## HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use ICLUSIG safely and effectively. See full prescribing information for ICLUSIG.**

**ICLUSIG® (ponatinib) tablets for oral use**
**Initial U.S. Approval: 2012**

**WARNING: ARTERIAL THROMBOSIS and HEPATOTOXICITY**

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

**Arterial Thrombosis:**

- **Cardiovascular, cerebrovascular, and peripheral vascular thrombosis, including fatal myocardial infarction and stroke have occurred in Iclusig-treated patients. In clinical trials, serious arterial thrombosis occurred in 8% of Iclusig-treated patients. Interrupt and consider discontinuation of Iclusig in patients who develop arterial thrombotic events *(2.3) (5.1)*.**

**Hepatotoxicity:**

- **Hepatotoxicity, liver failure and death have occurred in Iclusig-treated patients. Monitor hepatic function prior to and during treatment. Interrupt and then reduce or discontinue Iclusig for hepatotoxicity *(2.3) (5.2)*.**

**----------INDICATIONS AND USAGE----------**

Iclusig is a kinase inhibitor indicated for the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) that is resistant or intolerant to prior tyrosine kinase inhibitor therapy or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) that is resistant or intolerant to prior tyrosine kinase inhibitor therapy (1).
This indication is based upon response rate. There are no trials verifying an improvement in disease-related symptoms or increased survival with Iclusig.

**----------DOSAGE AND ADMINISTRATION----------**

- 45 mg taken orally once daily with or without food (2)
- Modify or interrupt dosing for hematologic and non-hematologic toxicity (2.2, 2.3)

**----------DOSAGE FORMS AND STRENGTHS----------**

- Tablets: 15 mg and 45 mg (3)

**----------CONTRAINDICATIONS----------**

- None (4)

**----------WARNINGS AND PRECAUTIONS----------**

- Congestive Heart Failure: Monitor patients for signs or symptoms of congestive heart failure and treat as clinically indicated (5.3, 6).
- Hypertension: Monitor for high blood pressure and treat as clinically indicated (5.4, 6).
- Pancreatitis: Monitor serum lipase monthly; interrupt or discontinue Iclusig (2.3, 5.5, 6).
- Hemorrhage: Interrupt Iclusig for serious or severe hemorrhage (5.6, 6).
- Fluid Retention: Monitor patients for fluid retention; interrupt, reduce, or discontinue Iclusig (5.7, 6).
- Cardiac Arrhythmias: Monitor for symptoms of arrhythmias (5.8, 6).
- Myelosuppression: Thrombocytopenia, neutropenia, and anemia may require dose interruption or reduction. Monitor complete blood counts every 2 weeks for 3 months and then monthly and as clinically indicated. Interrupt Iclusig for ANC < 1000/$mm^3$ or thrombocytopenia < 50,000/ $mm^3$ (2.2, 5.9, 6).
- Tumor Lysis Syndrome: Ensure adequate hydration and correct high uric acid levels prior to initiating therapy with Iclusig (5.10).
- Compromised Wound Healing and Gastrointestinal Perforation: Temporarily interrupt therapy in patients undergoing major surgical procedures (5.11).
- Embryo-fetal toxicity: Can cause fetal harm. Advise women of potential risk to a fetus (5.12, 8.1).

**----------ADVERSE REACTIONS----------**

The most common non-hematologic adverse reactions (≥ 20%) were hypertension, rash, abdominal pain, fatigue, headache, dry skin, constipation, arthralgia, nausea, and pyrexia. Hematologic adverse reactions included thrombocytopenia, anemia, neutropenia, lymphopenia, and leukopenia (6).

**To report SUSPECTED ADVERSE REACTIONS, contact ARIAD Pharmaceuticals, Inc. at (1-855-55-ARIAD) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**

**----------DRUG INTERACTIONS----------**

Strong CYP3A Inhibitors: Reduce Iclusig dose if co-administration cannot be avoided (7.1)

**----------USE IN SPECIFIC POPULATIONS----------**

The safety and efficacy of Iclusig in patients less than 18 years of age have not been tested (8.4).

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**

**Revised: [12/2012]**

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## FULL PRESCRIBING INFORMATION: CONTENTS*



*Sections or subsections omitted from the Full Prescribing Information are not listed.

