AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG Secretariat Assessment Report

Tirbanibulin (Klisyri®)
10 mg/g ointment

Reference number: 4076

Full submission

PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

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This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

AWMSG Secretariat Assessment Report
Tirbanibulin (Klisyri®▼) 10 mg/g ointment

1.0 Key facts

Assessment details	Tirbanibulin (Klisyri®▼) for the field treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis (Olsen grade 1) of the face or scalp in adults. ▼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 adverse reactions.
Current clinical practice	The applicant company suggest tirbanibulin should be positioned alongside other first-line treatment options for actinic keratoses (AK) of the face or scalp. Current topical therapies involve treatments over four weeks or more.
Clinical effectiveness and safety	In two identical phase III studies tirbanibulin was significantly more effective at clearing AK lesions than vehicle control ointment at Day 57. There was significant recurrence of AK in patients at a one year follow up after treatment with tirbanibulin. An indirect treatment comparison showed that tirbanibulin may be more effective than diclofenac gel 3% and has similar efficacy to 5-fluorouracil 5% and imiquimod 5%. Most adverse events of tirbanibulin were mild to moderate in severity, and reversible. Due to the need for longer term follow-up, the Committee for Medicinal Products for Human Use requested the company investigate the risk of progression of AK to squamous cell cancer in patients treated with tirbanibulin in a post-authorisation study over a three-year period.
Cost-effectiveness	A cost-utility analysis compares tirbanibulin with diclofenac 3%, imiquimod 5%, and 5-fluorouracil 5% in the first-line treatment of AK. The company base case suggests tirbanibulin dominates diclofenac gel 3%. Tirbanibulin has an incremental cost-effectiveness ratio (ICER) of £1,725/quality-adjusted life-year (QALY) gained compared to imiquimod 5% cream; and an ICER of £2,977/QALY compared to 5-fluorouracil 5% cream. AWTTC considers it more plausible to take the point estimate odds ratios for complete clearance rather than assuming equivalent clearance between tirbanibulin, 5-flourouracil 5% and imiquimod 5%. In this scenario, the

	ICER is £115,960/QALY and £4,697/QALY when compared to 5-fluorouracil 5% and imiquimod 5%, respectively. An alternative more plausible scenario includes incorporating recurrence of lesions resulting in ICERs of £3,936/QALY and £22,267/QALY compared to 5-fluorouracil 5% and imiquimod 5% respectively but tirbanibulin remains dominant compared to diclofenac 3%. The short time horizon does not consider progression to skin cancer, further treatment if the initial treatment is unsuccessful, nor the impact of adherence.
Budget impact	The company estimates that [commercial in confidence figure removed] people with AK are eligible to receive treatment with tirbanibulin in Wales each year from Year 1 to Year 5. The company estimate of the current market shares of the comparators is: fluorouracil [commercial in confidence figure removed], diclofenac [commercial in confidence figure removed] and imiquimod [commercial in confidence figure removed]. The company base case suggests additional costs of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5. The base case also predicts NHS resource savings valued at [commercial in confidence figure removed] in Year 2, increasing to [commercial in confidence figure removed] per year in Year 5, resulting from lower incidence of adverse events and less intensive monitoring requirements.

This assessment report is based on evidence submitted by Almirall Ltd[1] and an evidence search conducted by AWTTC on 18 October 2021.

2.0 Background

2.1 Condition and clinical practice

Actinic keratosis (AK) is characterised by premalignant skin lesions that occur on chronically light-exposed adult skin[2]. They present as discrete patches of erythema and scaling predominantly on the head and hands. The condition is graded on a three-point (Olsen) scale of increasing magnitude with grade 1 lesions being just visible and palpable, grade 2 lesions being usually red and scaly, and grade 3 being thicker hyperkeratotic lesions[2]. Prevalence of AK is higher in individuals with fairer skin types, increases with age and is higher in men than in women[3]. A study conducted in South Wales estimated the prevalence of AK in individuals aged 60 or over to be 33% in men and 16% in women[4]. Although the risk of an AK transforming into a squamous cell carcinoma is very low, this risk increases over time and with larger numbers of lesions[2]. The presence of ten AKs is associated with a 14% risk of developing a squamous cell carcinoma within five years[5]. AKs are believed to be part of a

spectrum that includes squamous skin cancers and prevention of skin cancer is therefore the reason for treatment[2].

