EU Risk Management Plan for

Klisyri 10 mg/g Ointment (Tirbanibulin)

RMP version to be assessed as part of this application:

RMP Version number:	1.1
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QPPV name:

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QPPV oversight declaration:

The content of this RMP has been reviewed and approved by the marketing authorisation Almirall's QPPV. The electronic signature is available on file.

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Part I: Product(s) overview

Table Part I.1: Product Overview

Active substance(s) **(INN or common name)**	Tirbanibulin
Pharmacotherapeutic group(s) (ATC Code)	Pharmacotherapeutic group: not yet assigned (ATC code: not yet assigned)
Marketing Authorisation Applicant	Almirall, S.A.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Klisyri
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Synthetic inhibitor of tubulin polymerisation
	Summary of mode of action: Tirbanibulin has potent anti-proliferative and anti-tumour activities *in vitro* and *in vivo* by virtue of its ability to induce cell cycle arrest and apoptotic cell death. Tirbanibulin is able to disrupt the cellular microtubule network via direct binding to tubulins, and is associated with disruption of Src tyrosine kinase signalling.
	Important information about its composition: The finished drug product is a white to off-white ointment containing the active drug substance, tirbanibulin, and the excipients, propylene glycol and glycerol monostearate 40-55.

Hyperlink to the Product Information	Tirbanibulin product information (Summary of Product Characteristics [SmPC]; label; package leaflet)
Indication(s) in the EEA	Current: N/A
	Proposed: Topical field treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis (AK) of the face or scalp in adults.
Dosage in the EEA	Current: N/A
	Proposed: Tirbanibulin 10 mg/g 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.
Pharmaceutical form(s) and strengths	Current: N/A
	Proposed: Each gram of ointment contains 10 mg of tirbanibulin.
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

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

Indication

Tirbanibulin 10 mg/g ointment is indicated for the topical field treatment of non-hyperkeratotic, non-hypertrophic AK of the face or scalp in adults.

- **Incidence and prevalence:**

  AK is an ultra-violet (UV) light-induced pre-cancerous lesion of the skin that represents the initial intra-epidermal manifestation of abnormal keratinocyte proliferation (Röwert-Huber, 2007; Fernandez Figueras, 2017). AK presents as erythematous, scaly patches on the skin of the face, scalp and extremities and can occur as a single lesion ormultiple lesions or as an entire field ("field cancerisation"), such as sun exposed areas onthe forehead or the back of the hand (Dodds, 2014; Figueras Nart, 2018).

  In Europe, the prevalence of AK ranges from 33% to 49% in males and 14% to 28% in females, depending on the country and the study population (Table SI.1). The prevalence of AK was consistent between countries and increased with age (Flohil, 2013).

Table SI.1: Prevalence of Actinic Keratosis in European Countries

Country	Reference	Prevalence		Study population
		Males	Females	
Austria	Eder, 2014	39%	24%	Dermatology outpatients
Germany	Tizek, 2019	41%	14%	Un-referred population at the Munich Oktoberfest
Italy	Fargnoli, 2017	34%	20%	Patients attending dermatology clinics
the Netherlands	Flohil, 2013	49%	28%	Participants ≥45 years of age
Spain	Ferrándiz, 2016	38%	21%	Patients attending dermatology clinics
Switzerland	Dziunycz, 2018	33%	19%	Patients attending general practitioners

- **Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:**

  Risk factors for the development of AK include older age, male gender, fair skin type, chronic UV exposure, outdoor occupations, history of AK or skin cancer, and concomitant immunosuppression (Flohil, 2013; Werner, 2015; Ferrándiz, 2016; Salmon, 2016; Fargnoli, 2017; Dziunycz, 2018; Schmitz, 2018; Tizek, 2019). Akdeniz et al. found that nearly every fifth nursing home resident in Berlin was affected by actinic keratosis (Akdeniz, 2019). AK was most strongly associated with male sex, probably because of the increased prevalence of alopecia in elderly males.

  In Fargnoli et al., AK was more frequent in patients with Fitzpatrick skin phototypes I-II (55% of patients) than in patients with skin phototypes III-IV (43% of patients) (Fargnoli, 2017). In Ferrándiz et al., the most frequent Fitzpatrick skin phototype in patients with AK was phototype II (45.7%), followed closely by phototype III (43.6%) (Ferrándiz, 2016). These data indicate that Fitzpatrick skin phototypes I-II are risk factorsfor the development of AK.

- **The main existing treatment options:**

  Currently, there is no standard of care for the treatment of AK lesions in the EU. The appropriate treatment is generally chosen based on the number of lesions present and therapy may be broadly categorised as either lesion-directed or field-directed. Lesion-directed treatments include physical modalities such as cryotherapy, laser, curettage, and ablative treatments. Cryotherapy is the recommended first-line lesion-directed treatment, followed by curettage (Werner, 2015; Fleming, 2017). Lesion-directed treatments are effective for clearing single lesions; however, they do nottarget underlying actinic changes in the surrounding skin (Cerio, 2017; Stockfleth, 2017).Field-directed therapies such as photodynamic therapy (PDT) and topical therapies, target visible and non-visible lesions and are used to treat multiple lesions on larger skinareas (Hofbauer, 2014; Stockfleth, 2015; Dirschka, 2017; Stockfleth, 2016; Werner, 2015; de Berker, 2017).

  Early diagnosis and treatment are key for minimising disease progression and severity of AK. The goals of AK treatment are to cure the lesions, clinically and histologically, minimise pain and adverse events, and reduce recurrence (Hofbauer, 2014;

Dirschka, 2017; Cerio, 2017). Considerations related to the patient's lifestyle, competence, and attitude toward treatment influences the treatment decision. Because AK is a visible marker of damage caused by chronic UV radiation exposure, the Swiss Registry of Actinic Keratosis Treatment Working Group recommended field-directed therapy as the optimal treatment approach for most patients (Hofbauer, 2014).

