▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – ONAKTA® (TIRBANIBULIN) OINTMENT

1 NAME OF THE MEDICINE

Tirbanibulin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of ointment contains 10 mg of tirbanibulin.

Each sachet contains 2.5 mg of tirbanibulin in 250 mg ointment. For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

White to off-white ointment.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

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.

If a dose is missed, the patient should apply the ointment as soon as they remember and then continue with the regular schedule. However, the ointment should not be applied more than once a day.

Special populations

Hepatic or renal impairment

Tirbanibulin has not been studied in patients with renal or hepatic impairment. Based on clinical pharmacology and *in vitro* studies, no dose adjustments are needed (see section 5.2 Pharmacokinetic Properties).

Elderly population

No dose adjustment is required (see section 5.1 Pharmacodynamic Properties).

Method of administration

ONAKTA® is for external use only on the face or scalp. Contact with eyes, lips, and the inside of nostrils or inside the ears should be avoided.

Each sachet is for single use only and should be discarded after use (see section 6.6 Special Precautions for Disposal).

Before applying ONAKTA®, patients should wash the treatment field with mild soap and water and dry it. Ointment from 1 single-use sachet should be squeezed onto a fingertip and a thin layer applied evenly over the entire treatment field, up to a maximum treatment area of 25 cm^2.

Hands should be washed with soap and water before and immediately after application of the ointment.

ONAKTA® should be applied at approximately the same time each day. The treated area should not be bandaged or otherwise occluded. Washing and touching of the treated area should be avoided for approximately 8 hours after application of ONAKTA®. After this period, the treated area may be washed with mild soap and water.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 List of Excipients.

ONAKTA® is contraindicated during pregnancy or in women of childbearing potential not using contraception. Pregnancy should be excluded before treating women of childbearing potential with ONAKTA®.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

ONAKTA® should not be applied until the skin is healed from treatment with any previous medicinal product, procedure or surgical treatment and should not be applied to open wounds or broken skin where the skin barrier is compromised.

Non-Treatment Area Exposure

Contact with the eyes should be avoided. ONAKTA® may cause eye irritation. In the event of accidental contact with the eyes, the eyes should be rinsed immediately with large amounts of water, and the patient should seek medical care as soon as possible.

ONAKTA® must not be ingested. If accidental ingestion occurs, the patient should drink plenty of water and seek medical care.

ONAKTA® should not be used on the inside of the ears, on the inside of the nostrils, or on the lips.

Repeat Use

The safety and efficacy of 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.

Local skin reactions

Local skin reactions in the treated area, including erythema, flaking/scaling, crusting, swelling, erosion/ulceration, and vesiculation/pustulation, may occur after topical application of ONAKTA®. Local skin reactions are common and the majority are mild to moderate. However, local skin reactions of severe intensity have been experienced by patients (see section 4.8 Adverse Effects (Undesirable Effects)). Treatment effect may not be adequately assessed until resolution of local skin reactions.

Hypersensitivity Reations

Serious hypersensitivity reactions, including systemic reactions (possible anaphylaxis) have been reported through post-marketing experience (see section 4.8 Adverse Effects (Undesirable Effects)).

Sun exposure

Due to the nature of the disease, excessive exposure to sunlight (including sunlamps and tanning beds) should be avoided or minimised.

Risk of progression to skin cancer

Whilst there is no signal for an increased risk of skin cancer development within the treatment field, longer term safety relating to the incidence of skin cancer in patients treated with ONAKTA® is currently under evaluation in a clinical trial.

Changes in the appearance of actinic keratosis could suggest progression to invasive squamous cell carcinoma. Ongoing monitoring of the treatment field is recommended and lesions clinically atypical for actinic keratosis or suspicious for malignancy should be appropriately managed.

Use in the elderly

The safety and efficacy profile observed in elderly patients was consistent with that in the overall patient population. No dose adjustment is required (see section 5.1 Pharmacodynamic Properties).

Paediatric use

There are no data to support safety and efficacy of ONAKTA® in the paediatric population.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

In vitro studies show that tirbanibulin does not inhibit or induce cytochrome P450 enzymes and it is not an inhibitor of efflux and uptake transporters at maximum clinical exposures.

There was no clinically relevant inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4/5, or induction of CYP1A2, 2B6 or 3A4 in vitro by tirbanibulin or metabolite KX2-5036. There was no clinically relevant inhibition of BCRP, OATP1B1, OATP1B3, BSEP, MRP2, OCT1, OCT2, P-glycoprotein, MATE1, MATE2-K, OAT1 or OAT3 transporters.

