For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

CLINDOXYL ONCE DAILY GEL

Benzoyl Peroxide and Clindamycin Gel BP

QUALITATIVE AND QUANTITATIVE COMPOSITION

Clindamycin Phosphate IP equivalent to Clindamycin 1% w/w

Hydrous Benzoyl Peroxide IP equivalent to Anhydrous Benzoyl Peroxide 5 % w/w

PHARMACEUTICAL FORM

White to slightly yellow homogeneous gel.

CLINICAL PARTICULARS

Therapeutic Indications

CLINDOXYL ONCE DAILY GEL is indicated for the topical treatment of mild to moderate acne vulgaris, particularly inflammatory lesions, in adults and adolescents aged 12 years and above.

Posology and Method of Administration

Adults and adolescents

CLINDOXYL ONCE DAILY GEL is for topical use only.

CLINDOXYL ONCE DAILY GEL should be applied in a thin film over the entire affected area once daily after washing gently with a mild cleanser and fully drying.

If the gel does not rub into the skin easily, too much is being applied.

Hands should be washed after application. Patients may also use a moisturiser as needed.

If excessive dryness or peeling occurs, frequency of application should be reduced or application temporarily interrupted. Efficacy has not been established for less than once daily dosing frequencies.

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

Two to five weeks of treatment may be required before a therapeutic effect is observed (*see Clinical Studies, Pharmacokinetic Properties).*

The safety and efficacy of clindamycin/benzoyl peroxide have not been studied beyond 12 weeks in acne vulgaris clinical trials. The prescriber should evaluate the benefit of continuing treatment beyond 12 weeks of uninterrupted use.

Use in Children

The safety and efficacy of clindamycin/benzoyl peroxide has not been established in children less than 12 years of age, therefore *CLINDOXYL ONCE DAILY GEL* is not recommended for use in this population.

Use in the Elderly

There are no specific recommendations for use in the elderly.

Renal impairment

No dosage adjustment is necessary.

As percutaneous absorption of clindamycin/benzoyl peroxide is low following topical application, renal impairment is not expected to result in systemic exposure of clinical significance.

Hepatic impairment

No dosage adjustment is necessary.

As percutaneous absorption of clindamycin/benzoyl peroxide is low following topical application, hepatic impairment is not expected to result in systemic exposure of clinical significance.

Contraindications

CLINDOXYL 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).

Special Warnings and Special Precautions for Use

Contact with the mouth, eyes, lips, other mucous membranes or areas of irritated or broken skin should be avoided. 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 *CLINDOXYL 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, *CLINDOXYL ONCE DAILY GEL* should be discontinued.

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 *CLINDOXYL ONCE DAILY GEL*.

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

Pseudomembranous colitis

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 *CLINDOXYL ONCE DAILY GEL*, 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.

Resistance to clindamycin

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 (*see Pharmacodynamic Properties*).

Cross-resistance

Cross-resistance has been demonstrated between clindamycin and lincomycin.

Resistance to clindamycin is often associated with inducible resistance to erythromycin (*see Interaction with other Medicaments and other Forms of Interaction*).

Interaction with Other Medicaments and Other Forms of Interaction

No formal drug-drug interaction studies have been conducted *with* clindamycin/benzoyl peroxide gel.

CLINDOXYL 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, *CLINDOXYL ONCE DAILY GEL* should be used with caution in patients receiving such agents.

Concomitant application of *CLINDOXYL 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).

Pregnancy and Lactation

Fertility

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

Pregnancy

There are no well-controlled studies in pregnant women treated with topical clindamycin/benzoyl peroxide 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 (*see Pre-Clinical Data*). No effects during pregnancy are anticipated since systemic exposure to clindamycin and benzoyl peroxide is low (*see Pharmacological Properties*).

However, *CLINDOXYL ONCE DAILY GEL* should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus.

Lactation

Topical clindamycin/benzoyl peroxide 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. Clindamycin is excreted in human milk following oral and parenteral administration.