In clinical practice, cryotherapy is the most frequently used treatment overall, except in instances of severe actinic damage, in which PDT is the first-choice treatment (Erlendsson, 2016). PDT is recommended as the first-line treatment for patients with multiple AKs, according to an international consensus (Fleming, 2017). In cases where AKs are hyperkeratotic, the use of combination treatments of curettage or cryotherapy with a field therapy can be considered (Fleming, 2017). The Italian expert consensus is to use ingenol mebutate, imiquimod 5%, and methyl aminolevulinate PDT as first-line treatments for multiple grade I/II AKs and cancerization field (Peris, 2016). For immunocompromised patients with AK, the European S3 guidelines recommend the use of cryotherapy or curettage (for single lesions or multiple discrete lesions, not the treatment of field cancerization), 5% fluorouracil (5-FU), 5% imiquimod, or PDT (Werner, 2015).

Therapy guidelines identify PDT as effective both as a lesion and field-directed treatment (reviewed in Morton, 2015 and Philipp-Dormston, 2015). PDT has been widely studied for thin and moderate thickness AK on the face and scalp with clearance rates of 81% to 92% three months after treatment, depending on the type of photosensitising agent used. Common reactions to PDT include erythema and oedema due to the basic phototoxic action of the procedure. Significant scaling may occur, diminished by emollient application. Pustulation occurs in 20 to 30% of cases, lasting up to 14 days. Less common unwanted effects include crusting, which occurs mostly after treating thicker lesions, and erosions.

Topical therapy is suited to address multiple lesions in the field of cancerisation, but patient compliance and willingness to initiate topical treatment are compromised by the potential for severe local skin reactions (LSRs) and/or prolonged duration of treatment (Dirschka, 2017). Adherence with topical AK treatments is poor with approximately 90% of patients being non-adherent or non-persistent with therapy as shown in a cross-sectional in 305 patients with AK who were on one of the following topical AK

treatments: 5-FU 5% cream, 5-FU 0.5% in 10% salicylic acid, imiquimod 5% cream, or diclofenac sodium 3% gel (Shergill, 2013).

In a recent review, Balcere et al. summarised the prevalence of LSRs among various topical treatments for AK, including severe LSRs (Balcere, 2019). Depending on the treatment and the study, the overall prevalence of LSRs ranged from 8.8% to 100%, the prevalence of severe LSRs ranged from 0% to 58.5%, and the prevalence of systemic symptoms ranged from 0% to 20%. The highest prevalence of severe LSRs and systemic symptoms was reported with imiquimod, followed by ingenol mebutate and 5-FU as 5% cream. Treatment discontinuation due to LSRs is also common, although the highest prevalence of treatment discontinuation due to LSRs is reported in studies with the longest treatment regimens, not in studies reporting the highest prevalence rates of severe LSRs.

Topical therapies currently approved and recommended in the consensus-based (S3) Guidelines of the International League of Dermatological Societies and the European Dermatology Forum are 5-FU, diclofenac, imiquimod, and ingenol mebutate (Werner, 2015). Ingenol mebutate (Picato® 150 or 500 µg/g gel) was used as short-term treatment of AK but is no longer a treatment option in Europe since July 2020. For long- term treatment, imiquimod (Aldara® 5% cream), 5-FU as 5% cream (Efudix® 5% cream) or in combination as 0.5% in 10% salicylic acid cutaneous solution (Actickerall®5 mg/g+100 mg/g cutaneous solution), and diclofenac sodium (Solaraze® 3% gel) can be used.

5-FU works by the inhibition of thymidylate synthetase, needed for DNA synthesis. 5-FU, either as 5% cream or in combination as 0.5% in 10% salicylic acid cutaneous solution, is indicated for the field treatment of AK (Efudix 5% cream SmPC, 2019; Actikerall5 mg/g+100 mg/g cutaneous solution SmPC, 2017). The side effects can be substantial,in particular for 5-FU as 5% cream, including soreness, redness and possible crusting (de Berker, 2017; Balcere, 2019). These are minimised through reduction in the frequency of application or short breaks in a course of therapy. In case of severe reaction, a steroid can be applied. Mild to moderate irritation and inflammation at the application site is frequently observed as 5-FU is known to induce pro-inflammatory cytokines, tumour necrosis factor-α and interleukin-8, which can lead to severe adverse skin reactions. In addition, 5-FU 5% cream has been related to systemic reactions, including severe neutropenia (Cohen, 2018).

Imiquimod is a topical immune-response modifier available as a 5%, 3.75%, and 2.5% cream. The side effects of imiquimod are similar to those of 5-FU, predominantly application site reactions including severe erythema, scabbing and crusting, and erosions or ulceration. Skin infections can also arise. Some systemic adverse reactions, including myalgia have also been reported by imiquimod-treated patients (Aldara 5% cream SmPC, 2017).

Diclofenac 3% in a 2.5% hyaluronic gel is licensed for application twice daily for 60 to 90 days and can be applied as a lesion- or field-based treatment. Its mechanism of action for AK is not known, but may be related to inhibition of the cyclooxygenase pathway leading to reduced prostaglandin E2 synthesis. Diclofenac sodium 3% gel usually causes less severe LSRs than other topical treatments, but has a lower efficacy than other topical treatments and it has a lengthy treatment duration (de Berker, 2017). Diclofenac is not among the first-line topical treatment options in the current European guidelines (Werner, 2015; Peris, 2016).

The choice of treatment for each patient depends on several factors, including lesion clearance, adverse effects, tolerability, cosmetic outcomes, and impact on the quality of life. In some instances, patients may opt for a less effective treatment if they feel the other options are intolerable (Khanna, 2017). With respect to patient preferences, dermatologists reported often applying shared decision making when choosing a specific treatment (Noels, 2019). All patients should be monitored for lesion recurrence regardless of treatment choice.

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

AK represents a carcinoma *in situ* in the skin, and when left untreated, AK can regress or progress to invasive SCC (Röwert-Huber, 2007; Werner, 2013; Fernandez Figueras, 2017). Rates of regression of single lesions reported in the literature range between 15% and 63% after 1 year (Werner, 2013). The data available on recurrence rates of single lesions 1 year after regression indicate a recurrence rate of 15% to 53%. Data on the relative change of total AK count over time range from -53% to +99%. Spontaneous complete field regression rates range from 0% to 21%, with recurrences in 57% of cases.

