

PRODUCT MONOGRAPH

Pr **BIACNA™ Topical Gel**

(clindamycin phosphate and tretinoin)

1.2% w/w and 0.025% w/w

Acne Therapy

Valeant Canada limitée/ Limited  
4787 Levy Street  
Montreal, Quebec H4R 2P9

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## **PART I: HEALTH PROFESSIONAL INFORMATION**

### **SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Clinically Relevant Nonmedicinal Ingredients</b>
Topical	Gel / Clindamycin 1% w/w (provided as clindamycin phosphate 1.2%) and tretinoin 0.025% w/w	Butylated hydroxytoluene (BHT)  <i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>

### **INDICATIONS AND CLINICAL USE**

BIACNA™ Topical Gel (clindamycin phosphate 1.2% w/w and tretinoin 0.025% w/w) is indicated for the topical treatment of acne vulgaris characterized by comedones, inflammatory papules/pustules, with or without an occasional nodule in adults and children 12 years or older. BIACNA™ Topical Gel is not indicated for the treatment of pustular and deep cystic nodular acne varieties (acne conglobata and acne fulminans).

**Pediatrics (<12 years of age):** Safety and effectiveness of BIACNA™ Topical Gel in children under the age of 12 years have not been established.

**Geriatrics (>65 years of age):** Safety and effectiveness of BIACNA™ Topical Gel in patients above the age of 65 years have not been established.

### **CONTRAINDICATIONS**

BIACNA™ Topical Gel (clindamycin phosphate 1.2% w/w and tretinoin 0.025% w/w) is contraindicated:

- In patients with regional enteritis, ulcerative colitis, or history of antibiotic-associated colitis.

- In patients who have a history of hypersensitivity to BIAACNA™ Topical Gel or any preparations containing clindamycin, lincomycin, tretinoin or to any ingredient in the formulation or component of the container. (See DOSAGE FORMS, COMPOSITION AND PACKAGING for a complete listing).

## **WARNINGS AND PRECAUTIONS**

### **General**

Patients should be advised to avoid having BIAACNA™ Topical Gel (clindamycin phosphate 1.2% w/w and tretinoin 0.025% w/w) come in contact with eyes and mucous membranes. BIAACNA™ Topical Gel is for external (dermatologic) use only. Not for ophthalmic use.

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.

Exposure to sunlight or unnecessary UV light should be minimized.

Occasional gram-negative folliculitis has been reported during treatment with clindamycin phosphate 1% topical products. If this should occur, therapy with BIAACNA™ Topical Gel should be discontinued and alternative therapy should be initiated.

Prolonged use of BIAACNA™ Topical Gel may result in overgrowth of non-susceptible organisms, including those initially sensitive to the clindamycin. Cross-resistance between clindamycin and erythromycin has been reported. If this should occur, therapy with BIAACNA™ topical Gel should be discontinued and alternative therapy should be initiated.

### **Carcinogenesis and Mutagenesis**

Carcinogenicity and mutagenicity of BIAACNA™ Topical Gel have not been assessed. Carcinogenicity and genotoxicity of each of the active ingredients in BIAACNA™ Topical Gel, clindamycin phosphate and tretinoin, have been assessed separately.

#### ***Clindamycin***

Clindamycin was not carcinogenic when applied topically daily to mice for two years in a 1.2% clindamycin phosphate topical gel similar to BIAACNA™ Topical Gel. Clindamycin was not carcinogenic when administered orally daily to rats for two years. Furthermore, clindamycin phosphate was not mutagenic or clastogenic in standard *in vitro* genotoxicity assays (See PART II: TOXICOLOGY).

#### ***Tretinoin***

Tretinoin was not carcinogenic when applied topically three times per week to mice for two years in a topical gel of higher strength than BIAACNA™ Topical Gel. Tretinoin has not been

examined for systemic carcinogenicity potential. Tretinoin was not mutagenic or clastogenic in standard *in vitro* and *in vivo* genotoxicity assays (See PART II: TOXICOLOGY).

## **Gastrointestinal**

### ***Clostridium Difficile-Associated Disease (CDAD)***

Systemic absorption of clindamycin has been demonstrated following topical use of BIAACNA™ Topical Gel. *Clostridium difficile*-associated disease (CDAD) has been reported with the use of topical clindamycin. 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 megacolon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur 2 months after the administration of antibacterial agents.

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**

Avoid BIAACNA™ Topical Gel contact with eyes, eyelids, angles of nose and mouth, mucous membranes (oral, intranasal or intravaginal), or other areas where treatment is not intended. In the event of accidental contact with such sensitive surfaces (mucous membranes, eyes, abraded skin), rinse with large amounts of lukewarm tap water (See ADVERSE REACTIONS and PART II: DETAILED PHARMACOLOGY).

## **Skin**

Excessive use of BIAACNA™ Topical Gel should be avoided. BIAACNA™ Topical Gel has a potential to cause reversible dermal irritation, co-allergic contact dermatitis, phototoxic reactions and photo allergy. Skin irritation was observed in humans and animals administered BIAACNA™ Topical Gel (See ADVERSE REACTIONS; DRUG INTERACTIONS; ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics and PART II: DETAILED PHARMACOLOGY and TOXICOLOGY).

In the event of sensitization or severe local irritation from BIAACNA™ Topical Gel, its usage should be discontinued, the Gel carefully wiped off, and appropriate alternative acne therapy should be instituted. BIAACNA™ Topical Gel should be prescribed with caution in atopic

subjects. Abrasive soaps, cleansers and cosmetics that have a strong drying effect and products with high concentrations of alcohol, astringents, spices or lime should be used with caution.

### **Photosensitivity and Photocarcinogenicity**

Because of heightened susceptibility to UV radiation as a result of using tretinoin, patients should avoid exposure to the sunlight, including sunlamp during the use of BIACNA™ Topical Gel. Daily uses of sunscreen products with a SPF of at least 30 and protective apparel (e.g., a hat) are recommended and patients with sunburn are advised not to use BIACNA™ Topical Gel until fully recovered. Patients who may be required to have considerable sun exposure due to occupation and those with inherent sensitivity to the sun should exercise particular caution. If sunburn occurs, discontinue therapy with BIACNA™ Topical Gel until the severe erythema and peeling subside.

### ***Clindamycin***

Evidence for enhancement of photocarcinogenesis by topical clindamycin is equivocal (See ADVERSE REACTIONS and PART II: TOXICOLOGY).

### ***Tretinoin***

Topical tretinoin enhances photocarcinogenicity in mice. A no-observed-adverse-effect level (NOAEL) for tretinoin photo-carcinogenicity is undefined (See ADVERSE REACTIONS and PART II: TOXICOLOGY).

### **Special Populations**

**Pregnant Women:** BIACNA™ Topical Gel should be given to woman of childbearing years only after contraceptive counseling. BIACNA™ Topical Gel should not be given to a pregnant woman unless the benefits to the mother clearly outweigh the possible risks to the fetus.

