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

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.

Excipients with known effects:
Propylene glycol 890 mg/g ointment

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 25cm^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

Propylene glycol may cause skin irritation.

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

Tirbanibulin ointment 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 national reporting system listed in Appendix V.

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. PHARMACOLOGICAL PROPERTIES

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≤0.0003), 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. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol
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(S)

EU/1/21/1558/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 July 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://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 RESPONSIBLE FOR BATCH RELEASE

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

Almirall Hermal GmbH
Scholtzstrasse 3
21465 Reinbek
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

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.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measure:

Description	Due date
Post-authorisation safety study (PASS): In order to further investigate the risk of progression of actinic keratosis (AK) to squamous cell carcinoma (SCC) in adult patients with non-hyperkeratotic, non-hypertrophic actinic keratosis (AK) treated with tirbanibulin, the MAH should conduct and submit the results of the phase 4, multi-centre, randomized, investigator-blinded, active-controlled, parallel-group study M-14789-41 conducted according to an agreed protocol.	Q4 2027

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF 10 mg/g OINTMENT

1. NAME OF THE MEDICINAL PRODUCT

Klisyri 10 mg/g ointment
tirbanibulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Propylene glycol
Glycerol monostearate 40-55

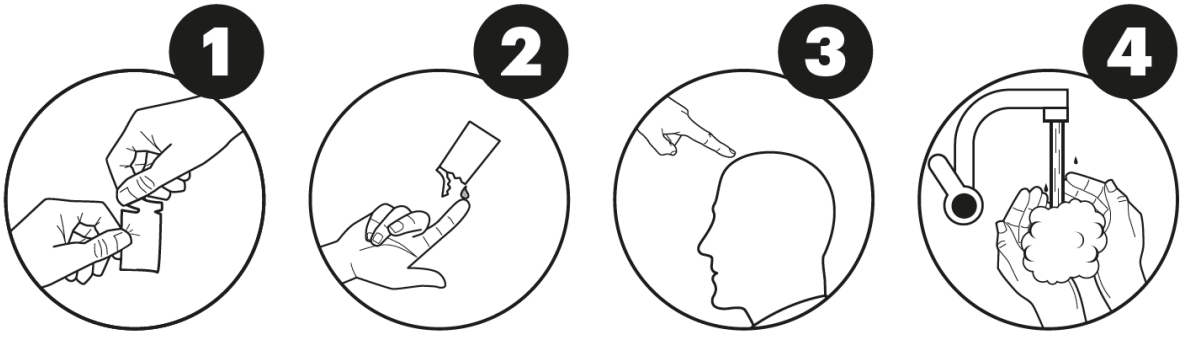
4. PHARMACEUTICAL FORM AND CONTENTS

Ointment
5 sachets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Cutaneous use
Read the package leaflet before use.
For single use only. Discard the sachet after use.

To be printed on the inside of the carton lid:



Open the sachet
Squeeze some ointment onto your fingertip
Apply the ointment to the affected area
Wash your hands
See package leaflet for further information.

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

Do not refrigerate or 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

Almirall, S.A.
Ronda General Mitre, 151
08022 Barcelona
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1558/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

klisyri

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET

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

Klisyri 10 mg/g ointment
tirbanibulin
Cutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

250 mg

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Klisyri 10 mg/g ointment
tirbanibulin

▼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 or pharmacist.
- 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 or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Klisyri is and what it is used for

Klisyri contains the active substance tirbanibulin. It is used for the treatment of mild actinic keratosis in adults. Actinic keratosis is a rough area of skin that has developed in people who have been exposed to too much sunshine over a long time. Klisyri should only be used for flat actinic keratosis on the face and scalp.

2. What you need to know before you use Klisyri

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

Warnings and precautions
Talk to your doctor or pharmacist before using Klisyri
- Do not use Klisyri until the area to be treated has healed from any previous medicine, procedure or surgical treatment. Do not apply Klisyri on open wounds or broken skin.
- Wash your hands if you happen to touch the area where you applied the ointment.
- Do not get Klisyri in your eyes. If it accidentally gets in your eye, rinse the eye thoroughly with plenty of water, seek medical assistance as soon as possible and take this leaflet with you.
- Do not apply the ointment internally, to the inside of the nostrils, the inside of the ear or on the lips. If the ointment accidentally touches any of these areas, wash it off by rinsing with water.
- Do not swallow this medicine. Drink plenty of water if you accidentally swallow this medicine, seek medical assistance and take this leaflet with you.
- Tell your doctor if you have problems with your immune system.
- Watch for any new scaly red patches, open sores, and raised or warty growths around the treatment area. If you see any, talk to your doctor immediately.

