PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr ONAKTA™

Tirbanibulin Ointment

Ointment, 1 % w/w, Topical

Microtubule inhibitor

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RECENT MAJOR LABEL CHANGES

Not applicable

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ONAKTA (tirbanibulin 1 % w/w ointment) is indicated for:

- the topical treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis (AK) (Olsen grade 1) on the face or scalp in adults.

1.1 Pediatrics

Pediatrics (< 18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥65 years): Evidence from clinical studies suggests that use in the geriatric population is not associated with differences in safety or effectiveness.

2 CONTRAINDICATIONS

- ONAKTA (tirbanibulin 1 % w/w ointment) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

The efficacy of ONAKTA (tirbanibulin 1 % w/w ointment) for more than 1 treatment course of 5 consecutive days have not been studied. If recurrences occur, or new lesions develop within the treatment area, other therapeutic options may be considered.

4.2 Recommended Dose and Dosage Adjustment

- ONAKTA should be applied to the affected field on the face or scalp once daily for 5 consecutive days using 1 single-dose sachet per application.
- Sufficient amount of ONAKTA ointment should be applied to form a thin layer to cover the treatment field of up to 25 cm^2.
- Each sachet is for single use only and should be discarded after use.
- ONAKTA has not been studied in patients with renal or hepatic impairment. Based on clinical pharmacology and *in vitro* studies, no dose adjustments are needed.
- Health Canada has not authorized an indication for pediatric use.

4.4 Administration

Before applying ONAKTA, patients should wash the treatment field with mild soap and water and dry it. Hands should be washed with soap and water before and immediately after application of the ointment.

The ointment should be applied at approximately the same time each day. The treated area should not be bandaged or otherwise occluded (see 7 WARNINGS AND PRECAUTIONS, 8 ADVERSE REACTIONS and 14 CLINICAL TRIALS). 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.

4.5 Missed Dose

If a dose is missed, the patient should apply the ointment as soon as he/she remembers and then he/she should continue with the subsequent schedule. However, the ointment should not be applied more than once a day.

5 OVERDOSAGE

Overdose of ONAKTA (tirbanibulin 1 % w/w ointment) could cause an increase in incidence and severity of local skin reactions.

No systemic signs of overdose are expected following topical application of ONAKTA due to the low systemic absorption of tirbanibulin. Management of overdose should consist of treatment of clinical symptoms.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Topical	1 % w/w Each gram of ONAKTA contains 10 mg of tirbanibulin (10 mg/g).	Glycerol monostearate 40-55 Type I and propylene glycol

ONAKTA (tirbanibulin 1 % w/w ointment) is a white to off-white ointment and is supplied in single-dose sachets containing 250 mg of ointment. Each sachet contains: 2.5 mg (1% w/w) of tirbanibulin. Each sachet should be discarded after single use. Available in box of 5 single-dose sachets.

7 WARNINGS AND PRECAUTIONS

General

The safety and efficacy of ONAKTA (tirbanibulin 1 % w/w ointment) treatment have not been evaluated in clinical trials on body areas apart from the face and scalp.

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

ONAKTA is for external topical use on the face or scalp only; not for oral or ophthalmic use. Application near and around the eyes, lips, mouth and the inside of nostrils or ears should be avoided.

Carcinogenesis and Mutagenesis

Tirbanibulin induced chromosomal damage and micronuclei in genotoxicity studies conducted in rats. Tirbanibulin was shown to be non-mutagenic in bacterial mutagenesis test (16 NON-CLINICAL TOXICOLOGY, Carcinogenicity, Genotoxicity).

Driving and Operating Machinery

ONAKTA has minimal influence on the ability to drive and use machines.

Immune

The safety and efficacy of ONAKTA treatment have not been evaluated in immunocompromised patients therefore, ONAKTA should be used with caution in immunocompromised patients.

Ophthalmologic

ONAKTA may cause eye irritation. Avoid transfer of the drug into the eyes and to the periocular area during and after application. Wash hands immediately after application. 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.

