PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrCABTREO™

Clindamycin Phosphate, Adapalene and Benzoyl Peroxide Gel,
1.2 % w/w, 0.15 % w/w and 3.1 % w/w, Topical

Acne Therapy

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

CABTREO (clindamycin phosphate, adapalene and benzoyl peroxide) is indicated for the topical treatment of acne vulgaris in patients 12 years of age and older.

CABTREO contains an antibacterial ingredient, clindamycin. To reduce the risk of development of drug-resistant bacteria and maintain the effectiveness of clindamycin, CABTREO should only be used for the authorized indication and clinical use.

1.1 Pediatrics

Pediatrics (< 12 years of age): The safety and efficacy of CABTREO in pediatric patients (12 years of age and older) have been established; therefore, Health Canada has authorized an indication for pediatric patients (see 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics (> 65 years of age): A limited number of subjects aged ≥ 65 years have been treated with CABTREO in clinical trials; therefore, the safety and efficacy of CABTREO have not been established in this patient population (see 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

- Patients who are hypersensitive to clindamycin phosphate, to adapalene, to benzoyl peroxide or to any ingredient in the formulation or component of the container. For a complete listing, see the 6 DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.
- CABTREO is contraindicated in patients with a history of regional enteritis (Crohn's disease), ulcerative colitis, or antibiotic-associated colitis.
- CABTREO is contraindicated in pregnant women and women planning a pregnancy (see 7.1.1 Pregnant Women).

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

Apply a thin layer of CABTREO to the affected area once daily.

CABTREO is for topical use only. Not for oral, ophthalmic, or intravaginal use.

Health Canada has not authorized CABTREO for pediatric use under the age of 12 years (see 7.1.3 Pediatrics).

4.4 Administration

Before applying CABTREO, wash the affected area, rinse with warm water, and pat the skin dry. Dispense a pea-sized amount of CABTREO onto one fingertip, dot onto the chin, cheeks, nose, and forehead, then gently rub over the entire face once daily. If a bath or shower is taken prior to application, the skin should be dry before applying the gel.

Wash hands thoroughly after applying CABTREO. If needed, use a moisturizer before or after the use of CABTREO and allow sufficient time for the skin to dry between both applications.

Avoid the eyes, mouth, paranasal creases of the nose, mucous membranes, and areas of broken, eczematous, or sunburned skin. If CABTREO gets in or near eyes, rinse thoroughly with water.

4.5 Missed Dose

Apply the missed dose as soon as you remember. Skip the missed dose if it is almost time for your next dose. Do not use extra medicine to make up the missed dose.

5 OVERDOSAGE

Acute overdosage with the topical use of CABTREO is unlikely. If CABTREO is applied excessively, no more rapid, or better results will be obtained and marked redness, peeling or discomfort may occur. The literature indicates that clindamycin could be absorbed topically (see 7 WARNINGS AND PRECAUTIONS, Gastrointestinal). In the event of accidental ingestion, treatment should be symptomatic.

Inadvertent oral ingestion of adapalene may lead to the same adverse effects as those associated with excessive oral intake of Vitamin A (hypervitaminosis) or other retinoids, including teratogenesis in women of childbearing age. If accidental oral ingestion occurs, the patient should be monitored, and appropriate supportive measures should be administered as necessary, including pregnancy testing in women of childbearing age.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients*
Topical	Gel Clindamycin Phosphate (1.2% w/w), Adapalene (0.15% w/w) and Benzoyl Peroxide (3.1% w/w)	Carbomer Homopolymer Type C (Carbomer 980), Potassium Hydroxide, Propylene Glycol and Purified Water

*Does not include any fragrance, colorant or alcohol

CABTREO is a triple combination of clindamycin phosphate, adapalene and benzoyl peroxide.

CABTREO is a white to off-white, opaque, smooth, water-based polymeric gel supplied in a 50 g pump. Physicians' samples are supplied in 3.5 g laminate tubes.

7 WARNINGS AND PRECAUTIONS

General

CABTREO is for external use only. Not for ophthalmic use.

Avoid contact with the eyes, eyelids, paranasal creases of the nose, lips, mucous membranes, severely inflamed skin. The product should not be applied to cuts, open lesions, abrasions, eczematous or sunburned skin or to other areas where treatment is not intended.

CABTREO should be applied only to the affected areas. Excessive use should be avoided.

Concomitant topical acne therapy is not recommended because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents. Avoid concomitant use of other potentially irritating topical products (medicated or abrasive soaps and cleansers, soaps and cosmetics that have strong skin-drying effect and products with high concentrations of alcohol, astringents, spices, or limes). Use of electrolysis, "waxing" and chemical depilatories for hair removal should be avoided on skin treated with CABTREO.

CABTREO may bleach hair and coloured fabric. Use caution when applying near hairline (see 9.3 Drug- Behavioral Interactions).

Patients should be advised to use non-comedogenic cosmetics (see 9.3 Drug- Behavioral Interactions).

Certain cutaneous signs and symptoms such as erythema, dryness, scaling, burning, or pruritus are associated with the topical application of retinoids and can also be expected with the use of CABTREO. These treatment-related effects generally occur during the first four weeks of therapy, are mostly mild to moderate in intensity, and usually lessen as the skin adjusts with continued use. Depending on the degree of the side effects, patients can be directed to use a moisturizer, use the medication less frequently or temporarily discontinue use until the symptoms subside (see 4.4 Administration).

Carcinogenesis and Mutagenesis

Only animal data are available (see 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity).

