Public Assessment Report

Decentralised Procedure

ClobaDerm 0.05% w/w Cream (clobetasol propionate)

Procedure No: UK/H/3207/001/DC

UK Licence No: PL 17507/0109

Auden Mckenzie (Pharma Division) Ltd
LAY SUMMARY

On 21 June 2012, the Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation to Auden Mckenzie (Pharma Division) Ltd. for the medicinal product ClobaDerm 0.5% w/w Cream (PL 17507/0109; UK/H/3207/001/DC). This is a prescription-only medicine (POM) used to help reduce the redness and itchiness of certain skin problems. These skin problems include eczema, psoriasis and dermatitis that have not responded to milder steroid creams or ointments.

ClobaDerm 0.5% w/w Cream contains the active ingredient clobetasol (as clobetasol propionate), which belongs to a group of medicines called steroids. Clobetasol propionate helps to reduce swelling and irritation.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of using ClobaDerm 0.5% w/w Cream outweigh the risks and a Marketing Authorisation was granted.
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## Module 1

### Information about the initial procedure

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<tr>
<td>Type of Application</td>
<td>Directive 2001/83/EC, Article 10(3) – hybrid application</td>
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<td>Active Substance</td>
<td>Clobetasol propionate</td>
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<tr>
<td>Form</td>
<td>Cream</td>
</tr>
<tr>
<td>Strength</td>
<td>500 micrograms/gram</td>
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</table>
| MA Holder | Auden Mckenzie (Pharma Division) Ltd  
McKenzie House  
Bury Street  
Ruislip  
Middlesex  
HA4 7TL  
UK |
| Reference Member State (RMS) | UK |
| Concerned Member State (CMS) | Ireland |
| Procedure Number(s) | UK/H/3207/001/DC |
| Timetable | Day 150 – 24 April 2012 |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
ClobaDerm 0.05% w/w Cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
1 g of cream contains 0.5 mg of clobetasol propionate (0.05% w/w).

Also contains 80 mg of cetostearyl alcohol, 475 mg of propylene glycol and 0.75 mg of chlorocresol in each gram of the cream.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Cream

White or almost white cream.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Clobetasol propionate is a very active topical corticosteroid which is of particular value when used in short courses for the treatment of more resistant dermatoses such as psoriasis (excluding widespread plaque psoriasis), recalcitrant eczemas, lichen planus, discoid lupus erythematosus, and other skin conditions which do not respond satisfactorily to less active steroids.

4.2 Posology and method of administration
Apply sparingly to the affected area once or twice daily until improvement occurs. As with other highly active topical steroid preparations, therapy should be discontinued when control is achieved. In the more responsive conditions this may be within a few days.

If no improvement is seen within two to four weeks, reassessment of the diagnosis, or referral, may be necessary.

Repeated short courses of ClobaDerm may be used to control exacerbations. If continuous steroid treatment is necessary, a less potent preparation should be used.

In very resistant lesions, especially where there is hyperkeratosis, the anti-inflammatory effect of ClobaDerm can be enhanced, if necessary, by occluding the treatment area with polythene film. Overnight occlusion only is usually adequate to bring about a satisfactory response. Thereafter improvement can usually be maintained by application without occlusion.

For topical administration.

4.3 Contraindications
• Rosacea
• Acne vulgaris
• Perioral dermatitis
• Perianal and genital pruritus
• Primary cutaneous viral infections (e.g. herpes simplex, chickenpox)
• Hypersensitivity to the preparation
• The use of ClobaDerm skin preparations is not indicated in the treatment of primary infected skin lesions caused by infection with fungi (e.g. candidiasis, tinea) or bacteria (e.g. impetigo); or dermatoses in children under one year of age, including dermatitis and napkin eruptions.

4.4 Special warnings and precautions for use
Long-term continuous therapy should be avoided where possible, particularly in infants and children, as adrenal suppression can occur even without occlusion. If ClobaDerm is required for use in children, it is recommended that the treatment should be reviewed weekly. It should be noted that the infant's napkin may act as an occlusive dressing.
If used in childhood or on the face, courses should be limited if possible to five days and occlusion should not be used.

