ACCUTANE™ ROCHE® (isotretinoin)

Blood Monitoring Guide

This material was developed by Hoffmann-La Roche, as part of the risk minimization plan for Accutane. This material is not intended for promotional use.

Clinical Use

Because of significant side effects associated with its use, ACCUTANE should be reserved for patients where the indicated conditions are unresponsive to conventional first line therapies.

ACCUTANE should only be prescribed by physicians knowledgeable in the use of retinoids systemically, who understand the risk of teratogenicity in females of child bearing age and who are experienced in counselling young adults for whom ACCUTANE is generally indicated.

A careful assessment of the patient's mental state should be made, including whether or not they have a history of previous psychiatric illness.

It is strongly recommended that each ACCUTANE prescription be limited to a one-month supply in order to encourage patients to return for follow-up to monitor side-effects. Prescriptions of ACCUTANE for women of child-bearing potential should be limited to 30 days of treatment and continuation of treatment requires a new prescription.

Pediatrics

The use of ACCUTANE in pediatric patients less than 12 years of age is not recommended. The use of ACCUTANE for the treatment of severe recalcitrant nodular acne in pediatric patients ages 12 to 17 years should be given careful consideration, especially for those patients where a known metabolic or structural bone disease exists.

Geriatrics

Clinical studies of ACCUTANE did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Although reported clinical experience has not identified differences in responses between elderly and younger patients, effects of aging might be expected to increase some risks associated with isotretinoin therapy.

Contraindications

- **ACCUTANE is contraindicated in pregnancy**. Females must not become pregnant while taking ACCUTANE or for at least one month after its discontinuation. ACCUTANE causes severe birth defects in a very high percentage of infants born to women who became pregnant during treatment with ACCUTANE in any amount, even for a short period of time. **See full Product Monograph for complete contraindication**.
- Breastfeeding women
- Hepatic and renal insufficiency
- Hypervitaminosis A
- Patients with excessively elevated blood lipid values
- Patients taking tetracyclines
- Patients who are sensitive to isotretinoin, or to any of the excipients

Most serious warnings and precautions

- **Pregnancy Prevention:** ACCUTANE is a known teratogen contraindicated in pregnancy. Physicians should **only** prescribe ACCUTANE to females of childbearing potential if **ALL** the conditions described below under "**Conditions of use**" are met. In addition, when prescribing this drug to female patients of childbearing potential, physicians must use Hoffmann-La Roche Limited's PREGNANCY PREVENTION PROGRAM®, which includes comprehensive information about the potential risks of this drug, a checklist for criteria which must be met prior to prescribing this drug to female patients of childbearing potential, detailed information on birth control options, a patient informed consent for review and signature, and monthly pregnancy reminders for physicians to use at each patient visit during the treatment period.
- **Conditions of Use:**
  1. The patient has severe disfiguring nodular and/or inflammatory acne, acne conglobata or recalcitrant acne that has not responded to standard therapy, including systemic antibiotics.
  2. The patient is reliable in understanding and carrying out instructions.
  3. All patients must sign the informed consent form prior to initiating therapy. This form is provided to the physician via the www.acneandu.ca website or by contacting the Roche Medical Information line at 1-888-762-4388.

