PRODUCT MONOGRAPH

PrBIACNA®
Clindamycin Phosphate and Tretinoin Gel
1.2% w/w and 0.025% w/w

Acne Therapy

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Topical	Gel / Clindamycin 1% w/w (provided as Clindamycin Phosphate 1.2%) and Tretinoin 0.025% w/w	Butylated Hydroxy Toluene, Citric Acid, Disodium Edetate, Polysorbate 80, Methylparaben, Propylparaben, Trometamol, Carbomer, Glycerine and Water.

INDICATIONS AND CLINICAL USE

BIACNA (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 is not indicated for the treatment of pustular and deep cystic nodular acne varieties (acne conglobata and acne fulminans).

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

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

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

CONTRAINDICATIONS

BIACNA (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 BIACNA 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 BIACNA (clindamycin phosphate 1.2% w/w and tretinoin 0.025% w/w) come in contact with eyes and mucous membranes. BIACNA 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 BIACNA should be discontinued and alternative therapy should be initiated.

Carcinogenesis and Mutagenesis

Carcinogenicity and mutagenicity of BIACNA have not been assessed. Carcinogenicity and genotoxicity of each of the active ingredients in BIACNA , 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 BIACNA . 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 BIACNA . 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 BIACNA . *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 BIACNA 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 BIACNA should be avoided. BIACNA 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 BIACNA · (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 BIACNA , its usage should be discontinued, the Gel carefully wiped off, and appropriate alternative acne therapy should be instituted. BIACNA 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 . 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 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 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 should be given to woman of childbearing years only after contraceptive counseling. BIACNA 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 . Topically administered BIACNA 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 BIACNA therapy to the mother.

It is not known whether clindamycin or tretinoin is excreted in human milk following topical use of BIACNA . 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 BIACNA is administered to a nursing woman.

Susceptibility/Resistance

Development of Drug-Resistant Bacteria
Prescribing BIACNA in the absence of the authorized indications is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

Potential for Microbial Overgrowth
Prolonged use of BIACNA 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 BIACNA should be discontinued and alternative therapy should be initiated.

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Overall, the frequency of investigator-determined drug-related adverse reactions that occurred with BIACNA (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 BIACNA 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 BIACNA 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 (≥1%) reported in these studies is shown in Table 1.

Table 1: Drug-Related Adverse Reactions Reported by ≥ 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 (%)
Skin and subcutaneous tissue disorders				
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 (≥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 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 with other topical products which have a drying effect. BIACNA 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 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 , 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 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 should be squeezed onto one fingertip, dot onto the chin; cheeks, nose, and forehead, then gently rub over the entire face once daily. BIACNA should be kept away from the eyes, the mouth, angles of the nose, and mucous membranes.

BIACNA is not for oral, ophthalmic, or intravaginal use.

Missed Dose

In case of a missed dose of BIACNA 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 (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 can be absorbed in sufficient amounts to cause systemic gastrointestinal side effects including abdominal pain, nausea, vomiting and diarrhea. In the case of overdosage BIACNA 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 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 , 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 or clindamycin.

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 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 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 , 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 to13.1 ng/mL (see PART II: DETAILED PHARMACOLOGY).

STORAGE AND STABILITY

Conserver entre 15 et 30 °C. The shelf life of BIACNA is 24 months.

SPECIAL HANDLING INSTRUCTIONS

- Protect from light.
- Keep out of the reach and sight of children.
- Keep the tube tightly closed.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each gram of BIACNA 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 also contains the following nonmedicinal ingredients: Butylated Hydroxy Toluene, Citric Acid, Disodium Edetate, Polysorbate 80, Methylparaben, Propylparaben, Trometamol, Carbomer, Glycerine and Water.