There are no adequate and well-controlled trials in pregnant women treated with BIACNA™ Topical Gel. Topically administered BIACNA™ Topical Gel did not impact fertility or embryo-fetal development in rabbits (See PART II: TOXICOLOGY).

### ***Clindamycin***

Systemically administered clindamycin did not affect fertility, mating ability, embryonic development, or post-natal development in animals (See PART II: TOXICOLOGY.)

### ***Tretinoin***

Birth defects among babies born to women exposed to topical tretinoin during pregnancy have been reported. However, there are no adequate and well controlled prospective studies of the use of topical tretinoin in pregnant women. In a well-conducted retrospective cohort study, no excess birth defects were identified in babies born to women exposed to topical tretinoin during the first trimester of pregnancy when compared to babies born to women who were not exposed to topical tretinoin.

Systemically administered tretinoin is well known to be a teratogen and to severely affect fertility and peri-/postnatal reproductive development. Systemic tretinoin produces dose-dependent and stage-dependent fetal malformations in several animal species (See PART II: TOXICOLOGY).

**Nursing Women:** Because of the potential for adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the BIAACNA™ Topical Gel therapy to the mother.

It is not known whether clindamycin or tretinoin is excreted in human milk following topical use of BIAACNA™ Topical Gel. Orally and parenterally administered clindamycin is excreted in breast milk. It is not known whether systemically administered tretinoin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BIAACNA™ Topical Gel is administered to a nursing woman.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

Overall, the frequency of investigator-determined drug-related adverse reactions that occurred with BIAACNA™ Topical Gel (clindamycin phosphate 1.2% w/w and tretinoin 0.025% w/w) in three Phase III studies and one 12-month open-label study in patients (n=2295) was 5%. The majority of drug-related adverse reactions were mild or moderate in severity. The most frequent drug-related adverse reactions were application site reactions, such as dryness, pruritus and rash, which generally peaked within two weeks of therapy, decreasing thereafter.

The incidence of discontinuations of BIAACNA™ Topical Gel due to drug-related adverse reactions was 0.5% and similar between treatment groups. The most commonly reported drug-related adverse reaction leading to withdrawal was rash.

### **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 reactions and for approximating rates.*

The safety profile of BIAACNA™ Topical Gel was assessed in three controlled 12-week phase III clinical studies in 1,853 patients, age 12 years of age and older with acne vulgaris and a 12-month open-label safety study in 422 patients, 12 years of age and older who used at least one dose from a once daily regimen.

The most common drug-related adverse reaction ( $\geq 1\%$ ) reported in these studies is shown in Table 1.

**Table 1: Drug-Related Adverse Reactions Reported by  $\geq 1\%$  of Patients Treated with BIACNA™ Gel in Phase III and Long Term Clinical Studies**

Adverse Drug Reaction	BIACNA™ Gel N = 2295 n (%)	Clindamycin N = 1428 n (%)	Tretinoin N = 846 n (%)	Vehicle N = 423 n (%)
<b>Skin and subcutaneous tissue disorders</b>				
Application Site Dry Skin/Dryness	40 (1.7%)	7 (0.5%)	20 (2.4%)	4 (0.9%)

**Less Common Clinical Trial Adverse Drug Reactions (<1%)**

**Eye disorders:** eye irritation

**Gastrointestinal disorders:** gastroenteritis, nausea

**General disorders:** feeling hot, pain

**Immune system disorders:** hypersensitivity

**Nervous system disorders:** headache

**Respiratory, thoracic, & mediastinal disorders:** influenza, nasal congestion, rhinitis

**Skin and subcutaneous tissue disorders:**

acne, herpes simplex, oily skin, photosensitivity reaction, rash, rash macular, rash scaly, skin bleeding, skin depigmentation, skin exfoliation, skin irritation, sunburn

application site reactions: burning, dermatitis, desquamation, erythema, excoriation, irritation, pigmentation changes, pruritus, reaction, swelling

The proportion of both adult ( $\geq 18$  years) and pediatric patients (12-17 years) reporting a specific drug-related adverse reaction was consistent with that which was reported in the overall population. The open-label 12-month safety study for BIACNA™ Topical Gel showed similar drug-related adverse drug reactions as seen in the 3-month studies.

**Post-Market Adverse Drug Reactions**

The post-marketing adverse drug reaction profile is consistent with the type of reactions reported in the controlled clinical trials.

**DRUG INTERACTIONS**

Patients should be advised to use caution when using BIACNA™ Topical Gel with other topical



products which have a drying effect. BIACNA™ Topical Gel should not be used with erythromycin or neuromuscular blocking agents.

### **Concomitant Topical Medication**

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 because of possible interaction with tretinoin.

### **Clindamycin and Erythromycin**

Clindamycin-containing products should not be used in combination with erythromycin-containing products. *In vitro* studies have shown antagonism between these two antimicrobials. The clinical significance of this *in vitro* antagonism is not known.

### **Neuromuscular Blocking Agents**

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, BIACNA™ Topical Gel should not be used in patients receiving such agents.

### **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 procedures have not been established.

### **Drug-Lifestyle Interactions**

Interactions with lifestyle have not been established.

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

BIACNA™ Topical Gel, a combination of a lincosamide antibiotic and a retinoid, contains clindamycin phosphate 1.2% w/w and tretinoin 0.025% w/w, formulated as a topical gel. Each gram of BIACNA™ Topical Gel contains, as dispensed, 10 mg (1.0%) clindamycin (as clindamycin phosphate), and 0.25 mg (0.025%) tretinoin in an aqueous based gel.

### **Duration of treatment**

12 weeks. Treatment beyond 12 weeks may call for evaluation by the physician.

### **Recommended Dose and Administration**

Adults, children 12 years of age and older: At bedtime the entire face should be washed with mild soap and dried. A pea-sized amount of BIACNA™ Topical Gel should be squeezed onto one fingertip, dot onto the chin; cheeks, nose, and forehead, then gently rub over the entire face once daily. BIACNA™ Topical Gel should be kept away from the eyes, the mouth, angles of the nose, and mucous membranes.

BIACNA™ Topical Gel is not for oral, ophthalmic, or intravaginal use.

### **Missed Dose**

In case of a missed dose of BIACNA™ Topical Gel the patient should wait for the next dose at the usual time. Patients should not double the dose to make up for the forgotten dose.

### **OVERDOSAGE**

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

If BIACNA™ Topical Gel (clindamycin phosphate 1.2% w/w and tretinoin 0.025% w/w) is applied excessively, marked redness, peeling or discomfort can occur. If excess application occurs accidentally or through over-enthusiastic use, the face should be gently washed with a mild soap and warm water. Topically applied clindamycin phosphate from BIACNA™ Topical Gel can be absorbed in sufficient amounts to cause systemic gastrointestinal side effects including abdominal pain, nausea, vomiting and diarrhea. In the case of overdose BIACNA™ Topical Gel should be discontinued for several days before resuming therapy.

