Public Assessment Report

UKPAR

Audavate 0.1% w/w Cream

(betamethasone valerate)

UK Licence No: PL 30306/0721

Actavis Group PTC ehf

Medicines and Healthcare Products Regulatory Agency

LAY SUMMARY

Audavate 0.1% w/w Cream (betamethasone valerate)

This is a summary of the Public Assessment Report (PAR) for Audavate 0.1% w/w Cream (PL 30306/0721). It explains how Audavate 0.1% w/w Cream was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Audavate 0.1% w/w Cream.

For practical information about using Audavate 0.1% w/w Cream, patients should read the package leaflet or contact their doctor or pharmacist.

What is Audavate 0.1% w/w Cream and what is it used for?
Audavate 0.1% w/w Cream is a cream containing the steroid betamethasone valerate. It is used to help reduce the redness and itchiness of certain skin problems including eczema, psoriasis and dermatitis.

How does Audavate 0.1% w/w Cream work?
Audavate 0.1% w/w Cream works by preventing the cell processes that can cause skin inflammation in response to certain skin conditions such as eczema, psoriasis and dermatitis.

How is Audavate 0.1% w/w Cream used?
Audavate 0.1% w/w Cream is topically applied onto the affected area of skin 1 to 3 times a day. This may be reduced as the affected skin becomes better or stopped when it is better. Audavate 0.1% w/w Cream must be applied as described in the patient information leaflet (PIL). The amount of Audavate 0.1% w/w Cream to be applied can be measured using a fingertip as described in the PIL. Amounts to be applied for adults and children are stipulated in the PIL.

What benefits of Audavate 0.1% w/w Cream have been shown in studies?
A clinical pharmacodynamic study demonstrated therapeutic equivalence of topically applied betamethasone valerate between Audavate 0.1% w/w cream and the reference product Betnovate 0.1% Cream (PL 10949/0014).

What are the possible side effects of Audavate 0.1% w/w Cream?
Like all medicines, Audavate 0.1% w/w Cream can cause side effects, although not everybody gets them.

The most common side effects with Audavate 0.1% w/w Cream (which affects less than 1 in 10 people) are: a feeling of burning, pain, and irritation or itching where the cream is applied.

For a full list of possible side effects, see the package leaflet.

Why was Audavate 0.1% w/w Cream approved?
The MHRA decided that the benefits of Audavate 0.1% w/w Cream outweigh the risks and recommended its approval.

What measures are being taken to ensure the safe and effective use of Audavate 0.1% w/w Cream?
Suitable safety information has been included in the summary of product characteristics and the package leaflet for Audavate 0.1% w/w Cream, including the appropriate precautions to be followed by healthcare professionals and patients.
Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Audavate 0.1% w/w Cream
The marketing authorisation for Audavate 0.1% w/w Cream was granted on 28th April 2017.
For more information about treatment with Audavate 0.1% w/w Cream, read the package leaflet or contact your doctor or pharmacist.

The full PAR for Audavate 0.1% w/w Cream follows this summary.

This summary was last updated in June 2017.

Audavate 0.1% w/w cream

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Actavis Group PTC ehf a marketing authorisation for the medicinal product Audavate 0.1% w/w Cream (PL 30306/0721). The product is a prescription-only medicine (POM) indicated in adults, the elderly and children over 1 year of age, for the treatment of corticosteroid responsive dermatoses including: atopic and discoid eczemas; prurigo nodularis; psoriasis (excluding widespread plaque psoriasis); neurodermatoses, including lichen simplex and lichen planus; seborrhoeic dermatitis; contact sensitivity reactions; discoid lupus erythematosus; and insect bite reactions. The product may also be used as an adjunct to systemic steroid therapy in generalised erythroderma

This is an abridged complex application submitted via a national procedure for Audavate 0.1% w/w Cream (PL 30306/0721) according to article 10(3) of Directive 2001/83/EC, as amended. The application satisfies the requirements for a hybrid application under Article 10(3), referring to a medicinal product that was authorised with a full dossier.

