PRODUCT MONOGRAPH

PrICLUSIG®

Ponatinib Tablets, 15 mg and 45 mg

(as ponatinib hydrochloride)

House Standard

Protein-tyrosine kinase inhibitor

L01XE24

ICLUSIG is indicated for the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom other tyrosine kinase inhibitor (TKI) therapy is not appropriate, including CML or Ph+ ALL that is T315I mutation positive or where there is prior TKI resistance or intolerance.

Marketing authorization with conditions is based on response rate. In the pivotal trial, the majority of the hematological responses occurred within 1 month. Consider discontinuing ICLUSIG if a hematological response has not been achieved by 3 months (90 days).

ICLUSIG for this indication has been issued marketing authorization with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the conditional nature of the authorization.

ARIAD Pharmaceuticals, Inc.
(A wholly owned subsidiary of Takeda Pharmaceutical Company Limited) 40 Landsdowne Street
Cambridge, MA, United States
02139

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Distributed by:
Paladin Labs Inc.,
Saint-Laurent, QC
H4M 2P2

Submission Control No: 212521

This product has been approved under the Notice of Compliance with Conditions (NOC/c) policy for one or all of its indicated uses.

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.

What will be different about this Product Monograph?

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol NOC/c. These sections may include, but are not limited to, the following:

- Indications and Clinical Uses;
- Action;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

Adverse Drug Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to Health Canada's Health Product Safety Information Division at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

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PART I: HEALTH PROFESSIONAL INFORMATION

ICLUSIG is indicated for the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom other tyrosine kinase inhibitor (TKI) therapy is not appropriate, including CML or Ph+ ALL that is T315I mutation positive or where there is prior TKI resistance or intolerance.

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SUMMARY PRODUCT INFORMATION

Route of Administration	Pharmaceutical Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet 15 mg and 45 mg	Lactose monohydrate *For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

NOC/c INDICATIONS AND CLINICAL USE

ICLUSIG (as ponatinib hydrochloride) is indicated for the treatment of adult patients with chronic phase (CP), accelerated phase (AP), or blast phase (BP) chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom other tyrosine kinase inhibitor (TKI) therapy is not appropriate, including CML or Ph+ ALL that is T315I mutation positive or where there is prior TKI resistance or intolerance.

Marketing authorization with conditions is based on a response rate endpoint (CP-CML: major cytogenetic response [MCyR] rate; AP-CML, BP-CML, Ph+ ALL: major hematologic response [MaHR] rate [see CLINICAL TRIALS]).

In the pivotal trial, the majority of the hematological responses occurred within 1 month. Consider discontinuing ICLUSIG if a hematological response has not been achieved by 3 months (90 days) (see CLINICAL TRIALS).

ICLUSIG should only be prescribed and monitored by a physician who has completed the certification with the **ICLUSIG Controlled Distribution Program** and who is experienced in the use of antineoplastic therapy and in the treatment of CML or Ph+ ALL.

ICLUSIG Controlled Distribution Program

ICLUSIG is only available through a controlled program referred to as the **ICLUSIG Controlled Distribution Program**. Under this program, only prescribers who have completed the certification and are registered with the program are able to prescribe ICLUSIG. Trained pharmacies will verify the prescriber's certified status prior to dispensing ICLUSIG to the patient. For further information about the program, please call 1-888-867-7426 (English and French) or visit www.iclusigcdp.ca.

A Patient Alert/Wallet Card describing the Serious Warnings and Precautions will be distributed to the patient (or included in packaging) at the time of dispensing and renewal. A copy of this information is on the last page of the product monograph.

Before starting treatment with ICLUSIG, the cardiovascular status of the patient should be assessed and cardiovascular risk factors should be actively managed. Cardiovascular status should continue to be monitored and therapy optimized during treatment with ICLUSIG (see Monitoring and Laboratory Tests).

An absolute distinction between patients at risk and patients not at risk of vascular occlusive events cannot be made. The optimal starting dose of ICLUSIG is not established. There are minimal data to support a 30 mg starting dose of ICLUSIG. Final data from a Phase 2 randomized dose-ranging study will help to clarify the optimal starting dose of ICLUSIG in adult patients with CML and Ph+ ALL.

The dose of ICLUSIG should be reduced to 15 mg daily in CP-CML patients who achieve a MCyR (see DOSAGE AND ADMINISTRATION). Do not resume ICLUSIG in patients with arterial or venous occlusive events unless the potential benefit outweighs the risk of recurrent arterial or venous occlusions and the patient has no other treatment options.

Geriatrics (≥ 65 years of age): Compared to patients < 65 years, older patients (with CP-CML) are more likely to experience adverse reactions.

Evidence from the clinical study suggests that use in the geriatric population (with CP-CML) is associated with reduced safety and effectiveness (see WARNINGS AND PRECAUTIONS).

Pediatrics (< 18 years of age): The safety and efficacy of ICLUSIG in patients less than 18 years of age have not been established. No data are available.

NOC/c CONTRAINDICATIONS

- Do not use in patients who are hypersensitive to ponatinib or to any ingredients in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.

- Do not use in patients who have unmanaged cardiovascular risk factors, including uncontrolled hypertension. Hypertension may contribute to the risk of arterial thrombotic events. Blood pressure should be monitored and managed to avoid hypertension (see also DRUG INTERACTIONS).

- Do not use in patients who are not adequately hydrated and with uncorrected high uric acid levels (see WARNINGS AND PRECAUTIONS).

NOC/c WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

ICLUSIG should only be prescribed and monitored by a physician who has completed the certification with the **ICLUSIG Controlled Distribution Program** and who is experienced in the use of antineoplastic therapy and in the treatment of CML or Ph+ ALL.

- Arterial occlusions have occurred in at least 25% (127/514) of ICLUSIG-treated patients (12% cardiac vascular, 9% cerebrovascular, 9% peripheral vascular; some patients experienced more than 1 type of event) with and without cardiovascular risk factors (including patients less than 50 years old). In the phase 2 trial, serious treatment-emergent arterial thrombosis (cardiovascular, cerebrovascular, and peripheral vascular, sometimes resulting in amputation) and occlusions were seen in 19% of the ICLUSIG-treated patients including fatal myocardial infarction, fatal cerebral infarction, stroke, disseminated intravascular coagulation, and arterial stenosis sometimes requiring urgent revascularization procedures. Peripheral arterial occlusive events, including fatal mesenteric artery occlusion have occurred in ICLUSIG-treated patients. Some of these events occurred within 2 weeks of starting treatment with ICLUSIG. Monitor for evidence of arterial occlusion. Interrupt or consider discontinuation in patients who develop arterial thrombotic events (see WARNINGS AND PRECAUTIONS, Arterial Occlusion).

- In the phase 2 trial, venous thromboembolism occurred in 6% of ICLUSIG-treated patients, 5% of which were serious. Cases of pulmonary embolism have been reported, some of which were fatal. Monitor for evidence of thromboembolism. Interrupt or consider discontinuation in patients who develop venous thromboembolism (see WARNINGS AND PRECAUTIONS, Venous Thromboembolism).

- Heart Failure (in some cases, fatal), including left ventricular dysfunction and ejection fraction decreases, occurred in 9% of ICLUSIG-treated patients, 6% of which were fatal or serious (see WARNINGS AND PRECAUTIONS, Congestive Heart Failure).

- Hemorrhage events (some fatal) including intracranial hemorrhage, hemorrhagic gastritis, (fatal), hemorrhagic cerebral infarction (fatal). Most hemorrhagic events, but not all, occurred in patients with grade 4 thrombocytopenia (see WARNINGS AND PRECAUTIONS, Hemorrhage).

- Hepatotoxicity (including fatal acute hepatic failure) has been reported. Monitor hepatic function prior to and during treatment. Consider ICLUSIG dose interruption followed by dose reduction or discontinuation in patients with hepatotoxicity (see WARNINGS AND PRECAUTIONS, Hepatotoxicity and DOSAGE AND ADMINISTRATION).

- Myelosuppression (thrombocytopenia, neutropenia, and anemia) (see WARNINGS AND PRECAUTIONS, Myelosuppression).

- Pancreatitis (7%) and elevations in amylase (3% grade 3 or greater) or lipase (13% grade 3 or greater) have been reported (see WARNINGS AND PRECAUTIONS, Pancreatitis).

- ICLUSIG has not been studied in patients with renal impairment.

General

Caution should be exercised and a reduction of the starting dose of ICLUSIG is recommended with concurrent use of ICLUSIG and strong CYP3A inhibitors (see DRUG INTERACTIONS).

Although no significant differences in pharmacokinetic parameters were observed in patients with various degrees of hepatic impairment (Child Pugh A, B and C) when compared to that of healthy volunteers following a single 30 mg dose, a higher incidence of adverse reactions was observed in patients with severe hepatic impairment. Therefore, the recommended starting dose of ICLUSIG is 30 mg once daily for patients with hepatic impairment (Child Pugh A, B, and C) (see DOSAGE AND ADMINISTRATION).

Cardiovascular

Before starting treatment with ICLUSIG, the cardiovascular status of the patient should be assessed and cardiovascular risk factors should be actively managed. Cardiovascular status should continue to be monitored and therapy optimized during treatment with ICLUSIG (see DRUG INTERACTIONS and Monitoring and Laboratory Tests).

Hypertension may contribute to the risk of arterial thrombotic events. Blood pressure should be monitored and managed to avoid hypertension (see Monitoring and Laboratory Tests).

Arterial Occlusion

In clinical trials arterial occlusions, including cardiovascular (e.g., fatal myocardial infarction, acute coronary syndrome), cerebrovascular (e.g., fatal cerebral infarction, stroke, stenosis of large arterial vessels of the brain), and peripheral vascular (e.g., retinal occlusion leading to vision loss, peripheral arterial occlusive disease, sometimes resulting in amputation) occlusions, some requiring the need for urgent revascularization procedures (cerebrovascular, coronary, and peripheral arterial), have occurred in 25% (127/514) of ICLUSIG-treated patients with and without cardiovascular risk factors (including patients less than 50 years old). Renal artery stenosis, associated with worsening, labile or treatment-resistant hypertension, has also occurred in some ICLUSIG-treated patients.

In the phase 2 trial, arterial occlusion has occurred in 23% (104/449) of ICLUSIG-treated patients with some patients experiencing events of more than one type.

Cardiovascular occlusion, including fatal and life-threatening myocardial infarction and coronary artery occlusion has occurred in 13% (56/449) of ICLUSIG-treated patients. Patients have developed heart failure concurrent or subsequent to the myocardial ischemic event.

Cerebrovascular occlusion, including fatal stroke, has occurred in 9% (39/449) of ICLUSIG-treated patients. ICLUSIG has been associated with stenosis over multiple segments in major arterial vessels that supply the brain (e.g., carotid, vertebral, middle cerebral artery).

Peripheral arterial occlusive events, including fatal mesenteric artery occlusion and life-threatening peripheral arterial disease have occurred in 9% (40/449) of ICLUSIG-treated patients. Patients have developed digital or distal extremity necrosis and have required amputations.

The median time to onset of arterial occlusion events was 12.7 months (range 3 days to 44.6 months). Arterial occlusion adverse events were more frequent with increasing age and in patients with prior history of ischemia, hypertension, diabetes, or hyperlipidemia (see Table 1). However, patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced arterial occlusive events.

ICLUSIG should not be used in patients with a history of myocardial infarction, prior revascularization or stroke unless the potential benefit of treatment outweighs the potential risk (see CONTRAINDICATIONS).

Before starting treatment with ICLUSIG, the cardiovascular status of the patient should be assessed and cardiovascular risk factors should be actively managed. Cardiovascular status should continue to be monitored during treatment with ICLUSIG (see Monitoring and Laboratory Tests). If decreased vision or blurred vision occurs, an ophthalmic examination (including fundoscopy) should be performed and ICLUSIG should be interrupted if arterial occlusion is suspected. Monitoring for evidence of arterial occlusion should be performed and ICLUSIG should be interrupted immediately in case of arterial occlusion. A benefit–risk consideration should guide a decision to restart ICLUSIG therapy (see DOSAGE AND ADMINISTRATION).

Inform patients that serious arterial occlusion (including arterial stenosis sometimes requiring revascularization) have occurred. Advise patients to immediately seek medical attention with any symptoms suggestive of a blood clot such as chest pain, shortness of breath, weakness on one side of the body, speech problems, leg pain, or leg swelling (see WARNINGS AND PRECAUTIONS).