The face, more than other areas of the body, may exhibit atrophic changes after prolonged treatment with potent topical corticosteroids. This must be borne in mind when treating such conditions as psoriasis, discoid lupus erythematosus and severe eczema.

If applied to the eyelids, care is needed to ensure that the preparation does not enter the eye, as glaucoma might result. If ClobaDerm does enter the eye, the affected eye should be bathed in copious amounts of water.

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

Appropriate antimicrobial therapy should be used whenever treating inflammatory lesions which have become infected. Any spread of infection requires withdrawal of topical corticosteroid therapy and systemic administration of antimicrobial agents. Bacterial infection is encouraged by the warm, moist conditions induced by occlusive dressings, and so the skin should be cleansed before a fresh dressing is applied.

There have been a few reports in the literature of the development of cataracts in patients who have been using corticosteroids for prolonged periods of time. Although it is not possible to rule out systemic corticosteroids as a known factor, prescribers should be aware of the possible role of corticosteroids in cataract development.

ClobaDerm 0.05% w/w Cream contains cetostearyl alcohol which can cause local skin reactions (e.g. contact dermatitis), propylene glycol which may cause skin irritation and chlorocresol which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction
None reported.

4.6 Fertility, pregnancy and lactation
There is inadequate evidence of safety in human pregnancy. Topical administration of corticosteroids to pregnant animals can cause abnormalities of fetal development including cleft palate and intrauterine growth retardation. The relevance of this finding to humans has not been established, therefore, topical steroids should not be used extensively in pregnancy, i.e. in large amounts or for prolonged periods.

The safe use of clobetasol propionate during lactation has not been established.

4.7 Effects on ability to drive and use machines
ClobaDerm is not expected to have any effects.

4.8 Undesirable effects
The following adverse reactions have been identified during post-approval use of clobetasol propionate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The frequency of these adverse events has therefore been classified as “unknown”.

Immune system disorders
Hypersensitivity
- Local hypersensitivity reactions such as erythema, rash, pruritus, urticaria and allergic contact dermatitis may occur at the site of application and may resemble symptoms of the condition under treatment.
- If signs of hypersensitivity appear, application should be stopped immediately.

Endocrine disorders
Features of Cushing's syndrome
- As with other topical corticosteroids, prolonged use of large amounts, or treatment of extensive areas can result in sufficient systemic absorption to produce the features of
Cushing's syndrome. This effect is more likely to occur in infants and children, and if occlusive dressings are used. In infants, the nappy may act as an occlusive dressing.

- Provided the weekly dosage is less than 50g in adults, any suppression of the HPA axis is likely to be transient with a rapid return to normal values once the short course of steroid therapy has ceased. The same applies to children given proportionate dosage.

**Vascular disorders**
Dilatation of the superficial blood vessels

- Prolonged and intensive treatment with highly-active corticosteroid preparations may cause dilatation of the superficial blood vessels, particularly when occlusive dressings are used, or when skin folds are involved.

**Skin and subcutaneous tissue disorders**
Local skin burning, local atrophy, striae, thinning, pigmentation changes, hypertrichosis, exacerbation of underlying symptoms, pustular psoriasis.

- Prolonged and intensive treatment with highly-active corticosteroid preparations may cause local atrophic changes, such as thinning and striae.
- Treatment of psoriasis with corticosteroids (or its withdrawal) is thought to have provoked the pustular form of the disease.

### 4.9 Overdose
Acute overdosage is very unlikely to occur, however, in the case of chronic overdosage or misuse, the features of hypercortisolism may appear and in this situation topical steroids should be reduced or discontinued gradually, under medical supervision.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties
Clobetasol propionate is a highly active corticosteroid with topical anti-inflammatory activity. The major effect of clobetasol propionate on skin is a non-specific anti-inflammatory response, partially due to vasoconstriction and decrease in collagen synthesis.

#### 5.2 Pharmacokinetic properties
Percutaneous penetration of clobetasol propionate varies among individuals and can be increased by the use of occlusive dressings, or when the skin is inflamed or diseased.