Reproductive Health: Female and Male Potential

- Fertility

No human data on the effect of ONAKTA on fertility are available.

Tirbanibulin has been assessed for effects on fertility or reproductive function in rats. In a non-clinical fertility and early embryonic development study, oral administration of 4 mg/kg/day of tirbanibulin to male rats caused fertility toxicity (16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

- Teratogenic Risk

No human data on the teratogenic effect of ONAKTA are available.

In non-clinical embryo-fetal development studies in rats and rabbits, fetal malformations occurred at oral doses of ≥1.25 mg/kg/day (rats) and 3 mg/kg/day (rabbits) (7.1.1 Pregnant Women, 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

Skin

Application of ONAKTA is not recommended until the skin is healed from 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.

Occlusion after topical application of ONAKTA is more likely to result in irritation (see 8 ADVERSE REACTIONS, Dermal Safety Studies). Propylene glycol may cause skin irritation.

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 (see 8 ADVERSE REACTIONS). Treatment effect may not be adequately assessed until resolution of local skin reactions.

- 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

Changes in the appearance of actinic keratosis could suggest progression to invasive squamous cell carcinoma. Clinically atypical lesions or lesions suspicious for malignancy should be appropriately managed (see 8 ADVERSE REACTIONS).

7.1 Special Populations

7.1.1 Pregnant Women

ONAKTA is not recommended during pregnancy and in women of childbearing potential not using contraception.

There are no clinical data regarding the use of ONAKTA in pregnant women or the impact on fertility, major birth defects, miscarriage or adverse maternal and fetal outcomes.

Tirbanibulin has been shown to have teratogenic properties. In non-clinical studies, oral administration of tirbanibulin in rats and rabbits is associated with maternal toxicity and embryo-fetal toxicity including implantation loss and teratogenicity (16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

7.1.2 Breast-feeding

It is unknown if ONAKTA or its metabolites are excreted in human milk. Precaution should be exercised because many drugs can be excreted in human milk, therefore a risk to the newborns/infants cannot be excluded.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ONAKTA and any potential adverse effects on the breastfed child from tirbanibulin or from the underlying maternal condition.

7.1.3 Pediatrics

Pediatrics (<18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use. Actinic keratosis is not a condition generally seen within the pediatric population.

7.1.4 Geriatrics

Of the 353 subjects with AK treated with ONAKTA in the 2 controlled Phase 3 trials, 246 (70%) were 65 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

In the pooled analysis of two phase 3 controlled clinical trials (up to Day 57), the majority of adverse reactions were mild in severity and the most common adverse reactions were: application site pruritus (9.1%) and pain (9.9%) in the treatment area. 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). Five subjects (1.4%) in the tirbanibulin group were treated with emollients. No subject withdrew from the trials due to adverse reactions.

Local skin reactions (LSRs) were collected independent of adverse reactions. LSRs peaked 8 days after starting the treatment and typically resolved within 2 to 3 weeks after completion of treatment with tirbanibulin ointment. LSRs at the application site were erythema (91%), flaking/scaling (82%), crusting (46%), swelling (39%), erosion/ulceration (12%), and vesiculation/pustulation (8%). Severe LSRs occurred in 46 patients (13%) in the pooled safety analysis. The incidence of patients with severe LSR was highest for flaking/scaling (9% patients), followed by erythema (6% patients), and then all other LSR categories (≤2% patients).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Two double-blind, vehicle-controlled clinical trials were conducted in 702 adult subjects with actinic keratosis on the face or scalp. Subjects were randomized 1:1 to ONAKTA or vehicle. Subjects enrolled in the trials had 4 to 8 clinically typical, visible, and discrete AK lesions in a contiguous area of 25 cm^2 on the face or scalp.