Gastrointestinal

Orally and parenterally administered clindamycin have been associated with severe colitis, which may result in patient death. Use of the topical formulation of clindamycin can result in absorption of the antibiotic from the skin surface. Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of oral and

parenteral therapy with clindamycin If significant diarrhea occurs, CABTREO should be discontinued. Antiperistaltic agents such as opiates and diphenoxylate with atropine may prolong and/or worsen severe colitis.

Studies indicate toxin(s) produced by Clostridia is one primary cause of antibiotic-associated colitis. The colitis is usually characterized by severe persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis. Stool cultures for *Clostridium difficile* and stool assay for *C. difficile* toxin may be helpful diagnostically. **When significant diarrhea occurs, the drug should be discontinued. Large bowel endoscopy should be considered to establish a definitive diagnosis in cases of severe diarrhea.**

Reproductive Health: Female and Male Potential

Teratogenic Risk (class effect)

Topical adapalene is contraindicated in pregnant women and women planning a pregnancy because of the possibility of an increased systemic exposure due to various factors (e.g. damaged skin barrier, excessive use) (see 2 CONTRAINDICATIONS).

Sensitivity/Resistance

Development of Drug-Resistant Bacteria

Prescribing CABTREO in the absence of the authorized indications is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

Potential for Microbial Overgrowth

Prolonged use of CABTREO may result in overgrowth of non-susceptible organisms including fungi. If this should occur, therapy with CABTREO should be discontinued and appropriate measures taken.

Cutibacterium acnes (C. acnes; previously called *Propionibacterium acnes)*resistance to clindamycin has been documented. Resistance to clindamycin is often associated with resistance to erythromycin. If this should occur, therapy with CABTREO should be discontinued and alternative therapy should be initiated.

Skin

Photosensitivity

CABTREO may increase sensitivity to ultraviolet light. Avoid or minimize sun exposure (including use of tanning beds, and sun lamps) following CABTREO application. Instruct patients to use sunscreen products (minimum SPF of 15) and wear protective apparel (e.g., hat) when exposure to sun cannot be avoided.

Local Irritation

Erythema, scaling, dryness, and stinging/burning may be experienced with use of CABTREO. These are most likely to occur during the first four weeks of treatment, are mostly mild to moderate in intensity, and usually lessen with continued use of the medication. Irritant and allergic contact dermatitis may occur. Depending upon the severity of these adverse reactions, patients should be instructed to use a moisturizer, reduce the frequency of the application of CABTREO, or discontinue use. The product should not be applied to cuts, abrasions, eczematous, or sunburned skin.

Avoid concomitant use of other potentially irritating topical products (medicated or abrasive soaps and cleansers, soaps and cosmetics that have strong skin-drying effect and products with high concentrations of alcohol, astringents, spices, or limes).

In case of sunburn, allow the skin to heal before using CABTREO. Weather extremes, such as wind or cold, may also be irritating to patients under treatment with adapalene.

7.1 Special Populations

7.1.1 Pregnant Women

CABTREO is contraindicated in women who are or may become pregnant (see 2 CONTRAINDICATIONS). There are no available data on CABTREO use in pregnant women to evaluate a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

There have been rare reports of birth defects among babies born to women exposed to topical retinoids such as adapalene during pregnancy. However, there are no well controlled prospective studies of the use of topical retinoids, including adapalene, in pregnant women. A retrospective study of mothers exposed to topical tretinoin during the first trimester of pregnancy found no increase in the incidence of birth defects. If the patient becomes pregnant while using these drugs, treatment should be discontinued.

In limited published trials in pregnant women administered clindamycin during the first trimester of pregnancy, there was no difference in the rate of major birth defects reported among in utero exposed infants compared to unexposed infants.

In limited published clinical trials with pregnant women, the systemic administration of clindamycin during the second and third trimesters has not been associated with an increased frequency of major birth defects.

The systemic exposure of benzoyl peroxide is unknown. Based on published literature, benzoyl peroxide is rapidly metabolized to benzoic acid (an endogenous substance), which is eliminated in the urine. Hence, maternal use is not expected to result in fetal exposure of the drug.

7.1.2 Breast-feeding

Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

If used during lactation, CABTREO should not be applied to the chest region and, care should be taken to avoid accidental exposure by the infant.

There are no data on the presence of clindamycin phosphate, adapalene and benzoyl peroxide in human milk, the effects on the breastfed infant, or the effects on milk production following topical administration. However, orally, and parenterally administered clindamycin has been reported to appear in breast milk.

7.1.3 Pediatrics

Pediatrics (< 12 years of age)

The safety and effectiveness of CABTREO in pediatric patients below the age of 12 years have not been established (see 1.1 Pediatrics).

7.1.4 Geriatrics

Geriatrics (> 65 years of age)

Clinical trials of CABTREO did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects (see 1.2 Geriatrics).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most frequent adverse reactions that may occur with CABTREO are mild to moderate application site reactions, such as skin irritation characterized by scaling, dryness, erythema, and burning/stinging.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

In 2 multicenter, randomized, double-blind, vehicle-controlled clinical trials, subjects aged 9 years and older applied CABTREO or vehicle once daily for 12 weeks. Adverse reactions reported by >1% of subjects treated with CABTREO and more frequently than subjects treated with vehicle are summarized in Table 2. Most adverse reactions were mild to moderate in severity. Severe adverse reactions represented 0.8% of the subjects treated.