In the event of accidental ingestion, the same adverse reactions effects as those expected with oral tretinoin and clindamycin including teratogenesis in women and gastrointestinal side effects including abdominal pain, nausea, diarrhea, bloody diarrhea and colitis are expected. In such cases, BIACNA™ Topical Gel should be discontinued and pregnancy testing should be carried out in women of childbearing years (See WARNINGS and PRECAUTIONS.)

### **ACTION AND CLINICAL PHARMACOLOGY**

#### **Mechanism of Action**

BIACNA™ Topical Gel, a combination of a lincosamide antibiotic and a retinoid, contains clindamycin phosphate 1.2% and tretinoin 0.025%, formulated as a topical gel.

#### ***Clindamycin***

Clindamycin is a semisynthetic derivative of the parent compound lincomycin that is produced by *Streptomyces lincolnensis* and is predominantly bacteriostatic. 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 has *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* was not examined with BIACNA™ Topical Gel or clindamycin.

*P. acnes* resistance to clindamycin has been documented. Resistance to clindamycin is often associated with resistance to erythromycin.

### ***Tretinoin***

The exact mode of action of tretinoin is unknown. Current evidence suggests topical tretinoin decreases cohesiveness of follicular epithelial cells resulting in decreased microcomedone formation. Additionally, tretinoin stimulates mitotic activity and increased turnover of follicular epithelial cells, causing extrusion of the comedones.

## **Pharmacodynamics**

Phase 1 dermal battery studies, i.e. potential for dermal irritation, contact sensitization, phototoxic and photo allergic reactions, demonstrated that BIACNA™ Topical Gel has potential to cause moderate skin irritation and low potential to cause allergic contact dermatitis, phototoxic reactions and photo allergic reactions (See PART II, DETAILED PHARMACOLOGY.)

## **Pharmacokinetics**

In a pharmacokinetic study of BIACNA™ Topical Gel in 12 patients with moderate to severe acne, tretinoin and clindamycin were absorbed percutaneously following 14 consecutive once daily applications of 4 g of BIACNA™ Topical Gel, i.e. approximately 4-times the recommended acne dose. Individual plasma concentrations of tretinoin, key tretinoin metabolites, and clindamycin ranged from 1.0-6.5 ng/mL. In one patient the plasma concentration of clindamycin reached to 13.1 ng/mL. (See PART II: DETAILED PHARMACOLOGY).

## **STORAGE AND STABILITY**

Store at controlled room temperature 25°C (77°F); excursions permitted to between 15–30°C. The shelf life of BIACNA™ Topical Gel is 24 months.

## **SPECIAL HANDLING INSTRUCTIONS**

Protect from light. Protect from freezing. Keep out of the reach of children. Keep away from heat. Keep the lid tightly closed.

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

Each gram of BIACNA™ Topical Gel contains, as dispensed, 10 mg (1.0% w/w) clindamycin (as clindamycin phosphate), and 0.25 mg (0.025% w/w) tretinoin in an aqueous based gel.

BIACNA™ Topical Gel also contains the following nonmedicinal ingredients: butylated hydroxytoluene NF, carbomer 981 NF, citric acid USP, edetate disodium USP, glycerin USP, methylparaben NF, polysorbate 80 NF, propylparaben NF, purified water USP, and tromethamine USP.

BIACNA™ Topical Gel is supplied as follows:

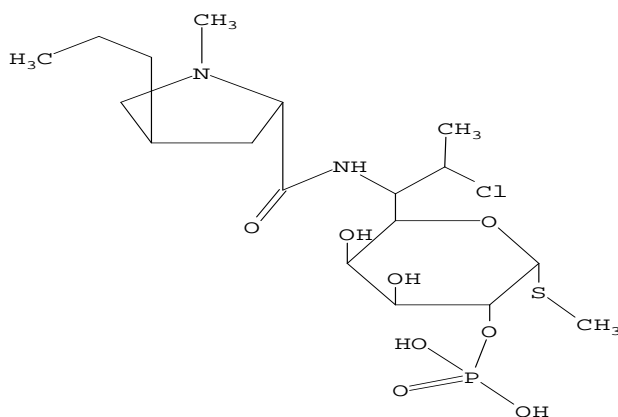
- 2 gram tube (sample size)
- 30 gram tube
- 60 gram tube

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance 1 – clindamycin phosphate

Proper name:	clindamycin phosphate
Chemical name:	Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl- <i>trans</i> -4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L- <i>threo</i> - $\alpha$ -D-galactooctopyranoside 2-(dihydrogen phosphate).
Molecular formula:	C <sub>18</sub> H <sub>34</sub> ClN <sub>2</sub> O <sub>8</sub> PS
Molecular mass:	504.97
Structural formula:	

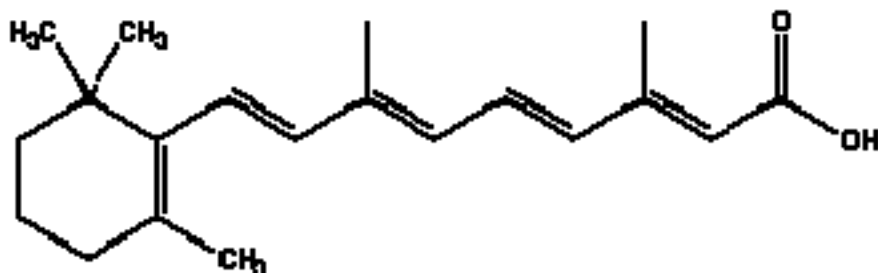


Physicochemical properties: Clindamycin phosphate is a water-soluble ester of the semi-synthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin.

#### Drug Substance 2 – Tretinoin

Proper name: Tretinoin  
Chemical name: 3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid (all-trans form).  
Molecular formula:  $C_{20}H_{28}O_2$   
Molecular mass: 300.44

Structural formula:



Physicochemical Properties: Tretinoin is a yellow to light-orange, crystalline powder. It is insoluble in water, slightly soluble in alcohol and in chloroform. Chemically, tretinoin is related to Vitamin A.

## CLINICAL TRIALS

The safety and efficacy of once daily use BIAACNA™ Topical Gel for the treatment of acne vulgaris were assessed in three 12-week prospective, multi-center, randomized, double-blind studies in patients 12 years and older. Studies 1 and 2 were of identical design and compared BIAACNA™ Topical Gel to clindamycin in the vehicle gel, tretinoin in the vehicle gel, and the vehicle gel alone. Study 3 compared BIAACNA™ Topical Gel to clindamycin in the vehicle gel.

Patients with 20 to 50 facial inflammatory lesions, 20 to 100 facial non-inflammatory lesions and two or fewer facial nodules were eligible to enroll in these studies. The infected acne lesions had to be suitable for topical acne treatment. Lesions on the back were not counted.