Table 2 Adverse Reactions Occurring in ≥ 1% of Subjects***

Adverse Reaction System Organ Class	**ONAKTA N = 353**	**Vehicle N = 349**
Number of Subjects (%) with any adverse reaction (at least possibly related to treatment)	56 (16%)	35 (10%)
General Disorders and Administration Site Conditions		
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.

* The Safety Population was defined as all randomized subjects who received at least one dose of study treatment.

** Defined as investigator determined at least possibly related to study treatment.

Table 3 Investigator Assessment of Maximal Post-Baseline Local Skin Reactions Greater Than Baseline in the Treatment Area (face or scalp)

	ONAKTA N = 353			Vehicle N = 349		
Local Skin Reactions	**Mild (1) n (%)**	**Moderate (2) n (%)**	**Severe (3) n (%)**	**Mild (1) n (%)**	**Moderate (2) n (%)**	**Severe (3) 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
Erosion/ Ulceration	32 (9%)	9 (3%)	0	10 (3%)	0	0
Vesiculation/ Pustulation	25 (7%)	2 (< 1%)	2 (< 1%)	3 (<1%)	0	0

4-point grading scale: 0 = absent, 1 = mild (slightly, barely perceptible), 2 = moderate (distinct presence), and 3 = severe (marked, intense).

For the 51 subjects (45 ONAKTA, 6 vehicle) who maintained complete clearance through the 12-month follow-up period, one isolated squamous cell carcinoma in the treatment field was reported in 1 patient following the Day 57 assessment; this event was considered by the investigator not to be related to treatment with ONAKTA.

8.3 Less Common Clinical Trial Adverse Reactions

General disorders and administration site conditions: application site paraesthesia, application site discomfort, application site dryness, application site warmth, application site inflammation, application site nodule, application site scab

Infections and infestations: carbuncle

Nervous system disorders: dysgeusia, headache

Skin and subcutaneous tissue disorders: blister, erythema, skin odour abnormal, skin tightness

Dermal Safety Studies

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

Clinical studies in healthy subjects demonstrated ONAKTA caused skin irritation under open patch, semi occlusive and occlusive patches. Skin irritation with a score of 3 or greater were lower in open patches condition 22% (n=8) vs occlusive/semi-occlusive patches 89% (n=32).

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No clinical studies evaluating the drug interaction potential of ONAKTA (tirbanibulin 1 % w/w ointment) have been conducted. Given the route of administration (topical), the short duration of dosing (5 days), the low systemic exposure (subnanomolar mean C_{max}), and the *in vitro* data, there is low potential for interaction with tirbanibulin ointment at maximum clinical exposure.

In Vitro Studies

CYP Enzymes: Tirbanibulin and the metabolite KX2-5036 directly or time-dependently inhibited CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4 with an IC_{50} value of >17 µM. Tirbanibulin up to 1 µM (431.5 ng/mL) and the metabolite KX2-5036 up to 3 µM (1024 ng/mL) did not induce CYP 1A2, 2B6, or 3A4. These findings suggest that ONAKTA has no clinically meaningful effect on the PK of drugs metabolized by CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4.

Drug Transporters: Neither tirbanibulin nor the metabolite KX2-5036 was a substrate of MDR1, BCRP, BSEP, MRP2, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 or OCT2. Tirbanibulin and the metabolite KX2-5036 inhibited MATE1, MATE2-K, OATP1B1, OATP1B3, OCT1 and/or OCT2 with an IC_{50} value of >1 µM. The results suggest that ONAKTA has no clinically meaningful effect on the PK of drugs mediated by MATE1, MATE2-K, OATP1B1, OATP1B3, OCT1 and OCT2.

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Tirbanibulin is a microtubule inhibitor. 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.

The mechanism of action of tirbanibulin for the topical treatment of actinic keratosis is unknown.

10.2 Pharmacodynamics

The pharmacodynamics of tirbanibulin in the treatment of actinic keratosis is unknown.

