Criteria for Use of
Highly Teratogenic Retinoids and High-dose Vitamin A
(Pregnancy Category D or X)

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Isotretinoin, most other systemic and topical retinoids, as well as high oral doses (≥ 25,000 IU per day) of vitamin A require pregnancy warnings or pregnancy risk management because of their teratogenic potential. The association of retinoids, particularly isotretinoin, and vitamin A with suicide, depression, and other serious adverse effects, such as hypertriglyceridemia, hypercholesterolemia, and bone abnormalities, have added to the growing need to ensure the safe use of these agents. The objectives of these criteria were to identify indications for which there is sufficient evidence to support the use of retinoids classified as **pregnancy category D or X**; and to identify potentially less teratogenic alternatives to these agents for medical conditions based on head-to-head (retinoid versus retinoid) and active-controlled (retinoid versus nonretinoid active comparator) trials. These criteria cover systemically administered acitretin, bexarotene, isotretinoin, tretinoin, and vitamin A (≥ 25,000 IU per day or equivalent), and topically applied alitretinoin, bexarotene, tazarotene, and tretinoin.

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Table 1 Criteria for Use of Acitretin

Oral	Pregnancy category X	Formulary

Criteria for Use	Yes	No
The response to ALL items below must be YES to use acitretin.		
Provider authorizing the initiation of therapy is a dermatologist. *Subsequent prescriptions may be renewed by dermatologists or other locally authorized clinicians (including nurse practitioners or physician assistants). Approved clinicians should be under the supervision of or, in a co-managed care situation, working with a Dermatologist, and appropriate patient monitoring must be followed*	☐	☐
Patient has chronic severe psoriasis **Criteria for severe psoriasis**[†] ☐ Disease is disabling or impairs the patient's quality of life (self-reported), including ability to work and activities of daily living AND ☐ Disease is extensive or does not have a satisfactory response to topical agents AND ☐ The patient is willing to accept life-altering adverse effects to achieve less disease or no disease AND ☐ Either description below pertains to patient: —Generally more than 10% of body surface area is involved with disease —Other factors apply (patient's attitude about disease; location of disease [e.g., face, hands, fingernails, feet, genitals]; symptoms [e.g., pain, tightness, bleeding, or severe itching]; arthralgias or arthritis). [†] Adapted from a Position Paper by Krueger, et al (2000)[1] and the National Psoriasis Foundation Medical Board Guidance for Managed Care Systems for Phototherapy or Systemic Treatments (including Biologics)[2]	☐	☐
Patient has been counseled to avoid donating blood during therapy and for at least 3 years after discontinuing therapy	☐	☐
If patient is a female of childbearing potential, she meets ALL three of the following requirements: ☐ Two negative urine or serum pregnancy tests (PGTs, with a sensitivity of at least 25 mIU / ml). The first PGT should be done when a trial of acitretin therapy is first decided for the patient and the second / confirmatory PGT must be done within the first 5 d of the menstrual period immediately before starting therapy, or at least 11 d after last unprotected sexual intercourse), and has negative monthly pregnancy tests during therapy. ☐ Patient has selected and committed to use 2 effective forms of contraception simultaneously, unless absolute abstinence is the chosen method, or the patient has undergone a hysterectomy, or is clearly postmenopausal. *The microdose progestin minipill is not recommended because acitretin interferes with its contraceptive effect.* ☐ Patient has agreed to use the 2 chosen effective forms of contraception simultaneously for at least 1 month prior to initiation of acitretin therapy, during therapy, and for *at least 3 years* after discontinuing acitretin therapy.	☐	☐
If patient is a female of childbearing potential, she has been counseled to avoid drinking alcohol during therapy and for 2 months following discontinuation of therapy (because of formation of etretinate, which has a long half-life of 120 days).	☐	☐
If patient is a female of childbearing potential, patient has been counseled to avoid taking St. John's Wort and avoid starting any new medications without first consulting a physician or pharmacist (because of a potential risk that these medications may interfere with hormonal contraceptives)	☐	☐
If female, patient has signed an *Acitretin Patient Agreement / Informed Consent for Female Patients* (see http://www.soriatane.com/include/pi.pdf , pp. 23–26)	☐	☐

Exclusion Criteria		
If the response to ANY item below is YES, then the patient should NOT receive acitretin.		
Patient is pregnant, nursing, planning to become pregnant, or unreliable about using contraceptive methods	☐	☐
Patient has severe hepatic or renal impairment	☐	☐
Patient has chronic, hyperlipidemia uncontrolled by lipid-lowering agents	☐	☐
Concomitant use with methotrexate (risk of hepatitis), tetracyclines (risk of pseudotumor cerebri), or vitamin A and / or other systemic retinoids (risk of hypervitaminosis A)	☐	☐
Hypersensitivity to acitretin, other product components, or other retinoids	☐	☐
Discontinuation Criteria	**Yes**	**No**
If the answer to ANY item below is YES, then acitretin should be discontinued and the patient referred for further evaluation.		
Lack of improvement in psoriasis symptoms after 3 months of acitretin therapy.	☐	☐
Patient develops any of the following adverse effects: Visual difficulties Papilledema, headache, nausea, vomiting, and visual disturbances (pseudotumor cerebri)	☐	☐
If the answer to the item below is YES, then acitretin should be discontinued and the patient counselled on potential risks of birth defects.		
Patient becomes pregnant, misses a period, stops using birth control, or has sexual intercourse without simultaneously using 2 effective contraceptive methods	☐	☐
Dispensing Limits		
Max. 30 days' supply (to encourage compliance with counseling)		
Monitoring		
Check blood lipid concentrations before starting therapy and every 1 to 2 weeks for the first 4 to 8 weeks or until lipid response is established; monitor more frequently or for a longer period in patients at risk (e.g., those with diabetes mellitus, patient or family history of hyperlipidemia, obesity, increased alcohol use, or pancreatitis)		
Check liver enzyme tests before starting therapy and every 1 to 2 weeks until stable, then as clinically indicated		
Perform periodic radiographic tests to evaluate patient for hyperostosis if acitretin is continued long-term or if patient develops symptoms consistent with hyperostosis		
Check blood glucose concentrations on a regular basis for possible development of diabetes mellitus		
Perform monthly pregnancy test		
Assess patient on a regular basis for potential depression and suicidality		
Counsel patient on a regular basis to reinforce avoidance of pregnancy		
Provide patient with a *Medication Guide* each time acitretin is dispensed, as required by law		

