ICLUSIG (ponatinib) tablets
45 mg, 15 mg

ICLUSIG is a kinase inhibitor that targets BCR-ABL1, an abnormal tyrosine kinase that is expressed in chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL).

In the U.S., ICLUSIG is indicated for:
- Treatment of adult patients with chronic-phase, accelerated-phase or blast-phase CML (CP-CML, AP-CML or BP-CML) or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated.
- Treatment of adult patients with T315I-positive CML (CP, AP or BP) or T315I-positive Ph+ ALL.

Limitations of Use:
ICLUSIG is not indicated and is not recommended for the treatment of patients with newly diagnosed CP-CML.

ABOUT CML

Leukemia is a blood cancer that forms in certain cells in a person's bone marrow. CML is one of four main types of leukemia; it is a result of a genetic mutation that takes place in early, immature versions of myeloid cells, which form red blood cells, platelets and most types of white blood cells. Subsequently, an abnormal gene called *BCR-ABL1* forms, turning the damaged cell into a CML cell. CML typically progresses slowly, but it can change into a fast-growing acute leukemia that is hard to treat.[1]

ICLUSIG CLINICAL DEVELOPMENT

ICLUSIG is a targeted cancer medicine developed using a computational and structure-based drug-design platform, specifically designed to inhibit the activity of BCR-ABL1 and its mutations. The PACE clinical trial supported ICLUSIG's U.S. Food and Drug Administration (FDA) approval.

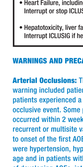
PACE
(Ponatinib Ph+ ALL and CML Evaluation)

The pivotal Phase 2 PACE trial evaluated the efficacy and safety of ICLUSIG in CML and Ph+ ALL patients resistant or intolerant to prior TKI therapy, or with the T315I mutation. Preliminary data supported the FDA's accelerated approval in December 2012. In November 2016, the FDA granted full approval based on 48-month follow-up data from the PACE trial.[2]

EFFECTIVE AGAINST THE T315I MUTATION

ICLUSIG targets native BCR-ABL1, as well as the BCR-ABL1 treatment-resistant mutations, including T315I, the most resistant mutation. ICLUSIG is the only approved TKI that demonstrates activity against the T315I gatekeeper mutation of BCR-ABL1. The mutation has been associated with resistance to all other approved TKIs.[3]

PATIENT SUPPORT



Takeda is committed to supporting people living with CML.

Takeda has a robust suite of services to help eligible patients access ICLUSIG.

Takeda strives to meet the needs of people living with cancer, their loved ones and the healthcare providers who support them.

For more information on ICLUSIG, visit www.ICLUSIG.com.
Additional information about Takeda Oncology is available through its website, www.takedaoncology.com.

U.S. IMPORTANT SAFETY INFORMATION

WARNING: ARTERIAL OCCLUSION, VENOUS THROMBOEMBOLISM, HEART FAILURE, and HEPATOTOXICITY
See full prescribing information for complete boxed warning.

- Arterial occlusion has occurred in at least 35% of ICLUSIG® (ponatinib)-treated patients including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures. Patients with and without cardiovascular risk factors, including patients less than 50 years old, experienced these events. Interrupt or stop ICLUSIG immediately for arterial occlusion. A benefit-risk consideration should guide a decision to restart ICLUSIG.
- Venous Thromboembolism has occurred in 6% of ICLUSIG-treated patients. Monitor for evidence of thromboembolism. Consider dose modification or discontinuation of ICLUSIG in patients who develop serious venous thromboembolism.
- Heart Failure, including fatalities, occurred in 9% of ICLUSIG treated patients. Monitor cardiac function. Interrupt or stop ICLUSIG for new or worsening heart failure.
- Hepatotoxicity, liver failure and death have occurred in ICLUSIG-treated patients. Monitor hepatic function. Interrupt ICLUSIG if hepatotoxicity is suspected.

