# ANNEX I

# SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

Winlevi 10 mg/g cream

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of cream contains 10 mg of clascoterone.

Excipients with known effect

Each gram of cream contains 25 mg of cetyl alcohol and 250 mg of propylene glycol (E1520).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Cream

White to almost white cream.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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.

### 4.2 Posology and method of administration

Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of acne vulgaris.

Posology

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).

*Adults*

Total daily dose should not exceed ten (10) fingertip units (corresponding to approximately 5 g of 10 mg/g clascoterone cream). The cream can be applied on the face, chest and/or back.

*Adolescents (from 12 to < 18 years of age)*

Total daily dose should not exceed four (4) fingertip units (corresponding to approximately 2 g of 10 mg/g clascoterone cream). The cream must be applied on the face only. No more than 60 g a month should be used (corresponding to one 60 g tube or two 30 g tubes).

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 (see sections 4.4 and 4.8).

*Renal or hepatic impairment*

No studies have been conducted in patients with renal or hepatic impairment. Given the very low systemic absorption, no dose adjustment or special considerations are anticipated for these patients (see section 5.2).

*Elderly*

There are no clinical data in patients aged 65 years or older. Winlevi is not recommended for use in patients aged 65 years or older.

Paediatric population

*Children from 9 to < 12 years*

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 but no recommendation on a posology can be made.

*Children below 9 years of age*

There is no relevant use of Winlevi in children aged less than 9 years for the treatment of acne vulgaris.

Method of administration

Winlevi is for cutaneous use only.

The affected areas should be clean and dry before application. Winlevi should not be applied to cuts, abrasions, eczematous or sunburned skin. The cream must be applied without using occlusive dressing to avoid an increased risk for systemic undesirable effects (see section 4.4).

Other cutaneous medicinal products used to treat other conditions on the same skin areas should be applied with a minimum of two (2) hours before or after the application of Winlevi. This is also applicable to the use of sunscreen or emollients.

The patient should be instructed to apply a thin, uniform layer of Winlevi to the affected area, massaging gently, avoiding the eyes, eyelids, lips and nostrils, and then wash hands after application.

The cream must be applied to the entire affected area and not to the acne lesions only.

## 4.3 Contraindications

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

Pregnancy (see section 4.6).

## 4.4 Special warnings and precautions for use

Hypothalamic-pituitary-adrenal (HPA) axis suppression

In a dedicated phase 2 clinical study in adults and adolescents from 12 to < 18 years of age, signs of HPA-axis suppression were limited to a laboratory-based assessment (adrenocorticotropic hormone [ACTH] stimulated cortisol levels, see section 5.1); no other clinical signs, symptoms or related endocrine adverse reactions were associated with such laboratory results. This laboratory-based evidence of HPA-axis suppression self-resolved without sequelae after treatment discontinuation (see section 4.8).

Conditions which augment systemic absorption (e.g. use over large surfaces, prolonged use, and the use of occlusive dressings), should be avoided (see section 4.2).

Typical symptoms of HPA-axis suppression include fatigue, weight loss, decreased appetite, low blood pressure, hypoglycemia, nausea, diarrhoea, vomiting, or abdominal pain (see section 4.8). Patients should be instructed to inform their physician if they develop any symptoms of HPA-axis suppression. 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.

*Adolescents (from 12 to < 18 years of age)*

The paediatric population may be at increased risk of HPA axis suppression. In the dedicated phase 2 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 than in adults (see section 5.1). In order to reduce the systemic absorption, use in adolescents must be limited to the face only (see section 4.2).

Local skin reactions

This medicinal product may induce local irritation (such as erythema, pruritus, scaling/dryness, stinging/burning), mostly of minimal or mild severity (see section 4.8). Caution should be used when applying to sensitive areas of the skin, such as the neck: if a local skin reaction in a sensitive area occurs, treatment discontinuation should be considered; emollients may also be applied with a minimum of two (2) hours before or after the application of this medicinal product (see section 4.2).

Local irritation could be increased in case of concomitant use of cutaneous anti-acneic medicinal products. 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 this medicinal product.

Application to abraded, eczematous skin or patients with inflammatory skin conditions that may coexist with acne, e.g. rosacea or perioral dermatitis, should be avoided.

The concomitant application of astringent cleansing cosmetic products and drying or irritating agents (such as perfumed or alcohol-containing products) should be avoided.

In patients, whose skin has been subjected to procedures such as depilation, chemical peels, dermabrasion or laser resurfacing, the skin should be allowed to recover before application is considered.

Concomitant use with photodynamic therapy is not recommended. Treatment with this medicinal product should be discontinued prior to initiating photodynamic therapy.