Table 2 Criteria for Use of Oral Bexarotene

Oral	Pregnancy category X	Nonformulary	
Inclusion Criteria		**Yes**	**No**
The response to ALL items below must be YES to use orally administered bexarotene			
Prescriber is a hematologist / oncologist or Provider authorizing the initiation of therapy is a dermatologist. *Subsequent prescriptions may be renewed by dermatologists or other locally authorized clinicians (including nurse practitioners or physician assistants). Approved clinicians should be under the supervision of or, in a co-managed care situation, working with a dermatologist, and appropriate patient monitoring must be followed*		☐	☐
Patient has refractory, advanced-stage cutaneous manifestations of cutaneous T-cell lymphoma (CTCL). *Advanced stage is defined as tumor stage or Sezary syndrome.*		☐	☐
Patient has documented inadequate response, intolerance, or contraindication to one form of systemic therapy		☐	☐
Patient meets one of the pregnancy risk management requirements described below. ☐ If patient is a male, he commits to using condoms during sexual intercourse while receiving bexarotene therapy and for 1 month after discontinuation of bexarotene ☐ If patient is a female of childbearing potential, she — has a negative serum pregnancy test (serum beta-human chorionic gonadotropin, beta-HCG) with a sensitivity of ≥ 25 mIU / ml within 1 week before starting bexarotene and monthly during therapy — AND selects and commits to using 2 effective contraceptive methods simultaneously, one of which should be nonhormonal, for 1 month prior to starting bexarotene, during bexarotene therapy, and for 1 month after discontinuation of bexarotene OR chooses abstinence as the contraceptive method. ☐ Patient is not of childbearing potential (i.e., has had a hysterectomy or bilateral oophorectomy)		☐	☐
Patient agrees to avoid donating blood during the period of teratogenic risk (during therapy and for 1 month after discontinuation of bexarotene)		☐	☐
Exclusion Criteria		**Yes**	**No**
If the response to ANY item below is YES, then the patient should NOT receive bexarotene.			
Patient is pregnant or nursing		☐	☐
Patient has contraindication to bexarotene (i.e., hypersensitivity)		☐	☐
Patient is taking gemfibrozil (risk of increasing bexarotene levels due to CYP3A4 inhibition); fenofibrate may be used safely		☐	☐
Patient is taking vitamin A > 15,000 IU daily (risk of hypervitaminosis A)		☐	☐
If the response to ANY item below is YES, use caution and weigh potential risks and benefits before deciding to use bexarotene.			
Patient has risk factors for pancreatitis (e.g., history of pancreatitis, hyperlipidemia uncontrolled by lipid-lowering agents, excessive alcohol consumption, uncontrolled diabetes mellitus, biliary tract disease, and medications known to increase triglyceride levels or to be associated with pancreatic toxicity)		☐	☐
Discontinuation Criteria		**Yes**	**No**
If the answer to the item below is YES, then bexarotene should be discontinued			
Lack of clinical improvement within 12 weeks after titrating bexarotene to 400 mg / m^2 daily or maximum tolerated dose		☐	☐
If the answer to the item below is YES, then the physician should consider discontinuing or temporarily stopping bexarotene therapy			
Increase in liver transaminases or bilirubin to more than 3 times the upper limit of normal		☐	☐
Dispensing and Administration Limits			
Quantity limit: 30-day supply			
Timing of initial dose: 2^{nd} or 3^{rd} day of normal menstrual period			
Monitoring			
Check lipid levels before starting therapy, weekly until the lipid response is established (usually within 2 to 4 weeks), then every 8 weeks			
Check liver function tests before starting therapy, at 1, 2, and 4 weeks after starting therapy, and if stable, then every 8 weeks thereafter			
Check thyroid function tests before starting and as indicated during therapy; monitor for signs and symptoms of potential hypothyroidism. Consider starting thyroid replacement after baseline thyroid function tests, particularly with high-dose bexarotene.			
Check white blood cell count with differential before starting therapy and periodically during therapy			
Perform monthly pregnancy test			

Monitor for visual difficulties and development of cataracts; if visual problems occur, refer patient for further evaluation
Counsel patient on a regular basis to reinforce use of effective contraceptive methods and avoidance of pregnancy and birth defects

