EU Risk Management Plan for Winlevi 10 mg/g cream (Clascoterone)

RMP version to be assessed as part of this application:

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EU QPPV name: Elena Alcaraz Garcia

EU QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

Table of content

Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Clascoterone
Pharmacotherapeutic group(s) (ATC Code)	Anti-acne preparations, other anti-acne preparations for topical use only. (D10AX06)
Marketing Authorisation Applicant	Cassiopea S.p.A.
Medicinal products to which this RMP refers	One (1)
Invented name(s) in the European Economic Area (EEA)	Winlevi 10mg/g cream
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Clascoterone is an androgen receptor inhibitor.
	Summary of mode of action: *In vitro* studies showed that clascoterone potently antagonises the effects of androgens in primary human sebocytes to reduce sebum production and accumulation and inflammatory mediators which are known drivers of the acne pathogenesis.
	Important information about its composition: Not applicable
Hyperlink to the Product Information	Please refer to Module 1.3.1 Summary of Product Characteristics (SmPC), Labelling and Package Leaflet.
Indication(s) in the EEA	Current: *Adults* Winlevi is indicated for the treatment of acne vulgaris. *Adolescents from 12 to < 18 years of age* Winlevi is indicated for the treatment of facial acne vulgaris.
	Proposed: Not applicable
Dosage in the EEA	Current: A thin uniform layer of cream should be applied to the affected area twice a day, in the morning and the evening, with at least eight hours between applications. Two (2) fingertip units of cream (corresponding to approximately 1 g of cream) will cover an area of about 28 x 22 cm (approximately 600 cm^2 of skin, corresponding to the average surface area of the face).

	In adults, the total daily dose should not exceed ten (10) fingertip units (corresponding to approximately 5 g of 10mg/g clascoterone cream). The cream can be applied on the face, chest and/or back. For adults and adolescents, to achieve the therapeutic effect, it is recommended to treat for three months. After three months of treatment, it is recommended that the physician evaluates the continued improvement of the patient. Thereafter, regular assessment every three months of the skin and of the status of the patient should determine if continued use of the product is needed taking into account the status of the disease and the safety profile of the treatment. In adolescents, the physician may decide to conduct the first evaluation visit earlier than three months, depending on the patient's adherence to treatment and/or safety considerations. *Adolescents (12 to < 18 years of age)* Total daily dose should not exceed four (4) fingertip units (corresponding to approximately 2 g of 10mg/g clascoterone cream). The cream must be applied on the face only. No more than 60 grams a month should be used (corresponding to one 60-gram tube or two 30-gram tubes).
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Winlevi is available as a white to almost white cream. Each gram of cream contains 10 mg of clascoterone.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Acne vulgaris

Acne is a chronic inflammatory skin condition of pilosebaceous glands that typically begins at puberty and may continue through adulthood with flares often coinciding with increasing serum androgens.[1,2]

Incidence:

It is one of the most common dermatological disorders worldwide with its incidence and severity influenced by genetics and environment.[1,3] Acne vulgaris affects approximately 9% of the population worldwide and approximately 85% of those aged 12 to 24 years.[4]

Prevalence:

The reported prevalence in adolescents ranges between 70% and 87%.[5] Although the prevalence of acne is highest in adolescents and young adults, it can also occur in younger children. However preadolescent acne is a rare disease, affecting only 3.5% of patients.[6]

Demographics of the population in the proposed indication and risk factors for the disease:

Acne is often the first sign of puberty in boys and girls, and this onset is thought to be secondary to hormonal surges leading to increased sebum production.[7] The pathogenesis of acne is multifactorial and includes abnormal follicular keratinization, increased production of sebum secondary to hyperandrogenism, proliferation of *Cutibacterium acnes* (formerly *Propionibacterium acnes*), and inflammation.[8,9] A strong association has been observed between several risk factors, including family history, age, body mass index and skin type, and acne presentation or severity.[10]

The main existing treatment options:

The major therapies currently used in the intended population for acne vulgaris are directed to reducing severity and recurrences of skin lesions as well as improving appearance. The approach depends on the severity of the acne, the age and treatment preferences (e.g., for cream, lotion, or gel) of the patient, and adherence and response to previous therapy. Various acne treatments target different steps in the pathogenesis of acne, from counteracting androgens and decreasing sebum production to preventing follicular occlusion, reducing *Cutibacterium acnes* proliferation, and decreasing inflammation.

In Europe, the European Evidence-based Guideline for the Treatment of Acne provides a framework for choosing appropriate treatments for acne vulgaris, based on clinical features and variants, severity and prognostic factors.[11]

First line treatment of acne vulgaris often involves topical therapies such as retinoids, benzoyl peroxide and azelaic acid, either as monotherapy or in combination. For more severe disease, or when topical therapy is insufficient or not tolerated, systemic agents (oral antibiotics such as doxycycline and minocycline, hormonal therapies such as combination oral contraception or spironolactone, or isotretinoin) are recommended.[4,8,12]

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Acne can lead to clinically relevant sequelae, such as erythema, hyperpigmentation, and scarring. Scarring is the most frequently investigated sequelae, and its prevalence estimates vary considerably from 43% to 90.8%. Patients frequently experience a combination of acne-induced sequelae and the burden of acne sequelae can be substantial.[13] Acne has a significant impact on a patient's quality of life, affecting both self-esteem and psychosocial development.

Important co-morbidities:

There is often significant physical and psychological morbidity in patients with acne, such as permanent scarring, poor self-image, depression, and anxiety.[14]

Part II: Module SII - Non-clinical part of the safety specification

A comprehensive non-clinical testing program was conducted to assess the pharmacologic, pharmacokinetic, and toxicologic properties of clascoterone when administered both topically and systemically.

Key safety findings from non-clinical studies and relevance to human usage are presented below:

Key Safety findings (from non-clinical studies)	**Relevance to human usage**
Toxicity	
Single and repeat dose toxicity: In female mice and rats, single intravenous (IV) administration produced a median lethal dose (LD50) of > 100 mg/kg and a single subcutaneous (SC) administration produced a LD50 of > 1,000 mg/kg.	*Single and repeat dose toxicity:* The non-clinical studies were reviewed, and no additional risks of clinical relevance were identified.
Following repeated SC administration to rats for 28 days or 13 weeks, effects included decreases in white blood cell and lymphocyte counts, decreases in adrenal and thymus weights, increases in liver weights, and microscopic changes in the liver (hypertrophy) and adrenal gland, lymph nodes, spleen, thymus and Peyer's patch (reported as atrophy or lymphocyte depletion). These effects occurred only at the high doses (25 and 50 mg/kg/day) in each study. There was no indication of systemic anti-androgenic activity. In rabbits, topical administration for 28 days produced changes in haematology (lymphocyte decrease) and blood chemistry (increase in alanine aminotransferase and alkaline phosphatase) as well as epidermal atrophy at application site, all of which were reversed almost completely after 14 days off-dose. The effects were noted primarily at 10 and 50 mg/kg/day.	Slightly more subjects treated in clinical settings in the clascoterone group vs the vehicle group showed a shift in alanine transaminase from normal to high (10% vs 5.5%), bilirubin from normal to high (4.3% vs 0%), cholesterol from normal to high (8.6% vs 3.6%), triglycerides from normal to low (2.9% vs 0%), white blood count from normal to low (2.9% vs 0%), absolute lymphocytes from normal to high (5.7% vs 1.8%), and absolute neutrophils from normal to low (10% vs 5.5%). The abnormal values were not generally considered to be clinically relevant.
Topical administration produced local changes that were observed in control and treated animals. In a 13-week minipig study, the 1% and 5% clascoterone creams applied topically produced minor effects that were limited to the site of application. Very slight erythema and oedema were noted with occasional observations of well-defined erythema. These dermal effects were also observed in the placebo-treated animals. Microscopic examination of the treated skin revealed reduced epidermal and dermal thickening that was generally minimal in severity at 1% (once per day or twice per day) and mild at 5% (once per day). The severity of the epidermal changes	Local skin reactions (such as erythema, pruritus, scaling/dryness, stinging/burning) were observed in clinical trials and are included in the SmPC with extensive warnings and recommendations to mitigate the risk of such reactions in Section 4.4.

