Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for Onakta

Active ingredient: Tirbanibulin

Sponsor: Seqirus Pty Ltd

August 2024

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- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
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- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACD	Allergic contact dermatitis
ACM	Advisory Committee on Medicines
AE	Adverse event
AK	Actinic keratosis
ARTG	Australian Register of Therapeutic Goods
ASA	Australia-specific annex
AUC	Area under the concentration curve
BCC	Basal cell carcinoma
C_{max}	Maximum observed blood concentration
CMI	Consumer Medicines Information
C_{min}	Minimum observed blood concentration
C_{trough}	Pre-dose blood concentration
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ITT	Intention to treat
KX-01	Tirbanibulin
KX2-391	Tirbanibulin
LSR	Local skin reaction
NOAEL	No observed adverse effect level
PK	Pharmacokinetics
PI	Product Information
PSUR	Periodic safety update report
RMP	Risk management plan
SAE	Serious adverse event
SCC	Squamous cell carcinoma
SD	Standard deviation
TEAE	Treatment-emergent adverse event
TGA	Therapeutic Goods Administration

Onakta (tirbanibulin) submission

Type of submission:	New chemical entity
Product name:	Onakta
Active ingredient:	Tirbanibulin
Decision:	Approved
Approved therapeutic use for the current submission:	Onakta is indicated for the topical field treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis of the face or scalp in adults.
Date of decision:	19 September 2023
Date of entry onto ARTG:	23 February 2024
ARTG number:	391198
, *Black Triangle Scheme*	Yes
Sponsor's name and address:	Seqirus Pty Ltd, 63 Poplar Road, Parkville, VIC 3052
Dose form:	Ointment
Strength:	10 mg/g
Container:	Sachet
Pack sizes:	1, 5 sachets
Route of administration:	Topical
Dosage:	Apply a thin layer of Onakta to evenly cover the treatment field of up to 25 cm^2 on the face or scalp once daily for 5 consecutive days using 1 single-dose sachet per application For further information regarding dosage, refer to the Product Information.
Pregnancy category:	D Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Onakta (tirbanibulin) – proposed indication

This AusPAR describes the submission by Seqirus Pty Ltd to register Onakta (tirbanibulin) for the following proposed indication:[1]

> *Onakta is indicated for the topical field treatment of actinic keratosis of the face or scalp in adults.*

Actinic (solar) keratosis

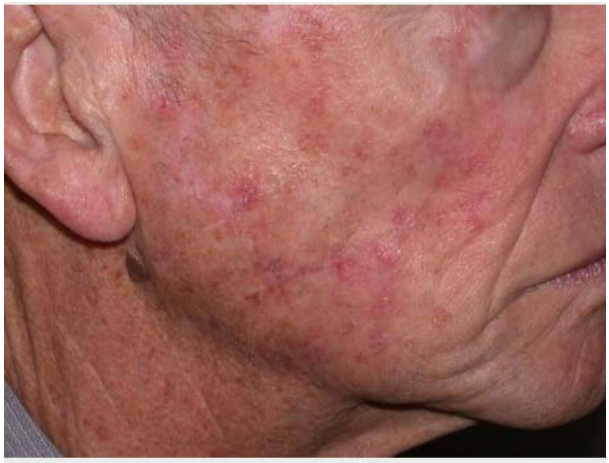
Actinic keratosis (AK; also known as solar keratosis) is a skin lesion resulting from the proliferation of atypical epidermal keratinocytes. Often presenting as red, scaly macules or papules[2], it can progress to squamous cell carcinoma (Figure 1).

Actinic keratosis typically affects older adults with fair skin. Chronic sun exposure is a major risk factor and induces mutations in the epidermal keratinocytes. Mutations in the p53 tumour suppressor gene have been detected in around half of actinic keratoses analysed.

The rationale for treating AK is the risk of progression to squamous cell carcinoma (SCC) if left untreated. The mean (95% CI) length of time for an AK to progress to SCC is 24.6 (21.04 to 28.16) months[3]. There is no precise estimate of the risk of progression for an individual lesion, with estimates ranging from 0.025% and 20% for each individual lesion[4].

The diagnosis is usually clinical, with biopsy employed in cases of uncertainty.

Figure 1. Actinic keratoses on the face (image from Fuchs A, Marmur E. The kinetics of skin cancer: progression of actinic keratosis to squamous cell carcinoma. Dermatol Surg 2007 Sep;33(9):1099-101).



[1] This is the original indication proposed by the Sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.

[2] Padilla, R. (2023, Jan) Actinic keratosis: Epidemiology, clinical features, and diagnosis. https://www.uptodate.com/contents/actinic-keratosis-epidemiology-clinical-features-and-diagnosis

[3] Fuchs A, Marmur E. The kinetics of skin cancer: progression of actinic keratosis to squamous cell carcinoma. Dermatol Surg 2007 Sep;33(9):1099-101

Current treatment options for actinic keratosis

Indications for treatment include symptoms, cosmesis, and extensive field keratoses (to reduce risk of invasive SCC, which may be difficult to detect in this context). There is some evidence that topical field treatment can reduce the risk of subsequent SCC[3].

When there are a few, isolated actinic keratoses the suitable treatments are:

- Cryotherapy (liquid nitrogen or "freezing" treatment)
- Curettage and cautery ("scraping and burning"): This may be used if early skin cancer is suspected.
- Surgical excision: This is usually only used when it is difficult to tell if the lesion is an actinic keratoses or an early skin cancer.

When there are multiple actinic keratoses (fields) the available treatments are:

- 5-Flourouracil cream: a cytotoxic agent which is normally applied twice daily for 2 -8 weeks. Its effects may be enhanced by the addition of calcipotriol.
- Imiquimod cream: an immune-response modifier which is normally applied 2-3 times a week for 4 to 16 weeks.
- Diclofenac gel: an anti-inflammatory which is applied twice daily for 3 months. This causes minimal inflammation but is less effective than other modalities.
- Photodynamic therapy: the combination of a photosensitising chemical applied to the skin and the application of visible light (using a machine or daylight).
- Chemical peels: the application of a chemical to the skin to remove the top layers of abnormal skin cells.
- Laser therapy: fractional and ablative lasers can be used to remove abnormal skin cells and "resurface" sun-damaged skin.