10.3 Pharmacokinetics

Table 4 Summary of Pharmacokinetic Parameters after 5 days of daily dosing of tirbanibulin in subjects with actinic keratosis

C_{max}	T_{max}	AUC_{0-24h}
0.258 ± 0.231 ng/mL	6.90 h	4.09 ± 3.15 ng·h/mL

Absorption

Following topical treatment of a mean daily dose of 138 mg (range: 54 to 295 mg) of ONAKTA to a 25 cm^2 contiguous area of the face or balding scalp, once daily for 5 consecutive days, the steady-state concentration of tirbanibulin was achieved by 72 hours with a mean ± SD trough concentration (C_{trough}) of 0.11 ± 0.08 ng/mL. On Day 5, systemic exposure to tirbanibulin mean ± SD values of steady-state AUC_{0-24h} and C_{max} were 4.09 ± 3.15 ng·h/mL and 0.258 ± 0.231 ng/mL, respectively. The mean C_{max} was equivalent to 0.598 nM. C_{max} and AUC_{0-24h} were slightly lower in the group with scalp application compared to face application (C_{max}: 0.176 ng/mL vs 0.34 ng/mL and AUC_{0-24h}: 3.18 ng·h/mL vs 5.0 ng·h/mL). The median time to reach C_{max} (T_{max}) was ~7 hours.

Distribution

Plasma protein binding of tirbanibulin is 88% and is independent of concentrations in the range of 0.01 to 10 µg/mL.

Metabolism

Following topical treatment with ONAKTA to adult subjects with actinic keratosis in a maximal use pharmacokinetic study, the plasma concentrations of the main metabolites (KX2-5036 and KX2-5163) were detectable with the highest plasma concentrations of 0.09 ng/mL and 0.12 ng/mL, respectively.

The *in vitro* study indicated that incubation of 1 or 10 µM tirbanibulin with human hepatocytes generated KX2-5036, KX-5163 and other unidentified metabolites.

In vitro, tirbanibulin is mainly metabolized by CYP3A4, and to a lesser extent, CYP2C8.

Elimination

Excretion of tirbanibulin has not been fully characterized in humans.

Special Populations and Conditions

- **Hepatic Insufficiency:** No formal studies of tirbanibulin ointment in patients with hepatic impairment have been conducted. Due to the low systemic exposure to tirbanibulin after topical application of tirbanibulin ointment once daily for 5 days, changes in hepatic function are unlikely to have any effect on the elimination of tirbanibulin. Therefore, no dose adjustments are considered needed (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment).

- **Renal Insufficiency:** No formal studies of tirbanibulin ointment in patients with renal impairment have been conducted. Due to the low systemic exposure to tirbanibulin after topical application of tirbanibulin ointment once daily for 5 days, changes in renal function are unlikely to have any effect on the elimination of tirbanibulin. Therefore, no dose adjustments are considered needed (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment).

11 STORAGE, STABILITY AND DISPOSAL

Store at 15°C - 30°C. Do not refrigerate or freeze.

Sachets should be discarded after single use.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

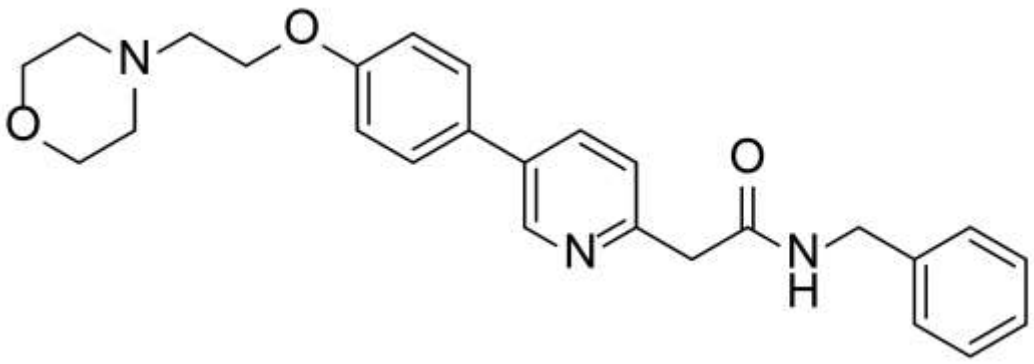
Drug Substance

Proper/Common name: Tirbanibulin (free base)

