NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Duac Once Daily Gel contains 1% w/w clindamycin (as phosphate) and 5% w/w benzoyl peroxide

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Duac Once Daily Gel contains 1% w/w clindamycin (as phosphate) and 5% w/w benzoyl peroxide.

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Gel

Duac Once Daily Gel is a white to slightly yellow homogenous gel for topical use.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the topical treatment of comedo, papular and pustular acne vulgaris, in adults and adolescents aged 12 years and above.

4.2 Dosage and method of administration

Dose

Duac Once Daily Gel is for topical use only.

Duac Once Daily Gel is recommended for a maximum duration of 11 weeks.

Australian Therapeutic Guidelines, Antibiotics, Version 12 recommend addition of topical antibiotics (topical clindamycin) if there is insufficient response to topical keratolytics alone in the treatment of acne vulgaris of moderate severity.

Adults and Adolescents (aged 12 years and above)

Duac Once Daily Gel should be applied once daily as a thin film in the evening, to affected areas after the skin has been thoroughly washed, rinsed with warm water, and gently patted dry.

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.

Paediatric population

The safety and efficacy of Duac 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

Duac 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

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.

During the first weeks of treatment, an increase in peeling and reddening will occur in most patients. Depending upon the severity of these side effects, patients can use a moisturiser, temporarily reduce the frequency of application of DUAC 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 may sometimes 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, DUAC Once Daily Gel should be discontinued.

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

If the patient experiences a reaction that indicates contact hypersensitivity or severe irritation, treatment with Duac Once Daily Gel should be discontinued immediately.

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 DUAC 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.

<u>Pseudomembranous colitis</u>

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clindamycin, and may range in severity from mild to life-threatening, 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. Duac Once Daily 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. Duac *Once Daily* Gel is recommended for a maximum duration of 11 weeks. If acne recurs, and a product containing a topical antibiotic or antiseptic is considered appropriate, the patient should be retreated with Duac Once Daily Gel to reduce the risk of development of cross-resistance to other topical antibiotics. Australian Guidelines* recommend addition of topical antibiotics (topical clindamycin) if there is insufficient response to topical keratolytics, such as benzoyl peroxide, alone in the treatment of acne vulgaris of moderate severity. The Australian Therapeutic Guidelines, Antibiotics Version 12 also recommend re-treating with the same drug if relapse occurs.

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

Clindamycin and erythromycin should not be used in combination.

Benzoyl peroxide reduces the potential for emergence of organisms resistant to clindamycin. However, 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 Interactions with other medicines and other forms of interaction).

Duac Once Daily Gel may not be adequate for severe nodulocystic acne.

4.5 Interaction with other medicines and other forms of interaction

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.

DUAC Once Daily Gel should not be used in combination with erythromycin-containing products due to possible antagonism to the clindamycin component.

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

Concomitant application of DUAC Once Daily Gel with tretinoin, isotretinoin and tazarotene should be avoided since benzoyl peroxide 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 sulphonamide-containing products may cause skin and facial hair to temporarily change colour (yellow/orange).

No clinical studies have been conducted to assess interactions between Duac Once Daily Gel and other topical medications.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category A.

Animal embryofoetal development studies have not been conducted with Duac Once Daily Gel or benzoyl peroxide. 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 foetus due to clindamycin. There are no well-controlled studies in pregnant women treated with DUAC 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 low.

It is not known whether Duac Once Daily Gel can cause foetal harm when administered to a pregnant woman or can affect reproductive capacity. Duac Once Daily Gel should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus.

Women of Child-Bearing Potential

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, Duac Once Daily Gel should be used with caution when adequate contraception is not being practised.

Breast-feeding

DUAC 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.

DUAC 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, DUAC Once Daily Gel should not be applied to the breast area.

Fertility

There are no data on the effect of topical clindamycin or benzoyl peroxide on fertility in humans.

Fertility was not impaired in rats given clindamycin phosphate 300 mg/kg/day in the diet.

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 Undesirable effects

Tabulated list of adverse reactions

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
Uncommon (≥1/1000, <1/100)	Dermatitis Paraesthesia Pruritus Erythematous rash Worsening of acne

In addition to the ADRs reported above for DUAC Once Daily Gel, 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 for DUAC Once Daily Gel, 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) are presented in the following table.

	Number of patients that experienced a treatment emergent sign or symptom			
	Duac *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: Duac Once Daily Gel (n=3), Clindamycin Gel (n=1) and Benzoyl Peroxide Gel (n=3). Of the three cases in the Duac *Once Daily* 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 Duac Once Daily 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

In the post marketing environment there have been instances of allergic reactions which can be sudden and severe.

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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via: https://nzphvc.otago.ac.nz/reporting

4.9 Overdose

Symptoms and signs

Excessive application of Duac Once Daily Gel may result in severe irritation. 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.

In the event of accidental ingestion of Duac Once Daily Gel, gastrointestinal adverse reactions similar to those seen with systemically administered clindamycin may be seen.

