PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] Taro-Clindamycin / Benzoyl Peroxide Gel

clindamycin and benzoyl peroxide gel, 1%/5%, w/w

(clindamycin as clindamycin phosphate)

Topical Acne Therapy

Professed Standard

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Topical	Gel Clindamycin 1% and benzoyl peroxide 5%, w/w (clindamycin as clindamycin phosphate)	*methylparaben*. *For a complete listing, see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Taro-Clindamycin / Benzoyl Peroxide Gel (clindamycin and benzoyl peroxide gel, 1% / 5%, w/w) is indicated in the topical treatment of moderate acne vulgaris characterized by the presence of comedones, papules and pustules.

Taro-Clindamycin / Benzoyl Peroxide Gel is not indicated for the treatment of cystic acne.

Taro-Clindamycin / Benzoyl Peroxide Gel contains an antibacterial ingredient, clindamycin. To reduce the development of drug-resistant bacteria and maintain the effectiveness of clindamycin, Taro-Clindamycin / Benzoyl Peroxide Gel should only be used for the authorized indication and clinical use.

Pediatrics (< 12 years of age): Safety and efficacy of Taro-Clindamycin / Benzoyl Peroxide Gel have not been established in patients under the age of 12 years.

CONTRAINDICATIONS

Taro-Clindamycin / Benzoyl Peroxide Gel (clindamycin and benzoyl peroxide gel, 1%/5%, w/w) is contraindicated in:

- Patients who have a history of hypersensitivity to either of the active ingredients (clindamycin or benzoyl peroxide), or the excipients. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

- Patients who have a history of hypersensitivity to medicines containing lincomycin.

- Patients with, or with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis (including pseudomembranous colitis).

WARNINGS AND PRECAUTIONS

General

For external (dermatological) use only. Not for oral, ophthalmic or intravaginal use.

Drug interactions: Concomitant topical acne treatments are not recommended because a possible cumulative irritancy effect may occur, which sometimes may be severe, especially with peeling, desquamating, or abrasive agents. If severe irritation develops, discontinue use and institute appropriate therapy.

Use of clindamycin phosphate or benzoyl peroxide with other drugs may lead to drug-drug interactions (see DRUG INTERACTIONS, Drug-Drug Interactions).

Benzoyl peroxide: Avoid contact with hair, fabrics, carpeting or other materials, as Taro-Clindamycin / Benzoyl Peroxide Gel may cause bleaching. 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 minimized. 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 Taro-Clindamycin / Benzoyl Peroxide Gel (clindamycin and benzoyl peroxide gel, 1%/5%, w/w).

Clindamycin phosphate: Gram-negative folliculitis has been reported in association with the long term use of clindamycin. Should gram-negative folliculitis occur, discontinue use of Taro-Clindamycin / Benzoyl Peroxide Gel, and institute appropriate therapy.

Gastrointestinal

***Clostridium difficile*-Associated Disease:** Systemic absorption of clindamycin has been demonstrated following topical use of clindamycin and benzoyl peroxide gel, 1%/5%, w/w. *Clostridium difficile*-associated disease (CDAD) has been reported with the use of topical, oral and parenteral administration of clindamycin, including with the use of clindamycin and benzoyl peroxide gel, 1%/5%, w/w (see ADVERSE REACTIONS). CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic mega

colon, or perforation of the colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur 2 months after the administration of antibacterial agents (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *Clostridium difficile*. *Clostridium difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *Clostridium difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridium difficile*. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases.

Ophthalmologic/Mucosal/Skin

Benzoyl peroxide: Avoid contact with the mouth, eyes, lips, other mucous membranes or areas of irritated or broken skin. In the event of accidental contact with sensitive surfaces (eyes, abraded skin, mucous membranes), rinse with copious amounts of cool tap water.
In addition, care should be taken when applying Taro-Clindamycin / Benzoyl Peroxide Gel to the neck and other sensitive areas.

During the first weeks of treatment, patients may experience peeling and reddening. In these patients, these symptoms will normally subside if treatment is temporarily interrupted and restarted after symptoms have subsided. Depending upon the severity of these side effects, patients can use a moisturizer, temporarily reduce the frequency of application of Taro-Clindamycin / Benzoyl Peroxide Gel 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.

If severe local irritation (e.g. severe erythema, severe dryness and itching, severe stinging/burning) develops, discontinue use of Taro-Clindamycin / Benzoyl Peroxide Gel, and institute appropriate therapy.

Patients should be advised that excessive application of Taro-Clindamycin / Benzoyl Peroxide Gel will not improve efficacy, but may increase the risk of skin irritation.

Susceptibility/Resistance

Development of Drug Resistant Bacteria

Prescribing Taro-Clindamycin / Benzoyl Peroxide Gel in the absence of the authorized indication is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

Cross-resistance and resistance

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

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 ACTION AND CLINICAL PHARMACOLOGY, Mechanism of Action and MICROBIOLOGY).