Table 1: Incidence of Arterial Occlusive Events in ICLUSIG-Treated Patients in the Phase 2 Trial (N=449) According to Risk Categories: Minimum Follow-up of 48 Cycles (1 Cycle = 28 Days)

Age (At time of Study Entry)	Prior history of ischemia, hypertension, diabetes, or hyperlipidemia N=218	No history of ischemia, hypertension, diabetes, or hyperlipidemia N=231
Age: 49 or younger	19% (7/37)	6% (6/107)
Age: 50 to 74 years	33% (50/153)	17% (19/110)
Age: 75 and older	54% (15/28)	50% (7/14)
All age groups	33% (72/218)	14% (32/231)
Total	**23% (104/449)**	

Source: Study AP24534-10-201 CSR, Data extraction date: August 03, 2015

Venous Thromboembolism

Venous thromboembolism occurred in 6% (25/449) of ICLUSIG-treated patients, including deep vein thrombosis, pulmonary embolism, superficial thrombophlebitis and retinal venous occlusions with vision loss.

Cases of pulmonary embolism have been reported, some of which were fatal. The incidence of thromboembolic events is higher in patients with Ph+ ALL or BP-CML than those with APCML or CP-CML.

If decreased vision or blurred vision occurs, an ophthalmic examination (including fundoscopy) should be performed and ICLUSIG should be interrupted if venous thromboembolism is suspected. Monitoring for evidence of thromboembolism should be performed and ICLUSIG should be interrupted immediately in case of venous thromboembolism. A benefit–risk consideration should guide a decision to restart ICLUSIG therapy (see DOSAGE AND ADMINISTRATION).

Inform patients that serious venous thromboembolism events have occurred. Advise patients to immediately seek medical attention with any symptoms suggestive of a blood clot such as chest pain, cough, fever, shortness of breath, feeling faint, weakness on one side of the body, speech problems, leg pain or leg swelling, rapid breathing or irregular heartbeat (see WARNINGS AND PRECAUTIONS).

Congestive Heart Failure and Left Ventricular Dysfunction

ICLUSIG has been reported to cause congestive heart failure and reduced left ventricular ejection fraction (LVEF) (see ADVERSE REACTIONS, ACTION and CLINICAL PHARMACOLOGY, Ventricular Performance).

In the phase 2 PACE trial in patients with refractory CML and Ph+ ALL receiving the 45 mg starting dose, 39 of 449 patients (9%) experienced cardiac failure or left ventricular dysfunction, including 28 patients (6%) with serious events and 4 patients (1%) with fatal events. The time from initiation of treatment to reporting of these adverse events averaged 196 days (range 1 - 981 days).

Patients receiving ICLUSIG should be monitored for signs and symptoms consistent with congestive heart failure, with treatment as clinically indicated, including interruption of ICLUSIG. Consider discontinuation of ICLUSIG in patients who develop new or worsening serious heart failure (see DOSAGE AND ADMINISTRATION).

LVEF should be evaluated in all patients prior to initiation of treatment with ICLUSIG, at three months after initiation of ICLUSIG, and whenever clinically indicated.

ICLUSIG should be used with caution in patients with a history of congestive heart failure or conditions that could impair left ventricular function. ICLUSIG should be permanently discontinued in patients who develop symptomatic congestive heart failure or asymptomatic left ventricular dysfunction that does not resolve within 4 weeks after interruption of ICLUSIG treatment or is of ≥ grade 3. In the presence of clinical manifestations of congestive heart failure, discontinuation of ICLUSIG is recommended. The dose of ICLUSIG should be interrupted and/or reduced in patients without clinical evidence of congestive heart failure but with an ejection fraction < 50% and > 10% below baseline.

Patients with significant or active cardiovascular disease were excluded from clinical trials, including patients with congestive heart failure within 3 months of starting ICLUSIG treatment.

Inform patients of the possibility of heart failure and abnormally slow or fast heart rates. Advise patients to contact their health care provider if they experience symptoms such as shortness of breath, chest pain, palpitations, dizziness, or fainting (see WARNINGS AND PRECAUTIONS).

Hypertension

Hypertension may contribute to the risk of arterial thrombotic and occlusion events, including renal artery stenosis. During ICLUSIG treatment, blood pressure elevations should be monitored and managed. Hypertension should be treated to normalize blood pressure. ICLUSIG treatment should be temporarily interrupted, dose reduced or stopped 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.

With a minimum of 48 cycles (1 cycle = 28 days) of follow-up for all ongoing patients, hypertension was noted as a treatment-emergent adverse event Treatment-emergent elevation of systolic or diastolic blood pressure (BP) occurred in 68% (306/449) of patients in the phase 2 clinical trial (48 months of follow-up); the adverse event of hypertension or worsening of hypertension was observed in 31% (137/449) of patients (12% grade 3 or greater). The estimated change in blood pressure for the CP-CML population (N= 270) is an increase of 1.18 mm Hg per year systolic and 0.07 mm Hg per year diastolic.

Seven patients (2%) treated with ICLUSIG in the phase 2 trial experienced treatment-emergent symptomatic hypertension as a serious adverse reaction, including hypertensive crisis. Patients may require urgent clinical intervention for hypertension associated with confusion, headache, chest pain, or shortness of breath (see ADVERSE REACTIONS).

Inform patients of the possibility of new or worsening of existing hypertension. Advise patients to contact their health care provider for elevated blood pressure or if symptoms of hypertension occur including headache, dizziness, chest pain, or shortness of breath (see WARNINGS AND PRECAUTIONS).

Cardiac Arrhythmias

Arrhythmia adverse events occurred in 19% (86/449; 7% [33/449] grade 3 or greater) of ICLUSIG-treated patients. Atrial fibrillation was the most common arrhythmia and occurred in 7% (31/449) of patients, approximately half of which were grade 3 or 4. Other grade 3 or 4 arrhythmia events included syncope (9 patients; 2.0%), tachycardia and bradycardia (2 patients 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 (1 patient each; 0.2%). For 27 patients, the event led to hospitalization.

Symptomatic bradyarrhythmias that led to a requirement for pacemaker implantation occurred in 1% (3/449) of ICLUSIG-treated patients. The cardiac rhythms (1 case each) identified were complete heart block, sick sinus syndrome, and atrial fibrillation with bradycardia and pauses.

Advise patients to report signs and symptoms suggestive of slow heart rate (fainting, dizziness) or rapid heart rate (chest pain, palpitations, dizziness). Interrupt ICLUSIG and evaluate.

Fluid Retention

Fluid retention adverse events occurred in 31% (4.5% grade 3 or greater) of patients treated with ICLUSIG. These events included peripheral edema, pericardial effusion, pleural effusion, and ascites. Patients should be monitored for fluid retention. Interrupt, reduce or discontinue ICLUSIG as clinically indicated.

Inform patients of the possibility of developing fluid retention and to contact their health care provider for symptoms such as leg swelling, abdominal swelling, weight gain, or shortness of breath.

Hematologic

Hemorrhage

Hemorrhage occurred in 28% (124/449) of ICLUSIG-treated patients. Severe hemorrhage events, including fatalities, occurred in 7% (32/449) of ICLUSIG-treated patients. The incidence of severe bleeding events was higher in patients with AP-CML, BP-CML, or Ph+ ALL than CP-CML. Gastrointestinal hemorrhage (fatal) and subdural hematoma were the most commonly reported severe bleeding events occurring in 1% (4/449 and 3/449, respectively). Some hemorrhagic events occurred in patients with grade 3 or 4 thrombocytopenia (see WARNINGS AND PRECAUTIONS, Myelosuppression). Interrupt ICLUSIG for serious or severe (grade 3 or greater) hemorrhage and evaluate (see DOSAGE AND ADMINISTRATION, Myelosuppression).

Inform patients of the possibility of serious bleeding and to immediately contact their healthcare provider with any signs or symptoms suggestive of hemorrhage such as unusual bleeding or easy bruising.

Myelosuppression

With 48 cycles (1 cycle = 28 days) of follow-up, myelosuppression was reported as an adverse event in 59% (266/449) of patients, and severe (grade 3 or greater) myelosuppression occurred in 50% (226/449) of patients treated with ICLUSIG. Severe (grade 3 or greater) events of thrombocytopenia (36%, 160/449), neutropenia (22%, 100/449) and anemia (16%, 70/449) were reported**.** The incidence of these events was higher in patients with AP-CML or BP-CML/Ph+ ALL than in patients with CP-CML. Of the patients who developed grade 3 or 4 platelet count decreased, most developed it within the first 3 months of treatment. A complete blood count should be performed every 2 weeks for the first 3 months and then monthly or as clinically indicated. Dose modification may be required. Myelosuppression was managed by withholding ICLUSIG temporarily or reducing the dose (see DOSAGE AND ADMINISTRATION).

Myelosuppression was reported in patients with normal baseline laboratory values as well as in patients with pre-existing laboratory abnormalities. Discontinuation due to myelosuppression occurred due to (thrombocytopenia (3.8%), neutropenia and anemia (< 1% each).

Inform patients of the possibility of developing low blood cell counts and to immediately report should fever develop, particularly in association with any suggestion of infection.

Hepatic/Biliary/Pancreatic

Hepatotoxicity

Hepatotoxicity, including acute fatal hepatic failure, has occurred in ICLUSIG-treated patients within 1 week of starting ICLUSIG treatment. With 48 cycles (1 cycle = 28 days) follow-up, 11% (50/449) of ICLUSIG-treated patients experienced grade 3 or 4 hepatotoxicity in the phase 2 trial. The most common forms of hepatotoxicity were elevations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase, bilirubin, alkaline phosphatase, and hypoalbuminemia. The incidence of adverse events of AST or ALT elevation was 16% (70/449) and 18% (81/449), respectively. ICLUSIG treatment may result in elevation in ALT, AST, bilirubin, and alkaline phosphatase. ALT or AST elevation was not reversed by the date of last follow-up in 5% of patients.

The median time to initial onset for the adverse events of ALT elevation was 141 days (range 2- 1457 days) and the median time to initial onset for the adverse events of AST elevation was 95 days (range 1-993 days). Liver function tests (LFTs), including transaminases, should be performed at baseline, then at least monthly or as clinically indicated. Dose interruption, reduction or discontinuation may be required (see DOSAGE AND ADMINISTRATION).

Inform patients of the possibility of developing liver function abnormalities and serious hepatic toxicity. Advise patients to immediately seek medical attention if signs of liver failure occur, including yellowing of the eyes or skin, “tea-colored” urine, or drowsiness.

Pancreatitis and Serum Lipase

With 48 cycles (1 cycle = 28 days) of follow-up in the phase 2 trial, ICLUSIG was associated with pancreatitis (7%; 6% grade 3) and elevations in serum lipase (42%; 16% grade 3 or greater). The frequency of pancreatitis is greater in the first 2 months of ICLUSIG use.

Check serum lipase and amylase every 2 weeks for the first 2 months and then periodically thereafter or as clinically indicated. Dose modification may be required (see Table 7 in DOSAGE AND ADMINISTRATION). If lipase elevations are accompanied by abdominal symptoms, ICLUSIG should be withheld and patients evaluated for evidence of pancreatitis (see DOSAGE AND ADMINISTRATION). Caution is recommended in patients with a history of pancreatitis or alcohol abuse. Patients with severe or very severe (grade 3 or greater) hypertriglyceridemia should be appropriately managed to reduce the risk of pancreatitis.

Inform patients of the possibility of developing pancreatitis that may be accompanied by nausea, vomiting, abdominal pain, or abdominal discomfort, and to promptly report these symptoms.

Immune

Hepatitis B Virus Reactivation

Reactivation of hepatitis B virus (HBV) has occurred in patients who are chronic carriers of this virus after receiving BCR-ABL tyrosine kinase inhibitors. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or death.

Patients currently receiving ICLUSIG should be tested for HBV infection, if clinically indicated, in order to identify chronic carriers of the virus. Patients should be tested for HBV infection before initiating treatment with ICLUSIG. Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with ICLUSIG should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.

