TOPICAL RETINOID AND COMBINATION PRODUCTS:
ATRALIN® (tretinoin) gel
AVITA® (tretinoin) cream and gel
DIFFERIN® (adapalene) cream, gel, lotion (Over-the-Counter Differin is a plan exclusion)
EPIDUO® (adapalene-benzoyl peroxide) gel
EPIDUO FORTE® (adapalene-benzoyl peroxide) gel
RETIN-A® (tretinoin) cream and gel
RETIN-A MICRO® (tretinoin) microsphere gel
TRETIN-X® (tretinoin) cream
VELTIN® (clindamycin phosphate and tretinoin) gel
ZIANA® (clindamycin phosphate and tretinoin) gel

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as “Description” defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as “Criteria” defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms “experimental” and “investigational” are considered to be interchangeable.

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Description:

Acne vulgaris is a chronic inflammatory dermatologic condition notable for open and/or closed comedones (blackheads and whiteheads) and inflammatory lesions that includes papules, pustules, or nodules. The prevalent bacterium implicated in acne is Propionibacterium acnes (P. acnes), a gram-positive anaerobe that is normally found on the skin and is implicated in the inflammatory phase of acne. P. acnes promotes lesions by secreting chemotactic factors that attract leukocytes to the follicle resulting in inflammation.

All anti-acne agents are effective in reducing inflammatory and non-inflammatory lesions when compared to placebo based on many years of clinical experience, multiple systematic reviews, and clinical practice guidelines. There is no evidence that confirms superiority of any one branded option over available brand or generic alternatives, including available over-the-counter (OTC) products. All anti-acne products have adequate track records of safety; most are generally well tolerated, but all cause skin irritation.

The American Academy of Dermatology has published guidelines for the care of acne vulgaris. The guidelines indicate that topical therapy is a standard of care in treatment and that topical retinoids and topical antibiotics are effective treatments. The effectiveness of topical retinoids in the treatment of acne is well documented. These agents act to reduce obstruction within the follicle and are useful in the management of both comedonal and inflammatory acne. The value of topical antibiotics in the treatment of acne has been investigated in many clinical trials. Topical erythromycin and clindamycin have been demonstrated to be effective and well tolerated. Monotherapy with topical antibiotics is not recommended due to the slow onset of action and likely emergence of antibiotic-resistant bacteria. Benzoyl peroxide may minimize the development of antibiotic resistance with P. acnes when used with topical or systemic antibiotics and these combinations are more effective than when the antibiotics are used alone. A combination of topical retinoids and topical erythromycin or clindamycin is more effective than either agent used alone.

Both Veltin® and Ziana® are topical acne products with 1.2% clindamycin phosphate and 0.025% tretinoin in an aqueous based gel. Each gram contains, as dispensed, 10mg (1%) clindamycin phosphate and 0.25mg (0.025%) tretinoin. Clindamycin phosphate and tretinoin are also available separately as topical preparations for the treatment of acne.

Definitions:

Drug related events:
Ineffective / failure
Use of a drug employing optimal doses (FDA-recommended doses) for optimal duration; where the condition being treated has not improved or worsened

A request for branded agent due to generic drug failure or ineffectiveness will be assessed for potential approval with documentation of use of optimal dose / duration of the generic product and meeting other criteria within the coverage guideline. When the drug in question is a combination product, there must be documentation of failure / ineffectiveness of concurrent use (each ingredient used at the same time) of individual generic components. When the drug in question is a low dose formulation, there must be documentation of failure / ineffectiveness of low dose generic formulation.
Adverse Drug Event: Allergic reaction / Hypersensitivity / Intolerance
Use of a drug produced a significant reaction where continued use of the drug places the individual at risk for either lack of improvement or worsening of the condition being treated or at risk for harm and the concern is documented in medical record. A significant adverse drug event is when an individual's outcome is death, life-threatening, hospitalization (initial or prolonged), disability resulting in a significant, persistent, or permanent change, impairment, damage or disruption in the individuals' body function/structure, physical activities or quality of life, or requires intervention to prevent permanent impairment or damage.

