Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2395

tirbanibulin 10mg/g ointment (Klisyri®) Almirall

05 November 2021

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC executive, advises NHS Boards and Area Drug and Therapeutics Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

tirbanibulin (Klisyri®) is accepted for use within NHSScotland.

Indication under review: field treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis (Olsen grade 1) of the face or scalp in adults.

In two phase III studies, a greater proportion of adults with actinic keratosis affecting an area of 25cm^2 on the face or scalp achieved complete clearance when treated with tirbanibulin ointment 1% compared with vehicle.

Chairman
Scottish Medicines Consortium

Indication

Field treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis (Olsen grade 1) of the face or scalp in adults.[1]

Dosing Information

Tirbanibulin ointment should be applied to the affected field on the face or scalp once daily for one treatment cycle of 5 consecutive days. A thin layer of ointment should be applied to cover the treatment field of up to 25cm^2. The ointment should be applied at approximately the same time each day. Tirbanibulin 10mg/g ointment is provided in sachets containing 2.5mg of tirbanibulin in 250mg ointment for single use only.

Tirbanibulin ointment should not be applied until the skin is healed from treatment with any previous medicinal product, procedure or surgical treatment and should not be applied to open wounds or broken skin.

Therapeutic effect can be assessed approximately 8 weeks after treatment starts. If the treated area does not show complete clearance at the follow-up examination, about 8 weeks after the treatment cycle started or thereafter, the treatment should be re-evaluated and management re-considered.

No clinical data on treatment for more than one treatment course of 5 consecutive days are available. If recurrence occurs, or new lesions develop within the treatment area, other treatment options should be considered. Treatment should be initiated and monitored by a physician.[1]

Product availability date

September 2021

Summary of evidence on comparative efficacy

By binding to tubulin directly, tirbanibulin disrupts microtubules, which induces cell cycle arrest and apoptotic death of proliferating cells. It is also associated with disruption of Src tyrosine kinase signalling. [1]

The key evidence supporting the efficacy and safety of tirbanibulin comes from KX01-AK-003 and KX01-AK-004, which were two identical, multicentre, randomised, double-blind, parallel group, phase III studies. Eligible patients were adults with four to eight clinically typical, visible, and discrete actinic keratosis (AK) lesions on the face or scalp within a contiguous area measuring 25cm^2. They had good general health and were willing to avoid excessive sunlight or ultraviolet light exposure to the face or scalp.[2, 3]

In each study, 351 patients were randomised equally to receive tirbanibulin ointment 1% or vehicle ointment, self-applied to treatment area once daily for 5 consecutive days. Patients were

prohibited from applying any topical products to the treatment area, including moisturizers or sunscreen up to day 57, unless prescribed by the investigator for the management of local skin reactions, or any treatment for AK lesions, other than the study drug.[2, 3]

The primary efficacy outcome was the complete (100%) clearance rate of AK lesions, defined as the proportion of patients at day 57 with no clinically visible AK lesions in the treatment area. The key secondary outcome was partial clearance rate of AK lesions, defined as the proportion of patients at day 57 with ≥75% reduction in the number of AK lesions identified at baseline in the treatment area. See results in Table 1. [2, 3]

Table 1: Primary and key secondary outcomes of KX01-AK-003 and KX01-AK-004 studies (ITT population) [2, 3]

	KX01-AK-003 study			KX01-AK-004 study		
	Tirbanibulin (n=175)	**Vehicle (n=176)**	**P-value**	**Tirbanibulin (n=178)**	**Vehicle (n=173)**	**P-value**
Complete clearance rate of AK lesions in the treatment area						
Overall, %	44%	5%	<0.0001	54%	13%	<0.0001
Face, %	50%	6%	-	61%	14%	-
Scalp, %	30%	2%	-	41%	11%	-
Partial clearance rate of AK lesions in the treatment area						
Overall, %	68%	16%	<0.0001	76%	20%	<0.0001
Face, %	76%	19%	-	80%	22%	-
Scalp, %	52%	11%	-	69%	15%	-

Abbreviations: AK, actinic keratosis; ITT, intention-to-treat.