Gastrointestinal Perforation and Impaired Wound Healing

Serious gastrointestinal perforation (fistula) was reported in a patient 38 days following cholecystectomy. ICLUSIG may impair wound healing based on the mechanism of action (see ACTION AND CLINICAL PHARMACOLOGY). Temporary interruption of ICLUSIG therapy should be considered in patients prior to undergoing major surgical procedures. Clinical judgment of adequate wound healing should guide the decision to resume ICLUSIG treatment after surgery.

Advise patients to inform their healthcare provider if they plan to undergo a surgical procedure or had recent surgery. Inform patients that cases of gastrointestinal perforation have been reported.

Neurologic

Peripheral and cranial neuropathies have occurred in ICLUSIG-treated patients. Overall, 20% (90/449) of ICLUSIG-treated patients in the pivotal phase 2 trial experienced a peripheral neuropathy event of any grade (2%, grade 3/4) (48-cycles follow-up). The most common peripheral neuropathies reported were paresthesia (5%, 23/449), peripheral neuropathy (4%, 19/449), hypoesthesia (3%, 15/449), dysgeusia (2%, (10/449), muscular weakness (2% (10/449) and hyperesthesia (1%, 5/449). Cranial neuropathy developed in 2% (10/449) of ICLUSIG-treated patients (<1%, 3/449 - grade 3/4). Cases of ataxia and convulsion were also reported.

Of the patients who developed neuropathy, 26% (23/90) developed neuropathy during the first month of treatment.

Inform patients of the possibility of developing peripheral or cranial neuropathy while being treated with ICLUSIG. Advise patients to report symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness.

Posterior Reversible Encephalopathy Syndrome (PRES)

Post-marketing cases of Posterior Reversible Encephalopathy Syndrome (PRES, also known as Reversible Posterior Leukoencephalopathy Syndrome – RPLS) have been reported in ICLUSIG-treated patients (see Post-Market Adverse Reactions). PRES is a serious neurological disorder that can present with signs and symptoms such as seizure with hemiplegia, 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 (MRI) of the brain.

If PRES is diagnosed during treatment, interrupt ICLUSIG treatment and resume treatment only once the event is resolved and if the benefit of continued treatment outweighs the risk of PRES.

Tumour Lysis Syndrome

Serious tumour lysis syndrome occurred in 2 patients (<1%). One case occurred in an AP-CML patient and one case occurred in a BP-CML patient. Hyperuricemia occurred in 31 patients (7%), most of whom were CP-CML patients (18 patients). Ensure adequate hydration and high uric acid levels should be corrected prior to initiating therapy with ICLUSIG.

Sexual Function/Reproduction

Women of childbearing age being treated with ICLUSIG should be advised of the potential risk to a fetus, and advised not to become pregnant. Men being treated with ICLUSIG should be advised not to father a child during treatment. Embryo-fetal toxicity has been reported in animal studies at exposures lower than human exposures at the recommended human dose. An effective method of contraception should be used during treatment (see TOXICOLOGY). It is unknown whether ICLUSIG affects the effectiveness of systemic hormonal contraceptives. An alternative or additional method of contraception should be used.

No human data on the effect of ponatinib on fertility are available. In rats, treatment with ponatinib has shown impairment of female fertility. Male fertility was not affected by ponatinib treatment. The clinical relevance of these findings to human fertility is unknown (see TOXICOLOGY).

Ophthalmologic

Serious ocular toxicities leading to blindness or blurred vision occurred in ICLUSIG-treated patients in the phase 2 trial (48 cycles follow-up). Retinal toxicities including macular edema, retinal vein occlusion, and retinal hemorrhage occurred in 2% of ICLUSIG-treated patients. Conjunctival irritation, corneal erosion or abrasion, dry eye, conjunctivitis, conjunctival hemorrhage, hyperemia and edema or eye pain occurred in 14% of patients. Visual blurring occurred in 5.1% of patients. Other ocular toxicities include cataracts, periorbital edema, blepharitis, glaucoma, eyelid edema, ocular hyperemia, iritis, iridocyclitis, and ulcerative keratitis. Conduct comprehensive eye exams at baseline and periodically during treatment. ICLUSIG should be interrupted if vascular occlusion is suspected (see ADVERSE REACTIONS).

A case of retinal artery occlusion (grade 4) while taking a 45 mg dose of ICLUSIG was reported. Patients should be monitored for the occurrence of vision problems (see WARNINGS AND PRECAUTIONS, Arterial Occlusion).

Inform patients of the possibility of ocular toxicity while being treated with ICLUSIG. Advise patients to report symptoms of ocular toxicity, such as blurred vision, dry eye, or eye pain.

Carcinogenesis and Mutagenesis

A statistically significant increased incidence of squamous cell carcinoma of the clitoral gland in rats was observed at a plasma exposure level lower or equal to the human exposure within the clinically recommended dose range. The clinical relevance of this finding is not known (see TOXICOLOGY).

Special Populations

Pregnant Women: Embryo-fetal toxicity has been reported in animal studies at exposures lower than human exposures at the recommended human dose (see TOXICOLOGY). There are no data regarding the use of ICLUSIG in pregnant women. The potential risk for humans is unknown. Patients must be informed of the potential risk to the fetus.

Inform patients that ICLUSIG can cause fetal harm when administered to a pregnant woman. Advise women of the potential hazard to a fetus and to avoid becoming pregnant during the treatment of ICLUSIG.

Nursing Women: It is unknown whether ICLUSIG is excreted in human milk. Available pharmacodynamic and toxicological data cannot exclude potential excretion in human milk. Breast-feeding should be stopped during treatment with ICLUSIG.

Men and Women with Childbearing Potential: Women of childbearing age being treated with ICLUSIG should be advised not to become pregnant and men being treated with ICLUSIG should be advised not to father a child during treatment. An effective method of birth control should be used during ICLUSIG treatment. It is unknown whether ICLUSIG affects the effectiveness of systemic hormonal contraceptives. An alternative or additional method of contraception should be used. No human data on the effect of ponatinib on fertility are available. In rats, treatment with ponatinib has shown impairment of female fertility. Male fertility was not affected by ponatinib treatment. The clinical relevance of these findings to human fertility is unknown.

Lactose intolerance: ICLUSIG contains 121 mg of lactose monohydrate in a 45 mg daily dose. Advise patients who have or may have an intolerance to lactose. Patients with rare hereditary disorders of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take ICLUSIG (see WARNINGS AND PRECAUTIONS, Special Populations and CONTRAINDICATIONS).

Hepatic Impairment: Administer ICLUSIG at a dose of 30 mg once daily in patients with hepatic impairment (Child Pugh A, B or C). Hepatic elimination is a major route of excretion for ICLUSIG.

A single dose of ICLUSIG 30 mg was administered to patients with mild, moderate, and severe hepatic impairment (Child-Pugh Classes A, B, and C, respectively) and to healthy subjects. Overall no major differences in ponatinib pharmacokinetics were observed in patients with varying degrees of hepatic impairment as compared to healthy subjects. However, there was an increased overall incidence of adverse reactions, in patients with severe hepatic impairment including a case of severe pancreatitis. The safety of multiple ICLUSIG dose, or doses higher than 30 mg has not been studied in patients with hepatic impairment. Caution is recommended when administering ICLUSIG to patients with hepatic impairment.

Renal Impairment: Renal excretion is not a major route of ponatinib elimination. ICLUSIG has not been studied in patients with renal impairment. Caution is recommended when administering ICLUSIG to patients with estimated creatinine clearance of < 60 mL/min (moderate to severe renal impairment) or end-stage renal disease.

Pediatrics (< 18 years of age): The safety and efficacy of ICLUSIG in patients less than 18 years of age have not been established. No data are available.

Geriatrics (≥ 65 years of age): Compared to patients < 65 years of age, older patients (≥ 65 years of age) are more likely to experience reduced efficacy and adverse reactions. Of the 449 patients in the clinical study of ICLUSIG, 155 (35%) were ≥ 65 years of age. CP-CML patients ≥ 65 years of age had a lower MCyR rate, 38%, compared with patients between 45 and 64 years of age (MCyR 59%) and patients between 18 and 44 years of age (MCyR 73%). Patients ≥ 65 years of age are more likely to experience adverse reactions, including decreased platelet count, peripheral edema, increased lipase, dyspnea, asthenia, muscle spasms, and decreased appetite.

In general, dose selection for an older patient should be done cautiously, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, of concomitant disease or other drug therapy.

Monitoring and Laboratory Tests

ICLUSIG is associated with serious events of vascular occlusion, thromboembolism, cardiac arrhythmias and cardiac failure. Before starting treatment with ICLUSIG, the cardiovascular status of the patient should be assessed and cardiovascular risk factors should be actively managed (see Drug-Drug Interactions). Cardiovascular status should continue to be monitored and therapy optimized during treatment with ICLUSIG (see WARNINGS AND PRECAUTIONS).

Hypertension may contribute to risk of arterial thrombosis and occlusion events. During ICLUSIG treatment, blood pressure should be monitored and managed to avoid hypertension.

ICLUSIG is associated with severe (grade 3 or greater) thrombocytopenia, neutropenia, and anemia. A complete blood count should be performed every 2 weeks for the first 3 months and

then monthly or as clinically indicated (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

ICLUSIG may result in elevation in ALT, AST, bilirubin, and alkaline phosphatase. Liver function tests should be performed at baseline and periodically, as clinically indicated (see WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATIONS, and TOXICOLOGY).

ICLUSIG is associated with pancreatitis. Check serum amylase/lipase every 2 weeks for the first 2 months and then periodically thereafter. Dose interruption or reduction may be required (see Table 7). If lipase elevations are accompanied by abdominal symptoms, ICLUSIG should be withheld and patients evaluated for evidence of pancreatitis (see DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS).

Left ventricular ejection fraction (LVEF) should be evaluated in all patients prior to initiation of treatment with ICLUSIG, at three months after initiation of ICLUSIG and whenever clinically indicated.

Monitor for evidence of thromboembolism. Interrupt treatment with ICLUSIG or consider discontinuation in patients who develop venous thromboembolism.

Serious ocular toxicities leading to blindness or blurred vision occurred in ICLUSIG-treated patients. Conduct comprehensive eye exams at baseline and periodically during treatment.

Ensure adequate hydration and correct uric acid levels prior to initiating therapy with ICLUSIG if tumour lysis syndrome is considered a substantial risk (see WARNINGS AND PRECAUTIONS).

Patients should be weighed and monitored regularly for signs and symptoms of fluid retention (see WARNINGS AND PRECAUTIONS).

Calcium and phosphate should be measured at baseline and monitored during ICLUSIG treatment, as clinically indicated.

NOC/c ADVERSE REACTIONS

Adverse Drug Reaction Overview

The adverse reactions described in this section were identified in a single-arm, open-label, international, multicenter trial in 449 CML and Ph+ ALL patients who were resistant or intolerant to prior TKI therapy including those with a BCR-ABL T315I mutation. All patients received a starting dose of 45 mg ICLUSIG once daily. Dose adjustments to 30 mg once daily or 15 mg once daily were allowed for the management of treatment toxicity. Additionally, after approximately 2 years of follow-up, patients who were still taking a 45 mg daily dose were recommended to undergo a dose reduction, in response to the continued occurrence of vascular

occlusive events in the clinical trial. At the time of reporting, all ongoing patients had a minimum follow-up of 48 cycles (1 cycle = 28 days). The median duration of treatment with ICLUSIG was 866 days in CP-CML patients, 590 days in AP-CML patients, and 86 days in BP-CML/Ph+ ALL patients. The trial is ongoing. At the time of the analysis, 71% (318/449) patients experienced a dose interruption of more than three days and 68% (304/449) experienced a dose reduction. The median dose intensity was 29 mg/day in CP-CML patients or, 64% of the expected 45 mg daily dose. The median dose intensity was greater in advanced disease states (34 mg/day in the AP-CML patients and 44 mg/day in the BP CML/Ph+ ALL patients). The rates of treatment-emergent adverse events resulting in discontinuation were 19% (50/270) in CP-CML, 12% (10/85) in AP-CML, 15% (9/62) in BP-CML, and 9% (3/32) in Ph+ ALL.