decreased after a 4-week recovery period but the severity of the dermal changes remained unchanged.	
The toxicological profile of clascoterone has been well characterized and the data suggest a minimal glucocorticoid-type response in the non-clinical species examined only at high doses and high systemic exposures. These exposures far exceed any that might occur during topical clinical use. Also, topical clascoterone formulated in the clinical cream caused no systemic effects in a 9-month minipig study at concentrations up to 5%. In the topical study, changes were limited to the site of application and included minor dermal irritation and minimal to mild reductions in epidermal and dermal thickening.	The material was well tolerated following topical application and no unmanageable concerns were identified that will limit the appropriate use of clascoterone in patients with acne.
Reproductive and developmental toxicity: A developmental and reproductive toxicology study battery was completed in rats and rabbits treated systemically with clascoterone. Overall, there is a very low potential risk for reproductive toxicity with clascoterone. In a fertility and early embryonic development study in rats, there was no effect on fertility at SC doses up to 12.5 mg/kg/day; increased preimplantation loss and sperm count changes were noted at this dose level but not at 2.5 mg/kg/day (4.7 to 8.0 times the human exposure based on area under curve [AUC] comparison). In an embryofoetal development study conducted in rats at subcutaneous doses of 1, 5, or 25 mg/kg/day, clascoterone-related malformations were noted at all dose levels, without a dose relationship: omphalocele was noted in a single foetus at each dose level, and external and visceral malformations (severe dilation of the lateral and third cerebral ventricles; thin skin, small size, and protruding tongue) were noted in two additional foetuses at 1 mg/kg/day (2.5 times the human exposure based on AUC comparison). In rabbits, postimplantation loss and resorptions were increased at a subcutaneous dose of 1.5 mg/kg/day whereas no treatment-related effect on embryofoetal development was observed at doses up to 0.4 mg/kg/day (3.7 times the human exposure based on AUC). In a pre- and postnatal development study performed in rats, no significant developmental toxicity was observed at subcutaneous doses up to 12.5 mg/kg/day.	*Reproductive and development toxicity:* Studies in animals have shown reproductive toxicity following subcutaneous administration. Although systemic absorption of cutaneous clascoterone and its main metabolite cortexolone, is negligible, there could be individual factors (e.g. use over large surfaces, prolonged use) that may contribute to an increased systemic exposure. As per Section 4.6 of the SmPC there are no data from the use of clascoterone in pregnant women. Based on animal studies and its mechanism of action (androgen receptor inhibition), clascoterone can cause foetal harm. Winlevi is contraindicated during pregnancy and women of childbearing potential have to use a contraceptive method during treatment with Winlevi and for at least 10 days after the last dose. The pregnancy status of women of childbearing potential should be verified prior to initiating treatment. 'Reproductive toxicity' is included as an important potential risk. It is unknown whether clascoterone/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Use of Winlevi is not recommended while breast-feeding or breast-feeding should be discontinued during treatment with Winlevi. Results from animal studies following subcutaneous administration showed no effect on fertility in male or female rats. There are no

Genotoxicity Clascoterone was generally inactive in genotoxicity studies. Clascoterone was not mutagenic in the Ames reverse mutation assay. A clastogen/aneugenic activity with clascoterone was found in two in vivo genotoxicity tests in rats at the highest tested dose, 2,000 mg/kg SC, with a threshold/no observed adverse effect level (NOAEL) of 1,000 mg/kg. Although clascoterone is an androgen receptor (AR) antagonist and weak glucocorticoid agonist, the highest test dose/exposure used in the rat micronucleus test is well into the range of its glucocorticoid agonism. It is therefore concluded that the observed high-dose clastogen/aneugen effect is caused by a well-known glucocorticoid agonist class effect. While no toxicokinetics (TK) data are available from the in vivo micronucleus assays performed in SD male rats, systemic exposure from repeat-dose study by the same s.c. route in Wistar male rats at 1/20 of the clastogen/aneugen threshold/NOAEL dose provided an exposure margin of > 150 times the human systemic exposure in a worst-case clinical dermal pharmacokinetics (PK) study with the intended clascoterone cream product. It can, therefore, safely be assumed that the observed clastogen /aneugen effect occurred at exposures with a threshold of well above 150 times the worst-case clinical systemic exposure. It is therefore concluded that the observed high-dose clastogen /aneugen activity in vivo in the rat is due to a well-known glucocorticoid class effect with a threshold/NOAEL 2-3 orders of magnitude above any systemic exposure that could occur from clascoterone cream in clinical use, and does not pose any risk to humans. Clascoterone was tested in the in vitro micronucleus assay on human peripheral lymphocytes both in the presence and absence of metabolic activation. Based on the results obtained, the test item was judged to be non-mutagenic in this in vitro test system. In an OECD 487 FISH human lymphocyte micronucleus test performed to clarify the mechanism of action it was found that the mechanism behind the weak micronuclei activity was due to aneugen effect only, with no clastogen effect detected. Since aneugen mechanisms have threshold, a normal margin assessment of risk is warranted, and the	data on the effect of clascoterone on human fertility. *Genotoxicity* Taking into account the very low systemic absorption of clascoterone following application of the cream, the resulting exposure to cortexolone 21-propionate is negligible. Overall, the weight of the evidence from non-clinical studies indicates that neither clascoterone nor its main degradation product, cortexolone 21-propionate, represent a genotoxic risk. While there has been an observed high-dose micronucleus effect in vivo in the rat, subsequent investigation with a FISH test in vitro has shown the micronucleus effect to be due to an aneugen mechanism without any clastogen activity, which allows for using thresholds/margins in safety assessment. The positive micronucleus finding is understood to be due to a well-known glucocorticoid class effect.

observed NOAEL in this assay provides for an aneugen margin of > 10,000 times the observed maximum human worst-case systemic exposure to topical clascoterone administration. Repeat-dose toxicity and genotoxicity studies with cortexolone 21-propionate, which is the main degradation product of clascoterone, were conducted to support anticipated clinical application of 1 to 2 grams of clascoterone cream 1% twice per day. Cortexolone 21-propionate was not mutagenic in the Ames test, nor clastogenic in human lymphocytes. A 4-week non-Good Laboratory Practice (GLP) study was conducted in Wistar rats (n=12/sex/group) via SC injection at doses of 0, 2, 10 and 50 mg/kg/day. The no-observed-effect level (NOEL) for this study was considered to be 2 mg/kg/day. The margin of safety using this NOEL dose is 74 (best case for 0.027 mg/kg/day) or 37 (worst case for 0.053 mg/kg/day). A 13-week GLP study was conducted in rats by s.c. administration at 0.6, 1.2 and 2.4 mg/kg/day. The NOEL for this study was considered to be 2.4 mg/kg/day. The multiple in vitro genetic toxicity studies showed that clascoterone was negative in an *in vitro* Ames, and equivocal in an in vitro micronucleus test in human peripheral lymphocytes assay at the concentration of 250 µg/mL. Clascoterone was found to be aneugenic in an *in vitro* micronucleus test with a threshold of 50 µg/mL. The *in vivo* micronucleus test in male rats was positive at doses in excess of 1000 mg/kg/day given twice by subcutaneous route. A weight-of-evidence approach indicates that clascoterone does not represent a genotoxic risk. No evidence of genotoxicity or mutagenicity was noted in any of the chronic toxicity studies conducted in rats or minipigs. *Carcinogenicity:* A carcinogenicity study assessed clascoterone cream when administered as a topical application to Sprague Dawley rats for up to 23 months. No evidence of local carcinogenicity was noted in female rats or systemic carcinogenicity in male or female rats following topical administration of clascoterone cream at concentrations ranging from 0.1% to 5%. In male rats, a slight increase in benign sebaceous cell adenomas at the site of application was noted following topical application of clascoterone 5% cream. These	*Carcinogenicity:* The carcinogenic risk in humans is considered to be very low. There is a considerable margin between systemic exposures causing micronuclei in the rat vs. worst case exposure in humans of well above 150-fold. In an in vivo micronucleus test, positive clastogen / aneugen effect was found in the high dose 2,000 mg/kg male group but no significant effect in the male 1,000 mg/kg group, indicating a clear high-dose phenomenon with a threshold. This finding is ascribed to a well-documented glucocorticoid agonist class effect occurring with CB-03-01 at high concentrations used in the in vitro assay. The skin effects when specifically discussed were ascribed to the injection procedure. Subcutaneous injection is intrinsically a contributory cause of skin damage and the resulting cell infiltration/proliferation. While long-term injection procedures could lead to

neoplastic tumours of sebaceous origin were only seen microscopically at the end of study. The increase occurred in the male 5% CB-03-01 Cream group (4/65) were considered test article related because they were statistically significant (p=0.049) compared to the vehicle control groups (as well as Envigo historical control data), were not present in any control animals, were associated with multiplicity of sebaceous cell tumours, and were observed at a higher incidence than published historical control databases. All other neoplasms occurred with comparable incidence in the test-article treated groups and untreated and/or vehicle control groups or they occurred sporadically and were not considered to be test-article related. These non-test article-related neoplasms included mammary gland adenomas and adenocarcinomas. In females dosed with 5% CB-03-01 Cream, statistically significant increases in incidence were observed for mammary adenoma and adenocarcinoma combined (p=0.009) in pairwise comparison with the vehicle control group. Because SD rat strains generally have high incidences of mammary gland neoplasms and because the incidence of mammary gland adenoma/adenocarcinoma combined (37%) was close to that of the Envigo historical control data (32%), the increased incidence in mammary adenomas and adenocarcinomas observed in this study is considered not related to test article administration. There was a dose threshold for the sebaceous cell adenomas, with significant effect in the 5 but not in the 1% CB-03-01 Cream group. There was also a time-dependency with no signs of tumour occurrence or signs of proliferative changes at the topical application site reported in the subchronic (13 weeks) rat study where the same high dose level was used. In the 13-week SC rat toxicity study, mostly moderate SC histiocytic cell infiltration was noted in all control and treated animals. This change was occasionally associated with abscess and/or cavity formation and overlying epidermal hyperplasia, ulcer and crust formation (CB-03-01/20). However, in the subsequent 26-week SC rat toxicity study, no treatment-related changes were noted. All observed changes were considered to be related to the SC route of administration or incidental, characteristic for Wistar rats of the same age. Statistically	skin tumours in rodents, this is still not relevant to the clascoterone cream product intended for cutaneous application without injection. The minimal observed effect is regarded as a known high dose anti-androgen effect not relevant to clinical use.

