DRUG NAME: Acitretin

SYNONYM(S):

COMMON TRADE NAME(S): SORIATANE®

CLASSIFICATION: miscellaneous

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Acitretin, like tretinoin, is a retinoid that is selective for the retinoic acid receptor (RAR).[1] Retinoids are derivatives of vitamin A and regulate various biological processes including: embryonic development, vision, reproduction, bone formation, metabolism, hematopoiesis, differentiation, proliferation, and apoptosis.[1,2] Etretinate, a prodrug of acitretin, has a much longer half-life and therefore prolonged risk of teratogenicity in women.[1,3] The exact mechanism of action is unknown; however, acitretin causes modulation of cellular differentiation in the epidermis, apoptosis, and DNA fragmentation in sensitive T-cell lines.[1,4,5] Acitretin also causes modulation of the immune response.[1,5]

PHARMACOKINETICS:

Oral Absorption	36-95%[3]; rate and extent approximately doubled with food; peak plasma concentration: 2-5 h; steady state: within 2 weeks	
Distribution	distributes into breast milk	
	cross blood brain barrier?	no information found
	volume of distribution[3]	9 L/kg
	plasma protein binding[5,6]	≥98%
Metabolism	extensive liver metabolism[3]; interconversion of acitretin to etretinate, the prodrug of acitretin, also occurs	
	active metabolite(s)	yes; including cis-acitretin and etretinate
	inactive metabolite(s)[5,6]	yes
Excretion	urine[6]	16-53%
	feces[6]	34-54%
	terminal half life[5,6]	49-53 h cis-acitretin: 63-64 h etretinate: 120 d; has been detected in serum for up to 3 years, likely due to storage in adipose tissue
	clearance	no information found
Elderly	half life: 37-96 h; higher plasma concentrations suggest age-related difference in clearance or volume of distribution[3]	

Adapted from standard reference[5] unless specified otherwise.

USES:

Primary uses:
Lymphoma, cutaneous T-cell[3,7]

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to vitamin A, its metabolites,[5] or other retinoids[6]
- severe hepatic or renal impairment[5]
- intractable hyperlipidemias[5]
- hypervitaminosis A[5]
- women of childbearing potential unless the patient[5]:
    - is reliable in understanding and carrying out instructions
    - is able to comply with mandatory contraceptive measures
    - has received and acknowledged understanding of a careful oral and printed explanation of the hazards of fetal exposure and the risk of possible contraception failure
    - avoids alcohol ingestion during treatment and for at least 2 months after discontinuing treatment
    - see **Pregnancy** section below

Hepatic function should be checked before starting treatment, every 1-2 weeks for the first 2 months after starting treatment, and then every 3 months during treatment. If abnormal results are obtained, institute weekly checks. If hepatic function fails to return to normal or deteriorates further, discontinue acitretin with continued hepatic monitoring for at least 3 months. In patients taking etretinate, of which acitretin is the active metabolite, hepatitis has rarely occurred.[5] Due to an increased risk of hepatitis the combined use of methotrexate and acitretin should be avoided.[5,8]

Blood lipid levels should be checked before starting treatment and again at intervals of one or two weeks until the lipid response to acitretin is established. Patients with an increased tendency to develop hypertriglyceridemia include those with diabetes mellitus, obesity, increased alcohol intake, or a familial history of these conditions.[5] See paragraph following the **Side Effects** table.

In diabetics, retinoids can either improve or worsen glucose tolerance. Blood glucose levels must be checked more frequently in the early stages of treatment.[5] Limited data, which could not be duplicated, also indicated that acitretin either increased insulin sensitivity directly or interacted with glyburide to do so. Careful monitoring of diabetic patients is recommended.[5]

Blood donation for transfusion purposes should be deferred during treatment and for at least 2-3 years after discontinuing treatment.[5,6] Theoretically, blood from donors may present a small risk to the fetus if transfused to a pregnant mother during the first trimester.[5]

Skeletal development: Calcification of ligaments of the spine, tendon insertions, and intraosseous membranes of the arms and legs have been reported. Skeletal hyperostotic changes may also occur. It is not know if these changes are progressive. Pretreatment radiographs and appropriate examinations during treatment should be periodically performed. If skeletal disorders arise, evaluate continuation of treatment. Due to the unknown effect of long-term treatment on growth and skeletal development, acitretin should only be used in **pediatric** patients when there are no effective alternatives.[5] Detailed monitoring recommendations available.[5]

