

BenzoTech® Gel Product Information

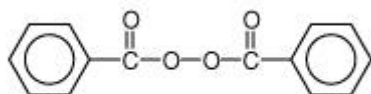
BENZOTECH® GEL **(Benzoyl peroxide 5%)**

DESCRIPTION

BenzoTech® Gel is a smooth aqueous gel, white to creamy white in colour. It contains hydrous benzoyl peroxide 5% as the active drug substance, which is dispersed in a water-based gel matrix.

Benzoyl peroxide is a fine, white or almost white, granular powder. It is practically soluble in water, sparingly soluble in alcohol, soluble in acetone, chloroform, benzene and ether, soluble in methylene chloride with separation of water.

The chemical formula for benzoyl peroxide is benzoyl superoxide, $(C_6H_5CO)_2O_2$.



Benzoyl
peroxide
 $(C_{14}H_{30}O_4)$
MW: 242.2

The excipient ingredients include purified water, glycerol, carbomer, sodium C₁₄-C₁₆ olefin sulfonate, disodium edetate, sodium hydroxide and citric acid. The product contains no alcohol, propylene glycol, parabens, dyes or perfumes that could potentially irritate the skin.

PHARMACOLOGY

Pharmacological Action

The mechanism of action of benzoyl peroxide is not fully established but its antibacterial activity against *Propionibacterium acnes* is thought to be a major mode of action. In addition, patients treated with benzoyl peroxide show a reduction in lipids and fatty acids and mild desquamation (drying and peeling activity) with a simultaneous reduction in comedones and acne lesions.

Pharmacokinetics

Little is known about the percutaneous penetration, metabolism and excretion of benzoyl peroxide, although it has been shown that benzoyl peroxide absorbed by the skin is metabolised to benzoic acid, then excreted as the benzoate in the urine. There is no evidence of systemic toxicity caused by benzoyl peroxide in humans.

INDICATIONS

For the topical treatment of mild or moderate acne vulgaris.

CONTRAINDICATIONS

BenzoTech Gel should not be used in patients with a known history of hypersensitivity to benzoyl peroxide or any other ingredients of the preparation.

WARNINGS

For External Use Only. Do not use in or near the eyes or on mucous membranes.

PRECAUTIONS

Patients receiving topical benzoyl peroxide treatment should be instructed to use the product only as directed. Skin reactions (e.g. dryness, erythema and peeling) may occur especially during the initial phase of treatment. If excessive skin irritation develops or increases, the patient should be instructed to use the drug less frequently, or to discontinue use until the integrity of the skin is restored, and depending on the severity of the reaction to institute appropriate palliative therapy (e.g. cold compresses).

After the reaction clears, treatment may often be resumed with reduced dosing schedule or less frequent application. However, if the condition worsens or persists, the patient should discontinue use and consult a doctor or a dermatologist.

Care should be taken to avoid contact with eyes, eyelids, lips, mucous membranes and open wounds. If the product accidentally gets into the eyes or membranous skin, rinse the affected area thoroughly with water.

Avoid contact with coloured materials (including hair, dyed fabrics or coloured sheets) because benzoyl peroxide has bleaching property and may cause discoloration.

Avoid using at high altitudes or on snow-covered ground as direct exposure to intense UV irradiation sources and abrasion in these places could potentiate the desquamating effect of benzoyl peroxide.

Carcinogenesis, mutagenesis, impairment of fertility

Based upon the updated assessment by the International Agency for Research on Cancer, there exists inadequate evidence in humans and limited evidence in experimental animals for the carcinogenicity of benzoyl peroxide. Overall benzoyl peroxide is not considered to be a carcinogen in humans.

Use in pregnancy

Reproduction studies in animal or human have not been performed with topical benzoyl peroxide. It is not known whether benzoyl peroxide can cause foetal harm when used topically by pregnant women. Since safety of the use of topical benzoyl peroxide in pregnant women has not been established, topical benzoyl peroxide should not be used during pregnancy unless clearly directed by a doctor or a pharmacist.

