Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Winlevi 10 mg/g cream

Clascoterone

PL 25258/0425

GLENMARK PHARMACEUTICALS EUROPE LIMITED

LAY SUMMARY

Winlevi 10 mg/g cream
Clascoterone

This is a summary of the Public Assessment Report (PAR) for Winlevi 10 mg/g cream. It explains how this product 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 this product.

This product will be referred to as Winlevi in this lay summary for ease of reading.

This application was approved under International Recognition procedure (IRP). The Reference Regulator (RR) was Health Canada. The reference regulator references are New Drug Submission Control Number 265619, Drug Identification Number (DIN) 02538881. The procedure followed route B.

This application was approved under Regulation 50 of the Human Medicines Regulation 2012, as amended (previously Article 8(3) of Directive 2001/83/EC, as amended).

For practical information about using Winlevi, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Winlevi and what is it used for?
Winlevi is used for the skin (topical) treatment of *acne vulgaris* in adults and adolescents aged 12 years and older.

How does Winlevi work?
Winlevi contains the active substance clascoterone, which belongs to a group of medicines known as ‘antiacne preparations for topical use’. The exact way that Winlevi works is not known. It is thought to treat acne by blocking androgens in the skin from making too much sebum (oils that keep the skin moist).

How is Winlevi used?
The pharmaceutical form of this medicine is cream and the route of administration is topical (used on the skin).

Winlevi should not be given to other people, even if they have the same symptoms as the patient, as it may harm them.

Winlevi is to be used on the skin only. Winlevi should not be used in or on the eyes, mouth or vagina.

Before this cream is applied, the patient should gently wash and dry the affected skin area. Next a thin, uniform layer of approximately 1 gram, corresponding to 2 fingertip units should be applied to the affected area twice a day, once in the morning and once in the evening. When spread on the skin, this should be enough to cover the size of two adult palms or one adult face. The patient should wash their hands after applying the cream.

For further information on how Winlevi is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take the medicine exactly as their doctor has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Winlevi have been shown in studies?
Winlevi was evaluated in two main clinical studies (Trial 1 and Trial 2) in patients 9 years of age or older with acne vulgaris. Collectively, 1,440 patients were enrolled in the two trials. Winlevi 1% (w/w) or the vehicle control was administered to the face twice daily.

More patients achieved a reduction in the number of acne lesions and clear, or almost clear, skin after 12 weeks of treatment with Winlevi in comparison to those who were treated with vehicle cream (placebo).

What are the possible side effects of Winlevi?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

The most common side effects with Winlevi (which may affect more than 1 in 10 people) are

- Redness of the skin
- Skin scaling
- Skin dryness

Why was Winlevi approved?
MHRA decided that the benefits are greater than the risks and recommended that this medicine can be approved for use.

What measures are being taken to ensure the safe and effective use of Winlevi?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Winlevi. The RMP details the important risks of Winlevi, how these risks can be minimised, any uncertainties about Winlevi (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Winlevi:

List of important risks and missing information	
Important identified risk(s)	• None
Important potential risk(s)	• Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression • Local skin reactions
Missing information	• Use in pregnancy and lactation • Long-term use

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Winlevi are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Winlevi
A marketing authorisation was granted in the United Kingdom on 30 January 2025.

The full PAR for Winlevi follows this summary.

This summary was last updated in March 2025.

TABLE OF CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Winlevi 10 mg/g cream (PL 25258/0425) could be approved.

The product is approved for the following indications:
The topical treatment of acne vulgaris in patients 12 years of age and older.

Paediatrics (<12 years): The safety and efficacy of Winlevi has not been established in paediatric patients under 12 years of age.

Mechanism of action

The active substance is clascoterone, which is an androgen receptor inhibitor. When applied topically to the skin, clascoterone acts locally, influencing multiple cellular and molecular acnegenic pathways with minimal systemic exposure. However, the exact mechanism of action of clascoterone for the topical treatment of acne vulgaris is not fully characterised.

This application was approved under International Recognition procedure (IRP). The Reference Regulator (RR) was Health Canada (New Drug Submission Control Number 265619, Drug Identification Number 02538881). The procedure followed route B.

