CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213189Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	213189
PDUFA Goal Date	December 30, 2020
OSE RCM #	2019-2685
Reviewer Name(s)	Donella Fitzgerald, PharmD
	Lindsey Crist, PharmD, BCPS
Acting Team Leader	Jacqueline Sheppard, PharmD
Acting Deputy Director	Doris Auth, PharmD
Review Completion Date	August 20, 2020
Subject	Evaluation of Need for a REMS
Established Name	Tirbanibulin
Trade Name	Klisyri
Name of Applicant	Athenex Inc.
Therapeutic Class	Microtubule inhibitor
Formulation(s)	Topical ointment, 1%
Dosing Regimen	(b) (4)

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Klisyri (tirbanibulin) is necessary to ensure the benefits outweigh its risks. Athenex Inc. submitted a New Drug Application (NDA) 213189 for tirbanibulin with the proposed indication for the topical treatment of actinic keratosis of the face or scalp. The risks associated with tirbanibulin include local skin reactions and potential skin cancer development. The applicant did not submit a proposed REMS or risk management plan with this application.

Actinic keratosis is a cutaneous lesion resulting from long-term sun exposure.[1,2] It is characterized by erythematous, scaly papules or plaques on areas exposed to the sun and has the potential to progress to squamous cell carcinoma.[1] Treatment with tirbanibulin resulted in an overall statistically significant improvement in the primary endpoint of complete clearance compared to the vehicle groups in the Phase 3 studies. Although local skin reactions occurred frequently in the trials, they are common with topical actinic keratosis treatments, were not serious and self-resolved. The causality of the single report of treatment site skin cancer development could not be determined, as skin cancer is common with disease progression.

Based on the safety profile and the efficacy demonstrated in the clinical trials, the Division of Risk Management and the Division of Dermatology and Dentistry (DDD) has determined that risk mitigation beyond labeling is unnecessary. A REMS is not needed to ensure the benefits of tirbanibulin outweigh its risks.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Klisyri (tirbanibulin) is necessary to ensure the benefits outweigh its risks. Athenex Inc. (Athenex) submitted a New Drug Application (NDA) 213189 for tirbanibulin with the proposed indication for the topical treatment of actinic keratosis (AK) of the face or scalp. This application is under review in the Division of Dermatology and Dentistry (DDD). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Klisyri (tirbanibulin), a new molecular entity[a], is a microtubule inhibitor proposed for the topical treatment of actinic keratosis (AK) of the face or scalp. The mechanism of action of tirbanibulin is unknown, though it has been shown to have antiproliferative effects in multiple cell lines in vitro,

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

including human keratinocytes, melanoma, and squamous cell carcinoma cells, and in mouse tumor models in vivo.

Tirbanibulin is proposed to be supplied as a topical ointment, 1%. It will be supplied as five (b) (4) packets containing 2.5 mg tirbanibulin in 250 mg ointment. The proposed dosage regimen is (b) (4) The duration of treatment is 5 days; however, actinic keratosis is a chronic condition and patients may require additional treatment courses for recurrences or new lesions.[b] Tirbanibulin will likely be administered in the outpatient setting. It is not currently approved in any jurisdiction and would be the first agent in its pharmacologic class for AK. None of the topical agents approved for AK have risk management strategies beyond labeling.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 213189 relevant to this review:

- 12/30/2019: NDA 213189 submission for the topical treatment of actinic keratosis of the face or scalp received.[3]
- 5/27/2020: A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues at this time that require a REMS for tirbanibulin.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Actinic keratosis (also known as solar keratosis) is a cutaneous lesion resulting from long-term sun exposure.[1,2] The lesions develop due to proliferation of atypical epidermal keratinocytes and have the potential to progress to squamous cell carcinoma (SCC).[1] The clinical presentation consists of solitary or multiple erythematous, scaly papules or plaques on areas exposed to the sun such as the face, balding scalp, neck, shoulders, and the back of the arms and hands. Patients may be asymptomatic, or they may experience burning, itching, or tenderness in the lesion area. Actinic keratosis affects between 40 to 58 million Americans, and is one of the most common reasons for dermatologist visits.[4,5,c] It is the most common precancerous lesion of the skin. About 60% of squamous cell carcinomas arise from preexisting actinic keratoses.[6] The risk is higher in older adults, people with fair skin, people with extensive sun exposure, and in men compared to women. It is difficult to predict whether AK will progress to squamous cell carcinoma; however, it is estimated that the risk of progression in studies ranges from 0.025 to 16% per lesion per year.[1,7,d] The risk of progression is higher in patients with