The submitting company conducted a Bayesian network meta-analysis (NMA) to compare the efficacy of tirbanibulin ointment with other therapies used to treat AK. These included topical therapies (diclofenac 3%; 5-fluorouracil 5%; 5-fluorouracil 0.5% with salicylic acid 10%) in the primary analysis, which assessed complete clearance after one course of treatment. Comparators including photodynamic therapy (plus methyl aminolevulinate or 5-aminolevulinic acid), cryotherapy, imiquimod 5% and 3.75% and the above topical therapies were assessed in a secondary analysis that could include multiple treatment courses. The results of the primary analysis indicated that tirbanibulin had similar efficacy to 5-fluorouracil 5% and 5-fluorouracil 0.5% with salicylic acid 10%. Tirbanibulin's credible intervals overlapped with each treatment, although tirbanibulin had a lower point estimate than 5-fluorouracil 5%, and higher point estimate than 5-fluorouracil 0.5% with salicylic acid 10%. Tirbanibulin was otherwise more effective than diclofenac 3% (higher point estimate and credible intervals did not overlap). In the secondary analysis, credible intervals overlapped for all comparators (including 5-fluorouracil 5%, 5-fluorouracil 0.5% with salicylic acid 10% and imiquimod 3.75% and 5%), except for diclofenac 3%, which was consistent with the primary analysis.

Summary of evidence on comparative safety

Tirbanibulin 1% ointment had a tolerable safety profile; most adverse events (AEs) were mild to moderate in severity, and reversible. In the pooled KX01-AK-003 and KX01-AK-004 studies, at day 57, any treatment-emergent AE was reported by 35% (124/353) of patients in the tirbanibulin group and 36% (124/349) in the control group respectively, of which 0.3% (1/353) and 1.7% (6/349) were serious. The most frequently reported treatment-emergent AEs of any grade with an incidence >2% in the tirbanibulin versus the control group were: application-site pain (9.9% versus 3.2%), application-site pruritus (9.1% versus 6.0%), upper respiratory tract infection (3.7% versus 4.9%), viral upper respiratory tract infection (3.1% versus 2.6%), skin abrasion (2.0% versus 2.3%).[2,3]

Summary of clinical effectiveness issues

Actinic keratosis is an ultraviolet light induced precancerous skin condition, occurring predominantly on the face, scalp, arms, and legs. It is common in older, fair-skinned people with a history of prolonged exposure to ultraviolet light, and is more frequently observed in men. If left untreated, AK has a low risk of progressing to invasive cutaneous squamous-cell carcinoma. Actinic keratosis lesions are manifest as ill-defined reddish to reddish-brown scaly lesions on erythematous base in areas damaged severely by sunlight. Current treatment options for AK include surgical destruction of the lesions (by cryosurgery or curettage with or without electrosurgery), photodynamic therapy and medical therapy. The appropriate treatment is generally chosen based on the number of lesions present and therapy may be broadly categorised as either lesion-directed (with cryosurgery) or field-directed (with topical products) or a combination of both. Field directed therapy is ideally suited to address multiple lesions and in particular in field cancerisation.[2, 3] Topical therapies include diclofenac (sometimes in combination with salicylic acid), 5-fluorouracil (alone or in combination with salicylic acid) and imiquimod. Tirbanibulin is a first in class treatment for field treatment of non-hyperkeratotic, non-hypertrophic AK (Olsen grade 1) of the face or scalp in adults.

In two identical clinical studies (KX01-AK-003 and KX01-AK-004), a significantly greater proportion of adults with AK lesions within a contiguous area of 25cm^2 on either the face or scalp (containing four to eight clinically typical, visible, and discrete AK lesions) achieved complete clearance when treated with tirbanibulin 1% ointment compared with vehicle.