Mean peak plasma clobetasol propionate concentrations of 0.63 ng/ml occurred in one study eight hours after the second application (13 hours after an initial application) of 30 g clobetasol propionate 0.05% ointment to normal individuals with healthy skin. Following the application of a second dose of 30 g clobetasol propionate cream 0.05% mean peak plasma concentrations were slightly higher than the ointment and occurred 10 hours after application.

In a separate study, mean peak plasma concentrations of approximately 2.3 ng/ml and 4.6 ng/ml occurred respectively in patients with psoriasis and eczema three hours after a single application of 25 g clobetasol propionate 0.05% ointment.

Following percutaneous absorption of clobetasol propionate, the drug probably follows the metabolic pathway of systemically administered corticosteroids, i.e. metabolised primarily by the liver and then excreted by the kidneys. However, systemic metabolism of clobetasol has never been fully characterised or quantified.

#### 5.3 Preclinical safety data
There are no preclinical data of relevance to the prescriber which are additional to that in other sections of the SmPC.
PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Cetostearyl alcohol
Glycerol monostearate
Arlacel 165 (glycerol monostearate & macrogol 100 stearate)
White beeswax
Propylene glycol
Chlorocresol
Sodium citrate
Citric acid monohydrate
Purified water

6.2 Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life
2 years.
In-use shelf life: 3 months

6.4 Special precautions for storage
Store below 30 °C.

6.5 Nature and contents of container
Collapsible aluminum tubes internally coated with an epoxy resin based lacquer and closed with a polypropylene cap.

Pack sizes: 30g or 100g.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Patients should be advised to wash their hands after applying ClobaDerm unless it is the hands that are being treated.

MARKETING AUTHORISATION HOLDER
Auden Mckenzie (Pharma Division) Ltd
McKenzie House
Bury Street
Ruislip
Middlesex
HA4 7TL
UK

MARKETING AUTHORISATION NUMBER(S)
PL 17507/0109

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
21/06/2012

DATE OF REVISION OF THE TEXT
21/06/2012
Module 3

PATIENT INFORMATION LEAFLET

ClobaDerm® 0.05% w/w Cream & Ointment
(Clobetasol Propionate)

Read all of this leaflet carefully because it contains important information for you.

• Keep this leaflet. You may need to read it again.
• If you have any further questions, ask your doctor or pharmacist.
• This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
• If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What is ClobaDerm and what is it used for?
2. Before you use ClobaDerm
3. How to use ClobaDerm
4. Possible side effects
5. Storing ClobaDerm
6. Further information

1. What is ClobaDerm and what is it used for?

ClobaDerm belongs to a group of medicines called steroids. It helps to reduce swelling and irritation.

ClobaDerm is used to help reduce the redness and thickness of certain skin problems. These skin problems include eczema, psoriasis and dermatitis that have not responded to milder steroid creams or ointments.

2. Before you use ClobaDerm

Do not use ClobaDerm:
• if you are allergic (hypersensitive) to clobetasol propionate or any of the other ingredients of ClobaDerm (listed in Section 6).
• if you have diabetes under 1 year old.
• to treat any of the following skin problems, it could make them worse:
  - acne
  - severe flushing of skin and around your nose (Rosacea)
  - spoty red rash around your mouth (perioral dermatitis)
  - itching around your back passage or private parts, unless your doctor has told you to do so
  - viral infections, such as cold sores, herpes or chicken pox
  - fungal infections, such as ringworm, athlete’s foot or thrush
  - skin blisters or sore that are caused by an infection.

Do not use this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before using ClobaDerm.

Special Precautions:

- Check with your doctor or pharmacist before using ClobaDerm if:
  • you are applying the cream or ointment under an adhesive dressing, including a child’s nappy. These dressings make it easier for the active ingredient to pass through the skin. It is possible to accidentally and up using too much cream or ointment.
  • you have psoriasis, your doctor will want to see you more often.

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before using this medicine.

Pregnancy and breast-feeding:

Talk to your doctor or pharmacist before using this medicine if you are pregnant, might become pregnant or are breast-feeding.