Table 2 : Adverse Reactions Reported by >1% of the CABTREO Group and More Frequently than the Vehicle Group

	CABTREO N = 242 n (%)	Placebo N = 121 n (%)
General disorders and administration site conditions	**48 (19.8)**	**2 (1.7)**
Application site pain1	33 (13.6)	1 (0.8)
Application site dryness	7 (2.9)	0
Application site exfoliation	4 (1.7)	0
Application site irritation	5 (2.1)	0
Xerosis	3 (1.2)	1 (0.8)
Application site dermatitis	3 (1.2)	0
Application site erythema	3 (1.2)	0
Investigations	**6 (2.5)**	**2 (1.7)**
Coronavirus test positive	3 (1.2)	0
Skin and subcutaneous tissue disorders	**7 (2.9)**	**1 (0.8)**
Erythema	3 (1.2)	0

[1]Application site pain defined as application site stinging, burning, or pain.

Local tolerability evaluations were conducted at each study visit in the clinical trials by assessment of erythema, scaling, itching, burning, and stinging. Table 3 presents the signs and symptoms of local facial tolerability at during the 12-week treatment period in subjects treated with CABTREO or vehicle. Both the assessments at week 12 and the maximum assessed incidence throughout the trial are presented.

Table 3 : Cutaneous Tolerability Assessment during 12-week treatment period in Subjects with Acne Vulgaris Treated with CABTREO in Trials 1 and 2

	Maximum During Treatment*			Week 12 (End of Treatment)**		
	Mild (%)	Moderate (%)	Severe (%)	Mild (%)	Moderate (%)	Severe (%)
CABTREO (N=242)						
Erythema	34.2	19.7	2.1	22.4	6.5	0.5
Burning	29.6	10.7	3.0	4.2	1.4	0.9
Scaling	26.7	3.4	0	7.0	0.9	0
Itching	24.3	3.4	0.4	6.0	0.9	0
Stinging	20.5	5.1	2.6	2.3	0.9	0.5

Vehicle (N=121)						
Erythema	22.5	21.7	1.7	25.5	5.5	0
Burning	2.5	0.8	0.8	0.9	0	0
Scaling	12.5	0	0	4.5	0	0
Itching	11.6	0.8	0	1.8	0	0
Stinging	3.3	0.8	0	1.8	0	0

*The denominators for calculating the percentages were the number of subjects with at least one post-baseline cutaneous tolerability assessment.
**The denominators for calculating the percentages were the number of subjects with Week 12 assessment.

Local tolerability scores for erythema, scaling, itching, burning, and stinging generally rose during the first two weeks of treatment and decreased thereafter. These reactions usually occur early in the treatment and tend to gradually lessen over time.

8.3 Less Common Clinical Trial Adverse Reactions (< 1%)

Psychiatric disorders: Depression.

Skin and subcutaneous tissue disorders: Dermatitis contact, dry skin, and swelling face.

8.5 Post-Market Adverse Reactions

There is no post-marketing experience with CABTREO.

The following adverse reactions have been identified during post-approval use of products containing clindamycin phosphate, adapalene and benzoyl peroxide as the active ingredients: anaphylaxis, allergic reactions, sunburn, blister, pruritis, hyperpigmentation, and hypopigmentation.

Because post-marketing adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

CABTREO is a topical product with low systemic availability. As CABTREO has the potential for local irritation, it is possible that concomitant use of abrasive cleansers, strong drying agents, or irritant products may produce additive irritant effects.

Clindamycin has been shown to have neuromuscular blocking properties and potential antagonism with erythromycin and aminoglycosides.

9.3 Drug-Behavioral Interactions

CABTREO should not come into contact with any coloured material including hair and fabrics as this may result in bleaching and discolouration.

As with other retinoids, use of electrolysis, “waxing” and chemical depilatories for hair removal should be avoided on skin treated with CABTREO.

Patients should be advised to use non-comedogenic cosmetics. Colour cosmetics such as blushers and powders are acceptable; however, make-up cosmetics should be water based. Cosmetics must be removed by thorough cleansing before the area is treated.

9.4 Drug-Drug Interactions

No formal drug-drug interaction studies have been conducted with CABTREO.

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction.

Table 4 : Established or Potential Drug-Drug Interactions

Common name	Source of Evidence	Effect	Clinical Comment
Aminoglycosides	T	Clindamycin is reported to antagonize bactericidal activity of aminoglycosides *in vitro. In vivo* antagonism has not been demonstrated.	CABTREO should be used with caution in patients receiving such agents.
Concomitant Topical Medication	T	Concomitant topical medication, medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect and products with high concentrations of alcohol, astringents, spices, or lime should be used with caution as they may produce additive irritant effects.	Particular caution should be exercised in using preparations containing sulphur, resorcinol, or salicylic acid in combination with CABTREO.
Erythromycin	T	Antagonism has been demonstrated between clindamycin and erythromycin *in vitro*. Clindamycin and erythromycin may compete for the same protein binding site in bacteria.	Due to possible clinical significance the two drugs should not be administered concurrently.

Neuromuscular blocking agents	CS	Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents.	CABTREO should be used with caution in patients receiving such agents.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.3 Mechanism of Action

Adapalene, clindamycin phosphate and benzoyl peroxide, have complementary mechanisms of action targeting the pathology of acne vulgaris. The active ingredients have an effect on three pathophysiologic factors known to contribute to acne vulgaris: altered follicular growth and differentiation (comedogenesis), colonization of the pilosebaceous unit with *Cutibacterium acnes (C. acnes*), and inflammation.

CABTREO combines these three active substances, which have complementary mechanisms of action targeting the physiopathology of acne vulgaris. The targets of their action are distinct, with no known pharmacodynamic interactions.

Clindamycin

Clindamycin is a semisynthetic derivative of the parent compound lincomycin that is produced by *Streptomyces lincolnensis* and is predominantly bacteriostatic (see 15 MICROBIOLOGY). Clindamycin binds to the 50S ribosomal subunits of susceptible bacteria and prevents elongation of peptide chains by interfering with peptidyl transfer, thereby suppressing bacterial protein synthesis.