BIACNA is supplied as follows:

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

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance 1 – clindamycin phosphate

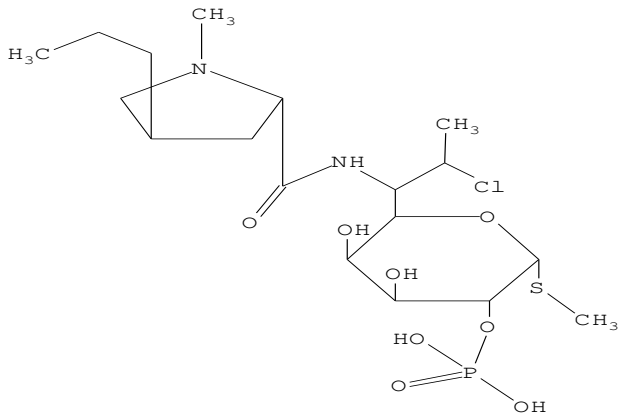
Proper name: clindamycin phosphate

Chemical name: Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-*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

Solubility: 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

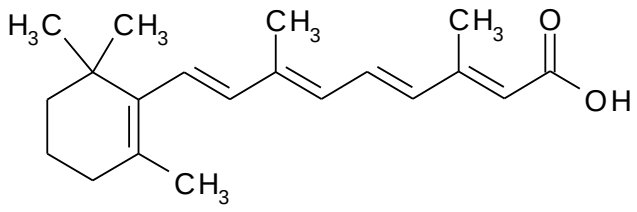
Proper name: Tretinoin

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 g/mol

Structural formula:



Physicochemical Properties

Description: Tretinoin is a yellow to light-orange, crystalline powder. Chemically, tretinoin is related to Vitamin A.

Solubility: It is insoluble in water, slightly soluble in alcohol and in chloroform.

CLINICAL TRIALS

The safety and efficacy of once daily use BIACNA 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 BIACNA to clindamycin in the vehicle gel, tretinoin in the vehicle gel, and the vehicle gel alone. Study 3 compared BIACNA 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 BIACNA is as follows:

Grade	**Description**
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 (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 (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 (clindamycin phosphate 1.2% w/w, tretinoin 0.025% w/w) clindamycin phosphate gel 1.2% w/w Topical: Once daily in the evening 12 weeks	1008 1002	19.1 (12 – 84) 19 (12 – 53)	51/49 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 845 Clindamycin 426 Tretinoin 846 Vehicle 423	48% 42%, 0.016 39%, <0.001 26%, <0.001	36% 27%, <0.001 31%, 0.007 16%, <0.001	41% 34%, <0.001 34%, <0.001 20%, <0.001	180 (21%) 70 (16%), 0.034 122 (14%), <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 1008 Clindamycin 1002	61% 55%, <0.001	50% 41%, <0.001	55% 47%, <0.001	381 (38%) 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 has potential to cause moderate skin irritation and low potential to cause allergic contact dermatitis, phototoxic reactions and photoallergic reactions. BIACNA contains 0.02% butylated hydroxytoluene (BHT). In clinical studies BHT at 2% strength (i.e. 10-times the strength in BIACNA) was a moderate sensitizer in a small number of patients.

Animal Pharmacodynamics

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

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

BIACNA has the potential to elicit skin irritation. BIACNA was mildly irritating to the skin of New Zealand White rabbits when applied under occlusion for 24h. Additionally, BIACNA

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 (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 , 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 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 , clindamycin, and tretinoin support the safety of BIACNA .

Acute Toxicity

The acute lethal oral dose of BIACNA 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 (1g drug product per 60kg person), assuming complete absorption and based on body surface area comparisons between species.

Repeat-dose Dermal Toxicity

BIACNA 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 (1g drug product per 60kg person), assuming complete absorption and based on body surface area comparisons between species.