Pseudotumour cerebri (benign intracranial hypertension) has rarely occurred with acitretin and other retinoids. Early signs and symptoms include severe headache, nausea and vomiting, and visual changes. Examine patients with these symptoms for papilledema. If present, discontinued acitretin immediately and refer for neurological diagnosis and care.[5] As tetracyclines can cause an increase in intracranial pressure, their combination with acitretin should be avoided.[5,8]

Carcinogenicity: not carcinogenic in animals[5]; no information found in humans

Mutagenicity: Not mutagenic in Ames test and mammalian *in vitro* mutation test.[5] Not clastogenic in mammalian *in vitro* chromosome tests.[5]

Fertility: no information found

Pregnancy: FDA Pregnancy Category X.[6] Studies with retinoids in animals or humans have shown fetal abnormalities, or there is evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. Contraindicated in women who are or may become pregnant.[5]

Acitretin is **highly teratogenic**. Contraception should be used even after menopause unless the patient has had a hysterectomy. The following measures should be taken for **women** of childbearing potential[5,6]:

- inform patient of the risks and hazards of pregnancy during and for at least 2-3 years after therapy is stopped
- perform a serum or urine pregnancy test in a licensed laboratory, with a negative result occurring within two weeks prior to starting treatment; repeat monthly during and for at least 2-3 years after therapy
- initiate therapy on the second or third day of a normal menstrual period
- use two reliable forms of contraception (unless abstinence is the chosen method) simultaneously during and for 2-3 years after therapy; thereafter, the risks and desirability of discontinuing effective contraception should be assessed
- avoid drugs that may interact with oral contraceptives

Men's seminal fluid contains small amounts of residual acitretin; the risk to a fetus is unknown.[3]

Breastfeeding is not recommended due to secretion into breast milk; women should not breastfeed for at least 2-3 years following discontinuation of acitretin.[5,6]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[9]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
auditory/hearing	tinnitus (1-10%)
blood/bone marrow/ febrile neutropenia	changes in blood counts (2-38%); including increased reticulocytes, WBC, platelets; decreased WBC, platelets; very low incidence of clinically significant cytopenias[9]
constitutional symptoms	fatigue (1-10%)
	insomnia (1-10%)
	rigors (>10%)
dermatology/skin	***alopecia*** (7-75%)[3,5,10]; including loss of eyebrows and eyelashes; variable and typically reversible upon discontinuation of therapy[9]
	dry lips and cheilitis (≤100%)[3,5,10]
	dry skin (≤70%)[3,5]; treatment with emollients may be beneficial[1]
	nail fragility (10-28%)[3,5,10]
	photosensitivity[5,10] (≤30%)[5,10]
	pruritis (10-50%)[3,5,10]
	rash (>10-30%)[5,10]; erythema (>10%)
	scaling of palms and soles (20-83%)[3,10]; scaling of other parts of the body (>10-47%)[3,5]
	skin atrophy (>10%)
	sticky skin (>10%)
gastrointestinal	*emetogenic potential: rare*[11]
	anorexia (1-10%); increased appetite (1-10%)
	dry mouth/mucous membranes[1] (>10%); treatment with emollients may be beneficial[1]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	nausea (1-10%)
	taste alteration (1-10%)
hemorrhage	***epistaxis*** (≤20%)[5,10]
infection	urinary tract infection[10]; may be due to thinning of the urethral mucosa[10]
lymphatics	edema (1-10%)
metabolic/laboratory	decreased high density lipoproteins (HDL) (30%); reversible upon discontinuation of therapy
	electrolyte changes (1-16%)
	elevated cholesterol (9%); reversible upon discontinuation of therapy
	elevated creatinine (5%)
	elevated liver function tests including ALT, AST, and LDH (11-28%); typically mild to moderate and reversible either during continuation or upon discontinuation of therapy; see **Special Precautions** section
	elevated triglycerides (65%); reversible upon discontinuation of therapy; see paragraph following the **Side Effects** table
	elevated uric acid (17%)
	worsened or improved glucose tolerance in diabetics
musculoskeletal	arthralgia (>10%); myalgia (≤35%)[5,10]
	arthritis (1-10%)
	calcification of ligaments, hyperostosis (1-10%); see **Special Precautions** section
	hypertonia (1-10%)
neurology	hyperesthesia (>10%)
	nervousness (1-10%)
	pseudotumour cerebri (<1%); see **Special Precautions** section
ocular/visual	ophthalmic effects; see paragraph following the **Side Effects** table
pain	abdominal, bone, or back pain (1-10%)
	earache (1-10%)
	headache (≤40%)[5,10]
	pain, not otherwise specified (1-10%)
pulmonary	rhinitis (>10%)
sexual/reproductive function	impotence (1-10%)

Adapted from standard reference[5] unless specified otherwise.