Special Populations

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

Pregnant Women: There are no well-controlled studies in pregnant women treated with topical clindamycin and benzoyl peroxide gel, 1%/5%, w/w. There are limited data on the use of topical clindamycin or benzoyl peroxide in pregnant women. Taro-Clindamycin / Benzoyl Peroxide Gel should not be administered to a pregnant woman unless the expected benefits to the mother outweigh the potential risks to the fetus.

Nursing Women: Topical clindamycin and benzoyl peroxide gel, 1%/5%, w/w has not been studied during breast-feeding. It is not known whether benzoyl peroxide or clindamycin are excreted in human milk following the topical use of clindamycin and benzoyl peroxide gel, 1%/5%, w/w. Orally and parenterally administered clindamycin have been reported to appear in breast milk. Taro-Clindamycin / Benzoyl Peroxide Gel should not be used during lactation unless the expected benefits to the mother outweigh the potential risks to the infant. If used during lactation, Taro-Clindamycin / Benzoyl Peroxide Gel should not be applied to the chest so as to avoid accidental ingestion by the infant.

Pediatrics (<12 years of age): Safety and efficacy of clindamycin and benzoyl peroxide gel, 1%/5%, w/w in patients under the age of 12 have not been established.

Geriatrics (>65 years of age): Safety and efficacy of clindamycin and benzoyl peroxide gel, 1%/5%, w/w in patients over the age of 65 have not been established.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

1% clindamycin / 3% benzoyl peroxide Gel: The number of subjects who experienced treatment-related adverse events was low and was similar in each treatment group . No individual treatment-related adverse event was reported by more than 2 subjects (≤ 1%) within any of the treatment groups. The most frequently- reported treatment-related adverse events were mild or moderate application site dermatitis and photosensitivity, with each occurring in 2 subjects (0.6%) in the 1% clindamycin / 3% benzoyl peroxide Gel group. One subject (0.3%) discontinued clindamycin / 3% benzoyl peroxide Gel due to application site dermatitis.

Clindamycin and benzoyl peroxide gel, 1%/5%, w/w: Nine of the 113 adverse events were related to clindamycin and benzoyl peroxide gel, 1%/5%, w/w. These adverse reactions were 1 case of mild application site paraesthesia, 1 case of acne worsening and 7 cases of mild to moderate pruritus and erythema, as well as dryness at the application site that lasted 3 to 48 days. There were no discontinuations due to adverse drug reactions with clindamycin and benzoyl peroxide gel, 1%/5%, w/w.

Clinical Trial Adverse Drug Reactions

Because 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 drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

1% clindamycin / 3% benzoyl peroxide Gel: In a controlled study where a total of 327 subjects (eligible subjects were between 12 and 45 years of age with mild-to-moderate acne vulgaris) applied 1% clindamycin / 3% benzoyl peroxide Gel once daily for 12 weeks, subjects were assessed for local cutaneous signs and symptoms of erythema, dryness, peeling, itching, and burning/stinging. The percentage of subjects that had symptoms present before treatment and present at week 12 are shown in Table 1 and Table 2.

Table 1 Percentage of Subjects Treated with 1% clindamycin / 3% benzoyl peroxide Gel with Symptoms of Local Skin Reactions – Burning/Stinging and Itching (N=327)

	Before Treatment (Baseline)			End of Treatment (Week 12)		
	Slight	Moderate	Strong	Slight	Moderate	Strong
Burning/ Stinging	15%	4%	0%	8%	2%	<1%
Itching	28%	6%	1%	17%	2%	0%

Table 2 Percentage of Subjects Treated with 1% clindamycin / 3% benzoyl peroxide Gel with Symptoms of Local Skin Reactions - Dryness, Erythema, and Peeling (N=327)

	Before Treatment (Baseline)				End of Treatment (Week 12)			
	Slight	Mild	Moderate	Severe	Slight	Mild	Moderate	Severe
Dryness	15%	2%	1%	0%	9%	1%	1%	0%
Erythema	19%	11%	5%	0%	19%	4%	2%	0%
Peeling	10%	2%	0%	0%	4%	<1%	0%	0%

Table 3 shows the most frequent adverse drug reactions determined by the investigator to be possibly, probably, or definitely treatment-related and reported in ≥1% subjects in the 1% clindamycin / 3% benzoyl peroxide Gel or comparator groups. No other adverse drug reactions (<1%) were reported for 1% clindamycin / 3% benzoyl peroxide Gel.