- After using Klisyri, avoid activities that might cause excessive sweating, and avoid exposure to sunlight as much as possible (including sunlamps and tanning beds). When outdoors, wear protective clothing and a hat.
- Do not cover the treated area with bandages after using Klisyri.
- Do not apply more ointment than your doctor has advised.
- Do not apply the ointment more than once a day.
- Do not allow other people or pets to touch the treated area for around 8 hours after applying the ointment. If the treated area is touched, the area of contact on the other person or pet should be washed.
- Contact your doctor if you get skin reactions to this medicine in the treated area that get severe (see section 4).

Children and adolescents
Do not give this medicine to children and adolescents under 18 years of age because they do not get actinic keratosis.

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

If you have previously used Klisyri or similar medicines, tell your doctor before starting the treatment.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
Klisyri should not be used during pregnancy.

Driving and using machines
This medicine is not expected to have any effect on your ability to drive or to use machines.

Klisyri contains propylene glycol
Propylene glycol may cause skin irritation

3. How to use Klisyri

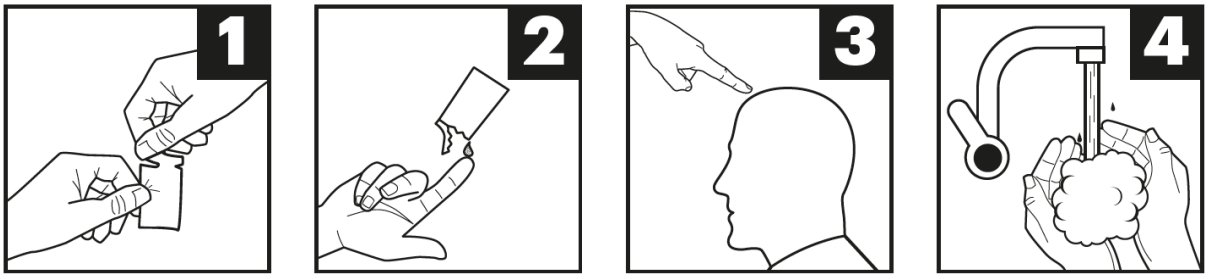
Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

This medicine is intended to treat an area of up to 25 cm^2 for only one treatment course of five days. If the treated area does not show complete clearance at about 8 weeks after the treatment cycle started, or new lesions develop within the treatment area, the treatment should be reconsidered by your doctor and other treatment options should be considered.

Apply a thin layer of Klisyri to the affected area on the face or scalp once daily for 5 days in a row. One sachet contains enough ointment to cover the treatment area. Do not save the opened sachet for use on another day, even if there is still ointment left.

Application instructions:
1. Wash your hands with soap and water before applying the ointment.
2. Wash the affected area with mild soap and water and dry it gently.
3. Open a new sachet each time you apply this medicine.
4. Open the sachet along the perforations (Figure 1).
5. Squeeze some ointment onto your fingertip (Figure 2).
6. Apply a thin layer of ointment evenly over the entire affected area (Figure 3).
7. Wash your hands with soap and water immediately after applying the ointment (Figure 4).
8. Do not wash or touch the treated area for about 8 hours. After this time, you may wash the treated area with mild soap and water.
9. Do not cover the treated area with bandages after you have applied Klisyri.

10. Repeat the above steps for each day of treatment at around the same time of the day.



If you use more Klisyri than you should
Wash the treated area with mild soap and water. Please contact your doctor or pharmacist if you get severe skin reactions.

If you forget to use Klisyri
If you miss a dose, apply the ointment as soon as you remember and then continue with your regular schedule. Do not apply the ointment more than once a day.

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

4. Possible side effects

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

After using this medicine, you may get side effects on the skin where you apply the ointment. These side effects may get worse for up to 8 days after you start the treatment, and they typically go away within 2 to 3 weeks after completing the treatment. Contact your doctor if these side effects get severe.

The most frequently occurring side effects in the treated area:

Very common (may affect more than 1 in 10 people)
- redness (erythema)
- skin scaling (flaking)
- scabs (crusting)
- swelling
- loss of the top layer of skin (erosion, ulcer)

Other possible side effects in the treated area:

Common (may affect up to 1 in 10 people)
- pain (tender, stinging, or burning feeling)
- itching (pruritus)
- blisters (vesicles, pustules)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. 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 Klisyri

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

Do not refrigerate or freeze.

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

For single use only. Do not re-use the sachets once opened.

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 Klisyri contains
- The active substance is tirbanibulin. Each sachet contains 2.5 mg of tirbanibulin in 250 mg ointment. Each gram of ointment contains 10 mg of tirbanibulin.
- The other ingredients are propylene glycol and glycerol monostearate 40-55.

What Klisyri looks like and contents of the pack
Each Klisyri sachet contains 250 mg of white to off-white ointment.
Each box contains 5 polyethylene/aluminium foil sachets.

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