Currently, no reliable estimates concerning the frequency of AK developing into invasive carcinoma can be given. In a study with a high-risk population, the risk of progression of AK to primary SCC (invasive or *in situ*) was estimated to be 0.60% at 1 year and 2.57% at 4 years (Criscione, 2009). Up to 65% of SCC arises from pre-existing AK, however the risk of progression to SCC of a single AK lesion per year has been reported to be very low, 0% to 0.075% in patients without a previous history of non-melanoma skin cancer (Marks, 1988), and up 0.53% per lesion in patients with prior history of non-melanoma skin cancer (Werner, 2013; Green, 2017). Furthermore, the rate of regression of single AK lesions has been reported to be generally between 20% and 30% (Werner, 2013).

While earlier guidelines proposed a conservative, clinically-directed approach to the treatment of AK (de Berker, 2007), the current treatment guidelines in Europe (Werner, 2015) recommend treatment of all AK, as it remains unknown whether aparticular lesion will progress to SCC. This recommendation reflects the growing recognition of AK lesions as *in situ* SCC (Röwert-Huber, 2007).

- **Important co-morbidities:**

The target population to be treated with tirbanibulin reflects the general adult population (>18 years of age), which consists of healthy subjects as well as subjects suffering from co-morbidities reflective of this population (age-related pre-existing diseases or co-morbidities). There are no specific co-morbidities in relation to AK.

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

Key safety findings from non-clinical studies and relevance to human usage

Toxicity:

- Key issues identified from acute or repeat-dose toxicity studies

Tirbanibulin toxicity is related to systemic exposure across species, irrespective of the route of administration and is reversible or shows a tendency toward recovery. Target organs include those that are highly proliferative (gastrointestinal [GI] epithelium, bone marrow, testes, and spleen), reflecting the pharmacologic action of the drug. Exposure-based safety margins for tirbanibulin for systemic toxicity at the proposed clinical dose and are ≥38- and ≥17-fold following repeated dermal application in rat and minipig, respectively, and >70-

fold following repeated oral administration in rat based on $AUC_{0-\ 24h}$. Systemic exposure (Day 5, AUC_{0-24h}) of metabolites KX2-5036 (6.17 to 66.3 ng/m.hL) and KX2-5163 (17.2 to 1090 ng.h/mL) in the rat and minipig is higher than that achieved in humans. Results from the MUsT study demonstrate that the maximum observed concentration of KX2-5036 and KX2-5163 in human plasma were0.0972 ng/mL (0.271 nM) and 0.121 ng/mL (0.353 nM), respectively.

In both the rat and minipig, tirbanibulin ointment caused mild to moderate dose-dependent skin irritation (e.g., erythema, oedema, and/or scabbing). In the repeat-dosestudies in rat and in minipig, these effects were shown to be transient. In the histopathology examinations in the 3-month repeated dose minipig study, the skin reactions were further categorised as primary (outcome of direct pharmacology) or secondary. The primary changes, consistent with exaggerated pharmacologic action of tirbanibulin, were limited to the basal cell layer of the epidermis and consisted of increased mitotic figures, apoptosis and/or diffuse basal cell loss. All remaining changesin the epidermis (subepidermal cleft formation, acute inflammation, ulcer and pustule formation, thickened epidermis and crusts) were interpreted to be sequelae to loss of the basal cell layer due to apoptosis and/or diffuse basal cell loss. Following the 4-weektreatment-free period, the basal cell layer in each treated animal was within normal limits.

Dedicated studies indicate that tirbanibulin has the potential to be an ocular irritant anda skin sensitizer but is not phototoxic.

- Reproductive/developmental toxicity

In a fertility and early embryonic development study in rats, tirbanibulin treatment resulted in a 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. The no observed adverse effects level (NOAEL) for female fertility and early embryonic development to implantation in rats was considered to be 1 mg/kg/day tirbanibulin. The NOAEL for male fertility was considered to be 2 mg/kg/day tirbanibulin. Plasma exposure to tirbanibulin based on AUC_{0-24h}. at that dose is projected to be 236 ng.h/mL, which is 58-times greater than human exposure in the clinical MUsT study (4.09 ng.h/mL).

In embryo-foetal development studies in rats and rabbits, embryo and foetal toxicity, including implantation loss and foetal malformations, occurred at oral doses of ≥1.25 mg/kg/day (rats) and 3 mg/kg/day (rabbits) tirbanibulin. The NOAELs for teratogenicity and reproductive effects were 0.5 mg/kg/day (rats) and 1 mg/kg/day(rabbits) tirbanibulin. At these doses, maternal area under the concentration-time curvefrom time 0 to 24 hours (AUC_{0-24h}) systemic exposures to tirbanibulin were 90.2 ng.h/mL(rats, Day 17) and 266 ng.h/mL (rabbits, Day 18), respectively, which are approximately >20- and >60-fold, respectively, greater than human exposure in the clinical MUsT study.

In a peri-/post-natal study in rats, statistically significant embryo-foetal lethality was observed in the F_1 generation for groups administered ≥0.5 mg/kg/day tirbanibulin. Based on these data, a NOAEL for F_1 foetal development could not be determined. TheNOAEL for maternal toxicity was 2.5 mg/kg/day tirbanibulin, the highest dose level tested in the study. However, animals administered 2.5 mg/kg/day were removed due to the high incidence of failure to produce a viable litter by gestation Day 24, resulting in an insufficient group size for data interpretation. Because of the removal of this group, F_1 behavioural and reproductive parameters were measured only for control, 0.5 and 1.25 mg/kg/day groups. The NOAEL for developmental, neurobehavioural, and reproductive performance in the F_1 generation is 1.25 mg/kg/day tirbanibulin.

- Genotoxicity

Tirbanibulin was negative in the Ames test for mutagenicity and weakly positive in the mouse lymphoma assay for mutagenicity, indicating clastogenic activity. Tirbanibulin was positive in the Chinese Hamster Ovary chromosomal aberration test following treatment with doses ≥25.7 µg/mL.

In an *in vivo* bone marrow micronucleus study in Sprague-Dawley rats treated with single oral doses of tirbanibulin, a significant increase in micronuclei was seen after doses ≥15 mg/kg. In a subsequent micronucleus study, using lower doses and 3 days of dosing, significant increases in micronuclei were detected at the highest test doses inboth males (25 mg/kg) and females (3.75 and 12.5 mg/kg). No increase of micronuclei was seen at the lower doses in absence of bone marrow toxicity, and the increases in micronuclei showed significant dose responses. In the same study, tirbanibulin induced small but significant increases in DNA strand breaks in the liver. However, in males this was only at the highest dose, and in females, there was no dose response. In addition, as all the comet tail values

in both sexes were clearly within the historical control values,the result was considered equivocal and probably not biologically relevant.