The reference product, authorised for at least 10 years in the UK, is Betnovate 0.1% Cream (PL 10949/0014) authorised to Glaxo Wellcome UK Limited. This product was authorised on 01/02/1993, on the basis of a full dossier, following a change of ownership application (COA) from PL 0004/5121R, which was authorised on 15/07/1987 to Glaxo Operations UK Limited.

The legal basis of the application according to article 10(3) and choice of reference product are acceptable.

The applicant has provided results from a clinical pharmacodynamic study of cutaneous vasoconstriction in healthy human volunteers *in lieu* of a clinical therapeutic equivalence study in patients. The UK reference product was used as a comparator in the clinical pharmacodynamic study.

Audavate 0.1% w/w Cream contains the steroid betamethasone valerate. It is used to help reduce the redness and itchiness of certain skin problems including eczema, psoriasis and dermatitis.

No non-clinical studies were conducted, which is acceptable given that reference is made to medicinal products which have been licensed for over 10 years. Audavate 0.1% w/w Cream and the reference product contain betamethasone at the same concentration and in the same esterified form.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and release of the product.

A satisfactory summary of the pharmacovigilance system and a detailed Risk Management Plan (RMP) has been provided with these applications.

A Marketing Authorisation was granted in the UK on 28th April 2017.

II QUALITY ASPECTS

II.1 Introduction

Audavate 0.1% w/w Cream is a white to almost white cream which contains 0.1% w/w of the active substance betamethasone valerate.

Other ingredients consist of the pharmaceutical excipients liquid paraffin, white soft paraffin, macrogol cetostearyl ether 20, cetostearyl alcohol, chlorocresol, sodium dihydrogen phosphate dihydrate, phosphoric acid 10%, sodium hydroxide 50%, purified water.

The finished products are packaged into collapsible aluminium tubes internally coated with an epoxy resin-based lacquer and closed with a polypropylene cap which are packed into cardboard tubes in pack sizes of 30g, 100g

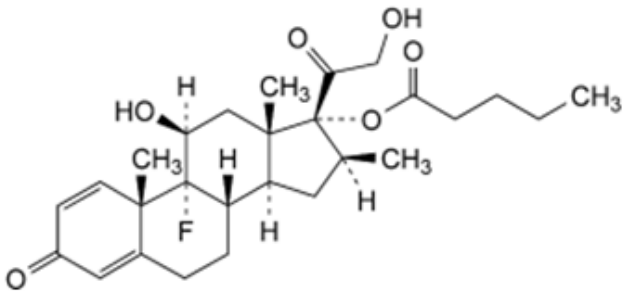
Specifications and certificates of analysis for all packaging materials have been provided.

Not all pack sizes may be marketed.

II.2. Drug Substance

INN: betamethasone valerate
Chemical name:

Structural formula:



Molecular formula: $C_{27}H_{37}FO_6$
Relative molecular mass: 476.6
Appearance: a white or almost white, crystalline powder
Solubility: practically insoluble in water, freely soluble in acetone and in methylene chloride, and soluble in ethanol (96 per cent).

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 European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability (CEP).The CEP also includes limits for particle size and controls the residual solvent acetone by the monograph test for loss on drying. The limits proposed for other residual solvents are in line with ICH Guideline for residual solvents.

II.3. Medicinal Product
Pharmaceutical Development

The aim of pharmaceutical development was to develop Audavate 0.1% Cream based on the lower strength Audavate RD 0.025%. The choice of excipients for the formulation is based on the excipients used in the UK reference product - Betnovate® Cream 0.1%.

A satisfactory account of the pharmaceutical development has been provided.

None of the excipients used contain material of animal or human origin.

All excipients are controlled by their respective European Pharmacopoeia monograph and no novel excipients are used.

A QP declaration has been provided and satisfactory GMP certificates have also been provided for all relevant sites.

Manufacture of the product

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at the commercial-scale batch size and shown satisfactory results.

A description and flow-chart of the manufacturing method has been provided.

Finished Product Specifications

The finished product specification is satisfactory. Analytical methods have been described and have been adequately validated, as appropriate.

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. The data from these studies support a shelf-life of 24 months, with the storage condition 'Do not store above 30°C'.