Chemical name: N-benzyl-2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl) acetamide

Molecular formula and molecular mass: $C_{26}H_{29}N_3O_3$; 431.5

Structural formula:



Physicochemical properties: White to off-white solid. Freely soluble in dimethyl sulfoxide, slightly soluble in ethanol, insoluble in water. Polymorphic Form B.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Actinic Keratosis of the Face or Scalp

Table 5 Summary of patient demographics for clinical trials in actinic keratosis

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
KX01-AK-003	Multicenter, randomized, double-blind, vehicle-controlled, parallel-group study in adult subjects with AK.	ONAKTA Ointment 1% Topical (face or scalp)	N =351 ONAKTA N = 175 Vehicle N = 176	ONAKTA 70.2 (48-86) Vehicle 69.5 (45-96)	86% Male 14% Female
KX01-AK-004	Multicenter, randomized, double-blind, vehicle-controlled, parallel-group study in adult subjects with AK.	ONAKTA Ointment 1% Topical (face or scalp)	N=351 ONAKTA N = 178 Vehicle N = 173	ONAKATA 69.1 (46-90) Vehicle 70.2 (46-92)	88% Male 12% Female

Two double-blind, vehicle-controlled clinical trials (KX01-AK-003 and KX01-AK-004) were conducted with 702 adult subjects with actinic keratosis (AK) on the face or scalp. Subjects were randomized 1:1 to ONAKTA (tirbanibulin 1 % w/w ointment) or vehicle (353 patients treated with tirbanibulin and 349 patients treated with vehicle). Subjects enrolled had 4 to 8 clinically typical, visible, and discrete AK lesions in a contiguous area of 25 cm^2 on the entire treatment field of the face or scalp. Subjects had an average age of 70 years (range 45 to 96 years), were predominantly Caucasian (>99%), male (87%), with Fitzpatrick skin types I or II (73%) and AK on the face (68%) or scalp (32%). A history of skin cancer was reported in 45 % of subjects (184 squamous cell carcinoma, 234 basal cell carcinoma, and 39 melanomas). ONAKTA was not offered to subjects with any previous use of medicinal product in the treatment area within 8 weeks of starting ONAKTA, and with any previous procedure or surgical treatment in the treatment area within 2 weeks of starting ONAKTA. Treatment groups were comparable across all demographics and baseline characteristics, including AK lesion count and distribution on the face or scalp.

Subjects received 5 consecutive days of once daily treatment with either ONAKTA (353) or vehicle control (349) to the treatment field. Subjects with complete (100%) clearance of AK lesions in the treatment area at Day 57 continued for assessment of Recurrence up to 12 months (assessments every 3 months) post-Day 57 visit.

Clinical efficacy

The primary efficacy endpoint was complete (100%) clearance of AK lesions in the treatment area on Day 57.

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 6).

Table 6 Complete and partial clearance rates at Day 57, ITT population (pooled data KX01-AK-003 and KX01-AK-004)

	Overall (face and scalp)	
	ONAKTA 10 mg/g ointment (N=353)	**Vehicle (N=349)**
Complete (100%) clearance rate[a]	49.3%[b]	8.6%
Partial (≥75%) clearance rate	72.2%[b]	18.1%

ITT=Intent-to-Treat

a. 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

b. p<0.0001; compared to vehicle by Cochran-Mantel-Hansel stratified by treatment location and study.

Complete clearance rate and partial clearance rate with ONAKTA on scalp and facial lesions were higher as compared to vehicle in an exploratory analysis (see Table 7).