Clinical rationale for Onakta in actinic keratosis treatment

Tirbanibulin has potent anti-proliferative and anti-tumour activities *in vitro* and *in vivo* by virtue of its ability to induce cell cycle arrest and apoptotic cell death. Tirbanibulin is able to disrupt the cellular microtubule network via direct binding to tubulins and is associated with disruption of Src tyrosine kinase signalling. This mechanism of action supports the use of tirbanibulin in the treatment of AK, a carcinoma, in situ, of the skin.

Current treatments for AK include local topical field treatments and local treatments including cryosurgery and excision. These local treatments are generally used for single or individual discreet lesions and can often be painful and likely to cause scarring and hypopigmentation. A major advantage of topical field treatments is that they can be used to treat multiple contiguous lesions. However, the use of current topical field treatments is limited by several factors including severe local skin reactions, prolonged treatment courses and poor treatment compliance. Given the high prevalence of AK in Australia and the limitations associated with current treatments, there is a need for an effective, better tolerated and cosmetically acceptable field treatment which can be given over a short period of time. Onakta® addresses some of the limitations by offering an effective treatment with high dosing compliance, a favourable local tolerability profile and requiring only once daily application for 5 days.

[3] Therapeutic Guidelines. Solar or actinic keratoses. Aug 2022. https://tgldcdp.tg.org.au/

Regulatory status

Australian regulatory status

This product is considered a new chemical entity for Australian regulatory purposes.

International regulatory status

The TGA referred to the Swissmedic review of Module 3 during evaluation.

Table 1 lists the regions where tirbanibulin ointment 1% has been approved.

Table 1. International registration status for tirbanilumab

Country	Indication	Approval Date
United States	KLISYRI® is a microtubule inhibitor indicated for the topical treatment of actinic keratosis of the face or scalp.	December 2020
European Union	KLISYRI® is indicated for the field treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis (Olsen grade 1) of the face or scalp in adults.	July 2021
Great Britain	For the field treatment of nonhyperkeratotic, non-hypertrophic actinic keratosis (Olsen grade 1) of the face or scalp in adults.	August 2021
Switzerland	For topical field therapy of non-hyperkeratotic, non-hypertrophic actinic keratoses of the face or scalp in adults.	February 2022
Taiwan	For the topical treatment of typical non-hyperkeratotic, non-hypertrophic actinic keratosis of the face or scalp in adults.	October 2022
Israel	For the field treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis (Olsen grade 1) of the face or scalp in adults.	January 2023
Canada	For the topical treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis (AK) (Olsen grade 1) on the face or scalp in adults.	May 2023

Registration timeline

This submission was evaluated under the standard prescription medicines registration process.

Table 2 captures the key steps and dates for this submission.

Table 2: Timeline for Onakta Submission (PM-2022-02492-1-1)

Description	Date
Submission dossier accepted and first round evaluation commenced	18 August 2022
First round evaluation completed	24 February 2023
Second round evaluation completed	26 May 2023
Delegate's[6] Overall benefit-risk assessment and request for Advisory Committee advice	4 July 2023
Sponsor's pre-Advisory Committee response	21 July 2023
Advisory Committee meeting	21 August 2023
Registration decision (Outcome)	19 September 2023
Administrative activities and registration in the ARTG completed	23 February 2024
Number of working days from submission dossier acceptance to registration decision*	272

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

The following guideline was referred to by the Delegate as being relevant to this submission:

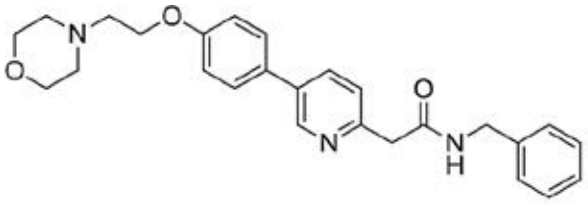
- Note for Guidance on Population Exposure: The Extent of Population Exposure to Assess Clinical Safety (CPMP/ICH/375/95).

The Delegate notes that this guideline is for drugs intended for long-term use (i.e. chronic or repeated intermittent use for longer than 6 months). It should be noted that Onakta is for use for 5 days and that this guideline is relevant to dosing outside the approved indication.

Quality evaluation summary

Tirbanibulin is a new chemical entity (Figure 2). It is not structurally related to other drugs which have been used for the treatment of actinic keratosis.

Figure 1. Tirbanibulin structure and molecular formula and weight

Structure	
Molecular formula	$C_{26}H_{29}N_3O_3$
Molecular weight	431.53 g/mol

Tirbanibulin is produced by chemical synthesis which is adequately described in the dossier. Impurity levels are well controlled. All test parameters and limits proposed for the drug substance specification are considered acceptable.

The drug product is a smooth, creamy, white to off-white ointment. It is formulated as an ointment with only two excipients – propylene glycol and 'glyceryl monostearate 40-55 percent'. Each gram of ointment contains 10mg tirbanibulin. Each sachet of ointment (which represents a single dose) contains a nominal 250mg of ointment (i.e. 2.5mg tirbanibulin). Each sachet is intended for single application to deliver 2.5mg of tirbanibulin. The contents of the ointment are shown in 2. Packs of 1 or 5 single-use sachets are proposed.

The quality of the drug product is controlled by specifications for appearance, identification, impurities, viscosity and microbial contamination. The specifications are acceptable.

The requested shelf life of 36 months when stored at or below 25°C (Do not freeze. Do not refrigerate) in the proposed laminated sachet is supported.

GMP clearances for the drug substance and drug product manufacturing sites are considered acceptable.

The Product Information (PI) document is finalised from a pharmaceutical chemistry and quality perspective.

The Product Labelling has been finalised from a pharmaceutical chemistry perspective and complies with the applicable requirements of Therapeutic Goods Order 91.

The quality Evaluator recommended approval from a quality control perspective.

Nonclinical (toxicology) evaluation summary

The nonclinical dossier was in accordance with the relevant ICH guidelines and its overall quality was high. There were no nonclinical objections to the registration of Onakta for the proposed indication.

In vitro studies demonstrated the mechanism of action of tirbanibulin, which is binding to tubulin and inhibition of polymerization, disruption of the microtubule network and keratinocyte cell cycle arrest and apoptosis. The major metabolite did not have an anti-proliferative effect on keratinocytes.

Tirbanibulin inhibited the growth of human keratinocytes *in vitro*. It also showed anti-proliferative effects in tumour cell lines, including renal cancer, lymphoma, melanoma, gastric cancer, squamous cell carcinoma. There were no studies using animal models of actinic keratosis.