Table 3 Most Frequent Adverse Drug Reactions Reported in ≥1% of Subjects in the 1% clindamycin / 3% benzoyl peroxide Gel or Comparator Groups

System Organ Class (Preferred Term)	1% clindamycin / 3% benzoyl peroxide Gel (N=327)	Clindamycin 1% Gel (N=328)	Benzoyl Peroxide 3% Gel (N=328)	Vehicle Gel (N=332)
General Disorders and Administration Site Conditions, n (%)				
Application site dermatitis	2 (1)	0	0	0
Application site irritation	0	0	2 (1)	0
Application site photosensitivity	2 (1)	1 (<1)	1 (<1)	2 (1)

Clindamycin and benzoyl peroxide gel, 1%/5%, w/w: In controlled clinical trials where a total of 172 subjects received clindamycin and benzoyl peroxide gel, 1%/5%, w/w, the reported adverse events considered to have a relationship to clindamycin and benzoyl peroxide gel, 1%/5%, w/w were comprised mainly of reactions at the site of application such as peeling (16.3%), erythema (7.6%), dryness (7%), burning (2.3%) and pruritus (1.7%). Mild paraesthesia and worsening of acne were noted in one subject each.

Post-Market Adverse Drug Reactions

Because these 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.

Gastrointestinal disorders: Diarrhea, abdominal pain, bloody diarrhea, colitis (including pseudomembranous colitis). (See WARNINGS AND PRECAUTIONS, *Clostridium difficile*-Associated Disease)

General disorders and administration site conditions: Application site reactions including discolouration.

Immune system disorders: Anaphylaxis, as well as allergic reactions leading to hospitalization, application site hypersensitivity such as urticaria, application site swelling and swelling of the face and tongue including angioedema.

DRUG INTERACTIONS

Drug-Drug Interactions

Table 4 Established or Potential Drug-Drug Interactions

Drug	Ref	Effect	Clinical comment
Neuromuscular blocking agents	CT	Clindamycin has been shown to have neuromuscular blocking properties that may enhance action of other neuromuscular blocking agents.	Use with caution.
Erythromycin	*In vitro*	Clindamycin and erythromycin have been shown to be antagonists.	Should not be used concomitantly.
Tretinoin, isotretinoin tazarotene	*In vitro*	Concomitant application of clindamycin and benzoyl peroxide gel, 1%/5%, w/w with tretinoin, isotretinoin and tazarotene should be avoided since benzoyl peroxide may reduce their efficacy and may 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).
Concomitant topical acne medication (to treat both inflammatory and non-inflammatory lesions)	CT	Possible cumulative irritancy may occur, which sometimes may be severe, especially with the use of peeling, desquamating or abrasive agents.	If severe irritation or dermatitis develops, discontinue use and institute appropriate therapy.
Topical sulphonamides	CT	When the use of topical benzoyl peroxide-containing preparation is followed by topical sulphonamide - containing products, this may cause skin and facial hair to temporarily change colour (yellow / orange).	Avoid concomitant use.

CT = Clinical Trial

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

For external (dermatological) use only. Not for oral, ophthalmic or intravaginal use.

Recommended Dose and Administration

The skin should be thoroughly washed with a mild, non-irritating cleanser, rinsed with warm water and gently patted dry.

Once daily gently apply Taro-Clindamycin / Benzoyl Peroxide Gel (clindamycin and benzoyl peroxide gel, 1%/5%, w/w) to lightly cover the entire affected areas of the face with a thin layer of gel. A pea-sized amount should be applied for each area of the face (e.g., forehead, chin, each cheek).

Hands should be washed with soap and water after application of Taro-Clindamycin / Benzoyl Peroxide Gel.

Patients with Renal Impairment
No dosage adjustment is necessary. As percutaneous absorption is low following topical application, renal impairment is not expected to result in systemic exposure of clinical significance.

Patients with Hepatic Impairment
No dosage adjustment is necessary. As percutaneous absorption is low following topical application, hepatic impairment is not expected to result in systemic exposure of clinical significance.

Missed Dose
If patients forget to apply Taro-Clindamycin / Benzoyl Peroxide Gel, they should be instructed to apply the next dose at the usual time. Patients should be instructed not to apply a double dose to make up for forgotten doses.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

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 Taro-Clindamycin / Benzoyl Peroxide Gel may cause severe skin irritation from the benzoyl peroxide and gastrointestinal side effects, including abdominal pain, nausea, vomiting and diarrhea, due to systemic absorption of clindamycin phosphate from Taro-Clindamycin / Benzoyl Peroxide Gel.

In the event of accidental ingestion of Taro-Clindamycin / Benzoyl Peroxide 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 of Taro-Clindamycin / Benzoyl Peroxide Gel (clindamycin and benzoyl peroxide gel, 1%/5%, w/w), Taro-Clindamycin / Benzoyl Peroxide 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 regional Poison Control Centre or healthcare professional, where available.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Clindamycin Phosphate: Clindamycin phosphate is a semi-synthetic antibiotic which is derived from the parent antibiotic, lincomycin. Although clindamycin phosphate is inactive *in vitro*, rapid *in vivo* hydrolysis converts this compound to the active antibiotic clindamycin. Like other macrolides, clindamycin inhibits bacterial protein synthesis by binding to the 50S subunit of ribosomes. Clindamycin *in vitro* inhibits *Propionibacterium acnes*, an organism that has been associated with acne vulgaris. Clindamycin also reduces inflammation by inhibiting leukocyte chemotaxis.