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

Location		**Complete (100%) Clearance Rate**		**Partial (≥75%) Clearance Rate**	
		Tirbanibulin 10 mg/g ointment (N=353)	**Vehicle (N=349)**	**Tirbanibulin 10 mg/g ointment (N=353)**	**Vehicle (N=349)**
All subjects	n/N	174/353	30/349	255/353	63/349
	%	49.3%	8.6%	72.2%	18.1%
Face	n/N	133/238	23/239	185/238	49/239
	%	55.9%	9.6%	77.7%	20.5%
Scalp	n/N	41/115	7/110	70/115	14/110
	%	35.7%	6.4%	60.9%	12.7%

ITT=Intent-to-Treat

Based on Mantel-Haenszel method

Recurrence, defined as the proportion of subjects with any identified AK lesion (new or previous lesion) in the previously treated area who achieved complete response at Day 57 up to 12 months post Day 57, was 73%.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Tirbanibulin was found to be a moderate contact sensitiser in dermal toxicity studies in rats and guinea pigs.

Carcinogenicity

No long-term animal studies have been performed to evaluate carcinogenic potential.

Genotoxicity

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. Tirbanibulin was negative in an *in vitro* bacterial reverse mutation (Ames) assay.

Reproductive and Developmental Toxicology

Tirbanibulin was assessed for effects on fertility or reproductive function in rats. Oral administration of 4 mg/kg/day of tirbanibulin (94 times the maximum recommended human dose (MRHD) on an AUC comparison basis) adversely affected spermatogenesis (including reduced sperm count, motility, morphology of sperm and degeneration of the seminiferous epithelium). No effects on sperm were observed in males treated at 2 mg/kg/day (47 times the MRHD on an AUC comparison basis).

Tirbanibulin induced fetal deaths and external, visceral, and skeletal malformations when administered orally to pregnant rats during the period of organogenesis at doses greater than or equal to 1.25 mg/kg/day, which resulted in systemic exposures at least 74 times the exposure associated with the MRHD on an AUC comparison basis. Tirbanibulin had no apparent effects on fetal development in rats at a dose of 0.5 mg/kg/day, which resulted in systemic exposures 18 times the exposure associated with the MRHD.

Tirbanibulin reduced mean fetal weight and size (crown-rump length) when administered orally to pregnant rabbits during the period of organogenesis at a dose of 3 mg/kg/day, which resulted in a systemic exposure 159 times the exposure associated with the MRHD on an AUC comparison basis. Tirbanibulin had no apparent effects on fetal development in rabbits at a dose of 1 mg/kg/day, which resulted in systemic exposures 53 times the exposure associated with the MRHD.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr ONAKTA™

Tirbanibulin Ointment

Read this carefully before you start taking **ONAKTA**. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ONAKTA**.

What is ONAKTA used for?

- ONAKTA is used in adults to treat a skin condition called actinic keratosis on the face or scalp.

What are the ingredients in ONAKTA?

Medicinal ingredient: Tirbanibulin

Non-medicinal ingredients: Glycerol monostearate 40-55 Type I and propylene glycol.

ONAKTA comes in the following dosage forms:

Ointment: 1 % w/w. Each gram of ONAKTA contains 10 mg of tirbanibulin (10 mg/g).

Do not use ONAKTA if:

- you are allergic to tirbanibulin or any of the other ingredients of this medicine or component of the container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you use ONAKTA. Talk about any health conditions or problems you may have, including if you:

- are being treated or have been treated for actinic keratosis with any other medicine, procedure, or surgery. You should not use ONAKTA until your skin has healed from other treatments.
- have opened wounds or broken skin or notice changes in the treatment area.
- have problems with your immune system.

Other warnings you should know about:

Skin reactions:

- ONAKTA may cause skin reactions around the treatment area.
- Watch for any new scaly red patches, open sores, and raised or warty growths around the treatment area. If you see any, talk to your healthcare professional right away.
- After applying ONAKTA, avoid activities that might cause a lot of sweating. Avoid exposure to sunlight as much as possible (including sunlamps and tanning beds). When outdoors, wear protective clothing and a hat.

