# NEW DRUG APPROVAL

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| **Brand Name** | Klisyri® |
| **Generic Name** | tirbanibulin |
| **Drug Manufacturer** | Athenex, Inc. |

## New Drug Approval

FDA Approval Date: December 14, 2020

Review Designation: Standard

Type of Review: Type 1 - New Molecular Entity

Dispensing Restrictions: Open Distribution

## Place in Therapy

### DISEASE DESCRIPTION & EPIDEMIOLOGY

Actinic keratosis (AK) is the most common type of precancer. AK also known as solar keratosis, is characterized by rough, scaly patches on the skin (most commonly found on the face, lips, ears, back of the hands, forearms, scalp, or neck), resulting from years of exposure to the sun. AK lesions can lead to squamous cell carcinoma (SCC). AK is routinely treated because AK lesions that progress to SCC are not distinguished from those that do not progress. The prevalence is likely underestimated given many people have AKs but do not know it or do not seek diagnosis or treatment. The prevalence of AK is directly correlated with age and is highest in countries near the equator with light-skinned populations. In the United States, the prevalence is not well characterized, but is approximately 10% in people between 20 and 30 years of age and more than 90% in people over 80 years of age.

## Efficacy

Actinic Keratosis of the Face or Scalp: Two double-blind, vehicle-controlled clinical trials (NCT03285477 and NCT03285490) were conducted with 702 adult subjects with actinic keratosis on the face or scalp. Subjects were randomized 1:1 to Klisyri® or vehicle. Subjects enrolled had 4 to 8 clinically typical, visible, and discrete AK lesions in a contiguous area of 25 $cm^2$ on the face or scalp. Subjects had an average age of 70 years (range 45 to 96 years), were predominantly Caucasian (99%), male (87%), with Fitzpatrick skin types I or II (72%) and actinic keratosis on the face (68%) or scalp (32%). Treatment groups were comparable across all demographics and baseline characteristics, including AK lesion count and distribution on the face or scalp. Subjects received 5 consecutive days of once daily treatment with either Klisyri® (353) or vehicle control (349) to the treatment field. Subjects with complete (100%) clearance of AK lesions in the treatment area at Day 57 returned to the clinic for recurrence assessment every 3 months for a total of 12 months post-Day 57.

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The primary efficacy endpoint was complete (100%) clearance of AK lesions in the treatment area, defined as the proportion of subjects at Day 57 with no clinically visible AK lesions in the treatment area and the secondary endpoint was partial (≥75%) clearance of AK lesions in the treatment area. Results from both studies are presented below.

**Table 1: Complete (100%) AK Clearance Rates on Day 57 for the Two Phase 3 Studies (Intent-to-Treat [ITT] Population**

| | Study 1 | | | | Study 2 | | | |
|---|---|---|---|---|---|---|---|---|
| | **KLISYRI N = 175 n/N (%)** | **Vehicle N = 176 n/N (%)** | **Treatment difference (KLISYRI -Vehicle)** | **95% Confidence Interval for the Treatment difference** | **KLISYRI N = 178 n/N (%)** | **Vehicle N = 173 n/N (%)** | **Treatment difference (KLISYRI -Vehicle)** | **95% Confidence Interval for the Treatment difference** |
| All subjects | 77/175 (44%) | 8/176 (5%) | 40%[a] | (31.6%, 47.5%)[a] | 97/178 (54%) | 22/173 (13%) | 42%[a] | (33.1%, 50.7%)[a] |
| Face | 60/119 (50%) | 7/121 (6%) | 45% | -- | 73/119 (61%) | 16/118 (14%) | 48% | -- |
| Scalp | 17/56 (30%) | 1/55 (2%) | 29% | -- | 24/59 (41%) | 6/55 (11%) | 30% | -- |

**Table 2: Partial (≥ 75%) AK Clearance Rates on Day 57 for the Two Phase 3 Studies (Intent-to-Treat [ITT] Population)**

| | Study 1 | | | | Study 2 | | | |
|---|---|---|---|---|---|---|---|---|
| | **KLISYRI N = 175 n/N (%)** | **Vehicle N = 176 n/N (%)** | **Treatment difference (KLISYRI -Vehicle)** | **95% Confidence Interval for the Treatment difference** | **KLISYRI N = 178 n/N (%)** | **Vehicle N = 173 n/N (%)** | **Treatment difference (KLISYRI -Vehicle)** | **95% Confidence Interval for the Treatment difference** |
| All subjects | 119/175 (68%) | 29/176 (16%) | 52%[a] | (42.9%, 60.3%)[a] | 136/178 (76%) | 34/173 (20%) | 57%[a] | (48.3%, 65.4%)[a] |
| Face | 90/119 (76%) | 23/121 (19%) | 57% | -- | 95/119 (80%) | 26/118 (22%) | 58% | -- |
| Scalp | 29/56 (52%) | 6/55 (11%) | 41% | -- | 41/59 (69%) | 8/55 (15%) | 55% | -- |

Efficacy was consistent across sex and age (<65 and ≥65 years) subgroups.

Subjects who achieved 100% clearance of AK lesions in the treatment area at Day 57 continued to be followed for up to 12 months following Day 57 to determine the recurrence rate. Recurrence was defined as the proportion of subjects with any identified AK lesion (new or previous lesion) in the previously treated area who achieved 100% clearance at Day 57. Of the 174 subjects treated with Klisyri® who were followed, the recurrence rate at 12 months post-Day 57 was 73%.

## Safety

### ADVERSE EVENTS

Most common adverse reactions (incidence ≥2%) are local skin reactions, application site pruritus, and application site pain.

### WARNINGS & PRECAUTIONS

- May cause eye irritation upon ocular exposure. Avoid transfer of the drug into the eyes and to the periocular area. If accidental exposure occurs, flush eyes with water and seek medical care.
- Local skin reactions can occur including severe reactions (e.g., vesiculation/pustulation, erosion/ulceration) in the treated area. Avoid use until skin is healed from any previous drug or surgical treatment.

### CONTRAINDICATIONS

None.

## Clinical Pharmacology

### MECHANISMS OF ACTION

Tirbanibulin is a topical microtubule inhibitor approved to treat actinic keratosis of the face or scalp. According to the FDA-approved product labelling, the mechanism of action of tirbanibulin for actinic keratosis is unknown; however, studies indicate the drug has a dual mechanism of action consisting of Src protein tyrosine kinase (PTK) inhibition and tubulin polymerization inhibition. Increased Src activity has been observed in hyperproliferative skin diseases, such as actinic keratosis.

## Dose & Administration

### ADULTS

Topical: Apply once daily to evenly cover up to a 25 $cm^2$ area (using no more than 1 single-dose packet per application) for 5 consecutive days.

### PEDIATRICS

Not available.

### GERIATRICS

Refer to adult dosing.

### RENAL IMPAIRMENT

Not available.

### HEPATIC IMPAIRMENT

Not available.

## Product Availability

### DOSAGE FORM(S) & STRENGTH(S)

Ointment: 1% tirbanibulin, single-dose packets.