Benzoyl Peroxide: The effectiveness of benzoyl peroxide in the treatment of acne vulgaris is primarily attributable to its bactericidal activity, especially with respect to *Propionibacterium acnes*, the predominant organism in sebaceous follicles and comedones. The antibacterial activity of this compound is presumably due to the release of active or free-radical oxygen capable of oxidizing bacterial proteins. This action, combined with a mild keratolytic effect, is believed to be responsible for its usefulness in acne. *P. acnes* resistance has not been reported with benzoyl peroxide. In acne patients treated topically with benzoyl peroxide, resolution of the acne usually coincides with the reduction in the level of *P. acnes* and free fatty acids.

Pharmacodynamics

Clinical studies in humans have demonstrated that-clindamycin and benzoyl peroxide gel, 1%/5%, w/w did not have detectable phototoxic potential or photocontact allergenic potential in human skin. Clindamycin and benzoyl peroxide gel, 1%/5%, w/w was found to possess an insignificant primary irritant potential. No instance of delayed contact sensitization was reported.

Pharmacokinetics

1% clindamycin / 3% benzoyl peroxide Gel: In an open-label study (24 patients with moderate-to-severe acne vulgaris in each treatment arm), topical administration of approximately 4 grams of 1% clindamycin / 3% benzoyl peroxide Gel under maximal- use conditions once daily for 5 days, resulted in systemic clindamycin concentrations that were quantifiable in all 24 patients in each treatment arm starting from 1 hour post dose. Clindamycin was slowly absorbed after topical application, reaching maximal observed plasma concentrations within 6 hours. All plasma clindamycin concentrations were ≤ 5.1 ng/mL on Day 5.

Benzoyl Peroxide: Benzoyl peroxide has been shown to be absorbed by the skin where it is converted to benzoic acid. Less than 5% of the dose enters the systemic circulation as benzoic acid.

STORAGE AND STABILITY

Prior to Dispensing: Store between 2°C and 8°C. Do not freeze.

SPECIAL HANDLING INSTRUCTIONS

To the Pharmacist:

Taro-Clindamycin / Benzoyl Peroxide Gel (clindamycin and benzoyl peroxide gel, 1%/5%, w/w):

Dispense with a 60 day expiration date and specify “Store at room temperature (15°C - 25°C). Do not freeze. Keep tube tightly closed. Keep out of the reach of children”.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Taro-Clindamycin / Benzoyl Peroxide Gel (clindamycin and benzoyl peroxide gel, 1%/5%, w/w):

Available in a 45 g tube.

Each gram of Taro-Clindamycin / Benzoyl Peroxide Gel contains 1% clindamycin (clindamycin as clindamycin phosphate) equivalent to 10 mg clindamycin in

combination with 5% (50 mg) benzoyl peroxide in a base consisting of carbomer homopolymer, dimethicone, disodium lauryl sulfosuccinate, edetate disodium, glycerin, silicon dioxide, methylparaben, poloxamer, purified water and sodium hydroxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance - Clindamycin Phosphate

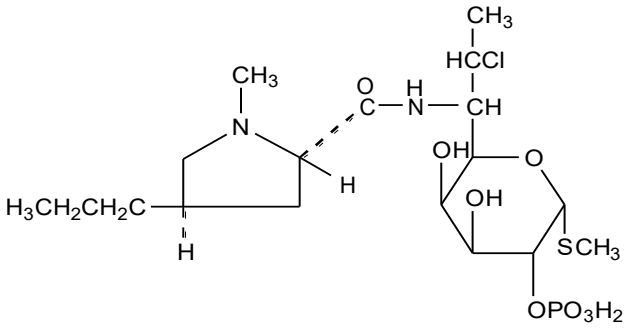
Proper name: Clindamycin Phosphate

Chemical name: Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-threo-α-D-galacto-octopyranoside 2-(dihydrogen phosphate)

Molecular formula: $C_{18}H_{34}ClN_2O_8PS$

Molecular mass: 504.97 g/mol

Structural formula:



Physicochemical properties: Clindamycin phosphate is a water soluble ester of the semi-synthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin. It occurs as a white to off-white, hygroscopic, crystalline powder. It is freely soluble in water, very slightly soluble in ethanol and practically insoluble in methylene chloride. It is odourless or practically odourless and has a bitter taste.

Drug Substance - Benzoyl Peroxide

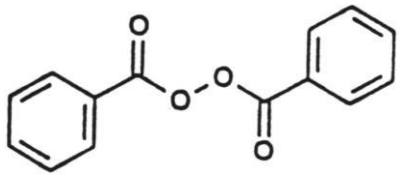
Proper name: Benzoyl Peroxide

Chemical name: Dibenzoyl peroxide

Molecular formula: $C_{14}H_{10}O_4$

Molecular mass: 242.23 g/mol

Structural formula:



Physicochemical properties: Benzoyl peroxide is a white powder, crystals or granules. Benzoyl peroxide has low solubility in water and is soluble in ether, diethyl ether and acetone.

