was therapeutically equivalent to the reference product, Betnovate RD ointment 0.025%w/w (Glaxo Wellcome UK Limited)

Suitable pharmaceutical development data have been provided for this application.

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

Manufacture

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 and has shown satisfactory results. Process validation data on commercial
batches have been provided. The results are satisfactory.

**Finished Product Specifications**
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

**Container Closure System**
The finished product is supplied in collapsible aluminium tubes internally coated with an epoxy resin based lacquer and closed with a polypropylene cap. The pack size is 100 g.

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with guidelines.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years for unopened tubes and 3 months after first opening are set, with a storage condition of “Do not store above 30°C”. These are satisfactory.

**Therapeutic Equivalence**
Bioequivalence can not be demonstrated for locally applied products. In accordance with the FDA Guidance for topical corticosteroid products, the applicant has submitted a pilot and pivotal studies to establish therapeutic equivalence of the vasoconstriction response between the proposed and the reference products. In addition, comparative dermal irritation study has been provided 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) and Labelling**
The SPC, PIL and labelling are pharmaceutically satisfactory.

User testing of the package leaflet has been accepted, based on a bridging report provided by the applicant making reference to the user-testing of the PIL for ClobaDerm 0.05% Ointment. (PL 17507/0110). The products are from the same therapeutic class and have similar indications. A critical analysis demonstrated that the key messages for safe and effective use for both leaflets were similar. The justification of the rationale for bridging is accepted.

**Marketing Authorisation Application (MAA) Forms**
The MAA form is pharmaceutically satisfactory.

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

**Conclusion**
There are no objections to the approval of this product from a pharmaceutical point of view.
III.2 NON-CLINICAL ASPECTS
PHARMACODYNAMICS, PHARMACOKINETICS, TOXICOLOGY
The pharmacological, pharmacokinetic and toxicological properties of betamethasone valerate are well-known.

No new non-clinical data have been supplied with this application and none are required for applications of this type. The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

A suitable justification has been provided for non-submission of the environmental risk assessment.

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

III.3 CLINICAL ASPECTS
Clinical Pharmacology
The clinical pharmacology of betamethasone valerate 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.

In accordance with the FDA Guidance, “Topical Dermatologic Corticosteroid in vivo bioequivalence 1995”, for topical corticosteroid products, the applicant has submitted a pilot and pivotal studies to establish therapeutic equivalence of the vasoconstriction response between the proposed product (Betamethasone valerate Ointment 0.025%) and the reference product (Betnovate RD Ointment 0.025%). In addition, comparative dermal irritation study has been provided to demonstrate comparable safety between the test and reference products.

Efficacy

Pilot Study
This is a single exposure, dose ranging study to evaluate the vasoconstriction activity of topically delivered Betnovate RD Ointment 0.025% in normal skin in healthy adult subjects.

Methodology
The study consisted of two parts:

Part A: to validate the vasoconstrictor assay precision
Part B: To evaluate the dose response vasoconstriction profile of Betnovate RD Ointment 0.025% at different dose durations, with occlusion, over a short period of time (30 - 360 minutes).

In Part A of the study subjects had four 4-cm² untreated sites on one forearm measured by chromameter (no dose) to assess reproducibility and precision of the test facility’s technique and instrumentation. These subjects continued into the next phase of the study.

In Part B of the study, subjects had eight 4-cm² sites on both forearms evaluated for vasoconstriction response to a single application of Betnovate RD Ointment 0.025% w/w following different durations of dose application ranging from 30 minutes to 360 minutes, in duplicate. Two sites on each forearm remained untreated to serve as control sites. All sites remained un-occluded after application. Vasoconstriction response was evaluated by
chromameter measurement at pre-dose, and after removal at 11 time points (1, 2, 4, 6, 8, 10, 12, 18, 20, 22, and 24 hours after dose removal).

Skin blanching quantification was determined by chromameter assessment.

Subjects were observed and queried for the occurrence of adverse events throughout the study.

The study was conducted in accordance to the guidance issued by the FDA Center for Drug Evaluation and Research in 1995. However, the number of subjects included in the study was higher compared to FDA’s recommendation and the method of removal of the corticosteroid was optimized. These changes to the method advised in the FDA guidance have been adequately justified and did not adversely affect the results of the study.