significant increased incidence of subcutaneous congestion was seen in group 2 males. This change was considered to be secondary, associated with the primary subcutaneous histiocytic infiltration, with no toxicological significance. The histiocytic infiltration had comparable incidence and severity in control and treated groups (CB-03-01/22). In the 14-day SC toxicity study in mice, there was mostly diffuse infiltration of macrophages, the severity of which ranged from minimal to moderate, in the test article treated male and female mice, in the subcutis. Macrophages contained phagocytized debris and often surrounded vacuolated tortuous tracks that contained homogenous to amorphous amphophilic material. This material was most likely composed of test article and the necrotic debris. In addition to macrophages, there was also sparse infiltration of lymphocytes and occasional neutrophils. Occasionally within these lesions, focal haemorrhages were present. In a few animals, ulceration and/or pustule formation was also noted. The epidermis adjacent to the ulceration and/or pustule was occasionally hyperplasic. However, in this study there were no control animals to assess the effects of needle trauma vs. a drug-related change.	
General safety pharmacology	
1. Nervous system Safety pharmacology assessments revealed no adverse effects on the central nervous system in rats at SC doses ≤ 250 mg/kg. 2. Cardiovascular system Safety pharmacology assessments revealed no adverse effects on the cardiovascular system in dogs at SC doses ≤ 250 mg/kg. In a pilot human Ether-a-go-go related gene (hERG) assay, clascoterone was considered a low-potency hERG-channel inhibitor with only 40% inhibition observed at the highest tested concentration, 3×10^{-5} M. This concentration is 1,500 times higher than the highest plasma concentration measured in the clinical studies (7.65 ng/mL). 3. Respiratory system No evidence of adverse respiratory system effects was noted based on the repeat-dose toxicity studies.	No clinical relevance has been identified. In the thorough QT (TQT) study conducted in healthy subjects who were exposed to clascoterone plasma levels that were well above the levels at the therapeutic dose, there was no evidence of corrected QT interval (QTc) prolongation. No clinical relevance has been identified.
Mechanisms for drug interactions	

In vitro studies did not show any potential or clinically relevant inhibition capacity toward the most important CYP450 enzymes. Indeed, although slight to moderate inhibition of CYP 2C8, 2C9, and 3A4 was observed, it is not likely that drug-drug interactions would occur *in vivo* given the limited systemic exposure.	No interaction clinical studies have been performed. The use of clascoterone cream at the same time as other cutaneous medicinal products has not been evaluated. Since the systemic exposure of the main component clascoterone and its metabolites following cutaneous application is negligible, no interaction with systemic treatments is expected; however caution is advised in concomitant use with other medicinal products.

Part II: Module SIII - Clinical trial exposure

The clinical development program for Winlevi for topical treatment of acne vulgaris included five studies in healthy subjects (including a thorough QT study with a solution formulation to achieve supratherapeutic plasma levels) and eight studies in subjects with acne vulgaris. A total of 2,318 subjects have been exposed to at least one application of study drug across all of the 13 studies. This included 1,757 subjects exposed to clascoterone at any concentration and regimen: 352 healthy subjects and 1,405 subjects with acne. Across the vehicle-controlled studies (171-7151-201, CB-03-01/25, and CB-03-01/26), 792 subjects with acne were treated with clascoterone 1% cream twice daily (BID) for 12 weeks.

Table SIII.1: Total Number of Subjects in the Safety Population by Study

Study ID (Type)	CB-03-01 N = 1,757	Placebo/ Vehicle N = 821	Retin-A 0.05% N = 30	Total N = 2,318
Healthy subjects				
CB-03-01/02 (single ascending dose)	18	6	0	24
CB-03-01/04 (multiple ascending dose)	24	0	0	24
CB-03-01/33 (TQT)	24	8	0	32
CB-03-01/05 (skin irritation)	36	0	0	36
CB-03-01/32 (repeat insult patch test)	250	0	0	250
Total healthy subjects	**352**	**14**	**0**	**366**
Subjects with acne				
171-7151-203 (steady-state PK)	8	0	0	8
171-7151-202 (maximum use HPA/PK)	42	0	0	42
CB-03-01/28 (maximum use HPA/PK)	27	0	0	27
CB-03-01/03	28	14	30	72
171-7151-201	288	75	0	363
CB-03-01/25	353	355	0	708
CB-03-01/26	369	363	0	732
CB-03-01/27[a]	290 [607[a]]	0	0	[607[a]]
Total subjects with acne	**1,405**	**807**	**30**	**1,952**

HPA = hypothalamic pituitary axis; PK = pharmacokinetic; TQT = thorough QT.

a Of the 607 subjects, all of whom were included in previous studies, 290 had received vehicle and 317 had received CB-03-01 in the previous controlled study, CB-03-01/25 or CB-03-01/26.

The extent of exposure in the safety populations of the Phase 2 dose escalation study, Phase 3 studies and active-controlled study are detailed below. Exposure to clascoterone twice daily was up to 12 months (including treatment period of the parent studies) for 123 subjects.

Table SIII.2: Extent of Exposure in the Safety Population by Study

Study Number	Treatment (Number Enrolled or Randomized/Completed)	Extent of Exposure – Daily Dose (mean ± SD)
CB-03-01/03	CB-03-01 cream 1%: 30/27 Retin-A® 0.05% cream: 32/26 Vehicle: 15/14 QD (evening) for 8 weeks	CB-03-01 cream 1%: 2.2 ± 1.2 g Retin-A® 0.05% cream: 2.1 ± 1.2 g Vehicle: 1.9 ± 0.9 g
171-7151-201	CB-03-01 cream 0.1% BID: 72/58 0.5% BID: 76/64 1% QD: 70/61 1% BID: 70/59 Vehicle QD or BID: 75/62 Applied for 12 weeks	CB-03-01 cream 0.1% BID: 1.3 ± 0.73 g 0.5% BID: 1.4 ± 0.62 g 1% QD: 0.7 ± 0.36 g 1% BID: 1.3 ± 0.55 g Vehicle QD or BID: 1.2 ± 0.66 g
CB-03-01/25	CB-03-01 cream 1%: 353/287 Vehicle: 355/290 BID for 12 weeks	CB-03-01 cream 1%: 1.96 ± 0.60 g Vehicle: 1.96 ± 0.58 g
CB-03-01/26	CB-03-01 cream 1%: 369/302 Vehicle: 363/282 BID for 12 weeks	CB-03-01 cream 1%: 1.97 ± 0.51 g Vehicle: 1.98 ± 0.51 g
CB-03-01/27	CB-03-01 cream 1%: 609 BID for up to 9 months	CB-03-01 cream 1%: 2.27 ± 1.24 g Vehicle: 2.30 ± 1.39 g [Subjects are summarized overall and according to the original test article they actually received in the Phase 3 pivotal studies (CB-03-01/25 and CB-03-01/26).]

BID = twice daily; QD = every day; SD = standard deviation.

The safety and efficacy of clascoterone applied twice daily for 12 weeks for the treatment of acne vulgaris were assessed in two identically-designed, multicentre, randomised, double-blind, vehicle-controlled clinical trials (CB-03-01/25 and CB-03-01/26). A total of 1,421 subjects 12 years and older with facial acne vulgaris were enrolled. Of these subjects, 641 (45%) were 12 to 17 years of age, and 780 (55%) were 18 years of age or older. In addition, 62% of the subjects were female and 91% were Caucasian. For safety analyses, data were pooled across the two Phase 3 pivotal studies (CB-03-01/25 and CB-03-01/26), in which 722 subjects were treated with clascoterone and 718 were treated with vehicle (designated Pool A) and also with the addition of the clascoterone 1% cream BID group from 171-7151-201 for a total of 792 subjects treated with clascoterone 1% cream BID for 12 weeks and 773 subjects treated with vehicle (designated Pool B).

Extent of exposure by subgroups of age, gender, and race for Pool B are shown below:

Table SIII.3: Extent of exposures by Subgroups of Age, Gender, Race in Phase 3 Pivotal Studies and Study 171-7151-201 (Pool B)

Demographics		Number of patients (N = 792)
Age[a]	9 - > 12	13
	12 - < 18	339
	≥ 18	440
Race n (%)	White	697
	Non-White	95
Gender	Male	291
	Female	501

a No subjects were ≥ 65 years old

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Pregnant women or women planning to become pregnant

Reason for exclusion: Studies in animals have shown reproductive toxicity and foetal harm. Based on animals studies and its mechanism of action (androgen receptor inhibition), clascoterone can cause foetal harm. Potential safety implications for the patient due to lack of data in this population clinically.

Is it considered to be included as missing information?: No

Rationale: There are no data from the use of clascoterone in pregnant women without any sequelae.

Breast-feeding women

Reason for exclusion: Potential safety implications for the patient due to lack of data in this population clinically.

Is it considered to be included as missing information?: No

Rationale: It is unknown whether clascoterone/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded.

Concomitant use with other cutaneous or systemic acne treatment

Reason for exclusion: Potential safety implications for the patient due to lack of clinical data.

