AUSTRALIAN PRODUCT INFORMATION

ACNATAC®

Clindamycin (as phosphate) 1% w/w and tretinoin 0.025% w/w

1 NAME OF THE MEDICINE

Clindamycin phosphate and tretinoin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ACNATAC is a fixed combination product containing the following active ingredients: clindamycin phosphate 1.2% w/w (equivalent to 1% w/w of clindamycin) and tretinoin 0.025% w/w. Each gram of ACNATAC contains 12 mg clindamycin phosphate (equivalent to 10 mg clindamycin) and tretinoin 0.25mg.

ACNATAC is formulated as an aqueous gel for topical administration.

Clindamycin phosphate is freely soluble in water.

Tretinoin is practically insoluble in water and is sensitive to air, heat and light, especially in solution.

ACNATAC contains the antimicrobial preservatives methyl hydroxybenzoate and propyl hydroxybenzoate. For the full list of excipients, see **Section 6.1 LIST OF EXCIPIENTS**.

3 PHARMACEUTICAL FORM

ACNATAC is an aqueous translucent yellow gel.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ACNATAC is indicated for the topical treatment of acne vulgaris when comedones, papules and pustules are present in patients 12 years or older.

Consideration should be given to official guidance on the appropriate use of antibacterial agents and acne treatment.

4.2 DOSE AND METHOD OF ADMINISTRATION

ACNATAC is indicated for external (dermatological use only). Patients should avoid the eyes, eyelids, lips and nostrils when applying ACNATAC. After applying ACNATAC the patient should wash their hands thoroughly.

Patient should minimise their exposure to sunlight and use appropriate sunscreen products with a SPF (Sun Protection Factor) of at least 30, together with suitable protective apparel (e.g. a hat).

Adults and adolescents (e.g. 12 years and older)

Once daily at night time the affected area should be washed with mild soap and dried. A small amount of ACNATAC should be squeezed onto one fingertip; dotted onto the affected area, then gently rubbed over the skin to ensure the entire affected area is covered. As guidance: a pea-sized amount of ACNATAC should be enough to cover the entire face.

Treatment with ACNATAC should not exceed 12 weeks of continuous use without careful evaluation. It should be noted that therapeutic improvement may not be observed for several weeks after starting treatment.

In case of a missed dose of ACNATAC, the patient should wait for the next dose at the usual time. Patients should not double the dose to make up for the forgotten dose.

Paediatric use
ACNATAC is not recommended for use in children below 12 years of age.

Use in the elderly (>65 years of age)
Safety and effectiveness of ACNATAC in patients above the age of 65 years have not been established.

Use in renal and hepatic impairment
In view of the low systemic exposure to clindamycin and tretinoin following topical administration of ACNATAC, moderate renal or hepatic impairment is not expected to result in systemic exposure of clinical concern. However, clindamycin and tretinoin serum concentrations have not been studied in patients with renal or hepatic disease following topical administration. Individual decisions are advisable in severe cases.

4.3 CONTRAINDICATIONS

ACNATAC is contraindicated:

- in patients who have a history of hypersensitivity to the active substances clindamycin and/or tretinoin, to any of the excipients, or lincomycin
- in patients with regional enteritis, ulcerative colitis, or history of antibiotic-associated colitis
- in patients who have a history of acute eczemas, rosacea and perioral dermatitis
- in patients with pustular and deep cystic nodular acne varieties (acne conglobate and acne fulminans)
- in pregnancy (see **Section 4.6 FERTILITY, PREGNANCY AND LACTATION – Use in Pregnancy**)
- in women planning a pregnancy

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

ACNATAC is not for oral, ophthalmic, intranasal or intravaginal use.

ACNATAC should be prescribed with caution in atopic subjects.

Contact with the mouth, eyes and mucous membranes and with abraded or eczematous skin should be avoided. Application to sensitive areas of skin should be made with caution. In the event of accidental contact with the eyes, bathe with large amounts of water.