Accidental exposure to mucous membranes

Accidental transfer of cream into eyes, mouth or other mucous membranes should be avoided. If contact with mucous membranes occurs, the area should be rinsed thoroughly with water.

Rebound effect

The rebound effect (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 corticosteroids) and cannot be excluded for this medicinal product. Should there be a reoccurrence of acne vulgaris within days to weeks after successful treatment of the condition with this medicinal product, 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.

Women of childbearing potential

Women of childbearing potential have to use an effective contraceptive method during treatment and for at least 10 days after the last dose (see section 4.6). The pregnancy status should be verified before initiating treatment with this medicinal product in women of childbearing potential (see section 4.6).

*Educational materials*

Educational materials regarding these precautions are available for healthcare professionals and patients (or parents/caregivers). A patient card is provided with the package of this medicinal product.

Excipients with known effect

*Cetyl alcohol*

This medicinal product contains 25 mg cetyl alcohol in each gram. Cetyl alcohol may cause local skin reactions (e.g. contact dermatitis).

*Propylene glycol*

This medicinal product also contains 250 mg propylene glycol in each gram. Propylene glycol may cause skin irritation.

## 4.5 Interaction with other medicinal products and other forms of interaction

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 (see section 4.2).

Since the systemic exposure of 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 glucocorticoid medicinal products.

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

No interaction clinical studies have been performed, therefore, an interaction with hormonal contraception cannot be excluded. The pregnancy status should be verified before initiating treatment with clascoterone in women of childbearing potential.

Pregnancy

There are no or a limited amount of data from the use of cutaneous clascoterone in pregnant women. Animal studies have shown reproductive toxicity following subcutaneous administration (see section 5.3). 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. Based on animals studies and its mechanism of action (androgen receptor inhibition), clascoterone can cause fetal harm. This medicinal product is contraindicated during pregnancy (see section 4.3).

The patient must be informed and understand the risks related to the use of this medicinal product during pregnancy.

Breast-feeding

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

Use of this medicinal product is not recommended while breast-feeding or breast-feeding should be discontinued during treatment with this medicinal product.

Fertility

There are no data on the effect of clascoterone on human fertility. Results from animal studies following subcutaneous administration showed no effect on fertility in male or female rats (see section 5.3).

## 4.7 Effects on ability to drive and use machines

Winlevi has no or negligible influence on the ability to drive and use machines.

## 4.8 Undesirable effects

Summary of the safety profile

The most frequently occurring adverse reactions are local skin reactions such as erythema (11.5%), scaling/dryness (10.0%), pruritus (7.4%) and stinging/burning (4.0%). These reactions were usually self-limiting and resolved during use of this medicinal product.

Tabulated list of adverse reactions

Adverse reactions reported with cutaneous clascoterone in both adult and adolescent (from 12 to < 18 years of age) patients, including clinical trials and post-marketing experience, are presented in Table 1 below, according to the MedDRA system organ classification.

The frequency of adverse reactions is defined as follows: very common ≥ 1/10; common ≥ 1/100 and to < 1/10; uncommon ≥ 1/1 000 and to < 1/100; rare ≥ 1/10 000 and to < 1/1 000; very rare < 1/10 000; not known (cannot be estimated from the available data).

**Table 1: Adverse reactions in adult and adolescent (from 12 to < 18 years of age) patients**

| System Organ Class | Adverse reaction | Frequency |
|---|---|---|
| Infections and infestations | Application site folliculitis | Rare |
| Immune system disorders | Hypersensitivity | Rare |
| Nervous system disorders | Headache | Rare |
| Respiratory, thoracic and mediastinal disorders | Oropharyngeal pain | Rare |
| Skin and subcutaneous tissue disorders | Acne<br>Dermatitis contact | Rare |
| General disorders and administration site conditions | Application site pain<br>Application site dryness<br>Application site erythema<br>Application site hypertrichosis | Common |
| Investigations | Adrenocorticotropic hormone (ACTH) stimulation test abnormal* | Common |

* assessed in the dedicated phase 2 study at supratherapeutic dosages, see section below.

Description of selected adverse reactions

*ACTH stimulation test abnormal*

Laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression(i.e., decreased serum cortisol levels at 30 minutes after ACTH stimulation) was observed in the dedicated phase 2 study 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 acne patients, corresponding to mean daily amounts of 11.3 g (adults) and 9.3 g (adolescents). No clinical signs or symptoms of adrenal suppression were observed. Upon discontinuation of treatment the laboratory test results normalised within 4 weeks (see section 4.4).

If HPA axis suppression occurs, treatment interruption should be considered (see section 4.4).

Paediatric population

Among the 444 subjects aged 12 to < 18 years enrolled in phase 2 and phase 3 vehicle-controlled studies for acne vulgaris and exposed to clascoterone cream, the overall incidence of adverse reactions was 4/444 (0.9%).