Secondary pharmacology studies did not identify potential off-target effects. Safety pharmacology studies did not reveal cardiovascular (including QTc), respiratory, gastrointestinal or CNS signals of concern.

Oral bioavailability was around 55% in mice, rats and dogs, and increased in rats with higher doses. Plasma protein binding was high in rats and rabbits and moderate in dogs, minipigs and humans. There is extensive metabolism in the liver with KX2-5036 the major metabolite in rat, dog and human hepatocytes. KX2-5036 has subsequently been found to be present in very low concentrations in human plasma. Metabolism is mainly via CYP3A4 (CYP2C8 to a lesser extent) and drug related material is mainly excreted in faeces (in rats).

Tirbanibulin had a low order of acute toxicity in minipigs. Oral administration of 50mg/kg in dogs resulted in 2 deaths. Repeat dose dermal and oral toxicology studies were conducted.

Systemic toxicity at high exposure in rats, minipigs and dogs was consistent with its known pharmacological action and included gastrointestinal necrosis, bone marrow and lymphoid hypocellularity, liver necrosis and reproductive organ degeneration with germ cell depletion.

Following dermal dosing, erythema, oedema and desquamation was observed in rats and minipigs. Fissuring and ulceration were also observed in minipigs. Histopathological changes included epidermal ulceration, hyperkeratosis, necrosis, atrophy and mixed cell infiltration. Findings occurred at subclinical doses in both species and were reversible.

Tirbanibulin was not mutagenic in the bacterial mutation assay. *In vitro* it was positive for chromosome aberrations (Chinese hamster ovary cells) and gene mutations (mouse lymphoma TK assay). It was clastogenic *in vivo* in the rat micronucleus test and Comet assay. Exposure to tirbanibulin in the *in vivo* study was high (24 times the AUC_{0-24h} in patients). No carcinogenicity data was submitted and this was considered acceptable.

Placental transfer and milk excretion were not studied. Reproductive performance was not impaired (4 mg/kg/day, oral, in male rats; 1mg/kg/day, oral, in female rats). Males at the high dose exhibited adverse effects on spermatogenesis. Oral administration during pregnancy produced embryofoetal lethality in rats (Exposure Ratio based on AUC (ER_{AUC}): 124). At a dose of 1.25mg/kg/day (ER_{AUC} :91) there was no adverse effects of tirbanibulin when administered during pregnancy through to lactation.

Tirbanibulin 1% was a dermal irritant in rats and rabbits and an eye irritant in rabbits. It may cause skin sensitisation. It was not phototoxic in rabbits following single dermal application.

Clinical evaluation summary

Summary of clinical studies

The clinical pharmacology program for tirbanibulin ointment 1% included 3 clinical trials with PK evaluations in adult subjects with AK: studies KX01-AK-01-US (Phase 1), KX01-AK-002 (Phase 2a) and KX01-AK-007, which was a MUSE study (Maximal Use Systemic Exposure Study).

The efficacy program consisted of two phase 3 studies, KX01-AK-003 and KX01-AK-004. These were identical Phase 3, double-blind, vehicle-controlled, randomised, multi-centre studies conducted to evaluate the efficacy and safety of tirbanibulin ointment 1% in subjects with AK on the face or scalp. These two Phase 3 studies were identical in terms of study design, subject entry criteria, and assessments, and were independently conducted at non-overlapping study sites.

Pharmacology

Pharmacokinetics

As tirbanibulin is being proposed for topical use, the main purpose of the pharmacokinetics (PK) studies was to determine the extent of systemic exposure with such use.

Three PK studies were included:

Study KX01-AK-01-US – this study could not provide any reliable PK data, according to the Sponsor, as some of the blood sampling occurred from the same arm that was being treated with tirbanibulin, leading to the study results being “not interpretable”. This is detailed in the Clinical Study Report:

> "Individual plasma KX2-391 concentrations at each sampling timepoint are described in Table 4. Several subjects in study KX01-AK-01-US have intermittently elevated concentrations followed by low or BLQ values that are inconsistent with the 6-hour plasma half-life seen in prior studies of oral KX2-391 in cancer patients. These aberrant values may be the result of collecting PK samples from the same arm where the treatment was applied. Since the protocol did not specify that the samples should be drawn from the opposite arm, the site drew samples based on ease of venous access and patient preference."

In KX01-AK-007 tirbanibulin was applied topically to the face or scalp in patients with AK (using 1% formulation intended for marketing) daily for 5 days. The dose used was 250mg of ointment (2.5mg of tirbanibulin). All participants had measurable daily trough and post-dose on day 5 concentrations. Steady state was achieved following the 3rd dose. Gender, age and lesion count did not significantly affect exposure. The majority of subjects had major metabolite (KX2-5036 and KX2-5163) concentrations below the limit of quantitation (0.05 ng/mL).

In vitro data demonstrated protein binding of 88% and metabolism via CYP3A4, and to a lesser extent CYP2C8. Other aspects of the systemic PK such as bioavailability, distribution and excretion were not assessed.

Study KX01-AK-002 was a phase 2 activity and safety study in subjects with AK of the scalp and face. It analysed concentrations following tirbanibulin application to the face or scalp. The dose used was 50mg of ointment or 0.5mg of tirbanibulin for 3 or 5 days. The five day course represents 1/5 of the proposed clinical dose. At 4 hours after the last dose, only about half of the subjects in both cohorts had quantifiable plasma concentrations (LLOQ 0.1ng/mL).

Another study included in the clinical module of the dossier was *in vitro* study AXC-02-B which examined the penetration of tirbanibulin 1% w/w ointment into and through human cadaveric skin. The study utilised vertical diffusion cells. A 1cm^2 area of skin was dosed with 10mg of the ointment. Four different formulations, with varying concentrations of propylene glycol, glyceryl monostearate and emulsifying wax, were tested. Cumulative recovery over 24h was similar for the four formulations.

Efficacy

The two pivotal efficacy studies were KX01-AK-003 and KX01-AK-004, which investigated the dose regimen intended for marketing. Studies KX01-AK-002 and KX01-AK-01-US were supportive.

KX01-AK-003 was a phase 3, double-blind, vehicle controlled, randomised study of the safety and efficacy of tirbanibulin 1% ointment for actinic keratosis of the face or scalp in adults. It was conducted at 31 sites in the US.