Use in lactation

Topical benzoyl peroxide may be absorbed through the mother's skin. However, it is not known whether it is distributed into breast milk. Benzoyl peroxide has not been reported to cause problems in nursing babies. Because many drugs are excreted into human milk, topical benzoyl peroxide should only be used during breastfeeding if clearly indicated by a doctor or a pharmacist.

Use in children

Safety and use of topical benzoyl peroxide in children below the age of 12 have not been studied. For children above 12 years old, although there is no specific study comparing use of topical benzoyl peroxide in children with use other age groups, this medicine is not expected to cause different sides effects or problems in children 12 years or older than it does in adults.

Use in geriatric patients

Safety and use of topical benzoyl peroxide have not been studied specifically in the old aged group. Therefore it is not known whether the drug works in the same way they do in younger adults. Although there is no specific information comparing use of benzoyl peroxide in the elderly with use in other age group, there are no published reports that it may cause different side effects or problems in geriatric people than it does in younger adults.

Interactions

Concomitant use of benzoyl peroxide and other topical medications (especially those containing exfoliative agents such as sulphur, resorcinol, salicylic acid or tretinoin) should be discouraged because of the possibility of interaction.

If patients have applied any of these medications prior to the use of topical benzoyl peroxide, sufficient time should elapse for the effects of these medications to subside before initiating treatment.

Use of medicated soaps, alkaline soaps and abrasive cleansers should be avoided because concomitant use may increase skin irritation. Sunscreens particularly those containing *p*-aminobenzoic acid may cause transient discoloration of skin in the presence of benzoyl peroxide.

Other topical preparations with high concentrations of alcohols, oils and surfactants such as shaving lotions, astringents and cosmetics should be avoided if possible. If used, the areas to be treated should be cleansed thoroughly before benzoyl peroxide is applied. Medicated cosmetics should not be used during benzoyl peroxide treatment.

ADVERSE REACTIONS

Topical benzoyl peroxide may produce a mild burning sensation on first application and a moderate reddening peeling of the skin within a few days. During the first few weeks of treatment, a sudden increase in peeling will occur in most patients; this is not harmful and will normally subside in a day or two if treatment is temporarily discontinued.

Contact sensitisation and dryness have been reported in some patients with topical benzoyl peroxide therapy.

DOSAGE AND ADMINISTRATION

Apply to the affected areas once or twice daily (morning and evening). Wash the affected areas prior to each application with a mild soap-free cleanser, rinse well with water, and pat dry with a soft cotton towel.

The frequency and duration of use should be adjusted to obtain the desired clinical response. Initially, apply once daily in the evening, gently massage into the skin, leave on skin for two hours and then wash off. After the first 3-4 days of treatment, if the skin tolerates well, apply before bedtime and allow the medication remain overnight. After the first week, if no discomfort occurs, apply twice a day, once in the morning and once before bedtime, leave on and wash off before the next application.

Changes to the frequency and duration of use should be closely monitored by careful observation of patient's response and tolerance.

Excessive or too frequent use may cause the skin to become flaming red, chapped or swollen. If occurred, reduce dosing or discontinue treatment temporary till the patient recovers well, then re-instate with less frequent or shorter duration applications (see PRECAUTIONS).

Once control is established, maintain the dosing schedule till satisfactory clinical response is attained. This usually takes approximately 8-12 weeks of drug use.

OVERDOSAGE

Excessive topical use may result in exacerbation of skin irritations. The symptoms of over application are erythema, scaling, itching, burning sensation, or swelling of skin. In such cases, discontinue use and apply emollients as necessary.

PRESENTATION

Water based gel: 50g tube

Poison Schedule: Benzoyl peroxide 5% preparations are non-scheduled.