The co-primary efficacy variables were:

- (1) Mean percent change from baseline at Week 12 in the following 3 lesion counts:
  - Inflammatory lesion counts
  - Non-inflammatory lesion counts, and
  - Total lesion counts

Success was defined if superiority was shown in the mean percent decrease from baseline at Week 12 for 2 of 3 lesion counts.

- (2) Percent of subjects who were graded clear or almost clear at Week 12 as judged by an Evaluator's Global Severity Score (EGSS) was used in Study 1 and Study 2. Percent of subjects who had at least a 2-grade improvement from baseline at Week 12 on the EGSS was used in Study 3.

The EGSS scale used in all of the clinical trials for BIAACNA™ Topical Gel is as follows:

<b>Grade</b>	<b>Description</b>
Clear	Normal, clear skin with no evidence of acne vulgaris
Almost Clear	Rare non-inflammatory lesions present, with rare non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red)
Mild	Some non-inflammatory lesions are present, with few inflammatory lesions (papules/pustules only; no nodulocystic lesions)
Moderate	Non-inflammatory lesions predominate, with multiple inflammatory lesions evident; several to many comedones and papules/pustules, and there may or may not be one small nodulo-cystic lesion
Severe	Inflammatory lesions are more apparent, many comedones and papules/pustules, there may or may not be a few nodulocystic lesions
Very Severe	Highly inflammatory lesions predominate, variable number of comedones, many papules/pustules and many nodulocystic lesions

## Study Design and Demographics

**Table 2 Summary of Patient Demographics for Phase III Clinical Trials**

Study Design	Dosage, Route of Administration and Duration of Therapy	Patients Total (n=number)	Age: Mean in Years (Range)	Gender % M/F
Study #7001. G2HP-06-02 Randomized, double-blind, active superiority and placebo controlled study N=1252 Sites: 28 in North America	BIACNA™ Topical Gel (clindamycin phosphate 1.2% w/w, tretinoin 0.025% w/w)	420	18.4 (12 – 54)	53/47
	clindamycin phosphate gel 1.2% w/w	208	19 (11 – 51)	56/44
	tretinoin gel 0.025% w/w	417	19 (11 – 47)	52/48
	vehicle gel	207	18.6 (12 – 47)	47/53
	Topical: Once daily in the evening 12 weeks			
Study #7001. G2HP-07-02 Randomized, double-blind, active superiority and placebo controlled study N=1288 Sites: 32 in North America	BIACNA™ Topical Gel (clindamycin phosphate 1.2% w/w, tretinoin 0.025% w/w)	425	19.2 (11 – 59)	45/55
	clindamycin phosphate gel 1.2% w/w	218	19.3 (12 – 52)	49/51
	tretinoin gel 0.025% w/w	429	19.4 (12 – 55)	45/55
	vehicle gel	216	19 (11 – 52)	49/51
	Topical: Once daily in the evening 12 weeks			



**Table 2 Summary of Patient Demographics for Phase III Clinical Trials (continued)**

Study Design	Dosage, Route of Administration and Duration of Therapy	Patients Total (n=number)	Age: Mean in Years (Range)	Gender % M/F
Study #MP 1501-02 Randomized, double-blind, active superiority controlled study N=2010 Sites: 47 in North America	BIACNA™ Topical Gel (clindamycin phosphate 1.2% w/w, tretinoin 0.025% w/w)	1008	19.1 (12 – 84)	51/49
	clindamycin phosphate gel 1.2% w/w  Topical: Once daily in the evening  12 weeks	1002	19 (12 – 53)	45/55

**Table 3 Mean Percentage Reduction from Baseline of Acne (Inflammatory, Non-Inflammatory and Total) Lesions and Dichotomized Success of Evaluator’s Global Severity Score at End of Therapy (Week 12) in ITT Population (Studies 06-02 and 07-02)**

Study # Total Patients	Treatment Patient No.	Mean % Reduction of Lesions at Week 12 from Baseline Mean, P value			Patients Achieving Dichotomized Success on EGSS* Total Number (%), P value
		Inflammatory	Non- Inflammatory	Total	
Combined Studies 06-02 and 07-02 N=2540	BIACNA™ Topical Gel 845	48%	36%	41%	180 (21%)
	Clindamycin 426	42%, 0.016	27%, <0.001	34%, <0.001	70 (16%), 0.034
	Tretinoin 846	39%, <0.001	31%, 0.007	34%, <0.001	122 (14%), <0.001
	Vehicle 423	26%, <0.001	16%, <0.001	20%, <0.001	34 (8%), <0.001

\* Success was defined as cleared or almost cleared at Week 12 on Evaluator’s Global Severity Score (EGSS). If no value was presented, then the patient was considered a failure.

**Table 4 Mean Percentage Reduction from Baseline of Acne (Inflammatory, Non-Inflammatory and Total) Lesions and Dichotomized Success of Evaluator’s Global Severity Score at End of Therapy (Week 12) in ITT Population (Study MP 1501-02)**

Study # Total Patients	Treatment Patient No.	Mean % Reduction of Lesions at Week 12 from Baseline Mean, P value			Patients Achieving Dichotomized Success on EGSS** Total Number (%), P value
		Inflammatory	Non- Inflammatory	Total	
MP 1501-02 N=2010	BIACNA™ Topical Gel 1008	61%	50%	55%	381 (38%)
	Clindamycin 1002	55%, <0.001	41%, <0.001	47%, <0.001	318 (32%), 0.002

\*\* Success was defined as at least 2-grade improvement from baseline at Week 12 on EGSS. If no value was presented, then the data was considered a failure.

## **DETAILED PHARMACOLOGY**

### **Mechanism of Action**

#### ***Clindamycin***

See PART II: MICROBIOLOGY.

#### ***Tretinoin***

The exact mode of action of tretinoin is unknown. Current evidence suggests topical tretinoin decreases cohesiveness of follicular epithelial cells resulting in decreased microcomedone formation. Additionally, tretinoin stimulates mitotic activity and increased turnover of follicular epithelial cells, causing extrusion of the comedones.

### **Human Pharmacodynamics**

Four Phase 1 dermal battery studies have been conducted; a 21-day cumulative dermal irritation study, a contact sensitivity repeat patch test study, a phototoxicity potential study, and a photoallergy study. These studies demonstrated that BIACNA™ Topical Gel has potential to cause moderate skin irritation and low potential to cause allergic contact dermatitis, phototoxic reactions and photoallergic reactions. BIACNA™ Topical Gel contains 0.02% butylated hydroxytolulene (BHT). In clinical studies BHT at 2% strength (i.e. 10-times the strength in BIACNA™ Topical Gel) was a moderate sensitizer in a small number of patients.

### **Animal Pharmacodynamics**

BIACNA™ Topical Gel is not a primary irritant, as defined by FHSA regulations. BIACNA™ Topical Gel did not induce any signs of ocular irritation when instilled in the eyes of New Zealand White rabbits.