Is it considered to be included as missing information?: No

Rationale: No interaction clinical studies have been performed. The use of clascoterone cream at the same time as other cutaneous medicinal products has not been evaluated, however the SmPC includes warnings to exercise caution when using clascoterone concurrently with others. Concomitant cutaneous acne therapy should be used with caution because a cumulative irritant effect may occur. The concomitant application of astringent cleansing cosmetic products and drying or irritating agents (such as perfumed or alcohol-containing products) should be avoided. Since the systemic exposure of the main component clascoterone and its main metabolite cortexolone following cutaneous application is negligible, no interaction with systemic treatments is expected, however caution is advised in concomitant use with other medicinal products.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme.
Population with relevant different ethnic origin	Not included in the clinical development programme.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme.
Paediatric patients <9 years	There is no relevant use of Winlevi in children aged less than 9 years for the treatment of acne vulgaris.
Paediatric patients from 9 to <12 years	In study CB-03-01/28, 27 children (aged 9 to 12 years) with acne received clascoterone 1% cream, 2 grams BID to the face and trunk for 2 weeks. In the Phase 3 Pivotal Studies CB-03-01/25 and CB-03-01/26, 13 children (aged 9 to 12 years) with acne received clascoterone 1% cream BID to the face for 12 weeks. Section 4.2 of the SmPC states that the safety and efficacy of Winlevi in children aged 9 to <12 years old has not been established. Currently available data are described in section 5.1 of the SmPC but no recommendation on a posology can be made.

BID = twice daily.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Post-marketing data

As per Winlevi USPI[1], WINLEVI (clascoterone) cream is an androgen receptor inhibitor indicated for the topical treatment of acne vulgaris in patients 12 years of age and older. Cleanse the affected area gently. After the skin is dry, apply a thin uniform layer of WINLEVI cream twice per day, in the morning and the evening, to the affected area.

As per World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology, no defined daily doses (DDDs) are assigned for topical preparations because the amount given per day can vary so much according to the intensity and distribution of the disease. The number of patients treated with Winlevi (clascoterone) cannot be precisely determined and therefore the patient exposure was estimated based on the available sales volumes and average per gram daily usage by the patient. In clinical studies with Winlevi, clinical efficacy was noted after 12 weeks of treatment. Hence the patient exposure is calculated in terms of Patient Treatment Days (PTD) considering the treatment duration of 3 months (90 days).

The available post marketing data till [redacted].

The cumulative patient exposure can be calculated as follows:

$$\text{Patient Exposure (Patient Treatment Days)} = \frac{\text{Total grams in sales}}{\text{Average per gram daily usage} \times 90 \text{ days}}$$

[1] United States Prescribing Information for Winlevi (clascoterone) 1% Cream; [redacted] (dated July 2022; NDA 213433)

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Based on the pharmacology and mechanism of action of clascoterone, non-clinical data, clinical trial data, and case reports from post-marketing experience, the potential for misuse for illegal purposes is considered to be negligible.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

The following safety concerns have been identified for clascoterone:

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Hypothalamic-pituitary-adrenal (HPA) axis suppression • Reproductive toxicity
Missing information	• None

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Local Skin Reactions: Clascoterone may induce local irritation (such as erythema, pruritus, scaling/dryness and stinging/burning). The excipients cetyl alcohol and propylene glycol may also cause local skin reactions. The proportion of subjects in clinical trials experiencing these local skin reactions was similar between the treatment groups. The most severe intensity of each treatment-emergent skin reaction during the studies was trace or mild for most subjects. Three clascoterone-treated subjects reported hypersensitivity of mild or moderate intensity. One of these subjects was discontinued from the study due to this event. These events were self-limiting and resolved during use of the product, without intervention.

  Clascoterone is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients in Section 4.3, with extensive warnings and recommendations to mitigate the risk of such reactions in Section 4.4. Most common local skin reactions such as erythema, scaling, dryness, and stinging/burning that occurred in the Phase 3 pivotal studies were included in the content of the SmPC section 4.8 independently of whether or not they had been reported as adverse events in the phase 3 studies. In addition, after three months of treatment as per Section 4.2, regular assessment of the skin and of the status of the patient should determine if continued use of the product is needed taken into account the status of the disease and the safety profile of the treatment. A recommendation is included in Section 4.4 that if a local skin reaction in a sensitive area occurs, treatment discontinuation should be considered; emollients may also be applied with a minimum of 2 hours before or after the application of clascoterone cream.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

- Hyperkalaemia: Clascoterone is structurally similar to the steroidal antiandrogen spironolactone and chronic treatment with spironolactone can produce hyperkalaemia. Because of the biological plausibility for similar effects with clascoterone, potassium shiftwas evaluated in 598 subjects ≥9 years of age for whom laboratory data was available. Shifts from normal, low or unknown to elevated potassium levels was observed, overall, in 5.3% (26/488) of clascoterone-treated subjects and 3.9% (4/103) of vehicle-treated subjects.

These values are inclusive of data from the paediatric group (9-11 years) which displayed the largest shift in potassium levels (33.3%); although, a placebo group was not studied in this age group precluding a comparison between active- versus vehicle-treated subjects. Notably, placebo-treated subjects displayed a larger shift to high potassium levels in the 12-17 years age group compared to the clascoterone group (5.4% and 3.3%). In adults, both treatment groups displayed similar shifts to high potassium levels (3.9% [clascoterone] and 3.0% [placebo]). The resultant risk difference in the shift to high potassium levels between clascoterone and placebo was -2.1% (12-17 years) and 0.9% (adults).

Proportion of Subjects with Shift[a] to High Potassium Levels

	WINLEVI®[b]	**Placebo**	**Treatment Difference (active-placebo)**
Overall (≥9 years)	26/488 (5.3%)	4/103 (3.9%)	1.4%
Approved Population (≥12 years)	17/461 (3.7%)	4/103 (3.9%)	-0.2%
By Age Group (years)			
9-11	9/27 (33.3%)	-	-
12-17	5/150 (3.3%)	2/37 (5.4%)	-2.1%
≥18	12/311 (3.9%)	2/66 (3.0%)	0.9%

[a] Shifts are described in terms of baseline potassium levels of normal, low or not done.

[b] Data excludes haemolysed samples.

Based on the totality of evidence, the paediatric (9-11 years) age group was the main driving force for the observed shift in potassium levels, which was substantially greater (but in the absence of a placebo comparator) than that observed in the indicated population of adolescents and adults (i.e., 12 years and older). Upon examination of shifts in potassium levels in the indicated population of ≥12 years for whom placebo-controlled data exists, the overall proportion of subjects with shift to high potassium levels was: 3.7% (17 out of 461) in the clascoterone group and 3.9% (4 out of 103) in the placebo group. In subjects of 12 years and older there is no evidence of increased incidence of elevated potassium serum levels in clascoterone-treated subjects compared to placebo.

In cases of elevated serum potassium during clinical trials, none were of clinical significance. Increased potassium did not have an effect on vital signs, including diastolic or systolic blood pressure, as demonstrated in Study CB-03-01/33, which dosed clascoterone 7.5% solution (1.5 mL BID, corresponding to 75 mg clascoterone b.i.d.) or vehicle twice daily to healthy volunteers).

No adverse reactions linked to the hyperkalaemia issue have been reported in the post-marketing experience in the US, with patient exposure of approximately 364,427patient treatment days. In the clinical trials conducted, there was no significant difference in the proportion of subjects who experienced a shift in potassium levels between the clascoterone and placebo groups.

Hyperkalaemia is followed up via routine pharmacovigilance.

- Concomitant use with other cutaneous or systemic acne treatment: No interaction clinical studies have been performed.

  The use of clascoterone cream at the same time as other cutaneous medicinal products has not been evaluated. The simultaneous use of multiple cutaneous agents, especially those with irritating properties (e.g., retinoids, benzoyl peroxide), can increase the risk of local skin irritation. As a potential interaction cannot be excluded, a recommendation is included in Section 4.2 that other cutaneous medicinal products used to treat other conditions on the

same skin areas should be applied with a minimum of 2 hours before or after the application of clascoterone cream. This is also applicable to the use of sunscreen or emollients. Warnings are included in Section 4.4 to inform that concomitant therapy with other anti-acneic cutaneous treatments and other products (i.e. medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect and products with high concentrations of alcohol, astringents, spices or lime) should be used with caution, applied with a minimum of two (2) hours before or after the application of clascoterone cream.

Since the systemic exposure of the main component clascoterone and its main metabolite cortexolone following cutaneous application is negligible, no interaction with systemic treatments is expected. Clascoterone has no induction potential of Cytochromes P450 (CYP) isozymes, and has no inhibitory potential except for CYP2C9, where it showed some inhibition at the highest concentrations tested (25 and 50 µM), which are several orders of magnitude higher than the systemic concentrations.

The findings from the clinical pharmacology program indicate that systemic exposure of clascoterone and its metabolites is low, and unlikely to interfere with any drugs potentially co-administered or endogenous corticosteroids.

Combining clascoterone with systemic anti-androgens could theoretically result in additive anti-androgen effects. No safety-related issues have been identified in the phase 3 studies CB-03-01/25 and CB-03-01/26 in those subjects who used concomitant medications with anti-androgen effects. These included various fixed dose combinations of oestrogen and progestogen, implant releasing progestogen, intramuscular medroxyprogesterone, and progestogen-only tablets.

