

PART III: CONSUMER INFORMATION

ICLUSIG is a medicine used to treat adults with the following types of leukemia who are no longer benefitting from treatment with other medicines:

- chronic myeloid leukemia (CML)
- Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL)

The approval with conditions is based on response rate. The majority of patients showed improvements within 1 month in the clinical study. Talk to your doctor if your condition has not improved after taking ICLUSIG for 3 months. Your doctor may advise you to stop taking ICLUSIG.

ICLUSIG for this indication has been approved with conditions. Results of studies to prove its clinical benefit have not been shown to Health Canada. Contact your health care providers for more information.

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products approved under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

P^rICLUSIG[®]
Ponatinib Tablets
(as ponatinib hydrochloride)

This leaflet is part III of a three-part "Product Monograph" published when ICLUSIG was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about ICLUSIG. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

ICLUSIG is a medicine used to treat adults with the following types of leukemia who are no longer benefitting from treatment with other medicines:

- Chronic myeloid leukemia (CML)
- Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL)

What it does:

ICLUSIG belongs to a group of medicines called tyrosine kinase inhibitors. In patients with CML and Ph+ ALL, the body produces abnormal white blood cells. ICLUSIG blocks a signal and stops the production of abnormal white blood cells.

When it should not be used:

Do not take ICLUSIG if:

- you are allergic to ponatinib
- you are allergic to any of the other ingredients of this medicine
- you are pregnant
- your doctor thinks you are at risk of heart problems
- you have high blood pressure that is not controlled by medication
- you are dehydrated or have severe vomiting, diarrhea, or sweating. This is more important if you have high uric acid in your blood.

What the medicinal ingredient is:

Ponatinib (as ponatinib hydrochloride)

What the nonmedicinal ingredients are:

Colloidal anhydrous silica, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, sodium starch glycolate, talc, titanium dioxide

What dosage forms it comes in:

Tablets; 15 mg and 45 mg

WARNINGS AND PRECAUTIONSSerious Warnings and Precautions

ICLUSIG can only be prescribed by a doctor:

- who is certified by the ICLUSIG Controlled Distribution Program
- who diagnoses and treats leukemia
- who has anti-cancer drug experience

Serious side effects with ICLUSIG include the following:

- Obstruction of your arteries that may lead to serious side effects, sometimes leading to amputation or death
- Blood clots in the veins especially in the legs which may travel through blood vessels to the lungs that may lead to death
- Heart problems that may lead to death
- Bleeding that may lead to death
- Liver problems that may lead to death
- Myelosuppression, a decreased production of blood cells
- Pancreatitis, inflammation of your pancreas

BEFORE you use ICLUSIG, talk to your doctor or pharmacist if you:

- have a liver or pancreas disorder, diabetes, or reduced kidney function
- have a history of alcohol abuse
- had a heart attack or stroke before
- had a recent surgery or plan to have a medical procedure
- have a history of blood clots in your blood vessels or heart problems, including heart failure or irregular heartbeats
- have a history of high cholesterol
- have high blood pressure and its complications, including separation of the layers of the arterial wall (artery dissection)
- you are intolerant to milk sugar. Or, have one of the following rare hereditary diseases:
 - Galactose intolerance
 - Lapp lactase deficiency
 - Glucose-galactose malabsorption
 because lactose is a non-medicinal ingredient in ICLUSIG
- had a history of narrowing of the blood vessels to one or both kidneys
- have ever had or might now have a hepatitis B virus infection (a viral infection of the liver). This is because during treatment with ICLUSIG, hepatitis B virus may

become active again, which can be fatal in some cases. Your doctor will check for signs of this infection before and during treatment with ICLUSIG.

Your doctor may want to take additional precautions.

- Eye problems can occur while you are taking ICLUSIG. Tell your doctor without delay if you experience any blurred vision, dry eye, or eye pain during treatment.

Driving and using machines

Before doing tasks which require special attention, wait until you know how you respond to ICLUSIG. Blurred vision, being dizzy, tired, lightheaded, or fainting can occur.