Frequency, type and severity of adverse reactions through week 12 were similar to those in adults as presented in Table 1, which covers both populations.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

## 4.9 Overdose

There is no specific treatment for an overdose with Winlevi.

In the dedicated phase 2 clinical study, a mean daily amount of 11.3 g and 9.3 g clascoterone cream 10 mg/g was administered for 2 weeks to 20 adult and 22 adolescent patients, respectively, resulting in laboratory-based HPA axis suppression in 5% of adults and 9% of adolescents respectively.

In the event of overdose, Winlevi should be discontinued and the patient monitored for potential occurrence of HPA axis suppression signs and symptoms.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-acne preparations, other anti-acne preparations for topical use, ATC code: D10AX06

Mechanism of action

Clascoterone is an androgen receptor inhibitor. *In vitro* studies showed that it potently antagonizes 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.

Pharmacodynamic effects

*Hypothalamic-pituitary-adrenal (HPA) axis suppression*

In the dedicated phase 2 study 171-7151-202 aimed at investigating the potential effects of clascoterone cream 10 mg/g on the HPA axis and pharmacokinetics in adults and adolescents with acne vulgaris, HPA axis suppression was evaluated in adults (n=20) and adolescents from 12 years of age (n=22) following application of supratherapeutical doses of clascoterone cream with a mean daily amount of 11.3 g in adults and 9.3 g in adolescents for 2 weeks (see section 5.2). HPA axis suppression indicated by 30-minute post-stimulation serum cortisol level of ≤ 18 mcg/dL was observed in 1/20 (5%) of adult subjects and 2/22 (9%) of adolescent subjects at Day 14. All subjects returned to normal HPA axis function at follow-up 4 weeks after the end of treatment.

*Cardiac electrophysiology*

At approximately 9-times the maximum treatment adult dose (5 g/day of cream), clascoterone does not prolong the QT interval to any clinically relevant extent.

Clinical efficacy and safety

The safety and efficacy of clascoterone cream 10 mg/g applied twice daily for 12 weeks for the treatment of acne vulgaris were assessed in two identically-designed phase 3, multicentre, randomised, double-blind, vehicle-controlled clinical trials (CB-03-01/25 and CB-03-01/26) enrolling in total 1 440 subjects with facial acne vulgaris. The trials enrolled subjects with Investigator's Global Assessment (IGA) of moderate or severe facial acne vulgaris (score of 3 or 4), 30 to 75 inflammatory lesions (papules, pustules and nodules), and 30 to 100 non-inflammatory lesions (open and closed comedones).

Of these 1 440 randomised subjects, 19 (1.3%) were 9 to 11 years of age, 641 (44.5%) were 12 to 17 years of age, and 780 (54.2%) were 18 years of age or older. Among adults and adolescents, 62% of the subjects were female and 91% were Caucasian. At baseline, subjects had a mean inflammatory lesion count of 42.4 and a mean non-inflammatory lesion count of 61.4. Approximately 83% of subjects had an IGA score of 3.

Efficacy was assessed by three co-primary endpoints: proportion of subjects in each treatment group achieving "success" at Week 12, with "success" defined as an IGA score of " clear (score=0)" or "almost clear (score=1)" AND at least a 2-point reduction in IGA compared to baseline, absolute

change from baseline in non-inflammatory lesions count (NILC) in each treatment group at Week 12, and absolute change from baseline in inflammatory lesions count (ILC) in each treatment group at Week 12.

*Adults and adolescents from 12 to < 18 years*

The IGA success rate and mean absolute and percent reduction from baseline in acne lesion counts after 12 weeks of treatment for patients 12 years of age and older are presented in Table 2.

**Table 2 Clinical efficacy of clascoterone cream 10 mg/g in adult and adolescent patients with facial acne vulgaris at week 12**

| | **Study CB-03-01/25** | | **Study CB-03-01/26** | |
|---|---|---|---|---|
| | **Clascoterone cream N = 342** | **Vehicle cream N = 350** | **Clascoterone cream N = 367** | **Vehicle cream N = 362** |
| **IGA Success[a]** | 18.8% | 8.7% | 20.9% | 6.6% |
| *Difference from vehicle* | 10.1% | | 14.3% | |
| *(95% CI)* | (4.1%, 16.0%) | | (8.9%, 19.7%) | |
| **Non-inflammatory lesions count (NILC)** | | | | |
| Mean absolute reduction | 20.4 | 13.0 | 19.5 | 10.8 |
| *Difference from vehicle* | 7.3 | | 8.7 | |
| *(95% CI)* | (3.5, 11.1) | | (4.5, 12.4) | |
| Mean percent reduction | 32.6% | 21.8% | 29.6% | 15.7% |
| *Difference from vehicle* | 10.8% | | 13.8% | |
| *(95% CI)* | (3.9%, 17.6%) | | (7.5%, 20.1%) | |
| **Inflammatory lesions count (ILC)** | | | | |
| Mean absolute reduction | 19.3 | 15.4 | 20.1 | 12.6 |
| *Difference from vehicle* | 3.9 | | 7.5 | |
| *(95% CI)* | (1.3, 6.5) | | (5.2, 9.9) | |
| Mean percent reduction | 44.6% | 36.3% | 47.1% | 29.7% |
| *Difference from vehicle* | 8.3% | | 17.5% | |
| *(95% CI)* | (2.2%, 14.4%) | | (11.8%, 23.1%) | |