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

II.4 Discussion on chemical, pharmaceutical and biological aspects

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

III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of betamethasone valerate are well-known. No new non-clinical data have been submitted for this application and none are required.

The applicant has provided an overview based on published literature. The non clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product's pharmacology and toxicology.

III.2 Pharmacology

No new pharmacology data are required for this application and none have been submitted.

III.3 Pharmacokinetics
No new pharmacokinetic data are required for this application and none have been submitted.

III.4 Toxicology
No new toxicology data are required for this application and none have been submitted.

III.5 Ecotoxicity/environmental risk assessment (ERA)
As this product is intended for generic substitution with other products already on the market, no increase in environmental exposure is anticipated. An ERA is, therefore, not deemed necessary.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this product from a non-clinical perspective.

IV CLINICAL ASPECTS
IV.1 introduction
With the exception of the pharmacodynamic study detailed below, no new clinical studies have been performed and none are required for this type of application. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
Topical corticosteroids can be systemically absorbed from intact healthy skin, to reach the systemic circulation. As a surrogate predictor of systemic absorption of topically corticosteroids, including betamethasone, the skin blanching assay (see clinical pharmacodynamic study) is considered sufficient; this is because the assay is reflective of penetration of steroid into the deeper cutaneous layers which is considered to correlate with the fraction that is systemically absorbed.

No new clinical pharmacokinetic studies have been performed and none are required.

IV.3 Pharmacodynamics
The Applicant has supplied a clinical pharmacodynamic study *in lieu* of a clinical study of therapeutic equivalence. The study to demonstrate equivalent cutaneous bioavailability of betamethasone valerate between the test and reference products consisted of two parts:

1) A pilot, dose-response study to test the reproducibility and precision of the chromameter method and the appropriate dose-duration for taking forwards to the pivotal study.
2) A pivotal study of vasoconstriction (skin blanching) in healthy volunteers to compare topically applied innovator product (Betnovate 0.1% Cream) with the test product (Audavate 0.1% Cream).

<u>Pilot study</u>

Title:
An open-label, randomised, evaluation of the dose duration-response relationship of topically delivered Betnovate Cream (Betamethasone Valerate 0.1%) with occlusion in healthy, adult human subjects between the ages of 18 and 65 years.

Methods
The vasoconstriction response to a single application of Betnovate cream was evaluated by chromameter method and visual observation following different treatment durations. Two sites on each forearm remained as untreated control sites.

Vasoconstriction response was evaluated by chromameter measurements at pre-dose and at defined intervals after dose removal.

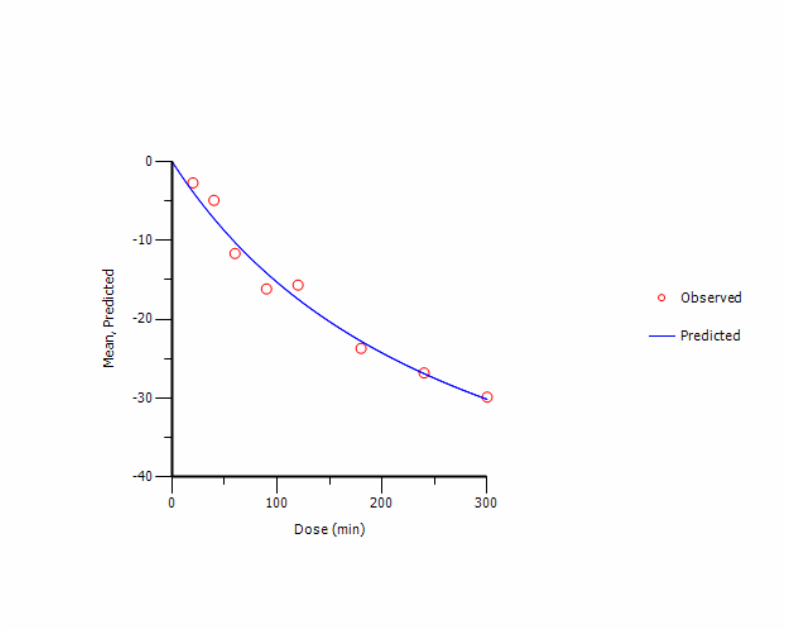
Test and reference products were acceptable.