There is limited specific evidence suggesting that the safety profile of clascoterone differs significantly in patients receiving concomitant treatment with other systemic acne treatments compared to those using clascoterone alone. A warning is included in Section 4.4 that concomitant use with other anti-acneic systemic treatments and other products (medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect and products with high concentrations of alcohol, astringents, spices or lime) should be avoided. Concomitant use with photodynamic therapy is not recommended. Treatment with this medicinal product should be discontinued prior to initiating photodynamic therapy.

Concomitant use with other topical or systemic acne treatment is followed up via routine pharmacovigilance and information is included in Sections 4.2, 4.4 and 4.5 of the SmPC.

- Overdose: Overdose risk is considered low due to the topical application. However, improper use, such as applying large quantities over extensive body areas or on damaged skin, may lead to an increase in local skin reactions or increased systemic absorption with potential systemic effects.

  In the long-term safety study (CB-03-01/27), although there were cases of much higher dosages than the recommended dose (maximum dosage recorded: 12.95 g per day), no treatment-emergent adverse events (TEAE) related to HPA suppression occurred, nor were there any cases of subjects discontinuing treatment due to suspected HPA inhibition.

  To date nine Periodic Adverse Drug Experience Reports (PADERs) were submitted to the Food and Drug Administration. There were no cases of overdose reported with clascoterone.

  Overdose is followed up via routine pharmacovigilance and as per SmPC section 4.9 in the event of overdose Winlevi should be discontinued and the patient monitored for potential occurrence of HPA axis suppression signs and symptoms.. In addition, a recommendation is included in Section 4.2 that clascoterone should not be applied to cuts, abrasions, eczematous or sunburned skin.

- Medication errors: In general, medication errors can occur at various stages, including prescribing, dispensing, and administration. Common errors with topical medications, which can be extrapolated to potential issues with clascoterone, may include incorrect application

method, applying an incorrect dose (too much or too little) or application on inappropriate body areas.

A review of the currently available data from post-market surveillance revealed a total number of 991 events in the Injury, poisoning and procedural complications system organ class (SOC), which were included in the PADERs. The most commonly received medication errors over the three-year period were product storage error (n=256), product dose omission issue (n=134) and product use issue (n=111). No safety related issues were identified as a result of the reported medication errors.

Medication errors are followed up via routine pharmacovigilance. There is clear wording in the SmPC regarding posology and method of administration. Additionally, Section 4.4 contains a warning and recommended action in the event of accidental exposure of clascoterone to mucous membranes.

- Off label use: Due to clascoterone's mechanism of action as an androgen receptor inhibitor, there is a potential for off label use in conditions such as hirsutism.

  A review of the currently available data from post-market surveillance revealed a total number of 33 reports of off label use have been received, as included in the PADERs. Four reports included off label indications of Fordyce spots, hair loss, hidradenitis and chin hirsutism in post-menopausal women. Two reports were received of use in unapproved body areas (scalp and vaginal area). The majority of cases concerned off label dosing frequency and one report concerned a prescription of '1 tube for 2 months' captured as off label use. No adverse events were reported in association with the off label use. No safety related issues were identified as a result of the off label use.

  Off label use is followed up via routine pharmacovigilance. There is clear wording in the SmPC regarding indication, posology and method of administration.

- Rebound effect: The rebound effect of clascoterone (i.e., an exacerbation of acne vulgaris) following treatment withdrawal was not assessed during the clinical studies. Rebound effect was reported for compounds structurally related to clascoterone (i.e. topical glucocorticoids) and cannot be excluded for clascoterone. There were no cases of rebound identified following withdrawal of clascoterone 1% cream during either the clinical development or the post-market experience.

  Rebound effect is followed up via routine pharmacovigilance. There is a warning included in Section 4.4 that should there be a reoccurrence of acne vulgaris within days to weeks after successful treatment of the condition with Winlevi, a withdrawal reaction should be suspected. Reapplication should be done with caution and medical advice is recommended in these cases, or other treatment options should be considered.

Other reasons for considering the risks not important:

- Psychiatric events: Depression is a common occurrence among adolescents; a recent review estimated that, in the US, about 1 in 4 female adolescents and 1 in 10 male adolescents are affected by depression, which is a significant risk factor for suicide, the cause of over one third of all adolescent deaths in the US.[15] Similar figures are found in Europe, where almost one in five young people were found to suffer from a mental disorder.[16]

  Acne vulgaris is associated with a significant psychosocial burden. Approximately 30–50% of patients aged 12–20 years with acne exhibit psychological responses, including anxiety, depression, lowered self-esteem, and low self-confidence.[17] A meta-analytic review of 42 studies confirmed an association between acne vulgaris and depression and anxiety.[18]

  One case of suicide attempt and three cases of depression occurred in the long-term study CB-03-01/27 which were considered not related to clascoterone and linked to the young age of the subjects, who are known to be at risk of mental health disorders which might lead to suicidality. Furthermore, in two patients who experienced depression, comorbid

conditions (pre-existing psychiatric disease, obesity and longstanding acne) may have been confounding factors.

A review of the currently available data from post-market surveillance, identified eight reports in the Psychiatric Disorders SOC, as included in the PADERs. This included two reports of anxiety, one report each of irritability, libido decreased, sleep disorder, stress, insomnia and purging.

Based on the above, there is no substantial evidence from currently available data from clinical trials or post-market surveillance suggesting a causal relationship between clascoterone and psychiatric events. Depression is a prevalent issue among adolescents and poses a serious risk for suicidality. Acne vulgaris, a common condition among adolescents, adds to this psychosocial burden. Evidence from a meta-analytic review underscores the association between acne and mental health issues. The psychosocial impact of acne is an important consideration for health care professionals and it is expected, as part of standard of care, that the psychological and social effects of acne will be assessed when planning and managing treatment. Suicidality ideation and behaviour (SMQ 'Depression and suicide/self-injury') will be monitored as part of routine pharmacovigilance activities and discussed in future Periodic Safety Update Reports (PSURs).

- Skin tumours / Carcinogenicity: An increased incidence of benign skin tumours of sebaceous origin was present in male rats treated with topical application of 5% cream for up to 23 months; this occurred in four animals. No evidence of local carcinogenicity was noted in female rats or systemic carcinogenicity in male or female rats following topical administration of CB-03-01 cream at concentrations ranging from 0.1% to 5%.

  Sebaceous cell adenomas in male rats with 5% cream were considered test article-related because they were statistically significant (p=0.049) compared to the vehicle control groups (as well as clinical research organization [CRO] historical control data), associated with multiplicity of sebaceous cell tumours and were observed at a higher incidence than published historical control databases. As observed in this study, epithelial tumours of the skin have been reported to be more common in males than females. On the whole, SC injection is intrinsically a contributory cause of skin damage and the resulting cell infiltration/proliferation. The skin effects were ascribed to the injection procedure. While long-term injection procedures could lead to skin tumours in rodents, this is still not relevant to the Winlevi cream product intended for cutaneous application without injection. Since androgen receptors in sebaceous glands are the pharmacological target of clascosterone, it would be expected that a persistent inhibition of such receptors by the antagonist would trigger a compensatory androgen receptors overexpression in the sebaceous glands in line to the observed benign adenomas. The fact that these occurred only in males further supports this proposal. Therefore, clascoterone did not induce genotoxic/malignant tumours at the site of contact, in line to a lack of mutagenicity. The effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. The minimal observed effect is regarded as a known high dose anti-androgen effect not relevant to clinical use.

  Clascoterone is considered clastogen/aneugen in vivo, and equivocal in the in vitro studies. Clascoterone tested in the in vitro micronucleus assay on human peripheral lymphocytes both in the presence and absence of metabolic activation was judged to be non-mutagenic in this in vitro test system.

  Based on these findings, it is considered that tumours do not constitute an important potential risk associated with clascoterone under anticipated conditions of human exposure.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Potential Risk: Hypothalamic-pituitary-adrenal (HPA) axis suppression

Risk-benefit impact: HPA axis suppression was observed and may occur during and shortly after treatment with clascoterone. In specific clinical studies, signs of HPA-axis suppression were limited to a laboratory-based assessment (ACTH stimulated cortisol levels); no other clinical signs or adverse reactions were associated with such laboratory results. This laboratory-based evidence of HPA-axis suppression self-resolved without sequelae after treatment discontinuation. In the current post-marketing surveillance data, there were no clinical signs or symptoms of HPA-axis suppression. The incidence of HPA axis suppression (ACTH stimulation test abnormal) is "common". 'HPA axis suppression' is included as an important potential risk.

Important Potential Risk: Reproductive toxicity

Risk-benefit impact: There are no data from the use of clascoterone in pregnant women. Animal studies have shown reproductive toxicity and foetal harm. Based on animal studies and its mechanism of action (androgen receptor inhibition), clascoterone can cause foetal harm. 'Reproductive toxicity' is included as an important potential risk.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Potential Risk: Hypothalamic-pituitary-adrenal (HPA) axis suppression

Potential mechanisms:

Cortexolone, the main metabolite of clascoterone, is a physiological component of the pool of endogenous corticosteroids, an intermediate in the synthesis of glucocorticoids, and exhibits weak glucocorticoid properties. Corticosteroids have the potential to interfere with the endogenous HPA axis, which regulates cortisol secretion in a controlled negative feedback loop.