Allergic reaction / hypersensitivity – may or may not involve the active ingredient. When the active ingredient is involved, use of same or a chemically similar agent places the individual at risk for harm when the same or chemically similar agent is used. The subsequent reaction may be the same as the original reaction or a more exaggerated response may be seen, potentially placing the individual at even greater risk for harm.

If the reaction occurred from the active/main generic ingredient; request for branded agent with same active ingredient will not be considered unless it is proven (documented) that active ingredient did not cause reaction and the request meets other criteria within the coverage guideline

Intolerance – these events represent circumstance(s) where use of a drug produced a significant reaction and continued use may result in non-adherence to proposed therapy and this concern is documented in medical record

Contraindication
Use of a drug that is not recommended by the manufacturer or FDA labelling

Use of any drug in the face of a contraindication is outside of the FDA and manufacturer's labelled recommendation and is considered investigational or experimental

Non-adherence
Individual does not follow prescribe regimen that places the individual at risk for lack of improvement or worsening of the condition being treated and this concern is documented in medical record

Precertification:

Precertification (Prior Authorization) is required for members with a Blue Cross Blue Shield of Arizona (BCBSAZ) pharmacy benefit for medication(s) or product(s) indicated in this guideline.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at [www.azblue.com/pharmacy](http://www.azblue.com/pharmacy).

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.
TOPICAL RETINOID AND COMBINATION PRODUCTS (cont.)

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Criteria:
Differin (adapalene) cream, gel, and lotion

See “Resources” section for FDA-approved dosage.

- Precertification for Differin (adapalene) requires completion of the specific request form in its entirety. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. Incomplete forms will be returned.

- **Initial therapy:** FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Differin (adapalene) is considered medically necessary when ALL of the following criteria are met:
  1. Individual is 12 years of age or older
  2. Individual has medical record documentation of a confirmed diagnosis of acne vulgaris
  3. Individual is unable to use ALL of the covered generic topical adapalene product(s) due to either of the following:
     - Covered generic product(s) failed or was not effective in controlling the condition
     - Covered generic product(s) caused a significant intolerant reaction
  4. Absence of ALL of the following contraindications:
     - Hypersensitivity to adapalene or any of the components in the cream or gel vehicle

- **Continuation of coverage (renewal request):** Differin (adapalene) is considered medically necessary with documentation of ALL of the following:
  1. The individual has benefited from therapy but remains at high risk
  2. The condition has not progressed or worsened while on therapy
  3. Individual has not developed any contraindications or other exclusions to its continued use

- Differin (adapalene) for all other indications not previously listed is considered experimental or investigational based upon:
  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
5. Insufficient evidence to support improvement outside the investigational setting.

This includes but is not limited to the following:
- Use of any of these agents for cosmetic purpose, the contract benefit language will be applied to determine coverage
- Liver spots
- Melasma
- Photo-aged skin
- Wrinkles

Criteria:
Epiduo (adapalene-benzoyl peroxide) gel
Epiduo Forte (adapalene-benzoyl peroxide) gel

See “Resources” section for FDA-approved dosage.

- Precertification for Epiduo (adapalene-benzoyl peroxide) and Epiduo Forte (adapalene-benzoyl peroxide) requires completion of the specific request form in its entirety. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. Incomplete forms will be returned.

