Date: 18 March 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Klisyri

International non-proprietary name: tirbanibulin
Pharmaceutical form: ointment
Dosage strength: 10 mg/g
Route(s) of administration: topical use
Marketing Authorisation Holder: Almirall AG
Marketing Authorisation No.: 68322
Decision and Decision date: approved on 3 February 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of the SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance tirbanibulin of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

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

2.2.2 Approved Indication

Klisyri is indicated for the topical field treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis of the face or scalp in adults.

2.2.3 Requested Dosage

Klisyri ointment should be applied to the affected field on the face or scalp once daily for one treatment cycle of 5 consecutive days. A thin layer of ointment should be applied to cover the treatment field of up to 25 cm^2.
Klisyri 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.
Optimal 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.
Clinical data on treatment for more than 1 treatment course of 5 consecutive days are not available.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	22 December 2020
Formal control completed	14 January 2021
List of Questions (LoQ)	12 May 2021
Answers to LoQ	23 July 2021
Predecision	21 October 2021
Answers to Predecision	29 November 2021
Final Decision	3 February 2022
Decision	approval

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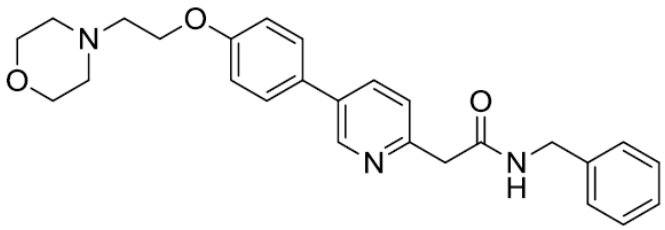
3 Quality Aspects

3.1 Drug Substance

INN: tirbanibulin (free base)
Chemical name: N-benzyl-2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl)acetamide
Molecular formula: $C_{26}H_{29}N_3O_3$
Molecular mass: 431.53 g/mol
Molecular structure:



Tirbanibulin is a white to off-white solid exhibiting polymorphic Form B. Tirbanibulin is insoluble in water.

The drug substance is manufactured by a multiple step chemical synthesis with final crystallisation. The synthesis of the drug substance and the necessary in-process controls are described in detail. The specifications are in line with the recommendations of the relevant ICH guidelines and are considered appropriate in order to ensure consistent quality of tirbanibulin.

Appropriate stability data have been generated, resulting in a suitable retest period.

3.2 Drug Product

Klisyri is a smooth, creamy white to off-white ointment (1% w/w) packaged in single-use sachets intended for topical use. Each sachet contains a nominal amount of 250 mg of drug product with an overfill averaging approximately 60 mg.

Klisyri ointment manufacturing involves the preparation of drug substance slurry in propylene glycol, addition of glycerol monostearate 40-55, homogenisation at high temperature to form a single phase, cooling to form the ointment and filling of the ointment into single-use sachets at ambient conditions using form-fill-seal technology.

For the control of the finished product, adequate tests and acceptance criteria for release and shelf-life have been established. The specifications include the parameters appearance, identity, assay, degradation products, viscosity and microbial tests. Analytical methods have been described and validated according to ICH requirements.

Appropriate stability data have been generated with production scale batches in the packaging material intended for commercial use and according to the relevant international guidelines.

3.3 Quality Conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

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4 Nonclinical Aspects

Regarding the marketing authorisation application of Klisyri (tirbanibulin), the Division Nonclinical Assessment conducted an abridged evaluation, which was based on the FDA assessment report (NDA 213189, dated 12 September 2019).
Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Klisyri in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised and all nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals.

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5 Clinical and Clinical Pharmacology Aspects

Swissmedic Clinical Review has not assessed the primary data relating to clinical pharmacology and clinical aspects of this application and its decision relies on the results of the assessment of the foreign reference authority, the FDA

5.1 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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6 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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7 Appendix

7.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Klisyri, ointment, was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

KLISYRI®

Composition

Active substances

Tirbanibulin

Excipients

Propylene glycol 890 mg/g, Glycerol monostearate 40-55.

Pharmaceutical form and active substance quantity per unit

Ointment with 10 mg/g tirbanibulin.
1 sachet contains 2.5 mg of tirbanibulin in 250 mg ointment.

Indications/Uses

Klisyri is indicated for the topical field treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis of the face or scalp in adults.

Dosage/Administration

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

Clinical data on treatment for more than 1 treatment course of 5 consecutive days are not available (see «warnings and precautions»).
If a dose is missed, it should be applied as soon as possible, then the regular schedule continued as foreseen. However, the ointment should not be applied more than once a day.