Study investigators may have been unblinded to treatment allocation due to the occurrence of local skin reactions. In addition, the study duration was short for a chronic condition, and limited longer term sustained efficacy and safety data are available. There is no evidence on retreatment with tirbanibulin in patients who have a recurrence of AK lesions.[2]

There is no direct evidence comparing tirbanibulin with relevant comparators and the submitting company therefore conducted a Bayesian NMA. There was considerable clinical and methodological heterogeneity in the included studies with respect to baseline severity of AK,

study duration and definition of study outcomes, which leads to uncertainty in the validity of the results and credible intervals were wide. Other outcomes such as lesion count reduction, disease recurrence rates and safety were not assessed in the NMA. Despite these limitations, the company's conclusion that tirbanibulin ointment has similar efficacy to 5-flourouracil 5% and 5-fluorouracil 0.5% with salicylic acid 10%, and is more effective than diclofenac 3%, seems reasonable.

Clinical experts consulted by SMC considered that tirbanibulin is a therapeutic advancement due to the shorter treatment period compared with other topical therapies.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis evaluating tirbanibulin ointment (Klisyri®) for the field treatment of non-hyperkeratotic, non-hypertrophic AK (Olsen grade 1) of the face or scalp in adults. Comparisons were provided versus diclofenac 3% gel, imiquimod 3.75% (Zyclara®) cream, imiquimod 5% cream, 5-fluorouracil 5% (Efudix®) cream, and 5-fluorouracil 0.5% with salicylic acid 10% (Actikerall®) solution. The company excluded cryotherapy and photodynamic therapy from the analysis following feedback from clinical experts that these treatments were not widely used in Scottish clinical practice.

A cohort-based decision-tree model over a 1-year time horizon was developed. Patients were assumed to receive treatment upon entry to the model before transitioning through a series of decision nodes; at the first set of nodes, patients were assumed to have complete clearance of AK ('successful treatment') or have incomplete clearance ('unsuccessful treatment'). At the second (and final) set of nodes, patients could either experience a severe local skin reaction or not. For patients for whom treatment was successful, it was assumed that complete clearance occurs at the time point of the maximum treatment effect as measured in the relevant clinical studies, and that there was no recurrence of the disease for the remainder of the model time horizon. Patients for whom treatment was unsuccessful were also assumed to cease treatment at the end of the recommended treatment duration but retain clinically visible lesions for the remainder for the time horizon.

The clinical evidence used in the economic evaluation is a combination of estimates derived from a Bayesian NMA conducted by the company and various clinical studies for individual comparators; specifically, the Bayesian NMA was used to inform the relative effectiveness of each medicine at achieving complete clearance of lesions while medicine-specific clinical studies were used to inform the time to maximum treatment effect and probability of experiencing a severe local skin reaction.

The health state utility values used to capture the impact of AK on patients' health-related quality-of-life (HRQoL) were identified via a systematic literature review. This identified one relevant publication by Chen et al that outlined a catalogue of utility values for a variety of skin diseases.[7] A group of nine patients with AK participated in a time trade-off exercise to help estimate the HRQoL impact of their condition; this exercise estimated an average health state utility value of 0.981 for a patient with AK (assuming a utility value of 1.0 for no AK). Baseline characteristics of

patients in the Phase 3 tirbanibulin studies (average age: 70 years; gender: 13% female) were used alongside previously estimated UK population factors to adjust for age and gender HRQoL effects over a patient's life. In addition, the disutility associated with a severe local skin reaction was set equal to the value estimated for patients experiencing pruritus and related conditions (0.085) in Chen et al.

Medicines acquisition costs were included for tirbanibulin and comparators, and the dose and duration of each treatment was assumed to be consistent with that stated in the relevant summary of product characteristics. Other non-medicines healthcare costs estimated included disease and adverse event management costs. The quantities of non-medicines resource use included in the analysis were based entirely on clinical expert opinion.

