AUSTRALIAN PRODUCT INFORMATION

NOVADAC ONCE DAILY GEL
(clindamycin phosphate/benzoyl peroxide) topical gel

1 NAME OF THE MEDICINE

Clindamycin phosphate/Benzoyl peroxide .

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

NOVADAC ONCE DAILY GEL contains 10 mg/g (1% w/w) clindamycin (as phosphate) and 50 mg/g (5% w/w) benzoyl peroxide.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

NOVADAC ONCE DAILY GEL is a white to slightly yellow homogenous gel with visible fine particles, for topical use.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the topical treatment of comedo, papular and pustular acne vulgaris.

4.2 DOSE AND METHOD OF ADMINISTRATION

NOVADAC ONCE DAILY GEL is for topical (external) use only.

NOVADAC ONCE DAILY GEL is recommended for a maximum duration of treatment of 11 weeks.

Adults and Adolescents (aged 12 years and above)

NOVADAC ONCE DAILY GEL should be applied as a thin film once daily in the evening, to affected areas after the skin has been thoroughly washed, rinsed with warm water and gently patted dry.

See Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and Section 4.9 OVERDOSE for sections for temporary interruptions or discontinuations of the treatment.

Use in Children

The safety and efficacy of NOVADAC ONCE DAILY GEL has not been established in prepubescent children (under 12 years of age), since acne vulgaris rarely presents in this age group.

4.3 CONTRAINDICATIONS

NOVADAC ONCE DAILY GEL is contraindicated in:

- patients who have demonstrated hypersensitivity to lincomycin, clindamycin, benzoyl peroxide or any components of the formulation.
- patients with, or with a history of, regional enteritis, ulcerative colitis, or antibiotic-associated colitis (including pseudomembranous colitis).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity reaction

If the patient experiences a reaction that indicates contact hypersensitivity or severe irritation, treatment with NOVADAC ONCE DAILY GEL should be discontinued immediately.

For dermatological (external) use only. Contact with the mouth, eyes, lips, other mucous membranes or areas of irritated or broken skin should be avoided. Application to sensitive areas of skin should be made with caution. In case of accidental contact, rinse well with water.

If excessive dryness or peeling occurs, frequency of application should be reduced, or application temporarily interrupted.

Patients should be advised that excessive application will not improve efficacy but may increase the risk of skin irritation.

During the first weeks of treatment, an increase in peeling and reddening may occur [see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)]. Depending upon the severity of these side effects, patients can use a moisturiser, temporarily reduce the frequency of application of NOVADAC ONCE DAILY GEL or temporarily discontinue use; however, efficacy has not been established for less than once daily dosing frequencies.

Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy may occur, which sometimes may be severe, especially with the use of peeling, desquamating, or abrasive agents.

If severe local irritancy (e.g. severe erythema, severe dryness and itching, severe stinging/burning) occurs, NOVADAC ONCE DAILY GEL should be discontinued.

The irritation potential of the agent may be increased if applied under occlusion.

Photosensitivity

As benzoyl peroxide may cause increased sensitivity to sunlight, sunlamps should not be used and deliberate or prolonged exposure to sunlight should be avoided or minimised. When exposure to strong sunlight cannot be avoided, patients should be advised to use a sunscreen product and wear protective clothing.

If a patient has sunburn, this should be resolved before using NOVADAC ONCE DAILY GEL.

The product may bleach hair and coloured or dyed fabrics. Avoid contact with hair, fabrics, furniture or carpeting.

Patients should be advised that, in some cases, 4–6 weeks of treatment may be required before the full therapeutic effect is observed.

Pseudomembranous colitis

Oral and parenteral clindamycin have been associated with severe diarrhoea and pseudomembranous colitis and may range in severity, with an onset of up to several weeks following cessation of therapy. Although this is unlikely to occur with topically applied clindamycin/benzoyl peroxide, if prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further, 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.