Klisyri 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 «warnings and precautions»).
Optimal 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.

Special dosage instructions

Patients with hepatic disorders

Klisyri has not been studied in patients with hepatic impairment. Based on clinical pharmacology and *in vitro* studies, no dose adjustments are needed (see «Pharmacokinetics»).

Patients with renal disorders

Klisyri has not been studied in patients with renal impairment. Based on clinical pharmacology and *in vitro* studies, no dose adjustments are needed (see «Pharmacokinetics»).

Immunocompromised patients

Clinical data on treatment in immunocompromised patients are not available (see «Warnings and precautions»).

Elderly patients

No dose adjustment is required (see «Properties/Effects»).

Children and adolescents

There is no relevant use of Klisyri in children and adolescents for the indication of actinic keratosis. There are no data on the efficacy and safety of Klisyri in children and adolescents.

Mode of administration

Klisyri is for external use only. Klisyri must not come into contact with the mucous membranes or the eyes. For indications on incorrect routes of administration, see «Warnings and precautions».

Each sachet is for single use only and should be discarded after use (see «Other information»).

The treatment is intended for self administration.
Before applying Klisyri, patients should wash the treatment field with mild soap and water and dry it. Some ointment from the single-use sachet should be squeezed onto a fingertip and a thin layer

applied evenly over the entire treatment field of up to 25 cm^2. Hands should be washed with soap and water before and immediately after application of the ointment.
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 Klisyri. After this period, the treated area may be washed with mild soap and water. The ointment should be applied at approximately the same time each day.

Contraindications

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

Warnings and precautions

Application errors

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.
Klisyri must not be ingested. If accidental ingestion occurs, the patient should drink plenty of water and seek medical care.
Klisyri should not be used on the inside of the nostrils, on the inside of the ears, or on the lips.
Application of Klisyri is not recommended until the skin is healed from treatment with any previous medicinal product, procedure or surgical treatment. The product must not be applied to open wounds or broken skin where the skin barrier is compromised (see «Dosage/Administration»).

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 Klisyri (see «Undesirable effects»). 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

Klisyri should be used with caution in immunocompromised patients (see «Dosage/Administration»).

Management of actinic keratosis

Topical treatment with tirbanibulin for more than one treatment course of 5 consecutive days has not been studied (see «Dosage/Administration»).

Excipients

This medicinal product contains 890 mg propylene glycol per gramm ointment.

Interactions

No *in vivo* pharmacokinetic and pharmacodynamic 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 Klisyri at maximum clinical exposure (see «Pharmacokinetics/*In vitro* drug interactions»).

Pregnancy, lactation

Pregnancy

There are insufficient data on the use of tirbanibulin in pregnant women. Studies in animals have shown reproductive toxicity (see «Preclinical Data»).
Pregnant women or women of childbearing potential not using contraception should not use Klisyri.
The risks to humans receiving topical treatment with Klisyri is estimated to be low as systemic absorption of tirbanibulin is low (see «Pharmacokinetics»). As a precautionary measure, Klisyri should not be used during pregnancy. If a pregnancy occurs during treatment, the patient should seek medical advice.

Lactation

It is unknown whether tirbanibulin or its metabolites are excreted in human milk.
A risk to the newborn/child cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue Klisyri therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No clinical data on the effect of topical Klisyri on fertility in humans are available. Animal studies have shown male reproductive toxicity (see «Preclinical data»). The risk for adverse effects on female and male fertility is estimated to be low as topically applied tirbanibulin is minimally absorbed (see «Pharmacokinetics»). However, Klisyri is not recommended for women and men who intend to become pregnant or conceive a child.

Effects on ability to drive and use machines

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

Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions in clinical studies are local skin reactions, which were mostly mild to moderate in degree and resolved without treatment. 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. 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 most of them did not require treatment.

List of adverse reactions

Table 1 lists the adverse reactions that were reported from 353 patients with actinic keratosis treated with Klisyri in two vehicle-controlled phase 3 clinical studies enrolling a total of 702 patients. Frequencies are defined as: very common (≥1/10*),* common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000); not known (frequency cannot be estimated from the available data).

Table 1:

System organ class	Adverse event	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 specific adverse reactions and additional information

Local skin reactions

Most local skin reactions were transient and mild to moderate in severity. Following the application of Klisyri, 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.
Local skin reactions after treatment with Klisyri peaked on day 8, decreased rapidly by day 15, and were at or below baseline by day 29.