Chromameter L*a*b*-a values, for each time point, were corrected for baseline reading and by the untreated site reading. 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. Maximal effect (E_{max}) and effective dose – 50% (ED_{50}) were determined using a software containing features specifically designed for population E_{max} modelling.

Data for 23 subjects (who completed the clinical phase of the study and who had complete data sets) were included in the statistical analysis.

Results

The figure below shows the mean negative a* areas under the effect curve (0-24 hour areas) against dose duration times and an overlay of the non-linear model fit equation.



The following table summarises the results of the analyses performed on the negative AUEC values for the non-linear model. The Akaike criteria (AIC) and Schwartz criteria (BIC) parameters were used to help determine the model that best fitted the data.

Summary of the Results of the Analysis Performed on the Negative AUEC Values for BETNOVATE® Cream (Betamethasone Valerate 0.1%)			
Cream, 0.1% (0-24 hour) Using Non-linear Model (N=23)			
E_{max}	**ED_{50} (Minutes)**	**AIC**	**BIC**
-58.53 a-scale units*Min	282.20 min	26.58	26.74

Conclusions:

Based on the ED_{50} estimate of 282.20min using non-linear model, a dose duration for evaluating bioequivalence using the study design for a pivotal bioequivalence study is nominally suggested as 282 minutes (ED_{50}) with D_1=141 min and D_2=564 min.

Betnovate cream (betamethasone valerate 0.1%) was well tolerated at a single topical dose of 20 µL total/4 cm^2 site when administered to healthy adult subjects.

The pilot study was designed in accordance with satisfactory guidance on equivalence demonstration for topical corticosteroids and executed appropriately. A suitable dose duration was identified for taking forwards to the pivotal study.

Pivotal study

Title: A single-blind, randomised, *in vivo*, single exposure study, to evaluate the vasoconstriction activity oftopically delivered Betamethasone Valerate 0.1% Creams in normal skin, with occlusion, in healthy adults aged 18 and 65 years.

Study objectives: To compare the vasoconstriction response profile and bioequivalence between Betnovate 0.1% cream and two test cream formulations containing betamethasone valerate 0.1% cream based on the ED_{50} identified in the DRC (dose response curve) pilot study and to monitor the safety of the subjects.

Methods:

Skin blanching quantification was determined by chromameter assessment.Subjects were observed and queried for the occurrence of adverse events (AEs) throughout the study. Urine samples were collected at the screening visit.

Potential subjects were screened for vasoconstrictor responsiveness using a single dose application of Betnovate cream (betamethasone valerate 0.1%) on normal skin. Ten sites on each forearm were dosed with reference product or two test formulations of betamethasone valerate 0.1% cream. Two sites on each forearm remained untreated to serve as control sites. All treated sites were occluded with a water impermeable film during the dose duration period. Vasoconstriction response was evaluated by chromameter measurements at pre-dose and at defined intervals after dose removal. The study was a single-blind, single exposure, randomised, vasoconstriction study conducted on healthy adult male and female subjects.

Protocol deviations

Minor protocol deviations were recorded and fully disclosed.

Statistical Methods:

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 pre-dose and post-dose removal were calculated from the final corrected (a*) values according to the trapezoidal rule.

Vasoconstriction response data from a total of 101 subjects were included in the final statistical analysis.

The dose duration-response criterion was: (AUEC at D_2/AUEC at D_1)$\geq$1.25

Demographic and baseline characteristics were summarised for all enrolled subjects.

A 90% confidence interval (CI) for the ratio of the mean test value to mean reference value was calculated for average AUEC response according to Locke’s method. The statistical analysis was performed using suitable software.

Results:

Vasoconstriction:

The following table summarises the means, standard deviations, and percentage coefficient of variations on the corrected a* values (0 – 24 hours) for the betamethasone valerate 0.1% creams (N=61).