Antibiotic-associated colitis (also known as Clostridium difficile-associated colitis or CDAD) has been reported with the use of some topical products containing clindamycin. This is unlikely to occur with ACNATAC, as plasma levels have been investigated and the percutaneous absorption of clindamycin found to be clinically negligible.

If prolonged or significant diarrhoea occurs or the patient suffers from abdominal cramps, treatment with ACNATAC should be discontinued immediately, as the symptoms may indicate antibiotic-associated colitis. Suitable diagnostic methods, such as the determination of Clostridium difficile and toxin and, if necessary, colonoscopy should be employed and treatment options for colitis considered.

Use of more than the recommended amount or too frequent application may cause redness, stinging and discomfort. If severe irritation occurs, especially in the early stages of therapy, patients should be advised to discontinue temporarily or reduce the frequency of application.

ACNATAC should not be applied at the same time as other topical preparations (including cosmetics) because of possible incompatibility and interaction with tretinoin. Particular caution should be exercised in the use of keratolytic agents such as sulfur, salicylic acid, benzoyl peroxide or resorcinol and chemical abrasives. If the

patient has been treated with such preparations, the effect of the peeling agents must subside before any commencement of ACNATAC therapy.

Some medicated cleansers and scrubbing solutions have a strong drying effect. They should not be used in patients receiving tretinoin topical therapy. Abrasive soaps, soaps and cosmetics as well as spices or lime should be used with caution.

Because of increased susceptibility to UV radiation, photosensitivity may occur during treatment with ACNATAC. Exposure to sunlight should therefore be minimised and appropriate sunscreen products with a SPF (Sun Protection Factor) of at least 30, together with suitable protective apparel (e.g. a hat), should be used. Use of sun lamps or sun beds should be avoided during treatment. Patients with sunburn should not use ACNATAC until recovered.

Patients who may be required to have considerable sun exposure due to occupation and those with inherent sensitivity to the sun, or family history of skin cancer should exercise particular caution. If sunburn occurs, discontinue therapy with ACNATAC until the severe erythema and peeling subside.

Resistance Development

Antibiotics

Long-term use of clindamycin alone may cause resistance and/or overgrowth of non-susceptible dermal bacteria or fungi and their overgrowth. Although this is a rare occurrence occasional gram-negative folliculitis has been reported during treatment with clindamycin 1% topical products. The prevalence of clindamycin resistance may vary geographically. Therefore, local information on resistance is desirable and consideration should be given to official guidance on the appropriate use of antibacterial agents when treating acne vulgaris.

Cross resistance may occur with other antibiotics such as erythromycin or lincomycin.

Simultaneous use of oral and topical antibiotics should be avoided, particularly if chemically different.

Combination clindamycin and tretinoin

Evidence suggests that when applied together, tretinoin (via its comedolytic, anti-comedogenic and anti-inflammatory effects) may increase the penetration of clindamycin and follicle exposure to the antibiotic and therefore may in turn minimises the resistant strains development.

If resistance and/or overgrowth occur, therapy with ACNATAC should be discontinued and alternative therapy should be initiated.

Paediatric Use

Safety and effectiveness of ACNATAC in paediatric patients below the age of 12 years have not been established.

Use in the Elderly

Safety and effectiveness of ACNATAC in adult patients above the age of 65 years have not been established.

Excipients

The excipients methyl hydroxybenzoate (E218) and propyl hydroxybenzoate (E216) may cause allergic reactions (possibly delayed). The excipient butylated hydroxytoluene (E321) may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Concomitant topical medication as well as medicated soaps and cleansers that have a strong drying effect and products with high concentrations of alcohol as well as astringents should be used with caution. The concomitant treatment with corticosteroids should be avoided.

ACNATAC should not be applied at the same time as other topical preparations (including cosmetics) because of possible incompatibility and interaction with tretinoin. Particular caution should be exercised in the use of keratolytic agents such as sulfur, salicylic acid, benzoyl peroxide or resorcinol and chemical abrasives. If the patient has been treated with such preparations, the effect of the peeling agents must subside before any commencement of ACNATAC therapy.

ACNATAC should not be used in combination with erythromycin-containing products. In vitro studies have shown antagonism between these two antimicrobials. The clinical significance of this in vitro antagonism is not known.