Sun exposure

Studies have been conducted to assess the effects of ultra-violet irradiation of the skin following single and multiple applications of Klisyri. Klisyri did not show any potential for photo-irritation or photo-allergic effects.

Long-term follow-up

In total, 202 of 204 patients with complete clearance at day 57 were followed for an additional 12 months (173 treated with Klisyri and 29 treated with vehicle). No adverse reactions were observed throughout the follow-up phase. The results did not change the safety profile of Klisyri (see «Properties/Effects»).

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Overdose following topical application with tirbanibulin may cause an increase in incidence and severity of local skin reactions. No systemic signs of overdose are expected following topical application of Klisyri due to the low systemic absorption of tirbanibulin. Management of overdose should consist of treatment of clinical symptoms.
For indications on incorrect routes of administration, see «Warnings and precautions».

Properties/Effects

ATC code

D06BX03

Mechanism of action

Tirbanibulin has potent anti-proliferative and anti-tumour activities *in vitro* and *in vivo*. Tirbanibulin disrupts the cellular microtubule network via direct binding to tubulin which induces cell cycle arrest and apoptotic cell death, and is associated with disruption of Src tyrosine kinase signalling.

Pharmacodynamics

See Mechanism of action.

Clinical efficacy

The efficacy of Klisyri applied on the face or scalp for 5 consecutive days was studied in two pivotal randomised, double-blind, vehicle-controlled Phase III studies (KX01-AK-003 and KX01-AK-004) including 702 adult patients (353 patients treated with Klisyri 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. The compliance rate was high, with >99% of the patients completing these studies. In the Klisyri 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 and partial clearance rate, as well as median percent reduction in actinic keratosis lesions, was assessed at day 57.

At day 57, patients treated with Klisyri had statistically significantly higher complete and partial clearance rates than patients treated with vehicle (p<0.0001). The median percent reduction in actinic keratosis lesions was also higher in the group treated with Klisyri compared with the vehicle group (see Table 2). The level of efficacy varied between the individual anatomical locations (face or scalp). Within each location, the complete and partial clearance rates were statistically significant higher in the group treated with Klisyri compared with the vehicle group (see Table 3).

Table 2: Complete and partial clearance rates and median percent (%) actinic keratosis lesion reduction at day 57, ITT population (KX01-AK-003 and KX01-AK-004)

	Overall (face and scalp)			
	KX01-AK-003		**KX01-AK-004**	
	Klisyri 10 mg/g ointment (N=175)	**Vehicle (N=176)**	**Klisyri 10 mg/g ointment (N=178)**	**Vehicle (N=173)**
Complete (100%) clearance rate[a]	77/175 44%[d]	8/176 5%	97/178 54%	22/173 13%
Partial (≥75%) clearance rate[b]	119/175 68%[d]	29/176 16%	136/178 76%	34/173 20%
Median % reduction in actinic keratosis lesions[c]	83.3%	20%	100%	25%

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] Median percent (%) reduction in actinic keratosis lesions compared to baseline.

[d] 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 (KX01-AK-003 and KX01-AK-004)

Location	KX01-AK-003		KX01-AK-004	
	Klisyri 10 mg/g ointment (N=175)	Vehicle (N=176)	Klisyri 10 mg/g ointment (N=178)	Vehicle (N=173)
	Complete (100%) Clearance Rate			
Face n/N	60/119	7/121	73/119	16/118
%	50%	6%	61%	14%
(95% CI)	(41-60%)[a]	(2-12%)	(52-70%)[a]	(8-21%)
Scalp n/N	17/56	1/55	24/59	6/55
%	30%	2%	41%	11%
(95% CI)	(19-44%)[a]	(0-10%)	(28-54%)[b]	(4-22%)
	Partial (>75%) Clearance Rate			
Face n/N	90/119	23/121	95/119	26/118
%	76%	19%	80%	22%
(95% KI)	(67-83%)[a]	(12-27%)	(71-87%))[a]	(15-31%)
Scalp n/N	29/56	6/55	41/59	8/55
%	52%	11%	69%	15%
(95% KI)	(38-65%)[a]	(4-22%)	(56-81%)[a]	(6-27%)

CI=confidence interval; ITT=Intent-to-Treat
a)p<0.0001; compared to vehicle by Cochran-Mantel-Haenszel stratified by study.
b)p<0.0003; 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 Klisyri compared with the vehicle group (p≤0.0003), both overall and by treatment location (face or scalp).

At day 57, there was a reduction in the median actinic keratosis lesion count of 83% and 100% in the Klisyri groups compared with 20% and 25% for the vehicle treatment groups for Study KX01-AK-003 and Study KX01-AK-004, respectively.