Resistance

Prolonged use of clindamycin may lead to selection of resistant micro-organisms and their overgrowth. NOVADAC ONCE DAILY GEL is recommended for a maximum duration of 11 weeks. There have been reports of *Propionibacterium acnes* resistance to clindamycin in the treatment of acne. If acne recurs, and a product containing a topical antibiotic or antiseptic is considered appropriate by their physician, the patient should be retreated with

clindamycin1%/benzoyl peroxide 5% (NOVADAC ONCE DAILY GEL) to reduce the risk of development of cross-resistance to other topical antibiotics.

Local recommendations about antibiotic use and prevalence of clindamycin resistance should be taken into consideration.

Benzoyl peroxide reduces the potential for emergence of organisms resistant to clindamycin (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Resistance development). Patients with a recent history of systemic or topical clindamycin or erythromycin use are more likely to have pre-existing anti-microbial resistant *Propionibacterium acnes* and commensal flora.

Cross-resistance has been demonstrated between clindamycin and lincomycin.

Resistance to clindamycin is often associated with inducible resistance to erythromycin (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Clindamycin and erythromycin should not be used in combination.

NOVADAC ONCE DAILY GEL may not be adequate for severe nodulocystic acne.

Use in the elderly

No data available.

Paediatric use

No data available.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Concomitant topical antibiotics, medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect, and products with high concentrations of alcohol and/or astringents, should be used with caution as a cumulative irritant effect may occur.

No clinical studies have been conducted to assess interactions between NOVADAC ONCE DAILY GEL and other topical medications.

NOVADAC ONCE DAILY GEL should not be used in combination with erythromycin-containing products. *In vitro* studies have shown antagonism between these two antimicrobials.

Oral clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. This effect is more common at higher doses of clindamycin. Therefore, NOVADAC ONCE DAILY GEL should be used with caution in patients receiving such agents.

Concomitant application of NOVADAC ONCE DAILY GEL with tretinoin, isotretinoin and tazarotene may reduce their efficacy and increase irritation. If combination treatment is required, the products should be applied at different times of the day (e.g., one in the morning and the other in the evening).

Using topical benzoyl peroxide-containing preparations at the same time as topical sulfonamide-containing products may cause skin and facial hair to temporarily change colour (yellow/orange).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no data on the effect of topical clindamycin or benzoyl peroxide on fertility in humans. Fertility was not impaired in male or female rats given benzoyl peroxide by oral gavage at doses up to 500 mg/kg/day, although male testes and epididymis weights were reduced at

1000 mg/kg/day, a dose which greatly exceeds that applied topically. Fertility was not impaired in rats given clindamycin phosphate 300 mg/kg/day in the diet.

There are no contraindications in women of child-bearing potential who are practising adequate contraception. However, due to the lack of clinical studies in pregnant women, NOVADAC ONCE DAILY GEL should be used with caution when adequate contraception is not being practised.

Use in pregnancy

(Pregnancy Category A)

Animal embryofetal development studies have not been conducted with NOVADAC ONCE DAILY GEL. Administration of benzoyl peroxide by oral gavage to female rats throughout gestation and 3 days post-partum resulted in reduced pup bodyweights at 1000 mg/kg/day, but no pup gross external abnormalities. Reproductive studies have been performed in rats and mice using oral and parenteral doses of clindamycin phosphate up to 300 mg/kg/day and have revealed no evidence of harm to the fetus due to clindamycin. There are no well-controlled studies in pregnant women treated with NOVADAC ONCE DAILY GEL.

There are limited data on the use of topical clindamycin or benzoyl peroxide alone in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. No effects during pregnancy are anticipated since systemic exposure to clindamycin and benzoyl peroxide is anticipated to be low.

It is not known whether NOVADAC ONCE DAILY GEL can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. NOVADAC ONCE DAILY GEL should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus.

Use in lactation

NOVADAC ONCE DAILY GEL has not been studied during breast-feeding.