CLINDOXYL 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, *CLINDOXYL ONCE DAILY GEL* should not be applied to the breast area.

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 *CLINDOXYL ONCE DAILY GEL*.

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 trial data

Safety and efficacy of clindamycin 1%/benzoyl peroxide 5% gel has been evaluated in five randomised double-blind clinical trials of 1319 patients (397 used clindamycin 1%/ benzoyl peroxide 5% gel) with facial acne vulgaris (*see Clinical Studies*). Patients 12 years or older were treated once daily in the evening for 11 weeks. All ADRs reported with clindamycin 1%/benzoyl peroxide 5% gel from these studies are shown in the summary table below:

Summary of ADRs in CLN 1%/BPO 5% Gel Controlled Clinical Trials (N=397) (Studies 150, 151, 152, 156 and 158)

MedDRA SOC	Very Common	Common	Uncommon
***Nervous system disorders**			Paraesthesia
***Skin and subcutaneous tissue disorders**	Erythema, peeling, dryness *(Generally reported as 'mild' in severity*)	Burning sensation	Dermatitis, pruritus, erythematous rash, worsening of acne

***At site of application**

In addition to the ADRs reported in the table above, in the pivotal trial conducted with topical clindamycin 1%/benzoyl peroxide 3% gel, application site photosensitivity reaction was also reported commonly.

In addition to the ADRs reported above, in studies conducted with topical clindamycin alone headache and application site pain were also reported commonly.

Local Tolerability

During five clinical trials with clindamycin 1%/benzoyl peroxide 5% gel, all patients were graded for facial erythema, peeling, burning, and dryness on the following scale: 0 = absent, 1 = mild, 2 = moderate and 3 = severe. The percentage of patients that had symptoms present before treatment (at baseline) and during treatment were as follows:

Local Tolerability Assessments for Subjects (N=397) in the CLN 1%/BPO 5% Gel Group during the Phase 3 Studies (Studies 150, 151, 152, 156 and 158)

	Before Treatment (Baseline)			**During Treatment**		
	Mild	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Erythema	28%	3%	0	26%	5%	0
Peeling	6%	<1%	0	17%	2%	0
Burning	3%	<1%	0	5%	<1%	0
Dryness	6%	<1%	0	15%	1%	0

Post-marketing data

MedDRA SOC	Rare
Immune system disorders	Allergic reactions including hypersensitivity and anaphylaxis
Gastrointestinal disorders	Colitis (including pseudomembranous colitis), haemorrhagic diarrhoea, diarrhoea, abdominal pain
***Skin and subcutaneous tissue disorders**	Urticaria
General disorders and Administration site conditions	Application site reactions including discoloration

***At site of application**

Overdose

Symptoms and signs

Excessive application of *CLINDOXYL 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 *CLINDOXYL 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.

Accidental ingestion should be managed clinically or as recommended by the National Poisons Centre, where available.

PHARMACOLOGICAL PROPERTIES

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

50S ribosomal subunit of the susceptible bacteria and prevent elongation of peptide chains by interfering with peptidyl transfer, thereby suppressing protein synthesis. The action of clindamycin is predominantly bacteriostatic although high concentrations may be slowly bactericidal against sensitive strains.

Clindamycin phosphate is inactive *in-vitro* and is hydrolysed *in vivo* to active clindamycin.

Benzoyl peroxide

Benzoyl peroxide is a highly lipophilic oxidising agent with bactericidal and mild keratolytic effects. It contributes a non-specific bactericidal mechanism (the formation of reactive oxygen species) to the combination therapy and thereby suppresses the emergence of drug-resistant organisms.

Pharmacodynamic effects

Clindamycin

Clindamycin has been shown to have *in vitro* activity against *Propionibacterium acnes,* an organism that has been associated with acne vulgaris. *P.acnes* resistance to clindamycin has been documented.

Clindamycin *in vitro* inhibits *P. acnes* (minimum inhibitory concentration (MIC) 0.4 µg/mL).

