# SUMMARY OF PRODUCT CHARACTERISTICS

**▼ WARNING: ARTERIAL OCCLUSION, VENOUS THROMBOEMBOLISM, HEART FAILURE, and HEPATOTOXICITY**

***See full prescribing information for complete boxed warning.***

**This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Health Care Professionals are asked to report any suspected adverse reactions.**

- **Arterial occlusion has occurred in at least 35% of Iclusig-treated patients including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures. Patients with and without cardiovascular risk factors, including patients less than 50 years old, experienced these events. Interrupt or stop Iclusig immediately for arterial occlusion. A benefit-risk consideration should guide a decision to restart Iclusig (4.4).**
- **Venous thromboembolism has occurred in 6% of Iclusig-treated patients. Monitor for evidence of thromboembolism. Consider dose modification or discontinuation of Iclusig in patients who develop serious venous thromboembolism (4.4).**
- **Heart failure, including fatalities, occurred in 9% of Iclusig-treated patients. Monitor cardiac function. Interrupt or stop Iclusig for new or worsening heart failure (4.4).**
- **Hepatotoxicity, liver failure and death have occurred in Iclusig-treated patients. Monitor hepatic function. Interrupt Iclusig if hepatotoxicity is suspected (4.2,4.4).**

## 1. NAME OF THE MEDICINAL PRODUCT

Iclusig 15 mg film-coated tablets
Iclusig 30 mg film-coated tablets
Iclusig 45 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Iclusig 15 mg film-coated tablets
Each film-coated tablet contains 15 mg of ponatinib (as hydrochloride).

*Excipients with known effect*
Each film-coated tablet contains 40 mg of lactose monohydrate.

Iclusig 30 mg film-coated tablets
Each film-coated tablet contains 30 mg of ponatinib (as hydrochloride).

*Excipients with known effect*
Each film-coated tablet contains 80 mg of lactose monohydrate.

Iclusig 45 mg film-coated tablets
Each film-coated tablet contains 45 mg of ponatinib (as hydrochloride).

*Excipients with known effect*
Each film-coated tablet contains 121 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Iclusig film-coated tablets are available in the following configurations.

Iclusig 15 mg film-coated tablets
White, biconvex, round film-coated tablet that is approximately 6.35 mm in diameter, with "A5" debossed on one side.

Iclusig 30 mg film-coated tablets
White, biconvex, round film-coated tablet that is approximately 7.8 mm in diameter, with "C7" debossed on one side.

Iclusig 45 mg film-coated tablets
White, biconvex, round film-coated tablet that is approximately 9.53 mm in diameter, with "AP4" debossed on one side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Iclusig (ponatinib) is a kinase inhibitor indicated for the:

- Treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated.

- Treatment of adult patients with T315I-positive CML (chronic phase, accelerated phase, or blast phase) or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).

Limitations of use:
Iclusig is not indicated and is not recommended for the treatment of patients with newly diagnosed chronic phase CML *[see Special warnings and precautions for use (4.4)]*.

### 4.2 Posology and method of administration

Posology

The optimal dose of Iclusig has not been identified. In clinical trials, the starting dose of Iclusig was 45 mg administered orally once daily. However, in the phase 2 trial, 68% of the patients required dose reductions to 30 mg or 15 mg once daily during the course of therapy.

Start dosing with 45 mg once daily. Consider reducing the dose of Iclusig for patients with chronic phase (CP) CP-CML and accelerated phase (AP) CML who have achieved a major cytogenetic response(MCyR).

Consider discontinuing Iclusig if a haematologic response has not occurred by 3 months (90 days).

Method of administration
Iclusig is for oral use. The tablets should be swallowed whole. Patients should not crush or dissolve the tablets. Iclusig may be taken with or without food. 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.

Patients should be advised not to swallow the desiccant canister found in the bottle.

Dose modifications for Myelosuppression

Dose modifications for neutropenia (ANC* < 1.0 x $10^9$/L) and thrombocytopenia (platelet < 50 x $10^9$/L) that are unrelated to leukemia are summarized in Table 1.

**Table 1 Dose modifications for myelosuppression**

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

Dose Modifications for Non-Hematologic Adverse Reactions

If a serious non-hematologic adverse reaction occurs, modify the dose, interrupt treatment, or consider discontinuation. Do not restart Iclusig in patients with arterial or venous occlusive reactions unless the potential benefit outweighs the risk of recurrent arterial or venous occlusions and the patient has no other treatment options. For serious reactions other than arterial or venous occlusion, do not restart Iclusig until the serious event has resolved or the potential benefit of resuming therapy is judged to outweigh the risk.

*Hepatotoxicity*
Recommended modifications for hepatotoxicity are summarized in Table 2

**Table 2 Dose Modifications for Hepatotoxicity**

| | |
|---|---|
| Elevation of liver transaminase > 3 × ULN* (Grade 2 or higher)<br><br>Persistent grade 2 (longer than 7 days) | Occurrence at 45 mg:<br>• Interrupt Iclusig and monitor hepatic function<br>• Resume Iclusig at 30 mg after recovery to ≤ Grade 1 (< 3 × ULN)<br><br>Occurrence at 30 mg:<br>• Interrupt Iclusig and resume at 15 mg after recovery to ≤ Grade 1<br><br>Occurrence at 15 mg:<br>• Discontinue Iclusig |
| Elevation of AST or ALT ≥ 3 × ULN concurrent with an elevation of bilirubin > 2 × ULN and alkaline phosphatase < 2 × ULN | Discontinue Iclusig |

*ULN = Upper Limit of Normal for the lab

*Pancreatitis and Elevation of Lipase/Amylase*

Recommended modifications for pancreatic adverse reactions are summarized in Table 3.

**Table 3 Dose Modifications for Pancreatitis and Elevation of Lipase/Amylase**

| | |
|---|---|
| Asymptomatic grade 1 or 2 elevation of serum lipase | Consider interruption or dose reduction of Iclusig |
| Asymptomatic Grade 3 or 4 elevation of lipase (> 2 x ULN*) or asymptomatic radiologic pancreatitis (Grade 2 pancreatitis) | Occurrence at 45 mg:<br>• Iclusig should be withheld and resumed at 30 mg after recovery to ≤ Grade 1 (< 1.5 x ULN)<br><br>Occurrence at 30 mg:<br>• Iclusig should be withheld and resumed at 15 mg after recovery to ≤ Grade 1 (< 1.5 x ULN)<br><br>Occurrence at 15 mg:<br>• Discontinue Iclusig |
| Symptomatic Grade 3 pancreatitis | Occurrence at 45 mg:<br>• Iclusig should be withheld and resumed at 30 mg after complete resolution of symptoms and after recovery of lipase enzymes to ≤ Grade 1<br><br>Occurrence at 30 mg:<br>• Iclusig should be withheld and resumed at 15 mg after complete resolution of symptoms and after recovery of lipase elevation to ≤ Grade 1<br><br>Occurrence at 15 mg:<br>• Discontinue Iclusig |
| Grade 4 pancreatitis | Discontinue Iclusig |
| *ULN = upper limit of normal for the lab | |

*Dose Modifications for Use with Strong CYP3A inhibitors*
The recommended dose should be reduced to 30 mg once daily when administering Iclusig with strong CYP3A inhibitors (see Interaction with other medicinal products and other forms of interaction {4.5}).

