

DATA SHEET

Name of Medicine

DUAC[®] ONCE DAILY GEL

STIEFEL

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

Presentation

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

Uses

Actions

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 trials

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.

Pharmacokinetics

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.

Indications

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

Dosage and Administration

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

Australian Guidelines* 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.

*Therapeutic Guidelines, Antibiotics, Version 12.

Adults

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

Use in Children

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.

Contraindications

Duac *Once Daily* Gel should not be used in patients with a known hypersensitivity to clindamycin, lincomycin, benzoyl peroxide or any of the excipients in the formulation.

Warnings and Precautions

Oral and parenteral clindamycin have been associated with severe diarrhoea and pseudomembranous colitis. Topical clindamycin has rarely been associated with pseudomembranous colitis, however if the patient suffers from abdominal cramps or diarrhoea, the product should be discontinued immediately. 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.

Duac *Once Daily* Gel should be used with caution in patients with a history of regional enteritis or ulcerative colitis, or a history of antibiotic-associated colitis.

Contact with the mouth, eyes, skin 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 eyes, bathe with copious amounts of water.

Duac *Once Daily* Gel should be used with caution in atopic individuals, and in combination with other topical therapy as this may lead to excessive peeling, dryness and irritation.

The frequency of application should be reduced if excessive irritation or dryness develops.

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.

The product may bleach hair or coloured fabrics.

Increased exposure to UV light, such as may occur at high altitudes, especially on snow-covered grounds, may result in excessive irritation of Duac *Once Daily* Gel-treated areas. It is recommended that exposure to sun or sunlamps should be minimised.

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

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 Guidelines 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.

*Therapeutic Guidelines, Antibiotics Version 12.

Clindamycin and erythromycin should not be used in combination.

Cross-resistance may occur with other antibiotics such as lincomycin and erythromycin when using antibiotic monotherapy.

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

Pregnancy and Lactation

Use in Pregnancy

Pregnancy Category A.

Animal embryofetal 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 however, no adequate and well-controlled studies in pregnant women.

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 given to a pregnant woman only if clearly needed.

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.

Use in Lactation

There is no restriction on the use of benzoyl peroxide during lactation.

It is not known whether clindamycin is excreted in human milk following the topical use of Duac *Once Daily* Gel, but oral and parenteral administration of clindamycin has been reported to result in the appearance of clindamycin in breast milk. For this reason, treatment of nursing mothers with Duac *Once Daily* Gel should be restricted to essential cases.

Effects On Ability To Drive And Use Machines

Not relevant.

Adverse Effects

Duac *Once Daily Gel* may cause erythema, peeling, dryness and pruritus at the site of application. Very rarely, paraesthesia, worsening of acne and contact dermatitis may occur. These localised effects are typically mild to moderate.

Reported frequencies in clinical trials are:

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

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 <i>Once Daily Gel</i> (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.

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

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 Duac *Once Daily* Gel and other topical medications.

Overdosage

No case of overdosage has been reported.

Pharmaceutical Precautions

Incompatibilities

None.

Shelf life

2 years.

Special precautions for storage

Instructions to the pharmacist: Store at 2°C to 8°C for up to 2 years. (Refrigerate. Do not freeze).

Instructions to the patient: Store at 2°C to 8°C for up to 2 months. (Refrigerate. Do not freeze).

Medicine Classification

Prescription Only Medicine

Package Quantities

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

Pack size: 25g.

Further Information

Preclinical Safety Information

Duac Once Daily Gel

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.

Effects on Fertility

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

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.

Excipients

Carbomer 980
Dimeticone 100
Disodium lauryl sulfosuccinate
Disodium edetate
Glycerol
Silicon dioxide
Poloxamer
Purified water
Sodium hydroxide

Name and Address

Distributed by
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