Table 3 Criteria for Use of Isotretinoin

Oral	Pregnancy category X	Formulary

Inclusion Criteria	**Yes**	**No**
The response to ALL items below must be YES to use orally administered isotretinoin		
Provider authorizing the initiation of therapy is a dermatologist and is registered in iPledge. *Subsequent prescriptions may be renewed by dermatologists or other locally authorized clinicians (including nurse practitioners or physician assistants). Approved clinicians should be under the supervision of or, in a co-managed care situation, working with a dermatologist, and appropriate patient monitoring must be followed. Prescribers, Delegated Prescribers, and Designees, as defined in the iPledge program, must be registered in iPledge (*www.iPLEDGEprogram.com).	☐	☐
Patient meets either ONE of the following criteria: ☐ Severe nodulocystic acne vulgaris (many inflammatory nodules ≥ 5 mm in diameter) AND has documented inadequate response, intolerance, or contraindication to at least 4 weeks of prior combined therapy with 2 anti-acne topical agents of different classes (e.g., benzoyl peroxide, retinoid, antibiotic) AND 1 non-retinoid systemic therapy ☐ Moderate to severe acne vulgaris (erythematous papules, pustules, nodules limited mostly to face, evidence of scarring, or acne lesions with potential for scarring) AND has documented inadequate response, intolerance, frequent relapses, or contraindication to prior treatment with topical benzoyl peroxide and at least 2 of each of the following types of formulary and nonformulary agents (at least 6-week trial for each agent alone or the combination of ≥ 2 agents): topical antibiotics, topical retinoids, systemic antibiotics, antiandrogen / hormonal therapies (females only). ***Examples of Formulary agents:*** *Topical — benzoyl peroxide ± erythromycin, erythromycin, tretinoin. Oral — clindamycin, doxycycline, erythromycin, minocycline, tetracycline, various oral contraceptives.* ***Examples of nonformulary agents:*** *Topical — adapalene, dapsone, tazarotene Oral —oxytetracycline*	☐	☐
Patient meets all requirements of iPLEDGE (regardless of condition to be treated with isotretinoin), summarized in part below ☐ Patient agrees to avoid donating blood during the period of teratogenic risk (during therapy and for 1 month after discontinuation of isotretinoin)	☐	☐
☐ If female, patient has been counseled and agrees to avoid pregnancy by using two effective forms of contraception simultaneously and continuously for one month before, during, and one month after isotretinoin therapy, unless patient is committed to continuous abstinence from heterosexual contact, has had a hysterectomy or bilateral oophorectomy, or is medically confirmed to be postmenopausal ☐ Patient has signed the isotretinoin *Patient Information/Informed Consent (for All Patients)* and, if patient is a female of childbearing potential, has signed an isotretinoin *Patient Information / Informed Consent About Birth Defects (for female patients who can get pregnant)* (see http://www.rocheusa.com/products/accutane/pi.pdf , pp. 31–39) ☐ If patient is a female of childbearing potential, she must have two negative urine or serum pregnancy tests with sensitivities of at least 25 mIU / ml before starting therapy: the first, a screening test, done by the prescriber when the decision is made to pursue qualification of the patient for isotretinoin therapy; and the second, a confirmation test, done at least 19 days after the screening test in a CLIA-certified laboratory and after the patient has used two contraceptive methods simultaneously for at least 1 month; the tests must be timed according to the regularity of the patient's menstrual cycles (check Product Information for details); patient must also have negative monthly pregnancy tests during therapy ☐ Provider and patient are registered and activated in the pregnancy risk management program, iPLEDGE		
Prescriber has questioned patient or patient's family about prior psychiatric disorders, and has determined that the potential benefits of isotretinoin outweigh its potential risks, which include depression, mood disorder, psychosis, or aggression)	☐	☐
Patient has been counseled on the possible association between isotretinoin and depression, psychosis, suicidality, psychiatric disorders, and aggression	☐	☐
There is insufficient (Grade I) evidence to recommend for or against the use of ***isotretinoin*** *for the following conditions (its use should be considered on a case-by-case basis): conglobate acne, hemodialysis-related nodulocystic acne, cervical condylomata acuminata (human papillomavirus infection), discoid lupus erythematosus, mycosis fungoides, oral leukoplakia (for resolution of lesions only–lack of evidence for prevention of malignant transformation), or early recurrence of prostate cancer*		

Exclusion Criteria	**Yes**	**No**
If the response to ANY item below is YES, then the patient should NOT receive isotretinoin.		
Patient has mild acne vulgaris (comedones with no or minimal inflammatory lesions)	☐	☐
Patient is pregnant, planning pregnancy, or is nursing	☐	☐
Patient has contraindication to isotretinoin (i.e., hypersensitivity to isotretinoin or its components, such as parabens)	☐	☐

Patient is taking tetracyclines (risk of pseudotumor cerebri), St. John's Wort (interaction with hormonal contraceptives), supplements containing vitamin A (risk of hypervitaminosis A)	☐	☐
Use of isotretinoin for any of the following conditions: cervical cancer, cancer chemoprevention, condylomata acuminata (venereal warts in men), cutaneous T-cell lymphoma—Sézary syndrome, myelodysplastic syndrome, ovarian cancer, renal cell carcinoma	☐	☐
Discontinuation Criteria	**Yes**	**No**
If the answer to the item below is YES, then isotretinoin should be discontinued		
Patient on isotretinoin for acne shows NO evidence of beneficial clinical effects within 4 months of starting therapy.	☐	☐
Patient is female and has unprotected heterosexual intercourse within one month before, during, or one month after isotretinoin therapy. *Restarting isotretinoin may be considered only after the patient has had a negative first pregnancy test at least 19 days after unprotected heterosexual intercourse and a negative second pregnancy test after using two effective forms of contraception simultaneously for at least 1 month (the pregnancy test should be timed according to regularity of menstrual periods—see product information for details).*	☐	☐
If the answer to the item below is YES, then isotretinoin should be discontinued and the patient referred for further evaluation	**Yes**	**No**
Patient becomes pregnant during isotretinoin therapy *Pregnancy must be reported to FDA MedWatch 1-800-FDA-1088 AND iPLEDGE pregnancy registry (*1-866-495-0654 or www.iPLEDGEprogram.com)	☐	☐
Patient develops depression, mood disorder, psychosis, or aggression	☐	☐
Patient develops any of the following adverse effects: ☐ Pseudotumor cerebri (papilledema, headache, nausea, vomiting, and visual disturbances) ☐ Uncontrolled hypertriglyceridemia or pancreatitis ☐ Unexplained hearing loss or tinnitus ☐ Persistent increase in liver enzymes or hepatitis ☐ Inflammatory bowel disease (abdominal pain, severe diarrhea, rectal bleeding) ☐ Visual difficulties	☐	☐
Dispensing Limits		
Wholesalers, providers, pharmacies, and patients must be registered, activated, and meet ALL requirements in iPLEDGE. To prescribe and dispense isotretinoin, the prescriber and pharmacy must access the iPLEDGE system via the internet (www.ipledgeprogram.com) or telephone (1-866-495-0654).		
Patients must have the prescription for isotretinoin filled within 7 days of the clinic visit and should receive no more than a 30-day supply of isotretinoin without automatic refills		
Monitoring		
Check urine or serum pregnancy test every month during isotretinoin therapy, at completion of therapy, and one month after discontinuation of therapy, as required by iPLEDGE. *Pregnancy tests should have a sensitivity of at least 25 mIU / ml and must be CLIA-certified (Clinical Laboratory Improvement Amendment). Authorization to dispense isotretinoin will not be granted by iPLEDGE without a monthly negative pregnancy test.*		
Counsel patient monthly to reinforce avoidance of pregnancy and the warning not to share isotretinoin with others, as required by iPLEDGE		
Pharmacists must provide patient with an isotretinoin *Medication Guide* each time drug is dispensed, as required by law		
Evaluate patient for possible depression, mood disturbance, psychosis, or aggression at each visit		
Check blood lipid concentrations before starting therapy and at weekly or biweekly intervals until lipid response is established (usually within 4 weeks); monitor more frequently or for a longer period in patients at risk (e.g., those with diabetes mellitus, hyperlipidemia, family history of hyperlipidemia, obesity, increased alcohol use, or pancreatitis)		
Check liver enzymes before starting therapy and at weekly or biweekly intervals until response is established.		