Pregnancy and Breast-Feeding

Ask your doctor or pharmacist for advice before taking this medicine if you are:

- pregnant or think you may be pregnant
- breast-feeding. Stop breast-feeding during treatment with ICLUSIG. It is not known if ICLUSIG passes into breast milk.
- planning to have a baby

Ability to have a child

ICLUSIG may make it harder to get pregnant or father a child. This has not been tested in humans.

Contraceptive (birth control) advice for men and women taking this medicine

- Women should avoid becoming pregnant. Use effective contraception (birth control) while taking this medicine. It is not known if this medicine affects how birth control pills work. Use a different or additional method of contraception while taking this medicine.
- Men should not father a child while taking this medicine.

Only use this medicine during pregnancy if your doctor tells you it is absolutely necessary. Potential risks exist for the unborn child.

Your doctor will perform:

- tests of the functions of your heart, arteries, and veins
- a complete blood count
 - during the first 3 months of treatment: every 2 weeks
 - after the first 3 months of treatment: once a month, or as directed by your doctor
- checks of the serum protein known as lipase
 - in the first 2 months of treatment: every 2 weeks
 - after the first 2 months of treatment: as directed by your doctor
- blood tests to check how well your liver works
 - as directed by your doctor
- eye exams at the start of and during treatment
- tests of hepatitis B infection before treatment with ICLUSIG and while on treatment if required

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

Drugs that may interact with ICLUSIG include:

- birth control pills may not work as well to prevent pregnancy. It is not known if ICLUSIG affects how oral contraceptives work. An alternative or additional method of contraception should be used.
- ketoconazole, itraconazole, voriconazole: medicines to treat fungal infections
- atazanavir, indinavir, nelfinavir, ritonavir, saquinavir: medicines to treat HIV infection
- clarithromycin, telithromycin, troleandomycin: medicines to treat bacterial infections
- nefazodone: a medicine to treat depression
- St. John's Wort: a herbal product used to treat depression
- carbamazepine: a medicine to treat epilepsy, euphoric/depressive stages and certain pain conditions
- phenobarbital, phenytoin: medicines to treat seizures
- rifabutin, rifampicin: medicines to treat tuberculosis or certain other infections
- digoxin: a medicine to treat heart weakness
- dabigatran: a medicine to prevent blood clots
- colchicine: a medicine to treat gout
- pravastatin, rosuvastatin: medicines to lower high cholesterol levels
- methotrexate: a medicine to treat severe joint inflammation (rheumatoid arthritis), cancer and the skin disease psoriasis
- sulfasalazine: a medicine to treat severe bowel and rheumatic joint inflammation

Avoid the following foods because they interact with ICLUSIG:

- grapefruit and grapefruit juice,
- star fruit,
- pomegranate,
- Seville oranges,
- other similar fruits

PROPER USE OF THIS MEDICATION

This is a long-term treatment. Unless told by your doctor, do not change the dose. Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Take ICLUSIG daily for as long as it is prescribed.

Swallow the tablets **whole**, with a glass of water. Do NOT crush or dissolve the tablets.

It does not matter if you take ICLUSIG with or without food.

Usual Recommended Dose: One 45 mg tablet a day

Your doctor may reduce your dose or tell you to stop taking this medicine if you experience certain side effects, including:

- abnormal blood test results
- inflammation of the pancreas
- heart or blood vessel problems

15 mg tablets are available if your doctor reduces your dose.

For 15 mg a day: Take one 15 mg tablet

For 30 mg a day: Take two 15 mg tablets

Overdose:

In case of drug overdose, contact a healthcare practitioner, hospital Emergency Department, or regional Poison Control Centre immediately, even if you have no symptoms.

Missed Dose:

Do not take a double dose or an extra dose to make up for a forgotten dose. Take your next dose at your regular time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Patients aged 65 and over are more likely to be affected by side effects.