The major inclusion criteria were as follows:

- Males and females ≥ 18 years old
- A treatment area on the face or scalp that was contiguous, measured 25cm^2 and contained 4 to 8 clinically typical AK lesions.
- Females to be postmenopausal, surgically sterile or using highly effective contraception.
- Sexually active males to avoid conception or donate sperm for 90 days following last study treatment.

The major exclusion criteria were as follows:

- clinically atypical and/or rapidly changing AK lesions on the treatment area (e.g. hypertrophic, hyperkeratotic, recalcitrant disease evidence by 2 previous cryosurgery occasions and/or cutaneous horn).
- Within 5cm of an incompletely healed wound or suspected BCC or SCC.
- Treatment with 5FU, imiquimod, ingenol mebutate, diclofenac, photodynamic therapy or other AK treatments within the treatment area (or 2cm of the treatment area) within the prior 8 weeks.
- Other treatments within the treatment area or within 2cm of the treatment area (cosmetic, acid containing, topical retinoids, light chemical peels, salves, corticosteroids). Use of artificial tanners within the treatment area or within 5cm of the treatment area.
- Treatment within 4 weeks with immunomodulators (e.g. azathioprine), cytotoxic drugs, interferon/interferon inducers, immune suppressants (e.g. cyclosporine, prednisolone).

Treatment was with 250mg of tirbanibulin 1% ointment, applied daily for five consecutive days to 25 cm^2. Vehicle was packaged in the same way. The following treatments were prohibited during the study: immunomodulators, immunosuppressives, cytotoxics, interferon/interferon inducers, topical/systemic steroids, 5FU, ingenol mebutate, imiquimod, diclofenac, topical or systemic retinoids, topical salicylic acid, bichloracetic acid, trichloroacetic acid, acid-containing therapeutic products, benzoyl peroxide, chemodestruction, medication/therapeutic topical salves, photodynamic therapy, psoralen plus ultraviolet A or ultraviolet D, artificial tanner, excessive/prolonged ultraviolet light exposure.

The primary efficacy outcome was the proportion of subjects at day 57 with no clinically visible AK lesions in the treatment area (i.e. 100% clearance rate of AK lesions).

The secondary efficacy endpoint was the proportion of subjects at day 57 with partial clearance (≥75% reduction in the number of AK lesions in the treatment area compared to baseline).

The additional efficacy endpoint was the recurrence rate in subjects who achieved complete clearance at day 57, 12 months post treatment completion.

Safety endpoints included local skin reactions, pigmentation, scarring, AEs, SAEs, events of special interest, clinical laboratory data and other general assessments.

Enrolment was stratified so that 2/3 of subjects were treated on the face and 1/3 on the scalp. Randomisation was 1:1 to tirbanibulin or vehicle. The main analysis population was the intention to treat (ITT) population. A sample size of 100 scalp-treated and 200 face treated was calculated to provide >90% power to detect a 20% difference between treatment allocation with a 2-tailed significant level of 0.05.

Of 408 subjects screened, 351 were allocated to treatment. Two participants in the vehicle group did not complete the study, as one died and one withdrew consent. The 85 subjects who achieved complete clearance (77 in tirbanibulin arm and 8 in vehicle arm) were eligible for recurrence follow-up (1 from vehicle arm withdrew consent before completion).

The subjects were mainly male (86%). The age range was 45 – 96 years, with most (74%) being ≥ 65 years. The median number of lesions at baseline was 6. Overall, 166 (47%) had a history of skin cancer, including SCCs (105), BCCs (124) and melanoma (24). Most subjects (83-87%) had previous AK treatments, with 34% overall having had prior field treatment. Baseline characteristics were balanced across the arms.

For the primary efficacy outcome, complete clearance occurred in 77/175 (44%) of the tirbanibulin group and 8/176 (5%) of the vehicle group. Findings were significant overall and in the face and scalp subgroups. The effect size appeared to be greater for treatment of face AK

compared to scalp AK. For the key secondary outcome, partial clearance occurred in 119/175 (68%) of the tirbanibulin group and 29/176 (16%) of the vehicle group. Treatment was effective for both face and scalp lesions (Table 3).

Table 3. Clearance rates at day 57 by treatment location - ITT population

Clearance Rate	Vehicle	Tirbanibulin 1%
100% [a]		
Overall	8/176 (5%)	77/175 (44%)
Face	7/121 (6%)	60/119 (50%)
Scalp	1/55 (2%)	17/56 (30%)
≥75%[b]		
Overall	29/176 (16%)	119/175 (68%)
Face	23/121 (19%)	90/119 (76%)
Scalp	6/55 (11%)	29/56 (52)

[a] Complete (100%) clearance rate of actinic keratosis lesions, defined as the proportion of subjects at day 57 with no clinically visible lesions in the treatment area.

[b] Partial (≥75%) clearance rate, defined as the proportion of subjects at Day 57 with a ≥75% reduction in the number of lesions identified at Baseline (Day I predose) in the treatment area.

Regarding the secondary endpoint of recurrence amongst subjects who achieved complete clearance, the Kaplan-Meier at 12 months was 0.74, i.e. 26% were free of recurrence.

Study KX01-AK-004 was a phase 3, randomised, double blind, vehicle controlled study of the safety and efficacy of tirbanibulin 1% ointment for the treatment of actinic keratosis on the face or scalp in adults. It was identical to KX01-AK-003 and also conducted at 31 centres in the US in 2017-2019.

Inclusion and exclusion criteria appeared to be the same as for the 003 trial, as were the study treatments (and prohibited concomitant treatments) and sample size calculations.

Of 410 subjects screened, 178 were randomised to tirbanibulin (119 to face, 59 to scalp) and 173 to vehicle (118 to face, 55 to scalp). All completed the study and were included in the ITT efficacy and safety population. Ninety six from the tirbanibulin arm and 22 from the vehicle arm entered the recurrence follow-up period.

The median age was 70, with 73% being ≥ 65 years. Most were male (88%), white (>99%) and were treated for lesions on the face (68%). The median number of AK lesions at baseline was 6. Fitzpatrick skin type II was most common (57%), followed by III (26%). Most subjects (72-74%) had had previous AK treatments and 36% overall had prior field treatment.

