Certificate Number: PP10168322

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY

On behalf of the Department of Health

CERTIFICATE OF A PHARMACEUTICAL PRODUCT (1)

This certificate conforms to the format recommended by the World Health Organisation
(explanatory notes are attached)

Exporting (certifying) country: **UNITED KINGDOM**

Importing (requesting) country: **LEBANON**

1 Name and dosage form of the product:

A) In the United Kingdom - Betnovate Scalp Application, TOPICAL SOLUTION

B) In LEBANON - Betnovate Scalp Application, Topical Solution, TOPICAL SOLUTION

1.1 Active ingredient(s) (2) and amount(s) (3) per unit dose:

Active Ingredient(s)	Amount per unit dose
BETAMETHASONE VALERATE	0.122 % W/W

For complete qualitative composition including excipients, see attached. (4)

1.2 Is this product licensed to be placed on the market for use in the exporting country? (5) Yes

1.3 Is this product actually on the market in the exporting country? Yes

1.4 The product is not on the market in the exporting country because

N/A

2A.1 Product Licence/Marketing Authorisation

Number [7]:	**PL 10949/0045**
Date of Issue:	01 April 1993

2A.2 The name and address of the Product Licence/Marketing Authorisation holder are:

Name: GLAXO WELLCOME UK LIMITED

Address: 980 GREAT WEST ROAD, BRENTFORD, MIDDLESEX, TW8 9GS, UNITED KINGDOM

2A.3 Status of the Product Licence/Marketing Authorisation holder [8]:

c) is not involved in manufacturing, packaging or labelling the dosage form but is responsible for the quality and release of the product

2A.3.1 For categories b,c and d the names and address of the manufacturing site where the dosage form is produced are [9]:

See attached page for Manufacturers/Packagers

2A.4 Is Summary Basis of Approval appended? [10] No

2A.5 Is the attached, officially approved product information complete and consonant with the licence? [11] Yes

2A.6 Applicant for certificate, if different from licence holder (name and address) [12] :

Name:

Address:

Section 2B is not included because the product named in this certificate is licensed in the UK[6]

3	Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced? (14)	N/A

IF NO OR NOT APPLICABLE PROCEED TO QUESTION 4

3.1	Periodicity of routine inspections (years)	
3.2	Has the manufacturer of this type of dosage form been inspected?	
3.3	Do the facilities and operations conform to GMP as recommended by the World Health Organisation ? (15)	
4	Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product including Good Manufacturing Practice (GMP)? (16)	Yes
	If No, explain	

Additional Information:

NONE

Address of certifying authority:

The Medicines and Healthcare products Regulatory Agency,
10 South Colonnade, Canary Wharf, London E14 4PU, United Kingdom

Telephone Number: +44 (0) 20 3080 6593

Name of authorised person: Mahmoodullah Khan

Signature: PLEASE SEE COVER LETTER

Stamp and Date: 16 September 2020

Names and Addresses of Manufacturers/Packagers (9)

Manufacturers

Name:	ASPEN BAD OLDESLOE GMBH
Address:	INDUSTRIESTRASSE 32-36, BAD OLDESLOE, D-23843, GERMANY

Excipient	Modifier	Amount per unit dose
CARBOMER 980		0.250 %W/W
ISOPROPYL ALCOHOL		39.300 %W/W
SODIUM HYDROXIDE	QS	
WATER PURIFIED	TO	100.000 %W/W

Explanatory Notes

1. This certificate, which is in the form recommended by WHO, establishes the status of the pharmaceutical product and of the applicant for the certificate in the UK. It is for a single product only since manufacturing arrangements and approved information for different dosage forms and different strengths can vary.

2. Whenever possible International Non-proprietary Names (Inns) or national non-proprietary names have been used.

3. The formula (complete composition) of the dosage form should be given on the certificate or be appended.

4. Details of the quantitative composition are preferred but their provision is subject to the agreement of the Marketing Authorisation holder.

5. When applicable, append details of any restriction applied to the sale, distribution or administration of the product that is specified in the Marketing Authorisation.