- Initial therapy: FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Epiduo (adapalene-benzoyl peroxide) and Epiduo Forte (adapalene-benzoyl peroxide) is considered medically necessary when ALL of the following criteria are met:

  1. Individual is 9 years of age or older for Epiduo
     Individual is 12 years of age or older for Epiduo Forte

  2. Individual has medical record documentation of a confirmed diagnosis of acne vulgaris

  3. The individual is unable to use the individual covered generic components of either Epiduo or Epiduo Forte simultaneously at the same time as demonstrated by either:
     - Simultaneous use of covered generic adapalene product and benzoyl peroxide failed or was not effective in controlling the condition
     - Simultaneous use of covered generic adapalene product and benzoyl peroxide caused a significant intolerant reaction
     - There is non-adherence with simultaneous use of individual components of covered generic adapalene product and benzoyl peroxide that is documented in medical records (documentation must be submitted)
TOPICAL RETINOID AND COMBINATION PRODUCTS (cont.)

- **Continuation of coverage (renewal request):** Epiduo (adapaline-benzoyl peroxide) and Epiduo Forte (adapaline-benzoyl peroxide) is considered *medically necessary* with documentation of ALL of the following:
  1. The individual has benefited from therapy but remains at high risk
  2. The condition has not progressed or worsened while on therapy
  3. Individual has not developed any contraindications or other exclusions to its continued use

- Epiduo (adapaline-benzoyl peroxide) and Epiduo Forte (adapaline-benzoyl peroxide) for all other indications not previously listed is considered *experimental or investigational* based upon:
  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

This includes but is not limited to the following:
- Use of any of these agents for cosmetic purpose, the contract benefit language will be applied to determine coverage
- Liver spots
- Melasma
- Photo-aged skin
- Wrinkles

**Criteria:**

Atralin (tretinoin) gel
Avita (tretinoin) cream and gel
Retin-A (tretinoin) cream and gel
Retin-A MICRO (tretinoin) microsphere gel
Tretin-X (tretinoin) cream

See “Resources” section for FDA-approved dosage.

- Precertification for Atralin (tretinoin), Avita (tretinoin), Retin-A (tretinoin), Retin-A Micro (tretinoin) and Tretin-X (tretinoin) requires completion of the specific request form in its entirety. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. Incomplete forms will be returned.
TOPICAL RETINOIDO AND COMBINATION PRODUCTS (cont.)

- **Initial therapy**: FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Atralin (tretinoin), Avita (tretinoin), Retin-A (tretinoin), Retin-A Micro (tretinoin) and Tretin-X (tretinoin) is considered *medically necessary* when ALL of the following criteria are met:

  1. Individual is 10 years of age or older for Atralin (tretinoin)
     Individual is 12 years of age or older for Avita (tretinoin), Retin-A (tretinoin), Retin-A Micro (tretinoin) and Tretin-X (tretinoin)
  2. Individual has medical record documentation of a confirmed diagnosis of acne vulgaris
  3. Individual is unable to use ALL of the covered generic topical tretinoin product(s) due to either of the following:
     - Covered generic product(s) failed or was not effective in controlling the condition
     - Covered generic product(s) caused a significant intolerant reaction
  4. Absence of ALL of the following contraindications:
     - Hypersensitivity to any of the ingredients

- **Continuation of coverage (renewal request)**: Atralin (tretinoin), Avita (tretinoin), Retin-A (tretinoin), Retin-A Micro (tretinoin) and Tretin-X (tretinoin) is considered *medically necessary* with documentation of ALL of the following:

  1. The individual has benefited from therapy but remains at high risk
  2. The condition has not progressed or worsened while on therapy
  3. Individual has not developed any contraindications or other exclusions to its continued use

- Atralin (tretinoin), Avita (tretinoin), Retin-A (tretinoin), Retin-A Micro (tretinoin) and Tretin-X (tretinoin) for all other indications not previously listed is considered *experimental or investigational* based upon:

  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

This includes but is not limited to the following:

- Use of any of these agents for cosmetic purpose, the contract benefit language will be applied to determine coverage
- Liver spots
- Melasma
- Photo-aged skin
- Wrinkles
Criteria:  
Veltin (clindamycin phosphate and tretinoin) gel  
Ziana (clindamycin phosphate and tretinoin) gel

See “Resources” section for FDA-approved dosage.

