Clarus®
Isotretinoin Capsules, USP

Blood Monitoring Guide

		Abbreviated	Normal Range	Testing Frequency	Possible Effect	Incidence	Comments
Complete Blood Count and Differential	Erythrocyte sedimentation rate	ESR	Male: ≤ 20 mm/h Female: ≤ 30 mm/h	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 1.5-7.8 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	≤ 3/ high power field	As clinically indicated	↑ Red blood cells	Less common than other parameters listed	
	White blood cells	WBC – urine	≤ 5/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	<1.80 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	>0.9 mmol/L	Baseline, first month, then as clinically indicated and at end of treatment	↓ HDL levels	16 %	• ↓ 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 %	
	Alkaline phosphatase (serum)	ALP	500-2000 nkat/L	Baseline, first month, then at 3 month intervals	↑ ALP	15 %	• If normalization does not readily occur, or if hepatitis is suspected, discontinue therapy and further investigate the etiology
	Aspartate aminotransferase (serum)	AST	0-585 nkat/L	Baseline, first month, then at 3 month intervals	↑ AST	15 %	
Pregnancy	Serum Or Urine	β-hCG serum β-hCG urine		Two negative pregnancy tests before starting CLARUS® therapy; the first pregnancy test should be conducted at initial assessment when the patient is qualified for Clarus® therapy by the physician; the second pregnancy test should be performed 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	8-150 μ/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)		120-140 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 isotretinoin 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: CLARUS® Mylan Pharmaceuticals ULC Product Monograph, January 31, 2017
Accutane™ Roche (isotretinoin) Product Monograph, November 29, 2016

For full prescribing and monitoring information, please consult the CLARUS® Product Monograph.

Mylan

INDICATIONS AND CLINICAL USE

CLARUS® (isotretinoin) is indicated for the treatment of Severe Nodular and/or Inflammatory Acne, Acne Conglobata and Recalcitrant Acne. **Because of significant side effects associated with its use, CLARUS® should be reserved for patients where the conditions listed above are unresponsive to conventional first line therapies.**

CLARUS® 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 CLARUS® is generally indicated (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS: Serious Warnings and Precautions and Special Populations, Pregnant Women in the prescribing information).

A careful assessment of the patient's mental state should be made, including whether or not they have a history of previous psychiatric illness (see WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions, Psychiatric in the prescribing information).

It is strongly recommended that each CLARUS® prescription be limited to a one-month supply in order to encourage patients to return for follow-up to monitor side-effects. Prescriptions of CLARUS® 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 CLARUS® in pediatric patients less than 12 years of age is not recommended. The use of CLARUS® 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 (see WARNINGS AND PRECAUTIONS: Special Populations, Pediatrics).

For more detailed prescribing information related to CLARUS®, including INDICATIONS, CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS, please consult the Clarus product monograph.

CONTRAINDICATIONS

► **CLARUS® is contraindicated in pregnancy.**

Females must not become pregnant while taking CLARUS® or for at least one month after its discontinuation. Isotretinoin causes severe birth defects in a very high percentage of infants born to women who became pregnant during treatment with isotretinoin in any amount, even for a short period of time.

- ► Potentially any exposed fetus can be affected. There are no accurate means of determining whether an exposed fetus has been affected (see WARNINGS AND PRECAUTIONS: Special populations, Pregnant Women in the prescribing information).
- ► If pregnancy does occur during treatment with CLARUS® or for one month after its discontinuation, CLARUS® treatment must be immediately stopped and the physician and patient should discuss the desirability of continuing the pregnancy.
- ► CLARUS® should only be prescribed by physicians knowledgeable in the use of retinoids systemically (see INDICATIONS AND CLINICAL USE in the prescribing information).

CLARUS® is also contraindicated in the following conditions:

- ► breastfeeding women,
- ► hepatic and renal insufficiency,
- ► hypervitaminosis A,
- ► patients with excessively elevated blood lipid values,
- ► patients taking tetracyclines (see WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions, Neurologic and DRUG INTERACTION: Drug-Drug Interactions in the prescribing information).
- ► patients who are sensitive to isotretinoin, or to any of the excipients. CLARUS® capsules contain hydrogenated vegetable oil and soybean oil (see DOSAGE FORMS, COMPOSITION AND PACKAGING: Composition in the prescribing information).