6. Sections 2A and 2B are mutually exclusive.

7. Indicate when applicable if the licence is provisional or the product has not yet been approved.

8. Specify whether the person responsible for placing the product on the market:

   (a) manufactures the dosage form and is responsible for the quality assurance and release of the product.
   (b) packages and/or labels a dosage form manufactured by another company but is responsible for the quality assurance and release of the product.
   (c) is not involved in manufacturing, packaging or labelling the dosage form but is responsible for the quality and release of the product.
   (d) is involved in none of the above.

9. This information is optional and can be provided only with the permission of the product-licence holder or, in the case of non-registered products, the applicant. Non-completion of this section indicates that the party concerned has not agreed to inclusion of this information.

   It should be noted that:

   information concerning the site of manufacture is part of the Marketing Authorisation. If the manufacturing site is changed the licence must be updated or it will cease to be valid.

   in the UK manufacture of pharmaceutical products is only permitted on licensed manufacturing sites. When the product-licence holder or applicant conforms to status (b), (c) or (d) as described in note 8 above the Manufacturing Licence holder is responsible for the manufacture of the dosage form.

10. This refers to the document prepared by some national regulatory authorities that summarises the technical basis on which the product has been licensed. The UK Medicines and Healthcare products Regulatory Agency does not prepare such a document.

11. This refers to product information approved by the Medicines and Healthcare products Regulatory Agency such as a Summary of Product Characteristics (SPC).

12. In this circumstance permission for issuing the certificate is required from the Marketing Authorisation holder. This permission must be provided to the Medicines and Healthcare products Regulatory Agency by the applicant.

13. Please indicate the reason that the applicant has provided for not requesting registration:

    (a) the product has been developed exclusively for the treatment of conditions - particularly tropical diseases - not endemic in the UK.
    (b) the product has been reformulated with a view to improving its stability under tropical conditions.
    (c) the product has been reformulated to exclude excipients not approved for use in pharmaceutical products in the UK.
    (d) the product has been reformulated to meet a different maximum dosage limit for an active ingredient.
    (e) this type of product does not require a Marketing Authorisation in the UK.
    (f) any other reason.

14. "Yes" means the Medicines and Healthcare products Regulatory Agency arranges periodic inspections of the manufacturing plant in which the dosage form is produced. "No" means that manufacture is taking place in a country other than the UK and inspections are not carried out by any Regulatory Authority. "Not applicable" means that manufacture is taking place in a country other than the UK and inspection is conducted under the aegis of the country of manufacture.

15. The requirements of good practices in the manufacture and quality control of drugs referred to in the certificate are those included in the thirty second report of the Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series, No. 823, 1992, Annex 1). Recommendations specifically applicable to biological products have been formulated by the WHO Expert Committee on Biological Standardisation (WHO Technical Report Series No. 822, 1992, Annex 1).

16. This section is to be completed when the product-licence holder or applicant conforms to status (b), (c) or (d) as described in note 8 above. It is of particular importance when foreign contractors are involved in the manufacture of the product. In these circumstances the applicant should supply the certifying authority with information to identify the contracting parties responsible for each stage of manufacture of the finished dosage form and the extent and nature of any controls exercised over each of these parties.

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SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

1 NAME OF THE MEDICINAL PRODUCT

Betnovate Scalp Application.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Betamethasone Valerate BP 0.122% $^{w}/_{w.}$

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Aqueous Suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Steroid responsive dermatoses of the scalp, such as psoriasis and seborrhoeic capitis, inflammation associated with severe dandruff.

4.2 Posology and Method of Administration

A small quantity of Betnovate Scalp Application should be applied to the scalp night and morning until improvement is noticeable. It may then be possible to sustain improvement by applying once a day, or less frequently.

For topical application.

This product is flammable. Keep the liquid away from open fire and flames and all sources of ignition including smoking during application and immediately after use.

Paediatric population
Betamethasone valerate is contraindicated in children under one year of age.
Children are more likely to develop local and systemic side effects of topical corticosteroids and, in general, require shorter courses and less potent agents than adults; therefore, courses should be limited to five days and occlusion should not be used.

Care should be taken when using betamethasone valerate to ensure the amount applied is the minimum that provides therapeutic benefit.