Warnings about some of the ingredients:

ClobaDerm Cream contains alcohol which can cause local skin reactions (e.g. contact dermatitis), propy-

ClobaDerm Ointment contains propylene glycol which may cause skin irritation.

3. How to use ClobaDerm

Always use ClobaDerm Cream or Ointment exactly as your doctor or pharmacist has told you. You should check with your doctor or pharmacist if you are not sure.

Using this medicine:
• You need to apply a thin layer of ClobaDerm 1 or 2 times a day. This may be reduced as your skin begins to get better, or stopped when it is better.
• This cream/ointment is for use on your skin only.
• Do not use on large areas of the body for a long time (such as every day for many weeks or months). If you need treatment for a long time, your doctor may decide you need to use a milder cream or ointment.
ClobaDerm 0.5% w/w Cream
UK/H/3207/001/DC

Guidance on how to apply the cream or ointment
1. Wash your hands.
2. Gently rub the correct amount of cream or ointment into the skin until it has all disappeared. You can measure how much ClobaDerm to use with your fingertip.

- This picture shows one fingertip unit.

3. Unless you are using spray ointment to your hands as a part of the treatment, wash them again after using the cream or ointment.

For an adult:
You should find this:

- Two fingertips of cream or ointment will cover both hands or one foot.
- Three fingertips of cream or ointment will cover one arm.
- Sixteen fingertips of cream or ointment will cover the front and back of the body.

Do not worry if you find you need a little more or a little less than this. It is only a rough guide.

For a child:

- Do not use on children under 1 year of age.
- Use ClobaDerm on the child for about 2 days a week you will need to use.
- A child of 4 years needs a child of the adult amount.
- A course of treatment for a child should not normally last more than 5 days—unless your doctor has told you to use it for longer. The doctor may want to see the child every week, while using the cream or ointment.

If you have powderbase:
If you have this powderbase on your elbow or knees, your doctor may suggest applying the cream ointment or ointment under an artifical dressing. It will only be at right to help the cream or ointment to start working. After a short period of time you will then apply the cream or ointment as normal.

If you apply ClobaDerm to the face:
You should only apply the cream or ointment to your face if your doctor tells you to. It should not be used for more than 5 days, as the skin on your face thins easily. Do not let the cream or ointment get into your eyes. If it does, wash it off with plenty of water.

If you use more ClobaDerm than you should:
If you mistake the cream or ointment or if you use more than you should, do not worry. If you apply a bit or if it is a little more than you need to, it will not do you any harm. If you are in any doubt, talk to your doctor or go to hospital as soon as possible.

If you forget to use ClobaDerm:
If you forget to apply cream or ointment, apply it as soon as you remember. If it is close to the time you are next meant to apply it, wait until the next time.

If you stop using ClobaDerm:
If you use ClobaDerm regularly make sure you talk to your doctor before you stop using it.

If you have any further question about this product, ask your doctor or pharmacist.

6. Possible side effects

Like all medicines, ClobaDerm can cause side effects, although not everybody gets them.

Stop using ClobaDerm and tell your doctor as soon as possible if:
- You find that your skin problem gets worse or your skin becomes swollen during treatment. You may be allergic to the cream or ointment, have an infection or need other treatment.

Other side effects you may notice when using ClobaDerm include:
- A feeling of burning, irritation or itching where the cream or ointment is applied.
- If you have psoriasis you may get raised bumps with pus under the skin. This can happen during or after the treatment and is known as psoriasis lesions.

Side effects if you use ClobaDerm for a long time, or you use it each time you apply it, or you apply it under an artifical dressing or a napkin:
- Stretch marks may develop.
- Viers under the surface of your skin may become more noticeable.
- Increased hair growth and changes in skin colour.
- Thinning of your hair that may also damage more easily.
- Weight gain, rounding of the face and high blood pressure. These are more likely to happen in infants and children.