The most common non-hematologic adverse reactions (≥ 20%) were abdominal pain (43%), rash (42%), constipation (37%), headache (37%), dry skin (36%), fatigue (30%), hypertension (30%), pyrexia (30%), arthralgia (29%), nausea (29%), diarrhea (22%), lipase increased (22%), vomiting (21%), myalgia (21%) and pain in extremity (20%). The most common adverse events (≥ 1%) that led to treatment discontinuation was platelet count decreased (4%). The most common adverse events (≥ 5%) that led to dose modification (interruption or dose reduction) were platelet count decreased (31%), neutrophil count decreased (14%), lipase increased (13%), arterial occlusive events (13%), abdominal pain (12%), rash (9%), anemia (6%), pancreatitis (6%), ALT increased (5%) and hypertension (5%).

Adverse drug reactions with a Very Common (≥ 10%) and Common (≥ 1% to < 10%) frequency are presented in Table 3. Overall, the very common adverse reactions (≥ 10%) were platelet count decreased, rash, constipation, headache, dry skin, abdominal pain, fatigue, hypertension, arthralgia, nausea, neutrophil count decreased, anemia, lipase increased, myalgia, ALT increased, AST increased.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 2: Serious Adverse Drug Reactions Occurring in ≥ 1% of Resistant or Intolerant CP-CML, AP-CML, BP-CML and Ph+ ALL Patients in Phase 2 Study AP24534-10-201 (PACE, N=449): Minimum Follow-up of 48 Cycles (1 Cycle = 28 Days)

MedDRA System Organ Class Preferred Term	**N (%)**
Blood and lymphatic system disorders	
Anemia	6 (1.3%)
Febrile neutropenia	5 (1.1%)
Pancytopenia	5 (1.1%)
Cardiovascular disorders	
Arterial occlusion	54 (12.0%)
Cardiac vascular	26 (5.8%)
Angina pectoris	12 (2.7%)
Acute myocardial infarction/myocardial infarction[a]	8 (1.8%)
Coronary artery disease	7 (1.6%)
Acute coronary syndrome	4 (0.9%)
Cerebrovascular	18 (4.0%)
Cerebral infarction	6 (1.3%)
Cerebrovascular accident	5 (1.1%)
Peripheral vascular	20 (4.5%)
Peripheral arterial occlusive disease	14 (3.1%)
Peripheral artery stenosis	3 (0.7%)
Venous thromboembolism[b]	8 (1.8%)
Atrial fibrillation	8 (1.8%)
Cardiac failure congestive	7 (1.6%)
Cardiac failure	5 (1.1%)
Pericardial effusion	5 (1.1%)
Gastrointestinal disorders	
Pancreatitis	25 (5.6%)
Abdominal pain	9 (2.0%)
General	
Pyrexia	5 (1.1%)
Investigations	
Lipase increased	9 (2.0%)
Platelet count decreased	8 (1.8%)
Neutrophil count decreased	5 (1.1%)
Vascular disorders	
Hypertension	7 (1.6%)

[a] Includes fatal events

[b] Individual venous thromboembolism events occurred at a frequency of < 1%

Source: Study AP24534-10-201 CSR, Data extraction date: August 03, 2015

Table 3: Most Common Adverse Drug Reactions Occurring in ≥ 5% of Resistant or Intolerant CP-CML, AP-CML, BP-CML and Ph+ ALL Patients in Phase 2 Study AP24534-10-201 (PACE, N=449); Minimum Follow-up of 48 Cycles (1 Cycle = 28 Days)

System Organ Class Preferred Term	CP-CML (N=270)		AP-CML (N=85)		BP-CML (N=62)		Ph+ ALL (N=32)	
	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)
Blood and lymphatic system disorders								
Anemia	11	6	21	13	23	21	16	13
Cardiac disorders								
Cardiac failure*	6	4	7	6	10	8	0	0
Eye disorders								
Dry eye	5	1	5	0	2	0	3	0
Gastrointestinal disorders								
Abdominal pain	29	7	18	5	10	2	19	6
Constipation	20	2	14	1	5	0	19	3
Nausea	16	0	12	0	21	0	3	0
Vomiting	8	1	8	0	13	0	3	0
Diarrhea	9	<1	11	0	2	0	3	3
Pancreatitis	7	7	8	6	5	3	0	0
Abdominal distension	6	0	5	0	5	0	0	0
General disorders and administration site conditions								
Fatigue	20	2	20	1	11	3	9	0
Asthenia	10	1	6	1	8	2	0	0
Pyrexia	9	0	8	1	3	0	13	0
Pain	7	1	7	0	7	2	0	0
Edema peripheral	6	0	7	0	5	0	9	0
Investigations								
Platelet count decreased	42	32	45	35	27	26	9	6
Lipase increased	25	11	15	13	13	11	9	6
Neutrophil count decreased	17	15	29	29	23	18	13	13
Alanine aminotransferase increased	15	4	17	2	10	3	6	3
Aspartate aminotransferase increased	12	2	14	4	8	2	6	3
Amylase increased	7	3	7	4	5	3	3	0
Gamma-glutamyltransferase increased	6	3	9	4	3	3	0	0

System Organ Class Preferred Term	CP-CML (N=270)		AP-CML (N=85)		BP-CML (N=62)		Ph+ ALL (N=32)	
	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)
Blood alkaline phosphatase increased	6	<1	11	1	3	0	0	0
Metabolism and nutrition disorders								
Decreased appetite	7	<1	7	1	5	0	9	0
Musculoskeletal and connective tissue disorders								
Arthralgia	19	2	19	2	13	0	3	0
Myalgia	18	1	19	0	13	0	6	0
Pain in extremity	12	2	6	0	5	0	0	0
Muscle spasms	11	0	4	0	2	0	6	0
Bone pain	9	<1	6	0	3	0	0	0
Back pain	9	1	2	0	0	0	0	0
Nervous system disorders								
Headache	25	3	13	0	11	2	13	0
Respiratory, thoracic and mediastinal disorders								
Dyspnea	8	2	8	0	7	2	0	0
Skin and subcutaneous tissue disorders								
Rash	42	4	34	4	24	3	19	3
Dry skin	40	3	25	1	18	2	22	0
Erythema	9	1	7	0	5	0	6	0
Rash pruritic	9	0	11	2	2	0	3	0
Pruritus	10	<1	4	0	2	2	0	0
Alopecia	6	0	7	0	5	0	6	0
Skin exfoliation	7	0	2	0	2	0	0	0
Vascular disorders								
Hypertension	22	6	13	6	3	3	3	3

Treatment related adverse events as assessed by the investigator. The incidence-rate reported in WARNINGS AND PRECAUTIONS section are treatment-emergent frequencies.

*Cardiac failure includes the following MedDRA preferred terms: cardiac failure, cardiac failure congestive, cardiac failure acute, cardiac failure chronic, left ventricular dysfunction, ejection fraction decreased.

Source: Study AP24534-10-201 CSR, Data extraction date: August 03, 2015

Other Common (≥ 1%) and Uncommon (< 1%) Clinical Trial Adverse Drug Reactions

Blood and lymphatic system disorders: febrile neutropenia, pancytopenia

Cardiac disorders: acute coronary syndrome, acute myocardial infarction/ myocardial infarction, angina pectoris, atrial fibrillation, atrial flutter, bradycardia, coronary artery disease, coronary artery occlusion, ischemic cardiomyopathy, myocardial ischemia, palpitations, pericardial effusion, tachycardia.

Uncommon: cardiac discomfort

Ear and labyrinth disorders: tinnitus**,** vertigo

Eye disorders: conjunctival hemorrhage, eye pain, eyelid edema, periorbital edema, vision blurred

Uncommon: retinal artery occlusion, retinal vein thrombosis and occlusion, visual impairment

Endocrine disorders: hypothyroidism

Gastrointestinal disorders: abdominal discomfort, dry mouth, dyspepsia, gastroesophageal reflux disease, gastrointestinal hemorrhage (includes fatal events), gingival bleeding, mouth ulceration, stomatitis

General disorders and administration site conditions: chest discomfort, chest pain, chills, face edema, influenza like illness, localised edema, malaise, non-cardiac chest pain, peripheral swelling

Hepatobiliary disorders:

Uncommon: Hepatic failure, hepatotoxicity, jaundice

Infections and infestations: cellulitis, conjunctivitis, folliculitis, herpes zoster, pneumonia, sepsis, upper respiratory tract infection, urinary tract infection

Injury, poisoning and procedural complications: contusion

Investigations: blood bilirubin increased, blood cholesterol increased, blood creatinine increased, blood uric acid increased, electrocardiogram QT prolonged, lymphocyte count decreased, transaminases increased, weight decreased, weight increased, white blood cell count decreased

Metabolism and nutrition disorders: dehydration, fluid retention, gout, hyperglycemia, hypertriglyceridemia, hyperuricemia, hypoalbuminemia, hypocalcemia, hypokalemia, hyponatremia, hypophosphatemia

Uncommon: tumour lysis syndrome

Musculoskeletal and connective tissue disorders: flank pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal stiffness, neck pain, upper extremity mass

Neoplasms benign, malignant unspecified (incl cysts and polyps): melanocytic nevus

Nervous system disorders: amnesia, carotid artery stenosis, cerebral infarction, cerebrovascular accident, dizziness, dysgeusia, hyperesthesia, hypoesthesia, lethargy, migraine, neuropathy peripheral, paraesthesia, syncope, transient ischemic attack, tremor

Uncommon: cerebral artery stenosis, cerebral hemorrhage

Psychiatric disorders: anxiety, confusional state, depression, disorientation, insomnia

Renal and urinary disorders: renal artery stenosis

Reproductive system and breast disorders: erectile dysfunction

Respiratory, thoracic and mediastinal disorders: cough, dry throat, dysphonia, dyspnea exertional, epistaxis, pleural effusion, pulmonary embolism (includes fatal events), pulmonary hypertension

Skin and subcutaneous tissue disorders: acne, actinic keratosis, dermatitis acneiform, dermatitis exfoliative, dermatitis psoriasiform, ecchymosis, erythema multiforme, exfoliative rash, generalised erythema, hyperhidrosis, hyperkeratosis, ichthyosis acquired, keratosis pilaris, night sweats, pain of skin, petechiae, skin discoloration, skin hyperpigmentation, skin lesion, skin ulcer, toxic skin eruption

Vascular disorders: arteritis, deep vein thrombosis, flushing, hot flush, intermittent claudication, peripheral arterial occlusive disease, peripheral artery stenosis, peripheral ischemia, poor peripheral circulation, splenic infarction

Uncommon: Embolism venous, hypertensive crisis

Abnormal Hematologic and Clinical Chemistry Findings

Myelosuppression was commonly reported in all patient populations of resistant or intolerant CML and Ph+ ALL. The frequency of Grade 3 or 4 thrombocytopenia, neutropenia, and anemia was higher in patients with AP-CML and BP-CML/Ph+ ALL than in patients with CP-CML (see Table 4). Myelosuppression was reported in patients with normal baseline laboratory values as well as in patients with pre-existing laboratory abnormalities.

Table 4: Incidence of Clinically Relevant Grade 3 or Greater Laboratory Abnormalities in ≥ 2% of Resistant or Intolerant CML and Ph+ ALL Patients from Study AP24534-10-201 (PACE, N=449): Minimum Follow-up of 48 Cycles (1 Cycle = 28 Days)

Laboratory Test	CP-CML (N=270) (%)	AP-CML (N=85) (%)	BP-CML (N=62) (%)	Ph+ ALL (N=32) (%)
Haematology				
Thrombocytopenia (platelet count decreased)	35	49	45	47
Neutropenia (ANC decreased)	23	52	48	59
Leukopenia (WBC decreased)	12	37	48	63
Anemia (Hgb decreased)	8	31	52	34
Lymphopenia	10	25	32	19
Biochemistry				
Lipase increased	13	13	15	13
Phosphorus decreased	9	13	11	3
Glucose increased	7	12	2	0
ALT increased	4	8	8	6
Sodium decreased	5	6	2	3
AST increased	3	6	5	0
Potassium increased	2	1	5	0
Alkaline phosphatase increased	2	4	3	0
Bilirubin increased	<1	2	0	3
Potassium decreased	<1	6	3	0
Amylase increased	3	4	5	0
Calcium decreased	<1	2	2	0

Source: Study AP24534-10-201 CSR, Data extraction date: August 03, 2015

Electrocardiogram Findings

In a phase 3 randomised, open-label study of ICLUSIG versus active comparator in adult patients with newly diagnosed CP-CML patients, the ICLUSIG group received once daily oral administration of 45 mg for 28 day continuous cycles, with dose adjustments based on tolerability. At the month 3 assessment, ICLUSIG was associated with statistically significant decreases from baseline in the QTcF interval and heart rate. The mean change from baseline in the QTcF interval (N=78) was -8.2 ms (90% CI -11.98, -4.88) and the mean change from baseline in heart rate (N=84) was -5.6 bpm (90% CI -7.81, -3.43).