Current treatment options include treatment with topical therapy, photodynamic therapy, cryosurgery and surgical excision[2]. The appropriate treatment is generally chosen based on the number of lesions present and therapy may be broadly categorised as either lesion-directed (e.g., cryosurgery) or field-directed (e.g., topical products)[3]. Topical therapy is ideally suited to address multiple lesions; options include 5-fluorouracil 5% cream (Efudix®), imiquimod 5% cream (Aldara®), diclofenac gel 3% (Solaraze®), and fluorouracil/salicylic acid solution (Actikerall®)[2]. Current topical therapies involve treatment regimens of four to twelve weeks[5].

2.2 Medicine

Tirbanibulin is a topical therapy indicated for the field treatment of non-hyperkeratotic, non-hypertrophic AK (Olsen grade 1) of the face or scalp in adults (UK licence October 2021)[6]. It disrupts microtubules by direct binding to tubulin, which induces cell cycle arrest and apoptotic death of proliferating cells and is associated with disruption of Src tyrosine kinase signalling[6]. The applicant company suggest tirbanibulin should be positioned alongside other first-line treatment options for AK of the face or scalp[1].

The course of treatment consists of tirbanibulin ointment applied once daily for five consecutive days[5]. A thin layer of ointment should be applied to cover the treatment field of up to 25 cm^2 [6]. Therapeutic effect can be assessed approximately eight weeks after treatment starts[6].

2.3 Comparators

The comparators included in the company's submission are:

- diclofenac gel 3% (Solaraze®)
- 5-fluorouracil 5% (Efudix®)
- imiquimod 5% (Aldara®)

2.4 Guidance and related advice

- Primary Care Dermatology Society. Actinic (solar) keratosis – primary care treatment pathway (2020)[5]
- British Association of Dermatologists' guidelines for the care of patients with actinic keratosis (2017)[2]
- Evidence- and consensus-based (S3) guidelines for the treatment of actinic keratosis – International League of Dermatological Societies in cooperation with the European Dermatology Forum – short version (2015)[7]

The All Wales Medicine Strategy Group (AWMSG) has previously recommended fluorouracil/salicylic acid (Actikerall®) for the topical treatment of slightly palpable and/or moderately thick hyperkeratotic actinic keratosis (grade I/II) in immunocompetent adult patients[8].

2.5 Prescribing and supply

AWTTC is of the opinion that, if recommended, tirbanibulin (Klisyri®) may be appropriate for prescribing by all prescribers within NHS Wales for the indication under consideration.

3.0 Clinical effectiveness

The company submission included evidence from two pivotal phase III studies (KX01-AK-003 and KX01-AK-004) that evaluate the efficacy and safety of Klisyri® compared with vehicle ointment in adults with AK[1]. The company also conducted a systematic literature review to assess the comparative efficacy and safety of Klisyri® and comparators in the treatment of AK using network meta-analysis[1].

3.1 Studies KX01-AK-003 and KX01-AK-004

KX01-AK-003 and KX01-AK-004 were two identically-designed, double-blinded, vehicle controlled, phase III studies involving adults (87% male, mean age 70 years) with four to eight clinically typical, visible, and discrete AK lesions in a 25 cm^2 contiguous treatment area on the face or scalp[9]. In each study, 351 patients were randomised 1:1 to receive either tirbanibulin or vehicle ointment to the treatment area once-daily for five consecutive days[9].

The primary endpoint in both studies was the percentage of patients with a complete (100%) reduction in the number of lesions in the application area at Day 57[9]. The key secondary endpoint was the percentage of patients with a partial (≥ 75%) reduction in the number of lesions within the application area at Day 57[9].

Results from both studies showed that tirbanibulin was superior to vehicle for the treatment of AK[9]. In KX01-AK-003 overall complete clearance occurred in 44% of patients in the tirbanibulin group and in 5% of those in the vehicle group (difference 40%; 95% confidence interval [CI], 32 to 47; $p < 0.0001$). In KX01-AK-004 the percentages were 54% and 13%, respectively (difference 42%; 95% CI, 33 to 51; $p < 0.0001$). In both studies, the percentages of patients with partial clearance were significantly higher ($p < 0.0001$) in the tirbanibulin groups than in the vehicle groups. See Table 1 for results[9].