BIACNA™ Topical Gel is not a contact sensitizer in animals. BIACNA™ Topical Gel did not elicit an allergic response in Hartley albino guinea pigs in the Guinea Pig Maximization Test.

BIACNA™ Topical Gel has the potential to elicit skin irritation. BIACNA™ Topical Gel was mildly irritating to the skin of New Zealand White rabbits when applied under occlusion for 24h. Additionally, BIACNA™ Topical Gel induced erythema and edema following 13 consecutive weeks of dermal dosing in Hanford minipigs. This local toxicity was similar in severity but more frequent in incidence compared to the vehicle control. The no-observed-adverse-effect-level (NOAEL) for local tolerance was 3 times the recommended therapeutic acne dose of BIACNA™ Topical Gel (1g drug product per 60kg person), assuming complete absorption and based on body surface area comparisons between species.

## **Human Pharmacokinetics**

In an open-label, multiple-dose study treating 12 subjects with moderate to severe acne, the percutaneous absorption of tretinoin and clindamycin was minimal following 14 consecutive daily applications of approximately 4 g of BIACNA™ Topical Gel, i.e approximately 4-times the recommended acne dose. Tretinoin plasma concentrations were below the lower limit of quantitation (LLOQ; 1 ng/mL) in 50% to 92% of subjects at any given time point following administration and were near the LLOQ in the remaining subjects, with individual values ranging from 1.0 to 1.6 ng/mL. The individual plasma concentrations of the key tretinoin metabolites, 13- cis -retinoic acid and 4-oxo-13-cis-retinoic acid, ranged from 1.0 to 1.4 ng/mL and from 1.6 to 6.5 ng/mL, respectively. Individual plasma concentrations for clindamycin generally did not exceed 3.5 ng/mL, with the exception of one subject whose highest plasma concentration was 13.1 ng/mL. Accumulation in plasma was not observed with repeated dosing.

## **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. Clindamycin has *in vitro* activity against *Propionibacterium acnes*, an organism which has been associated with acne vulgaris; however, the significance of this activity against *P. acnes* was not examined with BIACNA™ Topical Gel or clindamycin.

## **Development of Resistance**

*P. acnes* resistance to clindamycin has been documented. Resistance to clindamycin is often associated with resistance to erythromycin.

## **TOXICOLOGY**

Studies of BIACNA™ Topical Gel, clindamycin, and tretinoin support the safety of BIACNA™ Topical Gel.

### **Acute Toxicity**

The acute lethal oral dose of BIACNA™ Topical Gel in rat is >5000 mg formulation/kg. This dose is the human equivalent of >7.6 mg clindamycin/kg/day and >0.19 mg tretinoin/kg/day, or 46-times the recommended therapeutic acne dose of BIACNA™ Topical Gel (1g drug product per 60kg person), assuming complete absorption and based on body surface area comparisons between species.

### **Repeat-dose Dermal Toxicity**

BIACNA™ Topical Gel did not induce any signs of systemic toxicity attributed to the active pharmaceutical ingredients following 13 consecutive weeks of dermal dosing in Hanford

minipigs. The no-observed-adverse-effect-level (NOAEL) for systemic toxicity following dermal application was the high dose, 125 mg formulation/kg/day; this is human equivalent of 5 times the recommended therapeutic acne dose of BIACNA™ Topical Gel (1g drug product per 60kg person), assuming complete absorption and based on body surface area comparisons between species.

### **Repeat-dose Systemic Toxicity**

BIACNA™ Topical Gel has not been evaluated explicitly for toxicity following systemic administration. Toxicity of the active pharmaceutical ingredients, clindamycin phosphate and tretinoin, following systemic administration has been assessed separately in animals.

#### ***Clindamycin***

Little systemic toxicity is observed with systemic administration of clindamycin. Liver is the target organ of chronic high dose toxicity, and dog appears to be the most sensitive species to oral clindamycin. The dog oral no-observed-adverse-effect level (NOAEL), 100 mg/kg/day, is the human equivalent dose of 32 mg/kg; this is more than 150-times the recommended therapeutic acne dose of BIACNA™ Topical Gel (1g drug product per 60kg person), assuming complete absorption and based on body surface area comparisons between species.

#### ***Tretinoin***

Systemic toxicity is observed with systemic administration of tretinoin. Oral toxicity as reported in the literature is characterized as hypervitaminosis A syndrome, consists of decreased food consumption, decreased body weight gain, erythema, alopecia, mucosal changes, skeletal dissolution, and long-bone fractures. The rat appears to be the species most sensitive to oral tretinoin. The rat oral NOAEL, 1 mg/kg/day, is the human equivalent dose of 0.16 mg/kg; this is 32-times the recommended therapeutic acne dose of BIACNA™ Topical Gel (1g drug product per 60kg person), assuming complete absorption and based on body surface area comparisons between species.

### **Mutagenicity and Carcinogenicity**

Mutagenicity and carcinogenicity of the BIACNA™ Topical Gel formulation have not been assessed. Genotoxicity and mutagenicity of the active ingredients in BIACNA™ Topical Gel, clindamycin phosphate and tretinoin, have been assessed separately. Dermal carcinogenicity of a 1.2% clindamycin phosphate topical gel similar to BIACNA™ Topical Gel and of tretinoin topical gel of higher strength than BIACNA™ Topical Gel has been assessed in animals separately. Systemic carcinogenicity of clindamycin phosphate, but not tretinoin, has been assessed in animals.

### **Mutagenicity**

#### ***Clindamycin***

Clindamycin was not mutagenic or clastogenic in standard *in vitro* genotoxicity studies. Clindamycin (at the limit dose of 5000 µg/mL) did not induce structural or numerical

chromosome aberrations in human peripheral blood lymphocytes in non-activated and liver S9-activated test systems.

### ***Tretinoin***

Tretinoin was not mutagenic or clastogenic in standard *in vitro* and/or *in vivo* genotoxicity studies. Tretinoin (at the high dose of 200 µg/ml) did not induce structural or numerical chromosome aberrations in human peripheral blood lymphocytes in non-activated and liver S9-activated test systems. Tretinoin (at the limit dose of 5000 µg/plate) was non-mutagenic in the bacterial reversion test (Ames assay). Tretinoin (at the limit dose of 2000 mg/kg) was non-mutagenic and non-clastogenic in an *in vivo* rat micronucleus test.

## **Dermal Carcinogenicity**

### ***Clindamycin***

Clindamycin was not carcinogenic in mice over a lifetime of dermal application. The dermal carcinogenicity of clindamycin in a 1.2% clindamycin phosphate topical gel similar to BIACNA™ Topical Gel was evaluated by daily topical application to CD-1 mice for two years. The dermal clindamycin phosphate doses assessed were the human equivalent of 13 and 72 times the recommended therapeutic acne dose of BIACNA™ Topical Gel (1g drug product per 60kg person), assuming complete absorption and based on body surface area comparisons between species.