[a]Investigator Global Assessment (IGA) success was defined as at least a 2-point reduction in IGA compared to baseline and an IGA score of 0 (clear) or 1 (almost clear).

Among the 641 subjects aged 12 to < 18 years enrolled in phase 3 vehicle-controlled studies for facial acne vulgaris, 316 and 325 subjects were randomized to clascoterone cream and to vehicle, respectively.

Clascoterone cream was superior to vehicle in all the three co-primary endpoints: in the IGA success rate at Week 12 (14.9% vs 3.7%, respectively; Adjusted Odds Ratio [95% CI]: 4.3 [2.2; 8.4]; p-value: < 0.0001), in the absolute change from baseline in NILC at Week 12 (-17.6 vs -11.4, respectively; LS mean difference [95% CI]: -6.2 [-10.6; -1.9]; p-value: 0.0050) and in the absolute change from baseline in ILC at Week 12 (-17.9 vs -12.5, respectively; LS mean difference [95% CI]: -5.4 [-8.2; -2.7]; p-value: 0.0001).

*Children from 9 to < 12 years*

Among the 19 subjects aged 9 to 11 years enrolled in phase 3 vehicle-controlled studies for facial acne vulgaris, 13 and 6 subjects were randomized to clascoterone cream and to vehicle, respectively.
No statistically significant differences between clascoterone cream and vehicle were seen in any of the three co-primary endpoints: in the IGA success rate at Week 12 (15.4% vs 18.0%, respectively; Adjusted Odds Ratio [95% CI]: 0.8 [0.1; 11.8]; p-value: 0.8903), in the absolute change from baseline in NILC at Week 12 (7.3 vs -23.4, respectively; LS mean difference [95% CI]: 30.8 [-17.9; 79.4]; p-value: 0.2155) and in the absolute change from baseline in ILC at Week 12 (-20.6 vs -26.3; LS mean difference [95% CI]: 5.7 [-2.5; 13.9]; p-value: 0.1719).

## 5.2 Pharmacokinetic properties

Adults

*Absorption*

After repeated cutaneous administrations of 4 g to 12 g daily of clascoterone cream 10 mg/g in healthy adults and in adult patients with acne vulgaris for up to 6 consecutive weeks, the systemic exposure was less than 1% of the total administered dose.

No correlation between blood levels and adverse reactions could be established.

Following cutaneous treatment of clascoterone for 2 weeks with a mean dose of approximately 6 g applied twice daily (12 g/day of cream) to adult subjects with moderate to severe acne vulgaris (n=20), systemic concentrations of clascoterone were at steady state by Day 5. On Day 14, the mean ± SD maximum plasma concentrations ($C_{max}$) was 4.5 ± 2.9 ng/mL, the mean ± SD area under the plasma concentration-time over the dosing interval (AUCc) was 37.1 ± 22.3 h*ng/mL and the mean ± SD average plasma concentration ($C_{avg}$) was 3.1 ± 1.9 ng/mL.

*Distribution*

In *in vitro* studies, plasma protein binding of clascoterone was 84% to 89% and was independent of concentrations.

*Biotransformation*

Following cutaneous treatment with clascoterone, the plasma concentrations of cortexolone, the main metabolite of clascoterone, were detectable and generally below or near the lower limit of quantitation (0.5 ng/mL) in subjects with acne vulgaris.

*Elimination*

Excretion of clascoterone has not been fully characterised in humans. Because of the relatively low systemic bioavailability of clascoterone, the effects of renal or hepatic impairment were not evaluated.

Adolescents

In adolescent patients with acne vulgaris aged from 12 to < 18 years (n=22) after 2 weeks of treatment with a mean dose of approximately 4 g of clascoterone cream 10 mg/g applied twice daily (8 g/day), steady-state concentrations of clascoterone were achieved by Day 14. Clascoterone systemic exposure was similar to that observed in adult patients treated with 6 g twice daily.