Because tirbanibulin has apoptotic effects in proliferating tissues, and the doses that induced micronuclei were clearly associated with marked to severe bone marrow toxicityin both studies, it seems likely that the increase in micronuclei results from apoptosis and related chromosome breakage and therefore is associated with a threshold below which there is no induction of genotoxic events.

No bone marrow toxicity and accordingly no increase in micronuclei was seen *in vivo* at doses of up to 2.5 mg/kg in males and 1.25 mg/kg in females. Toxicokinetic investigations in the same study revealed maximum observed plasma concentration (C_{max}) values for males and females of 44.9 and 59.8 ng/mL, respectively, and AUC values of 91.5 and 96.8 ng.h/mL, respectively, at the NOAEL for genotoxicity. The C_{max}values are respectively 174- and 232-fold higher than C_{max} values in the clinical MUsT study. The AUC values are 22- and 24-fold higher than the patient AUC values obtainedin the clinical study.

Thus, based on the bone barrow micronucleus findings *in vivo*, tirbanibulin was found to exhibit a threshold for genotoxicity related to the bone marrow toxicity that is associated with tirbanibulin's anti-proliferative and pro-apoptotic effects. The threshold for these toxic effects represents a sufficient safety margin considered to pose no risk of treatment-induced genotoxicity in patients treated with therapeutic dosages.

- Carcinogenicity

No carcinogenicity studies have been performed with tirbanibulin based on the short duration of clinical treatment (5 days). In addition, no off targets were identified in 2 *in vitro* screens for activity against a battery of enzyme and receptor targets, including kinases. Because tirbanibulin was found to induce chromosome breaks in genotoxicity testing based on its anti-proliferative and pro-apoptotic action, and because it is knownthat compounds that disrupt microtubule polymerisation such as tirbanibulin induce positive results in genotoxicity assays, additional carcinogenity testing would not providesignificant additional scientific insight and is therefore not warranted.

Safety pharmacology:

The maximum observed tirbanibulin plasma concentration following dermal application at the proposed clinical dose regimen in the clinical MUsT study was 1.09 ng/mL, which corresponds to a free tirbanibulin concentration of 0.13 ng/mL (based on approximately 88% plasma protein binding in humans). This is several orders of magnitude below the concentration of 1.99 µM (855 ng/mL, >6500 fold) that did not produce any effect in the human ether-à-go go related gene (hERG) potassium current assay. The tirbanibulin major metabolite in human hepatocyte incubates, KX2-5036, had no significant effect on hERG tail current, with an IC_{50} of >30 µM (approximately 10200 ng/mL).

Concurrent exposure data are not available for the Applicant's cardiovascular and respiratory safety pharmacology studies in Beagle dogs administered intravenous (IV) tirbanibulin. However, based on the systemic tirbanibulin exposures observed in a pharmacokinetic (PK) and toxicity study in Beagle dogs, mean C_{max} values were estimated to be 1620 and 3320 ng/mL following doses of 2.5 mg/kg (IV) and 12.5 mg/kg(oral), respectively (corresponding to free tirbanibulin concentrations of 291.6 and 597.6 ng/mL based on plasma protein binding of 82% in dogs). The calculated mean oral bioavailability of tirbanibulin was 89% at 12.5 mg/kg and 56% at 25 mg/kg. Therefore, mean peak plasma concentrations following a 15 mg/kg IV dose of tirbanibulin, at which no adverse changes in the ECG, including QTc interval, were observed, are predicted to be significantly higher than 597.6 ng/mL, or >4500-fold higher than the maximum expected free peak plasma concentration in patients with AK(0.13 ng/mL).

Similarly, the safety margins for central nervous system (CNS) and GI safety of tirbanibulin were estimated, respectively, from the maximal oral doses of 50 mg/kg in rats (no effect observed in the modified Irwin's test) and 10 mg/kg in rats (no effect observed on either GI motility or gastric emptying). PK data for oral doses of 12.5 and 50 mg/kg provided mean C_{max} values of 2310 and 13400 ng/mL, respectively (corresponding to free tirbanibulin concentrations of 184.8 and 1072 ng/mL based on plasma protein binding of 92% in rats). Based on the maximum expected free peak plasma concentration in patients with AK (0.13 ng/mL), these provide safety margins of >8200-fold for CNS safety and >1400-fold for GI safety.

In conclusion, based on the exposure margins established between non-clinical cardiovascular safety assessments *in vitro* (hERG assay) and *in vivo* (Beagle dog), andGI and CNS (in rats) and maximal individual peak plasma concentrations observed in the MUsT study, the risk of cardiovascular adverse events following topical application of tirbanibulin 10 mg/g ointment under the intended clinical dosing regimen is low.

Other toxicity-related information or data:

- Mechanisms for drug interactions

In vitro, tirbanibulin is mainly metabolised by cytochrome P450 (CYP) 3A4, and to a lesser degree by CYP2C8. *In vitro* studies show that tirbanibulin does not inhibit or induce CYP enzymes and is not an inhibitor of membrane transporters at maximum clinical exposures. 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 no potential for drug-drug interaction potential with tirbanibulin 10 mg/g ointment at the maximum clinical exposure.

Part II: Module SIII – Clinical trial exposure

The clinical trial exposure for tirbanibulin 10 mg/g ointment is derived from 9 clinical studies, as shown in Table SIII.1.