Treatment	Mean	Standard Deviation	%CV
Betamethasone Valerate 0.1% cream (T1)	-30.923	13.755	-44.482
Betamethasone Valerate 0.1% cream (T2)	-30.635	15.249	-49.776
BETNOVATE® Cream (Betamethasone Valerate 0.1%) (R)	-27.746	13.503	-48.666

Bioequivalence using Locke's method

The following table summarizes the means of negative AUEC (0 – 24 h), percentage ratio of means, and 90% CI of betamethasone valerate 0.1% cream (N=61).

T1/R

Mean Negative AUEC (0 – 24 h)		% Ratio	90% CI
Betamethasone Valerate 0.1% cream	BETNOVATE® Cream (Betamethasone Valerate 0.1%)		
-30.92	-27.75	111.55%	(105.39%, 118.08%)

T2/R

Mean Negative AUEC (0 – 24 h)		% Ratio	90% CI
Betamethasone Valerate 0.1% cream	BETNOVATE® Cream (Betamethasone Valerate 0.1%)		
-30.63	-27.75	110.38%	(104.60%, 116.49%)

The 90% confidence intervals for the Test/Reference ratios for the mean negative AUEC (0-24h) lie within the acceptance limits (80.00 – 125.00%) specified in the guidance.

The respective confidence intervals for T1 and T2 were: (105.39%, 118.08%) and (104.60%, 116.49%).

The design and conduct of the pilot and pivotal studies were acceptable.

Overall conclusion: The data support the claim of equivalent cutaneous bioavailability of betamethasone valerate between the test and reference products. Equivalent clinical efficacy and safety of betamethasone valerate can also be inferred between the test and reference products.

IV.4 Clinical Efficacy

No new clinical efficacy studies have been conducted and none are required.

IV.5 Clinical Safety

No new studies of safety pertaining to systemic absorption of corticosteroids have been performed which is considered acceptable.

Due to the acceptable tolerance in the clinical vasoconstriction study and the similarities between the proposed and reference product, an additional clinical local tolerance study is not required.

IV.6 Risk Management Plan (RMP)
The Marketing Authorisation Holder (MAH) has submitted a Risk Management Plan (RMP), in accordance with the requirements of Directive 2001/83/EC, as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to this product.

A summary of safety concerns, as approved in the RMP is provided below:

Summary of safety concerns	
Important identified risks	• Hypersensitivity to the preparation • Local skin reactions e.g. contact dermatitis, allergic reactions • Use in Rosacea, Acne vulgaris, Perioral dermatitis, Perianal and genital pruritus, Primary cutaneous viral infections (e.g. herpes simplex, chickenpox). • The use of Betamethasone Valerate 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. • Adrenal suppression – long term continuous therapy particularly in infants and children. • Atrophic changes after prolonged treatment while treating psoriasis, discoid lupus erythematosus and severe eczema. • Use in psoriasis – risk of 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. • Spread of infections; Bacterial infection is encouraged by the warm, moist conditions induced by occlusive (airtight) dressing. • Hypercortisolism
Important potential risks	• Topical administration of corticosteroids to pregnant animals can cause abnormalities of fetal development including cleft palate and intrauterine growth retardation. • Glaucoma – if applied to eyelids • Cataracts • Features of Cushing's syndrome (more likely in infants and children) and dilatation of the superficial blood

Summary of safety concerns	
	vessels may occur if occlusive dressings are used
Missing information	None

Safety concern	Routine risk minimisation activities sufficient?	If yes, provide description of routine activity and justification
Important Identified Risks		
Hypersensitivity to the preparation	Yes	SmPC sections 4.3 (Contraindications) and 4.8 (Undesirable effects) of SmPC and in section 4 (Possible side effects) of PIL.
Local skin reactions e.g. contact dermatitis, allergic reactions	Yes	SmPC sections 4.3 (Contraindications) and 4.8 (Undesirable effects) of SmPC and in section 4 (Possible side effects) of PIL.
Use in Rosacea, Acne vulgaris, Perioral dermatitis, Perianal and genital pruritus, Primary cutaneous viral infections (e.g. herpes simplex, chickenpox).	Yes	SmPC section 4.3 (Contraindications) and in section 2 of PIL.
The use of Betamethasone Valerate 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.	Yes	SmPC section 4.3 (Contraindications) and in section 2 of PIL