### ***Tretinoin***

Tretinoin was not carcinogenic in mice over a lifetime of dermal application. The dermal carcinogenicity of tretinoin in a topical gel of higher strength (0.1%) than BIACNA™ Topical Gel was evaluated by three times per week topical application to CD-1 mice for two years. The tretinoin dose assessed was the human equivalent of 29- times the recommended therapeutic acne dose of BIACNA™ Topical Gel (1g drug product per 60kg person), assuming complete absorption and based on body surface area comparisons between species.

## **Systemic Carcinogenicity**

### ***Clindamycin***

Clindamycin was not carcinogenic in rats over a lifetime of oral administration. The oral carcinogenicity of clindamycin was evaluated by daily oral gavage of Sprague-Dawley rats with a 1% clindamycin phosphate gel for two years. The oral clindamycin phosphate doses assessed were the human equivalent of 9 and 29 times the recommended therapeutic acne dose of BIACNA™ Topical Gel, assuming complete absorption and based on body surface area comparisons between species.

### ***Tretinoin***

Tretinoin has not been assessed for systemic carcinogenicity.

## **Photocarcinogenicity**

Photocarcinogenicity of the BIACNA™ Topical Gel formulation has not been assessed. Photocarcinogenicity of a 1% clindamycin phosphate topical gel similar to BIACNA™ Topical Gel and of tretinoin topical gels have been assessed in animals separately.

### ***Clindamycin***

Evidence for enhancement of photocarcinogenesis by topical clindamycin phosphate is equivocal. Photocarcinogenicity of clindamycin in a 1.2% clindamycin phosphate topical gel similar to BIACNA™ Topical Gel was evaluated by 5 days per week UVR irradiation with or without topical application of the gel to SKH1(hr/hr)BR hairless albino mice for 40 weeks and observation for 52 weeks. Clindamycin did not decrease time to tumor formation relative to vehicle control. Clindamycin phosphate formulated as a 1.2% gel with 0.5% benzoyl peroxide (BPO) decreased time to tumor formation relative to vehicle control and 0.5% BPO gel, suggesting clindamycin may contribute to phototoxicity of the combination formulation. Clindamycin was assessed at the human equivalent dose of 43-times the recommended therapeutic acne dose of BIACNA™ Topical Gel (1g drug product per 60kg person), assuming complete absorption and based on body surface area comparisons between species.

### ***Tretinoin***

Topical tretinoin enhances photocarcinogenicity in hairless mice. Photocarcinogenicity of tretinoin gels were evaluated by UVR irradiation with daily topical application to SKH1 hairless albino mice for 28 weeks and observation for 55 weeks. Median time to tumor onset reduced and the abundance of tumors increased with exposure to UV radiation and topical tretinoin (0.001% and 0.01%) at doses the human equivalent of 0.2 and 2 times the recommended therapeutic acne dose of BIACNA™ Topical Gel (1g drug product per 60kg person), assuming complete absorption and based on body surface area comparisons between species. A no-observed-adverse-effect level (NOAEL) for tretinoin photo-carcinogenicity is undefined.

## **Reproductive and Developmental Toxicity**

BIACNA™ Topical Gel did not elicit any effects on fertility or embryofetal development in a topical study of fertility and embryofetal toxicity in rabbits. BIACNA™ Topical Gel was administered topically to New Zealand White Rabbits from two weeks prior to artificial insemination and until gestation day 18 at doses the human equivalent of 1.2, 3.5 and 12 times the recommended therapeutic acne dose of BIACNA™ Topical Gel (1g drug product per 60kg person), assuming complete absorption and based on body surface area comparisons between species. No adverse maternal or developmental toxicity was observed.

### ***Clindamycin***

Systemically administered clindamycin does not affect fertility, mating ability, embryonic development, or post-natal development. Oral clindamycin was not teratogenic in rat or mouse at doses the human equivalent of over 575 and 48 times the acne therapeutic dose of BIACNA™ Topical Gel (1g drug product per 60kg person), respectively, assuming complete absorption and based on body surface area comparisons between species. Subcutaneous clindamycin was not teratogenic in rats at doses the human equivalent of over 170 times the acne therapeutic dose of

BIACNA™ Topical Gel, assuming complete absorption and based on body surface area comparisons between species.

### ***Tretinoin***

Systemically administered tretinoin is well known to be a teratogen and to severely affect fertility and peri-postnatal development. Oral administration of tretinoin during embryonic development has produced adverse developmental anomalies, fetal death and behavioral impairment in a variety of animal models in a manner dependent on the dose, the level of maternal systemic exposure, the developmental stage of organogenesis, and the localization of tretinoin within the embryo. Additionally, tretinoin produces severe effects on fertility, labour, parturition, lactation, neonatal activity and viability, offspring growth and post natal development. The lowest developmental no-observed-adverse-effect-level (NOAEL) described in the literature for tretinoin is 1 mg/kg/day, based on oral administration to rat. This dose is the human equivalent dose of 0.15 mg/kg/day and is 37-fold greater than the maximum recommended acne therapeutic dose, based on body surface area comparisons between species. The systemic exposure to tretinoin is much lower following topical administration than oral administration. In nine of ten topical teratology studies conducted in rats and rabbits, various formulations of tretinoin did not elicit teratogenicity. In one of ten, topical tretinoin produced treatment-related fetal effects including delayed ossification of bones and an increase in supernumerary ribs at dermal doses the human equivalent of 40-times the acne therapeutic dose of BIACNA™ Topical Gel, assuming complete absorption and based on body surface area comparisons between species.

With widespread use of any drug, a small number of birth defect reports associated temporally with administration of the drug are expected by chance alone. Thirty cases of temporally associated congenital malformations have been reported during two decades of clinical use of a different topical tretinoin formulation. Although no definite pattern of teratogenicity and no causal association have been established from these cases, 5 of the reports describe the rare birth defect category, holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to the fetus is not known.

Summaries of toxicology studies conducted in support of BIACNA™ Topical Gel are presented in Table 5.