If any of the above side effects are troublesome or last more than a few days or if you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. Storing ClobaDerm
Keep all medicines out of the reach and sight of children.
Do not store above 30°C.
Do not use the ClobaDerm after the expiry date (EXP YYYY) which is shown on the tube and blister. The expiry date refers to the last day of that month.
This medicine should be disposed of 3 months after first opening.
Do not use the cream or ointment if any visible signs of deterioration, such as noticeable changes in colour or appearance are observed. If you are not sure please check with your pharmacist.

Medicines should not be disposed of via waste water or household waste. Ask your pharmacist how to dispose of medicines that are not longer required. This will help to protect the environment.

4. Further Information

What ClobaDerm contains:
The active ingredient is clobetasol propionate.
Each 1 g contains 0.5 mg of clobetasol propionate (0.05% w/w).
The other ingredients are:
- Cream: petrolatum, sodium chloride, water (aqua), glycerol monostearate, alcohol (isopropyl), propylene glycol, lactic acid, sorbitan monostearate, benzyl alcohol, and colorant (E127).
- Ointment: propylene glycol, sorbitan sesquioleate and white soft paraffin.

What ClobaDerm looks like and contents of the pack:
ClobaDerm Cream is a white or almost white cream.

ClobaDerm Ointment is a white cream.
Within each carton is a bottle of plastic screw-cap, which contain either 30 g or 100 g of cream or ointment.
Not all pack sizes may be marketed.

Marketing authorisation holder:
Axilad Pharmacuticals (Pharma division) Ltd. Melrose House Bury Street Rudgley Midleton HAM 7TL UK

Manufacturer:
Trophic Ltd. B.V. 3291 1UX, Oud-Beijerland The Netherlands

More Information
If you have any questions or are not sure about anything, ask your doctor or pharmacist who will advise you.

Other sources of information are:
- The Psoriasis Association, 2 Queneshill Road, Northampton, NN1 8BF
- You may also be able to find out more from books in public libraries.

This leaflet was last revised in June 2012.
For information in large print, on tape, or on CD or in Braille, phone +44 (0)1695 627 420.
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the UK and Ireland considered that the application for ClobaDerm 0.05% w/w Cream (PL 17507/0109; UK/H/3207/001/DC) could be approved. This product is a prescription-only medicine (POM).

ClobaDerm 0.05% w/w Cream contains the active ingredient, clobetasol propionate, which is a very active topical corticosteroid. ClobaDerm 0.05% w/w Cream is of particular value when used in short courses for the treatment of more resistant dermatoses such as psoriasis (excluding widespread plaque psoriasis), recalcitrant eczemas, lichen planus, discoid lupus erythematosus, and other skin conditions which do not respond satisfactorily to less active steroids.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Ireland as Concerned Member State (CMS). The application was submitted under Article 10(3) of Directive 2001/83/EC, as amended, as a hybrid application. The reference medicinal product for this application is Dermovate Cream (Glaxo Wellcome UK Limited, trading as Glaxo Laboratories and/or GlaxoSmithkline UK), which was first authorised in the UK in May 1993.

No new non-clinical data have been submitted, which is acceptable given that this is a hybrid application based on an originator product that has been in clinical use for over 10 years.

To support the application, the Marketing Authorisation Holder submitted three clinical studies. Two clinical studies (a pilot and pivotal) were submitted to establish equivalence of the vasoconstriction response between the proposed product Clobetasol Propionate 0.05% Cream (by Auden Mckenzie [Pharma Division] Ltd) and the reference product Dermovate Cream 0.05% (GlaxoSmithKline UK). A third clinical study was submitted to evaluate the skin sensitisation properties of the proposed product Clobetasol Propionate 0.05% Cream (Auden Mckenzie [Pharma Division] Ltd) compared to the reference product Dermovate Cream 0.05% (GlaxoSmithKline UK). During product development, Clobetasol Propionate 0.05% Cream (Auden Mckenzie [Pharma Division] Ltd) was the name used for ClobaDerm 0.05% w/w Cream (Auden Mckenzie [Pharma Division] Ltd). 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 at all sites responsible for the manufacture, assembly and batch release of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 150) on 24 April 2012. After a subsequent national phase, a licence was granted in the UK on 21 June 2012.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | ClobaDerm 0.05% w/w Cream |
| Name of the active substance (INN) | Clobetasol propionate |
| Pharmacotherapeutic classification (ATC code) | Corticosteroid, very potent (ATC Code: D07 AD01) |
| Pharmaceutical form and strength | Cream; 500 micrograms/gram |
| Reference number for the Decentralised Procedure | UK/H/3207/001/DC |
| Reference Member State (RMS) | United Kingdom |
| Concerned Member State (CMS) | Ireland |
| Marketing Authorisation Number | PL 17507/0109 |
| Name and address of the authorisation holder | Auden Mckenzie (Pharma Division) Ltd McKenzie House Bury Street Ruislip Middlesex HA4 7TL UK |