- Precertification for Veltin (clindamycin phosphate and tretinoin) and Ziana (clindamycin phosphate and tretinoin) requires completion of the specific request form in its entirety. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. Incomplete forms will be returned.

- **Initial therapy:** FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Veltin (clindamycin phosphate and tretinoin) and Ziana (clindamycin phosphate and tretinoin) is considered *medically necessary* when ALL of the following criteria are met:

  1. Individual is 12 years of age or older
  2. Individual has medical record documentation of a confirmed diagnosis of acne vulgaris
  3. The individual is unable to use the individual components of either Veltin (clindamycin phosphate and tretinoin) or Ziana (clindamycin phosphate and tretinoin) simultaneously at the same time as demonstrated by either:
     - Simultaneous use of covered generic clindamycin phosphate and covered generic tretinoin failed or was not effective in controlling the condition
     - Simultaneous use of covered generic clindamycin phosphate and covered generic tretinoin caused a significant intolerant reaction
     - There is non-adherence with simultaneous use of individual components of covered generic clindamycin phosphate and covered generic tretinoin that is documented in medical records (documentation must be submitted)
  4. Absence of **ALL** of the following contraindications:
     - Regional enteritis
     - Ulcerative colitis
     - History of antibiotic-associated colitis

- **Continuation of coverage (renewal request):** Veltin (clindamycin phosphate and tretinoin) and Ziana (clindamycin phosphate and tretinoin) is considered *medically necessary* with documentation of **ALL** of the following:

  1. The individual has benefited from therapy but remains at high risk
  2. The condition has not progressed or worsened while on therapy
  3. Individual has not developed any contraindications or other exclusions to its continued use
TOPICAL RETINOID AND COMBINATION PRODUCTS (cont.)

- Veltin (clindamycin phosphate and tretinoin) and Ziana (clindamycin phosphate and tretinoin) for all other indications not previously listed is considered experimental or investigational based upon:

  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

This includes but is not limited to the following:
- Use of any of these agents for cosmetic purpose, the contract benefit language will be applied to determine coverage
- Liver spots
- Melasma
- Photo-aged skin
- Wrinkles

Resources:


Epiduo. Package Insert. Revised by manufacturer 01/2013. Accessed 03/15/2016, 03-01-17

Epiduo Forte. Package Insert. Revised by manufacturer 07/2015. Accessed 03/15/2016, 03-01-17


TOPICAL RETINOID AND COMBINATION PRODUCTS (cont.)


Tretin-X. Package Insert. Revised by manufacturer 05/2013. Accessed 03/15/2016, 03-01-17


Ziana. Package Insert. Revised by manufacturer 03/2012. Accessed 03/15/2016, 03-01-17

FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ATRALIN</strong> Gel is a retinoid indicated for topical treatment of acne vulgaris.</td>
<td>Apply a thin layer of Atralin Gel once daily, before bedtime, to skin where lesions occur. Keep away from eyes, mouth, nasal creases, and mucous membranes. Atralin Gel is not for oral, ophthalmic, or intravaginal use.</td>
</tr>
<tr>
<td><strong>AVITA</strong> Cream and Gel is indicated for topical application in the treatment of acne vulgaris. The safety and efficacy of this product in the treatment of other disorders have not been established.</td>
<td>AVITA should be applied once a day, in the evening, to the skin where acne lesions appear, using enough to cover the entire affected area lightly. Application may cause a transient feeling of warmth or slight stinging. In cases where it has been necessary to temporarily discontinue therapy or reduce the frequency of application, therapy may be resumed or frequency of application increased when the patients become able to tolerate the treatment. Alterations of dose frequency should be closely monitored by careful observation of the clinical therapeutic response and skin tolerance. Efficacy has not been established for less than once-daily dosing frequencies. During the early weeks of therapy, an apparent increase in number and exacerbation of inflammatory acne lesions may occur. This is due, in part, to the action of the medication on deep, previously unseen lesions and should not be considered a reason to discontinue therapy. Therapeutic results should be noticed after two to three weeks but more than six weeks of therapy may be required before definite beneficial effects are seen. Patients treated with AVITA may use cosmetics, but the areas to be treated should be cleansed thoroughly before the medication is applied (see Precautions Section).</td>
</tr>
<tr>
<td><strong>DIFFERIN</strong> Cream is indicated for the topical treatment of acne vulgaris.</td>
<td>DIFFERIN Cream should be applied to affected areas of the skin, once daily at nighttime. A thin film of the cream should be applied to the skin areas where acne lesions appear, using enough to cover the entire affected areas lightly. A mild transitory sensation of warmth or slight stinging may occur shortly after the application of DIFFERIN Cream.</td>
</tr>
</tbody>
</table>
**DIFFERIN** Lotion is a retinoid product indicated for the topical treatment of acne vulgaris in patients 12 years and older.