**Table 5: Summary of Toxicology Studies**

Study Type	Species (strain) sex/group size	Route	Test Article	Dosage and Regimen	Results
<b>Acute Toxicity Study</b>					
Acute Oral Toxicity	Rats (Sprague-Dawley) Total: 12 5M+5F for test article 1M+1F for control	Oral (gavage)	BIACNA™ Topical Gel	5000 mg/kg of body weight. Single dose; fourteen subsequent days of observation.	There were no signs of toxicity observed in animals treated with the test or control article during the duration of the test. The test article did not cause mortality or gross signs of toxicity. LD <sub>50</sub> > 5000 mg/kg.
<b>Repeat-dose Dermal Toxicity Study</b>					
3-month repeat-dose dermal toxicity with 1-month recovery	Minipig (Hanford) Total: 72 6/group/sex	Dermal	BIACNA™ Topical Gel	25, 75 and 125 mg formulation/kg/day; 90 days dosing with subsequent 30 days of observation.	No signs of systemic toxicity at any dosage levels. No histopathological changes. Local irritation in all treatment groups with a slightly higher incidence of erythema observed in the 125 mg formulation/kg/day groups. NOAEL ≥125 mg formulation/kg/day for systemic toxicity and 75 mg formulation/kg/day for local tolerance.
<b>Genotoxicity of Clindamycin Phosphate</b>					
Mammalian chromosome aberration test	Human peripheral blood lymphocytes	<i>In vitro</i>	clindamycin phosphate	1250-5000 µg/mL	Clindamycin phosphate did not induce structural and numerical chromosome aberrations in HPBL cells in both the non-activated and the rat liver S9-activated test systems.

**Table 5: Summary of Toxicology Studies (continued)**

Study Type	Species (strain) sex/group size	Route	Test Article	Dosage and Regimen	Results
<b>Genotoxicity of Tretinoin</b>					
Ames test	Bacteria ( <i>Salmonella typhimurium</i> TA1535, TA 1537, TA98, TA100; <i>Escherichia coli</i> WP2 uvrA)	<i>In vitro</i>	tretinoin USP	1.5-5000 µg/plate	No substantial increases in revertant colony numbers were obtained at any dose level in either the presence or absence of S9 mix..
Chromosome Aberration Test	Human peripheral blood lymphocytes	<i>In vitro</i>	tretinoin USP	0.4-200 µg/mL	Tretinoin USP did not cause any statistically significant increases in the proportion of aberrant metaphases at any experimental point. No substantial increases in the incidence of chromatid or chromosome gaps or polyploidy were observed.
Micronucleus Test	Sprague Dawley (Hsd: SD)	Subcutaneous injection	tretinoin USP	500-2000 mg/kg	Rats treated with Tretinoin USP did not show any statistically significant changes in the proportion or in the numbers of micronucleated immature or mature erythrocytes.

**Table 5: Summary of Toxicology Studies (continued)**

Study Type	Species (strain) sex/group size	Route	Test Article	Dosage and Regimen	Results
<b>Carcinogenicity of Clindamycin</b>					
Dermal Carcinogenicity	Mice (CD:1); 60/group/sex	Topical	clindamycin 1% Gel	Once daily application of 2.7 and 15 mL/kg/day; 104 weeks observation	There were no noticeable neoplastic findings in either sex which could be attributed to the application of Clindamycin 1% Gel.
Oral Carcinogenicity	Rat (Sprague Dawley); 60/group/sex	Oral	clindamycin 1% Gel	9 and 30 mg/kg/ day once daily; 104 weeks observation	There were no noticeable neoplastic findings in either sex which could be attributed to the administration of Clindamycin 1% Gel.
<b>Photocarcinogenicity of Clindamycin</b>					
Phototoxicity and Photocarcino- genicity	Mice (Albino Hairless); 3M&3F/group	Topical	clindamycin 1% Gel	Once daily application 5 days per week for 40 weeks at 0.2 mL per mouse; 52 weeks observation	Clindamycin 1% Gel did not decrease time to tumor formation relative to vehicle control. Clindamycin 1%/ benzoyl peroxide (BPO) 0.5% Gel decreased time to tumor formation relative to vehicle control and BPO 0.5% Gel, suggesting clindamycin may contribute to phototoxicity of the combination formulation. The photocarcinogenicity of clindamycin was equivocal.
<b>Reproductive and Developmental Toxicity Study</b>					
Fertility and Developmental Toxicity Study	Rabbit (New Zealand White); Total: 120 20F/group	Dermal	BIACNA™ Topical Gel; 60, 180, 600 mg/kg/day	Dosing 14 days prior to insemination through gestation day 18 (total of 45 days).	No fetal or maternal toxicity observed; No signs of skeletal or visceral malformations. NOAEL ≥ 600 mg formulation/kg/day.

## REFERENCES

Lanigan RS, Yamarik TA. Final Report on the Safety Assessment of BHT(1). *Int J Toxicol* 2002; 21 Suppl 2:19-94.

Schlessinger J, Menter A, Gold M, Leonardi C, Eichenfield L, Plott RT, Leyden J, Wortzman M; Ziana Study Group. Clinical safety and efficacy studies of a novel formulation combining 1.2% clindamycin phosphate and 0.025% tretinoin for the treatment of acne vulgaris. *J Drugs Dermatol*. 2007 June;6(6):607 – 615.

**IMPORTANT: PLEASE READ****PART III: CONSUMER INFORMATION**

**Pr BIAcNA™ Topical Gel**  
**(clindamycin phosphate and tretinoin)**  
 1.2% w/w and 0.025% w/w

**Acne Therapy**

**This leaflet is part III of a three-part “Product Monograph” published when BIAcNA™ Topical Gel was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about BIAcNA™ Topical Gel. Contact your doctor or pharmacist if you have any questions about the drug.**

**ABOUT THIS MEDICATION****What the medication is used for:**

BIAcNA™ Topical Gel is an antibiotic and a retinoid (related to Vitamin A) combination medicine used for the topical treatment of facial acne in patients 12 years and older.

**What it does:**

Clindamycin helps prevent bacterial protein synthesis thereby limiting the growth of bacteria associated with acne..

Tretinoin is thought to normalize the growth of skin cells (keratinocytes) and to cause normal shedding of the cells (corneocytes) that clog the follicles in acne lesions, thereby preventing the build-up of sebum and the formation of microcomedones.

**When it should not be used:**

Do not use BIAcNA™ Topical Gel if:

- You have or have had regional enteritis (Crohn’s disease), ulcerative colitis, or antibiotic-associated colitis
- You are allergic to clindamycin, lincomycin, tretinoin or to any ingredient of this medication (See “What the nonmedicinal ingredients are”)

**What the medicinal ingredients are:**

Clindamycin phosphate 1.2% w/w and tretinoin 0.025% w/w

**What the nonmedicinal ingredients are:**

Butylated hydroxytoluene NF, carbomer 981 NF, citric acid USP, edetate disodium USP, glycerin USP, methylparaben NF, polysorbate 80 NF, propylparaben NF, purified water USP, and tromethamine USP.

**What dosage forms it comes in:**

BIAcNA™ is a gel for topical application available in a 2 gram sample tube, a 30 gram tube, and a 60 gram tube.

**WARNINGS AND PRECAUTIONS**

**This product is available only by prescription and should be used only according to your doctor’s instructions**

Safety and effectiveness in children below the age of 12 have not been established.

BIAcNA™ Topical Gel should not be applied to other areas of the body or to other growths or lesions, as the safety and effectiveness of this product have not been evaluated in other disorders.