The base-case cost-utility results versus each comparator are presented in Table 2 and imply that tirbanibulin is a 'dominant' treatment strategy (that it's less costly and more effective) than all comparators except 5-fluorouracil 0.5% with salicylic acid 10% where tirbanibulin is estimated to be marginally more expensive but also more effective - this is encapsulated in an incremental cost-effectiveness ratio of £2,946 per QALY. Disaggregated analyses provided by the company indicate that tirbanibulin's acquisition cost is less than diclofenac 3% gel and 5-fluorouracil 0.5% with salicylic acid 10% but more expensive than all other comparators considered. In addition, these analyses also showed that the majority of cost savings associated with tirbanibulin stem from an assumption of reduced healthcare resource use (for example up to 95% for the comparison versus imiquimod 5% cream) due to a higher proportion of patients initiating treatment in primary rather than secondary care therefore forgoing the need for an appointment with a consultant dermatologist.

Table 2: Base-case cost utility results

Comparator	Incremental costs	ICER (£ per QALY)
Diclofenac 3%	-£31.35	Dominant
Imiquimod 3.75%	-£88.61	Dominant
Imiquimod 5%	-£76.17	Dominant
5-fluorouracil 5%	-£92.84	Dominant
5-fluorouracil 0.5% with salicylic acid 10%	£11.91	2,946

Abbreviations: QALY, quality-adjusted life-year, ICER, incremental cost-effectiveness ratio

Given the size of the estimated incremental quality-adjusted life-years in the company's base-case results, the committee felt it more appropriate to view the decision problem as a cost-minimisation analysis; therefore, additional analyses were requested from the company. The base-case cost-minimisation results plus sensitivity analyses are shown in Table 3. These results help quantify the impact of assuming equal proportions of treatment initiation in primary versus secondary care, as well as providing a comparison versus photodynamic therapy among other scenarios.

Table 3: Base-case cost-minimisation results plus sensitivity analyses

Scenario	Description	Incremental costs				
		Diclofenac 3%	**Imiquimod 3.75%**	**Imiquimod 5%**	**5-fluorouracil 5%**	**5-fluorouracil 0.5% with salicylic acid 10%**
0	Base-case	-£31.35	-£81.61	-£76.17	-£92.84	£11.91
1	Equal proportions of patients initiate treatment in primary versus secondary care	-£31.35	-£0.42	£12.01	£12.98	-£23.36
2	Equal incidence of severe local skin reactions	-£31.13	-£83.94	-£71.90	-£79.72	£17.67
3	Equal time to maximum treatment effect	-£31.35	-£88.60	-£76.17	-£92.84	£11.91
4	Equal probability of complete clearance	-£14.00	-£88.60	-£76.17	-£92.84	£11.91
5	Scenarios 1, 2, 3 and 4 combined	-£13.78	£4.25	£16.29	£26.10	-£17.60
6	**Comparator:** photodynamic therapy	-£203.31				

Note: a negative incremental costs figure indicates cost savings associated with tirbanibulin

A number of limitations of the economic evaluation were identified such as the following:

- The vast majority of cost savings predicted from tirbanibulin stem from a reduction in health care resource use due to a greater number of patients initiating treatment in primary rather than secondary care. These assumptions have been entirely based on clinical expert opinion and there does not appear to be any other data to validate these assumptions. SMC clinical experts were asked to provide their opinion on the reasonableness of the company's assumptions which provided reassurance to the committee when considering a situation in the long-term once clinicians are familiar with this treatment.
- The company had originally excluded photodynamic therapy as a comparator from the analysis but this treatment was mentioned by SMC clinical experts as a potential comparator. The company provided a comparison versus photodynamic therapy upon request, which indicated that tirbanibulin was cost saving versus this comparator.

- No data were available to inform the relative effectiveness of tirbanibulin versus any comparator given the vehicle control design of the key clinical studies for this treatment. A Bayesian NMA was therefore carried out to estimate relative effectiveness across all comparators. The width of the credible intervals for achieving complete clearance of AK lesions is large for the majority of comparators, indicating uncertainty in their estimation; if comparator treatments are more effective than tirbanibulin then the economic results will not account for this.
- The methods used to derive the health state utility values associated with having AK were non-standard and inconsistent with the preferred approach for submissions to SMC; however, a comparison of the estimated utility gain following complete clearance with other available estimates suggests that the values used by the company are reasonable. Furthermore, given the committee preference for a cost-minimisation analysis, this limitation was of lesser importance.