Adapalene

Adapalene is a chemically stable, retinoid-like compound. Biochemical and pharmacological profile studies have demonstrated that adapalene is a potent modulator of cellular differentiation, keratinization, and inflammatory processes, all of which represent important

features in the pathology of acne vulgaris. Mechanistically, adapalene binds to specific retinoic acid nuclear receptors but, unlike tretinoin, does not bind to the cytosolic receptor protein. Although the exact mode of action of adapalene in acne vulgaris is unknown, current evidence suggests that topical adapalene normalizes the differentiation of follicular epithelial cells resulting in decreased microcomedone formation. *In vitro* studies with adapalene have shown inhibition of the AP-1 factors and the inhibition of the expression of toll like receptors 2. This profile suggests that the cell mediated inflammatory component of acne is reduced by adapalene.

Benzoyl Peroxide

Benzoyl peroxide is an oxidizing agent with a broad-spectrum bactericidal activity, in particular against *Cutibacterium acnes (C. acnes)*, which is abnormally present in the acne-affected pilosebaceous unit. Additionally, benzoyl peroxide has demonstrated exfoliative and keratolytic activities.

The use of benzoyl peroxide in combination with a topical antibiotic, clindamycin, has been shown to reduce the potential for emergence of organisms resistant to clindamycin.

10.3 Pharmacokinetics

Systemic exposure following topical application of CABTREO was evaluated in 20 subjects in an open label, randomized, pharmacokinetic study. Subjects aged 12 years and older with moderate to severe acne applied approximately 2.5 grams of CABTREO to the entire face (excluding eyes and lips), neck, upper chest, upper back, and shoulders once daily for 28 days.

Clindamycin Phosphate concentrations were measurable in the majority of samples following single and repeated topical administration of CABTREO (limit of quantification = 0.0500 ng/mL). The mean C_{max} and mean $AUC_{[0-t]}$ values for clindamycin phosphate were 2.52 ng/mL and 28.8 ng•h/mL on Days 28-29, respectively.

Clindamycin (C_{max} and $AUC_{[0-t]}$) accumulated up to approximately 3-fold between Days 1-2 and Days 28-29 following once daily application of CABTREO.

Adapalene concentrations were measurable in the majority of samples following single and repeated topical administration of CABTREO (LOQ = 0.100 ng/mL). The mean C_{max} and mean $AUC_{(0-t)}$ values for adapalene were 0.124 ng/mL and 2.74 ng•h/mL on Days 28-29, respectively.

In subjects ≥ 12 years of age, adapalene ($AUC_{[0-t]}$) accumulated up to approximately 3-fold between Days 1-2 and Days 28-29 for CABTREO.

Benzoyl peroxide has been shown to be absorbed by the skin where it is converted to benzoic acid. The percutaneous penetration of benzoyl peroxide is low; when applied topically, it is rapidly and completely converted into benzoic acid in the skin and eliminated in the urine.

Special Populations and Conditions

Pharmacokinetic studies have not been conducted in subjects with a medical condition which might interfere with the absorption, distribution, metabolism, or excretion of clindamycin phosphate, adapalene and benzoyl peroxide topical gel, in particular, a history of hepatic or renal disease.

11 STORAGE, STABILITY AND DISPOSAL

- Store pump upright.
- Protect from freezing.
- Keep away from heat.
- Keep container tightly closed.
- Keep out of sight and reach of children.

Healthcare Professional:

- Prior to Dispensing: Store in a refrigerator (2° to 8°C).

Patient:

- Store at room temperature (15° to 25°C).
- Use within 10 weeks after first opening.
- Do not freeze.

12 SPECIAL HANDLING INSTRUCTIONS

- Dispense CABTREO with a 10-week expiration date.
- Specify “Store at room temperature (15° to 25°C). Do not freeze.

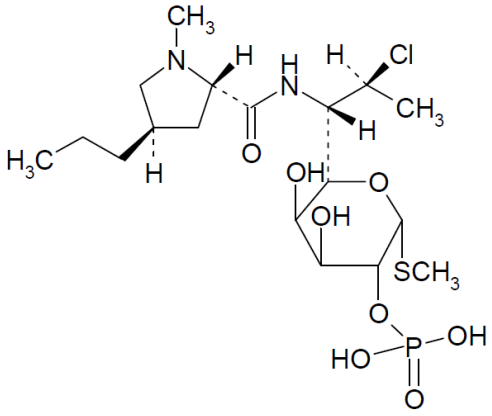
PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Clindamycin Phosphate	
Chemical name:	Methyl-7-chloro-6, 7, 8-trideoxy-6-(1-methyl-trans-4-propyl-L-2- pyrrolidinecarboxamido)-1-thio-L-threo-alpha-D-galacto- octopyranoside-2-(dihydrogen phosphate)	
Molecular formula and molecular mass:	$C_{18}H_{34}ClN_2O_8PS$	504.97 g/mol

Structural formula:

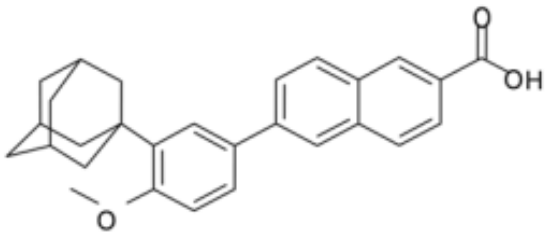


Physicochemical properties:

Description:	Clindamycin is a white to off-white, hygroscopic, crystalline powder.