## FULL PRESCRIBING INFORMATION

**WARNING: ARTERIAL THROMBOSIS and HEPATOTOXICITY**

**Arterial Thrombosis:**

- **Cardiovascular, cerebrovascular, and peripheral vascular thrombosis, including fatal myocardial infarction and stroke have occurred in Iclusig-treated patients. In clinical trials, serious arterial thrombosis occurred in 8% of Iclusig-treated patients. Interrupt and consider discontinuation of Iclusig in patients who develop arterial thrombotic events *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)]*.**

**Hepatotoxicity:**

- **Hepatotoxicity, liver failure and death have occurred in Iclusig-treated patients. Monitor hepatic function prior to and during treatment. Interrupt and then reduce or discontinue Iclusig for hepatotoxicity *[see Dosage and Administration (2.3) and Warnings and Precautions (5.2)]*.**

# 1 INDICATIONS AND USAGE

Iclusig® (ponatinib) is indicated for the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) that is resistant or intolerant to prior tyrosine kinase inhibitor therapy or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) that is resistant or intolerant to prior tyrosine kinase inhibitor therapy.

This indication is based upon response rate *[see Clinical Studies (14)]*. There are no trials verifying an improvement in disease-related symptoms or increased survival with Iclusig.

# 2 DOSAGE AND ADMINISTRATION

## 2.1 Recommended Dosing

The recommended dose and schedule for Iclusig is 45 mg administered orally once daily. Continue treatment as long as the patient does not show evidence of disease progression or unacceptable toxicity.

Iclusig may be taken with or without food. Tablets should be swallowed whole.

## 2.2 Dose Modifications for Myelosuppression

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

**Table 1: Suggested Dose Modifications for Myelosuppression**

| | |
|---|---|
| ANC* < 1 x $10^9$/L<br>or<br>platelet < 50 x $10^9$/L | First occurrence:<br>• Interrupt Iclusig and 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>• Interrupt 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>• Interrupt 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

## 2.3 Dose Modifications for Non-Hematologic Adverse Reactions

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

*Hepatic Toxicity*

Recommended modifications for hepatic toxicity are summarized in Table 2.

**Table 2: Recommended Dose Modifications for Hepatic Toxicity**

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

*ULN = Upper Limit of Normal for the lab

*Pancreatitis and Elevation of Lipase*

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

**Table 3: Recommended Dose Modifications for Pancreatitis and Elevation of Lipase**

| | |
|---|---|
| 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>• Interrupt Iclusig and resume at 30 mg after recovery to ≤ Grade 1 (< 1.5 x ULN)<br>Occurrence at 30 mg:<br>• Interrupt Iclusig and resume at 15 mg after recovery to ≤ Grade 1<br>Occurrence at 15 mg:<br>• Discontinue Iclusig |
| Symptomatic Grade 3 pancreatitis | Occurrence at 45 mg:<br>• Interrupt Iclusig and resume at 30 mg complete resolution of symptoms and after recovery of lipase elevation to ≤ Grade 1<br>Occurrence at 30 mg:<br>• Interrupt Iclusig and resume at 15 mg after complete resolution of symptoms and after recovery of lipase elevation to ≤ Grade 1<br>Occurrence at 15 mg:<br>• Discontinue Iclusig |
| Grade 4 pancreatitis | Discontinue Iclusig |

*ULN = Upper Limit of Normal for the lab

## 2.4 Dose Modification 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 Drug Interactions (7.1)]*.

# 3 DOSAGE FORMS AND STRENGTHS

15 mg and 45 mg round, white, film-coated tablets

# 4 CONTRAINDICATIONS

None

# 5 WARNINGS AND PRECAUTIONS

## 5.1 Thrombosis and Thromboembolism

Arterial Thrombosis

Cardiovascular, cerebrovascular, and peripheral vascular thrombosis, including fatal myocardial infarction and stroke have occurred in Iclusig-treated patients.

Serious arterial thrombosis occurred in 8% (34/449) of Iclusig-treated patients. Twenty-one patients required a revascularization procedure (16 patients with coronary revascularization, 4 patients with peripheral arterial revascularization, and 1 patient with cerebrovascular revascularization). Overall, fifty-one patients (11%) experienced an arterial thrombosis event of any grade.

Myocardial infarction or worsening coronary artery disease was the most common arterial thrombosis event and occurred in 21 patients (5%) of Iclusig-treated patients. Eleven of these patients developed congestive heart failure concurrent or subsequent to the myocardial ischemic event.