Safety concern	Routine risk minimisation activities sufficient?	If yes, provide description of routine activity and justification
Adrenal suppression – long term continuous therapy particularly in infants and children.	Yes	SmPC sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) of SmPC and in section 2 (Before you use Audavate) and section 4 (Possible side effects) of PIL.
Atrophic changes after prolonged treatment while treating psoriasis, discoid lupus erythematosus and severe eczema.	Yes	SmPC sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) of SmPC section 4 (Possible side effects) of PIL.
Use in psoriasis – risk of 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.	Yes	SmPC sections 4.4 (Special warnings and precautions for use), 4.8 (Undesirable effects) of SmPC and in section 2 (Before you use Audavate) of PIL
Spread of infections	Yes	SmPC sections 4.4 (Special warnings and precautions for use), in section 2 (Before you use Audavate) and section 4 (Possible side effects) of PIL.
Hypercortisolism	Yes	SmPC sections 4.9 (Overdose) and section 3 (How to use Audavate) of PIL.
Important Potential Risks		
Topical administration of corticosteroids to pregnant animals can cause abnormalities of fetal development including cleft palate and intrauterine growth retardation.	Yes	SmPC section 4.6 (Fertility, Pregnancy and Lactation) and section 2 (Before you use Audavate) of PIL
Glaucoma – if applied to eyelids	Yes	SmPC section 4.4 (Special warnings and precautions for use) and section 3 (How to use Audavate) of PIL
Cataracts	Yes	SmPC sections 4.4 (Special warnings and precautions for use)
Features of Cushing's syndrome (more likely in infants and children) and dilatation of the superficial blood vessels may occur if occlusive dressings are used	Yes	SmPC section, section 4.8 (undesirable effects) and section 4 (Before you use Audavate) of PIL

IV.7 Discussion on the clinical aspects

There are no objections to the approval of this product from a clinical perspective.

V User consultation

The package leaflet has been evaluated, in accordance with the requirements of articles 59(3) and 61(1) of 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 patients/users are able to understand and act upon the information that it contains.

VI Overall conclusion, benefit/risk assessment and recommendation

QUALITY
The important quality characteristics of Audavate 0.1% 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 and none are required for this type of application.

CLINICAL
With the exception of the data submitted in the clinical pharmacodynamics study, no new clinical data were submitted and none are required for this type of application. Results from the clinical pharmacodynamic study support the equivalent cutaneous bioavailability of topically applied betamethasone valerate between the proposed product and the reference product.

Therapeutic equivalence has been demonstrated between the proposed product Audavate 0.1% w/w Cream (Actavis Group PTC ehf) and the reference product Betnovate 0.1% Cream (Glaxo Wellcome UK Limited).

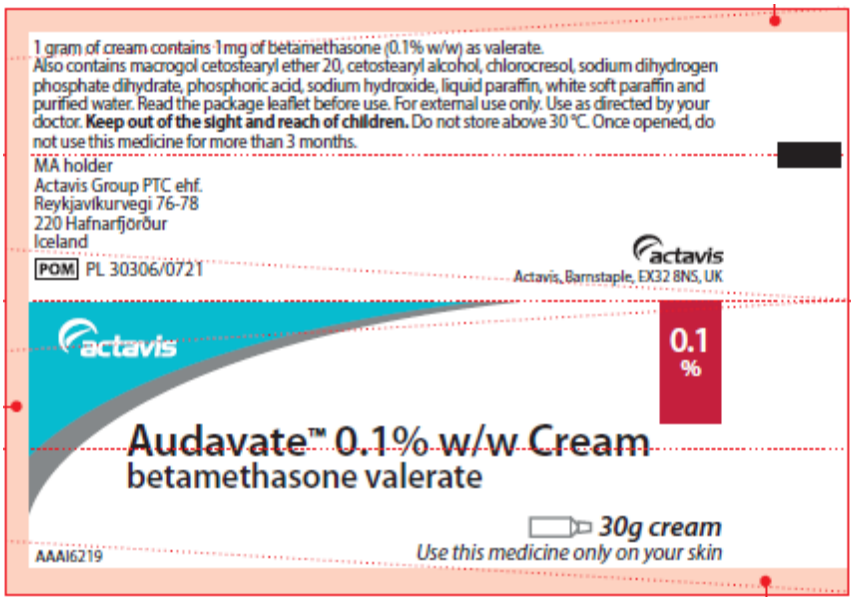
No new or unexpected safety issues arose during the clinical pharmacodynamics study. The proposed product has shown equivalence to the reference product such that the safety can be expected to be equivalent to the already licensed and marketed Betnovate 0.1% Cream (Glaxo Wellcome UK Limited).