Elderly
Clinical studies have not identified differences in responses between the elderly and younger patients. The greater frequency of decreased hepatic or renal function in the elderly may delay elimination if systemic absorption occurs. Therefore the minimum quantity should be used for the shortest duration to achieve the desired clinical benefit.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

Renal / Hepatic Impairment
In case of systemic absorption (when application is over a large surface area for a prolonged period) metabolism and elimination may be delayed therefore increasing the risk of systemic toxicity. Therefore the minimum quantity should be used for the shortest duration to achieve the desired clinical benefit.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed in section 6.1.

Infections of the scalp. Dermatoses in children under one year of age, including dermatitis.

4.4 Special warnings and precautions for use

Betamethasone valerate should be used with caution in patients with a history of local hypersensitivity to other corticosteroids. Local hypersensitivity reactions (*see section 4.8)* may resemble symptoms of the condition under treatment.
Manifestations of hypercortisolism (Cushing's syndrome) and reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, leading to glucocorticosteroid insufficiency, can occur in some individuals as a result of increased systemic absorption of topical steroids. If either of the above are observed, withdraw the drug gradually by reducing the frequency of application, or by substituting a less potent corticosteroid. Abrupt withdrawal of treatment may result in glucocorticosteroid insufficiency *(see section 4.8).*

Risk factors for increased systemic effects are:

- Potency and formulation of topical steroid
- Duration of exposure
- Application to a large surface area
- Increasing hydration of the stratum corneum
- Use on occluded areas of the skin
- Use on thin skin areas
- Use on broken skin or other conditions where the skin barrier may be impaired
- In comparison with adults, children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic adverse effects. This is because children have an immature skin barrier and a greater surface area to body weight ratio compared with adults.

Paediatric population
In infants and children under 12 years of age, treatment courses should be limited to five days and occlusion should not be used; long-term continuous topical corticosteroid therapy should be avoided where possible, as adrenal suppression can occur.

SUMMARY OF PRODUCT CHARACTERISTICS

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Infection risk with occlusion
Bacterial infection is encouraged by the warm, moist conditions within skin folds or caused by occlusive dressings. When using occlusive dressings, the skin should be cleansed before a fresh dressing is applied.

Use in Psoriasis
Topical corticosteroids should be used with caution in psoriasis as rebound relapses, development of tolerances, risk of generalised pustular psoriasis and development of local or systemic toxicity due to impaired barrier function of the skin have been reported in some cases. If used in psoriasis careful patient supervision is important.

Visual disturbance
Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Scalp Application
Patients should be advised to:

- Keep the preparation away from the eyes
- avoid smoking whilst applying Betnovate scalp application
- avoid fire, flame and heat including use of hair dryer after application

4.5. Interactions with other Medicaments and other forms of Interaction

Co-administered drugs that can inhibit CYP3A4 (e.g. ritonavir, itraconazole) have been shown to inhibit the metabolism of corticosteroids leading to increased systemic exposure. The extent to which this interaction is clinically relevant depends on the dose and route of administration of the corticosteroids and the potency of the CYP3A4 inhibitor.

4.6 Fertility, pregnancy and lactation

Fertility
There are no data in humans to evaluate the effect of topical corticosteroids on fertility.

Pregnancy
There are limited data from the use of betamethasone valerate in pregnant women.
Topical administration of corticosteroids to pregnant animals can cause abnormalities of foetal development. (*see section 5.3*).
The relevance of this finding to humans has not been established; however, administration of betamethasone valerate during pregnancy should only be considered if the expected benefit to the mother outweighs the risk to the foetus. The minimum quantity should be used for the minimum duration.

Lactation
The safe use of topical corticosteroids during lactation has not been established.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable amounts in breast milk. Administration of betamethasone valerate during lactation should only be considered if the expected benefit to the mother outweighs the risk to the infant.
If used during lactation betamethasone valerate should not be applied to the breasts to avoid accidental ingestion by the infant.

4.7 Effects on ability to drive and use machines

There have been no studies to investigate the effect of betamethasone valerate on driving performance or the ability to operate machinery. A detrimental effect on such activities would not be anticipated from the adverse reaction profile of topical betamethasone valerate.

4.8 Undesirable effects

Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥1/10,000 and <1/1,000) and very rare (<1/10,000), including isolated reports.