Post-Market Adverse Reactions

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Limited post-marketing data are available. The safety profile observed in post-marketing is similar to that observed during clinical studies. However, serious cases of Posterior Reversible Encephalopathy Syndrome (PRES, also known as Reversible Posterior Leukoencephalopathy Syndrome – RPLS) have occurred in patients receiving ICLUSIG. Blurred vision or bilateral blindness was reported in some patients after 5 days of treatment. Hepatitis B virus reactivation has been reported in patients who are chronic carriers of this virus after receiving BCR-ABL tyrosine kinase inhibitors.

In addition, the following adverse reactions have been identified during post-marketing use of ICLUSIG: urinary tract infection, chest pain, dehydration, peripheral swelling, and severe cutaneous reaction (e.g., Erythema multiforme, Stevens-Johnson Syndrome).

DRUG INTERACTIONS

Overview

Drug-Drug Interactions

Ponatinib is metabolized by esterases and/or amidases, and also by CYP3A4. Caution should be exercised and a reduction of the starting dose of ICLUSIG to 30 mg should be considered with concurrent use of ICLUSIG and strong CYP3A4 inhibitors.

In vitro studies indicate that drug-drug interactions are unlikely to occur as a result of ponatinib-mediated inhibition of the metabolism of substrates for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A or CYP2D6. An *in vitro* study in human hepatocytes indicated that drug-drug interactions are also unlikely to occur as a result of ponatinib-mediated induction of the metabolism of substrates for CYP1A2, CYP2B6, or CYP3A.

At therapeutic plasma concentrations, ponatinib did not inhibit OATP1B1 or OATP1B3, OCT1 or OCT2, organic anion transporters OAT1 or OAT3, or bile salt export pump (BSEP) *in vitro*. Clinical drug-drug interactions are unlikely to occur as a result of ponatinib-mediated inhibition of these transporter substrates. *In vitro*, ponatinib is an inhibitor of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Ponatinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp or BCRP and may increase their therapeutic effect and adverse reactions. Close clinical surveillance is recommended when ponatinib is administered with P-gp and BCRP substrates.

Substances that increase ponatinib serum concentrations

CYP3A4 inhibitors

Ponatinib is primarily metabolized by CYP3A4. Therefore, concomitant use of substances which inhibit CYP3A4 may increase ponatinib plasma concentrations.

Co-administration in healthy volunteers of a single 15 mg oral dose of ICLUSIG in the presence of ketoconazole (400 mg daily), a strong CYP3A4 inhibitor, resulted in increases in ponatinib systemic exposure, with ponatinib $AUC_{0-\infty}$ and C_{max} values that were 78% and 47% higher, respectively, than those seen when ponatinib was administered alone. Patients being co-administered ICLUSIG with strong CYP3A4 inhibitors may be at increased risk for adverse reactions.

Caution should be exercised and a reduction of the starting dose of ICLUSIG to 30 mg should be considered with concurrent use of ICLUSIG and strong CYP3A4 inhibitors such as clarithromycin, indinavir, itraconazole, ketoconazole, nelfinavir, ritonavir, saquinavir, voriconazole, and grapefruit juice (see Drug-Food Interactions).

Substances that decrease ponatinib serum concentrations

CYP3A4 inducers

Ponatinib is mostly metabolized by CYP3A4. Therefore, concomitant use of CYP3A inducers may decrease ponatinib serum concentrations. Co-administration of ICLUSIG with strong CYP3A inducers (such as carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, and St. John's Wort) should be avoided unless the benefit outweighs the possible risk of ICLUSIG underexposure. Monitor patients for signs of reduced efficacy.

Co-administration in healthy volunteers of a single 45 mg dose of ICLUSIG in the presence of rifampin (600 mg daily for 9 days), a strong CYP3A inducer, resulted in decreases in ponatinib systemic exposure, with ponatinib AUC_{0-inf} and C_{max} values that were 62% and 42% lower, respectively, than those seen when ponatinib was administered alone.

Gastric pH Elevating Drugs

The aqueous solubility of ponatinib is pH-dependent, with higher pH resulting in lower solubility.

Administration of a single 45 mg dose of ICLUSIG following multiple doses of a potent inhibitor of a proton pump inhibitor, lansoprazole, 60 mg QD for 2 days, in 18 healthy volunteers, resulted in reductions in ponatinib C_{max} by 25% without a change in overall systemic exposure (AUC_{0-inf}), respective to those seen when ICLUSIG was administered alone. Median T_{max} was increased by 1 hour when ICLUSIG was administered following lansoprazole pretreatment.

ICLUSIG may be administered concurrently with proton pump inhibitors or other drugs that raise gastric pH without the need for adjustment of ICLUSIG dose or separation of administration.

Substances that may have their serum concentrations altered by ponatinib

Transporter substrates

In vitro, ponatinib is an inhibitor of P-gp and BCRP. Therefore, ponatinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp (e.g., digoxin, dabigatran, colchicine, pravastatin) or BCRP (e.g., methotrexate, rosuvastatin, sulfasalazine) and may increase their therapeutic effect and adverse reactions. Close clinical surveillance is recommended when ICLUSIG is administered with these medicinal products substrates of P-gp or BCRP.

Drug-Food Interactions

Administration of ICLUSIG with a high- or low-fat meal, or without food, does not change the pharmacokinetics of ponatinib (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Products and juices containing grapefruit, star fruit, pomegranate, Seville oranges and other similar fruits that are known to inhibit CYP3A4 should be avoided at any time.

Drug-Herb Interactions

Interactions with herbal products have not been studied. St. John's Wort is a potent CYP3A4 inducer. Co-administration with ICLUSIG may lead to increased ponatinib metabolism and therefore decreased ponatinib serum concentrations (see Drug-Drug Interactions). Co-administration with ICLUSIG should be avoided.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been studied.

Drug-Lifestyle Interactions

Effects on Ability to Drive and Use Machines

The effect of ICLUSIG on the ability to drive or operate machinery was not specifically measured; however, in clinical studies with ICLUSIG, fatigue, dizziness, somnolence and syncope were reported. Patients experiencing dizziness, visual impairment or other undesirable effects should refrain from these activities until these effects cease (see ADVERSE REACTIONS).

Alcohol

No studies have been conducted on the potential interaction between ICLUSIG and alcohol consumption.

NOC/c DOSAGE AND ADMINISTRATION

Dosing Considerations

ICLUSIG must only be prescribed and used in treatment initiated by a physician who has completed certification with the **ICLUSIG Controlled Distribution Program**, and who is experienced in diagnosing patients with leukemia (in particular, CML or Ph+ ALL) and with treatments including antineoplastic therapy.

Before starting treatment with ICLUSIG, the cardiovascular status of the patient should be assessed and cardiovascular risk factors should be actively managed. Cardiovascular status should continue to be monitored and therapy optimized during treatment with ICLUSIG.

Hematologic support such as platelet transfusion and hematopoietic growth factors can be used during treatment if clinically indicated.

Recommended Dose

An absolute distinction between patients at risk and patients not at risk of arterial occlusive and venous thromboembolism events cannot be made. The optimal starting dose of ICLUSIG is not established. There are minimal data to support a 30 mg starting dose of ICLUSIG. Final data from a phase 2 randomized, dose-ranging study will help to clarify the optimal starting dose of ICLUSIG in adult patients with CML and Ph+ ALL.

The recommended starting dose is 45 mg of ICLUSIG once daily. Consider reducing the dose of ICLUSIG for patients with chronic phase (CP) CML and accelerated phase (AP) CML who have achieved a major cytogenetic response. ICLUSIG may be administered with or without food. ICLUSIG tablets should be swallowed whole. Patients should not crush or dissolve the tablets.

Advise patients to take ICLUSIG exactly as prescribed and not to change their dose or to stop taking ICLUSIG unless they are told to do so by their health care provider. Patients should not take two doses at the same time to make up for a missed dose.

Monitoring for evidence of venous thromboembolism and arterial occlusion should be performed and ICLUSIG should be interrupted immediately in case of vascular occlusion. A benefit–risk consideration should guide a decision to restart ICLUSIG therapy.

Advise patients who have intolerance to lactose that ICLUSIG contains lactose.

Dose Adjustment or Modifications

Dose modifications or interruption of dosing should be considered for hematologic (Table 5) or non-hematologic toxicity (Table 6 and Table 7). For a dose of 30 mg or 15 mg once daily, 15 mg tablets are available.

ICLUSIG may need to be temporarily withheld and/or dose-reduced for hematologic abnormalities (neutropenia, thrombocytopenia, leukopenia, anemia, lymphopenia) that are not related to underlying leukemia.

Consider reducing the dose of ICLUSIG from 45 mg once daily to 15 mg once daily for CP-CML patients who have achieved a MCyR.

Consider discontinuing ICLUSIG if a hematologic response has not been achieved by 3 months (90 days).

Myelosuppression

Dose modifications for neutropenia (ANC* < 1.0 x 10^9/L) and thrombocytopenia (platelets < 50 x 10^9/L) that are unrelated to leukemia are summarized in Table 5.

Table 5: Dose Modifications for Myelosuppression

ANC* < 1.0 x 10^9/L or platelets < 50 x 10^9/L	First occurrence: • Withhold ICLUSIG and resume initial 45 mg dose after recovery to ANC ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L
	Second occurrence: • Withhold ICLUSIG and resume at 30 mg after recovery to ANC ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L
	Third occurrence: • Withhold ICLUSIG and resume at 15 mg after recovery to ANC ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L
*ANC = absolute neutrophil count	

Hepatic Toxicity

Recommended dose modifications for hepatic toxicity are summarized in Table 6.

Table 6: Dose Modifications for Hepatic Toxicity

Elevation of liver transaminase > 3 × ULN* (grade 2 or higher)	Occurrence at 45 mg: • Interrupt ICLUSIG and monitor hepatic function • Resume ICLUSIG at 30 mg after recovery to ≤ grade 1 (≤ 3 × ULN) Occurrence at 30 mg: • Interrupt ICLUSIG and resume at 15 mg after recovery to ≤ grade 1 Occurrence at 15 mg: • Discontinue ICLUSIG
Elevation of AST or ALT ≥ 3 × ULN concurrent with an elevation of bilirubin > 2 × ULN and alkaline phosphatase < 2 x ULN	Discontinue ICLUSIG
*ULN = Upper Limit of Normal for the lab	

Non-hematologic Adverse Reactions

If a clinically significant or severe (grade 3 or greater) non-hematologic adverse reaction occurs, modify the dose, interrupt treatment or consider discontinuation. After the event is resolved or attenuated in severity, ICLUSIG may be resumed at the same dose or at a reduced dose according to initial grade of the adverse reaction.

Do not restart ICLUSIG until the severe (grade 3 or greater) adverse reaction has been resolved or the potential benefit of resuming therapy is judged to outweigh the risk.

In a patient suspected of developing an arterial or venous occlusive event, ICLUSIG should be immediately interrupted. A benefit-risk consideration should guide a decision to restart ICLUSIG therapy after the event is resolved.

Hypertension may contribute to risk of arterial thrombosis and occlusions. Hypertension should be treated to normalize blood pressure. ICLUSIG treatment should be temporarily interrupted if hypertension is not medically controlled (see CONTRAINDICATIONS).

Consider discontinuation in case of grade 4 non-hematological toxicity.

Pancreatitis and Elevation of Lipase/Amylase

Recommended modifications for pancreatic adverse reactions are summarized in Table 7.
In case lipase elevations are accompanied by abdominal symptoms, ICLUSIG should be interrupted and appropriate diagnostic tests should be considered in order to exclude pancreatitis (see WARNINGS AND PRECAUTIONS).