CLINICAL TRIALS

Comparative Bioavailability Studies

A Randomized, Double-Blind, Multiple-Site, Placebo-Controlled, Parallel Design Study Comparing Clindamycin 1%/Benzoyl Peroxide 5% Topical Gel (Taro Pharmaceuticals Inc.) to Clindoxyl® Topical Gel Clindamycin l %/Benzoyl Peroxide 5% (Stiefel) in the Treatment of Acne Vulgaris was performed in 450 eligible patients with acne vulgaris. The primary measure of bioequivalence was determined in the per-protocol population by evaluating the test/reference ratio of the mean percent change from baseline to Week 11 in the number of inflamed (papules/pustules) lesions and non-inflamed (open and closed comedones) lesions. The secondary measure was the proportion of patients who were considered a "clinical success" at Week 11 (Day 77±4 days). In addition superiority to placebo and safety was evaluated for test and reference treatments.
Bioequivalence of the test to reference product was considered to have been demonstrated for all efficacy endpoints.
Results of the primary efficacy analyses are summarized in the table below.

Table 5:

	Test	**Reference**
Primary Efficacy Endpoint[a]		
Number of Patients (N)	125	126
LSMeans	-74.20	-67.15
Test-to-Reference Ratio	--	110.49
90% CI Evaluation	--	105.49 -- 115.76
Co-Primary Efficacy Endpoint[b]		
Number of Patients (N)	125	126
LSMeans	-56.81	-52.59
Test-to-Reference Ratio	--	108.02
90% CI Evaluation	--	102.24 -- 114.16
Secondary Efficacy Endpoint[c]		
Number of Patients (N)	146	143
Number of Clinical Successes (n)	81	67
Proportion of Clinical Successes (%)	55.48	46.85
Difference Between Treatments		
Difference	--	8.63
90% CI Evaluation	--	-1.70 , 18.96

[a] Mean Percent Change from Baseline in Inflammatory Lesion Count between Treatment Groups
[b] Mean Percent Change from Baseline in Non-Inflammatory Lesion Count between Treatment Groups
[c] Proportion of Clinical Successes Between Treatment Groups

Pivotal Clinical Study

Clindamycin and benzoyl peroxide gel, 1%/5%, w/w:

In three double-blind clinical studies with a total of 673 patients, 188 patients were randomized to clindamycin and benzoyl peroxide gel, 1% / 5%, w/w, benzoyl peroxide and clindamycin, respectively, in addition to 109 patients randomized to vehicle. Clindamycin and benzoyl peroxide gel, 1% / 5%, w/w applied once daily for 11 weeks was significantly more effective than vehicle, benzoyl peroxide, and clindamycin in the treatment of inflammatory lesions of moderate to moderately severe facial acne vulgaris in two of the three studies (Studies 1 and 2). Clindamycin and benzoyl peroxide gel, 1% / 5%, w/w group showed greater overall improvement in the investigator's global assessment than the benzoyl peroxide, clindamycin and vehicle groups in two of the three studies (Studies 1 and 2). Patients were instructed to wash and dry the face, and then apply medication to the entire face, once daily, in the evening before retiring. Patients were evaluated and acne lesions counted at each clinical visit: weeks 2, 5, 8, 11. The primary efficacy measures were the lesion counts and the investigator's global assessment evaluated at week 11. Percent reductions in non-inflammatory lesion counts, inflammatory lesion counts, total inflammatory lesion counts and global improvement scores after treatment for 11 weeks in these three studies are shown in Table 6.

Table 6 Outcomes for Primary Endpoints (Preferred Data Set[1])

Week 11	**Mean Percent Reduction**		
	Study 1 (n=108)	**Study 2 (n=226)**	**Study 3 (n=250)**
Non-inflammatory Lesion Counts*			
Clindamycin and benzoyl peroxide gel, 1%/5%, w/w	26.5	40.4	25.7
Clindamycin 1% Gel	-5.2 (p=0.007)	15.3 (p=0.003)	11.2 (p<0.001)
Benzoyl Peroxide 5% Gel	14.2 (p=0.309)	34.9 (p=0.456)	18.8 (p=0.091)
Vehicle Gel	-12.6 (p=0.001)	-9.6 (p<0.001)	15.4 (p=0.037)