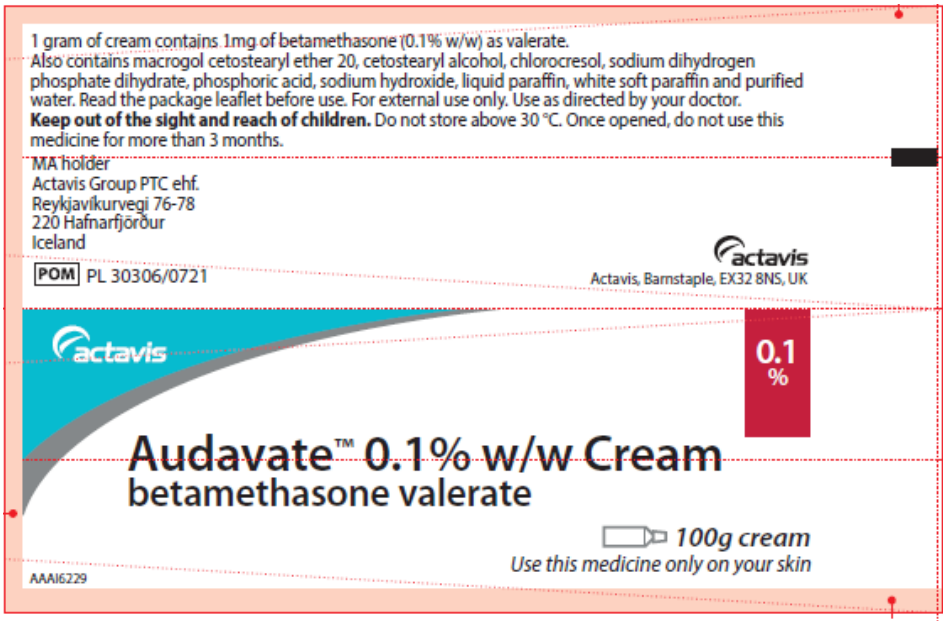
PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product, where appropriate and consistent with current guidelines.

BENEFIT/RISK ASSSESSMENT
The quality of the product is acceptable, and no new clinical safety concerns have been identified. Extensive clinical experience with betamethasone valerate is considered to have demonstrated the therapeutic value of the product. The benefit/risk balance, is, therefore considered to be positive.

Summary of Product Characteristics (SmPC), Package Leaflet and Labels
In accordance with Directive 2010/84/EU the Summary of Product Characteristics (SmPCs) and package leaflet for the product granted a Marketing Authorisation at a national level is available on the MHRA website.

The approved labelling for Prochlorperazine Maleate 3mg Buccal Tablets is presented below:




1 gram of cream contains 1mg of betamethasone (0.1% w/w) as valerate.
Also contains macrogol cetostearyl ether 20, cetostearyl alcohol, chlorocresol, sodium dihydrogen phosphate dihydrate, phosphoric acid, sodium hydroxide, liquid paraffin, white soft paraffin and purified water. Read the package leaflet before use. For external use only. Use as directed by your doctor.
Keep out of the sight and reach of children. Do not store above 30 °C. Once opened, do not use this medicine for more than 3 months.
MA holder
Actavis Group PTC ehf.
Reykjavíkurvegi 76-78
220 Hafnarfjörður
Iceland
POM PL 30306/0721
Actavis, Barnstaple, EX32 8NS, UK
actavis
0.1 %
Audavate™ 0.1% w/w Cream
betamethasone valerate
100g cream
Use this medicine only on your skin
AAAI6229