Proper name:	Adapalene
Chemical name:	6-(3-[1-adamantyl]-4-methoxyphenyl)-2-naphthoic acid
Molecular formula and molecular mass:	$C_{28}H_{28}O_3$ 412.5 g/mol

Structural formula:

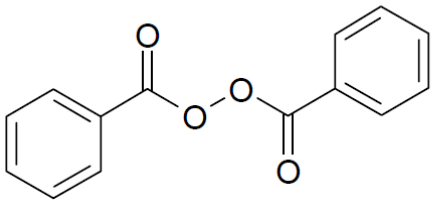


Physicochemical properties:

Description:	Adapalene is a white to off-white powder.
Solubility:	Sparingly soluble in tetrahydrofuran, practically insoluble in ethanol and in water.

Proper name:	Benzoyl Peroxide	
Chemical name:	Peroxide, dibenzoyl	
Molecular formula and molecular mass:	$C_{14}H_{10}O_4$	242.23g/mol

Structural formula:



Physicochemical properties:

Description:	Benzoyl peroxide is a white, granular powder
Solubility:	Soluble in acetone and methylene chloride, slightly soluble in alcohol and insoluble in water.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Treatment of Acne Vulgaris in Patients 9 Years of Age and Older

The safety and efficacy of once daily use of CABTREO for the treatment of facial acne vulgaris were assessed in two multicenter, randomized, double-blind clinical trials in subjects 9 years and older with facial acne vulgaris. Patient demographics that participated in the trials (N = 363) consisted of 73.6% white, 14.9% Black/African American and 7.2 % Asian. As assessed by the Evaluator's Global Severity Score (EGSS), 91.2% and 8.8% of participants had moderate or severe facial acne, respectively, at baseline.

While subjects aged 9 to less than 12 years were included in these trials, CABTREO is approved for use in patients of 12 years of age and above.

Table 5: Summary of Patient Demographics for Clinical Trials in The Treatment of Acne Vulgaris

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
301	Multicenter, double blind, randomized, parallel group study designed to assess the safety, tolerability, and efficacy of CABTREO in subjects with a clinical diagnosis of moderate to severe facial acne	Applied topically, once daily for 12 weeks	183 patients CABTREO (122 patients) Vehicle Gel (61 patients)	20.0 years old (10 to 44 years old)	77 Male (42.1 %) 106 Female (57.9 %)
302	Multicenter, double blind, randomized, parallel group study designed to assess the safety, tolerability, and efficacy of CABTREO Gel in subjects with a clinical diagnosis of moderate to severe facial acne	Applied topically, once daily for 12 weeks	180 patients CABTREO (120 patients) Vehicle Gel (60 patients)	20.6 years old (10 to 48 years old)	74 Male (41.1 %) 106 Female (58.9 %)

14.2 Study Results

Table 6: Results of Studies 301 and 302 in The Treatment of Acne Vulgaris

Primary Endpoints	Associated value and statistical significance for Placebo or active control
Absolute change in the facial inflammatory lesion count from baseline to Week 12	Both studies (301 and 302) met their coprimary efficacy endpoints and thereby demonstrated that CABTREO is superior to Vehicle Gel in the treatment of acne (Table 7). The percentages of subjects with treatment success were also markedly similar when compared by study drug group between studies.
Absolute change in the facial non-inflammatory lesion count from baseline to Week 12	
Percentage of subjects who achieved at least a 2-grade reduction at Week 12 from baseline in the EGSS and had an EGSS at Week 12 that equated to clear or almost clear (defined as treatment success)	

Table 7: Studies 301 and 302: Co-Primary Efficacy Results (ITT Population)

	301				302			
	CABTREO (N = 122)	**Vehicle Gel (N = 61)**	**Treatment Difference (95% CI)**	**P-value**	**CABTREO (N = 120)**	**Vehicle Gel (N = 60)**	**Treatment Difference (95% CI)**	**P-value**
Inflammatory Lesion Count Absolute change from baseline at Week 12								
LSM (LS SD)[a]	-27.7 (9.55)	-21.7 (8.79)	-5.94 (-8.73, -3.14)	< 0.001[b]	-30.1 (9.64)	-20.8 (9.90)	-9.30 (-12.38, -6.23)	< 0.001[b]
Percent change from baseline at Week 12								
LSM (LS SD)[a]	-75.70 (26.663)	-59.62 (24.348)	-16.08 (-23.72, -8.44)	< 0.001[b]	-80.13 (25.274)	-56.18 (25.149)	-23.95 (-31.73, -16.16)	< 0.001[b]
Non-inflammatory Lesion Count Absolute change from baseline at Week 12								
LSM (LS SD)[a]	-35.4 (15.52)	-23.5 (14.93)	-11.85 (-16.56, -7.14)	< 0.001[b]	-35.2 (14.48)	-22.0 (14.27)	-13.27 (-17.74, -8.80)	< 0.001[b]
Percent change from baseline at Week 12								
LSM (LS SD)[a]	-72.70 (32.364)	-47.61 (31.069)	-25.09 (-34.96, -15.22)	< 0.001[b]	-73.26 (27.640)	-48.99 (27.345)	-24.27 (-32.86, -15.68)	< 0.001[b]

EGSS reduction ≥ 2 grades from baseline and achieving clear or almost clear at Week 12								
Treatment Success, %	49.6	24.9	24.7 (10.7, 38.7)[c]	0.003[d]	50.5	20.5	30.0 (16.4, 43.6)[c]	0.001[d]

CI = confidence interval; EGSS = Evaluator's Global Severity Score; ITT = intent-to-treat; LS = least squares; LSM = least squares means; max = maximum; min = minimum; SD = standard deviation;