**Caution in the sun.** Therapy with BIAcNA™ Topical Gel may make your skin more susceptible to sunburn and other adverse effects of the sun, so unprotected exposure to natural or artificial light (such as a sunlamp) should be minimized. When outside, even on hazy days, areas treated with BIAcNA™ Topical Gel should be protected. An effective sunscreen should be used any time you are outside (consult your physician for a recommendation of an SPF level which will provide you with the necessary high level of protection). Use other protective clothing such as a hat when you are in the sun. If your face becomes sunburnt, stop medication until your skin has healed.

**Avoid excessive exposure to wind or cold.** Extremes of climate tend to dry or burn normal skin. Skin treated with BIAcNA™ Topical Gel may be more vulnerable to these extremes. Your physician can recommend ways to manage your acne treatment under such conditions.

**Use other medication only on your physician's advice.** You should avoid preparations that may dry or irritate your skin. These preparations may include certain astringents, toiletries containing alcohol, spices or lime, or certain medicated soaps, shampoos, and hair permanent solutions. Do not allow anyone else to use this medication.

**Pregnancy**

If you are pregnant, think you are pregnant, or of child-bearing age, do not use this medication until you check with your doctor. Birth defects have been reported among babies born to women exposed to topical tretinoin, although no well-controlled and adequate prospective studies of the use of topical tretinoin in pregnant women have been conducted to determine whether there is harm to the fetus or harm to the reproductive capacity of women. Talk to your doctor before using this medication.

**Nursing**

**It is not known whether clindamycin or tretinoin is excreted in human breastmilk. Discuss with your doctor.**

**BEFORE you use BIAcNA™ Topical Gel talk to your doctor or pharmacist if:**

- **You are using sunlamps or tanning booths.**
- **You have Crohn’s disease, ulcerative colitis.**
- **You have developed colitis with past antibiotic use.**
- **You are pregnant or planning to become pregnant. It is not known if BIAcNA™ Topical Gel may harm your unborn baby.**
- **You are breastfeeding. BIAcNA™ Topical Gel may pass through your milk and may harm your baby.**
- **You are taking other medicines, including drugs you can buy without a prescription.**
- **You are allergic to clindamycin, lincomycin or tretinoin, or any ingredients in the formulation or components of the container (See “What the nonmedicinal ingredients are” section).**

**AND WHILE YOU'RE ON BIAcNA™ Topical Gel THERAPY**

Use a gentle cleanser. Avoid frequent washings and harsh scrubbing. Acne is not caused by dirt, so no matter how hard you scrub, you can't wash it away. Washing too frequently (more than 2-3 times per day) or scrubbing too roughly may at times actually make your acne worse. Wash your skin gently and pat skin dry with a towel.

Avoid medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect, and skin products that contain alcohol, astringents, spices or lime. These products may cause increased skin irritation if used with BIAACNA™ Topical Gel.

## INTERACTIONS WITH THIS MEDICATION

BIAACNA™ Topical Gel should not be used with Erythromycin containing products.

Tell your doctor if you are using any other medications, such as neuromuscular blocking agents and any other topical medicine including those available without a prescription as they may interfere with each other.

## PROPER USE OF THIS MEDICATION

### Usual dose:

Adults and children 12 years and older: At bedtime, wash your face gently with mild soap and warm water and pat skin dry with a towel. Squeeze a pea-size amount of medication onto the fingertip. Cover the affected area lightly with BIAACNA™ Topical Gel by first dabbing it on your forehead, chin, and both cheeks, then spreading it evenly over your whole face. Smooth gently into the skin.

To help you use the medication correctly, keep these simple instructions in mind. Apply BIAACNA™ Topical Gel once daily before bedtime. Do not use more than a pea-size amount of BIAACNA™ Topical Gel as suggested by your physician or apply the product more frequently than instructed. Too much medication may irritate the skin, waste medication and will not give faster or better results.

Keep the medication away from the corners of the nose, mouth, eyes, and open wounds. Spread it away from these areas when applying. In case of accidental contact with these sensitive areas, rinse with plenty of lukewarm water.

Stop treatment and contact your doctor if symptoms persist for more than 12 weeks.

Do not wash your face more than 2-3 times a day. Washing your face too often or scrubbing may make your acne worse.

To get the best results with BIAACNA™ Topical Gel therapy, it is necessary to use it properly. AGAIN, FOLLOW INSTRUCTIONS - BE PATIENT - DON'T START AND STOP THERAPY ON YOUR OWN - IF YOU HAVE QUESTIONS, ASK YOUR DOCTOR.

### Overdose:

If medication is applied excessively, no more rapid or better results will be obtained and marked redness, peeling, or discomfort may occur. Oral ingestion of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.

Topically applied BIAACNA™ Topical Gel can be absorbed in sufficient amounts to produce systemic effects. [See “**WARNINGS AND PRECAUTIONS**”]

If you have taken too much BIAACNA™ Topical Gel, particularly by accidental oral ingestion, contact your doctor, hospital emergency department or your regional Poison Control Centre, even if there are no symptoms.

### Missed Dose:

If you forget to use BIAACNA™ Topical Gel at bedtime, you should wait for the next dose at the usual time. You should not double the dose to make up the forgotten dose.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

You may experience common side effects such as headache, sunburn, and upper respiratory tract infections..

You may develop a temporary skin colour change (lighter or darker) due to BIAACNA™ Topical Gel.

Stop use and immediately contact your doctor if:

- You develop skin irritation due to dryness, redness, peeling, burning or stinging from BIAACNA™ Topical Gel and your skin becomes very red, swollen, blistered or crusted.
- You develop serious side effects such as diarrhea, bloody diarrhea, and colitis (inflamed colon), which have been reported with the use of topical clindamycin.

## HOW TO STORE IT

- Store at controlled room temperature 25°C (77°F); excursions permitted to between 15–30°C.
- Protect from light.
- Protect from freezing.
- Keep the tube tightly closed
- Keep out of the reach of children.

### **General Information about BIAACNA™ Topical Gel**

Do not use BIAACNA™ Topical Gel for a condition for which it was not prescribed. Do not give BIAACNA™ Topical Gel to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about BIAACNA™ Topical Gel. If you would like more information, talk with your doctor. You can also ask your pharmacist or doctor for information about BIAACNA™ Topical Gel that is written for healthcare professionals.

**REPORTING SUSPECTED SIDE EFFECTS**

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)
  - Call toll-free at 1-866-234-2345
  - Complete a Canada Vigilance Reporting Form and:
    - Fax toll-free to 1-866-678-6789, or
    - Mail to: Canada Vigilance Program  
Health Canada  
Postal Locator 0701D  
Ottawa, Ontario  
K1A 0K9
- Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

***NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide Medical advice.***

**MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals can be found at:  
<http://www.website.document>  
or by contacting the sponsor, Valeant Canada limitée/Limited at:

1-800-361-4261

This leaflet was prepared by Valeant Canada limitée/Limited

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