Table 1. Complete and partial clearance of actinic keratosis lesions with tirbanibulin versus vehicle on Day 57 in studies KX01-AK-003 and KX01-AK-004[9]

Variable	KX01-AK-003			KX01-AK-004		
	Tirbanibulin (n = 175)	Vehicle (n = 176)	Difference (95% CI)	Tirbanibulin (n = 178)	Vehicle (n = 173)	Difference (95% CI)
Primary endpoint: complete (100%) clearance						
Overall*	77/175 (44%)	8/176 (5%)	40% (32%–47%) $p < 0.0001$	97/178 (54%)	22/173 (13%)	42% (33%–51%) $p < 0.0001$
Face	60/119 (50%)	7/121 (6%)	45% (34%–55%) $p < 0.0001$	73/119 (61%)	16/118 (14%)	48% (36%–58%) $p < 0.0001$
Scalp	17/56 (30%)	1/55 (2%)	29% (16%–42%) $p < 0.0001$	24/59 (41%)	6/55 (11%)	30% (12%–45%) $p < 0.0001$
Secondary endpoint: partial (≥ 75%) clearance						
Overall*	119/175 (68%)	29/176 (16%)	52% (43%–60%) $p < 0.0001$	136/178 (76%)	34/173 (20%)	57% (48%–65%) $p < 0.0001$
Face	90/119 (76%)	23/121 (19%)	57% (45%–67%) $p < 0.0001$	95/119 (80%)	26/118 (22%)	58% (46%–68%) $p < 0.0001$
Scalp	29/56 (52%)	6/55 (11%)	41% (23%–56%) $p < 0.0001$	41/59 (69%)	8/55 (15%)	55% (37%–69%) $p < 0.0001$

*face or scalp.
CI: confidence interval.

The incidence of recurrence was evaluated at one year among tirbanibulin-treated patients who had complete clearance at Day 57. In KX01-AK-003 77% (59/77) of patients developed recurrent lesions in the area treated with tirbanibulin: 73% (44/60) who received treatment on the face and 88% (15/17) who received treatment on the scalp[3]. In KX01-AK-004, 72% (70/97) of tirbanibulin-treated patients developed recurrent lesions: 68% (50/73) who received treatment on the face and 83% (20/24) who received treatment on the scalp[3].

3.2 Systematic review with indirect treatment comparison

In the absence of evidence directly comparing tirbanibulin to other AK treatments, the applicant company conduced a systematic review to identify suitable studies for inclusion in a Bayesian network meta-analysis[1].

The systematic review was designed to gather data relating to the treatment of AK worldwide; however, the results from the network meta-analysis are based only on treatments available in Wales[1]. Complete clearance was the only outcome that had a sufficient evidence base to enable network meta-analysis. The primary analysis of this outcome used data reported after one course of treatment, and a separate (secondary) analysis used data reported after any number of courses. The network meta-analysis results report the outcome of random effect models[1].

The systematic review identified twenty-one studies that assessed only one course of treatment and were therefore considered suitable for inclusion in the primary analysis[1]. An additional fourteen studies assessed more than one course of treatment and were therefore considered eligible only for the larger secondary analysis of all studies[1].

Mean odds ratios for complete clearance versus placebo are given together with credible intervals in Table 2. The results show that tirbanibulin is more effective than diclofenac and has similar efficacy to 5-fluorouracil[1].

The results for tirbanibulin, diclofenac and 5-fluorouracil were similar when studies involving more than one course of treatment were included in the network meta-analysis (secondary analysis)[1].

Table 2. Network meta-analysis results for complete clearance versus placebo

[Commercial in confidence figures removed].

3.3 Safety information

In pooled data from studies KX01-AK-003 and KX01-AK-004 the incidence of treatment-related adverse events up to Day 57 of application site pruritus (itching) and pain were 9% and 10% respectively in the tirbanibulin group versus 6% and 3% in the vehicle group[3]. Most adverse events were mild to moderate in severity, and reversible[3].

In the follow-up period of 1 year following Day 57, treatment-emergent skin cancers occurred in 10 of 353 (2.8%) patients in the tirbanibulin arm compared

to in 7 of 349 (2.0%) patients in the vehicle control arm[3]. Many cases were confounded by a history of skin cancers (approximately 45% of patients had a history of skin cancer): the short duration of safety follow-up suggests many of these skin cancers were pre-existing and only one occurred in the treatment area (in the tirbanibulin arm)[3].

