CONFIDENTIAL

Clindoxyl® Once Daily Gel

Clindamycin/benzoyl peroxide

Formulation and Strength

Topical gel containing clindamycin (1.2% clindamycin phosphate) at a concentration equivalent to 1% w/w (10 mg/g) and benzoyl peroxide 5% w/w (50 mg/g).
A white to slightly yellow coloured gel.

Excipients

Carbomers
Dimeticone
Disodium lauryl sulfosuccinate
Disodium edetate
Glycerol
Silica, colloidal hydrated
Poloxamer 182
Purified water
Sodium hydroxide

CLINICAL INFORMATION

Indications

Clindoxyl® Once Daily Gel is indicated for the topical treatment of mild to moderate acne vulgaris.

Clindoxyl® Once Daily Gel has not been demonstrated to have any additional benefit when compared to benzoyl peroxide alone in the same vehicle when used for the treatment of non-inflammatory acne.

Dosage and 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 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.

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

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.

Children

The safety and efficacy of Clindoxyl® Once Daily Gel have not been established in children less than 12 years of age, therefore clindamycin/benzoyl peroxide is not recommended for use in this population.

Elderly

There are no specific recommendations for use in the elderly.

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).

Warnings and Precautions

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.

Application to sensitive areas of skin should be made with caution.

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 clindamycin/benzoyl peroxide or temporarily discontinue use; however, efficacy has not been established for less than once daily dosing frequencies.

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.

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, clindamycin/benzoyl peroxide 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 clindamycin/benzoyl peroxide.

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 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.

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 Clinical Pharmacology*).

Cross-resistance
Cross-resistance has been demonstrated between clindamycin and lincomycin.
Resistance to clindamycin is often associated with inducible resistance to erythromycin (*see Interactions*).

Interactions

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

Clindamycin/benzoyl peroxide 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, clindamycin/benzoyl peroxide should be used with caution in patients receiving such agents.

Concomitant application of clindamycin/benzoyl peroxide 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 Clindoxyl® 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 (*see Non-Clinical Information*). No effects during pregnancy are anticipated since systemic exposure to clindamycin and benzoyl peroxide is low (*see Clinical Pharmacology*). However, Clindoxyl® Once Daily Gel should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus.

Lactation

Clindoxyl® 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. 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.

Ability to perform tasks that require judgement, motor or cognitive skills

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.

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 trial data

The 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 the 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**

Overdosage

For management of a suspected drug overdose, contact your National Poisons Centre, where available.

Symptoms

Topically applied benzoyl peroxide is not generally absorbed in sufficient amounts to produce systemic effects. Excessive application of topically applied clindamycin phosphate formulations can be absorbed in sufficient amounts to produce systemic effects (*see Warnings and Precautions*).

Excessive topical application of Clindoxyl® Once Daily Gel may cause severe skin irritation from the benzoyl peroxide and gastrointestinal side effects, including abdominal pain, nausea, vomiting and diarrhoea, due to systemic absorption of clindamycin phosphate from Clindoxyl® Once Daily Gel.

In the event of accidental ingestion of Clindoxyl® Once Daily Gel, the same gastrointestinal side effects as those expected with oral clindamycin are expected (*see Warnings and Precautions*).

Treatment

In the case of symptoms resulting from excessive topical application Clindoxyl® Once Daily Gel should be discontinued until the skin has recovered before resuming therapy (*see Warnings and Precautions*).

Appropriate symptomatic measures (e.g. cold compresses) should be taken to provide relief from irritation due to excessive topical application. Further management of excessive topical application or accidental ingestion should be as clinically indicated or as recommended by the National Poisons Centre or healthcare professional, where available.

Clinical Pharmacology

Pharmacodynamics

Anatomical Therapeutic Chemical (ATC) code

Pharmacotherapeutic group: Clindamycin, combinations

ATC code: D10AF51

Pharmacodynamic Properties

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 rRNA component of the 50S ribosomal 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 surface have been decreased from approximately 14 % to 2 % following application of clindamycin.

Clindoxyl® 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. The inclusion of benzoyl peroxide reduces the potential for the emergence of organisms resistant to clindamycin. The presentation of both active ingredients in one product is more convenient and ensures patient compliance.