Percutaneous absorption of clindamycin and benzoyl peroxide is low; however, it is not known whether clindamycin or benzoyl peroxide is excreted in human milk after topical application. Oral and parenteral administration of clindamycin has been reported to result in the appearance of clindamycin in breast milk.

NOVADAC ONCE DAILY GEL should be used during lactation only if the expected benefit justifies the potential risk to the infant.

To avoid accidental ingestion by the infant if used during lactation, NOVADAC ONCE DAILY GEL should not be applied to the breast area.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There have been no studies to investigate the effect of clindamycin/benzoyl peroxide on driving performance or the ability to operate machinery. A detrimental effect on such activities would not be anticipated from the adverse reaction profile of clindamycin/benzoyl peroxide.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse drug reactions (ADRs) are summarised below for topical clindamycin/benzoyl peroxide as a combination including any additional ADRs that have been reported for the single topical active ingredients, benzoyl peroxide or clindamycin. Adverse drug reactions are listed by MedDRA system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥ 1/1,000 and < 1/100), rare (≥ 1/10,000 and < 1/1,000) very rare (< 1/10,000).

Clinical trials:

Very common (> 1/10)	Erythema Peeling Dryness
Common (> 1/100, < 1/10)	Burning sensation Pruritus
Uncommon (> 1/1000, < 1/100)	Dermatitis, Paraesthesia Erythematous rash Worsening of acne

In addition to the ADRs reported above, in a clinical trial conducted with a topical clindamycin and benzoyl peroxide (1%/3%) gel product, application site photosensitivity reaction was reported commonly.

In addition to the ADRs reported above, in a clinical trial conducted with a topical clindamycin product, headache and application site pain were reported commonly.

Adverse events reported in five comparator clinical trials (studies 150, 151, 152, 156 and 158) by treatment arm are presented in the following table 1:

Table 1 – Adverse events reported in five comparator clinical trials

	Number of patients that experienced a treatment emergent sign or symptom			
	Clindamycin/ Benzoyl Peroxide Once Daily Gel (n = 397) Number (%)	**Benzoyl Peroxide (n = 396) Number (%)**	**Clindamycin Gel (n = 349) Number (%)**	**Vehicle Gel Control (n = 177) Number (%)**
Skin				
Erythema	38 (10)	46 (12)	17 (5)	20 (12)
Peeling	62 (16)	61 (16)	19 (6)	13 (8)
Burning	16 (4)	17 (4)	9 (3)	4 (2)
Dryness	52 (14)	47 (12)	30 (9)	14 (8)
Pruritus	11 (3)	7 (2)	5 (1)	4 (2)

Seven cases of diarrhoea were reported: Clindamycin/Benzoyl Peroxide Gel (n = 3), Clindamycin Gel (n = 1) and Benzoyl Peroxide Gel (n = 3). Of the three cases in the Clindamycin/Benzoyl Peroxide Gel group, one case was attributed to *E. coli* food poisoning, which was successfully treated with antibiotics. The other two patients experienced short episodes of mild diarrhoea with no treatment or change in usage of study medication.

Contact sensitivity was reported in a patch test study (study 157) conducted on healthy volunteers. A total of 218 subjects were tested of whom 18 (8.7%) developed allergic contact dermatitis after 3 weeks exposure to Clindamycin/Benzoyl Peroxide Gel. This incidence is similar to that observed historically (approximately 10%) at the investigative site for products containing benzoyl peroxide. It is anticipated that the incidence of sensitisation in clinical use will be much less than that reported in this study since semi-occlusive patching exaggerates any intrinsic effect of topically applied substances to cause contact sensitisation.

Post-marketing data:

Immune system disorders

Rare: Allergic reactions including hypersensitivity and anaphylaxis

Gastrointestinal disorders

Rare: Colitis (including pseudomembranous colitis), haemorrhagic diarrhoea, diarrhoea, abdominal pain

Skin and subcutaneous tissue disorders (at site of application)

Rare: Urticaria

General disorders and Administration site conditions

Rare: Application site reactions including discoloration

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

No case of overdosage has been reported.