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, ACNATAC should be used with caution in patients receiving such agents.

Tretinoin causes enhanced permeability for other topically applied medicinal agents.

Increased coagulation tests (PT/INR) and/or bleeding, have been reported in patients treated with clindamycin in combination with a vitamin K antagonist (e.g. warfarin, acenocoumarol and fluindione). Coagulation tests, therefore, should be frequently monitored in patients treated with vitamin K antagonists.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

ACNATAC did not affect the fertility of female rabbits at topical doses up to 600 mg/kg/day (6 mg/kg/day clindamycin and 0.15 mg/kg/day tretinoin) for two weeks prior to artificial insemination through gestation day 18 inclusive [8-fold the anticipated clinical exposure, based on body surface area (BSA)].

There are no available data on human fertility and ACNATAC.

Clindamycin

Reproduction studies in rats and mice, using subcutaneous and oral doses of clindamycin, revealed no evidence of impaired fertility.

Tretinoin

Systemically administered tretinoin severely affects fertility. Available data regarding fertility after topical administration in humans are limited.

Women of childbearing potential

ACNATAC should be given to women of childbearing potential only if effective contraception is used during treatment and for 1 month after discontinuation of treatment.

Use in Pregnancy

ACNATAC is contraindicated (see **Section 4.3 CONTRAINDICATIONS**) in pregnancy or in women of childbearing potential not using an effective method of contraception properly. If the product is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued.

Australian Pregnancy Category Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

No maternal or foetal toxicity was observed in rabbits given topical ACNATAC doses up to 600 mg/kg/day (6 mg/kg/day clindamycin and 0.15 mg/kg/day tretinoin) for two weeks prior to artificial insemination through gestation day 18 inclusive (8-fold the anticipated clinical exposure, based on BSA).

Clindamycin

A limited number of pregnancies exposed in the first trimester to clindamycin indicate no adverse effects of clindamycin on pregnancy or on the health of the foetus/new-born child. Clindamycin was not teratogenic in reproduction studies in rats and mice, using subcutaneous and oral doses of clindamycin.

Tretinoin

Tretinoin is a well-known human teratogen following systemic administration; however available data after topical administration in pregnant women is limited. Oral doses are teratogenic in animals and there is evidence of embryotoxicity from studies where tretinoin is applied dermally. When used in accordance with the prescribing information, topically administered retinoids are generally assumed to result in low systemic exposure due to minimal dermal absorption. However, there could be individual factors (e.g. damaged skin barrier, excessive use) that contribute to an increased systemic exposure.

Use in Lactation

It is not known whether tretinoin and clindamycin are secreted in breast milk following the use of ACNATAC. Oral and parenteral administration of clindamycin has been reported to result in the appearance of clindamycin in breast milk. It is known that orally administered retinoids and their metabolites are secreted in breast milk. Therefore, ACNATAC should not be used in women who are breast feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. It is unlikely that treatment with ACNATAC will have any effect on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse events reported in ≥1% of patients treated with ACNATAC compared to clindamycin, tretinoin or gel vehicle in three Phase III studies (see **Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical Trials**) are presented in Table 1. The majority of the adverse events were categorised by the investigator as mild and not considered to be related to treatment with the study medication.

Table 1: Adverse events reported in G2HP-06-02, G2HP-07-02 and MP1501-02 Studies

AE	**ACNATAC** N=1853 n (%)	**Clindamycin** N=1428 n (%)	**Tretinoin** N=846 n (%)	**Vehicle** N=423 n (%)
Number of subject with at least one AE	497 (27%)	342 (24%)	225 (27%)	91 (22%)
Nasopharyngitis	65 (4%)	64 (5%)	16 (2%)	5 (1%)
Headache	40 (2%)	24 (2%)	12 (1%)	11 (3%)
Upper respiratory tract infection	33 (2%)	25 (2%)	24 (3%)	11 (3%)
Pharyngolaryngeal pain	29 (2%)	18 (1%)	5 (1%)	7 (2%)
Dry skin	23 (1%)	7 (1%)	3 (<1%)	0 (0%)
Cough	19 (1%)	21 (2%)	9 (1%)	2 (1%)
Sinusitis	19 (1%)	19 (1%)	15 (2%)	4 (1%)