For the primary efficacy outcome 97/178 (54%) in the tirbanibulin arm and 22/173 (13%) in the vehicle arm achieved complete clearance at day 57. Partial clearance was achieved in 76% of subjects with tirbanibulin compared to 20% with vehicle. These results were all statistically significant, including in the face and scalp subgroups.

For recurrence at 12 months post day 57, the KM estimate for overall recurrence amongst those subjects who had achieved complete clearance was 0.72, i.e. 28% were free from recurrence at that stage.

The Sponsor has pointed out that, with regard to the recurrences at 12 months in the pivotal studies, only 1 or 2 lesions were recorded in 86% of subjects. Even though most subjects

experienced recurrence at 12 months, the severity of the AK in the field was substantially less than baseline. Furthermore, 42% of the recurrences were actually new lesions[4].

Supportive studies

Study KX01-AK-002 was a phase 2a, open label study of AK affecting the face or scalp (4-8 lesions within an area of 25cm^2). A dose of 50mg tirbanibulin 1% (i.e. 1/5 of the daily dose used in the pivotal studies) was used once daily for either 3 or 5 days. A total of 168 subjects completed day 57 and 26 completed 12 months post day 57 follow-up. The primary efficacy endpoint was 100% clearance rate. Secondary efficacy endpoints were reduction in AK lesion count, recurrence rate and sustained response rate.

Complete clearance at day 57 occurred in 43% treated for 5 days and 32% treated for 3 days. Partial clearance (≥75%) at day 57 occurred in 56% treated for 5 days and 52% for 3 days. Mean lesion counts decreased by 3.9 with 5 days of treatment and 3.4 with 3 days. Recurrence rates at 12 months in subjects with 100% clearance at day 57 were 57% with 5 days of treatment and 70% with 3 days.

Study AK-002 suggested that 5 days of treatment was probably better (at both day 57 and after 12 months).

It did not provide evidence that 250mg was the appropriate phase 3 dose of ointment.

Study KX01-AK-01-US was a phase 1, open label study of the treatment of dorsal forearm AK. Four cohorts were treated with once daily 1% tirbanibulin ointment, as follows:

- Cohort 1 (n=4) – 50mg over 25 cm^2 for 3 days
- Cohort 2 (n=10) – 200mg over 100 cm^2 for 3 days
- Cohort 3 (n=8) - 50mg over 25 cm^2 for 5 days
- Cohort 4 (n=8) – 200mg over 100 cm^2 for 5 days

Note the differences between this study and both the product and indication relevant to this submission (i.e. study used lower doses of ointment – either 50mg or 200mg – for a shorter duration in 2/4 cohorts – 3 days – and on AK at a different site – the forearm – and affecting a larger area in 2/4 cohorts – 100cm^2).

Complete clearance at day 45 occurred in 25% of subjects in cohort 1, 0% in cohort 2, 50% in cohort 3 and 12.5% in cohort 4. Partial clearance at day 45 occurred in 25% of subjects in cohort 1, 33% in cohort 2, 12.5% in cohort 3 and 37.5% in cohort 4. Median AK lesion counts at baseline / day 45 were 5/2.5 in cohort 1, 11.5/4 in cohort 2, 6/0.5 in cohort 3 and 11/4.5 in cohort 4.

Study AK-01 was essentially a proof of concept study showing the ointment as having activity in clearance of AK lesions.

Safety

The safety data is presented as 1) the main set, based on the two phase 3 studies and the phase 2a study and 2) the other set, based on six phase 1 studies. Across these 9 studies, 961 subjects were administered tirbanibulin 1% ointment. Of these, 569 subjects had actinic keratosis and

[4] Recurrence was considered any lesion within the field; new lesions were included as well as lesions that recurred in the same location as prior to initiation of therapy. Measurement was performed 14 months after the initial 5 day treatment course.

392 were healthy volunteers. The maximum dose any subject received was 250mg ointment daily for 5 days (i.e. the proposed clinical dose).

The total number of patients in the phase 3 program was 353 with 99.43% exposed for 5 days. This corresponds to 4.82 patient-years of exposure. Most (86.4%) of the patients were male and approximately 70% were aged ≥ 65 years.

In terms of length of follow up, 437 subjects were followed to day 57 and 83 subjects in the recurrence follow-up population (phase 2 and phase 3) were followed for 12 months after day 57.

Main safety data set

Studies KX01-AK-003 and 004 were identical phase 3 studies described above. Safety endpoints included adverse events (AEs), serious adverse events (SAEs), local skin reaction (LSR), hyper- and hypo-pigmentation and scarring assessments, events of special interest (ocular exposure, skin cancers, overdose, pregnancy), laboratory evaluation, vital signs, physical examination and ECGs.

Skin was assessed for erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation and erosion/ulceration. The grading scale was absent, mild, moderate and severe.

Study KX01-AK-002 was a phase 2a study, described above.

The incidence of subjects with any TEAEs, at least possibly related AEs, SAEs and severe AEs was generally similar across the 5 day treatment groups and vehicle. The number of subjects with AEs that were at least possibly related was higher in the tirbanibulin 1% 5 day arm from the 004 study (20%) than in the other tirbanibulin or vehicle groups (9-11%). All SAEs were considered as either unrelated or unlikely related. There was 1 death (due to suicide and considered unrelated) in the vehicle arm.

During the recurrence follow up period for the phase 3 trials, the following AEs (all not related) were reported in the tirbanibulin 1% group: mild cyst (in treatment area), mild thrombosis, moderate viral upper respiratory infection, severe sepsis/severe decrease haemoglobin/severe hairy cell leukaemia (these 3 were SAEs in the same subject), severe colon cancer and mild BCC (outside treatment area).

During the phase 3 studies, TEAEs occurring in > 2% subjects and also more commonly with tirbanibulin than vehicle, were application site pruritis (9% vs. 6%) and application site pain (10% vs 3%). These were also the most common related TEAEs. The moderate treatment related AEs in subjects administered tirbanibulin 1% were application site pruritis, application site pain, headache, application site nodule, application site scab, skin odour abnormal and viral upper respiratory tract infection. No treatment-related TEAEs led to discontinuation.

In terms of specifically reported skin reactions, across the phase 3 studies, were reported more commonly with tirbanibulin 1% than vehicle. Local reactions tended to peak by day 8 and were near resolved by day 29. Erythema and flaking/scaling were frequent and mostly mild to moderate severity. Crusting, swelling, vesiculation/pustulation and erosion/ulceration were less frequent and generally mild. Severe flaking/scaling at day 8 occurred in 6% and 8% of tirbanibulin treated subjects in 003 and 004, respectively. The LSRs were self-limited and did not require treatment.