*Elderly population*
Of the 449 patients in the clinical study of Iclusig, 155 (35%) were ≥ 65 years of age. In patients with CP-CML, patients of age ≥ 65 years had a lower major cytogenetic response rate (40%) as compared with patients < 65 years of age (65%). In patients with AP-CML, BP-CML, and Ph+ ALL, patients of age ≥ 65 years had a similar hematologic response rate (45%) as compared with patients < 65 years of age (44%). Forty percent of patients ≥ 65 years had arterial occlusion events. Compared to patients < 65 years, older patients are more likely to experience adverse reactions, including vascular occlusion, decreased platelet count, peripheral edema, increased lipase, dyspnea, asthenia, muscle spasms, and decreased appetite. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

*Hepatic impairment*
Hepatic elimination is a major route of Iclusig elimination. Iclusig has not been studied in patients with hepatic impairment (Childs-Pugh Classes A, B and C) at doses above 30 mg. Administer Iclusig at a dose of 30 mg once daily in patients with hepatic impairment (Child-Pugh A, B, or C) [See Posology and Method of Administration (section 4.2) and Pharmacokinetic Properties (section 5.2).

Single doses of Iclusig 30 mg were administered to patients with mild, moderate and severe hepatic impairment and to control healthy subjects. No major differences in ponatinib PK were observed in patients with varying degrees of hepatic impairment as compared to healthy controls. However, there was an increased overall incidence of adverse reactions (e.g. gastrointestinal disorders, including a case of severe pancreatitis) in the subjects with hepatic impairment following the single 30 mg dose compared to subjects with normal liver function. 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, or end-stage renal disease.

*Paediatric population*
The safety and efficacy of Iclusig in patients less than 18 years of age have not been established. No data are available.

## 4.3 Contraindications

Prior hypersensitivity to ponatinib or one of the ingredients of Iclusig drug product listed in section 6.1.

## 4.4 Special warnings and precautions for use

Important adverse reactions

*Arterial occlusion*

Arterial occlusions, including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease have occurred in at least 35% of Iclusig-treated patients from the phase 1 and phase 2 trials. With a minimum of 48 months follow-up for ongoing patients (N = 133) in the phase 2 trial, 33% (150/449) of Iclusig-treated patients experienced a cardiac vascular (21%), peripheral vascular (125) or cerebrovascular (9%) arterial occlusive event; some patients experienced more than 1 type of arterial occlusive event.

Iclusig can cause fatal and life-threatening arterial occlusion within 2 weeks of starting treatment, and at dose levels as low as 15 mg per day. Iclusig can also cause recurrent or multi-site vascular occlusion. Patients have required revascularization procedures (coronary, cerebrovascular, and peripheral arterial).

In the phase 2 trial, the median time to onset of the first cardiovascular, cerebrovascular, and peripheral vascular arterial occlusive events was 193 (range: 1 – 1355), 526 (range 5 – 1339), and 478 (range 3 – 1444) days, respectively.

Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. The most common risk factors observed in patients with arterial occlusive events were hypertension (62%; 93/150), hyperlipidemia (61%; 91/150), and history of cardiac disease (48%; 72/150). Arterial occlusion adverse events were more frequent with increasing age and in patients with history of ischemia, hypertension, diabetes, or hyperlipidemia *[see Table 4*].

**Table 4: Arterial Occlusion Incidence in Iclusig-Treated Patients in Phase 2 Trial According to Risk Categories: 4-year follow-up**

| **Age (At time of study entry)** | **History of ischemia, hypertension, diabetes, or hyperlipidemia N=218** | **No history of ischemia, hypertension, diabetes, or hyperlipidemia N=231** |
|---|---|---|
| 49 or younger | 31% (11/36) | 19% (21/108) |
| 50 to 74 years | 40% (64/158) | 30% (32/109) |
| 75 and older | 58% (14/24) | 57% (8/14) |
| All age groups | 41% (89/218) | 26% (61/231) |
| Total | 33% (150/449) | |

Cardiac vascular occlusion, including fatal and life-threatening myocardial infarction and coronary artery occlusion has occurred in 21% (94/449) of Iclusig-treated patients. Patients have developed heart failure concurrent or subsequent to the myocardial ischemic event *[see Special warnings and precautions for use (4.4)]*.

Cerebrovascular occlusion, including fatal stroke, has occurred in 9% (40/449) of Iclusig-treated patients. Iclusig can cause stenosis over multiple segments in major arterial vessels that supply the brain (e.g., carotid, vertebral, middle cerebral artery).

Peripheral arterial occlusion, including fatal mesenteric artery occlusion and life-threatening peripheral arterial disease, have occurred in 12% (52/449) of Iclusig-treated patients. Patients have developed digital or distal extremity necrosis and have required amputations. Renal artery stenosis, associated with worsening, labile or treatment-resistant hypertension, has occurred in some Iclusig-treated patients *[see Special Warnings and Precautions for use (4.4)]*.

Clinicians should consider whether the benefits of Iclusig treatment are expected to exceed the risks of therapy. In patients suspected of developing arterial occlusive events, interrupt or stop Iclusig. A benefit-risk consideration should guide a decision to restart Iclusig therapy *[see Posology and Method of Administration (4.2)]*.

*Venous thromboembolism*
Venous thromboembolic events occurred in 6% (25/449) of Iclusig-treated patients, including deep venous thrombosis (10 patients), pulmonary embolism (7 patients), superficial thrombophlebitis (3 patients), and retinal vein thrombosis (2 patients) with vision loss.

In the phase 2 trial, the incidence of venous thromboembolism was higher in Ph+ ALL or BP-CML patients (9% and 10%, respectively) than those with AP-CML (4%) and CP-CML (5%). Consider dose modification or discontinuation of Iclusig in patients who develop serious venous thromboembolism (see sections 4.2).

*Heart failure*
Fatal and serious heart failure or left ventricular dysfunction occurred in 6% Iclusig-treated patients (n = 29/449) in the phase 2 trial (48 months' follow-up). Nine percent of patients (N = 39) experienced any grade of heart failure or left ventricular dysfunction. The most frequently reported heart failure events were congestive cardiac failure and decreased ejection fraction (in 14 patients each; 3%).