  ACCUTANE is contraindicated in females of childbearing potential unless **ALL** of the following conditions apply:
  1. The patient is able and willing to comply with the mandatory effective contraceptive measures.
  2. The patient has received, and acknowledged understanding of, a careful oral and printed explanation of the hazards of fetal exposure to ACCUTANE and the risk of possible contraception failure. This explanation may include showing a line drawing to the patient of an infant with the characteristic external deformities resulting from ACCUTANE exposure during pregnancy.
  3. The patient has been informed and understands the need to rapidly consult her physician if there is a risk of pregnancy.
  4. The patient understands the need for rigorous follow-up on a monthly basis.
  5. The patient uses effective contraception without any interruption for one month before beginning ACCUTANE therapy, during ACCUTANE therapy and for one month following discontinuation of ACCUTANE therapy. It is recommended that two reliable forms of contraception be used simultaneously.
  6. The patient has had two negative pregnancy tests before starting ACCUTANE therapy with the first pregnancy test conducted at initial assessment when the patient is qualified for ACCUTANE therapy by the physician. The patient has had a second serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL with a negative result, performed in a licensed laboratory, within 11 days prior to initiating therapy. The patient has had two or three days of the next normal menstrual period before ACCUTANE therapy is initiated.
  7. In the event of relapse treatment, the patient must also use the same uninterrupted and effective contraceptive measures one month prior to, during and for one month after ACCUTANE.
- Even female patients who normally do not employ contraception due to a history of infertility, or claim absence of sexual activity, should be advised to employ contraception while taking ACCUTANE, following the above guidelines. Even female patients who have amenorrhea must follow all the advice on effective contraception unless the patient has undergone hysterectomy, bilateral oophorectomy, or has been medically confirmed to be postmenopausal.
- All patient materials and physician materials can be downloaded from the www.acneandu.ca website or by contacting the Roche Medical Information line at 1-888-762-4388.
- It is mandatory that all female patients of childbearing potential treated with ACCUTANE have regular monthly pregnancy tests during treatment and one month after the discontinuation of treatment. The dates and results of pregnancy tests should be documented. The blood monitoring chart can be used to document these results as well as to serve as a reminder of all the tests that should be carried out and their frequency. This physician material can be downloaded from the www.acneandu.ca website or by contacting the Roche Medical Information line at 1-888-762-4388.
- **Psychiatric:** Some patients treated with ACCUTANE have become depressed and some attempted or committed suicide. Although a causal relationship has not been established, all patients should be screened and monitored for signs of depression before and during therapy. Physicians should determine whether the patient may be depressed or has a history of depression including a family history of major depression before starting therapy with ACCUTANE. If symptoms of depression develop or worsen during treatment with ACCUTANE, the drug should be discontinued promptly and the patient referred for appropriate psychiatric treatment as necessary. However, discontinuation of ACCUTANE may not alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary.

  A Psychiatric Assessment Checklist is available to assist physicians in screening patients for depression/suicidality prior to treatment and in monitoring for the development of psychiatric symptoms during treatment. **This checklist is provided to the physician via the www.acneandu.ca website or by contacting the Roche Medical Information line at 1-888-762-4388**.
- **Neurologic:** ACCUTANE use has been associated with a number of cases of pseudotumor cerebri (benign intracranial hypertension), some of which involved concomitant use of tetracyclines. Early symptoms of pseudotumor cerebri include headache, nausea and vomiting, and visual disturbances. Patients with symptoms should be screened for papilledema and, if present, the drug should be discontinued immediately and the patient referred to a neurologist for diagnosis and care. Concomitant treatment with tetracyclines should be avoided.
- **Hepatic/Biliary/Pancreatic:** There have been some reports of acute pancreatitis, which is known to be potentially fatal.
- **Monitoring and Laboratory Tests:** The following tests are required before starting ACCUTANE, at first month, then as clinically indicated: serum blood lipid, complete blood count (CBC) and differential, liver function, and blood glucose levels.
- **Patient Medication Information:** Both male and female patients should be given a copy of the Patient Medication Information (Part III).