Table SIII.1: Overview of Clinical Studies with Tirbanibulin 10 mg/g Ointment

Development Phase	Study	Study design and type of control	Population
Phase III	KX01-AK-003	Randomised, double-blind, vehicle-controlled	Actinic keratosis
	KX01-AK-004		
Phase IIa	KX01-AK-002	Open-label, non-randomised, uncontrolled	Actinic keratosis
Phase I	KX01-AK-01-US	Open-label, uncontrolled	Actinic keratosis
	KX01-AK-007	Open-label, non-randomised, uncontrolled maximal usage trial	Actinic keratosis
	KX01-AK-006	Randomised, controlled, evaluator-blinded, within-subject comparison, contact sensitisation	Healthy subjects
	KX01-AK-008	Randomised, double-blind, controlled, within-subject comparison, phototoxicity	Healthy subjects
	KX01-AK-009	Randomised, double-blind, controlled, within-subject comparison, photoallergy	Healthy subjects
	KX01-AK-010	Randomised, controlled, evaluator-blinded, within-subject comparison, skin irritation	Healthy subjects

For the purpose of the safety assessment in this Risk Management Plan (RMP), pooled pivotal Phase III Studies KX01-AK-003 and KX01-AK-004 have been considered. Exposure data from these pooled Phase III study populations are presented in Table SIII.2 to Table SIII.6 of this module. Phase IIa and Phase I studies were not pooled, but are presented separately and commented thereafter.

Exposure in patient years was calculated as follows: exposure in days divided by 365.25.

Pivotal Phase III studies – pooled safety analysis

Overall, 353 patients with AK have been exposed to tirbanibulin 10 mg/g ointment (4.8241 patient years) in the pivotal clinical studies (KX01-AK-003 and KX01-AK-004).

Table SIII.2: Duration of Exposure in Patients with Actinic Keratosis

Duration of exposure	Patients	Patient years
0 to <3 days	0	–
3 to <5 days	2 (0.57%)	0.0192
5 days	351 (99.43%)	4.8049
>5 days	0	–
Total	**353 (100.00%)**	**4.8241**

Source: Section 5.3.5.3, Statistical Report for supporting the RMP, Table 1.

Table SIII.3: Extent of Exposure in Patients with Actinic Keratosis by Age Group and Gender

Age group	Patients		Patient years	
	Male	Female	Male	Female
<18	0 (0.00%)	0 (0.00%)	–	.
≥18 to <65	85 (27.87%)	22 (45.83%)	1.1636	0.3012
≥65 to <75	126 (41.31%)	15 (31.25%)	1.7194	0.2053
≥75 to <85	84 (27.54%)	9 (18.75%)	1.1499	0.1232
≥85	10 (3.28%)	2 (4.17%)	0.1342	0.0274
Total	**305 (100.00%)**	**48 (100.00%)**	**4.167**	**0.6571**

Source: Section 5.3.5.3, Statistical Report for supporting the RMP, Table 2.

Table SIII.4: Dose in Patients with Actinic Keratosis

Dose of exposure	Patients	Patient years
Tirbanibulin 10 mg/g ointment [a], 5 days	353 (100.00%)	4.8241

a) Patients applied a small amount of tirbanibulin 10 mg/g ointment to a 25 cm^2 treatment area from a single-use sachet containing 250 mg tirbanibulin 10 mg/g ointment (0.25 g/250 mg).

Source: Section 5.3.5.3, Statistical Report for supporting the RMP, Table 3.

Table SIII.5: Extent of Exposure in Patients with Actinic Keratosis by Ethnic Origin

Ethnic origin	Patients	Patient years
Hispanic or Latino	13 (3.68%)	0.1752
Not Hispanic or Latino	340 (96.32%)	4.6489
Total	**353 (100.00%)**	**4.8241**

Source: Section 5.3.5.3, Statistical Report for supporting the RMP, Table 4.

Table SIII.6: Fitzpatrick Skin Phototype in Patients with Actinic Keratosis

Fitzpatrick skin phototype	Patients	Patient years
Type I	49 (13.88%)	0.6708
Type II	200 (56.66%)	2.7296
Type III	88 (24.93%)	1.2047
Type IV	15 (4.25%)	0.2053
Type V	0 (0.00%)	.
Type VI	1 (0.28%)	0.0137
Total	**353 (100.00%)**	**4.8241**

Source: Section 5.3.5.3, Statistical Report for supporting the RMP, Table 5.

Phase IIa study

In Study KX01-AK-002, 168 patients with AK were exposed to tirbanibulin 10 mg/g ointment. All completed the study treatment period, 84 patients received 3 x 0.5 mg of tirbanibulin 10 mg/g ointment (2.5 mg/250 mL; total exposure for each patient: 1.5 mg), and 84 patients received 5 x 0.5 mg of tirbanibulin 10 mg/g ointment (total exposure for each patient: 2.5 mg).

Phase I studies

In Study KX01-AK-01-US, 30 patients with AK were exposed to tirbanibulin 10 mg/g ointment., 4 patients received 3 x 50 mg of tirbanibulin 10 mg/g ointment (0.25 mg/250 mL; total exposure for each patient: 1.5 mg), 10 patients received 3 x 200 mg of tirbanibulin 10 mg/g ointment (total exposure for each patient: 6 mg), 8 patients received 5 x 50 mg of tirbanibulin 10 mg/g ointment (total exposure for each patient: 2.5 mg), and 8 patients received 5 x 200 mg of tirbanibulin 10 mg/g ointment (total exposure for each patient: 10 mg). 29 patients completed the study.

In Study KX01-AK-007, 18 patients with AK were exposed to tirbanibulin 10 mg/g ointment. All completed the study and applied 5 x a small amount of a single-use sachet of tirbanibulin 10 mg/g ointment (containing 250 mg tirbanibulin 10 mg/g ointment [0.25 g/250 mg]) during the study.

In Study KX01-AK-006, 261 healthy subjects were exposed to tirbanibulin 10 mg/g ointment applied in skin patches (each containing 250 mg tirbanibulin 10 mg/g ointment [0.25 g/250 mg]) over 10 x 48- to 72-hour wear periods. 229 subjects completed the study.

In Study KX01-AK-008, 31 healthy subjects were exposed to tirbanibulin 10 mg/g ointment applied in skin patches (each containing 250 mg tirbanibulin 10 mg/g ointment [0.25 g/250 mg]) over one 24-hour wear period. 31 subjects completed the study.

In Study KX01-AK-009, 64 healthy subjects were exposed to tirbanibulin 10 mg/g ointment applied in skin patches (each containing 250 mg tirbanibulin 10 mg/g ointment [0.25 g/250 mg]) over 7 x 24-hour wear periods. 59 subjects completed the study.

In Study KX01-AK-010, 36 healthy subjects were exposed to tirbanibulin 10 mg/g ointment applied in skin patches (each containing 250 mg tirbanibulin 10 mg/g ointment [0.25 g/250 mg]) over 9 x 48- to 72-hour wear periods. 30 subjects completed the study.