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*
[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*
[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

multiple lesions.[8] SCC is the second leading cause of skin cancer deaths in the United States. The goal of treatment is to eliminate AK lesions to minimize the risk of progression to invasive SCC.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

There are varying approaches for the management of actinic keratosis. The decision to treat and the preferred treatment depend on the number and extent of lesions, presence of symptoms, and patient and clinician preferences. Spontaneous resolution of lesions may occur; however, untreated lesions may progress to SCC.[9] Current treatment strategies include lesion destructive therapies (e.g. surgery, cryotherapy, dermabrasion, and photodynamic therapy), field-directed therapies that can target multiple lesions over a continuous surface (topical agents, chemical peels, laser resurfacing), or sequential/combinations of these options. The treatment setting varies, some treatments are outpatient dermatologic procedures whereas others are self-administered at home. A summary of pharmacologic treatment options is provided in the table in the Appendix.

4 Benefit Assessment

The efficacy and safety of topical tirbanibulin 1% ointment for the treatment of AK was demonstrated in two pivotal phase 3 studies (Study KX01-AK-003, NCT03285477 and Study KX01-AK-004, NCT03285490).[10,11]

The two phase 3 studies were identical in design: multicenter, randomized, double-blind, and placebo (vehicle)-controlled. Eligible patients were required to have a continuous treatment area on the head or scalp of 25 cm^2 which contained 4 to 8 clinically typical, visible AK lesions. Patients were randomized (1:1) to tirbanibulin 1% ointment or a vehicle over the treatment area for 5 days. Randomization was stratified by treatment location (face or scalp).[e] The primary efficacy endpoint was complete clearance rate, defined as the proportion of subjects at Day 57 with 100% reduction in the number of AK lesions identified at baseline in the treatment area. The studies both consisted of a 28-day screening period, a 5-day treatment period, and a 52-day assessment period. Subjects with complete clearance of lesions entered a recurrence follow-up period and were assessed every 3 months until recurrence or up to 12 months after Day 57.

Results

The phase 3 studies enrolled a total of 702 subjects, 351 in Study KX01-AK-003 (Study 003) and 351 in KX01-AK-004 (Study 004). Treatment with tirbanibulin resulted in a statistically significant improvement in the primary endpoint of complete clearance at Day 57 compared to the vehicle groups in both studies. The clinical reviewer concluded that the Applicant provided substantial evidence of effectiveness.[12] Treatment results are summarized below in Table 1.

[e] Enrollment for both pivotal studies was controlled so that two-thirds of subjects were to receive treatment on the face and one-third received treatment on the scalp.

Table 1. Complete (100%) AK Clearance Rates on Day 57 from the two Phase 3 studies (Intent-to-Treat Population)[13]

	Study 003				Study 004			
	Tirbanibulin N = 175 n/N (%)	**Vehicle N = 176** n/N (%)	**Treatment difference (Tirbanibulin-Vehicle)**	**95% Confidence Interval for the Treatment difference**	**Tirbanibulin N = 178** n/N (%)	**Vehicle N = 173** n/N (%)	**Treatment difference (Tirbanibulin-Vehicle)**	**95% Confidence Interval for the Treatment difference**
All treatment locations	77/175 (44%)	8/176 (5%)	39.5%[a]	(31.6%, 47.5%)[a]	97/178 (54%)	22/173 (13%)	41.9%	(33.1%, 50.7%)[a]
Face	60/119 (50%)	7/121 (6%)	44.6%	(34.7%, 54.5%)[b]	73/119 (61%)	16/118 (14%)	47.8%	(37.1%, 58.5%)[b]
Scalp	17/56 (30%)	1/55 (2%)	28.5%	(16.0%,41.1%)[b]	24/59 (41%)	6/55 (11%)	29.8%	(14.8%, 44.8%)[b]

a. Based on Mantel-Haenszel risk limit

b. Based on Wald confidence interval.

5 Risk Assessment & Safe-Use Conditions

The primary safety analysis for tirbanibulin in actinic keratosis is based on the pooled data from the 702 subjects in the phase 3 trials, as well as supportive data from a Phase 2a study. The safety analysis included all randomized subjects who received at least one dose of study treatment and was collected through Day 57 and during the Recurrence Follow-up Period.

The most common treatment emergent adverse events (TEAEs) related to tirbanibulin were local skin reactions (LSR) which include erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation and erosion/ulceration. Application site pain and pruritis were also identified in ≥ 2% of subjects in the Phase 3 trials. All the LSR were self-limited and did not require treatment. If approved, labeling will include a warning and precaution for LSR and recommend that tirbanibulin not be used if skin is unhealed from any previous drug or surgical treatment.