Table 4 Criteria for Use of Oral Tretinoin / ATRA (all-*trans*-retinoic acid)

Oral	Pregnancy category D	Nonformulary

Inclusion Criteria	**Yes**	**No**
The response to ALL items below must be YES to use oral tretinoin		
Prescriber is a hematologist/oncologist	☐	☐
Patient has initial clinical (suspected) or new confirmed diagnosis of acute promyelocytic leukemia (APL), French American British (FAB) classification M3 (including M3 variant), characterized by the presence of the t(15;17) translocation or the PML / RARα gene AND requires remission induction or maintenance therapy (generally in combination with chemotherapy) (Grade A / B)	☐	☐
Patient meets the pregnancy risk management requirements summarized below:	☐	☐
☐ If female, patient has been counseled on the risk of birth defects and agrees to avoid pregnancy by using two effective forms of contraception simultaneously and continuously for one month before, during, and one month after isotretinoin therapy, unless patient is committed to continuous abstinence from heterosexual contact or has had a hysterectomy. *Even patients with a history of sterility or menopause must use two forms of contraception, unless a hysterectomy has been performed. The microdosed progesterone minipill may be an ineffective contraceptive method with tretinoin.*		
☐ If patient is a female of childbearing potential, she must have two negative urine or serum pregnancy tests with sensitivities of at least 25 mIU / ml before starting therapy and negative monthly pregnancy tests during therapy		
☐ The provider and patient feel that the potential benefits of tretinoin / ATRA therapy outweigh the potential risks, including risk of spontaneous abortions and birth defects should the patient be pregnant or be of childbearing potential		

Exclusion Criteria	**Yes**	**No**
If the response to ANY item below is YES, then the patient should NOT receive oral tretinoin.		
Use of tretinoin outside of a clinical trial protocol for either one of the following situations:	☐	☐
☐ Consolidation or salvage therapy for M3-type APL (Grade D / I)		
☐ Induction or maintenance therapy in combination with arsenic trioxide for newly diagnosed M3-type APL (Grade I)		
Concomitant intake of vitamin A supplements (risk of hypervitaminosis A)	☐	☐
Hypersensitivity to tretinoin or other product components, including parabens	☐	☐
Patients who are nursing	☐	☐

Discontinuation Criteria	**Yes**	**No**
If the answer to the item below is YES, then oral tretinoin should be discontinued		
Cytogenetics or molecular testing does not confirm t(15;17)	☐	☐
Increase in liver enzymes to > 5 times the upper limit of normal	☐	☐
Patient received tretinoin for 30 days after achieving complete remission or for 90 days, whichever comes first	☐	☐

Dispensing Limits

None

Monitoring

Follow local monitoring guidances to assess for therapeutic response and for rapidly evolving leukocytosis; however, evaluation of bone marrow for cytogenetic response should be done no sooner than 35 days after start of treatment

Monitor patient closely for retinoic acid syndrome, particularly during the first month of treatment
(Also called APL differentiation syndrome or retinoic acid–APL syndrome; characterized by fever, weight gain, edema, fluid retention, respiratory distress, pulmonary infiltrates, pulmonary and pleural effusions, and hepatic, renal, and multi-organ failure)

Monitor patient for possible signs and symptoms of pseudotumor cerebri
I.e., papilledema, headache, nausea, vomiting, visual disturbances; if symptoms are present, institute appropriate care and perform neurologic evaluation

Monitor for possible drug-drug interactions (e.g., with tetracyclines) that might increase the risk of pseudotumor cerebri

Check cholesterol and triglyceride levels on a regular basis

Check urine or serum pregnancy test every month during oral tretinoin therapy

Counsel patient monthly to reinforce avoidance of pregnancy

Table 5 Criteria for Use of High-dose Vitamin A (≥ 25,000 IU / day in adults)

Oral or intramuscular	Pregnancy category X	Nonformulary

Criteria for Use	**Yes**	**No**
The response to ALL items below must be YES to use high-dose vitamin A		
Patient meets either one of the following descriptions:	☐	☐
☐ A male or female NOT of childbearing potential who requires treatment for severe vitamin A deficiency with xerophthalmia		
☐ A female of childbearing potential who has severe signs of *active* xerophthalmia (i.e., acute corneal lesions) *(Women of childbearing potential with less than severe xerophthalmia [night blindness, Bitot's spots] should receive lower doses [5000 to 10,000 IU / d orally for at least 4 wk].)*		
There is insufficient (Grade I) evidence to recommend for or against the use of high-dose vitamin A in the treatment of patients with the following conditions (its use should be considered on a case-by-case basis): prevention of second primary tumors in patients with resected stage 1 non-small cell lung cancer (study dose: 300,000 IU daily, orally); and prevention of nonmelanoma squamous cell carcinoma of the skin in moderate / high-risk individuals (25,000 IU daily, orally)	☐	☐
Exclusion Criteria	**Yes**	**No**
If the response to ANY item below is YES, then the patient should NOT receive high-dose vitamin A (≥25,000 IU / d)		
Patient is pregnant	☐	☐
Hypersensitivity to vitamin A	☐	☐
Patient has hypervitaminosis A	☐	☐
Use of high-dose vitamin A for any of the following:	☐	☐
☐ Maintenance of remission of Crohn's disease		
☐ Prevention of lung cancer		
☐ Adjunctive therapy for chronic-phase chronic myelogenous leukemia		
☐ Prevention of malignant transformation and relapse of oral leukoplakia and resolution of lesions		
☐ Treatment of early-stage cutaneous melanoma		
☐ Prevention of nonmelanoma skin cancer in high / very high–risk individuals		
☐ Prevention of basal cell carcinoma in moderate / high-risk individuals		
Discontinuation Criteria	**Yes**	**No**
If the answer to the item below is YES, then high-dose vitamin A should be discontinued		
Completion of 2 weeks of high-dose vitamin A therapy (see dosing) for treatment of severe vitamin A deficiency. *Lower doses of 10,000 to 20,000 IU / d may be given for 2 months after high-dose vitamin A (≥ 25,000 IU / d) therapy.*		
Dispensing Limits		
None		
Monitoring		
Vitamin A should not be administered intravenously.		
Avoid prolonged use of mineral oil during oral vitamin A therapy (decreases absorption of oral vitamin A).		
Patients with malabsorption should not receive the oral formulation of vitamin A.		