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

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

The safety of tirbanibulin 10 mg/g ointment was established by the clinical studies included in the clinical development programme. These studies included healthy male and female subjects or patients with AK, ≥18 years of age, and the majority was white and had Fitzpatrick skin phototypes I, II, or III. Based on the intended indication of AK, which does not occur in paediatric populations, the clinical development programme excluded paediatric patients from enrolment in the clinical studies.

The key exclusion criteria from studies in patients with AK included in the clinical development programme (Studies KX01-AK-003, KX01-AK-004, KX01-AK-002, KX01-AK-007, and KX01-AK-01-US) are displayed in Table SIV.1.

Table SIV.1: Discussion of Exclusion Criteria and Implications for Missing Information

Exclusion criterion	Reason for exclusion	Missing information? (Yes/No)	Rationale
Clinically atypical and/or rapidly changing AK lesions on the treatment area, e.g., hypertrophic, hyperkeratotic, recalcitrant disease (had cryosurgery on 2 previous occasions) and/or cutaneous horn	To avoid confounding factors that can interfere with the interpretation of results.	No	This is a standard class level exclusion for clinical studies conducted with this type of product application.
Skin disease (e.g., atopic dermatitis, psoriasis, eczema) or condition (e.g., scarring, open wounds) that, in the opinion of the investigator, might have interfered with the study conduct or evaluations, or which exposed the subject to unacceptable risk by study participation	Unjustified safety risk for patient in the setting of a clinical study as they may have a higher risk of treatment complications.	No	The presence of these medical conditions is not expected to change the efficacy nor safety of tirbanibulin 10 mg/g ointment when used according to indication and correct dose.
Use of systemic retinoids within 6 months prior to screening	To avoid confounding factors that can interfere with the interpretation of results.	No	This is a standard class level exclusion for clinical studies conducted with this type of product application.

Exclusion criterion	Reason for exclusion	Missing information? (Yes/No)	Rationale
Treatment with immunomodulators or immunosuppressors, cytotoxic drugs, or interferons/interferon inducers	These are patients who, by virtue of their disease, may have been unable to comply with requirements of a clinical study, or were at increased or unknown risk (more than the average) of participating in a clinical study.	No	The presence of these serious medical conditions is not expected to change the efficacy nor safety of tirbanibulin 10 mg/g ointment when used according to indication and correct dose.
History of sensitivity and/or allergy to any of the ingredients in the study medication.	Hypersensitivity to the product is a standard contraindication to product use.	No	This is a standard exclusion criterion for controlled clinical studies and is kept as contraindication (SmPC section 4.3 “Hypersensitivity to the active substance or to any of the excipients listed in section 6.1”).
Females who were pregnant or nursing.	For ethical consideration in order to protect subsequent risks to the foetus.	No	Refer to the instructions in SmPC section 4.6 “Fertility, pregnancy, and lactation.”

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

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions (i.e., occurring in <1/1000 patients), adverse reactions with a long latency, or those caused by prolonged or cumulative exposure longer than 5 days. However, across the clinical studies, there has been no evidence of organ toxicity which suggests a potential toxicity by cumulative dose.

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

Table SIV.2: Exposure of Special Populations Included or not in Clinical Trial Development Programmes

Type of special population	Exposure	
	Patients (N=353)	**Patient years [a]**
Pregnant women	Not included in the clinical development programme.	
Breast-feeding women		
Patients with relevant co-morbidities:		
• Hepatic impairment		
• No hepatic impairment [b]	353 (100.00%)	4.8241
• Hepatic impairment [b]	0	–
• Renal impairment		
– No renal impairment [c]	119 (33.8%)	1.629
– Mild renal impairment [c]	193 (54.83%)	2.6366
– Moderate renal impairment [c]	38 (10.80%)	0.5175
– Severe renal impairment	2 (0.57%)	0.0274
• Cardiovascular impairment		
• No cardiovascular impairment [d]	331 (93.77%)	4.5229
• Cardiovascular impairment [d]	22 (6.23%)	0.3012
Population with relevant different ethnic origin	See Table SIII.5.	
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme.	
Children and adolescents (<18 years of age)	Not included in the clinical development programme, because the intended indication is limited to AK, which does not occur in paediatric populations. On 01-Feb-2019, the Paediatric Committee of the European Medicines Agency granted a product-specific waiver for all subsets of the paediatric population for tirbanibulin 10 mg/g ointment.	

Type of special population	Exposure	
	Patients (N=353)	Patient years [a]
Elderly	see Table SIII.3	

eGFR=estimated glomerular filtration rate ($141 \times \min[SCr/\kappa, 1]^{\alpha} \times \max[SCr/\kappa, 1]^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] ×1.159 [if Black]); GFR=glomerular filtration rate; HLGT=High-Level Group Term; HLT=High-Level Term; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term.

a) Exposure in patient years was calculated as exposure in days divided by 365.25.
b) Based on HLT 10019661, 10019664, and 10019669.
c) Renal impairment based on baseline GFR. No renal impairment when GFR ≥90 mL/min/1.73 m^2; mild renal impairment when GFR ≥ 60 to <90 mL/min/1.73 m^2; moderate renal impairment when eGFR ≥30 to <60 mL/min/1.73 m^2, severe renal impairment when GFR <30 mL/min/1.73 m^2.
d) Based on HLT 10019280 and 10011085, PT 10059056, and HLGT 10046973 per MedDRA v22.0.

Source: Section 5.3.5.3, Statistical Report for supporting the RMP, Table 6.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Internal sales data were used for calculation of exposure. Shipment data giving the total quantities of tirbanibulin distributed, expressed as Daily Defined Dose (DDD) of tirbanibulin - as defined by the WHO Collaborating Centre for Drugs Statistics Methodology - were used to make a crude estimate of the post-marketing exposure to tirbanibulin.

Considering that 1 treatment course is for 5 consecutive days using 1 single-dose sachet per application, it has been roughly estimated that 1 unit (containing 5 sachets) of tirbanibulin or 5 samples, corresponds to 1 patient exposed to the product.