Within the system organ classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories:

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 (cannot be estimated from the available data)

Immune system disorders
Rare: Hypersensitivity

Endocrine disorders
Rare: Hypothyroidism

Nervous system disorders
Rare: Headache

Eye disorders
Rare: Eye irritation

Gastrointestinal disorders
Rare: Gastroenteritis, nausea

Skin and subcutaneous tissue disorders
Uncommon: Acne, dry skin, erythema, seborrhoea, photosensitivity reaction, pruritis, rash, exfoliative rash, skin exfoliation, sunburn

Rare: Dermatitis, herpes simplex, rash macular, skin bleeding, skin burning sensation, skin depigmentation, skin irritation

General disorders and administration site conditions
Uncommon: Application site reaction, application site burning, application site dermatitis, application site dryness, application site erythema

Rare: Application site irritation, application site swelling, application site erosion, application site discolouration, application site pruritus, application site desquamation, feeling hot, pain

Paediatric population
The proportion of paediatric patients (12-17 years) reporting a specific drug-related adverse reaction was consistent with that which was reported in the overall population. The incidence of dry skin in the adolescent population (12-17 years) was slightly higher in clinical trials than in the overall population.

Reporting suspected adverse reactions
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

ACNATAC is for topical use only. If ACNATAC is applied excessively marked redness, peeling or discomfort can occur. If excess application occurs, the face should be gently washed with a mild soap and lukewarm water. ACNATAC should be discontinued for several days before resuming therapy.

In the case of overdosage, topically applied clindamycin phosphate from ACNATAC can be absorbed in sufficient amounts to produce systemic effects. Gastrointestinal side effects including abdominal pain, nausea, vomiting and diarrhoea may occur.

In the event of accidental ingestion, treatment should be symptomatic. The same adverse effects expected with clindamycin (i.e. abdominal pain, nausea, vomiting and diarrhoea) and tretinoin (including teratogenesis in women of childbearing years) are expected. In such cases, ACNATAC should be discontinued and pregnancy testing should be carried out in women of childbearing potential.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Pharmacotherapeutic group: Anti-Acne Preparations for Topical Use; clindamycin, combinations, ATC code: D10AF51.

ACNATAC is a novel formulation of clindamycin and tretinoin. The mechanisms of action described below are for the individual components of ACNATAC.

Clindamycin

Clindamycin is a semisynthetic derivative of the parent compound lincomycin that is produced by Streptomyces lincolnensis. It is primarily bacteriostatic in action. Clindamycin binds to the 50S ribosomal subunits of susceptible bacteria and prevents elongation of peptide chains by interfering with peptidyl transfer, thereby suppressing bacterial protein synthesis. Although clindamycin phosphate is inactive in vitro, rapid in vivo hydrolysis converts this compound to the active antibacterial compound clindamycin.

Clindamycin has been shown to have in vitro activity against Propionibacterium acnes, one pathological factor that influences the development of acne vulgaris. Clindamycin also exerts an anti-inflammatory effect on the acne vulgaris lesions.

Tretinoin

Topical tretinoin has comedolytic, anti-comedogenic and anti-inflammatory effects. Tretinoin decreases cohesiveness of follicular epithelial cells resulting in decreased microcomedone formation. Additionally, tretinoin stimulated mitotic activity and increased turnover of follicular epithelial cells, causing extrusion of the comedones. The comedolytic activity is related to a normalisation of the desquamation of the follicular epithelium. Tretinoin exerts anti-inflammatory effects via suppression of toll-like receptors (TLRs).

ACNATAC

The combination therapy of clindamycin and tretinoin, as is provided by ACNATAC, combines the complementary individual actions of each active ingredient. Evidence suggests that when applied together, tretinoin increases the penetration of clindamycin. Thus, the combination therapy targets multiple pathogenic factors of acne vulgaris: abnormal follicular keratinization, P. acnes proliferation and inflammation.