Table 6 Criteria for Use of Alitretinoin

Topical	Pregnancy category D	Nonformulary

Inclusion Criteria	**Yes**	**No**
The response to ALL items below must be YES to use alitretinoin		
Provider is an AIDS specialist, hematologist / oncologist, or Provider authorizing the initiation of therapy is a dermatologist. *Subsequent prescriptions may be renewed by dermatologists or other locally authorized clinicians (including nurse practitioners or physician assistants). Approved clinicians should be under the supervision of or, in a co-managed care situation, working with a dermatologist, and appropriate patient monitoring must be followed*	☐	☐
Patient requires topical treatment for cutaneous lesions of AIDS-related Kaposi's sarcoma	☐	☐
Patient is receiving highly active antiretroviral therapy (HAART)	☐	☐
Patient has documented inadequate response, intolerance, contraindication, or inconvenient access to local irradiation therapy AND intralesional vinblastine, AND, if patient has small lesions, cryotherapy	☐	☐
Exclusion Criteria	**Yes**	**No**
If the response to ANY item below is YES, then the patient should NOT receive alitretinoin		
Patient requires systemic treatment for AIDS-related Kaposi's sarcoma (> 10 new KS lesions in prior month, symptomatic lymphedema, pulmonary KS, or visceral involvement)	☐	☐
Hypersensitivity to alitretinoin or other product components	☐	☐
Concurrent topical therapy with DEET-containing products (N,N-diethyl-m-toluamide) (risk of DEET toxicity)	☐	☐
Patient is nursing *(Breastfeeding may be discontinued prior to starting alitretinoin therapy)*	☐	☐
Discontinuation Criteria	**Yes**	**No**
If the answer to the item below is YES, then alitretinoin should be discontinued		
Lack of documented initial beneficial effects despite 4 months of therapy Lack of documented continued benefit after 2 years of therapy (effectiveness has not been evaluated beyond 96 weeks in controlled trials).	☐	☐
Dispensing Limits		
No refills in first 4 months of therapy to reinforce reassessment of patient response. Thereafter, if patient has experienced a therapeutic benefit, refills may be prescribed for up to 1 year at a time.		
Monitoring		
Application to coexisting cutaneous T-cell lymphoma lesions may cause severe irritation		
Counsel patients of childbearing potential on avoiding pregnancy during therapy at each prescription refill.		
Advise patient to avoid exposing the treated areas to sunlight and sunlamps (risk of photosensitivity)		

Table 7 Criteria for Use of Topical Bexarotene

Topical **Pregnancy category X** **Nonformulary**

Inclusion Criteria	**Yes**	**No**
The response to ALL items below must be YES to use topical bexarotene		
Prescriber is a hematologist / oncologist or Provider authorizing the initiation of therapy is a dermatologist. *Subsequent prescriptions may be renewed by dermatologists or other locally authorized clinicians (including nurse practitioners or physician assistants). Approved clinicians should be under the supervision of or, in a co-managed care situation, working with a dermatologist, and appropriate patient monitoring must be followed*	☐	☐
Patient has cutaneous lesions of stage IA or IB cutaneous T-cell lymphoma (CTCL)	☐	☐
Patient has documented inadequate response, intolerance, or contraindication to topical nitrogen mustard, topical corticosteroids, and—for extensive disease—PUVA, if PUVA therapy is readily available.	☐	☐
Patient meets one of the pregnancy risk management requirements described below.	☐	☐
☐ If patient is a male, he commits to using condoms during sexual intercourse while receiving bexarotene therapy and for 1 month after discontinuation of bexarotene		
☐ If patient is a female of childbearing potential, she — has a negative serum pregnancy test (i.e., serum beta-human chorionic gonadotropin, beta-HCG) with a sensitivity of ≥ 25 mIU / ml within 1 week of starting bexarotene therapy and monthly during therapy — AND selects and commits to using 2 effective contraceptive methods simultaneously, one of which should be nonhormonal, for 1 month prior to starting bexarotene, during bexarotene therapy, and for 1 month after discontinuation of bexarotene OR chooses abstinence as the contraceptive method.		
☐ Patient is not of childbearing potential (i.e., has had a hysterectomy or bilateral oophorectomy)		

Exclusion Criteria	**Yes**	**No**
If the response to ANY item below is YES, then the patient should NOT receive topical bexarotene		
Concomitant therapy with other CTCL treatments (not studied)	☐	☐
Patient is pregnant, planning pregnancy, or is nursing	☐	☐
Patient has contraindication to bexarotene (i.e., hypersensitivity)	☐	☐
Patient is taking gemfibrozil (uncertain risk associated with increase in systemic levels of cutaneously absorbed bexarotene due to CYP3A4 inhibition) or vitamin A > 15,000 IU daily (risk of hypervitaminosis A) or using DEET (N, N-diethyl-m-toluamide) (potential for increased DEET toxicity)	☐	☐

Discontinuation Criteria	**Yes**	**No**
If the answer to the item below is YES, then topical bexarotene should be discontinued		
Documentation of lack of continued benefit after 3 years of therapy	☐	☐

Dispensing and Administration Limits
Quantity limit: 30-day supply
Timing of initial dose: 2nd or 3rd day of normal menstrual period

Monitoring
Since the effectiveness of bexarotene beyond 172 weeks of therapy has not been evaluated, reassess patients on a regular basis to determine whether the patient is benefiting from long-term therapy
Check monthly serum pregnancy test during therapy
Counsel patient on a regular basis to reinforce use of effective contraceptive methods and avoidance of pregnancy and birth defects