Serious cerebrovascular events were reported in 2% (8/449) of Iclusig-treated patients. Two patients experienced hemorrhagic conversion of the initial ischemic event. Four patients developed stenosis of large arterial vessels of the brain (e.g., carotid, vertebral, middle cerebral artery).

Serious peripheral arterial events were reported in 2% (7/449) of Iclusig treated patients. Three patients developed digital or distal extremity necrosis; 2 of these patients had diabetes mellitus and peripheral arterial disease and required amputations.

Thirty of 34 Iclusig patients who experienced a serious arterial thrombosis event had one or more cardiovascular risk factors (e.g., myocardial infarction, coronary artery disease, angina, stroke, transient ischemic attack, hypertension, diabetes mellitus, hyperlipidemia, and smoking). Patients with cardiovascular risk factors are at increased risk for arterial thrombosis with Iclusig. Interrupt and consider discontinuation of Iclusig in patients who develop arterial thrombotic events *[see Dosage and Administration (2.3)]*.

Venous Thromboembolism

Venous thromboembolic events occurred in 3% of Iclusig-treated patients, including deep venous thrombosis (9 patients), pulmonary embolism (4 patients), and 1 case each of portal vein thrombosis, and retinal vein thrombosis. Consider dose modification or discontinuation of Iclusig in patients who develop serious venous thromboembolism *[see Dosage and Administration (2.3)]*.

## 5.2 Hepatotoxicity

Hepatotoxicity that has resulted in liver failure and death occurred in Iclusig-treated patients. Fulminant hepatic failure leading to death occurred in an Iclusig-treated patient within one week of starting Iclusig. Two additional fatal cases of acute liver failure also occurred. The fatal cases occurred in patients with BP-CML or Ph+ALL. Severe hepatotoxicity occurred in all disease cohorts.

The incidence of aspartate aminotransferase (ALT) or alanine aminotransferase (AST) elevation was 56% (all grades) and 8% (grade 3 or 4). Iclusig-treatment may result in elevation in ALT, AST, or both. ALT or AST elevation was not reversed by the date of last follow-up in 5% of patients.

Monitor liver function tests at baseline, at least monthly or as clinically indicated. Interrupt, reduce or discontinue Iclusig as clinically indicated *[see Dosage and Administration (2.3)]*.

## 5.3 Congestive Heart Failure

Twenty patients treated with Iclusig (4%) experienced serious congestive heart failure or left ventricular dysfunction, with 4 fatalities. Thirty-three patients treated with Iclusig (7%) experienced any grade of congestive heart failure or left ventricular dysfunction. Monitor patients for signs or symptoms consistent with congestive heart failure and treat as clinically indicated, including interruption of Iclusig. Consider discontinuation of Iclusig in patients who develop serious congestive heart failure *[see Dosage and Administration (2.3)]*.

## 5.4 Hypertension

Eight patients treated with Iclusig (2%) experienced treatment-emergent symptomatic hypertension as a serious adverse reaction, including hypertensive crisis. These patients required urgent clinical intervention for hypertension associated with confusion, headache, chest pain, or shortness of breath.

Treatment-emergent hypertension occurred in 67% of patients (300/449) *[see Adverse Reactions (6)]*. In patients with baseline systolic BP<140 mm Hg and baseline diastolic BP<90mm Hg, 78% (220/282) experienced treatment-emergent hypertension; 49% (139/282) developed Stage 1 hypertension (defined as systolic BP≥140 mm Hg or diastolic BP≥90 mm Hg) while 29% developed Stage 2 hypertension (defined as systolic BP≥160 mm Hg or diastolic BP≥100 mm Hg. In 131 patients with Stage 1 hypertension at baseline, 61% (80/131) developed Stage 2 hypertension. Monitor and manage blood pressure elevations.

## 5.5 Pancreatitis

Clinical pancreatitis occurred in 6% (28/449) of patients (5% Grade 3) treated with Iclusig. Pancreatitis resulted in discontinuation or treatment interruption in 6% of patients (25/449). Twenty-two of the 28 cases of pancreatitis resolved within 2 weeks with dose interruption or reduction. The incidence of treatment-emergent lipase elevation was 41%.

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.