Local skin reactions (erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration) may occur with tirbanibulin treatment[3]. Most reactions were mild to moderate and reached a peak around Day 8 before dropping down to baseline levels by Day 57. The levels of dyspigmentation and scarring in patients was similar between tirbanibulin and vehicle control groups[3].

3.4 AWTTC critique

- Tirbanibulin offers a shorter duration of AK treatment (five days) compared to the four to twelve-week duration for existing topical treatments[5]. Adherence with current topical treatments is reported to be poor with approximately 90% of patients being non-adherent or non-persistent[3] - there is a need for additional treatment options. In the pivotal trials completion rates for tirbanibulin were high and it was well tolerated[3].
- Significant recurrence of AK occurred 12 months after Day 57. This occurred to a higher extent on the scalp than on the face. Recurrence is expected given the natural history of the disease[3]; however, there are no available data on retreatment with tirbanibulin in patients (including those who had a recurrence of their AK lesions, or on those who developed new lesions). The Summary of Product Characteristics states that if recurrence occurs, or new lesions develop within the treatment area, other treatment options should be considered[6]. Efficacy on retreatment will be investigated in the post-authorisation safety study following treatment over a three-year period (due 2026)[3]. This is a condition of the marketing authorisation to assess the long-term safety and efficacy of tirbanibulin. This will also include an active comparator arm.
- In the absence of comparative evidence, the network meta-analysis is presented for the other topical agents used in Wales. This is limited to complete clearance of AK lesions with no other clinical or safety comparisons made. The results should be interpreted with caution due to the limitations in the method and differences in study patient populations, such as the prior experience of skin cancer, previous treatments for AK, number of courses or sessions of treatment received, length of treatment, and definition of “complete clearance”.
- At one-year follow-up, the pivotal studies only analysed patients who successfully responded to the treatment, and excluded patients with residual AK who may have been at a higher risk of squamous-cell cancer. However, a conclusion on the risk of squamous-cell cancer would not have been possible due to the low rates of cancer occurrence as well as the confounding background rate of AK to squamous-cell cancer conversion in the absence of treatment. The risk of progression of AK to squamous-cell cancer in patients treated with tirbanibulin will be investigated in the post-authorisation safety study[3].

- Despite some of the limitations, clinical experts consulted by AWTTC highlight tirbanibulin is an important therapeutic development as an additional treatment option which has a different mechanism of action. As there is an increasing incidence of skin cancer in Wales, it was noted that skin field cancerisation in the form of AK is an important predisposing factor.

4.0 Cost-effectiveness

4.1 Context

The company submission includes a cost-utility analysis (CUA) comparing tirbanibulin 10 mg/g ointment with diclofenac gel 3%, imiquimod 5% cream, and 5-fluorouracil 5% cream, in patients with four to eight AK lesions in an area measuring 25 cm^2 on the face or scalp.

The CUA takes the form of a decision tree model. The model adopts a one-year time horizon for the base case analysis and an NHS Wales/Personal and Social Services perspective. Costs and outcomes are not discounted as the time horizon is one-year.

Treatment is deemed successful if 100% of lesions are cleared and unsuccessful if any clinically visible lesions remain. If complete clearance is achieved no further treatment is given and it is assumed that the specific lesions treated do not return for the remainder of the model time horizon. If treatments are not successful, clinically visible lesions are assumed to be present and no further treatment is taken for the remainder of the model time horizon.

The proportion of people achieving complete clearance for tirbanibulin was based on the phase III trials, and the odds ratios from the network meta-analysis estimated for each comparator were then applied to the odds ratio for tirbanibulin to generate odds of complete clearance with each comparator. For all comparators, except diclofenac gel 3%, there was no statistically significant difference in the probability of complete clearance when compared to tirbanibulin. It is therefore assumed that all interventions except diclofenac gel 3% would produce equivalent complete clearance outcomes in the base case.

A targeted literature search by the company suggested that there is no meaningful difference in the quality of life, nor resource use, associated with differing numbers of clinically visible lesions. Therefore, it is assumed that the probability of complete clearance following each treatment is independent of the number of clinically visible lesions present at baseline.

The company reported it was not possible to estimate the difference in frequency of severe local skin reactions between tirbanibulin and each comparator through the network meta-analysis due to difference in the definitions reported and insufficient/inconsistent data on the incidence of any specific severe local skin reactions. The model therefore estimates the number of people with severe local skin reactions with comparator treatment based on a targeted literature review and these are the only adverse events incorporated in

the analysis. Mortality is not incorporated in the model because it is assumed that people with AK would not face an increased risk of mortality due to the presence of clinically visible AK lesions and given the short time horizon.