NAME & ADDRESS OF THE SPONSOR

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CLINDATECH TOPICAL SOLUTION

Product Information

i. NAME OF THE DRUG

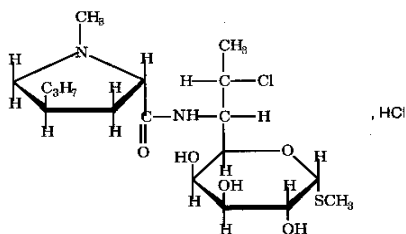
Tradename: ClindaTech Topical Solution
clindamycin (as hydrochloride)

Non-proprietary name: clindamycin hydrochloride

Chemical name: methyl 6-amino-7-chloro-6,7,8-trideoxy-N-[(2S,4R)-1-methyl-4-propylpropyl]-1-thio-L-threo- α -D-galacto-octopyranoside hydrochloride

Molecular formula: $C_{18}H_{33}ClN_2O_5 \cdot HCl$

Molecular Structure:



Molecular Weight: 461.5

1.086g of clindamycin hydrochloride (anhydrous form) is approximately equivalent to 1g of clindamycin.

ii. DESCRIPTION

ClindaTech Topical Solution is a clear hydroalcoholic solution containing clindamycin hydrochloride 1%.

Diocetyl malate, a noncomedogenic humectant, is incorporated to prevent skin dryness.

iii. PHARMACOLOGY

Pharmacological Action

Clindamycin is a lincosamide antibiotic obtained as a semi-synthetic derivative from cultures of *Streptomyces lincolnensis*. It is active *in vitro* and *in vivo* against most aerobic gram-positive cocci and several anaerobic and micro-aerophilic gram-negative and gram-positive organisms including *Propionibacterium acnes*, a resident anaerobe found in acne-susceptible follicles.

Cross-resistance has been demonstrated between clindamycin and lincomycin. Antagonism has been demonstrated between clindamycin and erythromycin.

Clindamycin may be bacteriostatic or bactericidal in action, depending on the concentration of the drug attained at the site of infection and the susceptibility

of the infecting organism. *In vitro* studies showed that the minimum inhibitory concentration of clindamycin against most wild strains of *P. acnes* (46 strains at the concentration of 10^8 /ml) ranged from 0.05 to 0.1 μ g/ml or below. The antibacterial action appears to relate to its ability in inhibiting ribosomal protein synthesis in susceptible organisms by binding to 50S ribosomal subunits.

The precise mechanism by which clindamycin reduces acne lesions has not been fully elucidated. Its therapeutic efficacy appears to act through its ability to decrease acne lesions, suppress or eliminate *P. acnes* in the sebaceous follicles, inhibit lipase activity, and reduce the levels of free fatty acids in skin surface lipids. Applied to the skin, clindamycin markedly reduces the follicular population of *P. acnes* and the concentration of skin surface free fatty acids.

Pharmacokinetics

Pharmacokinetic studies have not been undertaken with ClindaTech Topical Solution. Published results of studies which involved other clindamycin formulations are described below.

In an *in vitro* model using human skin, approximately 10% of the dose was absorbed into the stratum corneum following topical application of a 1% hydroalcoholic solution of radiolabelled clindamycin as the hydrochloride.

Absorption of clindamycin into comedones was assessed in an *in vivo* study in which comedones were removed from acne patients who had applied 1% clindamycin hydrochloride twice daily for 2 weeks or longer. The whole comedonal concentration of clindamycin ranged from 0-5 μ g/mg of comedonal material with a mean concentration of 0.824 μ g/mg. It was stated that these antibiotic concentrations are above the minimum inhibitory concentration of clindamycin for most wild strains of *P. acnes in vitro* at 0.05-0.1 μ g/ml or below.