Elderly

Clinical studies of clascoterone cream did not include sufficient number of subjects 65 years of age and older to determine whether they respond differently from younger subjects.

In vitro studies

*CYP enzymes*

Clascoterone inhibited CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4 with an $IC_{50}$ value of > 40 µM. Clascoterone up to 30 µM did not induce CYP 1A2, 2B6, or 3A4. These findings suggest that clascoterone has no clinically meaningful effect on the PK of substances metabolised by CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4.

### 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity studies.

Clascoterone was negative in an *in vitro* Ames and was aneugenic in an *in vitro* human lymphocyte micronucleus assay with a threshold of 50 mcg/mL, > 10 000 fold higher than the clinical $C_{max}$ reached with supratherapeutic doses.

*In vivo*, in male rats after double subcutaneous administration up to 2000 mg/kg, clascoterone was clastogenic in the micronucleous test, corresponding to > 100 safety margin calculated on the basis of animal versus clinical $C_{max}$ and AUC.

Clascoterone was not carcinogenic after daily topical administration of 0.1, 1 or 5 mg/mL cream (1 mg/g, 10 mg/g, or 50 mg/g) in a 2-year carcinogenicity study in rats. A statistically significant increase in benign sebaceous cell adenoma at the topical application site was observed only in males treated with the highest concentration of 50 mg/g clascoterone cream. An increased incidence of the non-neoplastic finding of atrophy of the skin and subcutis at the application site was reported in males and females treated with 10 mg/g and 50 mg/g clascoterone cream.

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 embryofetal 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 fetuses 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 embryofetal 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.

Environmental risk assessment (ERA)

Based on its endocrine mechanism of action, clascoterone may pose a risk to compartment(s), in particular the aquatic compartment(s).

## 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Cetyl alcohol
Citric acid monohydrate (E330) (for pH-adjustment)
Glycerol monostearate 40-55 Type I
Liquid paraffin
Polysorbate 80
Propylene glycol (E1520)
Purified water
Disodium edetate
all-*rac*-α-tocopherol (E307)

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

3 years

Discard the unused product 1 month after first opening.

## 6.4 Special precautions for storage

Prior to dispensing: store in a refrigerator (2 °C - 8 °C).
Once dispensed to patient: before opening, store in a refrigerator (2 °C – 8 °C). After the first opening, do not store above 25 °C.
Do not freeze.

## 6.5 Nature and contents of container

Epoxy-lined aluminium tube with a polypropylene screw cap.

Pack sizes: tubes of 10 g, 30 g or 60 g.

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal

This medicinal product may pose a risk to the environment (see section 5.3).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

# 7. MARKETING AUTHORISATION HOLDER

Cassiopea S.p.A.
Via C. Colombo, 1
Lainate, 20045
Milan
Italy

# 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1927/001
EU/1/25/1927/002
EU/1/25/1927/003

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

# ANNEX II

**A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Cosmo S.p.A.
Via C. Colombo 1,
20045 Lainate,
Milan, Italy.

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal. The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to 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 or use Winlevi, have access to/are provided with the following educational package:

Checklist for healthcare professionals

The Checklist for healthcare professionals should contain the following key elements:

- HPA-axis suppression:

o Provide clear instruction on correct use of Winlevi (dose, administration schedule and site of application for adult and adolescent, respectively)
o Inform patients about the risk of HPA-axis suppression and advice on signs and symptoms suggestive of this condition
o Monitor patient's adherence to the recommendation on correct use at follow-up visits
o 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:

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

Patient card (provided with each medicine pack)

The Patient Card should contain the following key elements:

– 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 III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Winlevi 10 mg/g cream
clascoterone

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each gram of cream contains 10 mg of clascoterone.

## 3. LIST OF EXCIPIENTS

Cetyl alcohol, citric acid monohydrate (E330), glycerol monostearate 40-55 Type I, liquid paraffin, polysorbate 80, propylene glycol (E1520), purified water, disodium edetate, all-*rac*-α-tocopherol (E307). See leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Cream
1 tube (10 g)
1 tube (30 g)
1 tube (60 g)

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Cutaneous use.
Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Once opened: do not store above 25 °C.

Do not freeze.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Cassiopea S.p.A.
Lainate, 20045
Italy

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1927/001 10 g tube
EU/1/25/1927/002 30 g tube
EU/1/25/1927/003 60 g tube

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Winlevi

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**TUBE**

## 1. NAME OF THE MEDICINAL PRODUCT

Winlevi 10 mg/g cream
clascoterone

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each gram of cream contains 10 mg of clascoterone.