Patients should be monitored for signs or symptoms consistent with heart failure and they should be treated as clinically indicated, including interruption of Iclusig. Consider discontinuation of Iclusig in patients who develop grade 4 heart failure (see sections 4.2 and 4.8).

*Hepatotoxicity*

Iclusig can cause hepatotoxicity, including liver failure and death.

Fulminant hepatic failure leading to death occurred in an Iclusig-treated patient within one week of starting Iclusig. Two additional fatal cases of liver failure also occurred. The fatal cases occurred in patients with blast phase (BP) CML or Ph+ ALL. Severe (grade 3 or 4) hepatotoxicity occurred in all disease cohorts.

With 48 months' 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) or alanine aminotransferase (ALT), bilirubin, and alkaline phosphatase. The incidence of AST or ALT elevation was 54% (all grades) and 8% (grade 3 or 4). ALT or AST elevation was not reversed by the date of last follow-up in 5% of patients.

Hepatotoxic events were observed in 29% of patients. The median time to onset of hepatotoxicity event was 3 months, with a range of <1 month to 47 months. Monitor liver function tests at baseline, then at least monthly or as clinically indicated. Interrupt, reduce or discontinue Iclusig as clinically indicated *[see Posology and Method of Administration 4.2]*.

*Hypertension*
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). Fifty three patients (12%) treated with Iclusig in this clinical 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.

In patients with baseline systolic BP<140 mm Hg and baseline diastolic BP<90 mm Hg, 80% (229/285) experienced treatment-emergent hypertension; 44% (124/285) developed Stage 1 hypertension (defined as systolic BP≥140 mm Hg or diastolic BP≥90 mm Hg) while 37% developed Stage 2 hypertension (defined as systolic BP≥160 mm Hg or diastolic BP≥100 mm Hg). In 132 patients with Stage 1 hypertension at baseline, 67% (88/132) developed Stage 2 hypertension.

Monitor and manage blood pressure elevations during Iclusig use and treat hypertension to normalize blood pressure. Interrupt, dose reduce, or stop Iclusig if hypertension is not medically controlled. In the event of significant worsening, labile or treatment-resistant hypertension, interrupt treatment and consider evaluating for renal artery stenosis.

*Pancreatitis*
Pancreatitis occurred in 7% (31/449, 6% serious or grade 3/4) of Iclusig-treated patients with 48 months of follow-up in the phase 2 trial. The incidence of treatment-emergent lipase elevation was 42% (16% grade 3 or greater).
Pancreatitis resulted in discontinuation or treatment interruption in 6% of patients (26/449). The median time to onset of pancreatitis was 14 days (range: 3 - 1452). Twenty-three of the 31 cases of pancreatitis resolved within 2 weeks with dose interruption or reduction.
Check serum lipase every 2 weeks for the first 2 months and then monthly thereafter or as clinically indicated. Consider additional serum lipase monitoring in patients with a history of pancreatitis or alcohol abuse. Dose interruption or reduction may be required. In cases where lipase elevations are accompanied by abdominal symptoms, interrupt treatment with Iclusig and evaluate patients for pancreatitis *[see Dosage and Administration (2.3)]*. Do not consider restarting Iclusig until patients have complete resolution of symptoms and lipase levels are less than 1.5 x ULN.

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

*Neuropathy*
Peripheral and cranial neuropathy 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 months follow-up). The most common peripheral neuropathies reported were paresthesia (5%, 23/449), neuropathy peripheral (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).
Of the patients who developed neuropathy, 26% (23/90) developed neuropathy during the first month of treatment. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness. Consider interrupting Iclusig and evaluate if neuropathy is suspected.

*Ocular Toxicities*
Serious ocular toxicities leading to blindness or blurred vision have occurred in Iclusig-treated patients in the phase 2 trial (48 months 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, hyperaemia and edema or eye pain occurred in 14% of patients. Visual blurring occurred in 6% of patients. Other ocular toxicities include cataracts, periorbital edema, blepharitis, glaucoma, eyelid edema, ocular hyperaemia, iritis, iridocyclitis, and ulcerative keratitis. Conduct comprehensive eye exams at baseline and periodically during treatment.

*Haemorrhage*
Serious hemorrhage events including fatalities, occurred in 6% (28/449) of patients treated with Iclusig in the phase 2 trial, with 48 months follow-up. Hemorrhage occurred in 28% (124/449) of patients. The incidence of serious bleeding events was higher in patients with AP-CML, BP-CML, and

Ph+ ALL. Gastrointestinal hemorrhage and subdural hematoma were the most commonly reported serious bleeding events occurring in 1% (4/449 and 4/449, respectively). Most hemorrhagic events, but not all, occurred in patients with grade 4 thrombocytopenia. Interrupt Iclusig for serious or severe hemorrhage and evaluate.

*Fluid Retention*
Fluid retention events judged as serious occurred in 4% (18/449) of patients treated with Iclusig in the phase 2 trial (48 months follow-up). One instance of brain edema was fatal. For fluid retention events occurring in more than 2% of the patients (treatment-emergent), serious cases included: pleural effusion (7/449, 2%), pericardial effusion (4/449, 1%), and edema peripheral (2/449, <1%).
In total, fluid retention occurred in 31% of the patients. The most common fluid retention events were peripheral edema (17%), pleural effusion (8%), pericardial effusion (4%) and peripheral swelling (3%).

Monitor patients for fluid retention and manage patients as clinically indicated. Interrupt, reduce, or discontinue Iclusig as clinically indicated.

*Cardiac Arrhythmias*
Arrhythmias occurred in 19% (86/449) of Iclusig-treated patients, of which 7% (33/449) were grade 3 or greater. Arrhythmia of ventricular origin was reported in 3% (3/86) of all arrhythmias, with one case being grade 3 or greater.

Symptomatic bradyarrhythmias that led to pacemaker implantation occurred in 1% (3/449) 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.

In patients with signs and symptoms suggestive of slow heart rate (fainting, dizziness) or rapid heart rate (chest pain, palpitations or dizziness), interrupt Iclusig and evaluate.

*Myelosuppression*
Myelosuppression was reported as an adverse reaction in 59% (266/449) of patients, and severe (grade 3 or 4) myelosuppression occurred in 50% (226/449) of patients treated with Iclusig. With 48 months of follow-up, the incidence of these events was greater in patients with AP-CML, BP-CML, and Ph+ ALL than in patients with CP-CML.

Severe myelosuppression (Grade 3 or 4) was observed early in treatment, with a median onset time of 1 month (range <1– 40 months). Obtain complete blood counts every 2 weeks for the first 3 months and then monthly or as clinically indicated, and adjust the dose as recommended (see section 4.2).