Systemic absorption of clindamycin was assessed by measurement of serum clindamycin in another open study of 18 acne patients. No clindamycin was detected in serum from any of the subjects obtained one to nine hours after application of a 1% clindamycin hydrochloride solution. The patients had been instructed to apply the solution with their fingertips to the affected areas 2 to 3 times daily. The duration of use ranged from 6-150 days with mean duration at 43.4 days, but the total volume of solution and surface area of application was not stated. The lower limit of quantification was 1 μ g/ml.

iv. INDICATION

ClindaTech Solution is indicated for the topical treatment of acne vulgaris, particularly forms in which comedones, papules and pustules predominate.

v. CONTRAINDICATIONS

ClindaTech is contraindicated in patients with known history of hypersensitivity reactions to preparations containing clindamycin, lincomycin or other ingredients in the formulation.

vi. **PRECAUTIONS**

FOR EXTERNAL USE ONLY

Clindamycin topical solution has an unpleasant taste. Caution should be exercised when applying the solution around the mouth to avoid any possible ingestion.

Avoid any contact with eyes, eyelids, abraded skin, nasal folds, lips or mucous membranes because of the irritating dryness caused by the alcoholic solvent. In the event of any accidental contact, bathe with copious amount of cool water.

Use with caution in the following circumstances

The topical solution contains alcohol and may cause a burning sensation especially in those patients with sensitive skins. Sensitivity reactions including contact dermatitis and rash are rare but may occur in individuals who are hypersensitive to clindamycin, lincomycin or any ingredient of the formulation.

Clindamycin should be prescribed with caution in atopic individuals or patients with impaired hepatic or renal functions. Safety has not been established when applied to areas affected concurrently with other dermatoses or to severely inflamed skin.

The use of clindamycin may cause overgrowth of non-susceptible organisms. Although rare, gram-negative folliculitis has been reported following topical application of clindamycin. If superinfection occurs, discontinue treatment.

Use of topical clindamycin has been associated with the development of strains of *P. acnes* resistant to clindamycin in some patients. If there is evidence of the development of clinical resistance during treatment, consideration should be given to discontinuation of treatment with topical clindamycin (ClindaTech Solution).

Check the following before use

ClindaTech Solution is not indicated in severe and deep nodulo-cystic acne.

The drug should not be used for patients with a history of ulcerative colitis, regional enteritis or antibiotic-associated colitis.

Oral and parenteral clindamycin have been associated with severe diarrhoea and pseudomembranous colitis which may result in patient death. Use of clindamycin hydrochloride topical solution results in absorption of the antibiotic from the skin surface. Diarrhoea, bloody diarrhoea and pseudomembranous colitis have been reported with the use of topical and systemic clindamycin.

It is important to consider the diagnosis of antibiotic associated colitis in patients who develop diarrhoea or colitis associated with antibiotic use. Antibiotic-associated colitis (whether pseudomembranous or not) appear to result from a toxin produced by *Clostridium difficile* in the alimentary tract. The severity of the colitis may range from mild watery diarrhoea to severe, persistent, life-threatening bloody diarrhoea. The diagnosis is usually made by

recognition of the clinical symptoms. The symptoms may occur during therapy or up to several weeks after cessation of therapy. Additional confirmatory signs of antibiotic-associated colitis include pseudomembrane formation seen with colonoscopy, *C. difficile* culture from the stool, or assay of the stool for *C. difficile* toxin.

Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *C. difficile* should be considered. Fluid, electrolytes and protein replacement should be provided when indicated.

Drugs which delay peristalsis, eg. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

Use in pregnancy Category A

Reproductive studies have been performed in rats and mice using oral and parenteral doses up to 300mg/kg/day and have revealed no evidence of harm to the fetus due to clindamycin. There exist, however, no adequate and well- controlled studies to demonstrate safety of use in pregnant women.

Use in lactation

It is not known if clindamycin is excreted in human milk following use of topically administered clindamycin. However, after oral or parenteral administration clindamycin has been detected in human milk. In the absence of any adequate and well controlled studies, topical clindamycin should not be used in lactating women.

Interactions with other drugs

Concurrent use of topical preparations containing alcohol (eg. astringents, after shave lotion, medicated cosmetics) should be avoided because they potentiate the drying action on the skin. The solvent vehicles in some abrasive cleansers, medicated soaps or cosmetics are alcoholic. They may cause a cumulative irritant effect in patients undergoing treatment.