Week 11	Mean Percent Reduction		
	Study 1 (n=108)	**Study 2 (n=226)**	**Study 3 (n=250)**
Inflammatory Lesion Counts*			
Clindamycin and benzoyl peroxide gel, 1%/5%, w/w	66.5	58.4	43.4
Clindamycin 1% Gel	34.5 (p=0.010)	35.9 (p<0.001)	39.8 (p=0.517)
Benzoyl Peroxide 5% Gel	39.5 (p=0.037)	39.4 (p=0.003)	33.5 (p=0.107)
Vehicle Gel	18.2 (p<0.001)	-7.6 (p<0.001)	28.6 (p=0.051)
Total Lesion Counts*			
Clindamycin and benzoyl peroxide gel, 1%/5%, w/w	41.5	47.7	32.5
Clindamycin 1% Gel	10.4 (p=0.003)	26.5 (p=0.001)	23.5 (p=0.021)
Benzoyl Peroxide 5% Gel	21.9 (p=0.066)	38.3 (p=0.097)	25.5 (p=0.076)
Vehicle Gel	-1.4 (p<0.001)	-6.0 (p<0.001)	20.6 (p=0.015)
Percentage of patients with Good to Excellent Global Improvement**			
Clindamycin and benzoyl peroxide gel, 1%/5%, w/w	75.0	62.7	31.5
Clindamycin 1% Gel	37.9 (p=0.010)	35.0 (p=0.002)	44.3 (p=0.197)
Benzoyl Peroxide 5% Gel	41.7 (p=0.030)	41.2 (p=0.013)	32.9 (p=0.745)
Vehicle Gel	14.8 (p<0.001)	6.5 (p<0.001)	35.1 (p=0.577)

[1] Only patients completing the study and compliant with the protocol were considered valid, and their data were included in the preferred data set.
* Comparisons between treatments and clindamycin and benzoyl peroxide gel, 1%/5%, w/w: p-values were calculated using one-way analysis of variance with treatment as the effect.
**Global improvement was defined on a scale of 0 to 4; 0 = worsening, 1 = poor, 2 = fair, 3 = good and 4 = excellent. Defined as dichotomous variable Success (global improvement scores of 3 or 4) or Failure (scores of 0, 1 or 2). Comparisons between treatments and clindamycin and benzoyl peroxide gel, 1%/5%, w/w: p-values were calculated using logistic regression with treatment as the effect.

MICROBIOLOGY

No microbiology studies were conducted in the clinical trials with clindamycin and benzoyl peroxide gel, 1%/5%, w/w.

Clindamycin and benzoyl peroxide individually have been shown to have *in vitro* activity against *Propionibacterium acnes*, an organism which has been associated with acne vulgaris; however, the clinical significance of this activity against *P. acnes* is not known and was not examined in clinical trials with clindamycin and benzoyl peroxide gel, 1%/5%, w/w.

Bacterial resistance may develop to macrolides, such as clindamycin, especially when used alone. Resistance to clindamycin is often associated with resistance to erythromycin and lincomycin. The use of clindamycin may be associated with the overgrowth of antibiotic-resistant organisms (e.g., *Propionibacterium acnes*, *Staphylococcus aureus*, *Streptococcus pyogenes*). However, the inclusion of benzoyl peroxide in the clindamycin and benzoyl peroxide gel, 1%/5%, w/w has been shown to reduce the potential for emergence of organisms resistant to clindamycin.

TOXICOLOGY

Acute Animal Toxicity

No single-dose toxicity studies were conducted with clindamycin and benzoyl peroxide gel, 1%/5%, w/w.

Clindamycin and benzoyl peroxide gel, 1%/5%, w/w**:** The ocular irritation index of clindamycin and benzoyl peroxide gel, 1%/5%, w/w was evaluated in rabbits. Evaluation of the cornea and of the iris showed no positive reactions following a single application (100 mg) of clindamycin and benzoyl peroxide gel, 1%/5%, w/w. No edema or suppuration of the conjunctiva was reported. Minor erythema of the conjunctiva lasting for a maximum of 24 hours was reported in one animal. With respect to possible ocular irritation, clindamycin and benzoyl peroxide gel, 1%/5%, w/w is considered very slightly irritant.

Chronic Animal Toxicity

Clindamycin and benzoyl peroxide gel, 1%/5%, w/w**:** Chronic toxicity of clindamycin and benzoyl peroxide gel, 1%/5%, w/w has been studied in rats and minipigs. Results from these studies are summarized in Table 7.

Table 7 Chronic toxicity of clindamycin and benzoyl peroxide gel, 1%/5%, w/w

Species	Treatment	Route	Length	Results
Rat (Sprague-Dawley)	Clindamycin and benzoyl peroxide gel, 1%/5%, w/w 80, 400, 2000 mg/kg/day; Vehicle gel 2000 mg/kg/day	Topical; 6 hours occluded exposure/day	28 days	No clinical signs observed, no effect on body weight change or food consumption; compared to controls, average weekly erythema score was increased for high dose females, low dose males showed increase in neutrophils and decrease in lymphocytes, mid dose females had fewer platelets, serum glucose levels were elevated for low and mid dose females, serum AST was elevated for mid dose males, no effect on necropsy, organ weights, relative organ weights, or histopathology; one accidental death in the control group on Day 1.
Minipig	Clindamycin and benzoyl peroxide gel, 1%/5%, w/w * 50, 500 mg/kg/day; non-aged Clindamycin and benzoyl peroxide gel, 1%/5%, w/w 500 mg/kg/day; Vehicle gel 500 mg/kg/day * Aged at room temperature for 60 days and subsequently kept at 2° to 8°C until application.	Topical; 6 hours nonoccluded exposure/day	90 days	No treatment related findings were found at terminal sacrifice for any dose group. Application of clindamycin and benzoyl peroxide gel, 1%/5%, w/w or its vehicle had no effect upon absolute organ weights, relative organ to body weight ratios or relative organ to brain ratios for any dose groups. Only a few gross lesions were observed in this study, and all were interpreted as incidental findings. No treatment related changes noted upon histopathological evaluation in any tissues.