Side effects may include:

- headache, dizziness or spinning feeling, ringing in the ears, state of confusion
- inflammation of hair follicles, hair loss
- skin that is red, abnormally darkened, dry, itchy, blistered, peeling, scaly, rash
- fatigue, sleeplessness, lack of energy, weakness, general feeling of being unwell, either emotionally or physically, or a combination of the two (malaise)
- vomiting, diarrhea, abdominal distension, discomfort, indigestion, decreased appetite, weight loss, dehydration, unpleasant taste, dry mouth, inflammation in the mouth, stomach acid reflux, nausea, constipation
- cough, upper airway infection, difficulty producing voice sounds, breathing difficulties, chills, flu-like illness, fever
- nosebleed
- dry or inflamed eyes
- hot flush, flushing, night sweats, increased sweating
- pain in bones, arms or legs, back, chest, neck, skeletal system, pain in joint, muscles
- pain in one or both legs when walking or exercising. This pain disappears after some rest. Muscle spasms.
- increased or reduced sense of touch. Prickling, tingling, itching, numbness and pain in the hands and feet.
- fluid retention in arms and/or legs
- inability to develop and maintain an erection
- high blood pressure or worsening of existing blood pressure (headache, dizziness, chest pain, or shortness of breath)

If you have had a hepatitis B virus infection before (a viral infection of the liver), the virus may become active again. In some patients who are long time carriers of this virus, the virus has become active again after receiving BCR-ABL tyrosine kinase inhibitors. The virus can cause death in some patients.

If any of these affects you severely, tell your doctor or pharmacist.

ICLUSIG can cause abnormal blood and urine test results. Your doctor will decide when to perform blood and urine tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom/Effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Common	Abdominal pain		√	
	Decreased number of blood cells called platelets: Bleeding or easy bruising		√	
	Decreased number of red blood cells: tiredness and lack of energy, shortness of breath, noticeable heartbeats, a pale complexion		√	
Common	Heart failure: swelling in ankles and legs, shortness of breath, cough, fluid retention, fatigue, lack of appetite, nausea		√	
	Abnormal accumulation of fluid around the heart: difficult or painful breathing, chest pain, cough, dizziness, rapid heart rate		√	

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Symptom/Effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
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	Heart weakness, heart attack: pain or discomfort in chest, arms, back, neck, jaw or stomach, shortness of breath		√	
	Pulmonary hypertension (high blood pressure that affects the blood vessels in the lungs and the right side of your heart): shortness of breath, fatigue, cough, chest pain, fainting and swelling of ankles and feet		√	
	Narrowing of the heart blood vessels: uncomfortable pressure, fullness, squeezing or pain in your chest (angina)		√	
	Fluid in the chest: chest pain, cough, fever, hiccups, rapid breathing, shortness of breath		√	
	Pancreatitis: severe stomach and back pain, nausea and vomiting		√	
	Blood circulation problems, including arterial thrombosis (blood clot), sometimes resulting in amputations or requiring revascularization (need for surgery to restore blood supply by way of a blood vessel graft)		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/Effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Lung infection/ pneumonia: fever, cough, shortness of breath, chills, chest pain, fatigue		√	
Sepsis/infection in blood: fever, rapid heart rate and breathing		√	
Low white blood cell count: fever, often with signs of infection		√	
Abnormal heart beat: rapid, irregular or slow		√	
Blood clot in a deep vein: swelling or pain in leg, ankle or foot, warmth or changes in skin color, such as turning pale, red or blue over affected area		√	
Blood clot in a lung artery: chest pain, shortness of breath, cough, rapid breathing		√	
Stroke (caused by bleeding in the brain due to a burst blood vessel, or blockage in the blood vessels supplying blood to the brain): trouble with speaking and understanding, weakness or numbness of face, arm or leg, trouble with seeing in one or both eyes, dizziness, severe headache, trouble with walking and loss of balance		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/Effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Un-Common		√	
Tumor lysis syndrome: metabolic disorders caused by the breakdown products of dying cancer cells (kidney failure, abnormal heartbeat)		√	
Eye Disorder: blocked eye veins, blurred vision, visual disturbance, or blindness		√	
Stomach bleeding: blood in stool, vomiting blood, dark or tarry stool		√	
Liver damage: yellow skin and whites of eyes, nausea, tiredness, loss of appetite, fever, skin rash, joint pain and inflammation, pain in the upper right abdomen, pale stools and dark-coloured urine		√	
Narrowing of blood vessels supplying blood to the kidneys. May lead to high blood pressure.		√	
Rare		√	
Artery Dissection (sudden severe pain in the back, chest or abdomen)		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/Effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Artery Aneurysm (a bulge in the wall of any artery including in the chest, arms, legs, heart, and brain): Symptoms will differ by the site. They can be cough, coughing up blood. Strong pain high in your neck or in your back when you didn't hurt yourself. Problems swallowing. Hoarse voice. Unusual pulsing in your chest or abdomen.		√	
Unknown Hepatitis B Virus Reactivation: see above symptoms under Liver damage		√	
Posterior Reversible Encephalopathy Syndrome, PRES – also known as Reversible Posterior Leukoencephalopathy Syndrome, RPLS (a rare neurological disorder): headaches, seizures, confusion, changes in vision or problems thinking		√	
Erythema multiforme (an allergic skin reaction): raised red or purple skin patches, possibly with blister or crust in the center. Possibly swollen lips. Mild itching or burning.		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/Effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Stevens Johnson syndrome (severe skin reaction): rash, red skin, red or purple skin patches possibly with blister or crust in the center, pus-filled rash, peeling skin, blisters on the lips, eyes, skin or in the mouth, itching, burning, flu-like feeling, fever.		√	