## 5.6 Hemorrhage

Serious bleeding events, occurred in 5% (22/449) of patients treated with Iclusig, including fatalities. Hemorrhagic events occurred in 24% of patients. The incidence of serious bleeding events was higher in patients with AP-CML, BP-CML, and Ph+ALL. Cerebral hemorrhage and gastrointestinal hemorrhage were the most commonly reported serious bleeding events. Most hemorrhagic events occurred in patients with grade 4 thrombocytopenia *[see Warnings and Precautions (5.9)]*. Interrupt Iclusig for serious or severe hemorrhage *[see Dosage and Administration (2.3)]*.

## 5.7 Fluid Retention

Fluid retention events judged as serious occurred in 3% (13/449) of patients treated with Iclusig. One instance of brain edema was fatal. Serious fluid retention events in more than 1 patient included: pericardial effusion (6/449, 1%), pleural effusion (5/449, 1%), and ascites (2/449, <1%).

In total, fluid retention occurred in 23% of the patients. The most common fluid retention events were peripheral edema (16%), pleural effusion (7%), and pericardial effusion (3%).

Monitor patients for fluid retention and manage patients as clinically indicated. Interrupt, reduce, or discontinue Iclusig as clinically indicated *[see Dosage and Administration (2.3)]*.

## 5.8 Cardiac Arrhythmias

Symptomatic bradyarrhythmias that led to a requirement for pacemaker implantation occurred in 3 (1%) 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 chest pain).

Supraventricular tachyarrhythmias occurred in 25 (5%) Iclusig-treated patients. Atrial fibrillation was the most common supraventricular tachyarrhythmia and occurred in 20 patients. The other supraventricular tachyarrhythmias were atrial flutter (4 patients), supraventricular tachycardia (4 patients), and atrial tachycardia (1 patient). For 13 patients, the event led to hospitalization. Advise patients to report signs and symptoms of rapid heart rate (palpitations, dizziness).

## 5.9 Myelosuppression

Severe (grade 3 or 4) myelosuppression occurred in 48% (215/449) of patients treated with Iclusig. The incidence of these events was greater in patients with accelerated phase CML (AP-CML), blast phase CML (BP-CML) and Ph+ALL than in patients with chronic phase CML (CP-CML). 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 Dosage and Administration (2.2)]*.

## 5.10 Tumor Lysis Syndrome

Two patients (<1%) treated with Iclusig developed serious tumor lysis syndrome. Both cases occurred in patients with advanced CML. Hyperuricemia occurred in 7% (30/449) of patients, the majority had chronic phase CML (19 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.

## 5.11 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 *[see Clinical Pharmacology (12.1)]*, 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.

## 5.12 Embryo-Fetal Toxicity

Iclusig can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. Ponatinib caused embryo-fetal toxicity in rats at exposures lower than human exposures at the recommended human dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Advise women to avoid pregnancy while taking Iclusig *[see Use in Specific Populations (8.1)]*.

# 6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The following adverse reactions are discussed in greater detail in other sections of the prescribing information:

- Thrombosis and Thromboembolism *[see Warnings and Precautions (5.1)]*
- Hepatotoxicity *[see Warnings and Precautions (5.2) and Dosage and Administration (2.3)]*
- Congestive Heart Failure *[see Warnings and Precautions (5.3)]*
- Hypertension *[see Warnings and Precautions (5.4)]*
- Pancreatitis *[see Dosage and Administration (2.3) and Warnings and Precautions (5.5)]*
- Hemorrhage *[see Warnings and Precautions (5.6)]*
- Fluid Retention *[see Warnings and Precautions (5.7)]*
- Cardiac Arrhythmias *[see Warnings and Precautions (5.8)]*
- Myelosuppression *[see Dosage and Administration (2.2) and Warnings and Precautions (5.9)]*

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. At the time of analysis, the median duration of treatment with Iclusig was 337 days in patients with chronic phase CP-CML, 362 days in patients with accelerated phase AP-CML, 89 days in patients with BP-CML, and 81 days in patients with Ph+ALL. The median dose intensity was 37 mg or, 83% of the expected 45 mg dose.

Adverse reactions reported in more than 10% of all patients treated with Iclusig in this trial are presented in Table 4. Overall, the most common non-hematologic adverse reactions (≥ 20%) were hypertension, rash, abdominal pain, fatigue, headache, dry skin, constipation, arthralgia, and nausea, and pyrexia.

The rates of treatment-emergent adverse events resulting in discontinuation were 13% in CP-CML, 11% in AP-CML, 15% in BP-CML, and 9% in Ph+ALL. The most common adverse events that led to treatment discontinuation were thrombocytopenia (4%) and infections (1%).