Free fatty acids on the skin surface have been decreased from approximately 14% to 2% following application of clindamycin.

Clindamycin also reduces inflammation by inhibiting leukocyte chemotaxis.

Benzoyl peroxide

The effectiveness of benzoyl peroxide in the treatment of acne vulgaris is primarily attributable to its bactericidal activity, especially with respect to *P. acnes.* The bactericidal activity of benzoyl peroxide is due to the release of active or free-radical oxygen capable of oxidising bacterial proteins. Benzoyl peroxide is also believed to be effective in the treatment of acne on account of its anti-inflammatory and mild keratolytic properties.

Resistance and cross-resistance

The treatment of acne with topical and oral antibiotics used as monotherapy such as clindamycin and erythromycin has been associated with the development of antimicrobial resistance in *P. acnes* as well as commensal flora (e.g. *Staphylococcus aureus, Streptococcus pyogenes*). The use of clindamycin may result in developing inducible resistance in these organisms.

Benzoyl peroxide has a bactericidal effect and it has not been shown to induce emergence resistance in *P. acnes.* The inclusion of benzoyl peroxide in clindamycin/benzoyl peroxide gel has been shown to reduce clindamycin resistant *P. acne* counts *(see Special Warnings and Special Precautions for Use).* This has not been studied with clindamycin 1%/benzoyl peroxide 3%.

The prevalence of acquired resistance may vary geographically and over time for selected organisms. Local information of resistance is desirable, particularly when treating severe infections.

Pharmacokinetic Properties

Absorption/Distribution/Metabolism

Clindamycin

Clindamycin phosphate is rapidly hydrolysed to clindamycin by skin phosphatases. Clindamycin is further metabolised to clindamycin sulfoxide. Significant levels of clindamycin have been detected in comedones of patients who have applied topical clindamycin phosphate for two weeks.

There is no evidence that the skin acts as a reservoir for clindamycin after repeated applications or that it accumulates systemically.

Clindamycin is metabolised in the liver to active and inactive metabolites.

Benzoyl peroxide

Benzoyl peroxide is absorbed by the skin where it is metabolised to benzoic acid. Following topical application, less than 5% of the dose enters systemic circulation as benzoic acid.

Clindamycin/benzoyl peroxide gel

A comparative study of the pharmacokinetics of clindamycin 1%/benzoyl peroxide 5% gel (1g applied to the face once daily) and 1% clindamycin solution (0.5g applied to the face twice daily) in 78 patients with moderate to severe acne indicated that mean plasma clindamycin levels during the four week dosing period were very low (< 0.5 ng/mL) for both treatment groups.

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

In an open-label study of patients with moderate-to-severe acne vulgaris, approximately 4 grams of clindamycin 1%/benzoyl peroxide 5% gel was applied once daily for 5 days to the face, upper chest, and upper back and shoulders. Two formulations were studied (24 patients in each group), one containing methylparaben and the other was preservative-free. Clindamycin was slowly absorbed after topical application, reaching maximal observed plasma concentrations within 6 to 8 hours. Geometric mean maximal plasma clindamycin exposure (C_{max} and $AUC_{o\text{-}infinity}$) on Day 5 was 1.095 ng/mL and 16.3 ng*h/mL, respectively, in the methylparaben formulation and 0.806 ng/mL and 11.4ng*h/mL, respectively, in the preservative-free formulation.

Systemic exposure to clindamycin sulfoxide was lower relative to clindamycin, as mean C_{max} and AUC values were approximately 4- to 5-fold higher on average for clindamycin compared with clindamycin sulfoxide. This ratio was comparable across all formulations, indicating that the conversion of clindamycin to its metabolite is not affected by formulation.

Elimination

Clindamycin

Clindamycin has an elimination half-life of approximately 9 hours and is excreted mainly in the urine as the parent compound.

Following multiple topical applications of clindamycin gel, less than 0.06% of the total dose was excreted in the urine.