WARNINGS AND PRECAUTIONS

Arterial Occlusions: The 35% of patients reported to have arterial occlusive events (AOEs) in the boxed warning included patients from both phase 1 and phase 2 trials. In the phase 2 trial, 33% of ICLUSIG-treated patients experienced a cardiac vascular (21%), peripheral vascular (12%), or cerebrovascular (9%) arterial occlusive event. Some patients experienced more than 1 type of event. Fatal and life-threatening events have occurred within 2 weeks of starting treatment, with doses as low as 15 mg per day. ICLUSIG can also cause recurrent or multisite vascular occlusion. Patients have required revascularization procedures. The median time to onset of the first AOE ranged from 193-526 days. The most common risk factors observed with these events were hypertension, hyperlipidemia, and history of cardiac disease. AOEs were more frequent with increasing age and in patients with a history of ischemia, hypertension, diabetes, or hyperlipidemia. In patients suspected of developing AOEs, interrupt or stop ICLUSIG.

Venous Thromboembolism: Venous thromboembolic events, including deep venous thrombosis, pulmonary embolism, superficial thrombophlebitis, and retinal vein thrombosis with vision loss, occurred in 6% of patients with an incidence rate of 5% (CP-CML), 4% (AP-CML), 10% (BP-CML), and 9% (Ph+ ALL). Consider dose modification or discontinuation of ICLUSIG in patients who develop serious venous thromboembolism.

Heart Failure: Fatal or serious heart failure or left ventricular dysfunction occurred in 6% of patients in the phase 2 trial. The most common heart failure events (3%) were congestive cardiac failure and decreased ejection fraction. Monitor patients for signs or symptoms consistent with heart failure and treat as clinically indicated, including interruption of ICLUSIG. Consider discontinuation if serious heart failure develops.

Hepatotoxicity: Hepatotoxic events were observed in 29% of patients (11% were grade 3 or 4). Severe hepatotoxicity occurred in all disease cohorts. Three patients with BP-CML or Ph+ ALL died: one with fulminant hepatic failure within one week of starting ICLUSIG and two with acute liver failure. The most common forms were elevations of AST or ALT (54% all grades, 8% grade 3 or 4, 5% not reversed at last follow-up), bilirubin, and alkaline phosphatase. The median time to onset of event was 3 months. Monitor liver function tests at baseline, then at least monthly or as clinically indicated. Interrupt, reduce or discontinue ICLUSIG as clinically indicated.

Hypertension: Treatment-emergent elevation of systolic or diastolic blood pressure (BP) occurred in 68% of patients, of which 12% were serious and included hypertensive crisis. Patients may require urgent clinical intervention for hypertension associated with confusion, headache, chest pain, or shortness of breath. In patients with baseline BP<140/90 mm Hg, 80% developed treatment-emergent hypertension (44% Stage 1 and 37% Stage 2). In 132 patients with Stage 1 hypertension at baseline, 67% developed Stage 2. Monitor and manage BP elevations during ICLUSIG use and treat hypertension to normalize BP. Interrupt, dose reduce, or stop ICLUSIG if hypertension is not medically controlled. In the event of significant worsening, labile or treatment-resistant hypertension, interrupt treatment and consider evaluating for renal artery stenosis.

Pancreatitis: Pancreatitis was reported in 7% of patients (6% were serious or grade 3/4). Many of these cases resolved within 2 weeks with dose interruption or reduction of ICLUSIG. The incidence of treatment-emergent lipase elevation was 42% (16% grade 3 or greater). Check serum lipase every 2 weeks for the first 2 months and monthly thereafter or as clinically indicated. Consider additional serum lipase monitoring in patients with a history of pancreatitis or alcohol abuse. Dose interruption or reduction may be required. In cases where lipase elevations are accompanied by abdominal symptoms, interrupt treatment with ICLUSIG and evaluate patients for pancreatitis. Do not consider restarting ICLUSIG until patients have complete resolution of symptoms and lipase levels are <1.5 x ULN.