Dose modifications (dose delays or dose reduction) due to adverse reactions occurred in 74% of the patients. The most common adverse reactions (≥5%) that led to dose modifications include thrombocytopenia (30%), neutropenia (13%), lipase increased (12%), rash (11%), abdominal pain (11%), pancreatitis (6%), and ALT, AST, or GGT increased (6%).

**Table 4: Adverse Reactions Occurring in >10% of Patients, Any Group**

| | CP-CML (N=270) | | AP-CML (N=85) | | BP-CML (N=62) | | Ph+ ALL (N=32) | |
|---|---|---|---|---|---|---|---|---|
| **System Organ Class** | **Any Grade (%)** | **CTCAE Grade 3 / 4 (%)** | **Any Grade (%)** | **CTCAE Grade 3 / 4 (%)** | **Any Grade (%)** | **CTCAE Grade 3 / 4 (%)** | **Any Grade (%)** | **CTCAE Grade 3 / 4 (%)** |
| **Cardiac or Vascular disorders** | | | | | | | | |
| Hypertension (a) | 68 | 39 | 71 | 36 | 65 | 26 | 53 | 31 |
| Arterial ischemia (b) | 13 | 7 | 12 | 6 | 8 | 5 | 3 | 0 |
| Cardiac Failure (c) | 6 | 4 | 6 | 2 | 15 | 11 | 6 | 6 |
| **Gastrointestinal disorders** | | | | | | | | |
| Abdominal pain (d) | 49 | 10 | 40 | 8 | 34 | 6 | 44 | 6 |
| Constipation | 37 | 2 | 24 | 2 | 26 | 0 | 47 | 3 |
| Nausea | 23 | 1 | 27 | 0 | 32 | 2 | 22 | 0 |
| Diarrhea | 16 | 1 | 26 | 0 | 18 | 3 | 13 | 3 |
| Vomiting | 13 | 2 | 24 | 0 | 23 | 2 | 22 | 0 |
| Oral mucositis (e) | 10 | 1 | 15 | 1 | 23 | 0 | 9 | 3 |
| GI hemorrhage (f) | 2 | <1 | 8 | 1 | 11 | 5 | 9 | 6 |
| **Blood and lymphatic system disorders** | | | | | | | | |
| Febrile neutropenia | 1 | <1 | 4 | 4 | 11 | 11 | 25 | 25 |
| **Infections and infestations** | | | | | | | | |
| Sepsis | 1 | 1 | 5 | 5 | 8 | 8 | 22 | 22 |
| Pneumonia | 3 | 2 | 11 | 9 | 13 | 11 | 9 | 3 |
| Urinary tract infection | 7 | 1 | 12 | 1 | 0 | 0 | 9 | 0 |
| Upper respiratory tract infection | 11 | 1 | 8 | 0 | 11 | 2 | 0 | 0 |
| Nasopharyngitis | 9 | 0 | 12 | 0 | 3 | 0 | 3 | 0 |
| Cellulitis | 2 | 1 | 4 | 2 | 11 | 3 | 0 | 0 |
| **Nervous system disorders** | | | | | | | | |
| Headache | 39 | 3 | 28 | 0 | 31 | 3 | 25 | 0 |
| Peripheral neuropathy (g) | 13 | 2 | 8 | 0 | 8 | 0 | 6 | 0 |
| Dizziness | 11 | 0 | 5 | 0 | 5 | 0 | 3 | 0 |
| **Respiratory, thoracic, and mediastinal disorders** | | | | | | | | |
| Pleural effusion | 3 | 1 | 11 | 2 | 13 | 0 | 19 | 3 |
| Cough | 12 | 0 | 17 | 0 | 18 | 0 | 6 | 0 |
| Dyspnea | 11 | 2 | 15 | 2 | 21 | 7 | 6 | 0 |
| **Skin and subcutaneous tissue disorders** | | | | | | | | |
| Rash and related conditions | 54 | 5 | 48 | 8 | 39 | 5 | 34 | 6 |
| Dry skin | 39 | 2 | 27 | 1 | 24 | 2 | 25 | 0 |
| **Musculoskeletal and connective tissue disorders** | | | | | | | | |
| Arthralgia | 26 | 2 | 31 | 1 | 19 | 0 | 13 | 0 |
| Myalgia | 22 | 1 | 20 | 0 | 16 | 0 | 6 | 0 |
| Pain in extremity | 17 | 2 | 17 | 0 | 13 | 0 | 9 | 0 |
| Back pain | 15 | 1 | 11 | 2 | 16 | 2 | 13 | 0 |
| Muscle spasms | 12 | 0 | 5 | 0 | 5 | 0 | 13 | 0 |
| Bone pain | 12 | <1 | 12 | 1 | 11 | 3 | 9 | 3 |
| **General disorders and administration site conditions** | | | | | | | | |
| Fatigue or asthenia | 39 | 3 | 36 | 6 | 35 | 5 | 31 | 3 |
| Pyrexia | 23 | 1 | 31 | 5 | 32 | 3 | 25 | 0 |