This application was approved under Regulation 50 of the Human Medicines Regulation 2012, as amended (previously Article 8(3) of Directive 2001/83/EC, as amended).

In line with the legal requirements for children's medicines, the application included a licensing authority decision on the agreement of a paediatric investigation plan (PIP) MHRA-101394-PIP01-24. The application included a licensing authority decision on the agreement of a partial waiver in the paediatric population from birth to less than 9 years of age.

The licensing authority issued an opinion on compliance of the PIP MHRA-101394-PIP01-24-C.

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

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A marketing authorisation was granted on 30 January 2025.

II. PRODUCT INFORMATION

Summary of Product Characteristics (SmPC)

The SmPC is in line with current guidelines and is satisfactory.

Patient Information Leaflet (PIL)

The PIL is in line with current guidelines and is satisfactory.

Label

The labelling is in line with current guidelines and is satisfactory.

III. QUALITY ASPECTS

This product consists of a homogenous cream. Each gram of cream contains 10 mg of clascoterone.

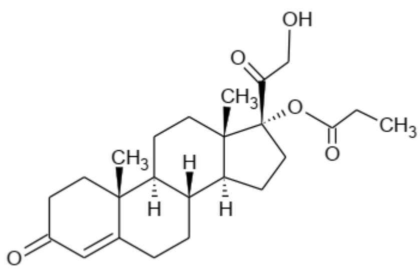
In addition to clascoterone, this product also contains the following excipients:
Cetyl alcohol
Citric acid monohydrate (E-330) (for pH-adjustment)
Glycerol monostearate 40-55 Type I
Liquid paraffin
Polysorbate 80
Propylene glycol (E-1520)
Purified water
Disodium edetate
all-rac-α-tocopherol (E-307)

The finished product is packaged in an epoxy-lined aluminium blind-end tube with a polypropylene cap closure, in a pack size of 10 g, 30 g or 60 g. Not all pack sizes may be marketed.

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

III.2 ACTIVE SUBSTANCE

rINN: Clascoterone
Chemical Name: 11-deoxy-hydrocortisone-17α-propionate
Molecular Formula: $C_{24}H_{34}O_5$
Chemical Structure:



Molecular Weight: 402.5
Appearance: A white or almost white powder
Solubility: Insoluble in water, very soluble in ethanol, sparingly soluble in propylene glycol, soluble in ethanol/propylene glycol (1:1)

The information related to the active substance was provided in an ASMF.

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

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards.

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

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

III.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the finished product.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

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

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years, with the storage conditions ‘Store in a refrigerator (2 °C - 8 °C) prior to dispensing. Once dispensed to patient, do not store above 25 °C. Do not freeze’, is acceptable.

The unused product should be discarded 180 days after the date of dispensing or 6 months after first opening, whichever comes first.

III.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a marketing authorisation is recommended.

IV. NON-CLINICAL ASPECTS

IV.1 Pharmacology

Clascoterone is a topically administered small molecule androgen receptor inhibitor for the treatment of acne vulgaris. *In vitro,* clascoterone exhibited high affinity for the human androgen receptor (AR) with a half-maximal inhibitory concentration (IC_{50}) value of 50 nM in human prostate adenocarcinoma cells.

Clascoterone administered subcutaneously at 1 mg/kg/day to female rabbits induced an increase in mean uterine horn weight (+92% and +105% for right and left horns, respectively), indicating progestational activity. This is reflected in the Summary of Product Characteristics (SmPC).

IV.2 Toxicology

Acute toxicity

The LD_{50} of clascoterone after a single subcutaneous injection to female rats over a period of 14 days is >1000 mg/kg body weight, and after a single intravenous injection the LD_{50} is >100 mg/kg body weight. Mortality was observed at 100 mg/kg as 3 out of 7 rats died (43%). This is reflected in the SmPC.

Repeated dose toxicity

Repeat-dose toxicity studies were conducted in mice (up to 5 days oral, up to 14 days subcutaneous), rats (up to 26 weeks subcutaneous, up to 13 weeks topical), rabbits (up to 28 days topical), and minipigs (up to 9 months topical). Treatment with clascoterone produced some systemic glucocorticoid effects at high doses when administered topically or subcutaneously in rabbits and rats, including decreased lymphocytes/leucocytes, increased plasma phospholipids, increased albumin, increased enzyme levels (AST, ALT, ALP).