Increased Toxicity in Newly Diagnosed CP-CML: In a prospective, randomized clinical trial in the first-line treatment of newly diagnosed patients with CP-CML, ICLUSIG 45 mg once daily increased the risk of serious adverse reactions 2-fold compared to imatinib 400 mg once daily. The median exposure to treatment was less than 6 months. The trial was halted for safety in October 2013. Arterial and venous thrombosis and occlusions occurred at least twice as frequently in the ICLUSIG arm compared to the imatinib arm. Compared to imatinib, ICLUSIG exhibited a greater incidence of myelosuppression, pancreatitis, hepatotoxicity, cardiac failure, hypertension, and skin and subcutaneous tissue disorders. ICLUSIG is not indicated and is not recommended for the treatment of patients with newly diagnosed CP-CML.

Neuropathy: Overall, 20% of patients experienced a peripheral neuropathy event of any grade (2% were grade 3/4). The most common were paresthesia (5%), neuropathy peripheral (4%), hypoesthesia (3%), dysgeusia (2%), muscular weakness (2%), and hyperesthesia (1%). Cranial neuropathy developed in 2% of patients (<1% grade 3/4). Of the patients who developed neuropathy, 16% developed neuropathy during the first 3 months of treatment. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness. Consider interrupting ICLUSIG and evaluate if neuropathy is suspected.

Ocular Toxicity: Serious ocular toxicities leading to blindness or blurred vision have occurred in patients. Retinal toxicities including macular edema, retinal vein occlusion, and retinal hemorrhage occurred in 2%. Conjunctival irritation, corneal erosion or ulceration, dry eye, conjunctivitis, conjunctival hemorrhage, hyperaemia and edema or eye pain occurred in 14%. Visual blurring occurred in 6%. Other ocular toxicities include cataracts, periorbital edema, blepharitis, glaucoma, eyelid edema, ocular hyperaemia, iritis, uveitis, and ulcerative keratitis. Conduct comprehensive eye exams at baseline and periodically during treatment.

Hemorrhage: Hemorrhage occurred in 28% of patients (6% serious, including fatalities). The incidence of serious bleeding events was higher in patients with AP- or BP-CML, and Ph+ ALL. Gastrointestinal hemorrhage and subdural hematoma were the most commonly reported serious bleeding events occurring in 1% each. Most hemorrhagic events occurred in patients with grade 4 thrombocytopenia. Interrupt ICLUSIG for serious or severe hemorrhage and evaluate.

Fluid Retention: Fluid retention occurred in 31% of patients. The most common events were peripheral edema (17%), pleural effusion (8%), pericardial effusion (4%) and peripheral swelling (3%). Severe events occurred in 4%. One instance of brain edema was fatal. Serious treatment-emergent events: included pleural effusion (2%), pericardial effusion (1%), and edema peripheral (<1%). Monitor patients for fluid retention and manage as clinically indicated. Interrupt, reduce, or discontinue ICLUSIG as clinically indicated.

Cardiac Arrhythmias: Arrhythmias occurred in 19% of patients (7% were grade ≥3). Arrhythmia of ventricular origin was reported in 3% of all arrhythmias, with one case being grade ≥3. Symptomatic bradyarrhythmias that led to pacemaker implantation occurred in 1% of patients. Atrial fibrillation was the most common arrhythmia (7%), approximately half of which were grade 3 or 4. Other grade 3 or 4 arrhythmia events included syncope (2%), tachycardia and bradycardia (each 0.4%), and electrocardiogram QT prolonged, atrial flutter, supraventricular tachycardia, ventricular tachycardia, atrial tachycardia, atrioventricular block complete, cardio-respiratory arrest, loss of consciousness, and sinus node dysfunction (0.2%). For 27 patients, the event led to hospitalization. In patients with signs and symptoms suggestive of slow heart rate (fainting, dizziness) or rapid heart rate (chest pain, palpitations or dizziness), interrupt ICLUSIG and evaluate.