**Table 4: Adverse Reactions Occurring in >10% of Patients, Any Group**

| | CP-CML (N=270) | | AP-CML (N=85) | | BP-CML (N=62) | | Ph+ ALL (N=32) | |
|---|---|---|---|---|---|---|---|---|
| Edema, peripheral | 13 | <1 | 19 | 0 | 13 | 0 | 22 | 0 |
| Pain | 8 | <1 | 7 | 0 | 16 | 3 | 6 | 3 |
| Chills | 7 | 0 | 11 | 0 | 13 | 2 | 9 | 0 |
| **Metabolism and nutrition disorders** | | | | | | | | |
| Decreased appetite | 8 | <1 | 12 | 1 | 8 | 0 | 31 | 0 |
| **Investigations** | | | | | | | | |
| Weight decreased | 6 | <1 | 7 | 0 | 5 | 0 | 13 | 0 |
| **Psychiatric disorders** | | | | | | | | |
| Insomnia | 7 | 0 | 12 | 0 | 8 | 0 | 9 | 0 |

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) includes cardiac, central nervous system, and peripheral arterial 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, hyperesthesia, hypoesthesia, neuralgia, neuropathy peripheral, paresthesia, peripheral sensorimotor neuropathy, polyneuropathy

**Table 5: Serious Adverse Reactions (SAR)**

| | N (%) |
|---|---|
| **Cardiovascular disorders** | |
| Arterial ischemic event | 34 (8%) |
| Myocardial infarction or worsening coronary artery disease | 21 (5%) |
| Stroke or TIA | 8 (2%) |
| Peripheral arterial disease | 7 (2%) |
| Hemorrhage | 22 (4%) |
| CNS hemorrhage | 10 (2%) |
| Gastrointestinal hemorrhage | 10 (2%) |
| Cardiac failure | 20 (4%) |
| Effusions* | 13 (3%) |
| Atrial fibrillation | 11 (2%) |
| Venous thromboembolism | 10 (2%) |
| Hypertension | 8 (2%) |
| **Gastrointestinal disorders** | |
| Pancreatitis | 23 (5%) |
| Abdominal pain | 17 (4%) |
| **Blood and lymphatic system disorders** | |
| Febrile neutropenia | 13 (3%) |
| Thrombocytopenia | 13 (3%) |
| Anemia | 12 (2%) |
| **Infections** | |
| Pneumonia | 24 (4%) |
| Sepsis | 11 (2%) |
| **General** | |
| Pyrexia | 14 (3%) |

*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 6).

**Table 6: Incidence of Clinically Relevant Grade 3/4* Hematologic Abnormalities**

| Laboratory Test | CP-CML (N=270) (%) | AP-CML (N=85) (%) | BP-CML (N=62) (%) | Ph+ ALL (N=32) (%) |
|---|---|---|---|---|
| ***Hematology*** | | | | |
| Thrombocytopenia (platelet count decreased) | 36 | 47 | 57 | 47 |
| Neutropenia (ANC decreased) | 24 | 51 | 55 | 63 |
| Leukopenia (WBC decreased) | 14 | 35 | 53 | 63 |
| Anemia (Hgb decreased) | 9 | 26 | 55 | 34 |
| Lymphopenia | 10 | 26 | 37 | 22 |