Long-term data

A total of 204 patients achieved complete clearance of actinic keratosis lesions in the treatment field at day 57 (174 treated with Klisyri and 30 treated with vehicle) and were eligible for a 12-months follow-up period to assess recurrence. After one year reappearance of lesions at baseline or new lesions resulted in a recurrence rate of 73% in Klisyri treated patients.

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 Klisyri (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 Klisyri.

Efficacy in elderly patients

Of the 353 patients treated with Klisyri 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 efficacy were observed between younger and older patients.

Pharmacokinetics

Absorption

Following topical treatment of Klisyri to a 25 cm^2 contiguous area of the face or balding scalp, once daily for 5 consecutive days, the steady-state concentration of tirbanibulin was achieved by 72 hours. On Day 5, systemic exposure to tirbanibulin was low with a mean maximum plasma concentration (C_{max}) of 0,34±0,30 ng/mL and 0,18±0,10 ng/mL, and a mean area under the plasma concentration curve from time zero to 24 hours (AUC_{24}) of 5,0±3,9 h*ng/mL and 3,2±1,9 h*ng/mL, in subjects who received the face and scalp topical treatment, respectively.

Distribution

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

Metabolism

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.

Elimination

Excretion of tirbanibulin has not been fully characterized in humans.

Kinetics in specific patient groups

Hepatic and renal impairment

No studies of Klisyri in patients with hepatic or renal impairment have been conducted. Due to the low systemic exposure after topical application of Klisyri 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 «Dosage/Administration»).

In vitro drug interactions

CYP Enzymes: Tirbanibulin and the metabolite KX2-5036 directly or time-dependently inhibited CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4 with an IC50 value of >17 μM. Tirbanibulin up to 1 μM (431.5 ng/mL) and the metabolite KX2-5036 up to 3 μM (1024 ng/mL) did not induce CYP 1A2, 2B6, or 3A4. These findings suggest that Klisyri has no clinically meaningful effect on the pharmacokinetics of drugs metabolized by CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4.
Drug Transporters: Neither tirbanibulin nor the metabolite KX2-5036 was a substrate of MDR1, BCRP, BSEP, MRP2, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 or OCT2. Tirbanibulin and the metabolite KX2-5036 inhibited MATE1, MATE2-K, OATP1B1, OATP1B3, OCT1 and/or OCT2 with an IC50 value of >1 μM. The results suggest that Klisyri has no clinically meaningful effect on the pharmacokinetics of drugs mediated by MATE1, MATE2-K, OATP1B1, OATP1B3, OCT1 and OCT2.

Preclinical data

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

Genotoxicity

Tirbanibulin was not mutagenic (Ames) but induced chromosomal damage and micronuclei in genotoxicity studies. Detailed testing suggested that tirbanibulin is 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.

Carcinogenicity

Studies on carcinogenicity of tirbanibulin have not been conducted.

Reproductive toxicity

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. The clinical relevance of these findings is unknown.
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. The clinical relevance of this finding is unknown.

Other data – (Local toxicity, phototoxicity)

Tirbanibulin caused slight to moderate irritation of the skin following dermal application b.i.d for 6 or 8 days in dermal irritation studies in rats and rabbits, respectively. In repeated dose toxicity studies in rat and minipig, tirbanibulin caused dermal toxicity following 5 and 28 days and 3 months of application (4 cycles of 5 consecutive days of treatment separated by 23 treatment-free days). Local toxicity, skin irritation and degeneration/necrosis in the epidermis/dermis, was reversible or showed a tendency toward recovery following the 2 to 3 week recovery period in the respective studies. Tirbanibulin was a moderate contact sensitiser in animal studies but this was not confirmed in humans.
Tirbanibulin did not display ocular irritation potential *in vitro* using the EpiOcular Eye Irritation Test. However, an *in vivo* ocular irritation study showed tirbanibulin was an irritant to the eyes of rabbits after a single application. In rabbit, tirbanibulin demonstrated no phototoxicity following single dermal application and ultraviolet A (UVA) irradiation.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date («EXP») stated on the pack.

Shelf life after opening

Sachets should be discarded after first use.

Special precautions for storage

Do not store above 30°C. Do not store in the refrigerator. Do not freeze.
Keep out of reach of children.

Authorisation number

68322 (Swissmedic)

Packs

Packs of 5 sachets à 250 mg ointment. [A]

Marketing authorisation holder

Almirall AG, 8304 Wallisellen

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