Medical Policy

BlueCross BlueShield of Kansas
An independent licensee of the Blue Cross Blue Shield Association

Title: Retinoids (topical)

- **Prime Therapeutics will review Prior Authorization**

  Prior Authorization Form:
  http://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth-6012KS-RETI.pdf

  Link to Drug List (Formulary):
  http://www.bcbsks.com/CustomerService/PrescriptionDrugs/drug_list.shtml

Professional
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Institutional
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State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

DESCRIPTION

The intent of the Retinoids Prior Authorization (PA) criteria is to discourage use of the listed target agents for the treatment of the cosmetic aspects of photoaging or photodamaged skin, and stretch marks, and also to promote utilization of cost-effective generic topical retinoid products before brand topical retinoid products. The retinoid agents approved for treatment of cosmetic aspects (e.g. Avage, Refissa, Renova, and Solage) are not considered medically necessary and are usually an excluded benefit. Patients 40 years of age and older will require prior authorization approval for retinoids; prior authorization criteria will not be applied to patients younger than 40 years of age. The topical retinoid agents may be approved through the prior authorization process for medical uses which are not for a cosmetic use: treatment of wrinkles, stretch marks, age spots, or skin lightening. Approval of brand topical retinoid products will require a history of use of a generic topical retinoid product or that the patient cannot be administered generic topical retinoid products due to documented intolerance, FDA labeled contraindication, or hypersensitivity. Requests for topical retinoid agents will be reviewed when patient-specific documentation has been provided.

Target Drugs

- **Atralin™** (tretinoin)[a]
- **Avita**® (tretinoin)[a]
- **Differin**® (adapalene)[a]
- **Fabior™** (tazarotene)
- **Retin-A**® (tretinoin)[a]
- **Retin-A Micro**® (tretinoin)[a]
- **Tretin-X™** (tretinoin)

a – generic available and included in program

FDA Approved Indications and Dosage[1-7,11,21,23]

Topical Retinoids	FDA Approved Indication	Administration and Dosing
	Acne Vulgaris	
Atralin • tretinoin gel 0.05%[a]	✓	Apply a thin layer to affected area once daily at bedtime.
Avita • tretinoin cream 0.025%[a] • tretinoin gel 0.025%[a]	✓	Apply a thin layer to affected area once daily at bedtime.
Differin • adapalene cream 0.1%[a] • adapalene gel 0.1%,[a] 0.3%[a] • adapalene lotion 0.1%	✓	Apply a thin layer to affected area once daily.
Fabior • tazarotene foam 0.1%	✓	Apply to affected area once daily in the evening.

Topical Retinoids	FDA Approved Indication Acne Vulgaris	Administration and Dosing
Retin-A • tretinoin cream 0.025%,[a] 0.05%,[a] 0.1%[a] • tretinoin gel 0.01%,[a] 0.025%[a] • tretinoin liquid 0.05%[a]	✓	Apply a thin layer to affected area once daily at bedtime.
Retin-A Micro • tretinoin gel microsphere 0.04%,[a] 0.08%, 0.1%[a]	✓	Apply a thin layer to affected area once daily at bedtime.
Tretin-X • tretinoin cream 0.025%, 0.0375%, 0.05%, 0.075%, 0.1% • tretinoin gel 0.025%, 0.01%	✓	Apply a thin layer to affected area once daily at bedtime.

a - generic available

POLICY

Prior Authorization Criteria for Approval

Generic Retinoid products will be approved when the following is met:

1. The patient is not using the requested agent for treatment of wrinkles, stretch marks, age spots, or skin lightening

Length of approval: 12 months

Brand Retinoid products will be approved when the following are met:

1. The patient is not using the requested agent for treatment of wrinkles, stretch marks, age spots, or skin lightening **AND**
2. ONE of the following:
   a. The patient's medication history includes use of a generic topical retinoid **OR**
   b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to an available generic topical retinoid

Length of approval: 12 months

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

RATIONALE

Acne

A review on treatment of acne (Lancet, 2012) suggests the large number of products and scarcity of comparative studies has led to disparate guidelines with few recommendations being evidence-based. Because of limited evidence, many guidelines rely on expert opinion with potential for conflicts of interest. Most guidelines base the choice of initial therapy on acne severity and whether acne is predominantly non-inflammatory or inflammatory.[9]

- Topical retinoids work for both comedonal and inflammatory acne. Placebo-controlled and non-inferiority studies may claim better tolerability with certain agents, but few trials guide clinical practice. Comparison trials between different retinoids and vs other acne agents are needed. Randomized controlled trials have shown higher strength retinoid preparations have greater activity vs lower strength ones, but at the expense of more irritation. All topical retinoids induce local reactions, and should be discontinued if severe.
- Data suggests that combinations of topical treatments with different mechanisms of action work better than single agents. However, few combinations have been tested properly against the relevant monotherapy. The trials tend to be methodologically flawed by factors such as suboptimal dose or frequency of monotherapy. Compliance can be increased with once-daily combination products due to convenience and faster speed of onset, although individual generic preparations used concomitantly might be more cost-effective.

Retinoids, although recommended in all forms of acne, have no apparent activity in preventing antibiotic resistance when used in combination with an antibiotic.[22]

Guidelines

American Academy of Pediatrics (2013)[24]

- Topical retinoids (tretinoin, adapalene, tazarotene) may be used as monotherapy or in combination products and in regimens of care for all types and severities of acne in children and adolescents of all ages. Isotretinoin is recommended for severe, scarring, and/or refractory acne in adolescents and may be used in younger patients. Extensive counseling, particularly regarding the avoidance of pregnancy as well as careful monitoring of potential side effects and toxicities, is recommended.
- The guideline recommends concomitant use of benzoyl peroxide with the fixed-combination of tretinoin and clindamycin, to avoid potential development of bacterial resistance.