Benzoyl peroxide

Benzoyl peroxide is excreted as benzoic acid in the urine.

Clindamycin /benzoyl peroxide gel

A comparative study of the pharmacokinetics of clindamycin 1%/benzoyl peroxide 5% gel (1g applied to the face once daily) and 1% clindamycin solution (0.5g applied to the face twice daily) in 78 patients for four weeks, indicated no statistically significant differences in the amounts of clindamycin and clindamycin sulphoxide excreted in the 24h period after the last dose were detected between treatments.

Special patient populations

Children

Not relevant for this product.

Elderly

See *section Posology and Method of Administration.*

Renal impairment

See *section Posology and Method of Administration.*

Hepatic impairment

See *section Posology and Method of Administration.*

Clinical Studies

The safety and efficacy of clindamycin 1%/benzoyl peroxide 5% were evaluated in five randomised double-blind clinical studies of 1319 patients with facial acne vulgaris with both inflammatory and non-inflammatory lesions. Treatment was applied once daily for 11 weeks and patients were evaluated and lesions counted at 2, 5, 8 and 11 weeks. The mean percentage reduction in the number of all lesions after 11 weeks is shown in the table below:

Summary table showing mean percent reduction in number of lesions from baseline after 11 weeks across studies 150, 151, 152, 156 & 158

	Study 150 (n = 120)	**Study 151 (n = 273)**	**Study 152 (n = 280)**	**Study 156 (n = 288)**	**Study 158** (n = 358)**
Inflammatory lesions					
CLN 1%/BPO 5%	65%	56%	42%	57%	52%
BPO	36%*	37%*	32%	57%	41%*
CLN	34%*	30%*	38%	49%*	33%*
Vehicle	19%*	-0.4%*	29%	n/a	29%*
Non-inflammatory lesions					
CLN 1%/BPO 5%	27%	37%	24%	39%	25%
BPO	12%	30%	16%	29%*	23%
CLN	-4%*	13%*	11%*	18%*	17%
Vehicle	-9%*	-5%*	17%	n/a	-7%
Total lesions (inflammatory plus non-inflammatory lesions)					
CLN 1%/BPO 5% (n=397)	41%	45%	31%	50%	41%
BPO (n=396)	20%	35%	23%	43%	34%
CLN (n=349)	11%*	22%*	22%*	33%*	26%*
Vehicle (n=177)	1%*	-1%*	22%*	n/a	16%*

*Statistically significant differences relative to CLN/BPO. **Pivotal study. Abbreviations: CLN= clindamycin, BPO= benzoyl peroxide.

The mean percentage reduction in total lesions was significantly greater with clindamycin 1%/ benzoyl peroxide 5% than clindamycin or vehicle in all five studies. The observed improvement was consistently greater with clindamycin 1%/ benzoyl peroxide 5% than benzoyl peroxide alone, but the difference did not achieve statistical significance in all individual studies.

Against inflammatory lesions, clindamycin 1%/ benzoyl peroxide 5% was significantly superior to clindamycin alone in four of five studies and to benzoyl peroxide alone in three of five studies. Against non-inflammatory lesions, clindamycin 1%/ benzoyl peroxide 5% was significantly superior to clindamycin alone in four of five studies.

Overall improvement in acne was assessed by the physician and was significantly superior with clindamycin 1%/ benzoyl peroxide 5% than with either benzoyl peroxide or clindamycin alone in three of five studies.

An effect on inflammatory lesions was apparent from week 2 of treatment. The effect on non-inflammatory lesions was more variable, with efficacy generally apparent after 2-5 weeks of treatment.

Preclinical Safety Data

Carcinogenesis/Mutagenesis

No genotoxicity or mutagenicity studies have been conducted with topical clindamycin/benzoyl peroxide gel.

Clindamycin

Clindamycin phosphate was not genotoxic in *Salmonella typhimurium,* a chromosome aberration assay or in a rat micronucleus test.

