PRIOR AUTHORIZATION CRITERIA

DRUG CLASS	**ISOTRETINOINS (ALL ORAL)**
BRAND NAME* **(generic)**	
	ABSORICA, ABSORICA LD (isotretinoin)
	ACCUTANE (isotretinoin)
	AMNESTEEM (isotretinoin)
	CLARAVIS (isotretinoin)
	MYORISAN (isotretinoin)
	ZENATANE (isotretinoin)
Status: CVS Caremark Criteria	
Type: Initial Prior Authorization	***Ref # 118-A***

** Drugs that are listed in the target drug box include both brand and generic and all dosage forms and strengths unless otherwise stated. OTC products are not included unless otherwise stated.*

FDA-APPROVED INDICATIONS

Absorica, Absorica LD

Absorica and Absorica LD are indicated for the treatment of severe recalcitrant nodular acne in non-pregnant patients 12 years of age and older with multiple inflammatory nodules with a diameter of 5 mm or greater. Because of significant adverse reactions associated with its use, Absorica and Absorica LD are reserved for patients with severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics.

Limitations of Use:

If a second course of Absorica/Absorica LD therapy is needed, it is not recommended before a two-month waiting period because the patient's acne may continue to improve following a 15 to 20-week course of therapy.

Accutane, Amnesteem, Claravis, Myorisan, Zenatane

Isotretinoin is indicated for the treatment of severe recalcitrant nodular acne. Nodules are inflammatory lesions with a diameter of 5 mm or greater. The nodules may become suppurative or hemorrhagic. "Severe," by definition, means "many" as opposed to "few or several" nodules. Because of significant adverse effects associated with its use, isotretinoin should be reserved for patients with severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics. In addition, isotretinoin is indicated only for those female patients who are not pregnant, because isotretinoin can cause severe birth defects.

A single course of therapy for 15 to 20 weeks has been shown to result in complete and prolonged remission of disease in many patients. If a second course of therapy is needed, it should not be initiated until at least 8 weeks after completion of the first course, because experience has shown that patients may continue to improve while off isotretinoin. The optimal interval before retreatment has not been defined for patients who have not completed skeletal growth.

Compendial Uses
Acne – refractory[8]
Cutaneous T-Cell Lymphoma (CTCL) (e.g., mycosis fungoides, Sézary syndrome)[7]
Keratosis follicularis (Darier Disease) – severe[8]
Lamellar ichthyosis – severe skin involvement[7]
Neuroblastoma[8]
Pityriasis rubra pilaris[7]
Rosacea – severe refractory[8]
Squamous Cell Cancers – to reduce the development of precancers and skin cancers in high risk patients[8]
Transient acantholytic dermatosis (Grover's Disease) – severe[8]

COVERAGE CRITERIA

The requested drug will be covered with prior authorization when the following criteria are met:

- The patient has any of the following diagnoses: A) severe recalcitrant nodular acne vulgaris, B) refractory acne vulgaris, C) severe refractory rosacea
  AND
  - The patient has tried and had an inadequate treatment response to any topical acne product AND an oral antibiotic
    AND
  - Treatment will be limited to 40 weeks (2 courses) or less AND with at least 8 weeks between each course

OR

- The patient has any of the following diagnoses: A) neuroblastoma, B) cutaneous T-cell lymphoma (CTCL) (e.g., mycosis fungoides, Sézary syndrome), C) is at high risk for developing skin cancer (squamous cell cancers), D) transient acantholytic dermatosis (Grover's Disease), E) keratosis follicularis (Darier Disease), F) lamellar ichthyosis, G) pityriasis rubra pilaris

RATIONALE

The intent of the criteria is to provide coverage consistent with product labeling, FDA guidance, standards of medical practice, evidence-based drug information, and/or published guidelines. Isotretinoin is indicated for the treatment of severe recalcitrant nodular acne. Nodules are inflammatory lesions with a diameter of 5 mm or greater. The nodules may become suppurative or hemorrhagic. "Severe," by definition, means "many" as opposed to "few or several" nodules. Because of significant adverse effects associated with its use, isotretinoin should be reserved for patients with severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics. In addition, isotretinoin is indicated only for those female patients who are not pregnant, because isotretinoin can cause severe birth defects.[1-6]