Health-related quality of life is estimated based on the number of days/weeks that a patient spends with one or more AK lesions with the assumption that the complete clearance of lesions would occur at the recommended time to maximum treatment effect. Utility scores were obtained from the literature and a disutility associated with AK lesions of 0.019[10] is applied. An additional disutility of 0.085 is applied to people that experience a severe local skin reaction.

Costs of treatment include drug acquisition costs, patient management, and adverse event costs. Dosing and acquisition costs are sourced from the British National Formulary[11]. All patients initially attend an appointment with a GP[12] and if treatment is unsuccessful patients attend a follow-up GP visit. If treatment is successful, patients have no further GP appointments within the time horizon of the model. If patients experience a severe local skin reaction they have a follow-up appointment with a GP, but no other costs related to managing the reaction are applied. The impact of referring a proportion of patients to a dermatologist following treatment failure or occurrence of a severe local skin reaction is explored in the sensitivity analysis.

Deterministic and probabilistic sensitivity analyses were conducted to test the influence of the uncertainty of individual parameters on the model results for the population base case. In the deterministic analysis, parameters are varied according to either their 95% confidence interval, or within a percentage of their base case value. The main deterministic analyses are of patients requiring a dermatologist appointment prior to a prescription, percentage of patients returning to a healthcare professional following an adverse event, and percentage visiting secondary care following a severe local skin reaction.

Additional, probabilistic sensitivity analysis is presented for 1,000 model simulations, and included varying the parameters relating to percentage of patients with complete clearance, patient management resource use, disutility associated with AK and proportion of patients experiencing a severe local skin reaction.

Several scenario analyses were run. The impact of recurrence is explored by extrapolation to a two-year time horizon, using recurrence data from a targeted literature review. It is assumed that patients will not receive further treatment if they experience a recurrence, and only one recurrence event can occur per patient. Patients that experience recurrence are assumed to have clinically visible AK lesions for the remainder of the model time horizon (from the end of Year 1 to the end of Year 2). Quality-adjusted life-years (QALYs) are discounted at a rate of 3.5% in the second year, as no further treatment is given after recurrence the costs were not discounted.

Separate scenario analyses using the point estimate odds ratios for each comparator, assuming equivalence between the time to maximum treatment effect and that all patients required a follow-up GP visit regardless of success of treatment were also conducted, as well as the inclusion of two topical therapies

less widely used in Wales, imiquimod 3.75% (Zyclara®) and 5-fluorouracil 0.5% plus salicylic acid 10% (Actikerall®).

4.2 Results

The results of the base case are detailed in Table 3. The results of the base case suggest tirbanibulin dominates diclofenac gel 3%. Tirbanibulin has an incremental cost-effectiveness ratio (ICER) of £1,725/QALY gained compared to imiquimod 5% cream; and an ICER of £2,977/QALY compared to 5-fluorouracil 5% cream. The main cost differences can be attributed to severe local skin reactions. The incremental QALY gains are predominantly driven by time to complete clearance and severe local skin reactions.

Table 3. Results of the base case analysis

	Tirbanibulin	Diclofenac 3%	Difference
Medicine acquisition costs	£59.00	£72.78	**−£13.78**
Patient management costs	£58.87	£70.70	**−£11.83**
AE costs	£5.08	£5.30	**−£0.22**
Total costs	£122.96	£148.79	**−£25.83**
Total QALYs	¶¶	¶¶	¶¶
ICER (£/QALY gained)	**Dominant**		
	Tirbanibulin	**Imiquimod 5%**	**Difference**
Medicine acquisition costs	£59.00	£48.60	**£10.40**
Patient management costs	£58.87	£58.87	**£0.00**
AE costs	£5.08	£9.36	**−£4.28**
Total costs	£122.96	£116.83	**£6.12**
Total QALYs	¶¶	¶¶	¶¶
ICER (£/QALY gained)	**£1,725**		
	Tirbanibulin	**5-fluorouracil 5%**	**Difference**
Medicine acquisition costs	£59.00	£32.90	**£26.10**
Patient management costs	£58.87	£58.87	**£0.00**
AE costs	£5.08	£18.20	**−£13.12**
Total costs	£122.96	£109.97	**£12.98**
Total QALYs	¶¶	¶¶	¶¶
ICER (£/QALY gained)	**£2,977**		

AE: adverse events; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year.
¶¶ commercial in confidence figure removed.