Decreased adrenal weights were observed in all species tested and correlated with adrenal atrophy in some of the studies, including the 9-month dermal toxicity study in minipigs. Anti-androgenic effects, such as hypertrophy of the interstitial cells in the testes and decreased hair regrowth were also observed. The no observed adverse effect level (NOAEL) in rats was 10 mg/kg/day (subcutaneous injection for 28 days), 1 mg/kg/day (subcutaneous injection for 13 weeks), 2.5 mg/kg/day (subcutaneous injection for 26 weeks) or 5% (dermal administration for 13 weeks). The
NOAEL in rabbits was 50 mg/kg/day (dermal administration for 28 days). The NOAEL in minipigs administered dermally daily for 13 weeks was reported as 5% clascoterone, although adrenal gland weights were reduced in animals treated with 2.5% and 5% clascoterone cream.

This information is reflected in the SmPC.

Reproductive and developmental toxicity

A complete battery of reproductive and developmental toxicology studies was conducted with subcutaneously administered clascoterone in rats and rabbits. Foetal malformations in rats and rabbits were observed at all tested doses, but also occurred in the control groups for rabbits. These include omphalocele, dilation of the lateral and third cerebral ventricles, thin skin, small size, and protruding tongue. A NOAEL for teratogenicity was not assigned for both species.

This information is reflected in the SmPC.

IV.3 Environmental risk assessment
An Environmental Risk Assessment (ERA) was submitted with this application.

The worst-case scenario for the Phase I predicted environmental concentration (PECSW) of clascoterone was above the action limit of 0.01 µg/L, therefore a Phase II Tier A environmental risk assessment is required. As clascoterone is endocrine active, tailored testing in fish is anticipated to be required for the Phase II ERA.

The applicant states that the Phase II ERA for clascoterone will be conducted as a post authorisation measure.

IV.4 Discussion on non-clinical aspects
MHRA considered that the non-clinical data submitted for this application is satisfactory. The grant of a marketing authorisation was recommended.

V. CLINICAL ASPECTS
V.1 Clinical efficacy
<u>Study CB-01-03/25 and /26</u>
The two phase III studies (study 25 and study 26) were similar in design, duration, intervention and comparison. Both compared clascoterone 1% 1g applied twice daily to vehicle cream. The treatments were double-blinded.

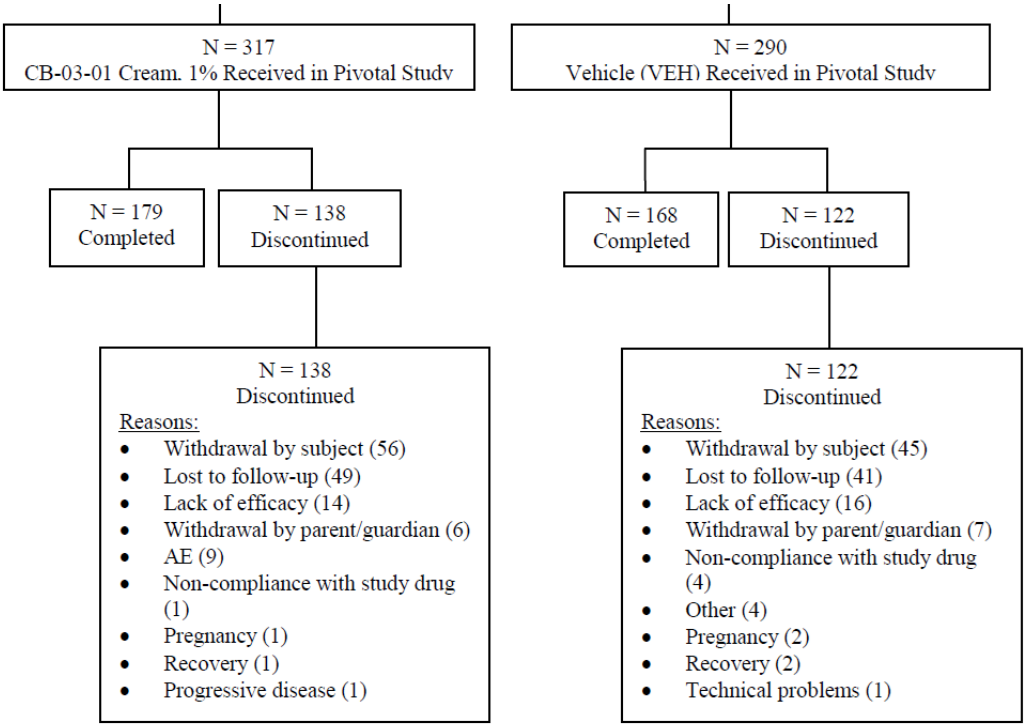
Three primary endpoints were assessed:
1. The proportional difference in the number of participants with successful improvements in Investigator's Global Assessment (IGA). IGA success was defined as a minimum 2-point IGA reduction after 12 weeks and a final IGA of 0 or 1.
2. The difference in the absolute change in non-inflammatory lesion counts at week 12
3. The difference in the absolute change in inflammatory lesion counts at week 12