Myelosuppression: Myelosuppression was reported in 59% of patients (50% were grade 3/4). The incidence of these events was greater in patients with AP- or BP-CML, and Ph+ ALL than in patients with CP-CML. Severe myelosuppression (grade 3 or 4) was observed early in treatment, with a median onset time of 1 month (range <1-40 months). Obtain complete blood counts every 2 weeks for the first 3 months and then monthly or as clinically indicated and adjust the dose as recommended.

Tumor Lysis Syndrome: Two patients (<1%, one with AP-CML and one with BP-CML) treated with ICLUSIG developed serious tumor lysis syndrome. Hyperuricemia occurred in 7% of patients. Due to the potential for tumor lysis syndrome in patients with advanced disease, ensure adequate hydration and treat high uric acid levels prior to initiating therapy with ICLUSIG.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): Post-marketing cases of RPLS have been reported in ICLUSIG-treated patients. RPLS is a neurological disorder that can present with signs and symptoms such as seizure, headache, decreased alertness, altered mental functioning, vision loss, and other visual and neurological disturbances. Hypertension is often present, and diagnosis is made with supportive findings on magnetic resonance imaging of the brain. If RPLS is diagnosed, interrupt ICLUSIG treatment and resume treatment only once the event is resolved and if the benefit of continued treatment outweighs the risk of RPLS.

Impaired Wound Healing and Gastrointestinal Perforation: Impaired wound healing occurred in patients receiving ICLUSIG. Withhold ICLUSIG for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of ICLUSIG after resolution of wound healing complications has not been established. Gastrointestinal perforation or fistula occurred in patients receiving ICLUSIG. Permanently discontinue in patients with gastrointestinal perforation.

Embryo-Fetal Toxicity: Based on its mechanism of action and findings from animal studies, ICLUSIG can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of ponatinib to pregnant rats during organogenesis caused adverse developmental effects at exposures lower than human exposures at the recommended human dose. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with ICLUSIG and for 3 weeks after the last dose.

ADVERSE REACTIONS

Most Common Adverse Reactions: The most common non-hematologic adverse reactions (≥20%) were abdominal pain, rash, constipation, headache, dry skin, arterial occlusion, fatigue, hypertension, pyrexia, arthralgia, nausea, diarrhea, lipase increased, vomiting, myalgia and pain in extremity. Hematologic adverse reactions included thrombocytopenia, anemia, neutropenia, lymphopenia, and leukopenia.

TO REPORT SUSPECTED ADVERSE REACTIONS, CONTACT TAKEDA AT 1-844-817-6468 OR FDA AT 1-800-FDA-1088 OR WWW.FDA.GOV/MEDWATCH.

DRUG INTERACTIONS

Strong CYP3A Inhibitors: Avoid concurrent use or reduce ICLUSIG dose if co-administration cannot be avoided.

Strong CYP3A Inducers: Avoid concurrent use.

USE IN SPECIFIC POPULATIONS

Females and Males of Reproductive Potential: Ponatinib may impair fertility in females and it is not known if these effects are reversible. Verify pregnancy status of females of reproductive potential prior to initiating ICLUSIG.

Lactation: Advise women not to breastfeed during treatment with ICLUSIG and for 6 days after last dose.

Please see full Prescribing Information, including boxed WARNING.

1. American Cancer Society. What is Chronic Myeloid Leukemia? https://www.cancer.org/cancer/chronic-myeloid-leukemia/about/what-is-cml.html. Accessed February 12, 2018.
2. ClinicalTrials.gov. Ponatinib for Chronic Myeloid Leukemia (CML) Evaluation and Ph+ Acute Lymphoblastic Leukemia (ALL) (PACE). https://clinicaltrials.gov/ct2/show/NCT01207440?term=NCT01207440&rank=1. Accessed February 12, 2018.
3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Myeloid Leukemia V.4.2016. ©National Comprehensive Cancer Network, Inc. 2016. All rights reserved. Accessed May 15, 2016. To view the most recent and complete version of the guideline, go online to NCCN.org.

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