A single course of therapy for 15 to 20 weeks has been shown to result in complete and prolonged remission of disease in many patients. If a second course of therapy is needed, it should not be initiated until at least 8 weeks after completion of the first course, because experience has shown that patients may continue to improve while off isotretinoin. The optimal interval before retreatment has not been defined for patients who have not completed skeletal growth. Long-term use of isotretinoin even in low doses, has not been studied, and is not recommended. It is important that isotretinoin be given at the recommended doses for no longer than the recommended duration. The effect of long-term use of isotretinoin on bone loss is unknown.[1-6]

Patients with acne vulgaris may be treated with antibacterial, comedolytic, retinoid, or antibiotic topical products (e.g., salicylic acid, benzoyl peroxide, azelaic acid, adapalene, tretinoin, tazarotene, clindamycin, erythromycin).[9] Combinations of products, if compatible, may be used when monotherapy is inadequate. Systemic antibiotics are a standard of care in the management of moderate and severe acne and treatment-resistant forms of inflammatory acne. There is evidence to support the use of tetracycline, doxycycline, minocycline, erythromycin, trimethoprim-sulfamethoxazole, trimethoprim, and azithromycin.[9] For patients with severe inflammatory acne that does not improve with other medications, isotretinoin may

be prescribed.[1-9] The compendia state that isotretinoin is effective in treating acne, however, should be reserved for patients who are unresponsive to conventional acne therapies, including oral and/or topical anti-infectives.[7,8]

The National Cancer Institute states that patients with neuroblastoma categorized as high risk are generally treated with dose-intensive multiagent chemotherapy, resection of the primary tumor, followed by myeloablative chemotherapy and autologous stem cell transplantation. Radiation of residual tumor and original sites of metastases is often performed. After recovery, patients are treated with oral isotretinoin for 6 months. Both myeloablative chemotherapy and isotretinoin improve outcomes in patients categorized as high risk.[7,8,13]

The National Comprehensive Cancer Network (NCCN) guidelines state that certain patient groups are at high risk for developing multiple squamous cell skin cancers and tumors that can behave aggressively. These include organ transplant recipients, other settings of immunosuppression (e.g., lymphoma, drug-induced, HIV), and patients with xeroderma pigmentosum. Use of oral retinoids (acitretin, isotretinoin) has been effective in reducing the development of actinic keratoses and cutaneous squamous cell cancer (CSCC) in some high-risk patients. Side effects may be significant. Therapeutic effects disappear shortly after cessation of the drug.[7,8,14]

Isotretinoin has also produced partial and complete responses in some patients with advanced cutaneous T-cell lymphomas, including mycosis fungoides and Sézary syndrome.[7] The NCCN guidelines also state that retinoic-acid receptor (RAT) agonists such as all-trans retinoic acid (ATRA), acitretin, and isotretinoin (13-cis retinoic acid) have been shown to be effect for the treatment of early-stage mycosis fungoides.[15]

According to Micromedex, based on the results of several studies, isotretinoin is highly effective in the treatment of severe, refractory rosacea at doses of 0.05 to 2 mg/kg/day. Good-to-excellent results were reported in 83% to 100% of patients receiving isotretinoin, after approximately 2 to 6 months of treatment. The papulopustular lesions in particular cleared promptly. A dose of 0.5 mg/kg/day is the preferred dosage in rosacea patients, since the incidence of adverse effects increases with increasing dose.[8] Oral and topical products are FDA-approved for rosacea, while isotretinoins are not. In addition, the Consensus Recommendations From the American Acne & Rosacea Society on the Management of Rosacea, Part 3: A Status Report on Systemic Therapies state that isotretinoin is an option to consider in selected cases of refractory papulopustular rosacea and early rhinophyma, though prolonged remissions are not likely after the drug is stopped. The recommendations also favor oral antibiotics over isotretinoin as the initial systemic therapy.[12]

For transient acantholytic dermatosis (Grover's Disease), treatment is usually based on a person's symptoms. Initial treatment options include topical steroids, topical antihistamines, or topical selenium sulfide. For more severe cases, tetracycline has been reported to be effective and the use of oral retinoids (acitretin or isotretinoin) has been reported. More troubling eruptions usually clear up after taking isotretinoin or tetracycline for one to three months.[8,16-18]