<u>Results for study – 25</u>
Endpoint 1: Intervention (success) = 18.8%; Vehicle (success) = 8.9%; odds ratio 2.36 (95%CI 1.43, 3.88)
Endpoint 2: Intervention = - 19.4; Vehicle = -6.3; Difference = -6.3 (95%CI -10.2, -2.4)
Endpoint 3: Intervention = - 19.4; Vehicle = -15.5; Difference = -3.9 (95%CI –6.5, -1.3)

<u>Results for study – 26</u>
Endpoint 1: Intervention (success) = 20.8%; Vehicle (success) = 6.5%; Odds ratio = 3.76 (95%CI 2.19, 6.43)
Endpoint 2: Intervention = - 19.5; Vehicle = - 10.9; Difference = -8.4 (95%CI –12.4, -4.5)
Endpoint 3: Intervention = - 20.0; Vehicle = -12.6; Difference = -7.4 (95%CI –9.8, -5.0)

<u>Study CB-01-03/27</u>
Study 27 was an open-label roll-over study that included patients enrolled in study 25 and study 26. The duration was an additional 9 months of treatment (a final total of 1 year of treatment for participants). This was primarily a safety study; however, efficacy data was still analysed according to changes in IGA over the 9 months.

In total 609 patients were rolled over. By the end of the study, 43% of rolled-over patients discontinued. Additionally, it was documented that the number of patients on study was as the table below.



	ITT N=609	**PP N=324**	**Safety N=607**
Subjects on-study at 3 months	539 (88.5)	324 (100.0)	538 (88.6)
Subjects on-study at 6 months	417 (68.5)	324 (100.0)	416 (68.5)
Subjects on-study at 9 months	304 (49.9)	274 (84.6)	303 (49.9)
Subjects on-study at 12 months	123 (20.2)	119 (36.7)	123 (20.3)

Results for study – 27
The majority (>=80.4%) of subjects, overall, in the ITT had facial IGA scores that were mild or moderate in severity at Baseline with the overall proportion of subjects who were clear or almost clear being greatest (ITT: 181/609, 29.8%; PP: 156/324, 48.1%) at the end of the study (Day 274).

For participants with moderate to severe IGA scores at baseline, the total number of patients from both CB-01-03 and Vehicle groups was 305. By day 274, the numbers decreased to 150 participants with moderate to severe IGA scores.

It is important to note that these results were not subjected to hypothesis testing, and significant dropout rates were observed by the end of the study.