Topical acne preparations containing desquamative or abrasive agents (eg. benzoyl peroxide, salicylic acid, resorcinol or tretinoin) may sensitise the skin to various local reactions. Concurrent use of these agents and topical clindamycin should be treated with caution in combination therapy. Concomitant use of other anti-acne or comedogenic cosmetic products should be avoided.

Both clindamycin and erythromycin appear to compete for the same ribosomal binding site in exerting their antibacterial action. Antagonism between the two anti-infective agents has been demonstrated. Concomitant use of either antibiotic in the topical treatment of acne is not recommended.

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the actions of other neuromuscular blocking agents.

vii. **ADVERSE REACTIONS**

The most frequent adverse effect associated with the use of topical clindamycin solution is dryness of skin. Other local reactions including erythema, peeling, oiliness, contact dermatitis, irritation, itching and burning have been reported. While the exact proportion of patients reporting skin reactions was not available in controlled clinical studies, these effects were generally mild and most skin intolerance did not cause discontinuation of treatment.

Patients very frequently (>10%) experience a sensation of warmth, irritating, dryness and/or burning experience following application of topical clindamycin, especially during the early phase of treatment. Many of these reactions can be attributed to the dehydrating effect of the hydroalcoholic vehicle.

Diarrhoea is commonly reported (>1%, <10%), and infrequently, abdominal pain, bloody diarrhoea (including pseudomembranous colitis) have also been reported following topical use of clindamycin hydrochloride. In one multi-centre, double-blind and placebo-controlled study comparing two formulations of 1% topical clindamycin in acne patients, it was noted that 6 of the 120 patients (~5%) in the clindamycin hydrochloride group, 6 of the 124 patients (~5%) in the clindamycin phosphate group and 2 of the 113 patients (~2%) in the placebo group reported diarrhoea during the 8-week study. The diarrhoea episode in one clindamycin-treated patient was considered by the investigator to be related to treatment. Sigmoidoscopy was performed and there was no evidence of pseudomembranous colitis. The other patients with diarrhoea continued the study and diarrhoea settled. No cause and effect relationship was established.

viii. **DOSAGE AND ADMINISTRATION**

ClindaTech Solution is for external use only and is applied directly on the skin.

Wash the entire face with mild, non-alkaline soap and warm water prior to any application. Using the Dab-O-Matic applicator provided, apply a thin film directly to each acne lesion or to areas having potential of eruption.

ClindaTech Solution is usually applied to affected areas twice daily, once every morning and once at bedtime. The frequency of treatment will depend on the severity of acne condition as well as skin tolerance, but should not be more than twice daily.

Treatment of acne vulgaris needs to be individualised according to the type of lesion predominate and the response of therapy. Application to the entire face of an average adult is equivalent to approximately 2ml of solution or clindamycin 20mg.

Generally, a decrease in the number of inflammatory lesions should be noticed after two or six weeks, but more than eight weeks of therapy may be required before any definite beneficial effects are observed. Therapy is usually continued

until a satisfactory response is obtained. If condition does not seem to improve or worsens, modification of treatment or alternative therapy should be considered.

Drug Incompatibilities

Information on the physical or chemical compatibility of topical clindamycin with other topical preparations is not available. ClindaTech should only be constituted using the base solution provided.

ix. **OVERDOSAGE**

No information is available concerning overdosage of topical clindamycin in humans.

x. **PRESENTATION**

ClindaTech Solution is packaged either in a kit pack for constitution prior to use, or in a ready-to-use pack.

The kit pack consists of a 1g amber glass vial of powder, a 100mL white HDPE bottle of diluent, a Dab-O-Matic applicator and a polypropylene closure.

The ready-to-use pack, in either 30mL, 50mL or 100mL, consists of a white HDPE bottle fitted with a screw-neck top and a Dab-O-Matic applicator and a polypropylene closure.

A package insert is included.

xi. **NAME AND ADDRESS OF THE SPONSOR**

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Australia

The above Product Information was approved by the Australian Therapeutic Goods Administration (TGA) on 7th September 1998, and revised on 19th February 2003.