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

Symptoms and signs

Excessive application of NOVADAC ONCE DAILY GEL may result in severe irritation (e.g., dermatitis, peeling and dryness). In this event, discontinue use and wait until the skin has recovered.

Topically applied benzoyl peroxide is not generally absorbed in sufficient amounts to produce systemic effects.

Excessive application of topically applied clindamycin may result in absorption of sufficient amounts to produce systemic effects (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

In the event of accidental ingestion of NOVADAC ONCE DAILY GEL, gastrointestinal adverse reactions similar to those seen with systemically administered clindamycin may be seen (e.g., nausea, vomiting and diarrhoea).

Treatment

Appropriate symptomatic measures should be taken to provide relief from irritation due to excessive topical application.

Accidental ingestion or application should be managed clinically or as recommended by the Poisons Information Centre (13 11 26).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Clindamycin

Clindamycin is a lincosamide antibiotic with bacteriostatic action against Gram-positive aerobes and a wide range of anaerobic bacteria. Lincosamides such as clindamycin bind to

the 23S subunit of the bacterial ribosome and inhibit the early stages of protein synthesis. The action of clindamycin is predominantly bacteriostatic although high concentrations may be slowly bactericidal against sensitive strains.

Although clindamycin phosphate is inactive *in-vitro*, rapid *in vivo* hydrolysis converts this compound to the antibacterial active clindamycin. Clindamycin activity has been demonstrated clinically in comedones from acne patients at sufficient levels to be active against most strains of *Propionibacterium acnes*. Clindamycin *in vitro* inhibits all *Propionibacterium acnes* cultures tested (MIC 0.4 mcg/mL). Free fatty acids on the skin have been decreased from approximately 14% to 2% following application of clindamycin.

Cross resistance may occur between clindamycin and other antibiotics such as lincomycin and erythromycin.

The prevalence of clindamycin resistance may vary geographically and with time for selected species. Local information of resistance is desirable, particularly when treating severe infections.

Resistance development

Prolonged use of clindamycin may lead to selection of resistant micro-organisms and their overgrowth. Clindamycin/Benzoyl Peroxide Gel was associated with reduced potential for emergence of resistance to clindamycin in *Propionibacterium acnes* compared to topical clindamycin alone in a clinical study of short duration.

Cross-resistance may occur between clindamycin and other antibiotics such as lincomycin and erythromycin.

The prevalence of clindamycin resistance may vary geographically and with time for selected species. Local information of resistance is desirable, particularly when treating severe infections.

Antibiotic-resistant propionibacteria may be transmissible between susceptible individuals. Physicians who routinely palpate patients' skin to assess acne severity should use cross infection control measures to avoid transferring resistant isolates between patients.

<u>Benzoyl peroxide</u>

Benzoyl peroxide is keratolytic acting against comedones at all stages of their development. It is an oxidizing agent with bactericidal activity against *Propionibacterium acnes*, the organism implicated in acne vulgaris. Furthermore, it is sebostatic, counteracting the excessive sebum production associated with acne.

NOVADAC ONCE DAILY GEL has a combination of keratolytic and antibacterial properties providing activity against all the inflamed and non-inflamed lesions of mild to moderate acne vulgaris.

Clindamycin/Benzoyl Peroxide Gel was associated with reduced potential for emergence of resistance to clindamycin in *Propionibacterium acnes* compared to topical clindamycin alone in a clinical study of short duration.

The presentation of both active ingredients in one product is more convenient and ensures patient compliance.

Clinical trials

In five randomised double-blind clinical studies of 1,319 patients with facial acne vulgaris with both inflammatory and non-inflammatory lesions, 397 used Clindamycin/Benzoyl Peroxide Gel, 396 used benzoyl peroxide, 349 used clindamycin and 177 used vehicle. Treatment was applied once daily for 11 weeks and patients were evaluated and lesions counted at 2, 5, 8 and 11 weeks.