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

INN: Clobetasol propionate

Chemical name: 21-Chloro-9-fluoro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-17-yl propanoate.

Structure:

![Chemical Structure of Clobetasol Propionate]

Molecular formula: \( C_{25}H_{32}ClFO_5 \)

Molecular mass: 467.0

Appearance: Clobetasol propionate is a white or almost white crystalline powder.

Solubility: Practically insoluble in water, freely soluble in acetone and sparingly soluble in ethanol (96%).

Clobetasol propionate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance clobetasol propionate are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.
MEDICINAL PRODUCT
Other Ingredients
Other ingredients consist of the pharmaceutical excipients, namely cetostearyl alcohol, glycerol monostearate, Arlacel 165 (glycerol monostearate and macrogol 100 stearate), white beeswax, propylene glycol, chlorocresol, sodium citrate, citric acid monohydrate, and purified water.

With the exception of Arlacel 165, all excipients comply with their respective European Pharmacopoeia monographs. Arlacel 165 is controlled to a suitable in-house specification, however its constituents (glycerol monostearate and macrogol 100 stearate) comply with their respective European Pharmacopoeia monographs. 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 excipients.

Pharmaceutical Development
The objective of the development programme was to formulate a stable topical preparation that was comparable in performance to the reference product Dermovate Cream (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 this product and the reference product.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, together with an appropriate account of the manufacturing process. The manufacturing process has been validated with production-scale batches and has shown satisfactory results.

Control of Finished Product
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 specification. Certificates of Analysis have been provided for all working standards used.

Container-Closure System
The finished product is supplied in collapsible aluminium tubes internally coated with an epoxy resin based lacquer fitted with polypropylene caps, in pack sizes of 30 g and 100 g. The tubes are packaged individually with the Product Information Leaflet (PIL) into cardboard outer cartons.

Not all pack sizes may be marketed.

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

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a
shelf-life of 2 years for the product stored in the unopened tubes has been set. The shelf-life after first opening a tube is 3 months. The storage instructions for the products are “Store below 30°C.”

Suitable post approval stability commitments have been provided to continue stability testing on two commercial batches of finished product.

**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 a pilot study and pivotal study to establish therapeutic equivalence of the vasoconstriction response between the proposed product and the reference product, and a third 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), Product Information Leaflet (PIL), Labels**

The SmPC, PIL and labels are satisfactory from a pharmaceutical perspective.

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 (Marketing Authorisation Application) Form**

The MAA form is satisfactory from a pharmaceutical perspective.

**Quality Overall Summary**

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**

The grant of a Marketing Authorisation is recommended.

**III.2 NON-CLINICAL ASPECTS**

The pharmacodynamic, pharmacokinetic and toxicological properties of clobetasol propionate are well-known. As clobetasol propionate is a widely used, well-known active substance, no new non-clinical data have been submitted and none are required.

The applicant’s non-clinical overview has been written by appropriately qualified persons and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics 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.

The grant of a Marketing Authorisation is recommended.
III.3 CLINICAL ASPECTS
Clinical Pharmacology
The clinical pharmacology of clobetasol propionate 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.

In support of the application, the Marketing Authorisation Holder submitted a pilot dose-response study and a further pivotal study to establish equivalence of the vasoconstriction response between the proposed product ClobaDerm 0.5%w/w Cream and the reference product Dermovate Cream 0.5% (GlaxoSmithKline UK).