Table 8 Criteria for Use of Tazarotene

Topical	Pregnancy category X	Nonformulary

Inclusion Criteria	**Yes**	**No**
The response to ALL items below must be YES to use topical tazarotene		
Patient meets at least ONE of the following conditions:	☐	☐
☐ Moderate to severe stable plaque psoriasis AND has documented inadequate response, intolerance, or contraindication to topical corticosteroids and calcipotriene (Grade I)		
☐ Mild to moderate facial acne vulgaris AND has documented inadequate response, intolerance, or contraindication to tretinoin 0.1% topical formulation (pregnancy category C–acne, Grade I evidence) AND adapalene 0.1% gel (pregnancy category C, Grade I evidence)		
☐ Maintenance therapy of chronic, stable, moderate to severe plaque psoriasis (a thrice-weekly dosing schedule with or without clobetasol) or acne vulgaris (alternate-day, similar to adapalene 0.1% once daily). There is insufficient (Grade I) evidence for or against the use of topical tazarotene for these uses (consider on a case-by-case basis).	☐	☐
If patient is female, she has had a negative serum pregnancy test with a sensitivity of ≥ 25 mIU / ml for human chorionic gonadotropin (hCG) within 2 weeks prior to starting tazarotene	☐	☐
There is insufficient (Grade I) evidence for or against the use of topical tazarotene for the following uses (case-by-case basis): a thrice-weekly dosing schedule with or without clobetasol as maintenance therapy of chronic, stable, moderate to severe plaque psoriasis; alternate-day tazarotene for acne vulgaris (similar to adapalene 0.1% once daily)	☐	☐
Exclusion Criteria	**Yes**	**No**
If the response to ANY item below is YES, then the patient should NOT receive topical tazarotene		
Patient is pregnant or planning pregnancy *(The extent of body surface exposure and transdermal absorption of tazarotene sufficient to cause teratogenic effects are unknown.)*	☐	☐
Patient has documented hypersensitivity to any product components	☐	☐
Patient has eczema or sunburn in the application area *(Do not start therapy until after the eczema or sunburn has resolved.)*	☐	☐
Discontinuation Criteria	**Yes**	**No**
If the answer to the item below is YES, then topical tazarotene should be discontinued		
Patient becomes pregnant *(Patient should be counselled on risk of birth defects.)*	☐	☐
Dispensing and Administration Limits		
If patient is of childbearing potential, start tazarotene therapy during a normal menstrual period		
If patient uses emollients, at least 1 hour should elapse before applying tazarotene		
Monitoring		
Counsel patients of childbearing potential on a regular basis to reinforce use of effective contraceptive methods and avoidance of pregnancy		
Counsel patients on avoidance of sunlight and sunlamps (unless medically prescribed), and use of sunscreens (SPF > 15) and protective clothing		
Use caution when tazarotene is used concomitantly with other photosensitizing drugs (e.g., fluoroquinolones, phenothiazines, sulfonamides, tetracyclines, thiazides)		
Monitor concomitant vitamin A intake		

Table 9 Criteria for Use of Topical Tretinoin

Topical	Pregnancy category X—photodamage Pregnancy category C–acne	Formulary

Inclusion Criteria	**Yes**	**No**
The response to ALL items below must be YES to use topical tretinoin		
Patient has mild to moderate facial acne vulgaris	☐	☐
There is insufficient (Grade I) evidence to recommend for or against the use of topical tretinoin for the following conditions (its use should be considered on a case-by-case basis): treatment of solar keratoses and warts in heart / kidney transplant recipients		
Exclusion Criteria	**Yes**	**No**
If the response to ANY item below is YES, then the patient should NOT receive topical tretinoin		
The sole intended purpose of topical tretinoin is to treat photodamage of the skin	☐	☐
Patient has contraindication to tretinoin (i.e., hypersensitivity)	☐	☐
Discontinuation Criteria	**Yes**	**No**
If the answer to the item below is YES, then topical tretinoin should be discontinued		
Patient develops severe location reaction at site of application (e.g., edema, erythema, blistering, crusting) *(Temporarily discontinue tretinoin until skin recovers or reduce dosage.)*	☐	☐
Dispensing and Administration Limits		
None		
Monitoring		
Counsel patients on avoidance of sunlight and sunlamps, and use of sunscreens and protective clothing		

Table 10 Evidence Rating: Indications for Use (Placebo-controlled Trials)

Strength of Recommendation and Evidence Rating	Reference†	Quality of Evidence	External Validity to VA
Grade A (always indicated and acceptable):			
Alitretinoin (topically) for HIV-related Kaposi's sarcoma (KS) in patients who do not require systemic anti-KS treatment and who have relatively high performance status	Overall:	Good	Possible
	Dedicoat (2005), CSR[14]	Good	Possible
	Product Information[4]	—	—
Grade B (may be useful / effective):			
Tretinoin (orally) in combination with anthracycline-based chemotherapy as induction or maintenance therapy for newly diagnosed APL	Overall:	Fair	Limited
	Sun (1993)[15]	Fair	Very limited
	Fenaux (1993)[16]	Fair	Limited
	Fenaux (1999)[17]	Fair	Limited
	Burnett (1999)[18]	Fair	Limited
	Also see related: Tallman (1997, 2002)[19, 20]	Fair	Limited
Tretinoin (0.01% to 0.1% topical cream) for photodamage on face or forearms	Overall:	Fair	Limited
	Samuel (2005), CSR[21]	Good	Limited
Grade C (may be considered):			
No clinical trials			
Grade D (may not be useful / effective; possibly harmful):			
Isotretinoin (orally) for cervical cancer, monotherapy or add-on therapy	Overall:	Poor	Limited
	Kim (1996)[22]	Poor	Limited
	Robinson (2002)[23]	Poor	Limited
	Veerasarn (1996)[24]	Poor	Limited
Isotretinoin (orally) for chemoprevention of head and neck cancer, second primary tumors	Overall:	Poor / Fair	Limited
	Toma (2004)[25]	Poor	Limited
	Lippman (1993),[26] Papadimitrakopoulou (1997),[27] Benner (1994)[28]	Poor	Limited
	Hong (1990),[29] Benner (1994)[30]	Fair	Limited
	Perry (2005)[31]	Fair	Limited
Isotretinoin (orally) for chemoprevention of lung cancer, second primary tumors or squamous metaplasia	Overall	Fair	Probable
	Lippman (2001)[32]	Fair	Probable
	Lee (1994)[33]	Poor	Limited
Isotretinoin (orally) for condylomata acuminata (venereal warts) in males	Olsen (1989)[34]	Poor	Limited
Isotretinoin (orally) for cutaneous T-cell lymphoma – Sézary syndrome	Molin (1987)[35]	Poor	Limited
Isotretinoin (orally) for myelodysplastic syndrome	Overall:	Poor	Limited
	Clark (1987)[36]	Poor	Limited
	Koeffler (1988)[37]	Fair	Limited
	Besa (1990)[38]	Poor (OS)	Limited
	Bourantas (1995)[39]	Poor (OS)	Limited
	Letendre (1995)[40]	Poor	Limited
	Hellstrom (1990)[41]	Poor	Limited
Isotretinoin (orally) for ovarian cancer (cancer antigen (CA) 125 levels or tumor progression)	Rustin (1996)[42]	Poor	Limited
Isotretinoin (orally) for renal cell carcinoma, add-on therapy	Overall:	Poor	Possible
	Fossa (2004)[43]	Poor	Possible
	Casali (1998)[44]	Poor	Limited
	Atzpodien (2004)[45]	Poor	Possible
	Atzpodien (2002)[46]	Poor	Possible
Isotretinoin (5–10 mg / d, orally) for chemoprevention of	Overall:	Fair	Possible