Apply a thin film of DIFFERIN Lotion to the entire face and other affected areas of the skin once daily, after washing gently with a mild soapless cleanser. Dispense a nickel size amount of DIFFERIN Lotion (3-4 actuations of the pump) to cover the entire face. Avoid application to the areas of skin around eyes, lips and mucous membranes.

DIFFERIN Lotion is for topical use only and not for oral, ophthalmic, or intravaginal use.

**DIFFERIN** Gel, 0.3%, is a retinoid, indicated for the topical treatment of acne vulgaris in patients 12 years of age and older.

Apply a thin film of DIFFERIN Gel, 0.3% to the entire face and any other affected areas of the skin once daily in the evening, after washing gently with a non-medicated soap.

**EPIDUO** gel is a combination of adapalene, a retinoid, and benzoyl peroxide, and is indicated for the topical treatment of acne vulgaris in patients 9 years of age and older.

EPIDUO gel is not for oral, ophthalmic, or intravaginal use.

Apply a thin film of EPIDUO gel to affected areas of the face and/or trunk once daily after washing. Use a pea-sized amount for each area of the face (e.g., forehead, chin, each cheek). Avoid the eyes, lips and mucous membranes.

**EPIDUO FORTE** gel is a combination of adapalene, a retinoid, and benzoyl peroxide, and is indicated for the topical treatment of acne vulgaris.

EPIDUO FORTE gel is not for oral, ophthalmic, or intravaginal use.

Apply a thin layer of EPIDUO FORTE gel to affected areas of the face and/or trunk once daily after washing. Use a peased amount for each area of the face (e.g., forehead, chin, each cheek). Avoid the eyes, lips, and mucous membranes.

**RETIN-A** is indicated for topical application in the treatment of acne vulgaris. The safety and efficacy of the long-term use of this product in the treatment of other disorders have not been established.

RETIN-A Gel, Cream or Liquid should be applied once a day, before retiring, to the skin where acne lesions appear, using enough to cover the entire affected area lightly.

Liquid: The liquid may be applied using a fingertip, gauze pad, or cotton swab. If gauze or cotton is employed, care should be taken not to oversaturate it to the extent that the liquid would run into areas where treatment is not intended. Gel: Excessive application results in “pilling” of the gel, which minimizes the likelihood of over application by the patient. Application may cause a transitory feeling of warmth or slight stinging. In cases where it has been necessary to temporarily discontinue therapy or to reduce the frequency of application, therapy may be resumed or frequency of application increased when the patients become able to tolerate the treatment.

Alterations of vehicle, drug concentration, or dose frequency should be closely monitored by careful observation of the clinical therapeutic response and skin tolerance.