Against inflammatory lesions, Clindamycin/Benzoyl Peroxide Gel was significantly more effective than clindamycin alone in four of five studies and to benzoyl peroxide alone in three of five studies. Against non-inflammatory lesions, Clindamycin/Benzoyl Peroxide Gel was significantly better than clindamycin in four of five studies. Against non-inflammatory lesions,

Clindamycin/Benzoyl Peroxide Gel was significantly better than benzoyl peroxide in only one of five studies.

Overall improvement was assessed by the physician and was significantly better with Clindamycin/Benzoyl Peroxide Gel than with either benzoyl peroxide or clindamycin alone in three of five studies.

The following table 2 reports results from the pivotal clinical study.

Table 2 - Results from the pivotal clinical study (Study 158)
(Intention To Treat Population)

	Clindamycin/ Benzoyl Peroxide Gel	**Benzoyl Peroxide**	**Clindamycin**	**Vehicle**
N	113	112	65	68
LS* mean % reduction in inflammatory lesions	60	46 (0.005)	37 (<0.001)	36 (<0.001)
LS* mean % reduction in non-inflammatory lesions	32	25 (0.521)	15 (0.204)	10 (increase) (0.002)
Global improvement (good to excellent)	58	44 (0.059)	30 (<0.001)	26 (<0.001)

* LS mean = least square mean (from analysis of variance with effects for site, treatment and interaction)

Values in brackets are raw p values.

5.2 PHARMACOKINETIC PROPERTIES

Clindamycin

In a maximised percutaneous absorption study the mean plasma clindamycin levels during a four-week dosing period for Clindamycin/Benzoyl Peroxide Gel were negligible (0.043% of applied dose).

The presence of benzoyl peroxide in the formulation did not have an effect on the percutaneous absorption of clindamycin.

Benzoyl peroxide

Benzoyl peroxide is absorbed by the skin where it is metabolised to benzoic acid. Benzoic acid is mostly conjugated to form hippuric acid, which is excreted via the kidneys. Benzoic acid too has a wide margin of safety and is an approved food additive.

In vivo data obtained with radiolabel procedures on urine specimens from rhesus monkeys indicated about 1.9% of the dose enters systemic circulation as benzoic acid.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

Benzoyl peroxide has been shown to be a tumour promoter and progression agent in a number of animal studies. Studies in mice have shown that benzoyl peroxide does not increase the growth of tumours initiated by UV light. Lifetime (104-week) carcinogencity studies with benzoyl peroxide dermally applied to mice (1%, 5%, 25/15% on approximately 6 cm^2) and rats (1.6%, 5%, 15% on approximately 17.5 cm^2) showed no evidence of carcinogenicity.

Long-term studies in animals to evaluate the carcinogenic potential of Clindamycin/Benzoyl Peroxide Gel and clindamycin phosphate have not been performed.

A photocarcinogenicity study, in which hairless albino mice were exposed to a cumulative tumourigenic dose of simulated sunlight, showed that dermal application of Clindamycin/Benzoyl Peroxide Gel, for 5 days per week for 40 weeks, caused a statistically significant reduction in the median time to skin tumour onset. A slight reduction was also observed with the gel vehicle only. It is unclear whether these results have any clinical significance. Clinical use of NOVADAC ONCE DAILY GEL is likely to be much less extensive than that tested in mice.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

NOVADAC ONCE DAILY GEL also contains carbomer 980, dimeticone 100, disodium lauril sulfosuccinate, disodium edetate, glycerol, poloxamer, silicon dioxide, sodium hydroxide and purified water.

6.2 INCOMPATIBILITIES

See Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

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 at 2ºC to 8°C. (Refrigerate. Do not freeze).