Other relevant warnings and precautions

- Serious skin reactions [e.g. erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN)]. These events may be serious and result in hospitalization, life threatening events, disfiguration, disability and/or death.
- Acute exacerbation of acne is occasionally seen during the initial period but this subsides with continued treatment, usually 7-10 days, and usually does not require dose adjustment.
- Exposure to intense sunlight or to UV rays should be avoided.
- It is recommended that the following be avoided in patients on ACCUTANE and for a period of 5-6 months after the end of treatment: aggressive chemical dermabrasion,cutaneous laser treatment, wax epilation, concurrent administration with keratolytic or exfoliative anti-acne agents.
- Special populations (pregnant women, females of child bearing potential, nursing women, pediatrics and geriatrics) and high risk patients (with diabetes, obesity, alcoholism or lipid metabolism disorder) undergoing treatment with ACCUTANE (See full Product Monograph for complete details).
- Male patients should be reminded that they must not share their medication with anyone, particularly not females.
- It is recommended that blood donation for transfusion purposes be deferred during therapy with ACCUTANE and for one month after discontinuation of treatment.
- Cardiovascular events (elevation in plasma triglycerides, decrease in high density lipoproteins, increase in cholesterol levels).
- Impaired hearing at certain frequencies
- Patients with diabetes or a family history of diabetes may experience problems with the control of their blood sugar during ACCUTANE therapy.
- ACCUTANE has been temporally associated with inflammatory bowel disease (including regional ileitis, colitis and hemorrhage) in patients without a prior history of intestinal disorders. Patients experiencing abdominal pain, rectal bleeding or severe diarrhea should discontinue ACCUTANE immediately.
- Clinical hepatitis, elevation of liver enzymes, acute pancreatitis which is known to be potentially fatal. Every attempt should be made to control significant triglyceride elevation. ACCUTANE should be discontinued if uncontrolled hypertriglyceridemia or symptoms of pancreatitis occur.
- Anaphylactic reactions, allergic cutaneous reactions and allergic vasculitis (often with purpura) of the extremities and extracutaneous involvement
- Effects on musculoskeletal system including osteoporosis, osteopenia, bone fractures, and delayed healing of bone fractures and hyperostosis
- Ophthalmologic effects (corneal opacities, dry eyes, decreased night vision, keratitis, blepharitis and conjunctivitis).
- Monitoring and Laboratory Tests (including pregnancy tests and signs of depression. See full Product Monograph for complete details)

For More Information

Please consult the Product Monograph at www.rochecanada.com/PMs/Accutane/Accutane_PM_E.pdf for important information relating to warnings and precautions, adverse reactions, drug interactions (e.g. St. John's Wort: ACCUTANE use is associated with depression in some patients. Patients should be cautioned to not self-medicate with St. John's Wort), and dosing information which has not been discussed in this piece. The product monograph is also available by calling us at 1-888-762-4388.

For more information, please call the birth control counselling line toll-free at 1-877-333-2263 or visit the ACCUTANE website at www.AcneandU.ca

If you require this information in an accessible format, please contact Roche at 1-800-561-1759.

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ACCUTANE is indicated for the treatment of:

- Severe Nodular and/or Inflammatory Acne
- Acne Conglobata
- Recalcitrant Acne

		Abbreviated	Normal Range	Testing Frequency	Possible Effect	Incidence	Comments
Complete Blood Count and Differential	Erythrocyte sedimentation rate	ESR	Male: 0-17 mm/hr Female: 1-25 mm/hr	Baseline, first month, then as clinically indicated	↑ sedimentation rate	40%	
	Hemoglobin	Hg	Men: 140–180 g/L Women: 115–155 g/L	Baseline, first month, then as clinically indicated	↓ Hg (Anemia)	Less common than other parameters listed	
	Neutrophils	NEU	Absolute neutrophils 2-7 x 10^9/L	Baseline, first month, then as clinically indicated	↓ NEU (Neutropenia)	Less common than other parameters listed	
	Platelet count	PLT	130–400 x 10^9/L	Baseline, first month, then as clinically indicated	↓ PLT (Thrombocytopenia) ↑ PLT	Less common than other parameters listed	
	White blood cells (Leukocytes)	WBC (LKC)	3.2–9.8 x 10^9/L	Baseline, first month, then as clinically indicated	↓ WBC (↓LKC) (Leukopenia)	Less common than other parameters listed	
Urinalysis	Protein	Protein – urine	Negative or < 150 mg/day	As clinically indicated	↑ protein (proteinuria)	Less common than other parameters listed	
	Red blood cells	RBC – urine	0-2/high-power field	As clinically indicated	↑ red blood cells	Less common than other parameters listed	
	White blood cells	WBC – urine	0-2/high-power field	As clinically indicated	↑ white blood cells	Less common than other parameters listed	
Lipids	Fasting cholesterol	Chol.	< 5.2 mmol/L	Baseline, first month, then as clinically indicated and at end of treatment	↑ cholesterol levels	7%	▪ ↑ cholesterol reversible upon dose reduction or cessation of therapy
	Fasting triglycerides	TG	< 1.7 mmol/L	Baseline, first month, then as clinically indicated and at end of treatment	↑ TG levels	25%	▪ ↑ in TG reversible upon dose reduction or cessation of therapy ▪ If serum triglycerides are >9 mmol/L, patient is at risk of acute pancreatitis ▪ Discontinue therapy if uncontrolled hypertriglyceridemia or symptoms of pancreatitis occur
	High density lipoproteins	HDL	> 1.3 mmol/L	Baseline, first month, then as clinically indicated and at end of treatment	↓ HDL levels	15%	▪ ↓ HDL reversible upon dose reduction or cessation of therapy
Liver Function	Alanine aminotransferase (serum)	ALT	0-585 nkat/L	Baseline, first month, then at 3 month intervals	↑ ALT	15%	▪ If normalization does not readily occur, or if hepatitis is suspected, discontinue therapy and further investigate the etiology
	Alkaline phosphatase (serum)	ALP	500-2000 nkat/L	Baseline, first month, then at 3 month intervals	↑ ALP	15%	
	Aspartate aminotransferase (serum)	AST	0-585 nkat/L	Baseline, first month, then at 3 month intervals	↑ AST	15%	
Pregnancy	Serum **or** Urine	ß-hCG serum ß-hCG urine		Two negative pregnancy tests before starting ACCUTANE therapy; the first pregnancy test should be conducted at initial assessment when the patient is qualified for ACCUTANE therapy by the physician; the second pregnancy test should be performed in a licensed laboratory within 11 days prior to initiating therapy; then monthly, including one month following discontinuation of treatment	Major human fetal abnormalities	≥ 25%	▪ Urine or serum pregnancy test with a sensitivity of at least 25 mIU/mL with a negative result, performed in a licensed laboratory
Blood Sugar	Fasting glucose (plasma)		3.9–6.1 mmol/L	As clinically indicated	↑ fasting blood sugar	Unknown	▪ Known or suspected diabetics should have periodic blood sugar determinations
Other Tests	Creatine phosphokinase (serum)[1]	CPK	5–130 u/L	As clinically indicated	↑ CPK, particularly in those patients undertaking vigorous physical activity[1]	12%	▪ ↑ CPK reversible after 2 to 4 weeks of therapy cessation[1]
	Urate, as uric acid (serum)		120–420 µmol/L	As clinically indicated	↑ uric acid (hyperuricemia)	Less common than other parameters listed	

[1] CPK elevation is based on the results of one study. In an open-label clinical trial (N=217) of a single course of therapy with ACCUTANE for severe recalcitrant nodular acne in pediatric patients 12 to 17 years, transient elevations in CPK were observed in 12% of patients, including those undergoing strenuous physical activity in association with reported musculoskeletal adverse events such as back pain, arthralgia, limb injury, or muscle sprain. In these patients, approximately half of the CPK elevations returned to normal within 2 weeks and half returned to normal within 4 weeks. No cases of rhabdomyolysis were reported in this trial.

References:
Current ACCUTANE™ ROCHE® Product Monograph.
Compendium of Pharmaceuticals and Specialties. Canadian Pharmacists Association.

For full prescribing information, please consult the ACCUTANE Product Monograph.