Strength of Recommendation and Evidence Rating	Reference†	Quality of Evidence	External Validity to VA
nonmelanoma skin cancer, basal or squamous cell carcinoma	Levine (1997),[47] Moon (1995)[48]	Fair	Possible
	Tangrea (1992)	Fair	Possible
	Moon (1997), Moon (1995)[48]	Fair	Possible
Tretinoin (oral) in combination with arsenic trioxide as salvage therapy for recurrent APL	Raffoux (2003)[49]	Poor	Limited
Tretinoin (< 0.01% topical cream) for photodamage (higher concentrations *are* effective)	Overall:	Fair	Limited
	Samuel (2005), CSR[21]	Good	Limited
Vitamin A (100,000 IU daily, orally) for maintenance of remission of Crohn's disease	Wright (1985)[50]	Fair	Limited
Vitamin A (25,000 IU daily, orally) for prevention of lung cancer	Overall:	Fair	Probable, high risk patients
	Omenn (1996),[51] Bowen (2003),[52] Omenn (1994),[53] Thornquist (1993),[54] Omenn (1993),[55] Goodman (1993),[56] Omenn (1991),[57] Goodman (1992),[58] Cullen (2005),[59] Redlich (1999),[60] Neuhouser (2003)[61]	Fair	Probable
	Caraballoso (2005), CSR[62]	Good	Probable
Vitamin A (retinol / retinol palmitate 50,000 IU / d, orally) as adjunctive therapy to busulfan for chronic-phase chronic myelogenous leukemia	Meyskens (1995)[63]	Poor	Very limited
Vitamin A for prevention of malignant transformation and relapse of oral leukoplakia and resolution of lesions	Overall:	Poor–Fair	Limited
	Stich (1988)[64]	Poor	Very limited
	Lodi (2005), CSR[65]	Good	Possible
Vitamin A (100,000 IU daily, orally) for early-stage, cutaneous melanoma	Meyskens (1994)[66]	Poor	Limited
Vitamin A (25,000 IU daily, orally) for prevention of nonmelanoma skin cancer in high / very high–risk individuals and prevention of basal cell carcinoma in moderate / high-risk individuals	Overall:	Poor	Possible
	Levine (1997)[47]	Fair	Possible
	Moon (1997, 1995),[48, 67] Cartmel (1999)[68]	Fair	Possible
Grade I (insufficient evidence to recommend for or against):			
Acitretin (20 to 70 mg / d) for severe, steroid-resistant lichen planus	Laurberg (1991)[69]	Fair	Limited
Acitretin (20 to 30 mg / d) for severe lichen sclerosis et atrophicus of vulva	Bousema (1994)[70]	Poor	Limited
Acitretin (50 mg / d) for discoid lupus erythematosus (LE) or subacute cutaneous LE is comparable to hydroxychloroquine 400 mg / d	Ruzicka (1992)[71]	Fair	Limited
Acitretin (25 to 30 mg / d or 0.25 to 0.30 mg / kg / d) for treatment or prevention of squamous or basal cell carcinoma of the skin in renal transplant recipients	Overall:	Poor	Limited
	de Sevaux (2003)[72]	Poor	Limited
	George (2002)[73]	Poor	Limited
	Bavinck (1995)[74]	Fair	Limited
	McKenna (1999)[75]	Poor (OS)	Very limited
Isotretinoin (orally) for acne conglobate	Overall:	Poor	Limited
	Hennes (1984)[76]	Poor	Unclear
	Peck (1982)[77]	Fair	Limited
Isotretinoin (orally) for hemodialysis-related nodulocystic acne	Lin (1999)[78]	Poor	Limited
Isotretinoin (orally) for cervical condylomata acuminata (human papillomavirus infection)	Georgala (2004)[79]	Fair	Limited
Isotretinoin (orally) for discoid lupus erythematosus	Jessop (2005), CSR[80]	Good	Unclear

Strength of Recommendation and Evidence Rating	Reference[†]	Quality of Evidence	External Validity to VA
Isotretinoin (orally) for cutaneous T-cell lymphoma – mycosis fungoides	Molin (1987)[35]	Poor	Limited
Isotretinoin (orally) for oral leukoplakia (resolves lesion, but high relapse rate; no data on malignant transformation)	Overall:	Poor	Possible
	Kaugars (1995, letter)[81]	Poor	Unclear
	Hong (1986)[82]	Fair	Possible[‡]
	Lodi (2005), CSR[65]	Fair	Possible[‡]
Isotretinoin (orally) for photodamaged skin	Hernandez-Perez (2000)[83]	Poor	Very limited
Isotretinoin (orally) for prostate cancer, using biomarker of antitumor effects, in patients with early recurrence (increasing prostate-specific antigen [PSA] levels); add-on therapy	DiPaola (1997)[84]	Poor	Probable
Tazarotene (0.01% to 0.1%) for mild to severe photodamage in patients who use comprehensive skin care and sunlight avoidance programs (need further studies) [Only 0.05% and 0.1% strengths are FDA-approved]	Overall:	Poor	Limited
	Samuel (2005), CSR[21]	Good	Limited
Tazarotene (0.1% gel once daily 3 days / week) with or without clobetasol (0.05% ointment 2 days / week) as maintenance therapy of chronic, stable, moderate to severe plaque psoriasis	Lebwohl (2001)[85]	Poor	Unclear
Tretinoin (orally) added on to arsenic trioxide as induction or maintenance therapy for newly diagnosed acute promyelocytic leukemia (conflicting evidence)	Shen (2004)[86]	Poor	Very limited
Tretinoin (0.05% topical cream) for treatment of solar keratoses and warts in heart / kidney transplant recipients	Euvrard (1992)[87]	Poor	Limited
Vitamin A (300,000 IU daily, orally) for prevention of second primary tumors in patients with resected stage 1 non-small cell lung cancer	Pastorino (1993, 1991, 1988)[88-90]	Poor	Limited
Vitamin A (25,000 IU daily, orally) for prevention of nonmelanoma squamous cell carcinoma of the skin in moderate / high-risk individuals	Moon (1997, 1995),[48, 67] Cartmel (1999)[68]	Fair	Possible