5.1 SERIOUS ADVERSE REACTIONS

5.1.1 Death

There was one death in the tirbanibulin clinical development program. One subject in the vehicle group of the Phase 3 trial, KX01-AK-003, died by suicide. The clinical reviewer did not attribute the patient death to treatment with the study drug.[14]

5.1.2 Non-fatal Serious Adverse Reactions

Two patients experienced at least one serious adverse event (SAE) in the tirbanibulin group compared to 6 patients in the vehicle group. One tirbanibulin treated patient experienced a pulmonary embolism and the other was diagnosed with sepsis, hairy cell leukemia and secondary anemia and pancytopenia.

Serious adverse events reported in the vehicle group include myocardial infarction, lumbar degenerative disk disease, complete heart block, chest pain and bacteremia. Per the clinical reviewer, the pulmonary embolism and sepsis experienced in the treatment group were unlikely attributable to study drug.[f] She stated in the multidisciplinary review draft that there is insufficient information to determine whether the hairy cell leukemia was related to tirbanibulin treatment.

5.2 ADVERSE EVENTS OF SPECIAL INTEREST

5.2.1 Skin Cancer

In study 003, nine skin cancers were reported in seven treatment group subjects, and four skin cancers in four vehicle group subjects. Of the reports in the treatment group, one occurred in a tirbanibulin treated area (scalp) on Day 74. The clinical reviewer stated that it is impossible to determine causality of tirbanibulin application 69 to 74 days prior to the diagnosis. In study 004, five skin cancers were reported in five treatment group subjects, compared to six skin cancers reported in four vehicle group subjects. In this study, none of the cancers were reported in an area treated with study drug. The clinical reviewer concluded in the multidisciplinary review draft that no pattern of development, nor association of skin cancer diagnosis and tirbanibulin application could be confirmed. A high proportion of study subjects (42%-47%) had a history of skin cancers, as is common with AK disease progression. She stated that it is possible the cancers reported were already developing.

6 Expected Postmarket Use

Tirbanibulin is expected to be prescribed by dermatologists involved in the treatment of actinic keratosis, though some primary care providers may prescribe it as well. The risks associated with tirbanibulin are similar to other topical therapies for actinic keratosis. The likely prescribers are familiar with managing a range of local skin reactions. Tirbanibulin is likely to be self-administered by patients in an outpatient setting for the 5-day treatment period.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for tirbanibulin beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of tirbanibulin based on the efficacy and safety information currently available.[14]

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

Actinic keratosis is a common cutaneous lesion resulting from long-term sun exposure that may progress to squamous cell carcinoma (SCC). Patients may present with one or multiple lesions. About 60% of squamous cell carcinomas arise from preexisting actinic keratoses. The goal of treatment is to eliminate actinic keratosis lesions to minimize the risk of progression to invasive SCC. Several treatment options exist including dermatologic procedures as well as topical therapies.

The benefit of tirbanibulin was demonstrated in two Phase 3 clinical trials. Treatment with tirbanibulin resulted in an overall statistically significant improvement in the primary endpoint of complete clearance at Day 57 compared to the vehicle groups in both studies. Mild to moderate local skin reactions were the most frequently occurring adverse events and have also been observed with approved topical AK treatments. The proposed prescribing information includes local skin reactions in the warning and precautions. One report of treatment site skin cancer also occurred, however skin cancer is common with AK disease progression and the clinical reviewer concluded that tirbanibulin causality could not be determined.

Therefore, based on the observed benefit and the safety data available, the risks associated with tirbanibulin do not pose unique considerations for a REMS and can be communicated with labeling. This reviewer is not recommending a REMS for management of the potential risks of tirbanibulin therapy.

9 Conclusion & Recommendations

Based on the information available, the benefit-risk profile is favorable therefore, a REMS is not necessary for tirbanibulin to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 References

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12. Epps R. Division of Dermatology and Dental Products draft Unireview for Tirbanibulin NDA 213189. July 23, 2020.
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10.2 SUMMARY OF TREATMENT OPTIONS FOR ACTINIC KERATOSIS (AK)[15]