Table 7: Dose Modifications for Pancreatitis and Elevation of Lipase/Amylase

Asymptomatic grade 2 pancreatitis and/or grade 2 elevation of lipase/amylase	Continue ICLUSIG at the same dose
Grade 3 or 4 asymptomatic elevation of lipase/amylase (> 2.0 x ULN*) only	Occurrence at 45 mg: • Withhold ICLUSIG and resume at 30 mg after recovery to ≤ grade 1 (≤ 1.5 x ULN) Occurrence at 30 mg: • Withhold ICLUSIG and resume at 15 mg after recovery to ≤ grade 1 (≤ 1.5 x ULN) Occurrence at 15 mg: • Discontinue ICLUSIG
Grade 3 pancreatitis	Occurrence at 45 mg: • Withhold ICLUSIG and resume at 30 mg after recovery to ≤ grade 1 Occurrence at 30 mg: • Withhold ICLUSIG and resume at 15 mg after recovery to ≤ grade 1 Occurrence at 15 mg: • Discontinue ICLUSIG
Grade 4 pancreatitis	Discontinue ICLUSIG
*ULN = upper limit of normal	

For patients whose adverse reactions are resolved, escalation of the dose should be considered, if clinically appropriate.

Hepatic Impairment

Caution is recommended when administering ICLUSIG to patients with hepatic impairment. The recommended starting dose is 30 mg once daily in patients with hepatic impairment (Child-Pugh A, B & C) (see WARNINGS AND PRECAUTIONS).

Renal Impairment

Renal excretion is not a major route of ponatinib elimination. ICLUSIG has not been studied in patients with renal impairment. Caution is recommended when administering ICLUSIG to patients with estimated creatinine clearance of < 60 mL/min, or end-stage renal disease.

Missed Dose

If a dose is missed, the patient should not take an additional dose. In this case, the patient should take the usual dose at the next scheduled time.

Administration

The tablets should be swallowed whole. Patients should not crush or dissolve the tablets. ICLUSIG may be administered with or without food.

OVERDOSAGE

Isolated cases of unintentional overdose with ICLUSIG were reported in clinical trials. Single doses of 165 mg and an estimated 540 mg in 2 patients did not result in any clinically significant adverse reactions. Multiple doses of 90 mg per day for 12 days in a patient resulted in pneumonia, systemic inflammatory response, atrial fibrillation, and asymptomatic, moderate pericardial effusion. Treatment was interrupted, the events resolved, and ICLUSIG was restarted at 45 mg, once daily. Multiple doses of 60 mg per day, administered due to lack of efficacy, in a Ph+ ALL patient resulted in hospitalization for pleural and pericardial effusions after 6 days of treatment. The patient was treated with diuretics and the events abated. ICLUSIG dosing was not interrupted.

In the event of an overdose of ICLUSIG, the patient should be observed and appropriate supportive treatment given.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

NOC/c ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Ponatinib is a kinase inhibitor. Ponatinib is a potent pan-BCR-ABL inhibitor with structural elements, including a carbon-carbon triple-bond that enables high affinity binding to native BCR-ABL and mutant forms of the ABL kinase. Ponatinib inhibits the *in vitro* tyrosine kinase activity of ABL and T315I mutant ABL with IC_{50}s values of 0.4 and 2.0 nM, respectively. Ponatinib inhibits the *in vitro* activity of additional kinases with IC_{50}s between 0.1 and 20, including members of the VEGFR, PDGFR, FGFR, EPH receptors and SRC families of kinases, and KIT, RET, TIE2, and FLT3.

Pharmacodynamics

In cellular assays, ponatinib was able to overcome imatinib, dasatinib, and nilotinib resistance mediated by BCR-ABL kinase domain mutations. In preclinical studies, 40 nM was determined as the concentration of ponatinib sufficient to inhibit viability of cells expressing all tested BCR-ABL mutants by > 50% (including T315I). In a cell-based accelerated mutagenesis assay, no mutation in BCR-ABL was detected that could confer resistance to 40 nM ponatinib.

Ponatinib elicited tumour shrinkage and prolonged survival in mice bearing tumours expressing native or T315I-mutant BCR-ABL.

The dose intensity-safety relationship indicated that there are significant increases in grade 3 or greater adverse events (arterial thrombosis, cardiac failure, hypertension, thrombocytopenia, pancreatitis, neutropenia, rash, ALT increase, AST increase, lipase increase, myelosuppression, arthralgia) over the dose range of 15 to 45 mg once-daily.

In the phase 1 study, plasma steady state trough concentrations of ponatinib typically exceeded 21 ng/mL (40 nM) at doses of 30 mg or greater. At daily oral doses of 15 mg or greater, 32 of 34 patients (94%) demonstrated a ≥ 50% reduction of CRKL phosphorylation, a biomarker of BCR-ABL inhibition, in peripheral blood mononuclear cells.

Cardiac Electrophysiology

The effect of ICLUSIG on ECG intervals was assessed in 39 leukemia patients who received 30 mg, 45 mg, or 60 mg ICLUSIG once daily in an open label, uncontrolled trial. Serial ECGs in triplicate were collected at baseline and at 2h, 4h, and 6h post-dosing at steady state (Day 29). The QTcF interval showed a decrease from baseline in all dose cohorts. At the therapeutic dose of 45 mg, the maximal observed mean change in QTcF from baseline was -7.5 ms at 6 h.

No large changes in the mean QTc interval (i.e., > 20 ms) from baseline were detected in the study. However, an increase in the mean QTc interval of < 10 ms cannot be excluded because of study design limitations, and due to the absence of a thorough QT study.

Ventricular Performance

The effect of ICLUSIG on LVEF was assessed by echocardiography in 24 patients with advanced or refractory leukemia who received 45 mg ICLUSIG once daily in the phase 1 open-label, uncontrolled trial. The mean change from baseline to minimum post-baseline LVEF was -9.9% (90% CI -13.0, -6.8). Minimum post-baseline ejection was < 50% in 5 (20.8%) of the subjects and < 40% in 2 (8.3%) subjects. The reduction from baseline to minimum post-baseline ejection fraction was ≥ 10% in 10 (41.7%) subjects, including 3 (12.5%) subjects with a reduction from baseline of ≥ 20%.

Pharmacokinetics

Absorption: Peak concentrations of ponatinib are observed approximately 6 hours after oral administration. Within the range of clinically relevant doses evaluated in patients (15 mg to 60 mg), ponatinib exhibited approximately dose-proportional increases in both C_{max} and AUC.

The geometric mean (CV%) C_{max} and $AUC_{(0-\tau)}$ exposures achieved for ponatinib 45 mg daily at steady state were 73 ng/mL (61%) and 1253 ng•hr/mL (58%), respectively. The absolute bioavailability of ponatinib is unknown.

Following either a high-fat or low-fat meal, in 22 healthy volunteers, plasma ponatinib exposures (C_{max} and AUC) were not different versus those in fasting conditions. ICLUSIG may be administered with or without food.

Distribution: *In vitro*, ponatinib is highly bound (> 99%) to plasma proteins. The blood/plasma partition ratio of ponatinib is 0.96. At daily doses of 45 mg, the geometric mean (CV%) apparent steady state volume of distribution is 1101 L (94%) suggesting that ponatinib is extensively distributed in the extravascular space. *In vitro* studies suggested that ponatinib is either not a substrate or is a weak substrate for both P-gp and BCRP. Ponatinib is not a substrate for the organic anion transporting polypeptides OATP1B1, OATP1B3 or the organic cation transporter OCT-1.

Metabolism: Ponatinib is metabolized to an inactive carboxylic acid by esterases and/or amidases, and metabolized by CYP3A4 to an N-desmethyl metabolite that is 4 times less active than ponatinib. The carboxylic acid and the N-desmethyl metabolite comprise 58% and 2% of the circulating levels of ponatinib, respectively.

Excretion: Following multiple 45 mg doses of ICLUSIG in patients, the terminal elimination half-life of ponatinib was 22 hours. With once-daily dosing, plasma exposures of ponatinib are increased by approximately 1.5-fold between first dose and steady state conditions. Ponatinib is mainly eliminated via feces. Following a single oral dose of [^{14}C] ponatinib, approximately 87% of the radioactive dose is recovered in the feces and approximately 5% in the urine. Unchanged ponatinib accounted for 24% and < 1% of the administered dose in feces and urine, respectively, with the remainder of the dose comprising metabolites.

Linearity/Non-linearity

A pharmacokinetic analysis conducted on the plasma concentration-time data from the 81 patients in the phase 1 study (AP24534-07-101) showed the increase in ponatinib concentrations was approximately proportional with increasing dose over the 15 mg to 60 mg dose range.

Special Populations and Conditions:

No specific studies have been performed to evaluate the effects of gender, age, race, and body weight on ponatinib pharmacokinetics. In CP-CML patients 65 years of age and over, there was a trend towards reduced efficacy.

Hepatic Insufficiency: Caution is recommended when administering ICLUSIG to patients with hepatic impairment. A single 30 mg oral dose of ponatinib was administered to subjects with normal liver function (N=8) and to subjects with mild [Child-Pugh A (N=6)], moderate [Child-Pugh B (N=6)], and severe [Child-Pugh C (N=4)] hepatic impairment. Compared to subjects with normal liver function, there was no trend of increased ponatinib exposure in subjects with hepatic impairment.

There was an increased incidence of adverse reactions in patients with severe hepatic impairment compared to subjects with normal liver function. Caution is recommended when administering ICLUSIG to patients with hepatic impairment. The recommended starting dose is 30 mg once daily in patients with hepatic impairment (Child-Pugh A, B, or C). The recommended starting dose is 30 mg once daily in patients with hepatic impairment (Child-Pugh A, B, or C) (see WARNINGS AND PRECAUTIONS, Special Populations).

Renal Insufficiency: Renal excretion is not a major route of ponatinib elimination. ICLUSIG has not been studied in patients with renal impairment. Caution is recommended when administering ICLUSIG to patients with estimated creatinine clearance of < 50 mL/min, or end-stage renal disease.

Pharmacogenomics: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product (see WARNINGS AND PRECAUTIONS and CONTRAINDICATIONS).

STORAGE AND STABILITY

ICLUSIG tablets should be stored at room temperature (15° to 30°C).

Store in the original package.

ICLUSIG must be kept out of reach and sight of children.

SPECIAL HANDLING INSTRUCTIONS

No special requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ICLUSIG (as ponatinib hydrochloride, 15 mg tablet)
Each tablet for oral administration contains 15 mg ponatinib (as ponatinib hydrochloride). The 15 mg tablet is a white, biconvex, round film-coated tablet that is approximately 6 mm in diameter, with “A5” debossed on one side. ICLUSIG 15 mg tablets are supplied in HDPE bottles with screw-top closures containing 30 or 60 tablets and one canister desiccant.

ICLUSIG (as ponatinib hydrochloride, 45 mg tablet)
Each tablet for oral administration contains 45 mg of ponatinib (as ponatinib hydrochloride). The 45 mg tablet is a white, biconvex, round film-coated tablet that is approximately 9 mm in diameter, with "AP4" debossed on one side. ICLUSIG 45 mg tablets are supplied in HDPE bottles containing 30 tablets and one canister desiccant.

Non-medicinal Ingredients
Tablet core: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, colloidal anhydrous silica, and magnesium stearate

Tablet coating: talc, polyethylene glycol, polyvinyl alcohol, titanium dioxide (E171)

Availability of Dosage Forms:
ICLUSIG (as ponatinib hydrochloride) 15 mg tablets are supplied in HDPE bottles containing 30 or 60 tablets.

ICLUSIG (as ponatinib hydrochloride) 45 mg tablets are supplied in HDPE bottles containing 30 tablets.

PART II: SCIENTIFIC INFORMATION

ICLUSIG is indicated for the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom other tyrosine kinase inhibitor (TKI) therapy is not appropriate, including CML or Ph+ ALL that is T315I mutation positive or where there is prior TKI resistance or intolerance.

Marketing authorization with conditions is based on response rate. In the pivotal trial, the majority of the hematological responses occurred within 1 month. Consider discontinuing ICLUSIG if a hematological response has not been achieved by 3 months (90 days).

ICLUSIG for this indication has been issued marketing authorization with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the conditional nature of the authorization.