*Tumor Lysis Syndrome*
Two patients (<1%) treated with Iclusig developed serious tumor lysis syndrome. One case occurred in a patient with advanced AP-CML and one case occurred in a patient with BP-CML.
Hyperuricemia occurred in 7% (31/449) of patients. Due to the potential for tumor lysis syndrome in patients with advanced disease (AP-CML, BP-CML, or Ph+ ALL), ensure adequate hydration and treat high uric acid levels prior to initiating therapy with Iclusig.

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

*Compromised Wound Healing and Gastrointestinal Perforation*
No formal studies of the effect of Iclusig on wound healing have been conducted. Based on the mechanism of action, Iclusig could compromise wound healing. Serious gastrointestinal perforation (fistula) occurred in one patient 38 days' post-cholecystectomy.

Interrupt Iclusig for at least 1 week prior to major surgery. The decision when to resume Iclusig after surgery should be based on clinical judgment of adequate wound healing.

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

## 4.5 Interaction with other medicinal products and other forms of interaction

Substances that may increase ponatinib serum concentrations
Based on *in vitro* studies, ponatinib is a substrate of CYP3A and to a lesser extent CYP2C8 and CYP2D6. In a drug interaction study in healthy volunteers, co-administration of Iclusig with ketoconazole increased plasma ponatinib $AUC_{0\text{-}inf}$ and $C_{max}$ by 78% and 47%, respectively.

Caution should be exercised and the recommended starting dose should be reduced when administering Iclusig with strong CYP3A inhibitors (e.g., boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole). Patients taking concomitant strong CYP3A inhibitors may be at increased risk for adverse reactions.

Substances that may decrease ponatinib serum concentrations
Co-administration of strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin, and St. John's Wort) with Iclusig should be avoided unless the benefit outweighs the risk of decreased ponatinib exposure. Monitor patients for reduced efficacy. Selection of concomitant medication with no or minimal CYP3A induction potential is recommended. In a drug interaction study in healthy volunteers, co-administration of Iclusig following multiple doses of rifampin resulted in decreased ponatinib $AUC_{0\text{-}inf}$ and $C_{max}$ values by 62% and 42%, respectively.

*Elevated Gastric pH*
Iclusig may be co-administered with gastric pH-elevating medications. The aqueous solubility of ponatinib is pH dependent, with higher pH resulting in lower solubility. Co-administration of a single 45 mg dose of ponatinib in the presence of lansoprazole (60 mg daily), a proton pump inhibitor, to 18 healthy volunteers decreased the $AUC_{0\text{-}inf}$ and $C_{max}$ of ponatinib by 6% and 25%, respectively, when compared to administration of ponatinib alone

Substances that may have their serum concentrations altered by ponatinib

*Cytochrome P450 Substrates*
In vitro studies indicate that ponatinib does not inhibit the metabolism of substrates for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A, or CYP2D6 and does not induce the metabolism of substrates for CYP1A2, CYP2B6, or CYP3A.

*Transporter substrates*
In vitro, ponatinib is an inhibitor of P-gp and ABCG2, and BSEP. 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 ponatinib is administered with these medicinal products.

In vitro, ponatinib did not inhibit the human organic anion transporting polypeptides OATP1B1 or OATP1B3, or the organic cation transporters OCT1, OCT2, OAT1, and OAT3.

Special populations

*Hepatic impairment*
Caution is recommended when administering Iclusig to patients with hepatic impairment (see sections 4.2 and 5.2).

*Renal impairment*
Caution is recommended in when administering Iclusig to patients with estimated creatinine clearance of < 50 mL/min or end-stage renal disease (see section 4.2).

*Paediatric population*
Interaction studies have only been performed in adults.

## 4.6 Fertility, pregnancy and lactation

Pregnancy Risk Summary

Based on its mechanism of action and findings in animals, Iclusig can cause fetal harm when administered to a pregnant woman *[see Data]*. There are no available data on Iclusig use in pregnant women. In animal reproduction studies, oral administration of ponatinib to pregnant rats during organogenesis caused adverse developmental effects at doses lower than human exposures at the recommended human dose *[see Data]*. Advise pregnant women of the potential risk to a fetus.
All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown.

*Animal Data*

Ponatinib was studied for effects on embryo-fetal development in pregnant rats given oral doses of 0.3, 1, and 3 mg/kg/day during organogenesis (25 rats per group). At the maternally toxic dose of 3 mg/kg/day (equivalent to the AUC in patients receiving the recommended dose of 45 mg/day), ponatinib caused embryo-fetal toxicity as shown by increased resorptions, reduced body weight, external alterations, multiple soft tissue and skeletal alterations, and reduced ossification. Embryo-fetal toxicities also were observed at 1 mg/kg/day (approximately 24% the AUC in patients receiving the recommended dose) and involved multiple fetal soft tissue and skeletal alterations, including reduced ossification.

Women of childbearing potential/Contraception in males and females
Verify the pregnancy status of females of reproductive potential prior to initiating Iclusig treatment.

Advise females of reproductive potential to use effective contraception during treatment with Iclusig and for 3 weeks after the last dose.

Pregnancy
Ponatinib has been shown to have adverse developmental effects in rats (see section 5.3) when given at doses lower than the human dose. There are no adequate and well-controlled studies in pregnant women. Iclusig should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Breastfeeding
There is insufficient/limited information on the excretion of ponatinib in human or animal breast milk. Physiochemical and available phamacodynamic/toxicological data on ponatinib cannot exclude ponatinib excretion in breast milk and a risk to the suckling child. Iclusig should not be used during breastfeeding.

Fertility
Based on animal data, ponatinib may impair fertility in females of reproductive potential. It is not known whether these effects on fertility are reversible.

**4.7 Effects on ability to drive and use machines**
There are no data on the effect of Iclusig on the ability to drive and use machines. Lethargy, dizziness, and blurred vision have been associated with Iclusig. Therefore, caution should be recommended when driving or operating machines.

**4.8 Undesirable effects**

Summary of the safety profile
The adverse reactions described in this section were identified in a single-arm, open-label, international, multicenter trial in 449 patients with CML or Ph+ ALL whose disease was considered to be resistant or intolerant to prior tyrosine kinase inhibitor (TKI) therapy including those with the BCR-ABL T315I mutation.

All patients received a starting dose of 45 mg Iclusig once daily. Interruptions and 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 arterial occlusive events and venous thromboembolic events in the clinical trial.

At the time of analysis (48 months of follow-up), 133 patients (30%) were ongoing (110 CP-CML; 20 AP-CML; 3 BP-CML; 0 Ph+ ALL), and the median duration of treatment with Iclusig was 32.2 months in patients with CP-CML, 19.4 months in patients with AP-CML, 2.9 months in patients with BP-CML, and 2.7 months in patients with Ph+ ALL. The median dose intensity in patients with CP-CML was 29 mg /day or 64% of the 45 mg starting dose; median dose intensity was greater in patients with advanced disease patients. Seventy one percent (318/449) of patients experienced a dose interruption of more than three days and 68% (304/449) experienced a dose reduction.