SV.1.2 Exposure

Cumulatively since tirbanibulin was first launched on the 14th December 2020 until the 13th of December 2023 (Data Lock Point of last PSUR) , it is estimated that 573,117 patients have been exposed to tirbanibulin

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

Potential for misuse for illegal purposes

Tirbanibulin is not structurally or pharmacologically related to any drug known to cause abuse or dependence. The PK and pharmacodynamic results do not suggest any potential effect on the CNS that may induce drug dependence. During the clinical development program, there were no adverse events that indicated abuse or a dependence potential, and no behaviour or withdrawal symptoms were observed after stopping treatment.

Part II: Module SVII – Identified and potential risks

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

Important identified risks:

- None

Based on the data observed in clinical studies, no important safety concerns have been identified for tirbanibulin 10 mg/g ointment.

Important potential risks:

Based on the natural progression of AK to SCC and the topical route of administration, the Applicant considers the following safety concerns to be potential risks for tirbanibulin 10 mg/g ointment:

- Skin tumours in treatment area

Missing information:

- None

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

There is either no associated relevant risk that impacts the risk-benefit profile of tirbanibulin 10 mg/g ointment, or the risk is considered to be minimal in relation to the severity of the indication for all the risks listed below:

- LSRs reported in the clinical studies are listed in section 4.8 of the SmPC as application site reactions, but they are not associated to a relevant risk. All LSRs were transient and did not require treatment. LSRs were mostly mild or moderate in severity; severe LSRs were infrequent and occurred at an overall incidence of 13%. No patients discontinued treatment due to LSRs, and no serious LSRs were reported across the clinical development programme.

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

The important safety concerns for Klisyri (tirbanibulin) are listed below:

Important Identified Risk: None

Important Potential Risk: Skin tumours in treatment area

Scientific evidence:

AK can progress to SCC (Röwert-Huber, 2007; Fernandez Figueras, 2017). Up to 65% of SCC arises from pre-existing AK, however the risk of progression to SCC of a single AK lesion per year has been reported to be very low, 0% to 0.075% in patients without a previous history of non-melanoma skin cancer (Marks, 1988), and up 0.53% per lesion in patients with prior history of non-melanoma skin cancer (Werner, 2013; Green, 2017). The calculated lifetime risk of malignant transformation for a patient with multiple AK lesions during a 10-year period is between 6% and 10% (Salasche, 2000). Furthermore, the rate of regression of single AK lesions has been reported to be generally between 20% and 30% (Werner, 2013).

In addition, cases of rapidly-growing SCC shortly after treatment with ingenol mebutate in patients with AK have been reported (Moreno Romero, 2015; Maglie, 2018). The mechanism of action of tirbanibulin is different from ingenol mebutate, and non-clinical data do not indicate a risk of development of skin cancers after tirbanibulin treatment.

In clinical studies, 1 isolated skin cancer (SCC) in the treatment area was reported in a patient treated with tirbanibulin 10 mg/g ointment following the Day 57 assessment in Study KX01-AK-003; this event was assessed by the investigator as not related to study treatment.

Risk-benefit impact:

Skin cancers in the treatment area are considered a potential risk based on the known risk of AK progression to SCC. Based on the low incidence of skin cancers in the treatment area observed across clinical studies, it is unlikely for treatment with tirbanibulin 10 mg/g ointment to cause events of skin cancers in the treatment area. The risk-benefit impact is acceptable.

Missing information: None

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

Not applicable.

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

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

Important Identified Risk: None

Important Potential Risk: Skin tumours in treatment area

Potential Mechanisms:

There is no known potential mechanism by which tirbanibulin could be associated with the development of skin tumours in the treatment area.

Evidence source(s) and strength of evidence:

AK can progress to skin cancer, in particular SCC (see Section SVII.1.2). In addition, cases of rapidly-growing SCC shortly after treatment with ingenol mebutate in patients with AK have been reported (Moreno Romero, 2015; Maglie, 2018). The mechanism of action of tirbanibulin is different from ingenol mebutate, and non-clinical data do not indicate a risk of development of skin tumours after tirbanibulin treatment.

Characterisation of the risk:

Of the 702 patients in the Safety Population of the randomised, vehicle-controlled Phase III studies (KX01-AK-003 and KX01-AK-004), 10 of 353 patients (2.83%) in the tirbanibulin 10 mg/g ointment group and 7 of 349 patients (2.01%) in the vehicle group had skin cancers (SCC, BCC, or melanoma) diagnosed after the start of treatment. All of these skin cancers were located outside the study treatment area except for 1 (0.28%) isolated SCC in the treatment area on the scalp in the tirbanibulin 10 mg/g ointment group in Study KX01-AK-003. All skin cancers were non-serious, of mild or moderate severity, and were consideredunrelated to the study treatment by the investigator. The majority of these skin cancers resolved or were resolving by the end of the study.

Although this is a potential safety concern, based on the low incidence of skin cancers in the treatment area observed across clinical studies, it is unlikely for treatment with tirbanibulin to cause events of skin cancers in the treatment area.

Risk factors and risk groups:

Risk factors for the progression of AK to skin cancer include advanced age, male gender, cumulative sun exposure, fair skin type, history of AK or skin cancer, and concomitant immunosuppression.

Preventability:

Successful treatment of AK will reduce the risk of the patient developing a serious and malignant cutaneous neoplasm.

Impact on the risk-benefit balance of the product:

The impact on the risk-benefit balance of the product is considered to be low.

Public health impact:

Given that only 1 (0.28%) isolated skin cancer (SCC) in the treatment area was observed in the integrated Safety Population, the impact on public health is estimated to be minimal.

SVII.3.2. Presentation of the missing information

Missing information: None

Part II: Module SVIII – Summary of the safety concerns

Table SVIII.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Skin tumours in treatment area
Missing information	None

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

III.1 Routine pharmacovigilance activities

Details of the Applicant's Pharmacovigilance System is provided in Module 1 as part of the Marketing Authorisation Application.

The Applicant has processes in place, supported by standard operating procedures, to ensure the collection, review, evaluation, and assessment of safety-related information. Processes are also in place to ensure the presentation of these data within product labelling and investigator brochures as well as reporting of these data to regulatory agencies, prescribers, investigators, and ethics committees.

As part of routine pharmacovigilance processes for marketed products, regular safety surveillance will be performed, and signal detection activities will be conducted according to internal procedures to identify specific areas for further review, along with single-case and multiple-case reviews. Medical safety assessments will be carried out to support regulatory agency requirements (such as Periodic Safety Update Reports), as well as for the purposes of updating the prescribing information whenever needed.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

None.