Evidence rating scheme based on methods used by the third U.S. Preventive Services Task Force[91] and the U.K. National Health Service Centre for Reviews and Dissemination[92]

Abbreviations: APL, Acute promyelocytic leukemia; CSR, Cochrane systematic review; IFNα2a, interferon alpha-2a; OS, Observational study; PRMP, Pregnancy Risk Management Program; PUVA, psoralen ultraviolet A; RCT, Randomized controlled trial

Routes of administration: Acitretin (orally), alitretinoin (topically), bexarotene (orally, topically), isotretinoin (orally), tazarotene (topically), tretinoin (orally, topically), vitamin A / retinol / retinyl palmitate (orally).

[†] Multiple references in a single cell indicate papers on the same trial

[‡] Study included U.S. veterans

[§] French American British (FAB) classification M3 (including M3 variant), characterized by the presence of the t(15;17) translocation or the PML/RARα gene. Alternative therapy should be considered for patients who lack the genetic marker.

Table 11 Evidence Rating: Less Teratogenic Alternative Agents (Head-to-head and Active-controlled Trials)

Strength of Recommendation and Evidence Rating	Reference†	Quality of Evidence	External Validity to VA
Grade A (always indicated and acceptable):			
No clinical trials			
Grade B (may be useful / effective):			
Isotretinoin (orally) is better than tetracycline for recalcitrant nodulocystic or conglobate acne	Lester (1985)[93]	Fair	Limited
Grade C (may be considered):			
Tazarotene 0.05% and 0.1% topically (pregnancy category X with PRMP) are, respectively, similar to and superior to tretinoin 0.05% (pregnancy category X–photodamage, no PRMP) for photodamage / wrinkles	Overall:	Fair	Limited
	Lowe (2004)[94]	Fair	Limited
	Kang (2001)[95]	Fair	Unclear
Grade D (may not be useful / effective; possibly harmful):			
No clinical trials			
Grade I (insufficient evidence to recommend for or against):			
Acitretin (50 mg / d) for discoid lupus erythematosus (LE) or subacute cutaneous LE is comparable to hydroxychloroquine 400 mg / d	Overall:	Poor	Limited
	Ruzicka (1992)[71]	Fair	Limited
Acitretin (25 to 50 mg / d) as add-on therapy to IFNα2a for stage I and II cutaneous T-cell lymphoma is inferior to add-on PUVA	Stadler (1998)[96]	Poor	Limited
Isotretinoin (orally) for recalcitrant or severe rosacea; low-dose isotretinoin has been shown to be similar in efficacy to topical tretinoin (however, no fair or good-quality placebo-controlled RCTs have evaluated efficacy of either agent)	Overall:	Poor	Limited
	Ertl (1994)[97]	Fair	Limited
	van Zuuren (2005), CSR[98]	No RCTs	No RCTs
Alternate-day tazarotene (0.1% gel, Category X with PRMP) is similar to adapalene (0.1% once daily, Category C) in efficacy, safety, and tolerability, and allows less frequent dosing for acne vulgaris	Overall:	Poor	Limited
	Leyden (2001)[99]	Fair	Limited
Tazarotene (0.05% and 0.1% gel once daily) as an alternative to fluocinonide (0.05% gel twice daily) for mild to moderate plaque psoriasis	Lebwohl (1998)[100]	Poor	Possible
Tazarotene (0.1% gel once daily) in combination with mometasone (0.1% cream once daily) as a more effective alternative to calcipotriene (0.005% ointment) for moderate to severe plaque psoriasis	Guenther (2000)[101]	Poor	Very limited
Tazarotene (0.1% gel once daily, Category X) is more efficacious than and as well tolerated as adapalene (0.1% gel once daily, Category C) for mild to moderate facial acne vulgaris	Overall:	Poor	Limited
	Webster (2002)[102]	Fair	Limited
Tazarotene (0.1% gel once daily; Category X with PRMP) is moderately more effective and as well tolerated as tretinoin (0.1% gel once daily, pregnancy category C–acne) but may be more irritating for mild to moderate acne vulgaris	Overall:	Poor	Very limited
	Webster (2001)[103]	Fair	Very limited
Vitamin A (25,000 IU daily, orally), as an "antioxidant" in patients with coronary heart disease, is second-line to fruits (400 g daily), vitamin E (400 IU daily), and vitamin C (1 g daily)	Singhal (2001)[104]	Poor	Limited

Evidence rating scheme based on methods used by the third U.S. Preventive Services Task Force[91] and the U.K. National Health Service Centre for Reviews and Dissemination[92]

Abbreviations: APL, Acute promyelocytic leukemia; CSR, Cochrane systematic review; IFNα2a, interferon alpha-2a; OS, Observational study; PRMP, Pregnancy Risk Management Program; PUVA, psoralen ultraviolet A; RCT, Randomized controlled trial

Routes of administration: Acitretin (orally), alitretinoin (topically), bexarotene (orally, topically), isotretinoin (orally), tazarotene (topically), tretinoin (orally, topically), vitamin A / retinol / retinyl palmitate (orally, parenterally).

† Multiple references indicate the primary article followed by other papers on the same trial

‡ Study included U.S. veterans

§ French American British (FAB) classification M3 (including M3 variant), characterized by the presence of the t(15;17) translocation or the PML/RARα gene. Alternative therapy should be considered for patients who lack the genetic marker.

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