The most common adverse reactions (≥5%) that led to dose modifications (interruption or dose reduction) include thrombocytopenia (31%), neutropenia (14%), lipase increased (13%), arterial occlusive events (13%), abdominal pain (12%), rash (9%), anemia (6%), pancreatitis (6%), ALT increased (5%) and hypertension (5%).

At the time of the analysis, 69% of the ongoing patients (92/133 patients) were reported to be receiving 15 mg; with 26% (35/133) and 5% (6/133) of Iclusig-treated patients receiving 30 mg and 45 mg, respectively.

Adverse reactions reported in all patients treated with Iclusig in this trial are presented in Table 5. Overall, the most common non-hematologic adverse reactions (≥ 20%) were abdominal pain, rash, constipation, headache, dry skin, arterial occlusion, fatigue, hypertension, pyrexia, arthralgia, nausea, diarrhea, lipase increased, vomiting, myalgia and pain in extremity.
The rates of treatment-emergent adverse reactions resulting in discontinuation were 19% in CP-CML, 12% in AP-CML, 15% in BP-CML, and 9% in Ph+ ALL. The most common adverse reactions that led to treatment discontinuation was thrombocytopenia (4%).

Tabulated summary of adverse reactions
Adverse reactions reported in all CML and Ph+ ALL patients are presented in Table 5. Frequency categories are very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), and not known (cannot be estimated from the available data).

**Table 5 Adverse reactions observed in CML and Ph+ ALL patients – frequency reported by incidence of treatment emergent events**

| System organ class | Frequency | Adverse reactions |
|---|---|---|
| Cardiac or vascular disorders | Very common | Hypertension[a], arterial ischemia[b] |
| | Common | Cardiac failure[c] |
| | Uncommon | Cardiac discomfort, embolism venous, hypertensive crisis, renal artery stenosis |
| Gastrointestinal disorders | Very common | Abdominal pain[d], constipation, nausea, diarrhea, vomiting, oral mucositis[e] |
| | Common | GI hemorrhage[f] |
| Blood and lymphatic system disorders | Common | Febrile neutropenia |
| Infections and infestations | Very common | upper respiratory tract infection, nasopharyngitis, urinary tract infection |
| | Common | pneumonia, sepsis, cellulitis |
| Nervous system disorders | Very common | Headache, peripheral neuropathy[g], dizziness |
| | Uncommon | Cerebral artery stenosis, cerebral haemorrhage |
| Respiratory, thoracic and mediastinal disorders | Very common | dyspnoea, cough |
| | Common | pleural effusion |
| Skin and subcutaneous tissue disorders | Very common | Rash and related conditions, dry skin, pruritus |
| | Common | Erythema, alopecia |
| Musculoskeletal and connective tissue disorders | Very common | Arthralgia, myalgia, pain in extemity, back pain, muscle spasms, bone pain |
| | Common | Musculoskeletal pain |
| General disorders and administrative site conditions | Very common | Fatigue or asthenia, pyrexia, edema, peripheral, pain |
| | Common | chills |
| Metabolism and nutrition disorders | Very common | Decreased appetite |
| | Common | Weight decreased |
| | Uncommon | Tumour lysis syndrome |
| Psychiatric disorders | Very common | Insomnia |

Adverse drug reactions, reported using MedDRA and graded using NCI-CTC-AE v 4.0 (NCI Common Terminology Criteria for Adverse Events) for assessment of toxicity.

Treatment-emergent, all causality events
(a) derived from blood pressure (BP) measurement recorded monthly while on trial
(b) cardiovascular, cerebrovascular, and peripheral vascular ischemia
(c) includes cardiac failure, cardiac failure congestive, cardiogenic shock, cardiopulmonary failure, ejection fraction decreased, pulmonary edema, right ventricular failure
(d) includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort
(e) includes aphthous stomatitis, lip blister, mouth ulceration, oral mucosal eruption, oral pain, oropharyngeal pain, pharyngeal ulceration, stomatitis, tongue ulceration
(f) includes gastric hemorrhage, gastric ulcer hemorrhage, hemorrhagic gastritis, gastrointestinal hemorrhage, hematemesis, hematochezia, hemorrhoidal hemorrhage, intra-abdominal hemorrhage, melena, rectal hemorrhage, and upper gastrointestinal hemorrhage
(g) includes burning sensation, skin burning sensation, hyperesthesia, hypoesthesia, neuralgia, neuropathy peripheral, paresthesia, peripheral sensorimotor neuropathy, peripheral motor neuropathy, peripheral sensory neuropathy, polyneuropathy, dysgeusia, muscular weakness, gait disturbance, nerve compression, areflexia, hypotonia, restless legs syndrome

**Table 6: Serious Adverse Reactions Occurring in > 2% of Patients from the Phase 2 Trial (N=449)**

| System Organ Class | Frequency |
|---|---|
| **Cardiovascular disorders** | |
| Arterial Occlusion | Very Common |
| Cardiac vascular | Very Common |
| Cerebrovascular | Common |
| Peripheral vascular | Common |
| Venous thromboembolism | Common |
| Hemorrhage | Common |
| CNS hemorrhage | Common |
| Gastrointestinal hemorrhage | Common |
| Heart failure | Common |
| Effusions(a) | Common |
| Atrial fibrillation | Common |
| Hypertension | Common |
| **Gastrointestinal disorders** | |
| Pancreatitis | Common |
| Abdominal pain | Common |
| **Blood and lymphatic system disorders** | |
| Febrile neutropenia | Common |
| Anemia | Common |
| Thrombocytopenia | Common |
| **Infections** | |
| Pneumonia | Common |
| Sepsis | Common |
| **General** | |
| Pyrexia | Common |

(a) includes pericardial effusion, pleural effusion, and ascites

*Laboratory Abnormalities*

Myelosuppression was commonly reported in all patient populations. The frequency of grade 3 or 4 thrombocytopenia, neutropenia, and anemia was higher in patients with AP-CML, BP-CML, and Ph+ ALL than in patients with CP-CML (see Table 7).