Mutagenicity and Carcinogenicity

No genotoxicity or mutagenicity studies have been carried out with clindamycin and benzoyl peroxide gel, 1%/5%, w/w.

Clindamycin phosphate: Clindamycin phosphate was not genotoxic in the Ames Assay or in a rat micronucleus test.

Benzoyl peroxide: Numerous *in vitro* studies and an *in vivo* genotoxicity study of benzoyl peroxide have been conducted and reported in the published literature. While a few *in vitro* studies have suggested that benzoyl peroxide may be a weak mutagen, the overall genotoxicity profile does not indicate a significant biological relevance.

Benzoyl peroxide has been found to be inactive as a mutagen in the Ames Assay and other assays, including the mouse dominant lethal assay.

Clindamycin and benzoyl peroxide gel, 1%/5%, w/w: In a 2-year study in mice, topical administration of clindamycin and benzoyl peroxide gel, 1%/5%, w/w at dose levels up to 8000 mg/kg/day (24000 mg/m^2/day) showed no evidence of increased carcinogenic risk. A 52-week photocarcinogenicity study in which hairless mice were exposed to UV radiation and clindamycin and benzoyl peroxide gel, 1%/5%, w/w at dose levels up to 2500 mg/kg/day (7500 mg/m^2/day), demonstrated a slight reduction in the median time to onset of tumours when compared to UV radiation alone.

Reproductive and Developmental Toxicity

Teratological studies were not conducted with clindamycin and benzoyl peroxide gel, 1%/5%, w/w.

Clindamycin Phosphate: Reproductive studies have been performed in rats and mice using subcutaneous and oral doses of clindamycin ranging from 100 to 600 mg/kg/day and have revealed no evidence of impaired fertility or harm to the fetus due to clindamycin.

Subcutaneous injections of clindamycin phosphate at 100 and 180 mg/kg/day (aqueous solution) on Gestation Days 6 through 15 in ICR and CF-1 mice and Sprague Dawley rats had no detrimental effects on the litter weight, number of live and dead pups per litter and the number of resorptions per litter. Fetuses of rats and CF-1 mice showed no sign of teratogenic activity as evidenced by examination for gross external, visceral and skeletal malformations. In fetus of ICR mice, a low incidence of cleft palate was observed. The incidence of cleft palate in the clindamycin phosphate treated litter was not significantly different from the incidence reported in the control litter.

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

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7. Product Monograph: ^{Pr} CLINDOXYL® Gel, GlaxoSmithKline Inc., Canada. Control No. 215840, Date of Revision: November 2, 2018

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

Taro-Clindamycin / Benzoyl Peroxide Gel

Clindamycin / Benzoyl Peroxide Gel

Read this carefully before you start taking Taro-Clindamycin / Benzoyl Peroxide Gel 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 Taro-Clindamycin / Benzoyl Peroxide Gel.

What is Taro-Clindamycin / Benzoyl Peroxide Gel used for?

Taro-Clindamycin / Benzoyl Peroxide Gel is used on the skin to treat moderate acne. It should not be used to treat severe (cystic) acne.

Taro-Clindamycin / Benzoyl Peroxide Gel contains an antibacterial ingredient called clindamycin that treats only bacterial infections. Clindamycin does not treat viral infections.

It is not known if Taro-Clindamycin / Benzoyl Peroxide Gel is safe and effective in people under the age of 12 years old and over the age of 65 years old.

How does Taro-Clindamycin / Benzoyl Peroxide Gel work?

Taro-Clindamycin / Benzoyl Peroxide Gel works by:

- slowing or stopping the growth of acne bacteria.
- killing acne bacteria.

What are the ingredients in Taro-Clindamycin / Benzoyl Peroxide Gel?

Medicinal ingredients in Taro-Clindamycin / Benzoyl Peroxide Gel: clindamycin phosphate and benzoyl peroxide.

Non-medicinal ingredients in Taro-Clindamycin / Benzoyl Peroxide Gel: Carbomer homopolymer, dimethicone, disodium lauryl, sulfosuccinate, edetate disodium, glycerin, methylparaben, poloxamer, purified water, silicon dioxide and sodium hydroxide.

Taro-Clindamycin / Benzoyl Peroxide Gel comes in a Topical Gel.

