▼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.

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Klisyri 10 mg/g ointment

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of ointment contains 10 mg of tirbanibulin.
Each sachet contains 2.5 mg of tirbanibulin in 250 mg ointment.

Excipient with known effect:

Each gram of ointment contains 890 mg of propylene glycol (E1520).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ointment
White to off-white ointment.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Klisyri is indicated for the field treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis (Olsen grade 1) of the face or scalp in adults.

4.2 Posology and method of administration

Posology

Tirbanibulin ointment should be applied to the affected field on the face or scalp once daily for one treatment cycle of 5 consecutive days. A thin layer of ointment should be applied to cover the treatment field of up to 25 cm^2.

If a dose is missed, the patient should apply the ointment as soon as he/she remembers and then he/she should continue with the regular schedule. However, the ointment should not be applied more than once a day.

Tirbanibulin ointment should not be applied until the skin is healed from treatment with any previous medicinal product, procedure or surgical treatment and should not be applied to open wounds or broken skin (see section 4.4).

Therapeutic effect can be assessed approximately 8 weeks after treatment starts. If the treated area does not show complete clearance at the follow-up examination, about 8 weeks after the treatment cycle started or thereafter, the treatment should be re-evaluated and management re-considered.

No clinical data on treatment for more than 1 treatment course of 5 consecutive days are available (see section 4.4). If recurrence occurs, or new lesions develop within the treatment area, other treatment options should be considered.

Special populations

Hepatic or renal impairment

Tirbanibulin has not been studied in patients with renal or hepatic impairment. Based on clinical pharmacology and *in vitro* studies, no dose adjustments are needed (see section 5.2).

Elderly population

No dose adjustment is required (see section 5.1).

Paediatric population

There is no relevant use of Klisyri in the paediatric population for the indication of actinic keratosis.

Method of administration

Tirbanibulin ointment is for external use only. Contact with eyes, lips, and the inside of nostrils or ears should be avoided.

Each sachet is for single use only and should be discarded after use (see section 6.6).

Treatment should be initiated and monitored by a physician.

Before applying tirbanibulin, patients should wash the treatment field with mild soap and water and dry it. Some ointment from 1 single-use sachet should be squeezed onto a fingertip and a thin layer applied evenly over the entire treatment field of up to a maximal treatment area of 25 cm^2.

The ointment should be applied at approximately the same time each day. The treated area should not be bandaged or otherwise occluded. Washing and touching of the treated area should be avoided for approximately 8 hours after application of tirbanibulin. After this period, the treated area may be washed with mild soap and water.

Hands should be washed with soap and water before and immediately after application of the ointment.

Tirbanibulin ointment is for application on the face or scalp. For information on incorrect route of administration, see section 4.4.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Incorrect route of administration

Contact with the eyes should be avoided. Tirbanibulin ointment may cause eye irritation. In the event of accidental contact with the eyes, the eyes should be rinsed immediately with large amounts of water, and the patient should seek medical care as soon as possible.

Tirbanibulin ointment must not be ingested. If accidental ingestion occurs, the patient should drink plenty of water and seek medical care.

Tirbanibulin ointment should not be used on the inside of the nostrils, on the inside of the ears, or on the lips.

Application of tirbanibulin ointment is not recommended until the skin is healed from treatment with any previous medicinal product, procedure or surgical treatment and should not be applied to open wounds or broken skin where the skin barrier is compromised (see section 4.2).

Local skin reactions

Local skin reactions in the treated area, including erythema, flaking/scaling, crusting, swelling, erosion/ulceration, and vesiculation/pustulation, may occur

after topical application of tirbanibulin ointment (see section 4.8). Treatment effect may not be adequately assessed until resolution of local skin reactions.

Sun exposure

Due to the nature of the disease, excessive exposure to sunlight (including sunlamps and tanning beds) should be avoided or minimised.

Immunocompromised patients

Tirbanibulin ointment should be used with caution in immunocompromised patients.

Risk of progression to skin cancer

Changes in the appearance of actinic keratosis could suggest progression to invasive squamous cell carcinoma. Clinically atypical lesions for actinic keratosis or suspicious for malignancy should be appropriately managed.

Propylene glycol

This medicine contains 222.5 mg propylene glycol in each sachet which is equivalent to 890 mg/g.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Given the route of administration (topical), the short duration of dosing (5 days), the low systemic exposure (subnanomolar mean C_{max}), and the *in vitro* data, there is low potential for interaction with tirbanibulin ointment at maximum clinical exposure.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of tirbanibulin in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Tirbanibulin ointment is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is unknown whether tirbanibulin/metabolites are excreted in human milk.

A risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from tirbanibulin ointment therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

No human data on the effect of tirbanibulin ointment on fertility are available. In a non-clinical fertility and early embryonic development study in rats, changes considered indicative of male fertility toxicity occurred (see section 5.3).

4.7 Effects on ability to drive and use machines

Klisyri 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 reported adverse reactions are local skin reactions. Local skin reactions included erythema (91 %), flaking/scaling (82 %), crusting (46 %), swelling (39 %), erosion/ulceration (12 %), and vesiculation/pustulation (8 %) at the application site. Furthermore, application site pruritus (9.1 %) and pain (9.9 %) have been reported in the treatment area.