Clinical Trials

Three randomised double-blind clinical studies, including a total of 4550 patients with acne vulgaris with both inflammatory and non-inflammatory lesions were performed. Of these 1853 patients were treated with ACNATAC Gel, 846 with tretinoin, 1428 with clindamycin phosphate and 423 with ACNATAC Gel vehicle.

Patients with 20-50 facial acne inflammatory lesions (papules and pustules), 20-100 facial acne non-inflammatory lesions (open and closed comedones), two or fewer nodules (defined as an inflammatory lesion greater than or equal to 5 mm in diameter) and without cysts were included. Lesions were counted at baseline and at weeks 2, 4, 8 and 12.

Primary measurements of efficacy for studies 7001.G2HP-06-02 and 7001.G2HP-07-02 were (1) mean percent change from baseline at Week 12 in inflammatory lesion counts, (2) mean percent change from baseline at Week 12 in non-inflammatory lesion counts, (3) mean percent change from baseline at Week 12 in total lesion counts, and (4) the percent of subjects who were clear or almost clear, at Week 12 as judged by an Evaluator's Global Severity Score (EGSS). Superiority vs. monotherapies was concluded if two of three lesion count variables and dichotomized EGSS were significant. Treatment was applied once daily for 12 weeks and patients were evaluated and lesions counted at week 12.

Studies 7001.G2HP-06-02 and 7001.G2HP-07-02 compared ACNATAC to both mono treatments (clindamycin phosphate 1.2% gel and tretinoin 0.025% gel) and vehicle using a double-blind treatment regimen. The third clinical study (MP1501-02) was conducted to compare ACNATAC to clindamycin alone.

The distribution of percent change in lesion counts was skewed, therefore the median percent change is shown in the following tables.

Table 2: Median percent change (decrease) in the number of lesions at Week 12

Lesion type	Treatment	Study			Meta-analysis All studies[1] (n=4550)
		G2HP-06-02 (n=1252)	G2HP-07-02 (n=1288)	MP1501-02 (n=2010)	
Inflammatory	**ACNATAC**	52.6	61.3	70.0	65.2
	Clindamycin	46.4*	52.1*	64.5*	60.0*
	Tretinoin	42.9*	50.0*	n.a.	46.4*
	Vehicle	25.0*	38.9*	n.a.	32.3*
Non-inflammatory	**ACNATAC**	43.8	42.3	57.6	51.6
	Clindamycin	27.5*	32.2	48.2*	43.5*
	Tretinoin	36.2*	40.0	n.a.	37.3*
	Vehicle	23.0*	24.2*	n.a.	23.9*
Total	**ACNATAC**	46.3	48.4	62.0	54.5
	Clindamycin	33.9*	40.9*	53.1*	48.1*
	Tretinoin	39.6*	39.7*	n.a.	39.6*
	Vehicle	22.2*	25.0*	n.a.	22.8*

p-values from ranked ANOVA

[1]for pairwise comparison vs Tretinoin and Vehicle, data from studies 7001-G2HP-06-02 and 7001-G2HP-07-02 were considered.

*$p \leq 0.05$

Table 3: Global Severity Score at Week 12 – presented as dichotomised values

	ACNATAC	Clindamycin	Tretinoin	Vehicle
Study 7001-G2HP-06-02 ITT-clear or almost clear				
Success	85 (20%)	32 (15%)	62 (15%)	18 (9%)
Failure[1]	335 (80%)	176 (85%)	355 (85%)	189 (91%)

Total	420	208	417	207
P-value		0.147	0.037	<0.001
Study 7001-G2HP-07-02 ITT-clear or almost clear				
Success	95 (22%)	38 (17%)	60 (14%)	16 (7%)
Failure[1]	330 (78%)	180 (83%)	369 (86%)	200 (93%)
Total	425	218	429	216
P-value		0.122	0.001	<0.001
Study MP-1501-02 ITT- clear, almost clear or at least 2-grade improvement				
Success	381 (38%)	318 (32%)	n.a.	n.a.
Failure[1]	627 (62%)	684 (68%)	n.a.	n.a.
Total	1008	1002	n.a.	n.a.
P-value		0.002	n.a.	n.a.