Multiple imputation (Markov Chain Monte Carlo) was used to impute missing data.

a Least squares means, SDs, differences in LSM, and associated 95% CIs were from an analysis of covariance with factors of treatment group and analysis center, and the respective baseline lesion count as a covariate. In the analysis of covariance for the inflammatory lesion count, an interaction of treatment by analysis center was significant and included in the model. Values have been adjusted for multiple imputation. Negative LSM values represent decreases from baseline.

b P-values were obtained from a ranked analysis of covariance with factors of treatment group and analysis center, and the respective baseline lesion count as a covariate. In the ranked analysis of covariance for the inflammatory lesion count, an interaction of treatment by analysis center was significant and included in the model. Values have been adjusted for multiple imputation.

c Treatment difference and corresponding 95% CI based on the reported percentages of success.

d P-value was obtained from a logistic regression (using Firth's penalized likelihood) with factors of treatment group and analysis center. Values have been adjusted for multiple imputation.

Percent changes from baseline in inflammatory and non-inflammatory lesion counts at weeks 4, 8, and 12 in addition to the percentage of participants achieving 2-grade reduction from baseline in EGSS at week 12 were also assessed in studies 301 and 302. All secondary endpoints from both studies were pre-planned, multiplicity-controlled and achieved statistical significance vs vehicle.

15 MICROBIOLOGY

No microbiology studies were conducted with CABTREO.

Clindamycin binds to the 50S ribosomal subunits of susceptible bacteria and prevents elongation of peptide chains by interfering with peptidyl transfer, thereby suppressing bacterial protein synthesis.

Clindamycin and benzoyl peroxide individually have been shown to have *in vitro* activity against *Cutibacterium acnes (C. acnes)*, an organism which has been associated with acne vulgaris. In an *in vitro* study, the minimum inhibitory concentration (MIC) for benzoyl peroxide against *C. acnes* is 128 mg/L. The clinical significance of this activity against *C. acnes* is not known.

Development of Resistance

Cutibacterium acnes (C. acnes) resistance to clindamycin has been documented. Resistance

to clindamycin is often associated with resistance to erythromycin.

16 NON-CLINICAL TOXICOLOGY

No carcinogenicity, genotoxicity, or reproductive and developmental toxicology studies were conducted with CABTREO. Data are available for individual components or a combination of two components (see Carcinogenicity, Genotoxicity, Reproductive and Developmental Toxicology and Special Toxicology).

General Toxicology

The dermal and systemic toxicity of CABTREO was investigated in a subchronic toxicity study in Göttingen minipigs following once daily dermal applications to 10% of total body surface area for 3 consecutive months. CABTREO was well tolerated and did not adversely affect any measured parameters. The no-observed-adverse-effect-level (NOAEL) was the high dose which used an enhanced formulation with 2.4% clindamycin phosphate, 6.2% benzoyl peroxide, and 0.3% adapalene (26 times the maximum recommended human dose, MRHD, of 2.5 grams of CABTREO, based on a mg/m^2 comparison).

Carcinogenicity

Carcinogenicity studies have been conducted with a gel formulation containing 1% clindamycin phosphate and 5% benzoyl peroxide. In a 2-year dermal carcinogenicity study in mice, treatment with the gel formulation at doses of 900, 2700, and 15000 mg/kg/day (1.2, 3.6 and 20 times the MRHD for clindamycin phosphate and 2.3, 7, and 39 times the MRHD for benzoyl peroxide, respectively, based on a mg/m^2 comparison) did not cause any increase in tumors.

Topical treatment with a different gel formulation containing 1% clindamycin phosphate and 5% benzoyl peroxide at doses of 100, 500, and 2000 mg/kg/day in a 2-year dermal carcinogenicity study in rats caused a dose-dependent increase in the incidence of keratoacanthoma at the treated skin site of male rats. In an oral (gavage) carcinogenicity study in rats, treatment with the gel formulation at doses of 300, 900, and 3000 mg/kg/day (0.8, 2.4 and 8 times the MRHD for clindamycin phosphate and 1.5, 4.6, and 16 times the MRHD for benzoyl peroxide, respectively, based on a mg/m^2 comparison) for up to 97 weeks did not cause any increase in tumors.

Carcinogenicity studies with adapalene were conducted in mice at topical doses of 0.4, 1.3, and 4.0 mg/kg/day, and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day. The highest dose levels are 4.3 (mice) and 3.2 (rats) times the MRHD based on a mg/m^2 comparison. In the rat study, an increased incidence of benign and malignant pheochromocytomas reported in the adrenal medulla of male rats was observed.

Benzoyl peroxide is a tumor promoter in several animal species. The significance of this finding in humans is unknown.

Genotoxicity

Clindamycin phosphate was not genotoxic in the human lymphocyte chromosome aberration assay.

Bacterial mutagenicity assays (Ames test) with benzoyl peroxide reported mutagenic potential in a few but not in the majority of investigations. Benzoyl peroxide has been shown to produce single-strand DNA breaks in human bronchial epithelial and mouse epidermal cells, DNA-protein cross-links in the human cells, and a dose-dependent increase in sister chromatid exchanges in Chinese hamster ovary cells.

Adapalene did not exhibit mutagenic or genotoxic effects *in vitro* (Ames test, Chinese hamster ovary cell assay, or mouse lymphoma TK assay) or *in vivo* (mouse micronucleus test).

Reproductive and Developmental Toxicology

Animal reproductive/developmental toxicity studies have not been conducted with CABTREO.