## 3. LIST OF EXCIPIENTS

Cetyl alcohol, citric acid monohydrate (E330), glycerol monostearate 40-55 Type I, liquid paraffin, polysorbate 80, propylene glycol (E1520), purified water, disodium edetate, all-*rac*-α-tocopherol (E307).

## 4. PHARMACEUTICAL FORM AND CONTENTS

Cream
30 g
60 g

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Cutaneous use.
Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Once opened: do not store above 25 °C.
Do not freeze.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Cassiopea S.p.A.
Lainate, 20045
Italy

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1927/002 30 g tube
EU/1/25/1927/003 60 g tube

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

## 17. UNIQUE IDENTIFIER – 2D BARCODE

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**TUBE**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Winlevi 10 mg/g cream
clascoterone
Cutaneous use

## 2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 g

## 6. OTHER

Cassiopea S.p.A.

**PATIENT CARD**

**Patient card for Winlevi 10 mg/g cream**– For women and girls who are able to become pregnant

**Contraception and pregnancy prevention**

What you must know

- Winlevi is a medicine for acne vulgaris.
- Winlevi can harm an unborn child if used during pregnancy.

What you must do

- Read the package leaflet carefully before use.
- Make sure you are not pregnant before starting use of this medicine.
- Use an effective method of contraception (birth control) during your treatment with clascoterone and for at least 10 days after the last clascoterone dose. Your doctor will advise you on the most suitable method for you.
- If you think you have become pregnant, stop using Winlevi and talk to your doctor.

Keep this card for at least 10 days after stopping treatment.

# B. PACKAGE LEAFLET

**Package leaflet: Information for the patient**

**Winlevi 10 mg/g cream**
clascoterone

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**
* Keep this leaflet. You may need to read it again.
* If you have any further questions, ask your doctor.
* This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
* If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What Winlevi is and what it is used for

Winlevi contains the active substance clascoterone that belongs to a group of medicines known as 'anti-acne preparations'.

Winlevi cream is a medicine used in adults and adolescents from 12 years of age and older to treat acne vulgaris. Acne vulgaris is a common skin condition that causes pimples, blackheads, and whiteheads that can affect the face, chest and back. In adolescents the use must be limited to the face only.

The active susbtance in Winlevi, clascoterone, blocks androgen receptors (a type of protein that binds to hormones called androgens). It also counteracts the effects of androgens in sebaceous glands (small glands in the skin that produce an oily substance called sebum) which improves acne vulgaris.

## 2. What you need to know before you use Winlevi

**Do not use Winlevi**
- if you are allergic to clascoterone or any of the other ingredients of this medicine (listed in section 6).
- if you are pregnant.

**Warnings and precautions**
* Talk to your doctor before using Winlevi. Your doctor should start and supervise the treatment.
* Winlevi is for external use only. It should only be applied to the skin.
* Do not use more Winlevi than the prescribed dose.
* Adolescents must apply the cream on the face only.

* Winlevi can cause irritation (for example, dryness, redness, itching or a stinging/burning sensation). In most cases, this is of minimal or mild severity.
* Use caution when applying to this medicine to sensitive areas of the skin, such as the neck. If a reaction in a sensitive area occurs, your doctor may instruct you to stop treatment. You may also apply emollients at least 2 hours before or after the application of Winlevi.
* Do not apply Winlevi to cuts, abrasions, eczema or on sunburnt skin, or to areas affected by inflammatory skin conditions that may coexist with acne (such as, for example, redness (blushing) across your face or red rash around the mouth).
* Do not use this medicine at the same time as photodynamic therapy. Your doctor may tell you to stop taking this medicine before starting photodynamic therapy.
* Do not cover the affected area with additional dressings or bandages, as this increases the risk of experiencing side effects.
* Avoid using this medicine on skin that has been exposed to other treatments, including cosmetic treatments (such as hair removal, chemical peels, dermabrasion or laser resurfacing), until the skin has recovered.
* Wash your hands after applying the cream.
* Avoid getting this medicine in your eyes, on your lips, mouth or corners of the nose, or on the mucous membranes on the inside of your nose and lips. If cream accidentally gets on these areas, rinse well with water.
* Avoid using this medicine at the same time as other cutaneous acne medicines. Using more than one acne medicine at the same time may cause more irritation. If treatment with more than one acne medicine is required, these should be applied or taken with at least 2 hours before or after the application of Winlevi.
* Avoid using skin products that may dry or irritate your skin.
* You may experience adrenal suppression (reduced activity of the adrenal glands, which produce a stress hormone called cortisol) as an undesirable effect of Winlevi during treatment. If you use Winlevi over large areas of your skin for a long time or if you cover the area with a bandage or dressing, this can increase the risk of developing adrenal suppression. If you develop one or more of the following symptoms, which are otherwise unexplained and do not get better, this may indicate adrenal suppression, and you should contact your doctor right away:
    * feeling tired,
    * weight loss,
    * decreased appetite,
    * low blood pressure,
    * feeling sick (nausea),
    * diarrhoea,
    * vomiting,
    * belly (abdominal) pain,
    * low blood glucose levels (hypoglycaemia),

  Your doctor could consider to test your blood cortisol levels and refer you to endocrinologist evaluation in the presence of signs or symptoms suggestive of adrenal suppression.
* Your doctor will monitor your condition and may stop or change the treatment if necessary. Regular follow-up is important, especially during long-term use.