In terms of LSRs in phase 2a study 002, the majority were minimal or mild erythema and flaking/scaling. The reactions were self-limited and did not require treatment. One subject had severe erythema and flaking/scaling at the day 8 visit.

AEs of special interest based on studies 003 and 004

The incidences of hypopigmentation, hyperpigmentation and scarring were similar between the tirbanibulin and vehicle arms.

There were no documented ocular exposures and all ocular adverse events were considered as not related or unlikely related.

In study KX01-AK-003 there were 10 subjects (2.8%) in the tirbanibulin arm and 7 (2%) in the vehicle arm who developed post treatment skin cancers. Only 1 of these cancers was found in the treatment area (a scalp SCC on day 74 in a tirbanibulin treated subject) and all were considered as not related to study medication.

In study KX-AK-004 7 subjects (2%) had skin cancer up to day 57 and these were not in the treatment field or considered related.

In phase 2a study 002, 3 subjects had SCC found post-treatment (day 3, day 36 and day 43; not in the treatment area).

During recurrence follow-up (i.e. out to 12 months post day 57 in the phase 2 and 3 studies), there were no events of within treatment field skin cancer. The small number of subjects in this cohort has been previously noted.

Other safety data set

In phase 1 study KX01-AK-01-US, the following TEAEs were reported: mild nasopharyngitis, mild headache, mild back pain, moderate procedural pain, moderate arthritis, mild arthralgia, mild urinary tract infection, moderate BCC (not in treatment area), moderate muscular weakness and moderate myositis. All subjects had LSRs and all were minimal to moderate severity, except for 1 subject each with transient severe erythema, transient severe flaking/scaling and transient severe pruritis. Skin reactions peaked around day 8. One subject had a TEAE of BCC (not in treatment area) on day 3.

In phase 1 study KX01-AK007, 4 subjects reported TEAEs of mild dry skin, mild erythema, moderate upper respiratory tract infection, mild dizziness and moderate rheumatoid arthritis. One subject had a related TEAE of dry skin (not in treatment area). All LSRs were mild to moderate in severity. Most of the reactions were erythema, flaking and scaling. Less frequently there was mild crusting and swelling. Two subjects had erosion/ulceration.

KX01-AK-010 was a dermal safety study in 36 healthy volunteers aged 25 to 73 years. Treatment was with 1% tirbanibulin ointment, vehicle or saline 3 times per week for 3 weeks, under occlusive, semi-occlusive and open patch conditions. There was one TEAE of mild contact dermatitis. Cumulative irritability was significant under occlusive and semi-occlusive conditions, compared with open conditions (2.33 and 2.41 vs. 0.80 respectively). Thirty-two subjects discontinued the occlusive and semi-occlusive dressing for tirbanibulin, compared to 2 with vehicle. The study demonstrated significant cumulative irritability with tirbanibulin 1% ointment under occlusion and semi-occlusion.

KX01-AK-006 was a dermal safety study in 261 healthy volunteers aged 18 to 75 years. Treatment was with tirbanibulin 1% ointment, vehicle or saline (control) using an induction followed by challenge to determine sensitizing potential. The three most frequent TEAEs were headache, nasopharyngitis and rhinorrhoea. There was one SAE (mild dyspnoea requiring hospitalisation) and one severe AE (headache). The mean irritation score was 2.09 for tirbanibulin, 0.06 for vehicle and 0.09 for saline. The study did not find a signal for sensitisation (i.e. worsening of skin effects following induction period).

KX01-AK-008 was a dermal safety study in 31 healthy volunteers aged 21 to 70 years. Treatment was with tirbanibulin 1% or vehicle plus/minus ultraviolet radiation to determine phototoxic potential. One subject reported a TEAE of mild headache that was considered possibly related. The study did not find a signal for phototoxic activity.

KX01-AK-009 was a dermal safety study in 64 healthy volunteers aged 26 to 75 years. Treatment was with tirbanibulin 1% ointment or vehicle plus 1 challenge with irradiation to determine photoallergic potential. There were 6 TEAEs – a mild and a moderate nasopharyngitis, moderate sinus headache, moderate upper respiratory tract infection and mild contusions. The study did not find a signal for photoallergy.

Post marketing data

The Sponsor has submitted the periodic safety update report (PSUR) for the period June 14, 2022, to December 13, 2022. In addition to the 961 subjects exposed to tirbanibulin in the trials described above, another 288 have been exposed across 6 trials either completed or ongoing by licensing partners. Cumulative post-marketing patient exposure is estimated at 270 315, of which 119 203 related to the current reporting period. The countries with the highest use were Germany and the USA. During the reporting period no new signals were found for tirbanibulin and the benefit-risk analysis remains favourable and unchanged.

Cumulatively, spontaneous post-marketing reporting consisted of 196 non-serious and 5 serious reports. These reports represent 431 non-serious ADRs and 12 serious ADRs. The most common system organ classes were “general disorders and administration site conditions”, “skin and subcutaneous tissue disorders” and “injury, poisoning and procedural complications”. The most commonly reported terms were “application site erythema”, “application site pain”, “off-label use”, “application site exfoliations”, “erythema”, “drug ineffective”, “application site vesicles”, “application site pruritis”, “product use issue”, “application site dryness” and “application site swelling”.

Two cases of skin cancer affecting the treatment field have been reported (cumulative):

- A 78 year old male with a history of AK of the face and scalp was diagnosed with basal cell carcinoma 14 days after tirbanibulin treatment commenced. Recovery was noted.
- An 82 year old male was diagnosed with SCC in a lesion that was present prior to therapy and did not respond to tirbanibulin.

In an ongoing phase 3 trial (M-14867-32) investigating treatment to a 100cm^2 field, one subject experienced a non-serious SCC within the treatment area. The causal relationship was assessed as not related.

Three cases of hypersensitivity have been reported (cumulative):

- One case involved facial swelling, facial redness, eye swelling, nausea, circulatory system disorder, change in blood pressure and hospitalisation.
- One case involved tongue swelling that was considered serious.
- One case reported mouth swelling, welts and cracked lips and was considered serious.