Despite the limitations outlined above, the economic case was demonstrated.

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from MASScot - Melanoma Action and Support Scotland, which is a Scottish Charitable Incorporated Organisation.
- MASScot has not received any pharmaceutical company funding in the past two years.
- Actinic keratosis is a common sun-induced precancerous condition. As such, it arises on exposed skin. It can coalesce creating a large patch of inflamed and weeping unsightly skin. It can also present as a pink/red smooth intensely itchy macule. If neglected there is the possibility of squamous cell cancer arising. Actinic keratosis can be embarrassing as it is unsightly. It can also be irritating with itch and weeping and lead to difficulties concentrating. Where there is a history of skin cancer, it can also create anxiety.
- There are other topical treatments available for actinic keratosis but they have a longer treatment period. They also produce redness and irritation, which makes some fear that it is making things worse. Freezing too creates a sore red blistering area.
- Five consecutive days of application with tirbanibulin may be adhered to, whereas a medicine with a longer treatment period may not. The benefit of a shorter course of treatment and hopefully a shorter time to healing would be welcomed.

Additional information: guidelines and protocols

British Association of Dermatologists (BAD) published in 2017: 'British Association of Dermatologists' guidelines for the care of patients with actinic keratosis 2017'. For patients with non-hypertrophic AK (Olsen grade 1) of the face or scalp these guidelines recommend indicate

that active topical therapy is suited to use in primary and secondary care as lesion- and field-based treatment. Recommended topical treatments include: emollient and sunscreen with advice on sun protection; 5-fluorouracil cream; 5- fluorouracil 0.5% in 10% salicylic acid; imiquimod 5% or 3.75% cream; diclofenac 3% in a 2.5% hyaluronic gel and ingenol mebutate cream (not authorised anymore). Non-topical treatment recommendations include: cryosurgery; methyl aminolaevulinate photodynamic therapy (MAL-PDT).[4]

The Primary Care Dermatology Society published in 2020: 'Actinic (Solar) Keratosis primary care treatment pathway'. For patients with grade 1 AK, these guidelines recommend: 5- fluorouracil cream; 5- fluorouracil 0.5% in 10% salicylic acid; imiquimod 5% and photodynamic therapy. For patients with larger areas of field change, 3% diclofenac gel and imiquimod 3.75% cream are also recommended. [5]

The European Academy of Dermatology and Venereology (EADV) published in 2014 'Management of actinic keratosis: a practical report and treatment algorithm from AKTeamTM expert clinicians'. Topical treatments recommended include: 5- fluorouracil cream; 3% diclofenac sodium; imiquimod 5% and 150µg/g and 500µg/g ingenol mebutate. Non topical treatments recommended include: cryosurgery, curettage and photodynamic therapy.[6]

Additional information: comparators

Diclofenac 3%, 5-fluorouracil 5%, imiquimod 3.75% and 5%, 5-fluorouracil 0.5% with salicylic acid 10%, photodynamic therapy.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per 5-day cycle (£)
Tirbanibulin 10mg/g ointment	**Application to the affected field once daily for one treatment cycle of 5 consecutive days.**	**£59**

Costs from company submission. Costs for five sachets calculated using the full cost of sachets assuming wastage.

Additional information: budget impact

SMC is unable to publish the estimated number of eligible patients or budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget impact.

*Other data were also assessed but remain confidential.**

References

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6. Dréno B, Amici JM, Basset-Seguin N, Cribier B, Claudel JP, Richard MA. Management of actinic keratosis: a practical report and treatment algorithm from AKTeam expert clinicians. Journal of the European Academy of Dermatology and Venereology. 2014;28(9):1141-9.
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This assessment is based on data submitted by the applicant company up to and including 15 October 2021.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.