During the early weeks of therapy, an apparent exacerbation of inflammatory lesions may occur. This is due to the action of the
medication on deep, previously unseen lesions and should not be considered a reason to discontinue therapy. Therapeutic results should be noticed after two to three weeks but more than six weeks of therapy may be required before definite beneficial effects are seen. Once the acne lesions have responded satisfactorily, it may be possible to maintain the improvement with less frequent applications, or other dosage forms. Patients treated with RETIN-A (tretinoin) acne treatment may use cosmetics, but the area to be treated should be cleansed thoroughly before the medication is applied. (See Precautions.)

RETIN-A MICRO MICROSPHERE, 0.1% and 0.04%, is indicated for topical application in the treatment of acne vulgaris. The safety and efficacy of the use of this product in the treatment of other disorders have not been established.

RETIN-A MICRO MICROSPHERE, 0.1% and 0.04%, should be applied once a day, in the evening, to the skin where acne lesions appear, using enough to cover the entire affected area lightly. Application of excessive amounts of gel may result in "caking" of the gel, and will not provide incremental efficacy. A transitory feeling of warmth or slight stinging may be noted on application. In cases where it has been necessary to temporarily discontinue therapy or to reduce the frequency of application, therapy may be resumed or the frequency of application increased as the patient becomes able to tolerate the treatment. Frequency of application should be closely monitored by careful observation of the clinical therapeutic response and skin tolerance. Efficacy has not been established for less than once daily dosing frequencies. During the early weeks of therapy, an apparent exacerbation of inflammatory lesions may occur. If tolerated, this should not be considered a reason to discontinue therapy. Therapeutic results may be noticed after two weeks, but more than seven weeks of therapy are required before consistent beneficial effects are observed. Patients treated with Retin-A Micro (tretinoin gel) microsphere, 0.1% and 0.04%, may use cosmetics, but the areas to be treated should be cleansed thoroughly before the medication is applied.

TRETIN•X cream is indicated for topical application in the treatment of acne vulgaris. The safety and efficacy of the long-term use of this product in the treatment of other disorders have not been established.

TRETIN•X cream should be applied once a day, before retiring, to the skin where acne lesions appear, using enough to cover the entire affected area lightly. Application may cause a transitory feeling of warmth or slight stinging. In cases where it has been necessary to temporarily discontinue therapy or to reduce the frequency of application, therapy may be resumed or the frequency of application increased when the patient becomes able to tolerate the treatment. Alterations of vehicle, drug concentration, or dose frequency should be closely monitored by careful observation of the clinical therapeutic response and skin tolerance. During the early weeks of therapy, an apparent exacerbation of inflammatory lesions may occur. This is due to the action of the medication on deep, previously unseen lesions and should not be considered a reason to discontinue therapy.
TOPICAL RETINOID AND COMBINATION PRODUCTS  (cont.)

<table>
<thead>
<tr>
<th><strong>VELTIN</strong> Gel is a lincosamide antibiotic and retinoid combination product indicated for the topical treatment of acne vulgaris in patients 12 years and older.</th>
<th>Therapeutic results should be noticed after two to three weeks but more than six weeks of therapy may be required before definite beneficial effects are seen. Once the acne lesions have responded satisfactorily, it may be possible to maintain the improvement with less frequent applications, or other dosage forms. Patients treated with TRETIN•X preparations may use cosmetics, but the areas to be treated should be cleansed thoroughly before the medication is applied (see Precautions).</th>
</tr>
</thead>
</table>
| • Apply a pea-sized amount once daily in the evening lightly covering the entire affected area. Avoid the eyes, lips, and mucous membranes.  
• Not for oral, ophthalmic, or intravaginal use. |  |
| **ZIANA** Gel is a lincosamide antibiotic and retinoid combination product indicated for the topical treatment of acne vulgaris in patients 12 years or older. |  |
| • Apply a pea-sized amount to the entire face once daily at bedtime. Do not apply to eyes, mouth, angles of the nose, or mucous membranes.  
• ZIANA Gel is not for oral, ophthalmic, or intravaginal use. |  |