Tabulated list of adverse reactions

Table 1 lists the adverse reactions that were reported in clinical studies. Frequencies are defined as: very common (≥ 1/10*);* common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (frequency cannot be estimated from the available data).

Table 1: Adverse reactions

MedDRA System Organ Class	Preferred term	Frequency
General disorders and administration site conditions	Application site erythema	Very common
	Application site exfoliation (flaking and scaling)	Very common
	Application site scab (crusting)	Very common
	Application site swelling	Very common
	Application site erosion (includes ulcer)	Very common
	Application site pain[a]	Common
	Application site pruritus	Common
	Application site vesicles (includes pustules)	Common

a) Application site pain includes pain, tenderness, stinging, and burning sensation at the application site.

Description of selected adverse reactions

Local skin reactions
Most local skin reactions were transient and mild to moderate in severity. Following the application of tirbanibulin ointment, the incidences of local skin reactions with a severity grade greater than baseline were erythema (91 %), flaking/scaling (82 %), crusting (46 %), swelling (39 %), erosion/ulceration (12 %), and vesiculation/pustulation (8 %). Severe local skin reactions occurred at an overall incidence of 13 %. Severe local skin reactions that occurred at an incidence >1 % were: flaking/scaling (9 %), erythema (6 %), and crusting (2 %). None of the local skin reactions required treatment.

Overall, local skin reactions peaked 8 days after starting the treatment and typically resolved within 2 to 3 weeks after completion of treatment with tirbanibulin ointment.

Site pruritus and pain
Events of application site pruritus and pain were mild to moderate in severity, transient in nature (mostly occuring during the first 10 days since the start of treatment), and the majority did not require treatment.

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 Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Overdose following topical application with tirbanibulin ointment may cause an increase in incidence and severity of local skin reactions. No systemic signs of overdose are expected following topical application of tirbanibulin ointment due to the low systemic absorption of tirbanibulin. Management of overdose should consist of treatment of clinical symptoms.

For information on incorrect routes of administration, see section 4.4.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibiotics and chemotherapeutics for dermatological use, other chemotherapeutics, ATC code: D06BX03

Mechanism of action

Tirbanibulin disrupts microtubules by direct binding to tubulin, which induces cell cycle arrest and apoptotic death of proliferating cells, and is associated with disruption of Src tyrosine kinase signalling.

Clinical efficacy and safety

The efficacy and safety of tirbanibulin applied on the face or scalp for 5 consecutive days was studied in 2 pivotal randomised, double-blind, vehicle-controlled Phase III studies (KX01-AK-003 and KX01-AK-004) including 702 adult patients (353 patients treated with tirbanibulin and 349 patients treated with vehicle).

Patients had 4 to 8 clinically typical, visible, discrete, non-hyperkeratotic, non-hypertrophic, actinic keratosis lesions within a contiguous 25 cm^2 treatment field on the face or scalp. On each scheduled dosing day, the ointment was applied to the entire treatment field. In the tirbanibulin group, the mean age was 69 years (range 46 to 90 years) and 96 % of patients had Fitzpatrick skin type I, II, or III. Efficacy, measured as complete (primary endpoint) and partial clearance rate, was assessed at day 57.

At day 57, patients treated with tirbanibulin had statistically significantly higher complete and partial clearance rates than patients treated with vehicle ($p< 0.0001$)(see Table 2). Efficacy was less in scalp lesions compared to facial lesions, though still statistically significant (see Table 3).

Table 2: Complete and partial clearance rates at day 57, ITT population (pooled data KX01-AK-003 and KX01-AK-004)

	Overall (face and scalp)	
	Tirbanibulin 10 mg/g ointment (N=353)	**Vehicle (N=349)**
Complete (100%) clearance rate[a]	49%[c]	9%
Partial (≥75%) clearance rate[b]	72%[c]	18%

ITT=Intent-to-Treat

a) Complete clearance rate was defined as the proportion of patients with no (zero) clinically visible actinic keratosis lesions in the treatment field.
b) Partial clearance rate was defined as the percentage of patients in whom 75 % or more of the number of baseline actinic keratosis lesions in the treatment field were cleared.
c) $p< 0.0001$; compared to vehicle by Cochran-Mantel-Hansel stratified by anatomical location and study.

Table 3: Complete and partial clearance rates at day 57 by anatomical location, ITT population (pooled data KX01-AK-003 and KX01-AK-004)

Location		Complete (100%) Clearance Rate		Partial (≥75%) Clearance Rate	
		Tirbanibulin 10 mg/g ointment (N=353)	**Vehicle (N=349)**	**Tirbanibulin 10 mg/g ointment (N=353)**	**Vehicle (N=349)**
Face	n/N	133/238	23/239	185/238	49/239
	% (95% CI)	56% (49% - 62%)[a]	10% (6% - 14%)	78% (72% - 83%)[a]	21% (16% - 26%)
Scalp	n/N	41/115	7/110	70/115	14/110
	% (95% CI)	36% (27% - 45%)[a]	6% (3% - 13%)	61% (51% - 70%)[a]	13% (7% - 20%)

CI=confidence interval; ITT=Intent-to-Treat

a) $p<0.0001$; compared to vehicle by Cochran-Mantel-Haenszel stratified by study.