Post-marketing data

Infections and Infestations
Very rare Opportunistic infection
Immune System Disorders
Very rare Hypersensitivity, generalised rash
Endocrine Disorders
Very rare Hypothalamic-pituitary adrenal (HPA) axis suppression

Cushingoid features (e.g. moon face, central obesity), delayed weight gain/growth retardation in children, osteoporosis, glaucoma, hyperglycaemia/glucosuria, cataract, hypertension, increased weight/obesity, decreased endogenous cortisol levels, alopecia, trichorrhexis

Skin and Subcutaneous Tissue Disorders

Common Pruritus, local skin burning /skin pain

Very rare Allergic contact dermatitis /dermatitis, erythema, rash, urticaria, pustular psoriasis, skin thinning* / skin atrophy*, skin wrinkling*, skin dryness*, striae*, telangiectasias*, pigmentation changes*,hypertrichosis, exacerbation of underlying symptoms

General Disorders and Administration Site Conditions

Very rare Application site irritation/pain

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

**Skin features secondary to local and/or systemic effects of hypothalamic-pituitary adrenal (HPA) axis suppression.*

Eye disorders

Not known	Vision, blurred (see also section 4.4)

Reporting of suspected reactions:
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9. Overdose

Symptoms and signs

Topically applied betamethasone valerate may be absorbed in sufficient amounts to produce systemic effects. Acute overdosage is very unlikely to occur, however, in the case of chronic overdosage or misuse the features of hypercortisolism may occur (*see section 4.8)*.

Treatment

In the event of overdose, betamethasone valerate should be withdrawn gradually by reducing the frequency of application, or by substituting a less potent corticosteroid because of the risk of glucocorticosteroid insufficiency.
Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code

D07AC Corticosteroids, potent (group III)

Mechanism of action

Topical corticosteroids act as anti-inflammatory agents via multiple mechanisms to inhibit late phase allergic reactions including decreasing the density of mast cells, decreasing chemotaxis and activation of eosinophils, decreasing cytokine production by lymphocytes, monocytes, mast cells and eosinophils, and inhibiting the metabolism of arachidonic acid.

SUMMARY OF PRODUCT CHARACTERISTICS

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Pharmacodynamic effects

Topical corticosteroids have anti-inflammatory, antipruritic, and vasoconstrictive properties.

5.2 Pharmacokinetic properties

Absorption

Topical corticosteroids can be systemically absorbed from intact healthy skin. The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle and the integrity of the epidermal barrier. Occlusion, inflammation and/or other disease processes in the skin may also increase percutaneous absorption.

Distribution

The use of pharmacodynamic endpoints for assessing the systemic exposure of topical corticosteroids is necessary because circulating levels are well below the level of detection.

Metabolism

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. They are metabolised, primarily in the liver.

Elimination

Topical corticosteroids are excreted by the kidneys. In addition, some corticosteroids and their metabolites are also excreted in the bile.

5.3 Preclinical safety data

Reproductive toxicity
Subcutaneous administration of betamethasone valerate to mice or rats at doses ≥0.1 mg/kg/day or rabbits at doses ≥12 micrograms/kg/day during pregnancy produced foetal abnormalities including cleft palate and intrauterine growth retardation.

The effect on fertility of betamethasone valerate has not been evaluated in animals.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Carbomer
Isopropyl Alcohol
Sodium Hydroxide
Purified Water.

SUMMARY OF PRODUCT CHARACTERISTICS

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6.2. Incompatibilities

None known.

6.3. Shelf life

24 months.

6.4. Special Precautions for Storage

Store below 25°C

Keep container tightly closed when not in use. Contents are flammable. Keep away from fire, flame or heat. Do not leave Betnovate Scalp Application in direct sunlight.

6.5 Nature and contents of container

White High Density Polyethylene (HDPE) bottle with a white Low Density Polyethylene (LDPE) nozzle and a white HDPE screw cap.

Pack size: 30 mL; 100 mL

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Glaxo Wellcome UK Ltd.
Trading as GlaxoSmithKline UK
980 Great West Road
Brentford
Middlesex
TW8 9GS

8. MARKETING AUTHORISATION NUMBER(S)

PL 10949/0045

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

1 April 1993.

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SUMMARY OF PRODUCT CHARACTERISTICS

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10 DATE OF REVISION OF THE TEXT

27/11/2019