Ophthalmic effects including dry eyes (≤30%),[5,10] eye irritation (>10%),[5] blepharitis and photophobia (>10%),[5] crusting of lids, redness, recurrent styes, pannus, and subepithelial corneal lesions may occur. Blurred vision (1-10%), abnormal lacrimation, and decreased night vision (<1%) have also been reported.[5] Advise patients to be cautious when driving or operating any vehicle at night and that they may experience decreased tolerance to contact lenses during the initial treatment period.[5] Discontinue therapy and undergo ophthalmic evaluation should visual difficulties occur.[5] The following additional ophthalmic effects have occurred in patients taking etretinate, of which

acitretin is the active metabolite: decreased visual acuity, minimal posterior subcapsular cataract, iritis, blot retinal hemorrhage, and scotoma.

Hypervitaminosis A produces a wide spectrum of signs and symptoms primarily of the mucocutaneous, musculoskeletal, hepatic, and central nervous systems. Nearly all of the adverse events reported with acitretin resemble those of hypervitaminosis A syndrome. Tolerability is a major factor affecting acitretin use[10]; headache, rash, musculoskeletal symptoms, and hyperlipidemias are common causes of withdrawal from treatment.[10] Side effects are typically dose-dependent.[1]

Lipids: Weight reduction and restriction of dietary fat and alcohol to control acitretin-related elevations of triglycerides or decreases of HDL should be attempted. If, despite these measures, hypertriglyceridemia and low HDL levels persist, consider discontinuing therapy. Dose-reduction or lipid lowering agents may also be of benefit.[2] Retinoids rarely have been associated with pancreatitis.[1]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
cimetidine[5]	no significant effect on cimetidine or acitretin pharmacokinetics		
digoxin[5]	no significant effect on digoxin or acitretin pharmacokinetics		
ethanol [3,5,6,8]	delayed; major; suspected; prolonged risk of teratogenicity in women	etretinate (a teratogenic retinoid with a much longer half life) may be formed	alcohol is contraindicated during acitretin treatment and for 2 months after discontinuing treatment in women of childbearing potential[3,6,9]
methotrexate[5,8]	delayed; major; suspected; increased risk of hepatitis	methotrexate and etretinate (a prodrug of acitretin) use has been associated with hepatitis; theoretical increased risk with acitretin; increased methotrexate plasma concentrations may occur[8]	avoid concurrent use
phenytoin[5]	increased risk of phenytoin toxicity	reduced phenytoin protein binding	monitor free phenytoin plasma levels; interpret total phenytoin plasma levels considering the increase in the free fraction of the drug
progesterone	no effect on progesterone plasma concentrations for most oral contraceptives; decreased contraceptive effect may occur with low-dose “minipills”	unknown	avoid low-dose progesterone “minipills”
retinoids and/or vitamin supplements containing vitamin A[5]	additive toxicity	acitretin is a vitamin A derivative	avoid combination

AGENT	EFFECT	MECHANISM	MANAGEMENT
tetracyclines[5,8]	delayed; moderate; suspected; risk of pseudotumour cerebri	theoretical additive or synergistic effect	avoid concurrent use

See ***Pregnancy*** under **Special Precautions** section regarding drugs that can interact with contraception.

SUPPLY AND STORAGE:

Oral: Hoffman-LaRoche Limited supplies acitretin as 10 and 25 mg capsules.[5] Store at room temperature and protect from light.[5]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BCCA usual dose noted in ***bold, italics***

Oral: 25 mg (range 25-75 mg/m^2) PO once daily[5]
- administer with food[5]

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"

Dosage in renal failure: contraindicated[5]

Dosage in hepatic failure: contraindicated[5]

Dosage in dialysis: neither acitretin or cis-acitretin are dialyzable[3,12]

Children:

safety and effectiveness have not been established[5]; growth potential may be affected[6]; see skeletal development in **Special Precautions** section

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