PRIOR AUTHORIZATION CRITERIA

DRUG CLASS	**ISOTRETINOINS (ALL ORAL)**
BRAND NAME* (generic)	
	ABSORICA (isotretinoin)
	AMNESTEEM (isotretinoin)
	CLARAVIS (isotretinoin)
	MYORISAN (isotretinoin)
	SOTRET (isotretinoin)
	ZENATANE (isotretinoin)
Status: CVS Caremark Criteria	***MDC-1***
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*

FDA-APPROVED INDICATIONS

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 the diagnosis of acne vulgaris (severe recalcitrant nodular or refractory) OR severe refractory rosacea AND
    - The patient has tried and had inadequate treatment responses 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

These criteria meet the Medicare Part D definition of a medically accepted indication. This definition includes uses which are approved by the FDA or supported by a citation included, or approved for inclusion, in one of the Medicare approved compendia.

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.

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.

Isotretinoin must not be used by female patients who are or may become pregnant. Because of isotretinoin teratogenicity and to minimize fetal exposure, isotretinoin is approved for marketing only under a special restricted distribution program approved by the Food and Drug Administration. This program is called iPLEDGE. Isotretinoin must only be prescribed by prescribers who are registered and activated with the iPLEDGE program. Isotretinoin must only be dispensed by a pharmacy registered and activated with iPLEDGE, and must only be dispensed to patients who are registered and meet all the requirements of iPLEDGE.

Patients with acne vulgaris may be treated with antibacterial, keratolytic, retinoid, or antibiotic topical products (e.g., salicylic acid, benzoyl peroxide, azelaic acid, adapalene, tretinoin, tazarotene, clindamycin, erythromycin). 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. For patients with severe inflammatory acne that does not improve with other medications, isotretinoin may

be prescribed.[1-10] 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 outcome 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), xeroderma pigmentosum. Use of oral retinoids (acitretin, isotretinoin) has been effective in reducing the development of precancers and skin cancers in some high risk patients. Side effects may be significant. Therapeutic effects disappear shortly after cessation of the drug. [7,8,14,16]

The NCCN guidelines also state that retinoids (all-trans retinoic acid, 13-cis retinoic acid and their synthetic analogs acitretin and isotretinoin) and interferons have been used for many years in the treatment of cutaneous T-cell lymphoma (CTCL; e.g., mycosis fungoides, Sézary syndrome). [7,8,15,16]

Isotretinoin has been used in the treatment of transient acantholytic dermatosis (Grover's Disease), keratosis follicularis (Darier Disease), lamellar ichthyosis, pityriasis rubra pilaris, and rosacea that are resistant to treatment with other agents; however, the specific role of isotretinoin in the treatment of these disorders and the safety of long-term use and high dosages of the drug have not been determined. In order to limit total isotretinoin dosage, isotretinoin should be used only if the disease is severe, the dosage is as low as possible and given intermittently, and should be combined with other topical therapy. [7, 8]

Based on the results of several studies, the compendia favor efficacy for isotretinoin in treating severe, refractory rosacea at a preferred dose of 0.05mg/kg/day for approximately 2 to 6 months of treatment. The National Institute of Arthritis and Musculoskeletal and Skin Diseases states that rosacea can be treated and controlled with a topical antibiotic. Topical keratolytics such as benzoyl peroxide and azelaic acid offer limited symptomatic control of inflammatory pustules. In addition, topical metronidazole may be helpful for mild disease and in addition to systemic therapy. For people with more severe cases oral antibiotics are often prescribed. Long-term, low-dose isotretinoin may be helpful for recalcitrant disease for some patients.[7,8,11,12]

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 (acetretin or isotretinoin) has been reported. More troubling eruptions usually clear up after taking isotretinoin or tetracycline for one to three months.[7,8,17-19]

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. [7,8,20,21]

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 to help increase the patient's ability to perspire, improve the ectropion, and reduce the severity of erythema, scaling, induration, and crusting. [7,8,22]

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. [7,8,23,24]

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Reviewed: CRC 12/1998, 8/1999, 02/2001, 09/10/2001, 04/2002, 02/2003, 03/2004; (MM) 10/2005, 09/2006; (WF) 08/2007, 08/2008; (DL) 09/2009; (KP) 08/2010, 03/2011, 08/2011; (LB) 07/2012; (LS) 08/2012; (KP) 04/2013, (SS) 06/2013; (LB) 06/2014; (MCM) 06/2015; (DHR) 05/2016; (ME) 06/2017
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CRITERIA FOR APPROVAL

1	Does the patient have the diagnosis of acne vulgaris (severe recalcitrant nodular or refractory) OR severe refractory rosacea? [If no, then skip to question 4.]	Yes	No
2	Has the patient tried and had inadequate treatment responses 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]	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

Guidelines for Approval			
Duration of Approval		**12 Months**	
Set 1		**Set 2**	
Yes to question(s)	**No to question(s)**	**Yes to question(s)**	**No to question(s)**
1	None	4	1
2			
3			

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	Your plan covers this drug when you meet all of these conditions: - You have acne or severe refractory rosacea - 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 use of this drug does not meet these requirements. This is based on the information we have.
3.	Approve, 12 Months	Deny	Your plan covers this drug when you do not use the drug for more than 40 weeks total with an 8-week break. Your use of this drug does not meet the

			requirement. This is based on the information we have.
4.	Approve, 12 Months	Deny	Your plan covers this drug when you meet one of these conditions: - You have acne - 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 use of this drug does not meet these requirements. This is based on the information we have.