For keratosis follicularis (Darier Disease), moisturizers with urea or lactic acid can help reduce scaling and thickening of the lesions. Low to medium potency topical steroids are sometimes useful for reducing inflammation and when bacterial growth is suspected, application of antiseptics can be helpful. Topical retinoids have been shown to be effective in reducing the localized symptoms of this disease in 3 months. The most effective medical treatment for severe cases has been the use oral retinoids such as acitretin and isotretinoin.[7,8,19,20]

For lamellar ichthyosis, petrolatum-based creams and ointments are used to keep the skin soft. As affected children become older, keratolytic agents such as alpha-hydroxy acid or urea preparations may be used to promote peeling and thinning of the stratum corneum. For individuals with ectropion, lubrication of the cornea with artificial tears or prescription ointments is helpful in preventing drying out of the cornea. Oral retinoid therapy such as acitretin or isotretinoin may be recommended for those with severe skin involvement.[7,8,21]

Management of pityriasis rubra pilaris (PRP) often involves systemic and topical therapies combined. Topical therapies can help with the symptoms and may be enough for people with mild PRP. Topical treatments used for PRP may include topical corticosteroids, keratolytics, tar, calcipotriol, topical tretinoin, and tazarotene. Topical treatments are usually combined with systemic therapy for PRP that affects a large part of the body. Oral retinoids (synthetic vitamin A derivatives) are usually preferred as a first-line systemic treatment. Methotrexate may be an alternative option for people who should not use systemic retinoids, or who don't respond to systemic retinoid therapy. For people who don't respond well to retinoid or methotrexate therapy, options may include biologic TNF-alpha inhibitors, azathioprine, cyclosporine, and/or phototherapy.[7,8,22,23]

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Date Written:	02/1995
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CRITERIA FOR APPROVAL

1	Does the patient have any of the following diagnoses: A) severe recalcitrant nodular acne vulgaris, B) refractory acne vulgaris, C) severe refractory rosacea? [If no, then skip to question 4.]	Yes	No
2	Has the patient tried and had an inadequate treatment response to any topical acne product AND an oral antibiotic? [Note: topical products include salicylic acid, benzoyl peroxide, azelaic acid, adapalene, tretinoin, tazarotene, clindamycin, erythromycin, or metronidazole for rosacea] [Note: oral antibiotics include minocycline, doxycycline, tetracycline, erythromycin, trimethoprim-sulfamethoxazole, trimethoprim, azithromycin] [If no, then no further questions.]	Yes	No
3	Will treatment be limited to 40 weeks (2 courses) or less AND with at least 8 weeks between each course? [No further questions.]	Yes	No
4	Does the patient have any of the following diagnoses: A) neuroblastoma, B) cutaneous T-cell lymphoma (CTCL) (e.g., mycosis fungoides, Sezary syndrome), C) is at high risk for developing skin cancer (squamous cell cancers), D) transient acantholytic dermatosis (Grover's Disease), E) keratosis follicularis (Darier Disease), F) lamellar ichthyosis, G) pityriasis rubra pilaris?	Yes	No

Mapping Instructions			
	Yes	**No**	**DENIAL REASONS – DO NOT USE FOR MEDICARE PART D**
1.	Go to 2	Go to 4	
2.	Go to 3	Deny	You do not meet the requirements of your plan. Your plan covers this drug when you meet all of these conditions: - You tried another topical acne product first, which did not work for you - You tried an oral antibiotic first, which did not work for you Your request has been denied based on the information we have. [Short Description: No trial of topical acne products and oral antibiotics]
3.	Approve, 12 Months	Deny	You do not meet the requirements of your plan. Your plan covers this drug when you meet all of the following conditions: - You will not use it for more than 40 weeks (2 treatment courses) - You will take an 8-week break between treatment courses Your request has been denied based on the information we have. [Short Description: Over max duration of use]
4.	Approve, 12 Months	Deny	You do not meet the requirements of your plan. Your plan covers this drug when you meet any of these conditions: - You have severe recalcitrant nodular acne vulgaris - You have refractory acne vulgaris - You have severe refractory rosacea - You have neuroblastoma - You have cutaneous T-cell lymphoma - You are at high risk for developing skin cancer - You have transient acantholytic dermatosis (Grover's Disease) - You have keratosis follicularis (Darier Disease)

			- You have lamellar ichthyosis - You have pityriasis rubra pilaris Your request has been denied based on the information we have. [Short Description: No approvable diagnosis]