This is not a complete list of side effects. For any unexpected effects while taking ICLUSIG, contact your doctor, nurse, or pharmacist.

HOW TO STORE IT

Keep this medicine out of the reach and sight of children.

Do not use this medicine after the expiry date which is stated on the bottle label after EXP. The expiry date refers to the last day of that month.

Store ICLUSIG at room temperature between 15° to 30°C. Store in the original container.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting <https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html> for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION**What does ICLUSIG Controlled Distribution Program mean?**

Only doctors who have been certified can write a prescription for ICLUSIG.

Pharmacist must be trained and must confirm that your doctor has been certified. The pharmacist cannot fill a prescription for ICLUSIG unless your doctor has been certified.

For information about the ICLUSIG Controlled Distribution Program, please call 1-888-867-7426 (English and French), or visit www.iclusigcdp.ca.

Where can I get my prescription filled?

Only pharmacies that have been trained on ICLUSIG and agree to the ICLUSIG Controlled Distribution Program requirements can fill your prescription. If you need help locating a trained pharmacy please call 1-888-867-7426.

How will my prescription be delivered?

Your prescription will be filled and shipped directly to you by a pharmacist trained in the ICLUSIG Controlled Distribution Program.

What will I receive with each shipment of ICLUSIG?

The pharmacy will mail your prescription of ICLUSIG directly to you along with other important materials, including a

- Patient Medication Guide
- Patient Wallet/Alert Card
- Contact information for the pharmacist

You will receive all of these materials with your first prescription and with each refill.

What is the Patient Alert/Wallet Card and what am I supposed to do with it?

The Patient Alert/Wallet Card contains important information about the serious side effects of ICLUSIG. The Patient Alert/Wallet Card contains information for you, your doctor, or

any other healthcare professional involved in your care. You should carry this card with you at all times. Show it to any doctor you consult for any reason.

What if I need more ICLUSIG than what my doctor usually prescribes, such as for travel?

If you need more ICLUSIG, contact your doctor.

What if I lost my medication or my medication was destroyed?

If you need more ICLUSIG, contact your doctor.

How do I contact my trained pharmacist if I have questions?

You may contact your pharmacist by using the contact information that was provided in your ICLUSIG shipment. If you have questions about ICLUSIG, you should also contact your doctor.

This document plus the full product monograph, prepared for health professionals can be found at www.iclusigcdp.ca; or by contacting Paladin Labs, Inc., at: 1-888-867-7426 (English and French)

This leaflet was prepared by ARIAD Pharmaceuticals, Inc. (a wholly owned subsidiary of Takeda Pharmaceutical Company Limited).

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