PHARMACEUTICAL INFORMATION

Drug Substance

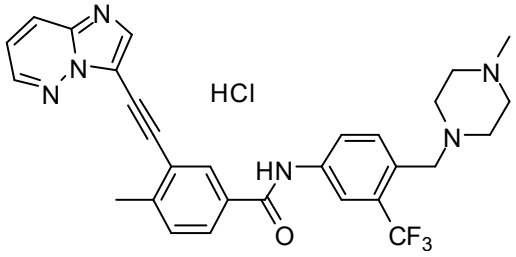
Proper name: ponatinib HCl

Chemical name: 3-(imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-{4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl}benzamide hydrochloride

Molecular formula and molecular mass:

$C_{29}H_{28}ClF_3N_6O$	569.02 g/mol (salt)
$C_{29}H_{27}F_3N_6O$	532.56 g/mol (free base)

Structural formula:



Physicochemical properties: Ponatinib HCl is an off-white to yellow powder with pKa of 2.77 and 7.8. The solubility of ponatinib in pH 1.7, 2.7, and 7.5 buffers is 7790 µg/mL, 3.44 µg/mL, and 0.16 µg/mL, respectively, indicating a decrease in solubility with increasing pH.

NOC/c CLINICAL TRIALS

The safety and efficacy of ICLUSIG (as ponatinib hydrochloride) in CML and Ph+ ALL patients who were resistant or intolerant to prior TKI therapy were evaluated in 444 patients in a single-arm, open-label, international, multicenter phase 2 trial AP24534-10-201 (PACE). All patients were administered a starting dose of 45 mg of ICLUSIG once-daily with the possibility of dose modifications, dose reductions, and/or interruptions. Patients were assigned to one of 6 cohorts based on disease phase (CP-CML; AP-CML; or BP-CML/Ph+ ALL), resistance or intolerance (R/I) to dasatinib or nilotinib, and the presence of the T315I mutation. Resistance in CP-CML was defined as failure to achieve either a complete hematologic response (CHR) (by 3 months), a minor cytogenetic response (by 6 months), or a major cytogenetic response (MCyR) (by 12 months) while on dasatinib or nilotinib.

CP-CML patients who experienced a loss of response or development of a kinase domain mutation in the absence of a complete cytogenetic response or progression to AP-CML or BP-CML at any time on dasatinib or nilotinib were also considered resistant. Resistance in AP-CML and BP-CML/Ph+ ALL was defined as failure to achieve either a major hematological response (MaHR) (AP-CML by 3 months, BP-CML/Ph+ ALL by 1 month), loss of MaHR (at any time), or development of kinase domain mutation in the absence of a MaHR while on dasatinib or nilotinib.

Intolerance was defined as the discontinuation of dasatinib or nilotinib due to toxicities despite optimal management in the absence of a complete cytogenetic response (CCyR) for CP-CML patients or MaHR for AP-CML, BP-CML, or Ph+ ALL patients.

The primary efficacy endpoint in CP-CML was MCyR, which included CCyR and partial cytogenetic responses (PCyR). The secondary efficacy endpoints in CP-CML were CHR and MMR.

The primary efficacy endpoint in AP-CML and BP-CML/Ph+ ALL was MaHR, defined as either a CHR or no evidence of leukemia (NEL). The secondary efficacy endpoints in AP-CML and BP-CML/Ph+ ALL were MCyR and MMR.

For all patients, additional secondary efficacy endpoints included confirmed MCyR, time to response, duration of response, progression-free survival, and overall survival.

The phase 2 PACE trial enrolled 449 patients, of which 444 were eligible for analysis (the unassigned patients comprised 5 patients in the safety population [3 CP-CML and 2 AP-CML] with a history of therapy with imatinib and a T315I mutation, but no detectable mutation at the centralized laboratory): 267 CP-CML patients (R/I Cohort: n=203, T315I Cohort: n=64), 83 AP-CML patients (R/I Cohort: n=65, T315I Cohort: n=18), 62 BP-CML (R/I Cohort: n=38, T315I Cohort: n=24), and 32 Ph+ ALL patients (R/I Cohort: n=10, T315I Cohort: n=22). A prior MCyR or better (MCyR, MMR, or CMR) to dasatinib or nilotinib was only achieved in 26% patients with CP-CML, and a prior MaHR or better (MaHR, MCyR, MMR, or CMR) was only achieved in 21%, and 24% of AP-CML and BP-CML/Ph+ ALL patients, respectively. At the time of analysis, ongoing patients had a median follow-up of 37.3 months (range: 0.07

months to 58.5 months). Baseline demographic characteristics are described in Table 8 below. There were 133 patients ongoing (110 CP-CML patients; 20 AP-CML patients; 3 BP-CML patients; 0 Ph+ ALL patients). With a minimum follow-up of 48 cycles (1 cycle = 28 days), a majority of the ongoing patients (92/133 patients; 69.2%) were reported to be receiving 15 mg at the last non-missing dose, while 35/133 patients (26.3%) were receiving 30 mg, and 6/133 (4.5%) were receiving 45 mg. Seventy-one percent (318/449) patients experienced a dose interruption of more than three days and 68% (304/449) experienced a dose reduction.

Table 8: Demographics and Disease Characteristics from Phase 2 Study AP24534-10-201 (PACE, N=449); Minimum Follow-up of 48 Cycles (1 Cycle = 28 Days)

Patient Characteristics at Entry	Total Safety Population N=449
Age	
Median, years (range)	59 (18 - 94)
Gender, n (%)	
Male	238 (53%)
Race, n (%)	
Asian	59 (13%)
Black/African American	25 (6%)
White	352 (78%)
Other	13 (3%)
ECOG Performance Status, n (%)	
ECOG=0 or 1	414 (92%)
Disease History	
Median time from diagnosis to first dose, years (range)	6.09 (0.33 - 28.47)
Resistant to Prior TKI Therapy[a], n (%)	374 (88%)
Prior TKI therapy– number of regimens, n (%)	
1	32 (7%)
2	155 (35%)
≥3	262 (58%)
BCR-ABL mutation detected at entry[b], n (%)	
None	198 (44%)
1	192 (43%)
≥2	54 (12%)

[a] Of 427 patients reporting prior tyrosine kinase inhibitor (TKI) therapy with dasatinib or nilotinib

[b] Of the patients with one or more BCR-ABL kinase domain mutations detected at entry, 37 unique mutations were detected.

Source: Study AP24534-10-201 CSR, Data extraction date: August 3, 2015

Overall, 55% of patients had one or more BCR-ABL kinase domain mutation at entry, with the most frequent being T315I (29%), F317L (8%), E255K (4%) and E359V (4%). In 67% of CP-CML patients in the R/I cohort, no mutations were detected at study entry. At the time of analysis, median duration of ICLUSIG treatment was 866 days in CP-CML patients, 590 days in AP-CML patients, 89 days in BP-CML, and 81 days in patients with Ph+ ALL. Efficacy results are summarized in Table 9 and Table 10.

Table 9: Efficacy of ICLUSIG in Resistant or Intolerant CP-CML Patients from Phase 2 Study AP24534-10-201 (PACE, N=449); Minimum Follow-up of 48 Cycles (1 Cycle = 28 Days)

	Overall (N=267)[a]	Resistant or Intolerant	
		R/I Cohort (N=203)	T315I Cohort (N=64)
Cytogenetic Response Rate			
Major (MCyR)[b] % n/N 95% CI (%)	55% (148/267) (49 - 62)	51% (103/203) (44 - 58)	70% (45/64) (58 - 81)
Complete (CCyR) % n/N 95% CI (%)	46% (123/267) (40 - 52)	40% (81/203) (–33-47)	66% (42/64) (53 - 77)
Major Molecular Response (MMR)[c] % n/N 95% CI (%)	39% (105/267) (–33-46)	34% (68/203) (–27-40)	58% (37/64) (45 - 70)

MCyR rates are unconfirmed (defined as response not necessarily confirmed at subsequent assessment).

[a] Includes 3 CP-CML patients who were not assigned to a cohort. These patients had a history of T315I that was not confirmed by mutation testing at study entry, and did not have prior therapy with either dasatinib or nilotinib.

[b] Primary endpoint for CP-CML Cohorts was MCyR (unconfirmed) by 12 months, which combines both complete (No detectable Ph+ cells) and partial (1% to 35% Ph+ cells) cytogenetic responses.

[c] Secondary endpoint for CP-CML Cohorts was MMR measured in peripheral blood. Defined as a ≤ 0.1% ratio of BCR-ABL to ABL transcripts on the International Scale (IS) (i.e., ≤ 0.1% BCR-ABL^{IS}; patients must have the b2a2/b3a2 [p210] transcript), in peripheral blood, measured by quantitative reverse transcriptase polymerase chain reaction (qRT PCR).

Source: Study AP24534-10-201 CSR, Data extraction date: August 3, 2015

94% (range 91% - 97%) of CP-CML patients achieved a CHR. The estimated median time to CHR was 14 days.

Of the CP-CML patients previously treated with 1, 2, 3 or 4 prior market authorised TKIs, 75% (12/16), 68% (66/97), 44% (63/142) , and 58% (7/12) achieved a MCyR while on ICLUSIG, respectively.

Of the CP-CML patients with no mutation detected at entry, 49% (66/136) achieved a MCyR.

In CP-CML patients who achieved MCyR, the median time to MCyR was 84 days (range: 49 to 334 days) and in patients who achieved MMR, the median time to MMR was 168 days (range: 55 to 965 days). At the time of reporting with minimum follow-up for all ongoing patients of 48 cycles (1 cycle = 28 days), the median durations of MCyR and MMR had not yet been reached. Based on the Kaplan-Meier estimates, 82% (95% CI: [74%- 88%]) of CP-CML (median duration of treatment: 32.2 months) patients who achieved a MCyR are projected to maintain

that response after 48 months; and 61% (95% CI: [51%-70%]) of CP-CML patients who achieved a MMR are projected to maintain that response at 36 months.

With a minimum follow-up of 48 cycles (1 cycle = 28 days), 3.4% (9/267) of CP-CML patients experienced transformation of their disease to AP-CML or BP-CML.

Table 10: Efficacy of ICLUSIG in Resistant or Intolerant AP-CML, BP-CML or Ph+ ALL Patients from Phase 2 Study AP24534-10-201 (PACE, N=449); Minimum Follow-up of 48 Cycles (1 Cycle = 28 Days)

	AP-CML		BP-CML		Ph+ ALL	
	R/I Cohort (N=65)	**T315I Cohort (N=18[a])**	**R/I Cohort (N=38)**	**T315I Cohort (N=24)**	**R/I Cohort (N=10)**	**T315I Cohort (N=22)**
Hematologic Response Rate						
Major (MaHR)[b] **%** **n/N** **95% CI (%)**	57% (37/65) (44 – 69)	56% (10/18) (31 – 79)	32% (12/38) (18 – 49)	29% (7/24) (13 – 51)	50% (5/10) (19 – 81)	36% (8/22) (17 – 59)
Complete (CHR)[c] **%** **n/N** **95% CI (%)**	49% (32/65) (–37 - 62)	56% (10/18) (31 – 79)	24% (9/38) (11 – 40)	17% (4/24) (5 – 37)	40% (4/10) (12 – 74)	32% (7/22) (14 – 55)
Major Cytogenetic Response (MCyR)[d] **%** **n/N** **95% CI (%)**	34% (22/65) (23 – 47)	56% (10/18) (31 – 79)	18% (7/38) (8 – 34)	29% (7/24) (13 – 51)	60% (6/10) (26 – 88)	41% (9/22) (21 – 64)

[a] Includes 2 AP-CML patients who were not assigned to a cohort. These patients had a history of T315I that was not confirmed by mutation testing at study entry, and did not have prior therapy with either dasatinib or nilotinib.
[b] Primary endpoint for AP-CML and BP-CML/Ph+ ALL cohorts was MaHR by 6 months, which combines complete hematologic responses and no evidence of leukemia.
[c] CHR (confirmed): WBC ≤ institutional ULN, ANC ≥1000/mm^3, platelets ≥100,000/mm^3, no blasts or promyelocytes in peripheral blood, bone marrow blasts ≤5%, <5% myelocytes plus metamyelocytes in peripheral blood, basophils <5% in peripheral blood, no extramedullary involvement (including no hepatomegaly or splenomegaly).
[d] MCyR combines both complete (no detectable Ph+ cells) and partial (1% to 35% Ph+ cells) cytogenetic responses.

Source: Study AP24534-10-201 CSR, Data extraction date: August 03, 2015

The median time to MaHR in patients with AP-CML (median duration of treatment: 19.4 months), BP-CML (median duration of treatment: 2.8 months) and Ph+ ALL (median duration of treatment: 2.7 months) among responders was 0.7 months (range: 0.4 to 5.8 months), 1.0 months (range: 0.4 to 3.7 months), and 0.7 months (range: 0.4 to 5.5 months), respectively.