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

Pilot Study
A single-exposure study to evaluate the dose vasoconstriction response of topically delivered clobetasol propionate cream 0.05% 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 Dermovate® Cream at different dose durations over a short period of time (10 minutes – 300 minutes).
Values for Maximum effect (E_max), Effective Dose – 50% (ED50) and D1 (half ED50) and D2 (twice ED50) were calculated.

Methodology
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 six 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 lot of Dermovate® Cream following different durations of dose application ranging from 10 minutes to 300 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 dose removal at 10 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.

The study was conducted in accordance to the guidance issued by the FDA Center for Drug Evaluation and Research in 1997. 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 do not adversely affect the results of the study.

**Statistical analysis**
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 using the trapezoidal rule. Maximum effect ($E_{max}$), Effective Dose - 50% ($ED_{50}$) and $D_1$ (half $ED_{50}$) and $D_2$ (twice $ED_{50}$) were calculated using software specifically designed for population modelling.

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

The figure below shows the mean negative a* areas (0 – 24 Hour Areas) under the effect curve (0 – 300 Minutes Dose Durations) using log normal distribution

![Graph showing mean negative a* areas](image)
Summary of the Results of the Analysis Performed on the Negative AUEC Values for Dermovate® Cream 0.05% (0-24 hr) Using Log Normal Distribution

<table>
<thead>
<tr>
<th>E_max</th>
<th>ED50 (MINUTES)</th>
<th>AIC</th>
<th>BIC</th>
<th>OBJ</th>
<th>NEGATIVE LOG LIKELIHOOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>58.74</td>
<td>29.90</td>
<td>3.77</td>
<td>3.79</td>
<td>1046.26</td>
<td>692.22</td>
</tr>
</tbody>
</table>

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. A smaller AIC, BIC, OBJ, and negative log likelihood indicate a better model fit.

Population E_max modelling using the log-normal distribution of ED50 provided the best fit of the data.

AUEC= Area Under the Effect Curve

Conclusion of the pilot study
Based on the ED50 estimate, a dose duration for evaluating equivalence using the FDA Guidance study design for pivotal equivalence study is nominally indicated as: 30 minutes (ED50) with D1=15 minutes and D2=60 minutes.

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

Objectives
The objective of the study was to compare the vasoconstriction response profile and therapeutic equivalence between Dermovate® Cream 0.05% (GlaxoSmithKline UK) and a test cream formulation containing Clobetasol Propionate 0.05% (by Auden Mckenzie [Pharma Division] Ltd.)

Methodology
The study was conducted by the methodology set out in the FDA Guidance for Industry published in 1997.

Enrolled subjects had a total of ten 4-cm² sites demarcated on each forearm, of which eight 4-cm² sites on each arm were dosed with two formulations (test and reference) of Clobetasol Propionate Cream. Two sites on each forearm remained untreated to serve as control sites. Dose durations were based on D1, D2, and ED50 values for the Reference Product B, Dermovate® Cream 0.05% w/w, as determined in the Dose Ranging Pilot Study. The Reference Product B formulation was dosed on two sites per arm for the D1, ED50, and D2 durations. The Test Product A, Clobetasol Propionate 0.05% Cream (Auden Mckenzie (Pharma Division) Ltd.), was dosed on two sites per arm using the same ED50 dose duration. All sites remained un-occluded after application.

Results
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:

\[
\frac{AUEC_{at\ D2}}{AUEC_{at\ D1}} \geq 1.25
\]
The following table summarizes the means of negative AUEC (0 – 24 hr), ratio of means, and 90% CI of Clobetasol Propionate Cream 0.05%:

<table>
<thead>
<tr>
<th>TEST PRODUCT A</th>
<th>REFERENCE PRODUCT B</th>
<th>% RATIO</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>32.48</td>
<td>32.75</td>
<td>99.15</td>
<td>(95.07, 103.42)</td>
</tr>
</tbody>
</table>

**Conclusion of the pivotal study**
The 90% confidence intervals of the test/reference ratio for the means of negative AUEC\(_{(0\text{-}24\text{hr})}\) lie within the equivalence interval of 80.00-125.00%. Thus the data support the claim that the test product Clobetasol Propionate 0.05% Ointment (Auden Mckenzie (Pharma Division) Ltd) is therapeutically equivalent to the reference product Dermovate Cream (Glaxo Wellcome UK Limited).