The results of the univariate sensitivity analysis show that adjusting key model parameters had minimal impact on the results. Tirbanibulin remained cost-effective when the probabilities were varied for complete clearance for both tirbanibulin and the comparators, the proportion of patients requiring treatment in secondary care, and the percentage of patients experiencing a severe local skin reaction.

Probabilistic sensitivity analysis indicates that tirbanibulin has a 100% probability of being cost-effective at a threshold of £20,000 and £30,000 per QALY gained, compared to diclofenac gel 3%; an 85.40% and 90.60% probability of being cost-effective at a threshold of £20,000 and £30,000 per QALY gained respectively compared to imiquimod 5% cream, and a 98.60% and 99.60% probability of being cost-effective at a threshold of £20,000 and £30,000 per QALY gained, respectively compared to 5-fluorouracil 5% cream.

In scenario analysis, tirbanibulin is associated with a higher probability of recurrence than all the comparators but remains dominant compared to diclofenac gel 3%, and has ICERs of £22,267 compared to imiquimod 5% cream and £3,936 compared to 5-fluorouracil 5% cream.

The base case assumed that all interventions apart from diclofenac gel 3% produce equivalent complete clearance outcomes as the network meta-analysis reported no statistically significant difference in the probability of complete clearance for imiquimod 5% cream and 5-fluorouracil 5% cream compared to tirbanibulin. When the point estimate odds ratios are applied to imiquimod 5% cream and 5-fluorouracil 5% cream, tirbanibulin remains cost-effective compared to imiquimod 5% (£4,697), however it is not cost-effective compared to 5-fluorouracil 5% (£115,960).

For other scenario analyses, including assuming an equivalent time to maximum effect of 90 days for all treatments, as well as the inclusion of a return appointment with the GP regardless of treatment success, the results remain the same, tirbanibulin dominates diclofenac gel 3%, and is cost-effective compared to imiquimod 5% cream and to 5-fluorouracil 5% cream. Tirbanibulin is also dominant compared to imiquimod 3.75% and 5-fluorouracil 0.5% plus salicylic acid 10%.

Table 4. Results of scenario and sensitivity analyses

Scenarios	ICER	Plausibility
Recurrence included with two-year time horizon	**Diclofenac 3% dominant** **Imiquimod 5% £22,267** **5-fluorouracil 5% £3,936**	This scenario provides a plausible alternative to the base case, given that recurrence of lesions occurs with all treatments included in the analysis.
Point estimate odds ratios for complete clearance rather than assuming equivalent clearance	**Imiquimod 5% £4,697** **5-fluorouracil 5% £115,960**	This scenario provides a plausible alternative to the base case, as although the complete clearance was not statistically significantly different compared to tirbanibulin, the point estimates would be most appropriate.
All patients have a return appointment with the GP regardless of treatment success	**Diclofenac 3% dominant** **Imiquimod 5% £1,725** **5-fluorouracil 5% £2,977**	This scenario is less plausible than only patients who do not have treatment success having a return GP appointment.
Equivalent time to maximum treatment effect	**Diclofenac 3% dominant** **Imiquimod 5% £4,280** **5-fluorouracil 5% £2,960**	This scenario is not as plausible as the base case which uses the reported times to maximum effect.
ICER: incremental cost-effectiveness ratio.		

4.3 AWTTC critique

The submission is characterised by both strengths and limitations:

Strengths:

- The submission gives a detailed, transparent account of the methods and data sources used in the analysis.
- Reasonable justifications are provided for the assumptions applied in the model.
- Appropriate comparators used to treat AK in Wales were included.
- Extensive sensitivity and scenario analyses have been conducted.

Limitations:

- AWTTC consider the point estimate odds ratios for complete clearance to be a more appropriate base case than the equivalent clearance approach applied in the company base case. The company assumes that the clearance rate for all comparators (except diclofenac) is identical. Applying equivalent clearance implies a cost-minimisation analysis approach but the clinical evidence provided does not include

comparative equivalence trials. Assuming equivalence of effectiveness will therefore introduce bias.