Fertility studies in rats treated orally with up to 300 mg/kg/day of clindamycin phosphate (approximately 80 times the MRHD based on a mg/m^2 comparison) revealed no effects on fertility or mating ability.

Developmental toxicity studies of clindamycin performed in pregnant rats and mice administered during the period of organogenesis at oral doses of up to 600 mg/kg/day clindamycin phosphate (160 and 80 times the MRHD, respectively, based on a mg/m^2 comparison) or subcutaneous doses of up to 200 mg/kg/day clindamycin phosphate (53 and 27 times the MRHD, respectively, based on a mg/m^2 comparison) revealed no malformations or embryo-fetal development toxicity.

In a combined repeated dose and reproduction/developmental toxicity study, benzoyl peroxide was administered to rats by oral gavage at 0, 250, 500, and 1000 mg/kg/day. Males were dosed for 29 days, and females were dosed for 41 to 51 days (from 14 days before mating to day 3 of lactation). No benzoyl peroxide -related changes in pre-coital time and rate of copulation, fertility, and gestation were noted. The NOAEL for reproductive toxicity was 500 mg/kg/day in males based on reproductive organ weight reduction and slight testes degeneration at 1000 mg/kg/day (52 and 103 times the MRHD, respectively, based on a mg/m^2 comparison). In females, slight uterine epithelial vacuolation and hyperplasia was observed at the high dose but considered not treatment related. The NOAEL for developmental toxicity was 500 mg/kg/day based on a high birthrate of runts and decreased pup body weight gain at 1000 mg/kg/day (52 and 103 times the MRHD, respectively, based on a mg/m^2 comparison).

In a rat oral reproduction study, 20 mg/kg/day adapalene (43 times the MRHD based on a mg/m^2 comparison) did not affect the reproductive performance and fertility of F0 males and females, or the growth, development, and reproductive function of F1 offspring.

No teratogenic effects were observed in rats treated with oral doses of 0.15 to 5.0 mg/kg/day adapalene (up to 11 times the MRHD based on a mg/m^2 comparison). However, teratogenic effects were observed in rats and rabbits at ≥ 25 mg/kg/day adapalene (53 and 107 times the MRHD, respectively, based on a mg/m^2 comparison). Findings included cleft palate, microphthalmia, encephalocele, and skeletal abnormalities in rats and umbilical hernia, exophthalmos, and kidney and skeletal abnormalities in rabbits.

Dermal teratology studies conducted in rats and rabbits at doses of 0.6-6.0 mg/kg/day adapalene (up to 13 and 26 times the MRHD, respectively, based on a mg/m^2 comparison) exhibited no fetotoxicity and only minimal increases in supernumerary ribs in both species and delayed ossification in rabbits.

Special Toxicology

The phototoxic potential of CABTREO was evaluated in the EpiDerm in vitro skin model and predicted to be not phototoxic. CABTREO was predicted to be minimally irritating/non-irritating to the eye in the EpiOcular in vitro model.

The combination of clindamycin and benzoyl peroxide (1% clindamycin and 5% benzoyl peroxide) was a mild primary ocular irritant in rabbit, not a primary rabbit skin irritant, and not a dermal sensitizer in the Buehler guinea pig test. There was no evidence of UVA-mediated dermal irritation in rabbits treated topically.

Skin sensitization tests with benzoyl peroxide have consistently shown positive results in non-clinical studies, which included the mouse local lymph node assay, the guinea pig Buehler and human patch tests. However, in a clinical repeated insult patch test (RIPT) to assess dermal sensitization, CABTREO had low sensitization potential.

PATIENT MEDICATION INFORMATION
READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrCABTREO™
Clindamycin Phosphate, Adapalene and Benzoyl Peroxide Gel

Read this carefully before you start receiving **CABTREO** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **CABTREO**.

What is CABTREO used for?

- CABTREO is used to treat acne (acne vulgaris) with comedones (clogged hair follicles - blackheads, whiteheads) and inflammatory papules and pustules (e.g., pimples) in patients 12 years of age and older.
- CABTREO contains an antibacterial ingredient called clindamycin, and it should be used exactly as directed by your healthcare professional. Misuse or overuse of CABTREO could lead to the growth of bacteria that will not be killed by clindamycin. This means that CABTREO or other medicines that contain clindamycin may not work for you in the future. Do not share your medicine.

How does CABTREO work?

CABTREO works in multiple ways. The 3 medicinal ingredients work together to unplug your blocked oil glands and to prevent these plugs from forming in the first place. They also help kill the bacteria present in acne and help reduce inflammation.

What are the ingredients in CABTREO?

Medicinal ingredients: Clindamycin Phosphate, Adapalene and Benzoyl Peroxide

Non-medicinal ingredients: Carbomer Homopolymer Type C (Carbomer 980), Potassium Hydroxide, Propylene Glycol and Purified Water.