Evidence source(s) and strength of evidence:

HPA axis suppression was observed in clinical trials and may occur during or after treatment with clascoterone. In a dedicated clinical study, signs of HPA-axis suppression were limited to a laboratory-based assessment (ACTH stimulated cortisol levels); no other clinical signs or adverse reactions were associated with such laboratory results. This laboratory-based evidence of HPA-axis suppression self-resolved without sequelae after treatment discontinuation within a few weeks. In the current post-marketing surveillance data, the incidence of HPA-axis suppression is unknown.

Characterisation of the risk:

Clascoterone has the potential for HPA suppression, but the risk is very low. Application of clascoterone to the face and truncal areas for long periods of time could potentially lower plasma cortisol but, due to the rapid metabolism of clascoterone, this is unlikely to happen; if it did occur, cortisol levels would recover in a few weeks upon treatment discontinuation. Typical symptoms of more severe HPA-axis suppression include fatigue, weight loss, decreased appetite, hyperpigmentation, low blood pressure, hypoglycaemia, nausea, diarrhoea, vomiting, or abdominal pain.

In a dedicated phase 2 clinical study signs of HPA-axis suppression were limited to a laboratory based assessment. Laboratory evidence of HPA axis suppression (i.e., decreased serum cortisol levels at 30 minutes after ACTH stimulation) was observed in 1/20 (5%) of adult and in 2/22 (9%) of adolescent patients under maximal usage conditions to the entire face, shoulders, upper chest and upper back of patients with moderate to severe acne, corresponding to mean daily amounts of 11.3 g (adults) and 9.3 g (adolescents). These amounts largely exceed the maximum recommended daily dose of clascoterone 1% cream as per the SmPC (5 g in adults, 2g in adolescents), which determines a >2-fold safety margin in adults and >4.5-fold in adolescents as compared to the future clinical use of the product. No clinical signs or symptoms of adrenal suppression were observed. Upon discontinuation of treatment the laboratory test results normalised within few weeks.

In study CB-03-01/28, assessing the potential for clascoterone 1% cream in inducing HPA suppression in paediatric acne patients aged 9 to <12 years (which is not the intended population to be treated with clascoterone 1% cream), 2 out of 23 (8.7%) subjects of the evaluable population demonstrated biochemical evidence of abnormal HPA axis response at Day 14 under maximum use conditions as documented by a 30-minute post-stimulation serum cortisol level of ≤ 18 µg/dL. In both cases, the subjects had borderline post-stimulation levels of cortisol, i.e., very close to the lower limit (18.0 and 16.1 µg/dL, respectively). Moreover, both subjects had no clinical symptoms nor TEAE attributable to HPA suppression. The two subjects fully recovered in the 4-week follow-up period.

No HPA-axis suppression events were recorded in the long-term extension safety study CB-03 01/27. Although there were cases of dosage much higher than the recommended dose (maximum dosage recorded: 12.95 g per day), no TEAE related to HPA suppression occurred, nor were there any cases of subjects discontinuing treatment due to suspected HPA inhibition.

In the post-market surveillance, the current marketing authorisation holder and licensee of Winlevi for the US market, [redacted], submitted to FDA, three cases with terms consistent with adrenal insufficiencies or HPA axis suppression (SOC term, 'Endocrine disorders'), all spontaneously reported: one reported by other healthcare professional and two by a consumer; all described as serious. One case of 'HPA axis suppression' was reported in a 20-year-old woman with a dosing duration of 3 months. A potential causal relationship could not be excluded. The other case of adrenal axis suppression was reported in a female patient of unknown age or dosing history. Due to the lack of clinical and exposure information, causality with Winlevi was ruled out. The final case of adrenal axis suppression submitted to FDA was reported in a female consumer of unknown age with a medical history of Down's Syndrome. The patient reported using Winlevi for an unknown indication. Causality with Winlevi was ruled out due to lack of confirmation of exposure. There were no clinical signs or symptoms reported which could be attributable to the event.

Finally, one case concerning a 31-year-old female patient who received a compound formulation of clascoterone (Winlevi) and experienced HPA axis suppression was submitted directly to the FAERs database by a consumer. Based on the limited available information and on the probable use of a compounded drug, a causal relationship between clascoterone and the observed events was ruled out.

Therefore, in total, the following HPA Axis Suppression/Adrenal Suppression events occurred:

Total HPA Axis Suppression/Adrenal Suppression Events Reported Per Age Group

Age group	**Case report type**	**Clinical study No.**	**No. of HPA axis suppression events**
≥18 years	Sponsored clinical study	171-7151-202	1
	Post-market surveillance	N/A	2*
≥12 to <18 years	Sponsored clinical study	171-7151-202	2

Age group	Case report type	Clinical study No.	No. of HPA axis suppression events
≥12 years (age unspecified)	Post-market surveillance	N/A	2
Total number of cases in subjects 12 years of age and older			**6**
9 to <12 years	Sponsored clinical study	CB-03-01/28	2
Total number of cases in subjects aged 9 to <12 years of age			**2**

Footnote:
* This includes one report that was submitted directly by a consumer to FDA (not by [redacted]) and pertains to a compounded formulation that seems to be unrelated to Winlevi (clascoterone).

From the adverse events on HPA Axis Suppression/Adrenal Suppression detected, only 1 case was assessed as related to suspect drug by Partner MAH's physician.

No cases have been identified in the post-marketing setting compatible with impaired growth. Similarly, there were no cases of Cushing syndrome identified and reported in [redacted] database.

The incidence of HPA axis suppression (ACTH stimulation test abnormal) is "common" (See SmPC section 4.8), however the potential of HPA axis suppression is minimal given the very low potency of clascoterone as glucocorticoid drug and the very low systemic absorption of the drug (which is needed to trigger a HPA axis suppression).

In the cases of laboratory evidence of HPA axis suppression, which occurred during the maximum use studies in adults and adolescents with moderate to severe acne, there were no associated symptoms, and the laboratory evidence was fully reversible with no clinical consequences or sequelae.

A meta-analysis by Heickman et al (2018)[20] confirms that the use of mid- to low-potency topical corticosteroids in children, even among those with significant atopic dermatitis, is associated with a low incidence of HPA axis suppression, often reversible and without clinical symptoms. Consequently, in paediatric practice, routine testing of the HPA axis is generally unnecessary in the absence of adrenal insufficiency symptoms.

Risk factors and risk groups:

The degree of inhibition of the HPA axis during (gluco-)corticosteroid therapy is predominantly linked to the type of compound, method of administration (parenteral, oral, inhalation, topical), cumulative dose, duration of treatment, frequency of administration and incidentally concomitant drugs that may increase the bioavailability of corticosteroids. However, there is considerable variation in individual physiology, probably related to different genetic profiles which regulate glucocorticoid receptor activity.[19]

Conditions which augment systemic absorption include use over large surface areas, prolonged use, and the use of occlusive dressings.

Paediatric patients may be more susceptible to systemic toxicity.

Preventability:

Treatment should be initiated and supervised by a medical doctor with experience in the diagnosis and treatment of acne vulgaris. These providers should be familiar with the management of potential adverse events associated with clascoterone. HPA axis suppression is followed up via routine pharmacovigilance. To minimise the risk, for adolescents (12 to <18 years of age) the total daily dose should not exceed four (4) fingerprint units (corresponding to approximately 2g of cream); the cream must be applied on the face only. Thereby reducing the adolescent maximum dose by more than half the adult maximum dose, consequently reducing the potential for systemic exposure. If

adrenal insufficiency is suspected, morning serum cortisol levels could be measured and the patient may be referred for endocrinological evaluation; treatment should be interrupted if HPA axis suppression is confirmed. Educational materials regarding these precautions are available for healthcare professionals.

Impact on the benefit-risk balance of the product:

HPA axis suppression may occur during or after treatment with clascoterone, however, as clascoterone is rapidly metabolised in vivo and the main metabolite is a physiological component of the pool of endogenous corticosteroids, systemic exposure is low.

Public health impact:

Unknown

Important Potential Risk: Reproductive toxicity

Potential mechanisms:

Based on its mechanism of action (androgen receptor inhibition), reproductive toxicity observed in animal studies (rats and rabbits) at all dose level tested and/or at non-maternotoxic doses without safety margin and a possible systematic effect after exposure, clascoterone can cause foetal harm.

Evidence source(s) and strength of evidence:

There are no data from the use of clascoterone in pregnant women. Animal studies have shown reproductive toxicity.

Characterisation of the risk:

In a fertility and early embryonic development study in rats, there was no effect on fertility at subcutaneous doses up to 12.5 mg/kg/day; increased preimplantation loss and sperm count changes were noted at this dose level but not at 2.5 mg/kg/day (4.7 to 8.0 times the human exposure based on AUC comparison). In an embryofoetal development study conducted in rats at subcutaneous doses of 1, 5, or 25 mg/kg/day, clascoterone-related malformations were noted at all dose levels, without a dose relationship: omphalocele was noted in a single foetus at each dose level, and external and visceral malformations (severe dilation of the lateral and third cerebral ventricles; thin skin, small size, and protruding tongue) were noted in two additional foetuses at 1 mg/kg/day (2.5 times the human exposure based on AUC comparison). In rabbits, post-implantation loss and resorptions were increased at a subcutaneous dose of 1.5 mg/kg/day whereas no treatment-related effect on embryofoetal development was observed at doses up to 0.4 mg/kg/day (3.7 times the human exposure based on AUC). In a pre- and postnatal development study performed in rats, no significant developmental toxicity was observed at subcutaneous doses up to 12.5 mg/kg/day.