Treatment

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Clindamycin, combinations, ATC Code: D10AF51

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 0.4mcg/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.

Benzoyl Peroxide

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.

Duac 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.

Duac Once Daily 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 efficacy and safety

In five randomised double-blind clinical studies of 1318 patients with facial acne vulgaris with both inflammatory and non-inflammatory lesions, 396 used Duac Once Daily 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, Duac Once Daily 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, Duac *Once Daily* Gel was significantly better than clindamycin in four of five studies. Against non-inflammatory lesions, Duac *Once Daily* 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 Duac Once Daily Gel than with either benzoyl peroxide or clindamycin alone in three of five studies.

The following table reports results from the pivotal clinical study.

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

Table 1

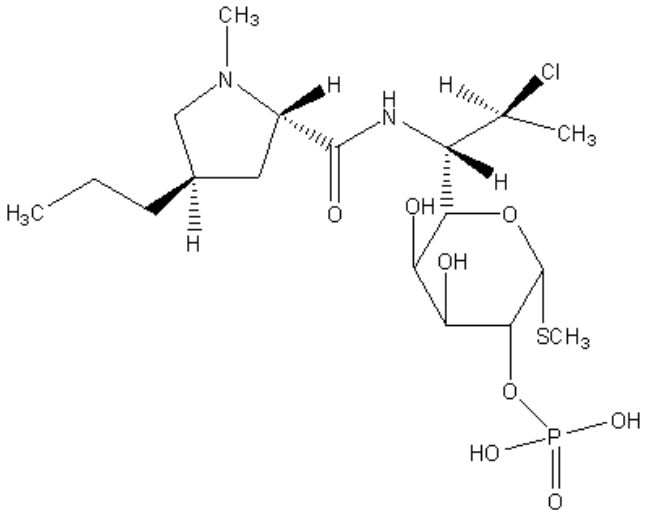
	DUAC	Benzoyl Peroxide	Clindamycin	Vehicle
N	113	112	65	68
LS* mean % reduction in inflammatory lesions	60	46 (0.005)	37 (<0.001)	36 (<0.001)
LS* mean % reduction in non-inflammatory lesions	32	25 (0.521)	15 (0.204)	10 (increase) (0.002)
Global improvement (good to excellent)	58	44 (0.059)	30 (<0.001)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

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

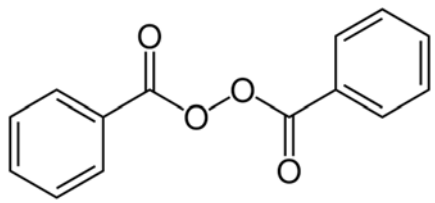
Values in brackets are raw p values.

Chemical Structure

Clindamycin phosphate



Benzoyl peroxide



5.2 Pharmacokinetic properties

Clindamycin

In a maximised percutaneous absorption study the mean plasma clindamycin levels during a four-week dosing period for Duac Once Daily 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

Radio-labelled studies have shown that absorption of benzoyl peroxide through the skin can only occur following its conversion to benzoic acid. Benzoic acid is mostly conjugated to form hippuric acid, which is excreted via the kidneys. Benzoic acid has a wide margin of safety and is an approved food additive.

5.3 Preclinical safety data

Repeat-dose dermal toxicity studies conducted on Duac Once Daily Gel, in two species, for up to 90 days, revealed no toxic effects, apart from minor local irritation.

An ocular irritation study found Duac Once Daily Gel to be only very slightly irritant.

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. The clinical significance of this is unknown.

Long-term studies in animals to evaluate the carcinogenic potential of Duac Once Daily Gel and clindamycin phosphate have not been performed.

A photocarcinogenicity study, in which hairless mice were exposed to a cumulative tumourigenic dose of stimulated sunlight, showed that derma application of Duac Once Daily 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 Duac is likely to be much less extensive than that tested in mice.

Genotoxicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carbomer 980
Dimeticone 100
Disodium lauryl sulfosuccinate
Disodium edetate
Glycerol
Silicon dioxide

Poloxamer
Purified water
Sodium hydroxide

6.2 Incompatibilities

None.

6.3 Shelf Life

2 years.

Shelf life of medicinal product after dispensing: 2 months.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Duac Once Daily Gel is presented in internally, lacquered membrane-sealed aluminium tubes fitted with a polyethylene screw-cap, packed into a carton.

Pack sizes: 5, 6, 25, 30, 45, 50, 55, 60 and 70 grams.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

GlaxoSmithKline NZ Limited
Private Bag 106600
Downtown
Auckland
New Zealand
Phone: (09) 367 2900
Facsimile: (09) 367 2910

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
2 March 2006

10. DATE OF REVISION OF THE TEXT

20 March 2018

Summary table of changes:

Section changed	Summary of new information
All	Data Sheet re-format
4.8	Added adverse reaction contact information
4.9	Revised information for advice on the management of overdose
5.1	Added Pharmacotherapeutic group and ATC code
6.6	Added information regarding disposal
9	Added date of first approval

Version 9.0

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