Benzoyl peroxide

Benzoyl peroxide is keratolytic acting against comedones at all stages of their development. It is an oxidising agent with bactericidal activity against *Propionibacterium acnes*, the organism implicated in acne vulgaris. Benzoyl peroxide is also believed to be effective in the treatment of acne on account of its anti-inflammatory 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 1%/benzoyl peroxide 5% has been shown to reduce clindamycin resistant *P. acne* counts (*see Warnings and Precautions*).

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.

Pharmacokinetics

Pharmacokinetic Properties

In a maximised percutaneous absorption study the mean plasma clindamycin levels during a four week dosing period for Clindoxyl® 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.

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.

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.

NON-CLINICAL INFORMATION

Clindamycin/benzoyl peroxide gel

In a two year carcinogenicity study in mice, topical administration of clindamycin/benzoyl peroxide gel showed no evidence of increased carcinogenic risk, compared with controls.

In a photococarcinogenicity study in mice, a slight reduction in the median time to tumour formation was observed relative to controls following concurrent exposure to clindamycin/benzoyl peroxide gel and simulated sunlight. The clinical relevance of the findings in this study is unknown.

Repeat-dose dermal toxicity studies conducted on clindamycin/benzoyl peroxide gel, in two species, for up to 90 days, revealed no toxic effects, apart from minor local irritation.

An ocular irritation study found clindamycin/benzoyl peroxide gel to be only very slightly irritant.

Benzoyl peroxide

In animal toxicity studies, benzoyl peroxide was well tolerated when applied topically.

Although high doses of benzoyl peroxide have been shown to induce DNA strand breaks, the available data from other mutagenicity studies, carcinogenicity studies and a photo co-carcinogenicity study indicate that benzoyl peroxide is not a carcinogen or a photocarcinogen.

No reproductive toxicity data are available.

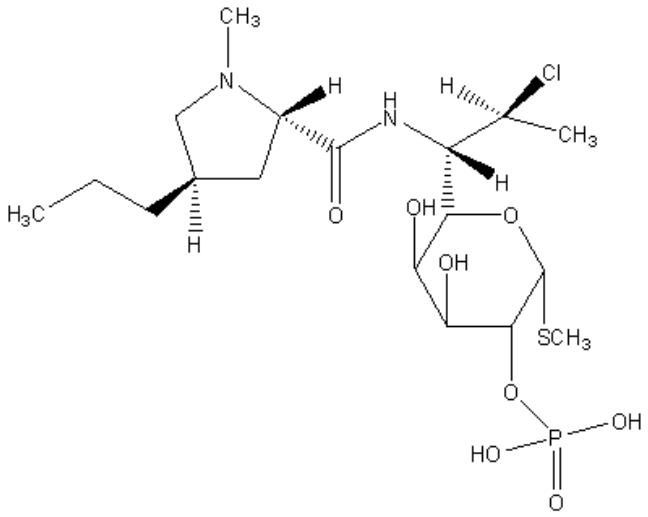
Clindamycin

In-vitro and in-vivo studies did not reveal any mutagenic potential of clindamycin. No long-term animal studies investigating the tumorigenic potential of clindamycin have been conducted. Otherwise, preclinical data reveal no special hazard for humans based on conventional studies of single and repeat-dose toxicity and toxicity to reproduction.

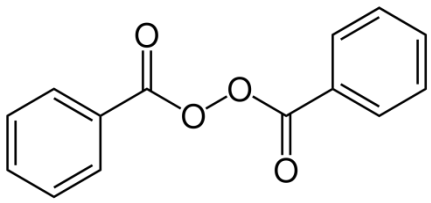
PHARMACEUTICAL INFORMATION

Chemical structure

Clindamycin phosphate:



Benzoyl peroxide:



Shelf-life

The expiry date is indicated on the packaging.

Storage

Storage conditions prior to dispensing: Store in a refrigerator (2°C to 8°C). Do not freeze.
Storage conditions after dispensing: Do not store above 25°C. Do not freeze. After 2 months, discard and use a new tube.

Nature and contents of container

Packaging description:
Aluminium tube internally coated with a phenolic resin lacquer and closed with a membrane seal and screw-on polyethylene cap.
Package sizes: 5g, 6g, 10g, 15g, 25g, 30g or 50g tube.

Not all pack sizes may be marketed.

Incompatibilities

Not applicable.

Use and handling

No special requirements.

Version number: GDS01(SI)

Date of issue: 30 October 2011

Product Owner
Stiefel Laboratories, Inc.
20 T.W. Alexander Drive, RTP, NC 27709, USA.