Medical Policy

BlueCross BlueShield of Kansas
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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):
  https://www.bcbsks.com/drugs/

Professional
Original Effective Date: April 1, 2017
Revision Date(s): April 1, 2017; December 18, 2017; January 1, 2018; October 22, 2018; December 1, 2018
Current Effective Date: December 1, 2018

Institutional
Original Effective Date: April 1, 2017
Revision Date(s): April 1, 2017; December 18, 2017, January 1, 2018; October 22, 2018; December 1, 2018
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DESCRIPTION

The intent of the Retinoids (topical) 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, 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 over 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 Agents

- **Altreno™** (tretinoin)
- **Atralin™** (tretinoin)[a]
- **Avita®** (tretinoin)[a]
- **Differin®** (adapalene)[a]
- **Fabior™** (tazarotene)
- **Retin-A®** (tretinoin)[a]
- **Retin-A Micro®** (tretinoin)[a]
- **Tazorac® cream 0.1%** (tazarotene cream 0.1%)[a]
- **Tretin-X™** (tretinoin) [b]

a – generic available and included in program
b - discontinued

FDA Approved Indications and Dosage[1-7,10,19,21,28-33]

Topical Retinoids	FDA Approved Indication	Administration and Dosing
Altreno • tretinoin lotion 0.05%	Topical treatment of acne vulgaris in patients 9 years of age and older	Apply a thin layer to affected areas once daily
Atralin • tretinoin gel 0.05%[a]	Topical treatment of acne vulgaris	Apply a thin layer to affected area once daily at bedtime.
Avita • tretinoin cream 0.025%[a] • tretinoin gel 0.025%[a]	Treatment of acne vulgaris	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%	▪ 0.1% cream is indicated for the topical treatment of acne vulgaris ▪ 0.1% gel is indicated for the topical treatment of acne vulgaris ▪ 0.3% gel is indicated for the topical treatment of acne vulgaris in patients 12 years of age and older ▪ 0.1% lotion is indicated for the topical treatment of acne vulgaris in patients 12 years of age and older	Apply a thin layer to affected area once daily.

Topical Retinoids	FDA Approved Indication	Administration and Dosing
Fabior • tazarotene foam 0.1%	Topical treatment of acne vulgaris in patients 12 years of age or older	Apply to affected area once daily in the evening.
Retin-A • tretinoin cream 0.025%,[a] 0.05%,[a] 0.1%[a] • tretinoin gel 0.01%,[a] 0.025%[a]	Treatment of acne vulgaris	Apply a thin layer to affected area once daily at bedtime.
Retin-A Micro • tretinoin gel microsphere 0.04%,[a] 0.06%, 0.08%, 0.1%[a]	Topical application in the treatment of acne vulgaris	Apply a thin layer to affected area once daily at bedtime.
Tazorac • tazarotene cream 0.05%, 0.1%[a] • tazarotene gel 0.05%, 0.1%	▪ 0.05% and 0.1% cream are indicated for the ▪ topical treatment of plaque psoriasis. ▪ 0.1% cream is indicated for the topical treatment of acne vulgaris. ▪ 0.05% and 0.1% gel are indicated for the topical treatment of patients with stable plaque psoriasis of up to 20% body surface area involvement. ▪ 0.1% gel is indicated for the topical treatment of patients with facial acne vulgaris of mild to moderate severity.	Apply a thin layer only to the affected area once daily in the evening
Tretin-X [b] • tretinoin cream 0.0375%, 0.075%	Treatment of acne vulgaris	Apply a thin layer to affected area once daily at bedtime.

a - generic available
b - discontinued

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 has tried and had an inadequate response to a generic topical retinoid
      OR
   b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to a 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 versus 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.[20]

American Academy of Pediatrics (2013)[22]

- 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)[23]
- 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 versus 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.

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.[24]

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.[11,12]

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.[25-27]

Photoaging [Off-Label Use][13-18]
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.[13-18]

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

04-01-2017	Policy published 03-01-2017. Policy effective 04-01-2017.
12-18-2017	Policy published 12-29-2017. Policy retro-effective to 12-18-2017.
	In Description section: ▪ Updated FDA Approved indication chart to add Retin-A Microgel 0.06% as a target
01-01-2018	In Description section: ▪ Updated FDA Approved Indication chart to specific indications, added Tazorac as a target and removed tretinoin gel as a target.
	Rationale section updated
	References updated
10-22-2018	Policy Published November 7, 2018. Policy retro-effective to October 22, 2018.
	Description section updated to add Altreno as a target agent.
	References updated
12-01-2018	Summary of Revisions: • Noted the discontinuation of Tretin-X • Updated fail language to standard 'Tried and had an inadequate response'
	Description section updated
	In Policy section: ▪ In Item 2 a added "has tried and had an inadequate response to" and removed "medication history includes use of" to read "The patient has tried and had an inadequate response to a generic topical retinoid"
	References updated

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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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