If you experience a reoccurrence (worsening) of acne in previously treated areas within days to weeks from treatment interruption, this may represent an exacerbation of acne due to the product (rebound). Do not re-treat the area without consulting a doctor.

If you are not sure about any of the warnings and precautions, you should discuss with your doctor.

**Children and adolescents**
This medicine is only for use in adolescents 12 years and over. Do not give this medicine to children under 12 years because no benefit of the medicine was seen in this age group.

**Other medicines and Winlevi**
Tell your doctor if you are using, have recently used or might use any other medicines.

**Pregnancy and breast-feeding**
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Winlevi may harm an unborn baby. If you're pregnant, do not use Winlevi. If you could become pregnant, you have to use effective contraception (birth control) while using Winlevi and for at least 10 days after stopping the treatment. You should talk to your doctor about which contraception method is right for you while you are taking Winlevi.

Your pregnancy status should be verified before starting the treatment.

It is not known if the active substance in Winlevi, clascoterone, or its by-products can be passed into breast milk. This means there may be a risk to the baby if you use Winlevi while breast-feeding. You should stop breast-feeding during treatment.

A patient card is provided with the Winlevi package to remind you of clascoterone risks in pregnancy.

**Driving and using machines**
Winlevi has no or negligible influence on the ability to drive and use machines.

**Winlevi contains cetyl alcohol.**
Cetyl alcohol may cause local skin reactions (e.g. contact dermatitis).

**Winlevi contains propylene glycol.**
Propylene glycol may cause skin irritation. Because this medicine contains propylene glycol, do not use it on open wounds or large areas of broken or damaged skin (such as burns).

## 3. How to use Winlevi

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

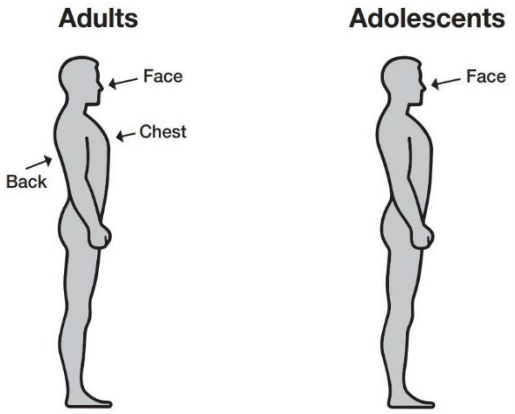
A thin and even layer of the cream should be applied twice a day, once in the morning and once in the evening. Adolescents must apply the cream on the face only. Ensure that you wait at least 8 hours between each application.

Before applying this cream, gently wash and dry the affected skin area. Apply a thin, even layer of cream to the affected area, massaging gently. Two (2) fingertip units of cream (which correspond to about 1 g) will cover an area of about 28 x 22 cm (approximately 600 $cm^2$) that corresponds to the average surface area of the face. A fingertip unit is the amount of cream squeezed out from a tube along the length of an adult's index finger, from the first finger crease to the tip. One fingertip unit dose is about 0.5 g of cream.


The cream must be applied to the entire affected area, and not to the acne lesions only.

Avoid applying the cream to the eyes, eyelids, lips and nostrils. Wash your hands after applying the cream. Do not cover the affected area with additional dressings or bandages, as this increases the risk of experiencing side effects.

In adults Winlevi can be applied to the face, chest and/or back. The daily dose should not exceed 10 fingertip units (about 5 g).
In adolescents Winlevi must be applied to the face only. The daily dose should not exceed 4 fingertip units (about 2 g). No more than one 60 g a month (corresponding to one 60 g tube or two 30 g tubes) should be used.




Apply other skin medicines or cosmetic products, such as moisturisers or sunscreens, with a minimum gap of 2 hours before or after you use Winlevi.

Your doctor will tell you how long you will need to use Winlevi. After three months of treatment, your doctor may need to assess if or how much your acne has improved. After that, your doctor will reassess regularly (every three months) if you should continue treatment.
If you are an adolescent, your doctor may decide to schedule a visit earlier than three months.