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

**Table 7 Incidence of Clinically Relevant Non-Hematologic Laboratory Abnormalities**

| Laboratory Test | Safety Population N=449 | |
|---|---|---|
| | Any Grade* (%) | G3-4 (%) |
| **Liver function tests** | | |
| ALT increased | 53 | 8 |
| AST increased | 41 | 4 |
| Alkaline phosphatase increased | 37 | 2 |
| Albumin decreased | 28 | 1 |
| Bilirubin increased | 19 | 1 |
| **Pancreatic enzymes** | | |
| Lipase increased | 41 | 15 |
| Amylase increased | 3 | <1 |
| **Chemistry** | | |
| Glucose increased | 58 | 6 |
| Phosphorus decreased | 57 | 8 |
| Calcium decreased | 52 | 1 |
| Sodium decreased | 29 | 5 |
| Glucose decreased | 24 | 0 |
| Potassium decreased | 16 | 2 |
| Potassium increased | 15 | 2 |
| Sodium increased | 10 | <1 |
| Bicarbonate decreased | 11 | <1 |
| Creatinine increased | 7 | <1 |
| Calcium increased | 5 | 0 |
| Triglycerides increased | 3 | <1 |

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

# 7 DRUG INTERACTIONS

Based on *in vitro* studies ponatinib is a substrate of CYP3A4/5 and to a lesser extent CYP2C8 and CYP2D6. Ponatinib also inhibits the P-glycoprotein (P-gp), ATP-binding cassette G2 (ABCG2) [also known as BCRP], and bile salt export pump (BSEP) transporter systems *in vitro [see Clinical Pharmacology (12.3)]*.

## 7.1 Drugs That Are Strong Inhibitors of CYP3A Enzymes

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 *[see Clinical Pharmacology (12.3)]*. 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), the recommended starting dose should be reduced to 30 mg once daily *[see Dosage and Administration (2.1)]*. Patients taking concomitant strong inhibitors may be at increased risk for adverse reactions *[see Clinical Pharmacology (12.3)]*.

## 7.2 Drugs That Are Strong Inducers of CYP3A Enzymes

Coadministration of Iclusig with strong CYP3A inducers was not evaluated *in vitro* or in a clinical trial; however, a reduction in ponatinib exposure is likely *[see Clinical Pharmacology (12.3)]*. Coadministration of strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin, and St. John's Wort) with Iclusig should be avoided unless the benefit outweighs the possible risk of ponatinib underexposure. Monitor patients for signs of reduced efficacy.

## 7.3 Drugs That Elevate Gastric pH

Coadministration of Iclusig with drugs that elevate the gastric pH was not evaluated in a clinical trial. Based on the chemical properties of ponatinib, elevated gastric pH may reduce bioavailability and exposure *[see Clinical Pharmacology (12.3)]*. Coadministration of Iclusig with drugs that elevate the gastric pH (e.g., proton pump inhibitors, H2 blockers, or antacids) should be avoided unless the benefit outweighs the possible risk of ponatinib underexposure. Monitor patients for signs of reduced efficacy.

## 7.4 Drugs That Are Substrates of the P-gp or ABCG2 Transporter Systems

*In vitro* studies demonstrate that Iclusig inhibits the P-gp and ABCG2 [also known as BCRP] transporter systems. The effect of coadministration of Iclusig with sensitive substrates of the P-gp (e.g., aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, tolvaptan, topotecan) and ABCG2 [also known as BCRP] (e.g., methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan) transporter systems on exposure of these substrates has not been evaluated in clinical studies.

# 8 USE IN SPECIFIC POPULATIONS

## 8.1 Pregnancy

**Pregnancy Category D**

*Risk Summary*

Based on its mechanism of action and findings in animals, Iclusig can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies with Iclusig in pregnant women. Advise women to avoid becoming pregnant while taking Iclusig. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

*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. 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.

### 8.3 Nursing Mothers

It is unknown whether ponatinib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ponatinib, a decision should be made whether to discontinue nursing or to discontinue Iclusig, taking into account the importance of the drug to the mother.

### 8.4 Pediatric Use

The safety and efficacy of Iclusig in patients less than 18 years of age have not been established.

### 8.5 Geriatric Use

One hundred and fifty-five of 449 patients (35%) in the clinical trial of Iclusig were 65 years of age and over. In patients with CP-CML, patients of age ≥ 65 years had a lower major cytogenetic response rate (38%) as compared with patients < 65 years of age (64%). In patients with AP-CML, BP-CML, and Ph+ ALL, patients of age ≥ 65 years had a higher major hematologic response rate (47%) as compared with patients < 65 years of age (40%). Patients of age ≥ 65 years may be 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 elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

### 8.6 Hepatic Impairment

Iclusig has not been studied in patients with hepatic impairment.