Pregnancy and breastfeeding:

- There are specific risks you should discuss with your healthcare professional if you:
    - are pregnant, plan to become pregnant, able to get pregnant or think you are pregnant,
    - are breastfeeding or will be breastfeeding.
- You should not use ONAKTA if you are pregnant, or if you can get pregnant and do not use birth control.
- Tell your healthcare professional right away if you become pregnant or think you may be pregnant during your treatment with ONAKTA.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ONAKTA:

No relevant interactions with ONAKTA are known at this time.

How to use ONAKTA:

- Use ONAKTA as instructed by your healthcare professional. Check with your healthcare professional if you are not sure.
- ONAKTA is for use on your skin only (face or scalp). Do not apply the ointment internally, to the inside of your nose, the inside of the ears or on the lips. If ONAKTA accidentally touches any of these areas, wash it off by rinsing with water.
- Do not get ONAKTA in, around, or near your eyes. Do not touch your eyes while you are applying ONAKTA.
- Wash your hands right away with water and soap after applying ONAKTA. After applying ONAKTA, be careful to keep ONAKTA on the treated area from coming into contact with your eyes. Irritation may happen if you get ONAKTA in your eyes. If you accidently get ONAKTA into your eyes, rinse the eyes fully with water and seek medical care as soon as possible.
- Do not allow other people or pets to touch the treated area for around 8 hours after applying ONAKTA. If the treated area is touched, the area of contact on the other person or pet should be washed.
- Avoid transferring the product to other areas after application.
- Throw away any open sachet of ONAKTA after use even if there is medicine still left in it.
- Do not use more ONAKTA than you need to cover the treatment area. Using too much ONAKTA, or using it too often, or for too long can increase your chances of having a severe skin reaction or other side effects.
- Do not swallow this medicine. Drink plenty of water if you accidentally swallow this medicine and seek medical help immediately.

Application instructions:

1. Wash your hands with soap and water before applying the ointment.
2. Wash the affected area with mild soap and water and dry it gently.
3. Open the sachet along the perforations (Figure 1). Use a new sachet each time you apply this medicine.
4. Squeeze some ointment onto your fingertip (Figure 2).
5. Apply a thin layer of ointment evenly over the entire affected area (Figure 3).

6. Wash your hands with soap and water immediately after applying the ointment (Figure 4).
7. Do not wash or touch the treated area for about 8 hours. After this time, you may wash the treated area with mild soap and water.
8. Do not cover the treated area with bandages or dressing after you have applied ONAKTA.
9. Repeat the above steps for each day of treatment at around the same time of the day.

Usual adult dose:

- Apply a thin layer of ONAKTA to the affected area on the face or scalp once a day for 5 days in a row. Use 1 single dose sachet per application.
- One sachet contains enough ointment to cover the treatment area.
- Do not use more than 1 single dose sachet per day.

Overdose:

Overdose of ONAKTA might cause severe skin reactions. Please contact your healthcare professional if you develop severe skin reactions. Wash the treated area with mild soap and water.

If you think you, or a person you are caring for, have applied too much ONAKTA, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, apply the ointment as soon as you remember and then continue with your dosing schedule. Do not apply the ointment more than once a day.

What are possible side effects from using ONAKTA?

These are not all the possible side effects you may have when taking ONAKTA. If you experience any side effects not listed here, tell your healthcare professional.

- Altered taste
- Headache
- Application site skin reactions:
    - Skin odours
    - Tight skin
    - Loss of top layer of skin
    - Skin prickling
    - Dry skin
    - Skin infection around hair

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Severe Application Site Skin Reactions: skin scaling/flaking, blistering, itching, scabs (crusting), swelling, redness, pain (stinging, tenderness, burning feeling)	✓		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store at room temperature, between 15 and 30 °C. Do not refrigerate or freeze.
- Keep out of reach and sight of children.

If you want more information about ONAKTA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.avirpharma.com), or by calling 1-888-430-0436.

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