Medical Letter (2012)[25]

- Topical retinoids (e.g., tretinoin, adapalene, and tazarotene) can be used to treat both inflamed and noninflamed acne lesions, alone or in combination with antibiotics, or for maintenance treatment. Many dermatologists now use them as first-line treatment. It is not clear that any one of these agents is more effective vs others. Retinoid/antimicrobial combinations are more effective than either component alone, but simultaneous application of tretinoin and benzoyl peroxide can cause oxidation of tretinoin and loss of effectiveness. Oral isotretinoin is the most effective drug available for severe nodulocystic acne, potentially clearing lesions, leading to remission that can persist for years after treatment is stopped.

European evidence based guidelines (2012) on treatment of acne made the following treatment recommendations.[10]

- Comedonal acne: Due to the mild/moderate severity of comedonal acne, a topical therapy is recommended. The best efficacy was found for azelaic acid, benzoyl peroxide (BPO) and topical retinoids. Use of fixed-dose combinations of BPO + clindamycin does not lead to a clinically relevant increase in efficacy against non inflammatory lesions (NIL). BPO + adapalene trended towards better efficacy against NIL vs the components as monotherapy. However, there was a trend towards inferiority for tolerability profile. Tolerability of topical retinoids and BPO is comparable; there is a trend towards azelaic acid having a better tolerability profile. Limited data suggests a patient preference for adapalene vs topical retinoids.
- Papular pustular acne: The best efficacy against inflammatory lesions was with fixed-dose combinations of BPO + adapalene and BPO + clindamycin, vs topical monotherapies. Monotherapy with azelaic acid, BPO or topical retinoids all had comparable efficacy vs each other. Systemic antibiotic monotherapy shows no superiority vs topical treatment; therefore combining systemic therapy with topical agents is preferred.
- Nodular/conglobate acne: Systemic isotretinoin shows superior or comparable efficacy in treatment of conglobate acne vs combination systemic antibiotics + topical therapy. Experts suggest the greatest effectiveness in the treatment of conglobate acne in clinical practice is seen with systemic isotretinoin; this can only be partly supported by published evidence, due to lack of clinical trials in conglobate acne.

According to the American Academy of Dermatology (2007) the effectiveness of topical retinoids in the treatment of acne is well documented. These agents act to reduce obstruction within the follicle and therefore are useful in management of both comedonal and inflammatory acne. There is no consensus about relative efficacy of topical retinoids (e.g., tretinoin, adapalene, tazarotene). The concentration and/or vehicle of any particular retinoid may impact tolerability. A combination of topical retinoids and topical erythromycin or clindamycin is more effective than either agent used alone.[8]

Psoriasis

A review (U.S., 2013) on treatment of psoriasis suggests tazarotene is as effective as topical corticosteroids in alleviating symptoms of psoriasis, and is associated with a longer disease-free interval. The perilesional adverse effects (e.g., itching, burning) are common but can be managed with alternate-day application or use with topical corticosteroids and moisturizers.[26]

Guidelines

American Academy of Dermatology Guidelines (AAD, 2009-2011) consider tazarotene a first line therapy, best used in combination with a corticosteroid, increasing efficacy vs tazarotene alone and reducing tazarotene irritation. Topical tazarotene is a corticosteroid-sparing agent with the major limitation of irritation, which can be minimized by applying it sparingly, avoiding perilesional areas, and/or used in combination with a topical corticosteroid, producing synergistic effects, longer treatment benefit, and remission.[12,14]

European Guidelines (German 2012) suggest that after 12 weeks of treatment with tazarotene 0.1 % once daily, 50% of patients achieve > 50% improvement in skin lesions. Combination therapy with topical steroids may optimize treatment success and reduce skin irritation. Contact with healthy skin should be avoided to prevent irritation.[13]

Other Medical Uses

Additional therapeutic uses for topical retinoids (tretinoin primarily) are supported by current compendia, including flat and facial warts and keratinization disorders, such as actinic keratosis, keloids, hypertrophic scars, and keratosis follicularis.[27-29]

Photoaging [Off-Label Use][15-20]

Photoaging is the superimposition of photodamage on intrinsically aged skin resulting in premature aging. Photodamage of the skin occurs by chronic exposure to ultraviolet light. The skin develops wrinkles, irregular pigmentation, lentigines, and possibly premalignant lesions (e.g., actinic keratoses). Among the retinoids, tretinoin has been the most widely investigated for photoaging therapy; however, tazarotene and adapalene are also accumulating data.[15-20]

Treatment of various benign photoaging lesions may be considered a lesser priority if treated only for cosmetic reasons. However, other types of lesions (e.g., actinic keratoses, etc.) may potentially be precancerous, and treatment for those lesions may be considered a higher priority to prevent progression to carcinoma.

REVISIONS

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Additional Information

The age limit of 40 years or older as the edit parameter has been based on analysis of National Ambulatory Medical Care Survey (NAMCS) data (1990-1994)[1] and (1990-2004).[2] In the initial analysis, acne-related treatment with tretinoin was equal to non-acne conditions around 44 years of age.[1] The second analysis confirmed that there was a "minute probability" of non-acne-related use of topical retinoids in the population aged 40 years and younger.[2] The authors of the NAMCS data evaluations suggest a minimum age of 40 years as a cut-off to determine coverage of retinoid agents for acne.[1,2] These analyses were consistent with a study of the prevalence of acne in adults in the United Kingdom (UK).[3] Data from the UK study indicated the prevalence of acne did not substantially decline between the ages of 24 and 44 years of life but fell significantly after 45 years of age.[3]

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