In the individual studies, total and partial clearance rates at day 57 (the primary and key secondary endpoints in these studies) were statistically significantly higher in the group treated with tirbanibulin compared with the vehicle group ($p\leq0.0003$), both overall and by treatment location (face or scalp).

Long-term efficacy

A total of 204 patients achieved complete clearance of actinic keratosis lesions in the treatment field at day 57 (174 treated with tirbanibulin and 30 treated with vehicle) and were eligible for a 1-year follow-up period for safety monitoring and to evaluate sustained efficacy by assessing actinic keratosis lesions in the treatment field.

After one year, the recurrence rate in patients treated with tirbanibulin was 73 %. There was a higher recurrence rate for scalp lesions compared to facial lesions. Of the patients who developed recurrences, 86 % had either 1 or 2 lesions. Furthermore, 48 % of patients developing recurrences reported at least 1 lesion that was not identified at the time of the initial treatment (i.e., newly occurring lesions counted as recurrences).

Risk of progression to squamous cell carcinoma (SCC)
By day 57, there were no reports of SCC in the treatment field in patients treated with tirbanibulin (0 of 353 patients) or vehicle (0 of 349 patients). One isolated SCC in the treatment field was reported in 1 patient following the day 57 assessment; this event was considered by the investigator not to be related to treatment with tirbanibulin.

Elderly population

Of the 353 patients treated with tirbanibulin in the 2 randomised, double-blind, vehicle-controlled Phase III studies conducted, 246 patients (70 %) were 65 years of age or older. No overall differences in safety or efficacy were observed between younger and older patients.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Klisyri in all subsets of the paediatric population in the treatment of actinic keratosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Tirbanibulin ointment was minimally absorbed in 18 patients with actinic keratosis after topical application once daily for 5 consecutive days over an area of 25 cm^2. Tirbanibulin plasma concentrations were low at steady state (mean maximum concentration [C_{max}] of 0.258 ng/mL or 0.598 nM and AUC_{0-24h} of 4.09 ng·h/mL).

Distribution

The protein binding of tirbanibulin to human plasma proteins is approximately 88 %.

Biotransformation

In vitro, tirbanibulin is mainly metabolised by CYP3A4, and to a lesser degree by CYP2C8. The main metabolic pathways are N-debenzylation and hydrolysis reactions. The most relevant metabolites were characterised in patients with actinic keratosis in a maximal use pharmacokinetic study and showed minimal systemic exposure.

In vitro studies show that tirbanibulin does not inhibit or induce cytochrome P450 enzymes and it is not an inhibitor of efflux and uptake transporters at maximum clinical exposures.

Elimination

Elimination of tirbanibulin has not been fully characterized in humans.

Hepatic and renal impairment
No formal studies of tirbanibulin ointment in patients with hepatic or renal impairment have been conducted. Due to the low systemic exposure to tirbanibulin after topical application of tirbanibulin ointment once daily for

5 days, changes in hepatic or renal function are unlikely to have any effect on the elimination of tirbanibulin. Therefore, no dose adjustments are considered needed (see section 4.2).

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. Tirbanibulin was a moderate contact sensitiser in animals but this was not confirmed in humans.

Tirbanibulin was not mutagenic but induced chromosomal damage and micronuclei in genotoxicity studies. Detailed testing suggested that tirbanibulin is clastogenic/aneugenic and associated with a threshold, below which there is no induction of genotoxic events. *In vivo*, genotoxicity occurred at plasma levels > 20 times higher than the human exposure in the maximal use pharmacokinetic study.
In embryo-foetal development studies in rats and rabbits, embryonic and foetal toxicity, including foetal malformations, occurred at multiples of 22 times and 65 times greater than human exposure in the maximal use pharmacokinetic human study. In a pre- and postnatal development study in rats, reductions in fertility and increased embryo-foetal lethality were seen in the offspring of treated females.

In a fertility and early embryonic development study in rats, decrease in testes weight which correlated with decreased sperm count, decreased sperm motility, increased incidences of abnormal sperm, and increased incidence of degeneration of the seminiferous epithelium, considered indicative of male fertility toxicity, occurred at multiples of 58 times greater than human exposure in the maximal use pharmacokinetic human study. However, there were no changes in male mating or fertility indices.

6.1 List of excipients

Propylene glycol (E1520)
Glycerol monostearate 40-55

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not refrigerate or freeze.

6.5 Nature and contents of container

Sachets with an inner layer of linear low-density polyethylene. Each sachet contains 250 mg of ointment.

Packs of 5 sachets.

6.6 Special precautions for disposal

Sachets should be discarded after first use.

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

7 MARKETING AUTHORISATION HOLDER

Almirall, S.A.

Ronda General Mitre, 151

08022 Barcelona

Spain

8. MARKETING AUTHORISATION NUMBER

PLGB 16973/0043

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02/04/2026

10 DATE OF REVISION OF THE TEXT

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