**If you use more Winlevi than you should**
If you use Winlevi over large areas of your skin for a long time or if you cover the area with a bandage or dressing, this can increase the risk of developing side effects including adrenal suppression (see sections 2 and 4).

**If you forget to use Winlevi**
Wait for at least eight (8) hours between applications.
Do not apply a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor.

## 4. Possible side effects

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

In some cases, laboratory tests may show lower-than-normal levels of a stress hormone called cortisol. This usually does not cause any symptoms and returns to normal within few weeks after stopping treatment.
There is a possibility that specific symptoms may develop such as: feeling tired, weight loss, decreased appetite, feeling sick (nausea), diarrhoea, vomiting, belly (abdominal) pain, low blood glucose levels (hypoglycemia).
See section 2 “Warnings and precautions” for information on what to do if you experience such symptoms.

Application site reactions such as redness, peeling, dryness, itching, stinging/burning of the skin, may be experienced with the use of Winlevi. See section 2 “Warnings and precautions” for information on what to do if you experience such symptoms.

Winlevi may cause the following side effects:

**Common** (may affect up to 1 in 10 people)
- Application site pain, dryness, redness, and excessive hair growth
- Lower-than-normal levels of a stress hormone called cortisol

**Rare** (may affect up to 1 in 1 000 people)
- Hypersensitivity (allergic reactions) at the site of application,
- Acne
- Itchy, blistered, dry and cracked skin (dermatitis contact)
- Headache
- Inflammation of hair follicles (folliculitis) at the site of application
- Sore throat (oropharyngeal pain)

**Reporting of side effects**
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Winlevi

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and tube after EXP. The expiry date refers to the last day of that month.

Discard the unused product 1 month after first opening.

Store in a refrigerator (2 °C – 8 °C). Once opened: do not store above 25 °C. Do not freeze.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What Winlevi contains**
- The active substance is clascoterone.
- The other ingredients are cetyl alcohol, citric acid monohydrate (E330) (for pH-adjustment), glycerol monostearate 40-55 Type I, liquid paraffin, polysorbate 80, propylene glycol (E1520), purified water, disodium edetate, all-rac-α-tocopherol (E307). See section 2. Winlevi contains cetyl alcohol. Winlevi contains propylene glycol.

**What Winlevi looks like and contents of the pack**
Winlevi is a white to almost white cream.

Winlevi is available in tubes containing 10 g, 30 g or 60 g of cream. There is one tube per carton. Not all pack sizes may be marketed.

**Marketing Authorisation Holder**
Cassiopea S.p.A.

Via C. Colombo, 1
Lainate, 20045
Milan
Italy

**Manufacturer**
Cosmo S.p.A.
Via C. Colombo, 1
Lainate, 20045
Milan
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**BE, BG, CY, EE, HR, IE, LT, LU, LV, MT, SI**
Cassiopea S.p.A.
Italy
info@cassiopea.com

**Česká republika**
Glenmark Pharmaceuticals s.r.o.
Tel: + 420 227 629 511
recepce@glenmarkpharma.com

**DK, FI, IS, NO, SE**
Glenmark Pharmaceuticals Nordic AB
Sweden
Tlf./Puh/Tel/Sími: + 46 40 35 48 10
info@glenmarkpharma.se

**AT, DE**
INFECTOPHARM Arzneimittel und Consilium GmbH
Germany
Tel: + 49 6252 957000
kontakt@infectopharm.com

**España**
Glenmark Farmacéutica, S.L.U.
Tel: + 34 911 593 944
infospain@glenmarkpharma.com

**France**
Laboratoires Bailleul
Tél: + 33 (0)1 56 33 11 11
vigilance-reclamation@bailleul.com

**Ελλάδα**
IASIS PHARMA
Τηλ: + 30 210 2311031
iasis@iasispharma.gr

**Magyarország**
Mediner Kft.
Tel.: +36 52 535 708
info@mediner.hu

**Italia**
InfectoPharm S.r.l.
Tel: + 39 02 007066 1
info-ita@infectopharm.com

**Nederland**
Glenmark Pharmaceuticals BV
Tel: + 31 (0)8003355533
nlinfo@glenmarkpharma.com

**Polska**
Glenmark Pharmaceuticals Sp. z o. o.
Tel.: + 48 22 35 12 500
poland.receptionist@glenmarkpharma.com

**Portugal**
Laboratório Medinfar - Produtos Farmacêuticos
Tel: + 351 214 997 461
medinfar@medinfar.pt

**România**
IASIS PHARMACEUTICALS SRL
Tel.: +40 720 536008
iasis@iasispharma.ro

**Slovenská republika**
Glenmark Pharmaceuticals SK, s.r.o.
Tel: + 421 2 20 255 041
info-sk@glenmarkpharma.com

**This leaflet was last revised in**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.