Pharmacokinetic drug interactions are unlikely with tirbanibulin.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

In a fertility and early embryonic development study in rats, reproductive performance was not affected at doses (oral administration) up to 4 mg/kg/day (240 times the AUC at maximum recommended human dose [MRHD]) in males and 1 mg/kg/day (147 times the AUC at the MRHD) in females. However, in male rats, tirbanibulin at 4 mg/kg/day (oral administration), adversely affected spermatogenesis, including reduced sperm count and motility, and increased observations of morphologically abnormal sperm. The observed decrease in testes weight correlated with an increased incidence of degeneration of the seminiferous epithelium. No effects on sperm were observed in males treated at 2 mg/kg/day (166 times the AUC at the MRHD).

Use in pregnancy – Pregnancy Category D

There are no or limited amount of data from the use of tirbanibulin in pregnant women.

In embryofetal development studies in rats, tirbanibulin induced increased post implantation loss, reduced embryofetal survival, reduction in mean fetal bodyweight, reduced mean fetal crown-rump length in live fetuses, and external, visceral, and skeletal malformations following oral administration to pregnant rats at >1.25 mg/kg/day during the period of organogenesis (91 times the AUC at the MRHD). No effect on fetal development was seen at 0.5 mg/kg/day (22 times the AUC at the MRHD) in rats. Reduced mean fetal weight and crown-rump length were observed following oral administration of tirbanibulin to pregnant rabbits at 3 mg/kg/day during the period of organogenesis (194 times the AUC at the MRHD). Tirbanibulin had no effect on fetal development at a dose of 1 mg/kg/day (65 times the AUC at the MRHD) in rabbits.

In a pre- and post-natal development study in rats, tirbanibulin was orally administered to pregnant rats (from implantation through gestation and lactation) at doses up to 1.25 mg/kg/day (91 times the AUC at the MRHD). No adverse effects on maternal function or developmental, neurobehavioral, or reproductive performance of offspring were observed.

ONAKTA® is contraindicated during pregnancy or in women of childbearing potential not using contraception. Pregnancy should be excluded before treating women of childbearing potential with ONAKTA®.

Use in lactation

It is unknown whether tirbanibulin/metabolites are excreted in human or animal milk, or its effects on milk production.

A risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from ONAKTA® therapy, considering the benefit of breast feeding for the child and the benefit of therapy for the woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

ONAKTA® has no or negligible influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

In two double-blind, Phase III vehicle-controlled clinical trials, the safety of ONAKTA® was investigated in 702 adults with actinic keratosis on the face or scalp. 353 patients were treated with tirbanibulin for 5 consecutive days and 349 patients received vehicle. Patients were followed until Day 57, and those with complete clearance at Day 57, followed for up to a further 12 months. The incidence of adverse events (Table 1) was reported separately to information on local skin reactions (LSRs)(Table 2).

Adverse events and local skin reactions were predominantly mild to moderate in severity and transient. No subjects withdrew from the trials due to adverse events related to tirbanibulin ointment.

Treatment-Related Adverse Events

Table 1 presents the incidence of treatment-related adverse events occurring in ≥2% of subjects in the phase III controlled clinical trials (pooled analysis).

Table 1. Treatment-Related Adverse Events Occurring in ≥2% of Subjects in Two Controlled Clinical Trials – Pooled Safety Population.

Preferred Term	ONAKTA® N=353	Vehicle N = 349
Number of Subjects (%) with any treatment-related adverse reaction	56 (16%)	35 (10%)
Application site pruritus	32 (9%)	21 (6%)
Application site pain[a]	35 (10%)	11 (3%)

[a] Application site pain includes pain, tenderness, stinging and burning sensation at the application site.

Events of application site pruritus and pain were mild to moderate in severity, transient in nature (mostly occurring during the first 10 days since the start of treatment), and the majority did not require treatment.

No additional local adverse reactions were reported in patients who maintained complete clearance through a 12-month follow-up period.

Local skin reactions

Local skin reactions were assessed by the investigators using a grading scale of 0 = absent, 1 = mild (slightly, barely perceptible), 2 = moderate (distinct presence), and 3 = severe (marked, intense).

Most local skin reactions were transient and mild to moderate in severity. Following the application of tirbanibulin ointment, the incidences of local skin reactions with a severity grade greater than baseline were erythema (91%), flaking/scaling (82%), crusting (46%), swelling (39%), erosion/ulceration (12%), and vesiculation/pustulation (8%). Severe local skin reactions occurred at an overall incidence of 13%. Severe local skin reactions that occurred at an incidence >1% were flaking/scaling (9%), erythema (6%), and crusting (2%). None of the local skin reactions required treatment.

The percentages of subjects with the maximal post-baseline grades for each local skin reaction greater than baseline by treatment group are provided in Table 2.