A total of 43% (260/609) of patients discontinued in the study, out of which 31 patients were assessed due to lack of efficacy or disease progression. Among the discontinued patients, 5.4 % (14/260) patients had worsening of the acne (7 patients progressed from mild to moderate and 7 patients from moderate to severe). Additionally, there were 11.2% (29/260) of the discontinued patients with moderate and severe acne severity at baseline and maintained their acne severity prior to discontinuation: 9.6 % (25/260) in 'moderate to moderate' and 1.5 % (4/260) in 'severe to severe'. Considering these patients, conservatively, in the respective categories for estimation of percentage of patients with moderate or severe acne at Day 274, the percentages are: 26.8% [(131+7+25)/609] moderate and 4.9% [(19+7+4)/609] severe. Even with this conservative assumption, the percentage of patients with moderate or severity acne decreased from baseline to Day 174: from 43% to 26.8% for moderate acne and from 7.1% to 4.9% for severe acne.

V.2 Clinical safety

Key phase III studies

Major safety issues were not observed in the phase III trials. No deaths or severe adverse events related to the drug were reported in Study 25, 26 and 27.

The total number of treatment emergent adverse events (TEAEs) were similar in both groups, with only 81 (11.4%) and 92 (12.6%) subjects in study 25 and 26, respectively, reporting TEAEs, in total between the studies of 82 subjects treated with CB-03-01 and 91 treated with vehicle.

For study 26, 110 (18.1%) of the subjects experienced TEAEs.

For all studies, local skin reactions were monitored such as erythema, edema, scaling/dryness, stinging/burning, pruritis. It is noted that blood tests as well as vitals were not measured in any of the studies.

Key phase II studies

Two maximal dose hypothalamic-pituitary-adrenal suppression studies were undertaken – study 171-7151-202) and study CB-03-01/28 (referred from here onwards as study 202 and 28 respectively).

Both studies were of similar design conducted over 2 weeks but with differing age groups – study 202 assessing adolescents aged 12 to 18 and adults, and study 28 assessing children between the ages of 9 and 12.

The doses used for both studies are as follows:

- Adult = Clascoterone 6g applied twice daily
- Adolescents = Clascoterone 6g twice daily if Body Surface Area (BSA) >1.6 m2. 4 grams of test article if BSA <1.6m2
- Children = 2g twice daily

The outcome of a suppressed HPA axis is defined as a post-stimulation serum cortisol level of ≤ 18μg/dL) measured via adrenocorticotropic stimulation test.

The results indicated that systemic circulation of the drug was present:

1. 1 (5%) out of 20 adult participants had CST levels ≤ 18μg/dL (Study 202)
2. 2 (9%) out of 22 adolescent participants had CST levels ≤ 18μg/dL (Study 202)
3. 2 (8.7%) out of 23 children had CST levels ≤ 18μg/dL (Study 28)

In terms of potassium levels, high potassium levels in 9 participants were noted in study 28 and none in study 202.

V.3 Discussion on clinical aspects

Key efficacy endpoints demonstrated clinically relevant results in terms of improvements in the Investigator's Global Assessment (IGA), inflammatory lesion count, and non-inflammatory lesion count.

In terms of safety, the primary focus of the phase III safety studies was on local skin reactions, which are appropriately described in the Summary of Product Characteristics (SmPC). No significant safety concerns were highlighted in this area.

Some safety concerns were noted, particularly in relation to HPA axis suppression and potential hyperkalaemia. Although these concerns were noted, the product information and risk management plan have been designed to address and mitigate these risks.

MHRA considered that the clinical data submitted for this application is satisfactory.
The grant of a marketing authorisation was recommended.

VI. RISK MANAGEMENT PLAN (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

VII. USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

VIII. OVERALL CONCLUSION, BENEFIT/RISK AND RECOMMENDATION

The quality of the product is acceptable. The non-clinical and clinical data submitted have shown the positive benefit/risk of this product in the topical treatment of acne vulgaris in patients 12 years of age and older. The safety and efficacy of Winlevi has not been established in paediatric patients under 12 years of age.

The following post-authorisation measures are recorded which should be fulfilled by the Marketing Authorisation Holder by the dates shown:

Description	**Due date**
A phase II environmental risk assessment is required	18/12/2026
A GLP-compliant partition coefficient (n-octanol/water) study is required.	18/12/2026

The Summaries of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory.

In accordance with legal requirements, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

IX. TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations, where significant changes are made, are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPCs and/or PIL available on the MHRA website.

Application type	Scope	Product information affected	Date of grant	Outcome	Assessment report attached Y/N