[1]missing values are imputed as failures

Paediatric population

The percentage change in the number of lesions at Week 12 for adolescents, between 12 and 17 years, in the individual trials and the meta-analysis of these trials are provided below.

Table 4: Median percent change (decrease) in the number of lesions at Week 12 – Adolescents

Lesion type	Treatment	Study			Meta-analysis All studies[1] (n=2915)
		G2HP-06-02 (n=800)	G2HP-07-02 (n=795)	MP1501-02 (n=1320)	
Inflammatory	**ACNATAC**	50.0	56.2	66.7	62.5
	Clindamycin	40.4	46.7	64.0*	58.3*
	Tretinoin	38.5*	47.3*	n.a.	40.7*
	Vehicle	16.7*	25.4*	n.a.	21.4*
Non-inflammatory	**ACNATAC**	43.4	40.2	55.6	50.0
	Clindamycin	23.4*	26.5*	48.7*	42.2*
	Tretinoin	30.2*	36.9	n.a.	32.8*
	Vehicle	13.5*	13.7*	n.a.	13.5*
Total	**ACNATAC**	42.0	44.8	59.4	52.5
	Clindamycin	31.3*	34.2*	53.0*	46.4*
	Tretinoin	31.9*	38.1*	n.a.	35.6*
	Vehicle	14.6*	14.6*	n.a.	14.6*

p-values from ranked ANOVA

[1]for pairwise comparison vs Tretinoin and Vehicle, data from studies 7001-G2HP-06-02 and 7001-G2HP-07-02 were considered.

*$p \leq 0.05$

Although the studies were not powered for the subgroups and the results are not as consistent as for the changes in lesion counts in the overall population, they do provide evidence for superiority of the combination product.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Tretinoin

Tretinoin occurs in the body as a metabolite of retinol, and it exhibits a certain degree of Vitamin A growth-promoting activity. Representative well-controlled clinical studies conclude that topically applied tretinoin does not increase plasma all trans retinoic acid (tretinoin). Following a single topical application of radiolabelled

tretinoin, the blood concentration of retinoic acid was found to be unchanged from 2-48 hours. Neither single-dose nor long term treatment with topical tretinoin formulations does alter systemic retinoid levels, which remain within the range of body's natural endogenous levels.

Clindamycin

Clindamycin phosphate is converted within the skin by phosphatases, leading to the more potent form of clindamycin. Thus, conversion to clindamycin is a major determinant of antimicrobial activity in the skin layers following topical application of clindamycin phosphate.

ACNATAC

In an open-label, multiple dose study treating 12 subjects with moderate to severe acne, the percutaneous absorption of tretinoin following 14 consecutive daily applications of approximately 4 g of ACNATAC was minimal. Tretinoin plasma concentrations were below the lower limit of quantitation (LLOQ; 1 ng/mL) in 50% to 92% of subjects at any given time point following administration and were near the LLOQ in all remaining subjects, with values ranging from 1.0 to 1.6 ng/mL. The plasma concentrations of the key tretinoin metabolites, 13-cis-retinoic acid and 4-oxo-13-cis-retinoic acid, ranged from 1.0 to 1.4 ng/mL and from 1.6 to 6.5 ng/mL, respectively. Plasma concentrations for clindamycin generally did not exceed 3.5 ng/mL, with the exception of one subject who recorded a value of 13.1 ng/mL.

Distribution
No data available.

Metabolism
No data available.

Excretion
No data available.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
There are no available data on the genotoxicity of ACNATAC.

Clindamycin was negative in assays evaluating the potential to cause gene mutations and chromosomal damage.

Tretinoin was negative in assays for gene mutations in bacteria (Ames test) and mammalian cells (Chinese hamster lung cells). A two-fold increase in sister chromatid exchange (SCE) frequency was found in human diploid fibroblasts, but other chromosomal aberration assays (human lymphocytes in vitro, mouse micronucleus test in vivo) did not show a clastogenic or aneuplodogenic effect.