**Table 7: Clinically Relevant Grade 3/4* Hematologic Laboratory Abnormalities in Patients from the Phase 2 Trial (N=449)**

| Laboratory Test | CP-CML (N=270) (%) | AP-CML (N=85) (%) | BP-CML (N=62) (%) | Ph+ ALL (N=32) (%) |
|---|---|---|---|---|
| **Hematology** | | | | |
| Thrombocytopenia (platelet count decreased) | 35 | 49 | 45 | 47 |
| Neutropenia (ANC decreased) | 23 | 52 | 48 | 59 |
| Leukopenia (WBC decreased) | 12 | 36 | 48 | 63 |
| Anemia (Hgb decreased) | 8 | 31 | 52 | 34 |

| | | | | |
|---|---|---|---|---|
| Lymphopenia | 10 | 25 | 32 | 19 |

ANC=absolute neutrophil count, Hgb=hemoglobin, WBC=white blood cell count
*Reported using NCI-CTC-AE v 4.0

**Table 8: Clinically Relevant Non-Hematologic Laboratory Abnormalities**

| Laboratory Test | Safety Population N=449 | |
|---|---|---|
| | Any Grade* (%) | CTCAE Grade 3 / 4 (%) |
| **Liver function tests** | | |
| ALT increased | 41 | 6 |
| AST increased | 35 | 4 |
| Alkaline phosphatase increased | 40 | 2 |
| Albumin decreased | 27 | <1 |
| Bilirubin increased | 13 | <1 |
| **Pancreatic enzymes** | | |
| Lipase increased | 38 | 13 |
| Amylase increased | 18 | 3 |
| **Chemistry** | | |
| Glucose increased | 54 | 7 |
| Phosphorus decreased | 33 | 10 |
| Calcium decreased | 30 | <1 |
| Sodium decreased | 27 | 5 |
| Glucose decreased | 13 | 0 |
| Potassium decreased | 18 | 2 |
| Potassium increased | 19 | 2 |
| Sodium increased | 10 | <1 |
| Bicarbonate decreased | 19 | <1 |
| Creatinine increased | 21 | <1 |
| Calcium increased | 12 | 0 |
| Triglycerides increased | 3 | <1 |

ALT=alanine aminotransferase, AST=aspartate aminotransferase.
*Graded using NCI-CTC-AE v 4.0

Post marketing Experience

The following adverse reactions have been identified during post approval use of Iclusig. 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:

**Nervous system disorders:** Reversible posterior leukoencephalopathy syndrome (RPLS) – also known as Posterior Reversible Encephalopathy Syndrome (PRES)

**Metabolism and nutrition disorders:** Dehydration

**Skin and subcutaneous tissue disorders:** Severe cutaneous reaction (e.g. Erythema multiforme, Stevens-Johnson syndrome)

Description of selected adverse reactions

*Vascular occlusion (see section 4.2 and 4.4).*
Serious vascular occlusion has occurred in patients treated with Iclusig, including cardiovascular, cerebrovascular and peripheral vascular events, and venous thrombotic events. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these

events. Arterial occlusive adverse events were more frequent with increasing age and in patients with history of ischaemia, hypertension, diabetes, or hyperlipidaemia.

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

*Severe Cutaneous Adverse Reactions (SCARs)*
Severe skin reactions (such as Stevens-Johnson Syndrome) have been reported with some BCR-ABL Tyrosine Kinase Inhibitors. Patients should be warned to immediately report suspected skin reactions, especially if associated with blistering, peeling, mucosal involvement or systemic symptoms.

With a minimum of 48 cycles (approximately 46 months) for all ongoing patients, the incidence of clinically relevant grade 3 or 4 laboratory abnormalities in ≥2% of patients in any disease group is presented in Table 8.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions. Please contact the relevant competent authority.

### 4.9 Overdose

Overdoses with Iclusig were reported in clinical trials. One patient was accidentally administered the entire contents of a bottle of study medication via nasogastric tube. The investigator estimated that the patient received 540 mg of Iclusig. Two hours after the overdose, the patient had an uncorrected QT interval of 520 ms. Subsequent ECGs showed normal sinus rhythm with uncorrected QT intervals of 480 and 400 ms. The patient died 9 days after the overdose from pneumonia and sepsis. Another patient accidentally self-administered 165 mg on cycle 1 day 2. The patient experienced fatigue and non-cardiac chest pain on day 3. Multiple doses of 90 mg per day for 12 days in a patient resulted in pneumonia, systemic inflammatory response, atrial fibrillation, and a moderate pericardial effusion. In the event of an overdose of Iclusig, stop Iclusig, observe the patient and provide appropriate supportive treatment.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

*Pharmacotherapeutic group*: antineoplastic agents, protein kinase inhibitors, ATC code: L01XE24

*Mechanism of Action:*
Ponatinib is a kinase inhibitor. Ponatinib inhibited the *in vitro* tyrosine kinase activity of ABL and T315I mutant ABL with $IC_{50}$ concentrations of 0.4 and 2.0 nM, respectively. Ponatinib inhibited the *in vitro* activity of additional kinases with $IC_{50}$ concentrations between 0.1 and 20 nM, including members of the VEGFR, PDGFR, FGFR, EPH receptors and SRC families of kinases, and KIT, RET, TIE2, and FLT3. Ponatinib inhibited the *in vitro* viability of cells expressing native or mutant BCR-ABL, including T315I. In mice, treatment with ponatinib reduced the size of tumors expressing native or T315I mutant BCR-ABL when compared to controls.

*Pharmacodynamic effects*

In a cell-based assay, ponatinib concentrations of 20 nM (10.65 ng/mL) were sufficient to suppress most BCR-ABL mutant clones. However, ponatinib concentrations of 40 nM (21.3 ng/mL) were required to suppress T315I mutants. The median and range of steady-state $C_{max}$ and trough ($C_{min}$) concentrations of ponatinib following 29 days of once-daily dosing of 15 mg, 30 mg and 45 mg are listed in Table 9.

**Table 9: Median, Maximum, and Minimum Ponatinib Exposure at Steady-State by Dose Group: PK Evaluable Population**

| Dose | Median $C_{max}$ (Range) (nM) | Median $C_{min}$ (Range) (nM) |
|---|---|---|
| 15 mg QD (n = 8) | 49 (23 – 105) | 28 (11 – 68) |
| 30 mg QD (n = 9) | 125 (67 – 178) | 54 (41 – 89) |
| 45 mg QD (n = 21) | 161 (64 – 336) | 67 (22 – 137) |

Concentrations of ponatinib shown in cell-based assays to suppress unmutated BCR-ABL and most mutant BCR-ABL clones may be achieved at once daily dosing of 15 mg or 30 mg.

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

In vitro, there was no significant inhibition of platelet aggregation with ponatinib at concentrations seen clinically and up to 0.7 μg/mL (1.23 μM).

*Cardiac Electrophysiology*
A QT assessment was performed in 39 patients with cancer who received 30 mg, 45 mg, or 60 mg Iclusig once daily. No large changes in the mean QTc interval (i.e., > 20 msec) from baseline were detected in the study. However, a small increase in the mean QTc interval (i.e., < 10 msec) cannot be excluded because of study design limitations. In a phase 3 trial comparing ponatinib with imatinib, the mean change from baseline to worst QTcF value in ponatinib-treated patients (n=124) was < 10 msec.