CABTREO comes in the following dosage forms:

- Gel; 3.5 g tubes (sample) and 50 g pumps

Do not use CABTREO if:

- You are allergic to clindamycin phosphate, adapalene, benzoyl peroxide or any of the other ingredients in CABTREO.
- You have a history of regional enteritis (Crohn’s disease), ulcerative colitis, or antibiotic-associated colitis.
- You are pregnant or plan to become pregnant.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you receive CABTREO. Talk about any health conditions or problems you may have, including if you:

- have Crohn's disease, ulcerative colitis.
- have developed colitis with past antibiotic use.
- plan to have surgery. CABTREO may affect how certain medicines work that may be given during surgery.
- are breastfeeding or plan to breastfeed. It is not known if CABTREO passes into your breast milk. Talk to your healthcare professional about the best way to feed your baby during treatment with CABTREO.
- use during breastfeeding, do not apply CABTREO to the chest region. Make sure to avoid accidental contact to your baby.
- have other skin problems, including cuts, abrasions, sunburn, or eczema.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with CABTREO:

- Topical or oral erythromycin-containing products
- Neuromuscular blocking agents
- Aminoglycoside antibiotics
- Other acne products that have a drying effect on the skin (e.g. products containing sulphur, resorcinol, or salicylic acid)

How to take CABTREO:

- Use CABTREO exactly as your healthcare provider tells you to use it.
- CABTREO is for use on the skin only.
- Do not use more CABTREO than you need to cover the treatment area. Using too much CABTREO or using it more than 1 time a day may increase your chance of skin irritation.
- Avoid sunlight, including sunlamps during treatment with CABTREO. CABTREO can make you more sensitive to the sun, and the light from sunlamps and tanning beds. You could get severe sunburn. Use sunscreen (minimum SPF of 15) and wear a wide-brimmed hat and clothes that cover your skin if you have to be in sunlight.
- If you get sunburnt, let your skin heal before using CABTREO.
- Cold weather and wind may irritate skin treated with CABTREO.
- Avoid applying CABTREO to cuts, abrasions, skin with eczema, and sunburned skin.
- Avoid skin products that may dry or irritate your skin such as medicated or harsh soaps, astringents, cosmetics that make your skin dry, and products containing high levels of alcohol, spices, or limes.
- Avoid the use of "waxing" as a hair removal method on skin treated with CABTREO.
- Avoid getting CABTREO in your hair or on colored fabric. CABTREO may bleach hair or colored fabric.
- Do not use other topical acne preparations or other topical products, including cosmetics, on the affected area unless directed to do so by your healthcare

professional. Many cosmetic products may also contain other peeling agents, which may interfere with the medication or make possible side effects worse.
- You may use a moisturizer after applying CABTREO as needed. Make sure to allow skin to dry after you apply CABTREO.

Usual dose
- Apply a thin layer of CABTREO to your face one (1) time each day.
- Before you apply CABTREO, wash your face gently, rinse with warm water, and pat your skin dry.

Step 1:
Wash your face gently, rinse with warm water and pat it dry with a clean towel.

Step 2:

To apply CABTREO, use the pump to dispense one pea-sized amount only of CABTREO onto your fingertip (see Figure 1).

One pea-sized amount of CABTREO should be enough to cover your entire face.

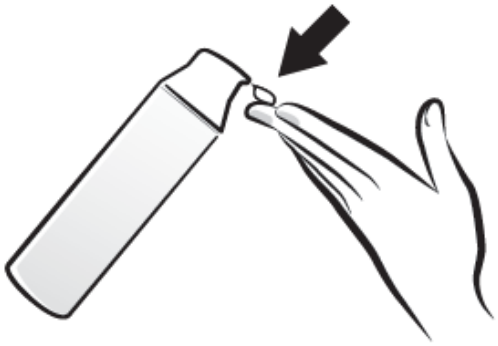


Figure 1

Step 3:
Dot CABTREO onto the five (5) areas of your face (chin, left cheek, right cheek, nose, and forehead).

Step 4:
Spread the gel over your face and gently rub it in. It is important to spread the gel over your entire face. If your healthcare professional tells you to put CABTREO on other areas of your skin with acne, be sure to ask how much you should use.

Step 5:
Wash your hands with soap and water after applying CABTREO.

Overdose:

If you apply too much CABTREO, you will not get faster or better results. This may cause redness, peeling or discomfort. Taking CABTREO by mouth by accident may cause the same side effects as that of taking too much Vitamin A by mouth. If you accidentally take CABTREO by mouth, talk to your healthcare professional.

If you think you, or a person you are caring for, have been given too much CABTREO, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to apply CABTREO on your skin at the usual time, apply it when you remember, unless it is almost time for your next application, in which case wait and apply at the next application time. The dose should not be doubled to make up for a missed dose.

What are possible side effects from using CABTREO?

These are not all the possible side effects you may have when taking CABTREO. If you experience any side effects not listed here, tell your healthcare professional.

- burning or stinging sensation
- dryness
- itching
- peeling of skin
- rash
- redness
- scaling
- swelling
- sunburn
- blisters
- dark or light skin patches (hyperpigmentation or hypopigmentation)

Do not be discouraged if CABTREO causes side effects when you first start to use it. This happens when your skin is adjusting to CABTREO action of unplugging clogged pores. If these problems continue to happen or if they are getting worse, talk to your healthcare professional. Your healthcare professional may recommend the use of a moisturizer, a change in your dose, or a change to how often you use CABTREO.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Skin Irritation: redness, scaling, dryness, stinging, burning, itching, and swelling		√	
UNKNOWN			
Allergic reactions (anaphylaxis): hives, rash, or severe itching, swelling of your face, eyes, lips, tongue, or throat, trouble breathing or throat tightness, feeling faint, dizzy, or lightheaded			√
Clostridium difficile colitis (bowel inflammation): severe or persistent diarrhea, abdominal pain, nausea, and vomiting.			√

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store CABTREO at room temperature (15 to 25°C).
- Do not freeze.
- CABTREO should be used within 10 weeks after first opening. Any unused CABTREO should be thrown away 10 weeks after first opening.
- Keep CABTREO out of light and away from heat.
- Keep the container tightly closed.
- Keep out of reach and sight of children.
- Store pump upright.

If you want more information about CABTREO:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.bauschhealth.ca), or by calling 1-800-361-4261.

This leaflet was prepared by Bausch Health, Canada Inc.

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