Risk factors and risk groups:

Women of childbearing potential and pregnant women.

Preventability:

Winlevi is contraindicated during pregnancy as per Section 4.3 of the SmPC and women of childbearing potential have to therefore use an effective contraceptive method during treatment with Winlevi and for at least 10 days after the last dose. No clinical interaction studies have been performed, therefore, an interaction with hormonal contraception cannot be excluded.. The pregnancy status of women of childbearing potential should be verified prior to initiating treatment with clascoterone. Educational materials regarding these precautions are available for healthcare professionals and patients (or parents/caregivers). A patient card is provided with the package of the medicinal product.

Impact on the risk-benefit balance of the product:

Due to clascoterone's mechanism of action and toxicity observed in animal studies, clascoterone can cause foetal harm and is therefore contraindicated during pregnancy and women of childbearing

potential have to use an effective contraception during treatment and for at least 10 days after the last dose.

Public health impact:

Unknown

SVII.3.2. Presentation of the missing information

Not applicable

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Hypothalamic-pituitary-adrenal (HPA) axis suppression • Reproductive toxicity
Missing information	• None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for clascoterone:

Cassiopea S.p.A. is not using any specific adverse reaction follow-up questionnaires for clascoterone.

However, targeted follow-up will be completed if any adverse event reports are received that warrant specific questioning to the reporter to clarify details within the report.

Other forms of routine pharmacovigilance activities for clascoterone:

No other forms of routine pharmacovigilance activities are considered necessary.

III.2 Additional pharmacovigilance activities

Study CB-03-01/43 summary

Study short name and title:

Post-marketing safety study to characterise the potential risk of HPA axis suppression with long-term use of Winlevi in adolescents.

Rationale and study objectives:

This PASS aims to monitor the long-term safety of clascoterone on HPA axis in adolescents. Should such an effect be detected there will be an assessment for any risk factors. The impact of treatment, if any, on growth and sexual maturation will also be evaluated.

The study will be conducted in two parts. Part A will be a feasibility assessment and Part B will be the execution of the chosen study design.

Study design:

Part A will involve assessment of feasibility of the data sources to be considered with a preference for real world data (RWD) and appropriate healthcare databases, including EEA. Feasibility of other designs, including a registry approach, may also be considered.

Study population:

The study will include adolescent patients (≥12, <18 years) with acne vulgaris, covering a broad range of countries and regions in the EU and UK.

Patients will be included if they are at least 12 years old and less than 18 years old at the time of commencing clascoterone, and have a diagnosis of facial acne vulgaris.

Milestones:

Part A: Feasibility assessment is to be conducted within 3 months of the European Commission Decision on Winlevi being granted.

Part B: Once feasibility is endorsed by the EU Competent Authorities, the MAH will develop the full protocol and conduct the PASS to timelines agreed with the EMA.

Study progress reports: Submission of interim reports and inclusion of updates in Periodic Benefit-Risk Evaluation Reports (PBRERs).

Final study report for Part B: Within one year of the end of data collection.

III.3 Summary Table of additional Pharmacovigilance activities

Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization.

N/A

Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances.

N/A

Category 3 - Required additional pharmacovigilance activities: Please see table below:

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 - Required additional pharmacovigilance activities				
Study ID: CB-03-01/43 **Title:** Post-marketing safety study to characterise the potential risk of HPA axis suppression with long-term use of Winlevi in adolescents. (Planned)	**Part A:** To assess the feasibility of relevant data sources suitable for evaluation of the potential risk of HPA axis suppression with the use of clascoterone for facial acne vulgaris in adolescents. **Part B:** Execution of the chosen study design following the feasibility assessment.	Potential risk of HPA axis suppression in adolescents	Submission of feasibility assessment Protocol to be completed Interim reports Final study report	3 months after EC Decision on Winlevi Subject to feasibility Defined within the specific post-marketing procedure Within one year of the end of data collection

Part IV: Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies are planned and none are considered required.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
HPA axis suppression	**Routine risk communication:** As per SmPC Section 4.2 the total daily dose in adolescents, that must be limited to the face, should not exceed four (4) fingertip units (corresponding to approximately 2 g of cream). Additionally, the application must be done without using occlusive dressings as per Section 4.2. Sections 4.4 and 4.8 include warnings of HPA axis suppression with potential risk factors and symptoms. PL Sections 2 and 4. **Routine risk minimisation activities recommending specific clinical measures:** SmPC Sections 4.1 and 4.2 recommend that in adolescents, use must be limited to the face. A warning that the application must be done without using occlusive dressings is included in Section 4.2 of the SmPC. In Section 4.4 of the SmPC there is the recommendation that if adrenal insufficiency is suspected, morning serum cortisol levels could be measured, and the patient may be referred for endocrinological evaluation; treatment should be interrupted if HPA axis suppression is confirmed. A recommendation to patients in Section 2 of the PL to not use Winlevi over large areas of skin for a long time or cover the area with a bandage or dressing, as this can increase the risk of developing adrenal suppression and to stop treatment if feeling unusually tired or unwell when using and to discuss with doctor. The doctor could consider to test the patient's blood cortisol levels and to refer them to an endocrinologist. **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine Pack size (60 grams maximum pack size, corresponding to approximately one month of treatment for adolescents) Legal status (restricted medical prescription)
Reproductive toxicity	**Routine risk communication:** SmPC section 4.3 includes a contraindication during pregnancy and Section 4.4 states a warning for women of childbearing potential have to therefore use an effective contraceptive method during treatment with Winlevi and for at least 10 days after the last dose. The pregnancy status

	of women of childbearing potential should be verified prior to initiating treatment with clascoterone. PL Section 2 reports the recommendation to patients to ask their doctor for advice if pregnant or planning a pregnancy and to use birth control while using Winlevi and for at least 10 days after stopping treatment. **Routine risk minimisation activities recommending specific clinical measures:** SmPC Section 4.6 states that women of childbearing potential have to use an effective contraceptive method during treatment with Winlevi and for at least 10 days after the last dose. Additionally, in section 4.4 is reported that the pregnancy status of women of childbearing potential should be verified prior to initiating treatment with clascoterone. A recommendation to patients is included in Section 2 of the PL to ask their doctor for advice if pregnant or planning a pregnancy and to use birth control while using Winlevi and for at least 10 days after stopping the treatment. **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine Legal status (restricted medical prescription)

V.2. Additional Risk Minimisation Measures

Additional risk minimisation 1: Healthcare professional checklist for risk minimisation

Objectives:

The healthcare professional (HCP) checklist is to be provided to prescribing HCPs for the important potential risks of HPA axis suppression and reproductive toxicity. The objective is to ensure awareness and support adherence to recommended prescribing and monitoring steps, to facilitate early identification of signs and symptoms suggestive of HPA axis suppression, particularly in adolescent patients, and to ensure that patients receive clear and consistent counselling on the risk of embryo–foetal toxicity, the contraindication during pregnancy, and the need for verified negative pregnancy status before treatment initiation. The HCP checklist also aims to reinforce the importance of recommending and confirming the use of appropriate contraception for women of childbearing potential during treatment and for the required post-treatment period, thereby supporting patients' adherence to these measures.

Rationale for the additional risk minimisation activity:

There is a potential risk of HPA axis suppression, especially in the adolescent population from 12 to < 18 years of age. In a specific study assessing the potential of clascoterone cream to cause HPA axis suppression, laboratory-based evidence of HPA axis suppression was more frequently observed in adolescents.

Based on animal studies and its mechanism of action (androgen receptor inhibition), clascoterone can cause foetal harm.

Although systemic absorption of cutaneous clascoterone and its main metabolite cortexolone, is negligible, there could be individual factors (e.g. use over large surfaces, prolonged use) that may contribute to an increased systemic exposure.

Given the potential risk of adolescents applying more than the recommended daily dose and the possibility for long-term treatment with clascoterone, it is considered that strengthening HPCs' awareness of the potential risks is necessary. This measure is intended to ensure that healthcare professionals are aware of the occurrence of the risks specified above and the appropriate management of these risks.

Target audience and planned distribution path:

The target audience is healthcare professionals who intend to prescribe Winlevi.

Plans to evaluate the effectiveness of the interventions and criteria for success:

The effectiveness of the HCP checklist will be evaluated through the review of any cases received pertaining to these risks on an ongoing basis and summarised at the time of periodic safety update reports (PSURs).

Additional risk minimisation 2: Patient card

Objectives:

The objective of the patient card is to notify patients of the important potential risk of reproductive toxicity with a reminder that clascoterone should not be used in pregnancy and that pregnancy status must be confirmed prior to initiating treatment with Winlevi in women of childbearing potential. The patient card also aims to enhance awareness of the necessity for effective contraception for at least 10 days following treatment discontinuation.

Rationale for the additional risk minimisation activity:

Considering the potential for long-term treatment with clascoterone, risk awareness by the patients beyond the initial consultation and prescription is required. In the context of repeated prescribing or dispensing, patient-physician counselling may not consistently occur, increasing the risk that compliance with the contraindication can therefore be more easily overlooked. It is considered that strengthening patients' awareness of the important potential risk of reproductive toxicity is necessary. This measure is intended to ensure that patients are aware of the risk and how to follow the necessary precautions to minimise the risk.