At the time of reporting with minimum follow-up for all ongoing patients of 48 cycles (1 cycle = 28 days), the median duration of MaHR for patients with AP-CML, BP-CML and Ph+ ALL was

12.9 months (range: 1.2 to 52.3+ months), 6.0 months (range: 1.8 to 47.4+ months), and 3.2 months (range: 1.8 to 12.8+ months), respectively. In the patients with AP-CML, the probability of remaining in MaHR was estimated to be 51% (95% CI: [36%-65%]) and 29% (95% CI: [17%-43%]) at 52 weeks and 104 weeks, respectively. In the patients with BP-CML/Ph+ ALL, the probability of remaining in MaHR was estimated to be 28% (95% CI: [14%-44%]) and 16% (95% CI: [6%-30%]) at 52 weeks and 104 weeks, respectively.

DETAILED PHARMACOLOGY

Animal Pharmacodynamics

In cellular assays, ponatinib was shown to inhibit native BCR-ABL (0.5-0.8 nM IC_{50}) with potency approximately 500-fold greater than that of imatinib, 25-fold greater than that of nilotinib, and comparable to that of dasatinib.

Ponatinib also inhibited 14/14 BCR-ABL mutants known to confer resistance to other approved BCR-ABL inhibitors. In addition to T315I (8-11 nM IC_{50}), these include Y253H, E255K, E255V, T315A, F317L, F317V, and F359V. In a cell based accelerated mutagenesis assay that has successfully identified mutations that confer clinical resistance to imatinib, dasatinib, and nilotinib, no mutation in BCR-ABL was detected that could confer resistance to 40 nM (21 ng/mL) ponatinib. In *in vivo* models, oral administration of ponatinib inhibited BCR-ABL signaling, induced tumor shrinkage and prolonged survival in mice bearing tumors expressing native BCR-ABL or T315I mutant BCR-ABL.

Animal Pharmacokinetics

A series of *in vitro* studies and *in vivo* studies in mice, rats, and monkeys were performed to determine the absorption, distribution, metabolism and excretion of ponatinib.

Ponatinib was readily absorbed after oral dosing with a T_{max} of 4 to 6.5 hours in rats and monkeys. The oral bioavailability in rats and monkeys was 54% and 21%, respectively. The terminal half-life of ponatinib in plasma after an I.V. dose was 9.7 and 5.3 hours in rats and monkeys, respectively. After an oral dose of [^{14}C]ponatinib, radioactivity was mainly excreted in feces of rats, monkeys, and humans. Approximately 10% or less of the radioactive dose was excreted in urine; urinary excretion was an insignificant pathway in rats, monkey and humans. Ponatinib was largely eliminated by metabolism in rats, monkeys, and humans.

[^{14}C]Ponatinib was widely and rapidly distributed throughout the body following oral administration to rats. Ponatinib was highly bound to plasma proteins (> 99%) in mice, rats, monkeys, and humans. Ponatinib did not show preferential binding to erythrocytes and equilibrium distribution of ponatinib in whole blood and plasma was not concentration dependent. Ponatinib is a weak or non-substrate of P-gp and BCRP. Ponatinib is not a substrate of OATP1B1, OATP1B3, or OCT1. Ponatinib is not an inhibitor of OATP1B1, OATP1B3, OCT1, OAT1, OAT3, and OCT2. Ponatinib is an inhibitor of P-gp, BCRP and BSEP with IC_{50} (μM) of 0.491, 0.013 and 31.5, respectively.

Ponatinib is a reversible inhibitor of CYP450 enzymes *in vitro* with IC_{50}s in the range 5.2 to 13.6 μM. Ponatinib is unlikely to inhibit the CYP mediated metabolism of concomitant drugs *in vivo* at plasma concentrations of ≤ 0.260 μM (Bjornsson et al, 2003). As the geometric mean maximum plasma ponatinib concentration at the recommended clinical dose of 45 mg was 0.145 μM, the risk of ponatinib inhibiting metabolism of other drugs is low. Ponatinib is not a metabolism or time dependent inhibitor. The major human plasma metabolite, AP24600 was a very weak inhibitor of CYPs (IC_{50} > 100 μM).

In vivo, ponatinib is hydrolyzed by non-specific esterases or amidases. The amide hydrolysis metabolite AP24600 was the major metabolite in rat and human plasma but was a trace metabolite in monkeys. In rat, monkey and human plasma, AP24600 was 50.2%, < 1%, and 14.9% of the ponatinib levels. In rats, the metabolism of ponatinib is dominated by formation of the N-desmethyl metabolite AP24567 which is excreted in feces, and AP24600 (and its downstream metabolites) which is excreted in urine. In monkeys, renal excretion was insignificant. In monkey feces, drug-related radioactivity was present mostly as the parent compound or as N-desmethyl ponatinib, hydroxy ponatinib, a double lactam at piperazine moiety, and N-oxide ponatinib.

TOXICOLOGY

Single-dose Toxicity

In mice, single doses of 50 and 150 mg/kg ponatinib were asymptomatic. At 450 mg/kg, rough hair coats, reversible decreased body weight gain, and decreased food consumption were observed. The no-observed-adverse-effect level (NOAEL) for ponatinib was 150 mg/kg when administered as a single oral dose to mice.

Rats administered single oral doses of 10 mg/kg ponatinib were asymptomatic, except for thinning fur in one animal/sex. Transient decreases in reticulocytes, albumin and A:G ratio were noted. At doses of 30 and 100 mg/kg, histopathologic examination revealed that moribundity and mortality in many of these animals appeared to be associated with ponatinib-mediated immunosuppression (due to lymphoid depletion). Bacterial sepsis was a sequela to the immunosuppression, and there were numerous systemic tissue alterations that were deemed secondary to sepsis/hypoperfusion/shock. In addition, single-cell necrosis involving the exocrine pancreas and intestinal crypt epithelial cells was observed at 100 mg/kg. Clinical signs were also observed in the 30 and 100 mg/kg dose groups. The NOAEL for ponatinib was 10 mg/kg when administered as a single oral dose to rats.

Ponatinib doses of 5, 15, and 45 mg/kg administered to cynomolgus monkeys were well tolerated; the only noteworthy clinical observations were dry flaky skin and mild to moderate skin erythema at 15 and 45 mg/kg. Reversible, slight body weight loss and reduced food consumption were observed at the 15 and 45 mg/kg doses during the first week post-dose. There were no ponatinib-related changes in hematology, clinical chemistry, coagulation, or urinalysis parameters. Systolic heart murmurs were noted in individual animals treated with 5 and

45 mg/kg. Heart murmurs were also noted in some animals near the end of a 28-day repeat dose toxicity study on ponatinib in cynomolgus monkeys that were shown to be reversible. In both studies, no macroscopic or microscopic correlates were noted.

Repeat-dose Toxicity

Pivotal repeat-dose toxicity studies were conducted in rats and cynomolgus monkeys. In the 28-day study in rats, animals were administered doses of 0, 1.5, 3 and 6 mg/kg ponatinib and in the 6-month study in rats, doses of 0, 0.25, 0.75, and 2 mg/kg were administered. Slight elevations in liver enzyme levels were observed at clinically relevant or lower exposure levels. However, there were no histologic correlates observed upon microscopic examination of liver specimens. Dry flaky skin was observed in rats after repeated dosing.

In monkeys, ponatinib doses were 0, 1, 2.5, and 5 mg/kg in the 28-day study, and 0, 0.25, 0.75, and 2 mg/kg in the 6-month study. The pancreas was identified as a target organ of toxicity in the 28-day toxicity study in monkeys. Skin changes in the form of crusts, hyperkeratosis, or erythema were observed in toxicity studies in cynomolgus monkeys. The heart murmurs observed in single dose toxicity in monkeys were also observed in the repeat-dose studies.

In addition, the adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use are described below. Depletion of lymphoid organs was observed in repeat-dose toxicity studies in rats and cynomolgus monkeys. The effects were shown to be reversible after withdrawal of the treatment. Hyper-/hypoplastic changes of the chondrocytes in the physis were noted in repeat-dose toxicity studies in rats. In rats, inflammatory changes accompanied by increases in neutrophils, monocytes, eosinophils, and fibrinogen levels were found in the preputial and clitoral glands following chronic dosing. In cynomolgus monkeys, thyroid gland follicular atrophy mostly accompanied by a reduction in T3 levels and a tendency toward increased TSH levels were observed in the 4-week repeat-dose toxicity study in cynomolgus monkeys. Ponatinib-related microscopic findings in the ovaries (increased follicular atresia) and testes (minimal germ cell degeneration) in animals treated with 5 mg/kg ponatinib were noted in repeat-dose toxicity studies in cynomolgus monkeys.

Ponatinib at doses of 3, 10, and 30 mg/kg produced increases in urine output and electrolyte excretions and caused a decrease in gastric emptying in safety pharmacology studies in rats.

Carcinogenesis and Mutagenesis

Ponatinib was not mutagenic in a bacterial mutagenesis (Ames) assay, was not clastogenic in a chromosome aberration assay in human lymphocytes, nor was it clastogenic in an *in vivo* mouse micronucleus assay at oral doses up to 2000 mg/kg.

In a two-year carcinogenicity study, male rats were orally administered ponatinib at 0.05, 0.1 and 0.2 mg/kg/day and females were orally administered 0.2 and 0.4 mg/kg/day. A 0.8 mg/kg/day dose in females resulted in a plasma exposure level generally lower or equivalent to the human exposure at the range of dose from 15 mg to 45 mg daily. A statistically significant increased incidence of squamous cell carcinoma of the clitoral gland was observed at a 0.8 mg/kg/day

dose. At doses of 0.4 and 0.8 mg/kg/day in females, there was increased incidence of sex cord stromal hyperplasia and of mixed sex cord stromal benign tumours in the ovaries. The clinical relevance of these findings is not known.

Reproductive Toxicity

Ponatinib may impair fertility in female patients. In a rat fertility study with 0.25, 0.75, and 1.50 mg/kg/day ponatinib, there was no effect observed on male fertility parameters, but female fertility parameters were reduced. There was increased pre- and post-implantation embryo-fetal lethality observed in the 1.50 mg/kg/day female group. The NOAEL for paternal toxicity was 0.25 mg/kg/day based on reduced body weight and reduced body weight gain at ≥0.75 mg/kg/day. The NOAEL for reproductive performance and fertility was 1.50 mg/kg/day in males and 0.75 mg/kg/day in females.

Ponatinib was administered orally to pregnant female rats at doses of 0.3, 1, and 3 mg/kg/day from Gestation Day 7 through 17. Embryo-fetal toxicity in the form of post-implantation loss, reduced fetal body weight, and multiple soft tissue and skeletal alterations were observed at maternal toxic dosages. Multiple fetal soft tissue and skeletal alterations were also observed at maternal nontoxic dosages. The maternal NOAEL was considered to be 1 mg/kg/day and the developmental NOAEL was considered to be 0.3 mg/kg/day.

Other Toxicity Studies

In a phototoxicity study in rats, diffuse corneal edema with neutrophilic cell infiltration, and hyperplastic changes in the lenticular epithelium suggestive of a mild phototoxic reaction were observed in animals treated with 5 and 10 mg/kg ponatinib.

Ponatinib inhibited aggregation of human platelets in vitro only at a test concentration 100 times higher than the estimated plasma C_{max} in human patients at the recommended therapeutic dose. No inhibition of platelet aggregation was detected at concentrations 10 times higher than the therapeutic C_{max}.

In juvenile rats, daily oral administration of 3 mg/kg/day ponatinib to juvenile rats beginning on Day 15 postpartum resulted in mortality related to inflammatory effects within 6 to 7 days of treatment initiation. Lower doses (0.75 and 1.5 mg/kg/day) caused adverse reductions in body weight gain, but no other adverse effects on juvenile rat developmental parameters (vaginal opening, preputial separation or bone measurements).

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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.

PrICLUSIG®
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 PRECAUTIONS

Serious 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 blood pressure or high cholesterol
- 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		√	
	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.		√	
Unknown	**Hepatitis B Virus Reactivation:** see above symptoms under Liver damage		√	

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	
	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.		√	
	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)

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