Trade Name (Generic), Approval Year	Indication[a]	Dosage form; dosage for AK	Important Safety and Tolerability Issues	Risk Management Approaches
FDA Approved Topical Treatments				
Carac (fluorouracil cream), 1962	Topical treatment of multiple AK of the face and anterior scalp	0.5% cream; once daily for up to 4 weeks	Contraindicated in pregnancy, dihydropyrimidine dehydrogenase deficiency Application site adverse reactions (erythema, scaling/dryness, edema, crusting, erosions, stinging/burning, and pruritus); hypersensitivity (may be delayed); ophthalmic adverse reactions; photosensitivity; embryofetal toxicity	Labeling – Contraindications, Warnings and Precautions
Efudex (fluorouracil cream), 1962	Treatment of multiple AK	5% cream; 2% and 5% topical solution; twice daily for 2 to 4 weeks		
Fluoroplex (fluorouracil cream), 1962	Topical treatment of multiple AK	1% cream; twice daily for 2 to 6 weeks		
Tolak (fluorouracil cream), 1962	Topical treatment of AK lesions of the face, ears, and scalp	4% cream; once daily for 4 weeks		
Aldara (imiquimod cream), 1997	Clinically typical, nonhyperkeratotic, nonhypertrophic AK on the face or scalp in immunocompetent adults	5% cream; 2 times per week for 16 weeks to treatment area	Local inflammatory reactions (e.g. skin weeping and erosion); systemic reactions (e.g. flu-like symptoms); photosensitivity; data not available for repeated use for AK in same area	Labeling – Warnings and Precautions
Zyclara (imiquimod	Clinically typical, visible or palpable AK of the full	2.5% and 3.75% cream;	Local inflammatory reactions (e.g. skin	Labeling – Warnings and

cream), 1997	face or balding scalp in immunocompetent adults	Once daily to treatment area for 2-week treatment cycles separated by 2-week no-treatment period	weeping and erosion); systemic reactions (e.g. flu-like symptoms); photosensitivity; avoid with other imiquimod creams; caution in patients with autoimmune conditions	Precautions
Picato (ingenol mebutate gel), 2012	Topical treatment of AK	0.015% and 0.05% gel; Face or scalp: 0.015% once daily for 3 days; Trunk or extremities: 0.05% once daily for 2 days	Ophthalmic adverse reactions (e.g. severe eye pain, chemical conjunctivitis, corneal burn, eyelid edema, eyelid ptosis, periorbital edema); Hypersensitivity reactions (including anaphylaxis, allergic contact dermatitis); local skin reactions (e.g. erythema, crusting, vesiculation, erosion)	Labeling – Warnings and Precautions
Solaraze (diclofenac gel), 2000	Topical treatment of AK. Sun avoidance indicated during therapy.	3% gel, Applied to lesion areas twice daily for 60 to 90 days	Boxed Warning – cardiovascular (CV) thrombotic events[b] Contraindicated in the setting of coronary artery bypass surgery Nonsteroidal inflammatory class warnings /precautions (CV thrombotic events, heart failure and edema, caution in GI ulceration/bleeding, severe renal or hepatic impairment, anaphylaxis); local dermal adverse reactions	Labeling – Boxed Warning, Contraindications, Warnings and Precautions
Levulan Kerastick (aminolevulinic acid topical solution), 1999	For photodynamic therapy (treatment) of minimally to moderately thick AK of the face or scalp, or	20% topical solution; Administered only by healthcare provider	Contraindicated in cutaneous photosensitivity; porphyria or allergies to porphyrins	Labeling – Contraindications, Warnings and Precautions

	upper extremities *Must be used in combination with Blue Light Photodynamic therapy		Transient amnestic episodes; photosensitivity; irritation; not studied in patients with coagulation disorders	
Ameluz (aminolevulinic acid gel), 1999	For the lesion-directed and field-directed treatment of AK of mild to moderate severity on the face and scalp *Must be used in combination with photodynamic therapy	10% gel; Administered only by healthcare provider	Contraindicated in cutaneous photosensitivity; porphyria, allergies to porphyrins, photodermatoses Transient amnestic episodes; risk of eye injury, protective eyewear needed for patient and provider; photosensitivity; risk of bleeding – caution in patients with coagulation disorders, ophthalmic adverse reactions, mucous membrane irritation	Labeling – Contraindications, Warnings and Precautions
Metvixia (methyl aminolevulinate), 2004	For treatment of thin and moderately thick, non-hyperkeratotic, non-pigmented AK of the face and scalp in immunocompetent patients when used in conjunction with lesion preparation in the physician's office when other therapies are considered medically less appropriate *Must be used with red light illumination therapy	16.8% cream; Administered only by healthcare provider for treatment session	Contraindicated in cutaneous photosensitivity; porphyria or allergies to porphyrins Not been studied for more than one course; Hypersensitivity	Labeling – Contraindications, Warnings and Precautions
Other Treatments Retinoids and salicylic have been used off label for actinic keratosis				

[a]Indication is not a comprehensive list of all FDA approved indications, only the AK indication; [b]Diclofenac gel shares the NSAID class Boxed Warning for CV events and Warnings/Precautions

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