**Statistical methods**

Vasoconstriction data analyses were conducted as described in the FDA Guidance. Chromameter L*a*b*-a values, for each time point and site 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. Maximum Effect (E_{max}), Effective Dose – 50% (ED_{50}), D_{1} (half ED_{50}) and D_{2} (twice ED_{50}) were determined using a software containing features specifically designed for population modelling.

**Results**

The results are presented below

**Mean negative a* areas under the effect curve (0-24 hour areas) for dose duration times 0 to 360 minutes (Log-Normal Model)**

![Graph showing mean negative a* areas under the effect curve](image)

The Akaike criteria (AIC), Schwartz criteria (BIC), objective function (OBJ), and negative log likelihood goodness of fit parameters were used to help determine the model that best fit the data.
Summary of the Results of the Analysis Performed on the Negative AUEC Values for Betnovate RD Ointment 0.025% Using Log Normal Model

<table>
<thead>
<tr>
<th>F_{crit}</th>
<th>ED_{50} (Minutes)</th>
<th>AIC</th>
<th>BIC</th>
<th>OBJ</th>
<th>Negative Log Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>42.75</td>
<td>136.22</td>
<td>3.92</td>
<td>3.94</td>
<td>1149.79</td>
<td>751.33</td>
</tr>
</tbody>
</table>

**Conclusion on the pilot study**

Based on the ED_{50} estimate of 136.22 minutes for the log-normal model, a dose duration for evaluating bioequivalence using the FDA Guidance study design for a pivotal bioequivalence study is nominally indicated as: 140 minutes (ED_{50}) with D_{1}=70 minutes and D_{2}=280 minutes

**Pivotal Study**

A single-blind, single-exposure study to evaluate the vasoconstriction activity of topically delivered betamethasone valerate ointment 0.025% in normal skin in healthy adult subjects. (Pivotal bioequivalence study)

**Objectives**

The objective of the study was to compare the vasoconstriction response profile (bioequivalence) between the test formulation containing Betamethasone valerate Ointment 0.025% (Auden Mckenzie [Pharma Division] Ltd.) and Betnovate RD Ointment 0.025% (GlaxoSmithKline UK).

**Methodology**

The study was based on the pivotal vasoconstriction study design as recommended in the FDA Guidance for Industry published in 1997. Potential subjects were screened for vasoconstriction responsiveness using a single dose application of Betnovate RD Ointment 0.025% on normal skin.

Enrolled subjects had a total of ten 4-cm² sites demarcated on each forearm, of which eight 4-cm² sites on each forearm were dosed with two formulations which contained betamethasone valerate Ointment 0.025%. Two sites on each forearm remained untreated to serve as control sites. Dose durations were based on D_{1} (70 minutes), D_{2} (280 minutes), and ED_{50} (140 minutes) values for the Reference Product, Betnovate RD Ointment 0.025%, as determined in the dose ranging pilot study.

The reference formulation, Betnovate RD Ointment 0.025% (GlaxoSmithKline UK), was dosed on 2 sites per arm for the D_{1}, ED_{50}, and D_{2} durations. The test product, Betamethasone valerate Ointment 0.025% (Auden Mckenzie (Pharma Division) Ltd) was dosed on 2 sites per arm using the same ED_{50} dose duration.

All site remained non-occluded after application.

**Statistical methods**

Vasoconstriction data analyses were conducted as described in the FDA Guidance. Chromameter L*a*b*-a* values, for each 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.
There were a total of 20 sites per subject (10 sites on each forearm). Of these, 6 pairs of sites (3 pairs per arm) were dosed with reference product, with dose durations of one-half the Effective Dose – 50% (D₁), twice the Effective Dose – 50% (D₂) and the Effective Dose – 50% (ED₅₀). One pair of sites per arm was dosed with test product, with a dose duration of the Effective Dose – 50% (ED₅₀).

Only the data of ‘detectors’, i.e., individual subjects whose negative AUEC values at D₁ and D₂ were both positive and that met the dose duration-response criterion below, were included in the final analysis. The dose duration-response criterion was:

\[
\frac{AUEC \text{ at } D₁}{AUEC \text{ at } D₂} \geq 1.25
\]

A 90% confidence interval (CI) about the ratio of the mean test value to the mean reference value was calculated for average AUEC response according to Locke’s method.

**Results**

*Mean corrected a* values (0-24 hours) for the comparison of the Test and Reference formulations (n=67)*

The following table summarizes the means of negative AUEC (0 – 24 hr), ratio of means, and 90% CI for the comparison of the test and reference formulations.