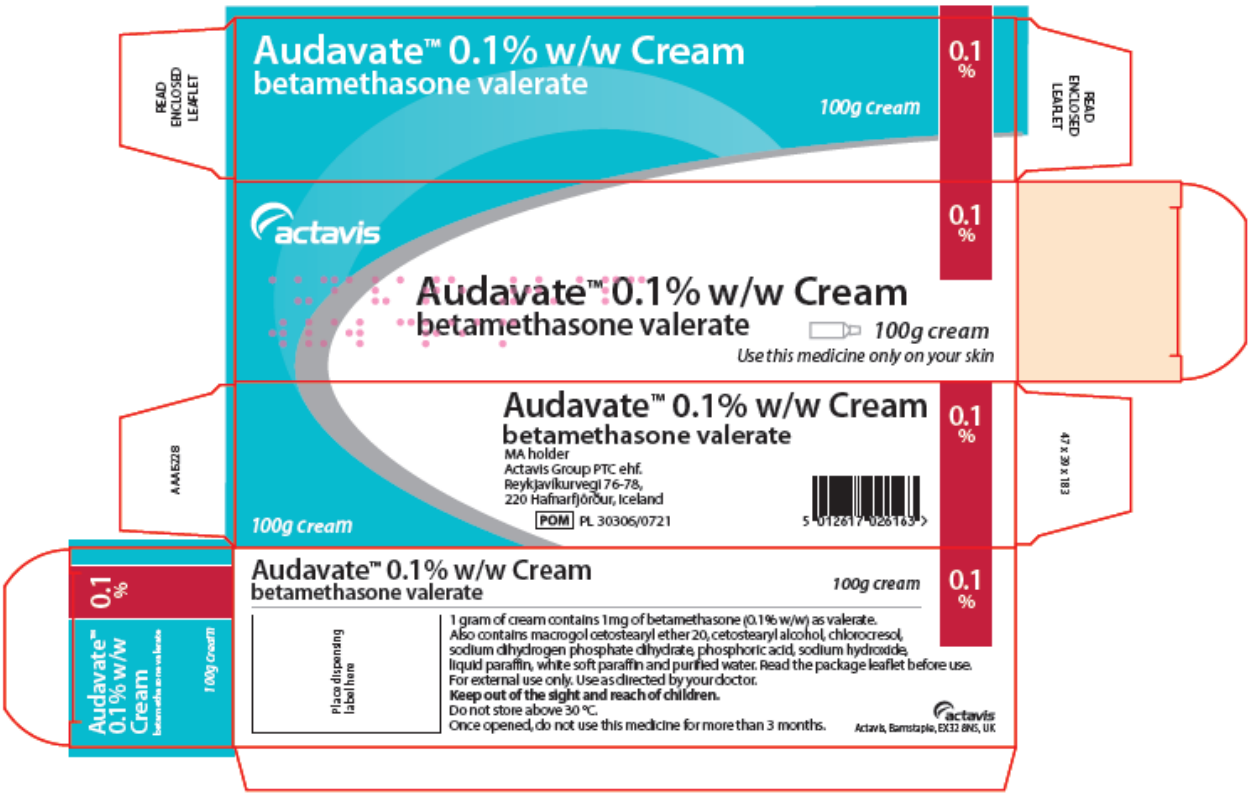

READ ENCLOSED LEAFLET
Audavate™ 0.1% w/w Cream
betamethasone valerate
100g Cream
0.1 %
actavis
Use this medicine only on your skin
MA holder
Actavis Group PTC ehf.
Reykjavíkurvegi 76-78,
220 Hafnarfjörður, Iceland
POM PL 30306/0721
AAAE218
47 x 36 x 183
Place dispensing label here
1 gram of cream contains 1mg of betamethasone (0.1% w/w) as valerate.
Also contains macrogol cetostearyl ether 20, cetostearyl alcohol, chlorocresol, sodium dihydrogen phosphate dihydrate, phosphoric acid, sodium hydroxide, liquid paraffin, white soft paraffin and purified water. Read the package leaflet before use.
For external use only. Use as directed by your doctor.
Keep out of the sight and reach of children.
Do not store above 30 °C.
Once opened, do not use this medicine for more than 3 months.
Actavis, Barnstaple, EX32 8NS, UK

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)