Table 2. Investigator Assessment of Maximal Post-Baseline Local Skin Reactions Greater Than Baseline in the Treatment Area (face or scalp) - Pooled Data from Two Controlled Clinical Phase 3 Trials

	ONAKTA® N= 353			Vehicle N = 349		
Local Skin Reactions	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**
Erythema	76 (22%)	223 (63%)	22 (6%)	98 (28%)	20 (6%)	0
Flaking/ Scaling	92 (26%)	166 (47%)	31 (9%)	86 (25%)	33 (9%)	1 (<1%)
Crusting	107 (30%)	50 (14%)	7 (2%)	31 (9%)	8 (2%)	0
Swelling	102 (29%)	32 (9%)	2 (<1%)	15 (4%)	1 (<1%)	0
Vesiculation/ Pustulation	25 (7%)	2 (<1%)	2 (<1%)	3 (<1%)	0	0
Erosion/ Ulceration	32 (9%)	9 (3%)	0	10 (3%)	0	0

Overall, local skin reactions peaked 8 days after starting the treatment and typically resolved within 2 to 3 weeks after completion of treatment with ONAKTA®.

Tabulated list of adverse reactions

Table 3 lists the adverse reactions, including local skin reactions, reported in the clinical trials with ONAKTA®. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (frequency cannot be estimated from the available data).

Table 3. Adverse Reactions

MedDRA System Organ Class	Preferred term	Frequency
General disorders and administration site conditions	Application site erythema	Very common
	Application site exfoliation (flaking and scaling)	Very common
	Application site scab (crusting)	Very common
	Application site swelling	Very common
	Application site erosion (includes ulcer)	Very common
	Application site pain[a]	Common
	Application site pruritus	Common
	Application site vesicles (includes pustules)	Common

[a] Application site pain includes pain, tenderness, stinging, and burning sensation at the application site.

Dermal Safety Studies

Clinical studies in healthy subjects demonstrated ONAKTA® did not cause contact sensitisation (261 subjects), phototoxic skin reactions (31 subjects), or photoallergic skin reactions (64 subjects).

Post-marketing experience

During post-marketing use of ONAKTA® serious hypersensitivity reactions, including systemic reactions (possible anaphylaxis) have been reported.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Overdose following topical application with ONAKTA® may cause an increase in incidence and severity of local skin reactions. There is no data available on oral overdose or the extent of oral absorption of ONAKTA®. Management of overdose should involve monitoring and supportive care.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antibiotics and chemotherapeutics for dermatological use, other chemotherapeutics, ATC code: D06BX03

Mechanism of action

Tirbanibulin 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.

Clinical trials

The efficacy and safety of tirbanibulin applied on the face or scalp for 5 consecutive days was studied in 2 pivotal randomised, double-blind, vehicle-controlled Phase III studies (KX01-AK-03 and KX01-AK-004) including 702 adult patients (353 patients treated with tirbanibulin and 349 patients treated with vehicle). Of these, 247 patients (70%) were 65 years of age or older and 308 (88%) were male.

Patients had 4 to 8 clinically typical, visible, discrete, non-hyperkeratotic and non-hypertrophic actinic keratosis lesions within a contiguous 25 cm^2 treatment field on the face or scalp. On each scheduled dosing day, the ointment was applied to the entire treatment field. In the tirbanibulin group, the mean age was 69 years (range 46 to 90 years) and 96% of patients had Fitzpatrick skin type I, II, or III. The primary efficacy endpoint was complete (100%) clearance of AK lesions in the treatment area, defined as the proportion of subjects at Day 57 with no clinically visible AK lesions in the treatment area and the secondary endpoint was partial (≥75%) clearance of AK lesions in the treatment area. Results from both studies are presented below.

Table 4. Complete (100%) AK Clearance Rates on Day 57 for the Two Phase 3 Studies (Intent-To-Treat [ITT] Population)

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

[a] Based on Mantel-Haenszel method

Table 5. Partial (≥ 75%) AK Clearance Rates on Day 57 for the Two Phase 3 Studies (Intent-To-Treat [ITT] Population)

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

[a] Based on Mantel-Haenszel method

At day 57, patients treated with tirbanibulin had statistically significantly higher complete and partial clearance rates than patients treated with vehicle ($p<0.0001$) (see Table 5). Efficacy was less in scalp lesions compared to facial lesions, though still statistically significant ($p<0.0001$) (see Table 6).

Table 6. Complete and partial clearance rates and median percent (%) actinic keratosis lesion reduction at day 57, ITT population (pooled data KX01-AK-003 and KX01-AK-004)

	Overall (face and scalp)	
	ONAKTA® (N=353)	**Vehicle (N=349)**
Complete (100%) clearance rate[a]	49%[c]	9%
Partial (≥75%) clearance rate[b]	72%[c]	18%

ITT=Intent-to-Treat

[a] Complete clearance rate was defined as the proportion of patients with no (zero) clinically visible actinic keratosis lesions in the treatment field.

[b] Partial clearance rate was defined as the percentage of patients in whom 75% or more of the number of baseline actinic keratosis lesions in the treatment field were cleared.