Clinical Evaluator recommendation

The Clinical Evaluator did not recommended authorisation in round 1 and in round 2 recommended rejection of the submission. The main reasons advanced by the Evaluator are summarised as:

- A single field treatment is "not plausible" due to the relatively low complete clearance rate at one year when considering all patients treatment. Such retreatment – either with tirbanibulin or other AK therapies – is not supported by data.
- Day 57 outcomes represents "short term" rather than "long term" and any efficacy data beyond day 57 were not placebo-controlled.
- The safety data is insufficient due to 569 subjects being in the primary AK safety dataset and 73 phase 3 subjects being followed for 12 months. This was thought to only be able to detect "common" adverse reactions. This dataset is insufficient given the potential for use in "hundreds and thousands of patients".
- Deficiencies in safety data include uncommon and rare reactions, adverse reactions with long latency, cumulative toxicity with repeated use, safety related interactions with other AK treatments.
- Absence of comparator-controlled trials.

Risk Management Plan evaluation summary

The EU-RMP Version is 0.7 (dated 10 May 2021; data lock point 10 October 2019).

The ASA Versions are 1.0 (9 June 2022) and 2.0 (10 March 2023).

The summary of safety concerns are outlined in Table 4.

Table 4. Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None	–	–	–	–
Important potential risks	Skin tumours in treatment area	✓	✓*	✓	–
Missing information	Effects on fertility†	✓	–	✓	–
	Use in pregnancy and lactation†	✓	–	✓	–
	Long term safety and efficacy (3 years) †	✓	✓*	✓	–

*EU PASS study (M-14789-41)
† Australia-specific safety concern

The RMP Evaluator found the above summary acceptable. The pharmacovigilance plan (i.e. routine pharmacovigilance and the EU PASS) is also acceptable. Routine risk minimisations activities are proposed.

The Delegate notes the Evaluator's recommendation to add the following to Important Missing Information:

- uncommon and rare adverse reactions - all new chemical entities have some degree of uncertainty about "uncommon and rare adverse reactions" and it is reasonable not to include this general phrase in the RMP.
- adverse reactions with a long latency – covered by "long term safety and efficacy"
- cumulative toxicity from repeated use – this would be outside the prescribing recommendations and clinical trials

- safety related interactions with other treatments for AK – this would also be covered adequately by "long term safety and efficacy".

The RMP Evaluator also considered text about contraception duration that was removed by the Sponsor during the course of the submission.

Women of childbearing potential should be advised to use effective contraception during and up to 6 months after treatment. Male patients should take adequate contraceptive measures during and up to 3 months after the discontinuation of the therapy.

The Sponsor explained that the safety margins are sufficiently large to not require such stringent contraception instructions. The EU and US labelling do not include these durations. RMP considered this acceptable. The Delegate also considers this acceptable.

RMP Evaluator recommendations regarding conditions of registration

- The Onakta EU-Risk Management Plan (RMP) (version 0.7, dated 10 May 2021, data lock point 10 October 2019), with Australian Specific Annex (version 2.0, dated 10 March 2023), included with submission PM-2022-02492-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs). Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter. The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.
- Onakta (tirbanibulin) is to be included in the Black Triangle Scheme. The PI and CMI for Onakta must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the Sponsor notifies the TGA of supply of the product.

Risk-benefit analysis

Efficacy

The two pivotal studies adequately demonstrated efficacy in terms of achieving complete or partial clearance after 5 days of treatment at day 57. The 12 month follow up data suggests that recurrence of lesions for those who had initial total clearance is expected to be relatively high. The severity of AK field recurrence at 12 months was generally less than baseline (i.e. there was still improvement even without maintaining 100% clearance). Such recurrence could presumably be managed with other available AK treatments.

The Clinical Evaluator considered the day 57 timepoint (at which point most subjects completed the trial) as representing less reliable short-term data, and the longer-term data were not placebo controlled. The Delegate considers short-term efficacy as established and the long term efficacy data as consistent with modest benefit (i.e. approximately 70% of subjects with initial complete clearance had recurrence at 12 months, but most of this recurrence represented only 1 – 2 lesions, compared with the study entry requirement of 4 – 8 lesions). The Delegate considers that a long-term placebo-controlled trial may be difficult to justify ethically. An active

comparator trial could have been used to allow controlled long-term data and this would be welcome.

Tirbanibulin ointment has potential additional benefits such as a relatively short treatment duration (e.g. compared with fluorouracil, imiquimod and diclofenac) and being generally well tolerated with acceptable self-limiting skin changes.

Given that tirbanibulin is being proposed as a one-off treatment, there is a high likelihood of a patient needing other AK treatments. There are no direct efficacy data about how such sequential treatment combinations may fare. The high history of use of previous AK treatments amongst the pivotal trial subjects does shed some light on sequential treatment. The Clinical Evaluator considered the lack of direct data prohibitive for registration. The Delegate considers it acceptable if tirbanibulin is used within the boundaries of the submitted data.

Finally, the Delegate notes the addition of tirbanibulin to the American Academy of Dermatology guidelines of care for the management of actinic keratosis (Eisen, 2022). Tirbanibulin was assigned a *strong* recommendation with a *high* certainty of evidence.

Safety

ICH guidelines anticipate 1500 individuals to be exposed to a drug during development, 300-600 to be exposure for 6 months and at least 100 for a year (ICH Topic E 1 Population Exposure: The Extent of Population Exposure to Assess Clinical Safety. CPMP/ICH/375/95). The Sponsor has noted that the guideline applies to long-term treatment, which is different to tirbanibulin when used as a single 5 day course.

Across the tirbanibulin 1% ointment development program 961 individuals were exposed. As 300-600 subjects exposed is generally required to detect common AEs, this was achieved. The Clinical Evaluator considered the dataset as insufficient to detect uncommon, rare reactions, adverse reactions with long latency, cumulative toxicity and safety related interactions with other treatments.

The Delegate acknowledges that a safety dataset of 961 is somewhat below the number required to detect uncommon reactions and this may have been questionable at initial registration. However, there is now a significant post marketing dataset which can capture these (especially clinically significant reactions within 8 weeks of treatment). The long latency reactions will be addressed by both the formal EU PASS, as well as through post marketing data. Cumulative toxicity represents use not within the confines of the PI and should not necessarily preclude registration.