Target audience and planned distribution path:

The target population is women of childbearing potential who are prescribed Winlevi. The patient card will be provided with the package of the medicinal product.

Plans to evaluate the effectiveness of the interventions and criteria for success:

The effectiveness of the patient card will be evaluated through the reporting of any identified pregnancy cases in the post-marketing setting. Any spontaneous cases received will be evaluated at the time of receipt and follow-up questionnaires will be sent if further information is required. Regular updates on pregnancies and their outcomes will be presented in PSURs.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hypothalamic-pituitary-adrenal	**Routine risk minimization measures:**	**Routine pharmacovigilance activities beyond adverse**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
(HPA) axis suppression	SmPC Section 4.1 and 4.2 recommend that, in adolescents, the use of clascoterone cream must be limited to the face. SmPC Section 4.2 states that in adolescents, the total daily dose should not exceed four (4) fingertip units (corresponding to approximately 2 g of 10mg/g clascoterone cream). A warning that the application must be done without using occlusive dressings is included in Section 4.2 of the SmPC. Sections 4.4 and 4.8 of the SmPC include a warning of HPA axis suppression with potential risk factors and symptoms and recommendation to consider measuring morning serum cortisol levels if HPA axis suppression is suspected and referring the patient for endocrinological evaluation. Treatment should be interrupted if HPA axis suppression is confirmed. A recommendation to patients is included in Section 2 of the PL, not to use Winlevi over large areas of skin for a long time or cover the area with a bandage or dressing, as this can increase the risk of developing adrenal suppression and to stop treatment if feeling unusually tired or unwell when using and to discuss with doctor. The doctor could consider to test the patient's blood cortisol levels and to refer them to an endocrinologist. Pack size is limited to 60 grams maximum, corresponding to approximately one month of treatment for adolescents. **Additional risk minimisation measures:** Healthcare professional checklist	**reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study CB-03-01/43 Post-marketing safety study to characterise the potential risk of HPA axis suppression with long-term use of Winlevi in adolescents. (Planned) Final study report: Within one year of the end of data collection.
Reproductive toxicity	**Routine risk minimisation measures**	**Routine pharmacovigilance activities beyond adverse**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	SmPC section 4.3 includes a contraindication during pregnancy and Section 4.6 states that women of childbearing potential have to therefore use an effective contraceptive method during treatment with Winlevi and for at least 10 days after the last dose. Additionally, in section 4.4 it is specified the warning on the pregnancy status of women of childbearing potential that should be verified prior to initiating treatment with clascoterone. A recommendation to patients in Section 2 of the PL to ask their doctor for advice if pregnant or planning a pregnancy and to use birth control while using Winlevi and for at least 10 days after stopping treatment. **Additional risk minimisation measures:** Healthcare professional checklist Patient card	**reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Part VI: Summary of the risk management plan

Summary of risk management plan for Winlevi 10mg/g cream (clascoterone)

This is a summary of the risk management plan (RMP) for Winlevi 10mg/g cream. The RMP details important risks of Winlevi 10mg/g cream, how these risks can be minimised, and how more information will be obtained about Winlevi 10mg/g cream's risks and uncertainties (missing information).

Winlevi 10mg/g cream's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Winlevi 10mg/g cream should be used.

This summary of the RMP for Winlevi 10mg/g cream should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Winlevi 10mg/g cream's RMP.

I. The medicine and what it is used for

Winlevi 10mg/g cream is authorised for the treatment of acne vulgaris in patients from 12 years of age and older (see SmPC for the full indication). It contains clascoterone as the active substance and it is given by topical administration.

Further information about the evaluation of Winlevi 10mg/g cream's benefits can be found in Winlevi 10mg/g cream's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Winlevi 10mg/g cream, together with measures to minimise such risks and the proposed studies for learning more about Winlevi 10mg/g cream's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Winlevi 10mg/g cream, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Winlevi 10mg/g cream are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Winlevi 10mg/g cream. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• None
Important potential risks	• Hypothalamic-pituitary-adrenal (HPA) axis suppression • Reproductive toxicity
Missing information	• None

II.B Summary of important risks

Important potential risk: Hypothalamic-pituitary-adrenal (HPA) axis suppression	
Evidence for linking the risk to the medicine	HPA axis suppression was observed in clinical trials and may occur during or after treatment with clascoterone. In dedicated clinical studies, signs of HPA-axis suppression were limited to a laboratory-based assessment (ACTH stimulated cortisol levels); no other clinical signs or adverse reactions were associated with such laboratory results. This laboratory-based evidence of HPA-axis suppression self-resolved without sequelae after treatment discontinuation. In the current post-marketing surveillance data, the incidence of HPA-axis suppression is unknown.
Risk factors and risk groups	The degree of inhibition of the HPA axis during (gluco-) corticosteroid therapy is predominantly linked to the type of compound, method of administration (parenteral, oral, inhalation, topical), cumulative dose, duration of treatment, frequency of administration and incidentally concomitant drugs that may increase the bioavailability of corticosteroids. However, there is considerable variation in individual physiology, probably related to different genetic profiles which regulate glucocorticoid receptor activity.[19] Conditions which augment systemic absorption include use over large surface areas, prolonged use, and the use of occlusive dressings.

	Paediatric patients may be more susceptible to systemic toxicity.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.1 and 4.2 recommend that, in adolescents, the use of clascoterone cream must be limited to the face. SmPC Section 4.2 states that in adolescents, the total daily dose should not exceed four (4) fingertip units (corresponding to approximately 2 g of 10 mg/g clascoterone cream). A warning that the application must be done without using occlusive dressings is included in Section 4.2 of the SmPC. Sections 4.4 and 4.8 of the SmPC include a warning of HPA axis suppression with potential risk factors and symptoms and recommendation to consider measuring morning serum cortisol levels if HPA axis suppression is suspected and referring the patient for endocrinological evaluation. Treatment should be interrupted if HPA axis suppression is confirmed. A recommendation to patients is included in Section 2 of the PL not to use Winlevi over large areas of skin for a long time or cover the area with a bandage or dressing, as this can increase the risk of developing adrenal suppression and to stop treatment if feeling unusually tired or unwell when using and to discuss with doctor. The doctor could consider to test the patient's blood cortisol levels and to refer them to an endocrinologist. Additional risk minimisation measures: Healthcare professional checklist
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study CB-03-01/43 Post-marketing safety study to characterise the potential risk of HPA axis suppression with long-term use of Winlevi in adolescents. (Planned) See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Reproductive toxicity

Evidence for linking the risk to the medicine	There are no data from the use of clascoterone in pregnant women. Animal studies have shown reproductive toxicity.
Risk factors and risk groups	Women of childbearing potential and pregnant women.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.3 includes a contraindication during pregnancy and Section 4.6 states that women of childbearing potential have to therefore use an effective contraceptive method during treatment with Winlevi and for at least 10 days after the last dose. Additionally, in section 4.4. there is a warning on the pregnancy status of women of childbearing potential that should be verified prior to initiating treatment with clascoterone. A recommendation to patients in Section 2 of the PL to ask their doctor for advice if pregnant or planning a pregnancy and to use birth control while using Winlevi and for at least 10 days after stopping treatment. Additional risk minimisation measures: Healthcare professional checklist Patient card

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Winlevi 10mg/g cream.

II.C.2 Other studies in post-authorisation development plan

Study CB-03-01/43

Purpose of the study:

This PASS aims to monitor the long-term safety of clascoterone on HPA axis in adolescents. Should such an effect be detected there will be an assessment for any risk factors. The impact of treatment, if any, on growth and sexual maturation will also be evaluated.

The study will be conducted in two parts. Part A will be a feasibility assessment and Part B will be the execution of the chosen study design.

Part VII: Annexes

Table of contents

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Prior to the launch of Winlevi in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where Winlevi is marketed, all healthcare professionals, patients/carers who are expected to prescribe, dispense or use Winlevi have access to/are provided with the following educational package:

Healthcare professional checklist for risk minimisation:

The Healthcare professional checklist shall contain the following key messages:

Hypothalamic-pituitary-adrenal (HPA) axis suppression

- Provide clear instruction on correct use of Winlevi (dose, administration schedule and site of application for adult and adolescent, respectively)
- Inform patients about the risk of HPA-axis suppression and advice on signs and symptoms suggestive of this condition
- Monitor patient's adherence to the recommendation on correct use at follow-up visits
- Consider measuring morning serum cortisol levels if HPA axis suppression is suspected and referring the patient for endocrinological evaluation. Treatment should be interrupted if HPA axis suppression is confirmed

Reproductive toxicity

- Inform patient about the contraindication during pregnancy due to the risk of potential fetal harm and congenital malformations
- Verify pregnancy status prior to initiating treatment
- Counsel on contraception during treatment with Winlevi, recommending use of an effective method of contraception
- Advise on continued use of contraception for at least 10 days after last administration

Patient card:

The Patient card shall contain the following key messages:

Reproductive toxicity

- Inform patient about the contraindication during pregnancy due to the risk of potential fetal harm and congenital malformations
- Verify pregnancy status prior to initiating treatment
- Counsel on contraception during treatment with Winlevi, recommending use of an effective method of contraception
- Advise on continued use of contraception for at least 10 days after last administration

Annex 7 - Other supporting data (including referenced material)

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