Once opened, store at 2ºC to 8°C. (Refrigerate. Do not freeze). Discard 2 months after opening.

6.5 NATURE AND CONTENTS OF CONTAINER

NOVADAC ONCE DAILY GEL is presented in single 30 g internally, lacquered membrane-sealed aluminium tubes fitted with a polyethylene screw cap.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Clindamycin phosphate is a water-soluble ester of the semisynthetic antibiotic produced by a 7(*S*)-chloro-substitution of the 7(*R*)-hydroxyl group of the parent antibiotic lincomycin. Synthesis also involves phosphorylation of the C(2)-OH group. It is a white to off-white, odourless, hygroscopic, crystalline powder. It is soluble in water, slightly soluble in dehydrated alcohol, very slightly soluble in acetone, and in alcohol; and practically insoluble in chloroform, methylene chloride and ether.

Chemical name: 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).

Molecular formula: $C_{18}H_{34}ClN_2O_8PS$.

Molecular weight: 504.97.

Benzoyl peroxide is a white amorphous or granular powder with a characteristic odour which is practically insoluble to sparingly insoluble in water, slightly to sparingly soluble in alcohol, soluble in acetone, chloroform and ether and also soluble in methylene chloride with separation of water.

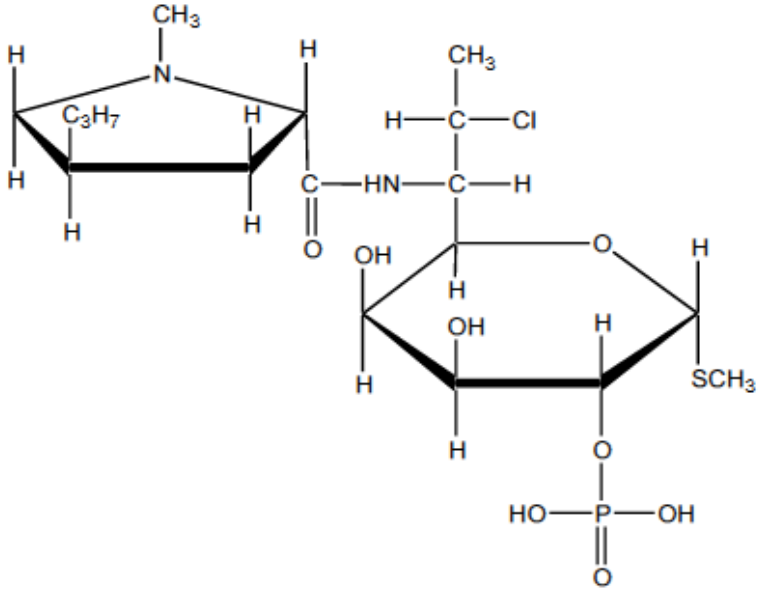
Chemical Name: dibenzoyl peroxide.

Molecular formula: $C_{14}H_{10}O_4$

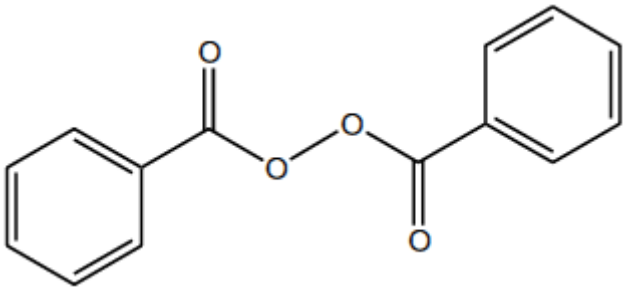
Molecular weight: 242.23.

Chemical structure

Clindamycin phosphate



Benzoyl peroxide



CAS number

CAS Number: 24729-96-2 – Clindamycin phosphate

CAS Number: 94-36-0 – Benzoyl peroxide

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8 SPONSOR

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9 DATE OF FIRST APPROVAL

29 May 2024

10 DATE OF REVISION

not applicable

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	New PI