<table>
<thead>
<tr>
<th>BETAMETHASONE VALERATE OINTMENT 0.025% (TEST)</th>
<th>BETNOVATE RD OINTMENT 0.025% (REFERENCE)</th>
<th>% RATIO</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.42</td>
<td>19.61</td>
<td>88.85</td>
<td>(80.29,97.75)</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 Betamethasone valerate Ointment 0.025% (Auden Mckenzie (Pharma Division) Ltd) is therapeutically equivalent to the reference product Betnovate RD Ointment 0.025% (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, Betnovate RD ointment 0.025%.

**Skin Irritation Study**

A randomized, single-centre, phase 1 study to evaluate the 21-day cumulative irritation potential of Betamethasone valerate Ointment 0.025% in normal skin in healthy adult subjects.

**Methodology**

The 21-day, cumulative skin irritation study, utilizing standard methodology was used to detect the skin sensitization properties of the test product Betamethasone valerate Ointment 0.025% (Auden Mckenzie (Pharma Division) Ltd) in comparison with the reference innovator Betnovate RD Ointment 0.025% (GlaxoSmithKline UK), placebo (sterile Water for Injection) as a negative control and the irritant sodium lauryl sulfate 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 re-applied to the same sites each day (± 1 hour) for a total of 21 applications. Scoring of skin reactions was performed before the first patch application and then 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 compare the mean cumulative irritation score (sum of all combined “Dermal Response” and “Other Effects” scores) after 21 consecutive daily applications of Betnovate RD Ointment 0.025% and Betamethasone valerate Ointment 0.025% and to compare the results with the irritation scores of the positive and negative controls to determine whether the Test formulation was non-inferior to the Reference formulation in terms of cumulative irritation.

The relevant hypotheses were:

\[ H_0: median_{T} - 1.25median_{R} > 0 \text{ (not non-inferior)} \]

\[ H_1: median_{T} - 1.25median_{R} \leq 0 \text{ (non-inferior)} \]

It was pre-specified that to demonstrate non-inferiority of the Test formulation compared to the Reference formulation, 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 \( median_R \) had to be \( \leq 0 \).

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.
The Table below summarises the bootstrapping CIs based on the cumulative irritation scores

<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>-3</td>
<td>-0.875</td>
</tr>
<tr>
<td>Positive Control vs. Negative Control</td>
<td>45.5</td>
<td>49.75</td>
</tr>
</tbody>
</table>

The results therefore indicate that the proposed formulation of Betamethasone valerate Ointment 0.025% was non-inferior to its respective Reference product (Betnovate RD Ointment 0.025%) in terms of irritation potential.

In addition, the Positive Irritant Control produced greater cumulative irritation compared to the negative control.

Overall, Betamethasone valerate Ointment 0.025% was well tolerated as single site application of 1 x 0.2 ml daily for 21 consecutive days, applied topically to healthy adults. The Positive Irritant Control demonstrated local skin irritation as anticipated for a known topical irritant.

**Conclusion of the skin irritation study**

The results of this study confirm that the proposed product, Betamethasone valerate Ointment 0.025% has no greater propensity to cause dermal irritation than the corresponding licensed reference product Betnovate RD Ointment 0.025% (Glaxo Wellcome UK Limited).

**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 pilot, pivotal or the skin irritation studies. The proposed product has shown equivalence to the reference product such that the safety can be expected to be equivalent to the marketed Betnovate RD Ointment 0.025% (Glaxo Wellcome UK Limited).

**Clinical Expert Report**

The clinical expert report is 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.
Marketing Authorisation Application (MAA) Forms
The MAA form is medically satisfactory.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
The SmPC, PIL and labelling are medically satisfactory and consistent with those for the reference product.

Clinical Conclusion
There are no objections to the approval of this product from a clinical point of view.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Audavate RD 0.025% 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 betamethasone valerate are well-known, no additional data were required.

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

Therapeutic equivalence has been demonstrated between the proposed product Betamethasone valerate Ointment 0.025% (Auden Mckenzie [Pharma Division] Ltd.) and the reference product Betnovate RD Ointment 0.025% (GlaxoSmithKline UK).

SAFETY
The safety profile of betamethasone valerate is well-known. With the exception of the safety data generated during the pilot and pivotal vasoconstrictor assay studies and the skin irritation study, no new safety data were submitted and none are required for this application. No new or unexpected safety issues arose during the pilot and pivotal vasoconstrictor 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 Betnovate RD Ointment 0.025% (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 betamethasone valerate is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
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<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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