[c] p<0.0001; compared to vehicle by Cochran-Mantel-Hansel stratified by anatomical location and study.

Table 7. Complete and partial clearance rates at day 57 by anatomical location, ITT population (pooled data KX01-AK-003 and KX01-AK-004)

Location	**Complete (100%) Clearance Rate**		**Partial (≥75%) Clearance Rate**	
	ONAKTA® (N=353)	**Vehicle (N=349)**	**ONAKTA® (N=353)**	**Vehicle (N=349)**
Face n/N % (95% CI)	133/238 56% (49% -62%)[a]	23/239 10% (6% -14%)	185/238 78% (72% - 83%)[a]	49/239 21% (16% - 26%)
Scalp n/N % (95% CI)	41/115 36% (27% - 45%)[a]	7/110 6% (3% - 13%)	70/115 61% (51% - 70%)[a]	14/110 13% (7% - 20%)

CI=confidence interval; ITT=Intent-to-Treat

[a] p<0.0001; compared to vehicle by Cochran-Mantel-Haenszel stratified by study.

Long-term efficacy

Patients that achieved complete (100%) clearance of AK lesions in the treatment area at Day 57 continued to be followed as part of an open-label extension for up to 12 months following Day 57 (n=84). Recurrence was defined as the proportion of patients with any identified AK lesion (new or previous lesion) in the previously treated area who achieved 100% clearance at day 57.

After one year, the estimated incidence of any lesions within the application area was 73%. There was a higher recurrence rate for scalp lesions compared to facial lesions. Of the patients who developed recurrences, 86% had either 1 or 2 lesions. Furthermore, 48% of patients developing recurrences reported at least 1 lesion that was not identified at the time of the initial treatment (i.e., newly occurring lesions counted as recurrences).

The safety and efficacy of ONAKTA® retreatment has not been evaluated in clinical trials.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Tirbanibulin ointment was minimally absorbed in 18 patients with actinic keratosis after topical application once daily for 5 consecutive days over an area of 25 cm^2 . Tirbanibulin plasma concentrations were low at steady state (mean maximum concentration [C_{max}] of 0.258 ng/mL or 0.598 nM and AUC_{0-24h} of 4.09 ng·h/mL).

Distribution

The protein binding of tirbanibulin to human plasma proteins is approximately 88%.

Metabolism

In vitro, tirbanibulin is mainly metabolised by CYP3A4, and to a lesser degree by CYP2C8. The main metabolic pathways are N-debenzylation and hydrolysis reactions. The most relevant metabolites were characterised in patients with actinic keratosis in a maximal use pharmacokinetic study and showed minimal systemic exposure.

Excretion

Elimination of tirbanibulin has not been fully characterized in humans.

Hepatic and renal impairment

No formal studies of ONAKTA® in patients with hepatic or renal impairment have been conducted. Due to the low systemic exposure to tirbanibulin after topical application of ONAKTA® once daily for 5 days, changes in hepatic or renal function are unlikely to be clinically significant. Therefore, no dose adjustments are considered needed (see section 4.2 Dose and Method of Administration).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Tirbanibulin was not mutagenic, *in vitro,* in the bacterial reverse mutation assay (Ames test). Tirbanibulin was positive in an *in vitro* chromosomal aberration assay with Chinese hamster ovary (CHO) cells, an *in vitro* mouse lymphoma assay with L5178/TK+/- cells, and an *in vivo* micronucleus assay in rats. Exposure to tirbanibulin in the *in vivo* study was 24 times the exposure in patients at the maximum recommended dose.

Carcinogenicity

No carcinogenicity studies have been conducted with tirbanibulin.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Propylene glycol
Glyceryl monostearate 40-55 per cent

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Do not refrigerate. Do not freeze.

6.5 NATURE AND CONTENTS OF CONTAINER

Sachets with an inner layer of linear low-density polyethylene. Each sachet contains 250 mg of ointment.

Packs of 1 or 5 single-use sachets*.

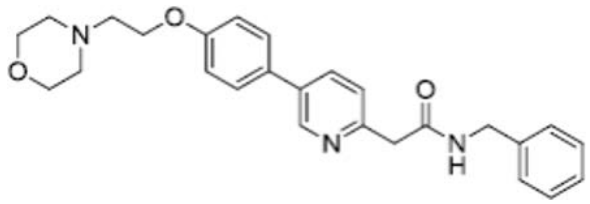
*Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Each sachet is for single-use only. Discard sachet after use. Any unused medical product or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Molecular Formula: $C_{26}H_{29}N_3O_3$
Molecular Weight: 431.5

CAS number

897016-82-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

TBC

10 DATE OF REVISION

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information

ONAKTA® is a registered trademark of Avir Pharma Inc., used pursuant to a sublicense from Athenex Inc., the exclusive licensee of Avir Pharma Inc.