The significant safety signals with tirbanibulin 1% generally relate to local toxicity, especially acute reactions peaking by day 8. The commonest reactions were mild to moderate, self-limited and self-resolving. Local reactions graded as severe were uncommon. This suggests acceptable local toxicity; however, its nature should be made clear in the PI.

An ongoing question is the potential for tirbanibulin to be associated with increased incidence of skin malignancy within the treatment field after a more prolonged period. The reasons for this concern include the carcinogenic potential of tirbanibulin itself (positive mutagenicity and clastogenicity) in patients with high background risk, as well as experience with other agents that have had an associated malignancy risk (i.e. ingenol mebutate, although its different mechanism of action is acknowledged). The small (83) and select (i.e. only subjects who experienced 100% clearance with treatment) cohort that was followed up to 12 months, is probably not sufficient to answer this with certainty. Furthermore, remote occurrences of skin cancer associated with previous tirbanibulin use may be difficult to detect in the post-market setting.

The concern is somewhat mitigated by the post-marketing safety data which has not found a signal for skin malignancy. Also, given the treatment will be given on the face and scalp, close monitoring of the treatment area for concerning changes can occur and is relatively straight forward. The EU has requested a post-marketing safety study which will help address the issue. The ACM will be asked to comment on these issues.

The Delegate notes the occurrence in the post-market setting of 3 hypersensitivity reactions,. These significant events should be included in the PI.

With regard to the pregnancy category, the Delegate considers "D" as appropriate. This is consistent with the Nonclinical Evaluator. It is noted that fluorouracil cream, another cytotoxic teratogen used for treatment of AK, has a pregnancy category D. In addition, tirbanibulin ointment is mainly going to be used in a population that is over the age of 50 and male. The choice of pregnancy category is going to have a minor impact on the product's use and the Delegate considers it appropriate and consistent with TGA practice to assign it category D.

Proposed Indications

The proposed indication should include the terms "one-off course" and "non-hypertrophic, non-hyperkeratotic":

> *Onakta, as a one-off course, is indicated for the topical field treatment of actinic keratosis of the face or scalp in adults (non-hypertrophic, non-hyperkeratotic).*

Uncertainties and limitations of the data

The limitations in the safety data include whether there is potential for long term toxicity (in particular increased skin malignancy) and also whether there are safety related interactions when other treatments are used sequentially (as they are likely to be). There are also no data about retreatment or active comparator data, and this was considered significant by the Clinical Evaluator. The Delegate notes that retreatment would not be consistent with the current proposed use and retreatment or active comparator trials would not necessarily be required for registration purposes.

The Delegate considers the submitted data as sufficient for establishing safety and efficacy for the proposed use in the proposed population (i.e. single use as field treatment). The identified deficiencies in the data should be noted in the PI to assist with good quality prescribing.

Proposed conditions of registration

Submission to the TGA of the PASS (that has been mandated by the EMA) when it becomes available.

Conclusions

The Delegate considers that ONKATA may have a role in field treatment of head or scalp AK in certain patients, such as those desiring a short treatment period or who have not tolerated other field treatments. The limitations of its efficacy and the potential for long-term safety concerns will be further addressed by ACM and should be made clear to prescribers and patients in the PI and CMI.

Advisory Committee considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the Sponsor's response to these documents, advised the following:

1. ***Could the ACM comment on the potential increased risk of skin cancer within the treatment field and whether this is appropriately addressed in the PI?***

The ACM noted that there is currently no strong signal of an increased risk of skin cancer within the treatment field. The ACM noted that the biological plausibility of an association is low, however, advised the there is no long-term follow-up safety data relating to the incidence of SCC in patients' treatment with tirbanibulin. The ACM did acknowledge that the PASS study is currently underway and should address these data gaps.

On balance the ACM was supportive of the PI including statements about skin malignancy.

The ACM supported the PI wording proposed by the Delegate:

> *It is currently unknown whether Onakta may increase the risk for skin malignancy within the treatment field*

and/or an alternative such as:

> *Whilst there is no signal for an increased risk of SCC development within the treatment field, longer term safety data relating to incidence of SCC in patients treated with Onakta is currently under evaluation in clinical trials.*

2. ***Does ACM have any comments on the adequacy of safety data put forward to support the proposed single course of treatment?***

The ACM was of the view that the safety data provided is adequate. The ACM considered the PSUR for the period 14 June 2022 to 13 December 2022 and noted the cumulative post-marketing exposure is estimated at 270,315 patients. There were no changes to the product safety information identified in the PSUR and no signal regarding any increased risk of progression to skin malignancy within the treatment area.

3. ***What is ACM's view about whether the PI is sufficient to ensure Onakta is used in a way that is supported by the data submitted (including the deficiencies in long term safety and use of retreatment/combination, and effect durability)?***

The ACM noted that retreatment and combination treatment approaches are common for this condition.

The ACM acknowledged that there are deficiencies in the data in relation to use of Onakta for retreatment and combination treatment. However, the ACM noted that there was no evidence of drug accumulation within the non-clinical studies. The ACM also noted that a clinical study on repeat dosing is currently underway.

The ACM was satisfied with the following PI wording in relation to repeat dosing:

The safety and efficacy for more than 1 treatment course of 5 consecutive days has not been studied in clinical trials. If recurrence occurs, or new lesions develop within the treatment area, other treatment options should be considered.

4. ***Should the PI specify treatment of 'non-hyperkeratotic, non-hypertrophic actinic keratosis' as a 'one-off course'?***

The ACM was supportive of the indication specifying non-hypertrophic and non-hyperkeratotic actinic keratosis. The ACM noted that this aligned with the clinical study inclusion criteria.

The ACM discussed the inclusion of 'one-off course' within the indication and was of the view that this is not required, particularly noting elimination within 5 days and the small treatment area (25 cm^2). On balance the ACM recommended that the 'one-off course' wording should be removed from the indication.

ACM conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *Onakta~~, as a one-off course,~~ is indicated for the topical field treatment of actinic keratosis of the face or scalp in adults (non-hypertrophic, non-hyperkeratotic).*

Outcome

Based on a review of quality, safety, and efficacy, and following PI negotiations with the Sponsor, the TGA decided to register Onakta (tirbanibulin) for the following indication:

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

Attachment 1. Product Information

The Product Information (PI) approved with this submission for Onakta which is referred to in this AusPAR (and can be accessed on this AusPAR's webpage) may have been superseded. For the most recent PI and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6203 1605
https://www.tga.gov.au