*Clinical efficacy and safety*

The safety and efficacy of Iclusig in patients with CML and Ph+ ALL whose disease was considered to be resistant or intolerant to prior tyrosine kinase inhibitor (TKI) therapy were evaluated in a single-arm, open-label, international, multicenter trial. Efficacy results described below should be interpreted within the context of updated safety information

All patients were administered a starting dose of 45 mg of Iclusig once daily. Patients were assigned to one of six cohorts based on disease phase (chronic phase CML [CP-CML]; accelerated phase CML [AP-CML]; or blast phase CML /Philadelphia-positive acute lymphoblastic leukemia [BP-CML/Ph+ ALL]), resistance or intolerance (R/I) to prior TKI therapy, and the presence of the T315I mutation.

Resistance in CP-CML while on prior TKI therapy, was defined as failure to achieve either a complete hematologic response (by 3 months), a minor cytogenetic response (by 6 months), or a major cytogenetic response (by 12 months). Patients with CP-CML 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 prior TKI therapy were also considered resistant. Resistance in AP-CML, BP-CML, and Ph+ ALL was defined as failure to achieve either a major hematologic response (by 3 months in AP-CML, and by 1 month in BP-CML and Ph+ ALL), loss of major hematologic response (at any time), or development of a kinase domain mutation in the absence of a complete major hematologic response while on prior TKI therapy.

Intolerance was defined as the discontinuation of prior TKI therapy due to toxicities despite optimal management in the absence of a complete cytogenetic response in patients with CP-CML or major hematologic response for patients with AP-CML, BP-CML, or Ph+ ALL.

The primary efficacy endpoint in CP-CML was major cytogenetic response (MCyR), which included complete and partial cytogenetic responses (CCyR and PCyR). The primary efficacy endpoint in AP-CML, BP-CML, and Ph+ ALL was major hematologic response (MaHR), defined as either a complete hematologic response (CHR) or no evidence of leukemia (NEL).

The trial enrolled 449 patients, of which 444 were eligible for efficacy analysis: 267 patients with CP-CML (R/I Cohort: n=203, T315I: n=64), 83 patients with AP-CML, 62 patients with BP-CML, and 32 patients with Ph+ ALL. Five patients were not eligible for efficacy analysis due to lack of confirmation of T315I mutation status, and these patients had not received prior dasatinib or nilotinib.

At the time of analysis, the median duration of follow-up for the trial (all cohorts) was 37.3 months (minimum of 48 months of follow-up for all ongoing patients). Baseline demographic characteristics are described in Table 10.

**Table 10: Demographic and Disease Characteristics**

| **Patient Characteristics at Entry** | **Efficacy Population N=444** |
|---|---|
| **Age** | |
| Median, years (range) | 59 (18 to 94) |
| **Gender, n (%)** | |
| Male | 236 (53%) |
| **Race, n (%)** | |
| Asian | 57 (13%) |
| Black or African American | 25 (6%) |
| White | 349 (79%) |
| Other | 13 (3%) |
| **ECOG Performance Status, n (%)** | |
| ECOG=0 or 1 | 409 (92%) |
| **Disease History** | |
| Median time from diagnosis to first dose, years (range) | 6.1 (0.3 to 28.5) |
| Resistant to Prior TKI Therapy, n (%) | 374 (88%) |
| Presence of one or more BCR-ABL kinase domain mutations* | 244 (55%) |
| Prior TKI therapy– number of prior approved TKIs, n (%) | |
| 1 | 29 (7%) |
| 2 | 166 (37%) |
| ≥3 | 249 (56%) |

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

At the time of analysis, there were 133 patients ongoing (110 patients with CP-CML; 20 patients with AP-CML; 3 patients with BP-CML; 0 patients with Ph+ ALL), and the median duration of Iclusig treatment was 32.2 months in patients with CP-CML, 19.4 months in patients with AP-CML, 2.9 months in patients with BP-CML and 2.7 months in patients with Ph+ ALL.

Efficacy results are summarized in Table 11, and Table 12.

**Table 11: Efficacy of Iclusig in Patients With Resistant or Intolerant Chronic Phase CML**

| | Overall (N=267) | Cohort | |
|---|---|---|---|
| | | R/I Cohort (N=203) | T315I Cohort (N=64) |
| **Cytogenetic Response** | | | |
| Major [a] (MCyR)<br>%<br>(95% CI) | <br>55%<br>(49,62) | <br>51%<br>(44,58) | <br>70%<br>(58,81) |
| Complete (CCyR)<br>%<br>(95% CI) | <br>46%<br>(40,52) | <br>40%<br>(33,47) | <br>66%<br>(53,77) |
| **Major Molecular Response [b]**<br>%<br>(95% CI) | <br>39%<br>(33,46) | <br>34%<br>(27,40) | <br>58%<br>(45,70) |

[a] Primary endpoint for CP-CML Cohorts was MCyR by 12 months, which combines both complete (no detectable Ph+ cells) and partial (1% to 35% Ph+ cells in at least 20 metaphases) cytogenetic responses.

[b] Secondary endpoint for CP-CML Cohorts was MMR (proportion of patients who met the criteria for MMR at least once after the initiation of study treatment) measured in peripheral blood. Defined as a ≤0.1% ratio of BCR-ABL to ABL transcripts on the International Scale (IS) (ie, ≤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).

In patients with CP-CML who achieved MCyR or MMR, the median time to response was 2.8 months (range: 1.6 to 11.3 months) and 5.5 months (range: 1.8 to 47.4 months), respectively. With a minimum follow-up of 48 months, the median durations of MCyR (range: 2.7 to 50.3+ months) and MMR (range: 1.7 to 50.3+ months) had not yet been reached.

**Table 12: Efficacy of Iclusig in Patients With Resistant or Intolerant Advanced Disease (includes R/I and T315I cohorts)**

| | AP-CML Overall (N=83) | BP-CML Overall (N=62) | Ph+ ALL Overall (N=32) |
|---|---|---|---|
| **Hematologic Response** | | | |
| Major[a] (MaHR)<br>%<br>(95% CI) | <br>57%<br>(45,68) | <br>31%<br>(20,44) | <br>41%<br>(24,59) |
| Complete[b] (CHR)<br>%<br>(95% CI) | <br>51%<br>(39-62) | <br>21%<br>(12,33) | <br>34%<br>(19,53) |

[a] Primary endpoint for patients with AP-CML, BP-CML, and Ph+ ALL was MaHR by 6 months, which combines complete hematologic responses and no evidence of leukemia.

[b] CHR: 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).