III.2 Additional pharmacovigilance activities

The Applicant plans to perform the following additional pharmacovigilance activity:

- 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.

The main safety concerns that will be addressed with this study will be skin tumours in treatment area.

Study name and title:

Study M-14789-41: A Phase 4, Multi-centre, Randomized, Investigator-blinded, Active-controlled Study to Determine the Incidence of Squamous Cell Carcinoma and Evaluate the Long-term Safety and Efficacy of Tirbanibulin 10 mg/g Ointment for the Treatment of Adult Patients with Actinic Keratosis on the Face or Scalp.

Rationale and study objectives:

Tirbanibulin 10 mg/g ointment has been studied in multiple Phase II and Phase III studies to evaluate the efficacy, pharmacodynamics, pharmacokinetics, safety, and tolerability in patients with AK. Tirbanibulin ointment is applied as a short-duration therapy, consisting of once daily application for 5 consecutive days, and has been shown to be an effective and safe treatment for AK of the face or scalp. This study will investigate the effect of tirbanibulin ointment on the inhibition of the potential progression of AK lesions to squamous cell carcinoma (SCC) and will evaluate long-term safety over 3 years in patients treated with tirbanibulin; moreover, it will assess the efficacy of tirbanibulin versus an active comparator, and will generate data to support common clinical practice in the management of the AK. The study is investigator-blinded to avoid bias in the evaluation of safety and the efficacy data from the 2 randomised groups.

The primary study objective is to evaluate the incidence of invasive SCC confirmed by biopsy in the treatment field after administration of topical tirbanibulin ointment or active comparator over the 3-year study period.

The secondary study objectives are to evaluate the safety and tolerability of topical tirbanibulin ointment over the 3-year study period and to evaluate the short-term efficacy and long-term efficacy of topical tirbanibulin ointment over the full 3-year study period.

Study design:

This is a Phase 4, multi-centre, randomized, investigator-blinded, active-controlled, parallel-group study to determine the incidence of invasive SCC, long-term safety, tolerability and efficacy of tirbanibulin 10 mg/g ointment administered topically over 25 cm^2 of the face or scalp in adult patients with AK.

Study population:

The study population will consist of male and female patients, aged 18 years or older, with a contiguous field on the face or scalp measuring 25 cm^2 that contains 4 to 8 clinically typical, non-hypertrophic, non-hyperkeratotic, visible, and discrete AK lesions.

Milestones:

Protocol submission to Competent Authorities: Q4 of 2021

Interim Results: Q4 of 2025

Final Clinical Study Report: Q4 of 2027

III.3 Summary table of additional pharmacovigilance activities

Table Part III.1: On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Tirbanibulin Post-Authorisation Safety Study (PASS). (Study M-14789-41)	To evaluate the incidence of invasive SCC and to assess the long-term safety and efficacy of tirbanibulin 10 mg/g ointment.	Skin tumours in treatment area	Study Protocol submission to Competent Authorities Interim Results Final Clinical Study Report	Q4 of 2021 Q4 of 2025 Q4 of 2027

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Not applicable				
Other additional pharmacovigilance activities				
Not applicable				

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

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

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine risk minimisation measures

Table Part V.1: Description of Routine Risk Minimisation Measures by Safety Concern

Potential risks

Safety concern	Routine risk minimisation activities
Skin tumours in treatment area	**Routine risk communication:** • SmPC Section 4.2, Section 4.4. and Section 5.1 • PL Section 2 and Section 3. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimisation measures beyond the Product Information:** • Legal status: Prescription only medicine

V.2. Additional risk minimisation measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3. Summary of risk minimisation measures

Table Part V.3: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Skin tumours in treatment area	**Routine risk minimisation measures:** • SmPC section 4. 2, section 4.4 and section 5.1. • PL Section 2 and Section 3 **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • Study no.: M-14789-41 • Final Clinical Study Report Date: Q4 of 2027

Part VI: Summary of the risk management plan

Summary of risk management plan for Klisyri (tirbanibulin)

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

Klisyri's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Klisyri should be used.

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

Important new concerns or changes to the current ones will be included in updates of Klisyri's RMP.

I. The medicine and what it is used for

Klisyri is authorised for topical field treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis (AK) of the face or scalp in adults (SmPC). Klisyri contains tirbanibulin (10 mg/g) as the active substance and should be applied once daily to the affected field for 5 consecutive days. A thin layer of ointment should be applied to cover the treatment field.

Further information about the evaluation of Klisyri's benefits can be found in Klisyri's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage <link to the EPAR summary landing page>.

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

Important risks of Klisyri, together with measures to minimise such risks and the proposed studies for learning more about Klisyri's risks, are outlined below.

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;

- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

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

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

II.A List of important risks and missing information

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

List of important risks and missing information	
Important identified risks	None
Important potential risks	Skin tumours in treatment area
Missing information	None

II.B Summary of important risks

Important potential risk – Skin tumours in treatment area	
Evidence for linking the risk to the medicine	Skin tumours in the treatment area are considered a potential risk based on the known risk of AK progression to skin cancer, in particular squamous cell carcinoma. However, non-clinical data do not indicate a risk of development of skin tumours after Klisyri treatment. Furthermore, based on the low incidence observed across clinical studies, it is unlikely for treatment with Klisyri to cause skin cancers in treatment area.
Risk factors and risk groups	Advanced age, male gender, cumulative sun exposure, fair skin type, history of AK or skin cancer, and concomitant immunosuppression.
Risk minimisation measures	Routine risk minimisation measures • SmPC section 4. 2, section 4.4 and section 5.1. • PL. section 2 and section 3
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study M-14789-41 See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

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

Study short name: Study M-14789-41

Purpose of the study:

This study will investigate the effect of tirbanibulin ointment on the inhibition of the potential progression of AK lesions to squamous cell carcinoma (SCC) and will evaluate long-term safety over 3 years in patients treated with tirbanibulin; it will also assess the efficacy of tirbanibulin versus an active comparator.

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

Not applicable

Part VII: Annexes

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Annex 4 – Specific adverse drug reaction follow-up forms

Not applicable.

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

Not applicable.