Carcinogenicity
Long-term animal studies have not been performed to evaluate the carcinogenic potential of ACNATAC.

Clindamycin

Clindamycin phosphate 1% gel did not cause any tumourigenic response in mice at topical doses of up to 150 mg clindamycin/kg/day for 2 years (50-fold the anticipated clinical exposure, based on BSA). Clindamycin phosphate 1% gel did not accelerate tumour development in mice at topical doses of up to 100 mg/kg and UVR Exposure at 120 RBU 5 days/week for 40 weeks (24-fold the anticipated clinical exposure, based on BSA).

Tretinoin

In a 91-week dermal study in mice, tretinoin treatment at 0.5 and 1 mg/kg for three days per week was associated with the development of squamous cell carcinomas and papillomas in females at the site of application. These

skin tumours occurred in the context of severe dermal irritation; the relevance to humans is unclear. No carcinogenicity was observed at a dose of 0.025 mg/kg (less than the anticipated clinical exposure, based on BSA).

Tretinoin has been shown to enhance photocarcinogenicity following concurrent or intercurrent exposure to the drug and UV radiation in animal skin. In hairless albino mice, the tumourigenic potential of UV irradiation was increased with concurrent dermal exposure to tretinoin at a dose of 100 mg/kg. Although the relevance of this finding to humans is unclear, patients should minimise exposure to sunlight or artificial UV sources.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- glycerol
- carbomer 981
- trometamol
- propyl hydroxybenzoate
- methyl hydroxybenzoate
- polysorbate 80
- disodium edetate
- citric acid
- butylated hydroxytoluene
- purified water

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

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.

Discard after 3 months of first opening the tube.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Do not refrigerate. Do not freeze. ACNATAC should be kept out of reach of children.

6.5 NATURE AND CONTENTS OF CONTAINER

ACNATAC clindamycin (as phosphate) 1% w/w and tretinoin 0.025% w/w Topical Gel is supplied in aluminium tubes with an epoxyphenolic internal lacquer, fitted with a polyethylene cap, in pack sizes of 30 g and 60 g. Not all pack sizes may be marketed.

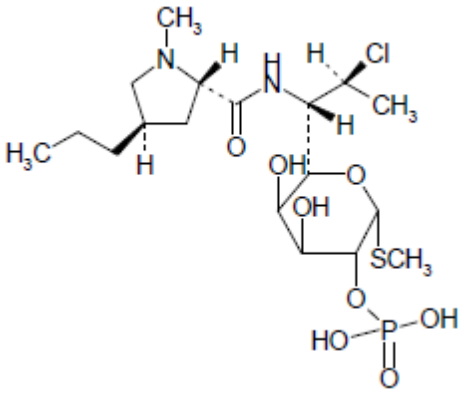
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

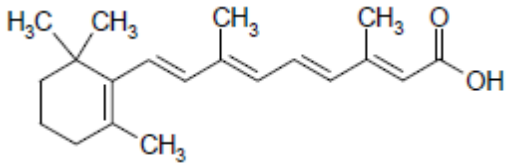
Chemical Structure

The chemical name for clindamycin phosphate is Methyl-7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-threo-α-D-galacto-octopyranoside 2-(dihydrogen phosphate). Clindamycin phosphate has the following chemical structure:



$C_{18}H_{34}ClN_2O_8PS$ Molecular weight: 504.97 g mol^{-1}

The chemical name for tretinoin is 3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid. Tretinoin has the following chemical structure:



$C_{20}H_{28}O_2$ Molecular weight: 300.44 g mol^{-1}

CAS Number

Clindamycin phosphate: 24729-96-2

Tretinoin: 302-79-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

29 March 2016

10 DATE OF REVISION

8 May 2019

Summary Table of Changes

Section Changed	Summary of New Information
4.3	Added cross-reference to Section 4.6 FERTILITY, PREGNANCY AND LACTATION – Use in Pregnancy.
4.6	Added information on Women of childbearing potential. Added cross-reference to Section 4.3 CONTRAINDICATIONS for use in pregnancy.

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