WARNINGS AND PRECAUTIONS

The Information/Consent/Agreement should be signed by *all* patients prior to starting therapy with isotretinoin. This consent form is designated to ensure that patients have been counselled on and understand the psychiatric and teratogenic risks associated with isotretinoin, prior to starting treatment. The consent form can be obtained by downloading it from the CLARUS® Clear Program Website, www.clarusclearprogram.ca, or by contacting Customer Service centre at customerservice@mylan.ca.

Serious Warnings and Precautions

All patients must sign the informed consent form prior to initiating therapy.

► ***Pregnancy Prevention:*** Isotretinoin is a known teratogen contraindicated in pregnancy (see boxed CONTRAINDICTIONS in the prescribing information). Physicians should **only** prescribe CLARUS® 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 Mylan Pharmaceuticals ULC's CLEAR™ Program, which includes the following:

- 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
- monthly pregnancy reminders for physicians to use at each patient visit during the treatment period

► ***Psychiatric:*** Some patients treated with isotretinoin have become depressed and some attempted or committed suicide. Although a casual relationship has not been established, all patients should be screened and monitored for signs of depression during therapy (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests in the prescribing information). Physicians should determine whether the patient may be depressed or has a history of depression including a family history or major depression before starting therapy with CLARUS®. If symptoms of depression develop or worsen during treatment with isotretinoin, the drug should be discontinued promptly and the patient referred for appropriate psychiatric treatment as necessary. However, discontinuation of CLARUS® may not alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary.

A Psychiatric Screening 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.

► ***Neurologic:*** Isotretinoin use has been associated with a number of cases of pseudotumor cerebri (benign intracranial hypertension), some of which involved concomitant use of tetracyclines (see CONTRAINDICATIONS and DRUG INTERACTIONS: Drug-Drug Interactions in the prescribing information). Early symptoms of pseudotumor cerebri include headache, nausea and vomiting, and visual disturbances. Patients with these 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 (see CONTRAINDICATIONS and DRUG INTERACTIONS: Drug-Drug Interactions in the prescribing information).

Serious Skin Reactions

There have been very rare post-marketing reports of severe skin reactions (e.g., erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN)) associated with isotretinoin use. These events may be serious and result in hospitalization, life threatening events, disfiguration, disability and/or death. CLARUS® treatment should be discontinued if the patient develops any of the following reactions: rash, especially if associated with fever and/or malaise, conjunctivitis (red or inflamed eyes); blisters on legs, arms or face and/or sores in mouth, throat, nose or eyes; peeling skin or other serious skin reactions.

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.clarusclearprogram.ca website or by contacting Mylan Pharmaceuticals Customer Service line at 1-844-596-9526.**

CLARUS® is contraindicated in females of childbearing potential unless **ALL** of the following conditions apply:

4. The patient is able and willing to comply with the mandatory effective contraceptive measures.
5. The patient has received, and acknowledged understanding of, a careful oral and printed explanation of the hazards of fetal exposure to isotretinoin 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 isotretinoin exposure during pregnancy.
6. The patient has been informed and understands the need to rapidly consult her physician if there is a risk of pregnancy.
7. The patient understands the need for rigorous follow-up on a monthly basis.
8. The patient uses effective contraception without any interruption for one month before beginning CLARUS® therapy, during CLARUS® therapy and for one month following discontinuation of CLARUS® therapy. It is recommended that two reliable forms of contraception be used simultaneously (see WARNINGS AND PRECAUTIONS: Special Populations, Pregnant Women in the prescribing information).
9. The patient has had two negative pregnancy tests before starting CLARUS® therapy, with the first pregnancy test conducted at initial assessment when the patient is qualified for CLARUS® 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 CLARUS® therapy is initiated.
10. 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 CLARUS®.

(Re items 4 to 10 see WARNINGS AND PRECAUTIONS: Special Populations, Pregnant Women in the prescribing information).

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 CLARUS®, 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.

Adverse Reactions

The most common side effects are mucocutaneous or dermatologic. The common side effects include: cheilitis (96%), facial erythema/dermatitis (55%), dry nose (51%), desquamation (50%), pruritus (30%), dry skin (22%), conjunctivitis (19%), alopecia (13%), irritation of the eyes (11%), rash (<10%). Dryness of the nasal mucosa and pharynx may be associated with mild epistaxis and hoarseness, respectively. Mild-to-moderate conjunctivitis may be alleviated by use of an ophthalmic ointment. In rare cases, hair loss persisted after treatment was completed.

For full prescribing information, please consult the CLARUS® Mylan Pharmaceuticals ULC Product Monograph.