Repeat-dose Systemic Toxicity

BIACNA 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 (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 (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 formulation have not been assessed. Genotoxicity and mutagenicity of the active ingredients in BIACNA , clindamycin phosphate and tretinoin, have been assessed separately. Dermal carcinogenicity of a 1.2% clindamycin phosphate topical gel similar to BIACNA and of tretinoin topical gel of higher strength than BIACNA 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 mcg/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 mcg/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 mcg/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 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 (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 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 (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 , 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 formulation has not been assessed. Photocarcinogenicity of a 1% clindamycin phosphate topical gel similar to BIACNA 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 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 (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 (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 did not elicit any effects on fertility or embryofetal development in a topical study of fertility and embryofetal toxicity in rabbits. BIACNA 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 (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 (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 , 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 , 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 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
Acute Toxicity Study					
Acute Oral Toxicity	Rats (Sprague-Dawley) Total: 12 5M+5F for test article 1M+1F for control	Oral (gavage)	BIACNA	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_{50} > 5000 mg/kg.
Repeat-dose Dermal Toxicity Study					
3-month repeat-dose dermal toxicity with 1-month recovery	Minipig (Hanford) Total: 72 6/group/sex	Dermal	BIACNA	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.
Genotoxicity of Clindamycin Phosphate					
Mammalian chromosome aberration test	Human peripheral blood lymphocytes	*In vitro*	clindamycin phosphate	1250-5000 mcg/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
Genotoxicity of Tretinoin					
Ames test	Bacteria (*Salmonella typhimurium* TA1535, TA 1537, TA98, TA100; *Escherichia coli* WP2 uvrA)	*In vitro*	tretinoin USP	1.5-5000 mcg/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	*In vitro*	tretinoin USP	0.4-200 mcg/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
Carcinogenicity of Clindamycin					
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.
Photocarcinogenicity of Clindamycin					
Phototoxicity and Photocarcinogenicity	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.
Reproductive and Developmental Toxicity Study					
Fertility and Developmental Toxicity Study	Rabbit (New Zealand White); Total: 120 20F/group	Dermal	BIACNA ; 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.

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PART III: CONSUMER INFORMATION

PrBIACNA®
Clindamycin phosphate and tretinoin gel
1.2% w/w and 0.025% w/w

This leaflet is part III of a three-part "Product Monograph" published when BIACNA 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 . Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
BIACNA 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.

BIACNA contains an antibacterial ingredient called clindamycin, and it should be used exactly as directed by your healthcare professional. Misuse or overuse of BIACNA could lead to the growth of bacteria that will not be killed by clindamycin. This means that BIACNA or other medicines that contain clindamycin may not work for you in the future. Do not share your medicine.

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 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 Hydroxy Toluene, Citric Acid, Disodium Edetate, Polysorbate 80, Methylparaben, Propylparaben, Trometamol, Carbomer, Glycerine and Water.

What dosage forms it comes in:
BIACNA is a gel for topical application available in a 2-gram sample 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 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 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 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 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 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 may harm your unborn baby.
- **You are breastfeeding.** BIACNA 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 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 BIACNA .

INTERACTIONS WITH THIS MEDICATION

BIACNA 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 BIACNA 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 BIACNA once daily before bedtime. Do not use more than a pea-size amount of BIACNA 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 BIACNA 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 BIACNA can be absorbed in sufficient amounts to produce systemic effects (see "**WARNINGS AND PRECAUTIONS**"]

If you have taken too much BIACNA , 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 BIACNA 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 BIACNA .
Stop use and immediately contact your doctor if:

- You develop skin irritation due to dryness, redness, peeling, burning or stinging from BIACNA 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 15–30°C.
- Protect from light.
- Keep the tube tightly closed
- Keep out of reach and sight of children.

General Information about BIACNA
Do not use BIACNA for a condition for which it was not prescribed. Do not give BIACNA to other people, even if they have the same symptoms you have. It may harm them.

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

Reporting Side Effects

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

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

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

MORE INFORMATION

If you want more information about Biacna:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); by contacting the sponsor: Bausch Health, Canada Inc., 2150 St-Elzéar Blvd. West, Laval, (Quebec) H7L 4A8; or by calling 1-800-361-4261.

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