**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, Dermovate Cream (Glaxo Wellcome UK Limited).

**Skin Irritation Study**
A randomized, single-centre, phase 1 study to evaluate the 21-day cumulative irritation potential of clobetasol propionate cream 0.05% 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 Clobetasol Propionate 0.05% Cream (Auden Mckenzie (Pharma Division) Ltd) in comparison with the reference innovator Dermovate Cream 0.05% (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. The study was conducted in accordance with the FDA Guidance for Industry on Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products published in 1999.

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 Dermovate® in terms of cumulative irritation.

The relevant hypotheses were:

\[ H_0: \text{median}_T - 1.25\text{median}_R > 0 \ (\text{not non-inferior}) \]
\[ H_1: \text{median}_T - 1.25\text{median}_R \leq 0 \ (\text{non-inferior}) \]

A 95% bootstrap CI (confidence interval) of the median difference between Test (Treatment B) and Reference (Treatment A) was used for evaluating non-inferiority. In addition, the
comparison of Treatment C (positive irritant control) and Treatment D (negative irritant control) was performed in an identical manner.

If the degree of irritation for a given test article was such that a new application of the test article could not be applied to the same site, the product was discontinued from further application at that site. The test site was still observed and scored at each subsequent visit; however, the last score observed prior to test article discontinuation was carried forward and used in the primary analysis.

**Results**

**Cumulative dermal irritation scores**

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>MEAN</th>
<th>STANDARD DEVIATION</th>
<th>MEDIAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment A (Reference Cream)</td>
<td>19.40</td>
<td>4.31</td>
<td>19.00</td>
</tr>
<tr>
<td>Treatment B (Test Cream)</td>
<td>19.66</td>
<td>4.88</td>
<td>19.00</td>
</tr>
<tr>
<td>Treatment C (Positive Control)</td>
<td>50.54</td>
<td>13.72</td>
<td>53.00</td>
</tr>
<tr>
<td>Treatment D (Negative Control)</td>
<td>16.43</td>
<td>7.59</td>
<td>16.00</td>
</tr>
</tbody>
</table>

Treatment A: Dermovate® Cream 0.05% w/w  
Treatment B: Clobetasol propionate 0.05% cream  
Treatment C: Sodium Lauryl Sulfate Solution 0.1% w/v  
Treatment D: Sterile Water for Inj., USP

**Summary of 95% Bootstrapping Confidence Interval**

<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>Treatment B (Clobetasol Propionate Cream 0.05%) vs Treatment A (Dermovate® Cream 0.05%)</td>
<td>-5.125</td>
<td>-3.5</td>
</tr>
<tr>
<td>Treatment C (Positive Irritant Control) vs Treatment D (Negative Irritant Control)</td>
<td>24.625</td>
<td>34.375</td>
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</table>

A bootstrap CI for the median cumulative irritation score for Treatment B minus the median of 1.25 times the Cumulative Irritation Score (CIS) score for Treatment A had an upper 95% confidence limit of -3.5, indicating that Clobetasol Propionate Cream 0.05% was non-inferior to Dermovate Cream 0.05% in terms of irritation.
Conclusion of the skin irritation study
The methodology of this study is appropriate to assess the potential of the test product to cause irritation of the skin and its equivalent irritation to the reference product Dermovate Cream.

The results support the claim that the test product is no more irritant than the reference product Dermovate Cream (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 pivotal study 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 marketed Dermovate Cream (Glaxo Wellcome UK Limited).

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 ClobaDerm 0.05% w/w Cream 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 clobetasol propionate 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 ClobaDerm 0.5% w/w Cream and the reference product Dermovate Cream (Glaxo Wellcome UK Limited).

SAFETY
The safety profile of clobetasol propionate 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 Dermovate Cream (Glaxo Wellcome UK Limited).

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 clobetasol propionate 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

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