Benzoyl peroxide

Both the carcinogenicity and photocarcinogenicity of benzoyl peroxide have been extensively assessed in both mice and hamsters, by various routes of administration, in studies ranging from 42 to 100 weeks in duration. The overall conclusion is that benzoyl peroxide is considered to be neither carcinogenic nor photocarcinogenic in topical acne products at a concentration of 2.5% to 10%.

The genotoxicity of benzoyl peroxide was extensively assessed *in vitro* and *in vivo*. While in a few *in vitro* studies benzoyl peroxide showed weak mutagenicity, the overall genotoxicity profile did not indicate significant biological relevance.

Clindamycin/benzoyl peroxide gel

In a 2-year carcinogenicity study in mice, topical administration of clindamycin 1%/benzoyl peroxide 5% gel at dose levels up to 8000 mg/kg/day (24000 mg/m^2/day) showed no evidence of increased carcinogenic risk, compared with controls.

In a 52-week photococarcinogenicity study in which hairless mice were exposed to both ultraviolet radiation and clindamycin 1%/benzoyl peroxide 5% gel at dose levels up to 2500 mg/kg/day (7500 mg/m^2/day), a slight reduction in the median time to onset of tumours was observed, as compared to ultraviolet radiation alone.

Reproductive Toxicology

Fertility and Pregnancy

No fertility studies were conducted with topical clindamycin/benzoyl peroxide gel.

Clindamycin

Fertility studies in rats treated orally with up to 300 mg/kg/day of clindamycin revealed no effects on fertility or mating ability.

Reproduction studies have been performed in rats and mice using subcutaneous and oral doses of clindamycin phosphate, clindamycin hydrochloride and clindamycin palmitate. These studies revealed no evidence of foetal harm.

The highest dose used in the rat and mouse teratogenicity studies was equivalent to a clindamycin phosphate dose of 432 mg/kg. For a rat, that dose is 84-fold higher, and for a mouse 42-fold higher, than the anticipated human dose of clindamycin phosphate from 1% clindamycin phosphate foam based on a mg/m^2 comparison.

Benzoyl peroxide

In a combined repeat dose and reproduction/development toxicity study, benzoyl peroxide (250, 500, or 1000 mg/kg/day) was administered orally to male rats for 29 days and female rats for 41-51 days. There were no treatment-related changes observed in the mating period, mating rate, conception rate, delivery rate, birth rate, pregnancy period, luteinisation number, implantation number and the rate of losing embryos and fetuses after implantation. In pups, body weight was significantly decreased in the high-dose group. The no-observed-adverse-effect level (NOAEL) for reproductive toxicities was considered to be 500 mg/kg/day.

PHARMACEUTICAL PARTICULARS

List of Excipients

Carbomer (50000 mPa.s), Dimeticone (100 $mm^2.s^{-1}$) Disodium Lauryl Sulfosuccinate, Edetate Disodium, Glycerol, Silica (Colloidal Hydrated), Poloxamer 182, Purified Water, Sodium Hydroxide.

Incompatibilities

There are no relevant data available.

Shelf life

Shelf life of medicinal product as packaged for sale: 18 months.

Expiry date is indicated on the label and packaging.

Shelf life of medicinal product after dispensing (after the seal has been broken): 2 months.

Special precautions for storage

Store in refrigerator (2^o to 8^o C). Do not freeze. Discard after 2 months after the seal has been broken.

Storage conditions after dispensing

Do not store above 25° C.

Keep out of reach of children.

Nature and contents of container

Internally lacquered membrane-sealed aluminium tubes fitted with a polyethylene screw-cap, packed into a carton.

All pack presentations may not be marketed in the country.

Instructions for Use / Handling

For application to the skin. For external use only.

There are no other special requirements for use or handling of this product.

Manufactured by:
Glaxo Operations UK Limited,
(trading as Glaxo Wellcome Operations),
Harmire Road, Barnard Castle,
County Durham, DL12 8DT,
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Imported and marketed by:
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