Do not use Taro-Clindamycin / Benzoyl Peroxide Gel if:

You are allergic to:

- clindamycin.
- benzoyl peroxide.
- lincomycin, an antibiotic.
- any of the other ingredients in Taro-Clindamycin / Benzoyl Peroxide Gel. See **What are the ingredients in Taro-Clindamycin / Benzoyl Peroxide Gel?**

You have or have had the following:

- inflammatory bowel disease, such as Crohn's disease or ulcerative colitis.
- bloody, severe, or long-lasting diarrhea after using antibiotics.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Taro-Clindamycin / Benzoyl Peroxide Gel. Talk about any health conditions or problems you may have, including if you are:

- pregnant or planning to become pregnant.
- breast-feeding or planning to breast-feed.

If you do breast-feed:

- Do not apply to the chest or breast area to prevent the infant from ingesting Taro-Clindamycin / Benzoyl Peroxide Gel.

Other warnings you should know about:

- Taro-Clindamycin / Benzoyl Peroxide Gel is for external use only.
- Keep Taro-Clindamycin / Benzoyl Peroxide Gel away from:
    - your eyes.
    - inside your nose.
    - your mouth and lips.
    - other mucous membranes, like inside your vagina.
    - areas of broken or irritated skin.
    - sunburned skin, until it has healed
- If contact occurs with any of the above areas, flush with water for at least 5 minutes. If discomfort continues, talk to your healthcare professional.
- Do not apply too much. Applying too much may cause skin irritation. If this happens, use the gel less often.
- Limit your time in the sun. If you have to be in the sun, wear protective clothing and sunscreen. Do not use sunlamps or tanning beds.
- Do not use other acne medications applied to the skin unless your healthcare professional tells you to do so.
- If you have recently used other medicines with clindamycin or erythromycin, Taro-Clindamycin / Benzoyl Peroxide Gel may not work as well as it should. Tell your healthcare professional if you have recently used these other medicines.

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 Taro-Clindamycin / Benzoyl Peroxide Gel:

- Medicines used to relax muscles during surgery.
- Erythromycin, an antibiotic.
- Medicines applied to the skin that contain tretinoin, isotretinoin or tazarotene.
- Medicines called sulphonamides that are applied to the skin such as dapsone or sulfacetamide.
- Other acne medications applied to the skin.

How to take Taro-Clindamycin / Benzoyl Peroxide Gel:

- Before you apply:
  - wash your skin with a mild cleanser that doesn't irritate your skin.
  - rinse with warm water.
  - gently pat dry.
- Apply only to your skin.
- After you apply:
  - wash your hands with soap and water.
- Although you may feel better early in treatment, use only as directed by your healthcare professional.
- Misuse or overuse of Taro-Clindamycin / Benzoyl Peroxide Gel could lead to the growth of bacteria that will not be killed by clindamycin (resistance). This means that Taro-Clindamycin / Benzoyl Peroxide Gel may not work for you in the future.
- Do not share your medicine.

Usual dose:

- Apply a thin layer to the affected area, once a day.
- For the face, apply a pea-sized amount for each affected area of your face, for example, to:
  - your chin.
  - each cheek.
  - your forehead.

Overdose:

If you accidently swallow Taro-Clindamycin / Benzoyl Peroxide Gel seek medical advice.

If you think you have taken too much Taro-Clindamycin / Benzoyl Peroxide Gel, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed dose:

If you missed a dose of this medication, apply it as soon as you remember. Do not apply two doses at the same time.

What are possible side effects from using Taro-Clindamycin / Benzoyl Peroxide Gel?

These are not all the possible side effects you may feel when taking Taro-Clindamycin / Benzoyl Peroxide Gel. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- skin rash that is red or bumpy.
- dry or itchy skin.
- numbness or tingling of the skin.
- burning or stinging of the skin.
- peeling skin.

- a change in colour of the skin where the medicine was applied.
- sensitivity to the sun.
- worsening of acne.

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	
RARE Colitis (inflammation of the intestines): • cramps. • severe pain. • bloating. • severe or long lasting diarrhea (bloody or watery). • nausea. • vomiting.			✓
Folliculitis (an infection of your hair follicles): • tiny red or white bump at the base of a hair. • painful or tender skin. • blisters. • skin itching.			✓
Severe allergic reaction: • raised and itchy rash (hives). • swelling of the mouth, face or tongue, making it hard to breathe. • collapsing.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

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/adverse-reaction-reporting.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 at room temperature (15° - 25°C). Do not freeze. Keep tube tightly closed. Keep out of reach and sight of children.

If there is any Taro-Clindamycin / Benzoyl Peroxide Gel left 60 days after you receive it, you should throw it out and talk to your healthcare professional.

If you want more information about Taro-Clindamycin / Benzoyl Peroxide Gel:

- 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 (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website http://www.taro.ca, or by calling 1-800-268-1975.

This leaflet was prepared by Taro Pharmaceuticals Inc.

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