The median time to MaHR in patients with AP-CML, BP-CML, and Ph+ ALL was 0.7 months (range: 0.4 to 5.8 months), 1.0 month (range 0.4 to 3.7 months), and 0.7 months (range: 0.4 to 5.5 months), respectively. The median duration of MaHR for patients with AP-CML, BP-CML, and Ph+ ALL was 12.9 months (range: 1.2 to 52+ months), 6.0 months (range: 1.8 to 47.4+ months), and 3.2 months (range: 1.8 to 12.8+ months), respectively.

## 5.2 Pharmacokinetic properties

Absorption
The absolute bioavailability of ponatinib is unknown. Peak concentrations of ponatinib are observed within 6 hours after Iclusig oral administration. Following ingestion of either a high-fat or low-fat meal by 22 healthy volunteers, plasma ponatinib exposures (AUC and $C_{max}$) were not different when compared to fasting conditions.

Distribution
Ponatinib is greater than 99% bound to plasma proteins *in vitro*. There was no plasma protein binding displacement of ponatinib (145 nM) *in vitro* by other highly protein bound medications (ibuprofen, nifedipine, propranolol, salicylic acid, and warfarin). The geometric mean (CV%) apparent steady state volume of distribution is 1223 liters (102%) following oral administration of Iclusig 45 mg once daily for 28 days in patients with cancer. Ponatinib is a weak substrate for both P-gp and ABCG2 *in vitro*. Ponatinib is not a substrate for organic anion transporting polypeptides (OATP1B1, OATP1B3) and organic cation transporter 1 (OCT1) *in vitro*.

Biotransformation
At least 64% of a ponatinib dose undergoes phase I and phase II metabolism. CYP3A4 and to a lesser extent CYP2C8, CYP2D6 and CYP3A5 are involved in the phase I metabolism of ponatinib *in vitro*. Ponatinib is also metabolized by esterases and/or amidases.

Elimination
The geometric mean (range) terminal elimination half-life of ponatinib was approximately 24 (12 to 66) hours following Iclusig 45 mg oral administration once daily for 28 days in patients with cancer. Exposure increased by approximately 90% (median) [range: 20% to 440%] between the first dose and presumed steady state. Ponatinib is mainly eliminated via feces. Following a single oral dose of [$^{14}$C]-labeled ponatinib, approximately 87% of the radioactive dose is recovered in the feces and approximately 5% in the urine.

Renal impairment
Iclusig has not been studied in patients with renal impairment. Although renal excretion is not a major route of ponatinib elimination, the potential for moderate or severe renal impairment to affect hepatic elimination has not been determined (see section 4.2). Caution is recommended when administering Iclusig to patients with estimated creatine clearance of < 60 mL/min, or end-stage renal disease

Hepatic impairment
A single dose of 30 mg ponatinib was administered to patients with mild, moderate, or severe hepatic impairment and to healthy volunteers with normal hepatic function. 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 hepatic impairment compared to subjects with normal liver function {see Posology and method of administration}.

Iclusig has not been studied at doses above 30 mg in patients with hepatic impairment (Childs-Pugh Classes A, B & C). The recommend starting dose is 30 mg once daily in patients with hepatic impairment (Child-Pugh A, B or C).

Caution is recommended when administering Iclusig to patients with hepatic impairment (see sections 4.2 and 4.4).

Intrinsic factors affecting ponatinib pharmacokinetics
No specific studies have been performed to evaluate the effects of gender, age, race, and body weight on ponatinib pharmacokinetics. An integrated population pharmacokinetic analysis completed for ponatinib did not identify gender, age, race or body weight as having a meaningful effect on intersubject variability, and no dose adjustments are recommended.

## 5.3 Preclinical safety data

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.

In a 2-year carcinogenicity study, male and female rats were administered daily oral doses of ponatinib of 0.05, 0.1, 0.2 and 0.2, 0.4, and 0.8 mg/kg/day, respectively. Exposures in animals at the highest dose tested were 0.3- to 0.8-fold the human exposure (based on AUC) at doses of 15 and 45 mg daily. Ponatinib induced a statistically significant increase in malignant squamous neoplasms of the clitoral gland in females at 0.8 mg/kg/day.

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.

Ponatinib may impair female fertility. In a fertility study in male and female rats, female fertility parameters were reduced at 1.5 mg/kg/day with exposure equivalent to 0.43 and 1.23 times, of human daily steady state AUC at the recommended dose of 45 mg/day (AUC = 1296 h·ng/mL) and 15 mg/day (451.8 h·ng/mL), respectively. Evidence of pre- and post-implantation loss of embryos was observed in female rats. Although there were no effects on male fertility parameters in the rat fertility study, repeat dose toxicology studies in monkeys showed degeneration of epithelium of the testes in monkeys at exposures approximately 3.3 times the plasma drug exposure (AUC) in patients receiving the recommended dose of 45 mg/day.

A juvenile toxicity study in 15-day-old rats was conducted with daily oral gavage administration of ponatinib at 0.75, 1.5, or 3 mg/kg/day for 21 days. There were no adverse effects of ponatinib on juvenile rat developmental parameters (vaginal opening, preputial separation or bone measurements) observed in this study. Once daily oral administration of 3 mg/kg/day ponatinib to juvenile rats beginning on Day 15 postpartum (pp) resulted in mortality related to inflammatory effects after 6 to 7 days following initiation of treatment. The dose of 3 mg/kg/day is approximately 0.32 times the clinical dose on a mg/m$^2$ basis for a child.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Tablet core
Lactose monohydrate
Microcrystalline cellulose
Sodium starch glycolate
Colloidal anhydrous silica
Magnesium stearate

Tablet coating
Talc
Macrogol 4000
Poly (vinyl alcohol)
Titanium dioxide (E171)

## 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

Do not store above 30° C. Keep away from children.

### 6.5 Nature and contents of container

Iclusig 15 mg film-coated tablets
30 film-coated tablets in a wide-mouth white, high density polyethylene (HDPE) bottles with a plastic canister containing a molecular sieve desiccant and induction sealed child resistant closure.

Iclusig 30 mg film-coated tablets
30 film-coated tablets in a wide-mouth white, high density polyethylene (HDPE) bottles with a plastic canister containing a molecular sieve desiccant and induction sealed child resistant closure.

Iclusig 45 mg film-coated tablets
30 film-coated tablets in a wide-mouth white, high density polyethylene (HDPE) bottles with a plastic canister containing a molecular sieve desiccant and induction sealed child resistant closure.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

Disposal

No special requirements for disposal.

## 7. MARKETING AUTHORISATION HOLDER

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

## 8. MARKETING AUTHORISATION NUMBER(S)

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: DD /MM/YYYY

## 10. DATE OF REVISION OF THE TEXT

MM/YYYY