- The pivotal studies compared tirbanibulin to vehicle ointment and no direct comparisons of tirbanibulin to the comparators used in the model exist. The company therefore undertook a systematic review of the literature and network meta-analysis for indirect comparison. While the systematic review and network meta-analysis appear well conducted, there is large heterogeneity within the included studies in regards to study population, outcomes, follow-up periods, number of treatment cycles and definition of complete clearance. Furthermore, certain comparisons are supported by small amounts of data with high uncertainty. Considering the heterogeneity and uncertainties surrounding the network meta-analysis results, it is unclear how accurate the ICERs are.
- The disutility applied for lesions in the model was based on a published time trade off exercise conducted with nine participants with AK in the United States in the early 2000s[10] which was then adjusted to the UK population of people with AK lesions. While the company states that this is the best available evidence, the small sample size, location and age of the evidence and data manipulation will introduce uncertainty and bias into the analysis as the QALY differences in the model are solely driven by lesion disutility.
- The network meta-analysis could not include other outcomes such as lesion count reduction, AEs and local skin reactions, and discontinuations due to differences in the definitions reported and insufficient or inconsistent data. The rate of local skin reactions applied in the model was therefore taken from a targeted literature search with different values extracted from different publications for different comparators directly compared. Considering the heterogeneity of evidence, this will introduce bias.
- Furthermore, the difference in frequency of recurrence could not be estimated through the network meta-analysis and recurrence was therefore not included in the base case. Including the recurrence rate (which is higher for tirbanibulin) increases the ICERs (see Table 4). However, even when recurrence is captured in the scenario analysis, no further treatment costs beyond the first recurrence treatment were included which may not reflect real-world practice.
- The probability of complete clearance in the model was assumed to be independent of the number of clinically visible lesions present at baseline. It is unclear whether this would be the case in practice. Any dependence of clearance rate on lesion number will affect the ICERs as the analysis is mainly driven by this parameter.
- The model provided includes an option for a longer time horizon and progression to skin cancer, however these scenarios have not been included in the submission. Since these lesions can develop into skin cancer, a longer-term time horizon may have been preferable.
- The model assumes that only one treatment course is given even if clearance is not achieved. This may not be a realistic assumption in routine practice and will underestimate costs for all treatments considered.

- Treatment adherence is not included in the analysis presented which could introduce bias if adherence differs between different treatment options.

4.4 Review of published evidence on cost-effectiveness

A literature review conducted by AWTTC did not identify any studies relevant to the cost-effectiveness of tirbanibulin in the treatment of people with AK.

5.0 Budget impact

5.1 Context and methods

It is assumed that people currently receiving treatment for AK would not receive tirbanibulin and only newly diagnosed patients were included in the budget impact model. The company has estimated that there will be 76,209 people with AK in 2020[13]. This estimate is based on Office for National Statistics population statistics and Welsh specific incidence data[14]. To calculate the number of people who chose treatment, the company has applied incidence estimates for people with AK on their face (8.8%) and scalp (78%[15]), and the number of people who chose treatment after being reassured that their lesion was not cancerous (40%, based on Welsh clinician opinions), and applied an annual mortality rate (0.73% for people aged ≥ 75 years in Wales[16]. The annual net number of people with AK eligible for treatment was estimated to be [commercial in confidence figure removed].

The company estimate of the market shares for comparator topical treatments for AK is: fluorouracil [commercial in confidence figure removed], diclofenac [commercial in confidence figure removed] and imiquimod [commercial in confidence figure removed]. An assumed market share of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5 is applied to estimate the number of people likely to be prescribed tirbanibulin in Wales for the indication covered in the submission. Comparators are displaced by tirbanibulin in proportion to their current market share.

5.2 Results

The budget impact is presented in Table 5. The company estimates that introducing tirbanibulin would lead to an overall cost of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5.

Table 5. Company-reported costs associated with use of tirbanibulin for the treatment of actinic keratosis

[Commercial in confidence figures removed].

The company estimated that net resource implications arising from the introduction of tirbanibulin will lead to a saving of [commercial in confidence figure removed] in Year 1 rising to a saving of [commercial in confidence figure removed] in Year 5. This is a consequence of reduced adverse events and

reduced monitoring. These resource implications are included for potential planning purposes but may not be realised in practice.

5.3 AWTTC critique

- The submission gives a detailed, transparent account of the methods and data sources used to estimate budget impact.
- The company has not factored population growth and mortality in subsequent years into the calculations.
- Sensitivity analysis was not conducted for adherence, treating recurrence, or subsequent treatments due to treatment failure.
- Appropriate comparators used to treat AK in Wales were included.

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