As hepatic elimination is a major route of excretion for Iclusig, hepatic impairment may result in increased ponatinib exposure. Avoid Iclusig in patients with moderate to severe (Child-Pugh B or C) hepatic impairment unless the benefit outweighs the possible risk of ponatinib overexposure *[see Clinical Pharmacology (12.3)]*. Patients with moderate to severe hepatic impairment may be at increased risk for adverse reactions *[see Clinical Pharmacology (12.3)]*.

### 8.7 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 Clinical Pharmacology (12.3)]*.

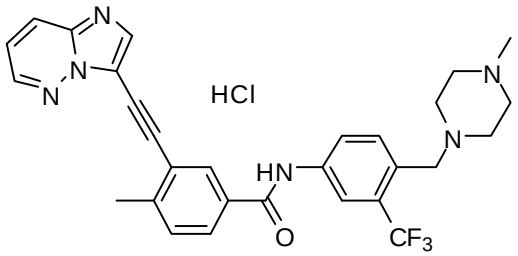
## 10 OVERDOSAGE

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.

## 11 DESCRIPTION

Iclusig (ponatinib) is a kinase inhibitor. The chemical name for ponatinib hydrochloride is 3-(imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-{4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl}benzamide hydrochloride. The molecular formula is $C_{29}H_{28}ClF_3N_6O$ which corresponds to a formula weight of 569.02 g/mol. Its structure is shown below:



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 mcg/ml, 3.44 mcg/ml, and 0.16 mcg/ml, respectively, indicating a decrease in solubility with increasing pH. Iclusig tablets are available as white, round, film-coated tablets for oral administration. Each tablet contains ponatinib hydrochloride equivalent to 15 or 45 mg ponatinib with the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (type B), colloidal silicon dioxide, magnesium stearate and a tablet coating. The tablet coating consists of talc, polyethylene glycol, polyvinyl alcohol, and titanium dioxide.

# 12 CLINICAL PHARMACOLOGY

## 12.1 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.

## 12.3 Pharmacokinetics

The geometric mean (CV%) $C_{max}$ and $AUC_{(0-\tau)}$ of Iclusig 45 mg daily at presumed steady state in patients with advanced hematologic malignancies were 73 ng/mL (74%) and 1253 ng•hr/mL (73%), respectively. Ponatinib administered as an investigational capsule formulation to patients with cancer exhibited approximately dose proportional increases in both $C_{max}$ and AUC over the dose range of 15 to 60 mg. A dose intensity safety analysis showed a significant increase in grade 3 or higher adverse reactions (i.e., thrombocytopenia, neutropenia, rash, ALT elevation, AST elevation, pancreatitis, and lipase elevation) with an increase in dose intensity.

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. The aqueous solubility of ponatinib is pH dependent, with higher pH resulting in lower solubility *[see Description (11)]*. Drugs that elevate the gastric pH may reduce ponatinib bioavailability *[see Drug Interactions (7.3)]*.

Distribution

Ponatinib is greater than 99% bound to plasma proteins *in vitro*. 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 [also known as BCRP] *in vitro*. Ponatinib is not a substrate for organic anion transporting polypeptides (OATP1B1, OATP1B3) and organic cation transporter 1 (OCT1) *in vitro*.

Metabolism

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.

**Drug Interactions**

Coadministration of Ponatinib and CYP3A Inhibitors

Coadministration of a single 15 mg oral dose of ponatinib in the presence of ketoconazole (400 mg daily), a strong CYP3A inhibitor to 22 healthy volunteers, increases the $AUC_{0-\infty}$ and $C_{max}$ of ponatinib by 78% and 47%, respectively, when compared to administration of ponatinib alone *[see Drug Interactions (7.1)]*.

Coadministration of Ponatinib and CYP3A Inducers

Since the human oxidative metabolism of ponatinib via the cytochrome P450 system primarily involves CYP3 isozymes, a reduction in ponatinib exposure is likely and was observed in simulations using a mechanistic model *[see Drug Interactions (7.2)]*.

Coadministration With Other CYP 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.

Coadministration With Substrates of Transporters

*In vitro*, ponatinib is an inhibitor of P-gp and ABCG2 [also known as BCRP], and BSEP *[see Drug Interactions (7.4)]*.

*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.

**Pharmacokinetics in Specific Populations**

Hepatic Impairment

Iclusig has not been studied in patients with hepatic impairment. As hepatic elimination is a major route of excretion for ponatinib, hepatic impairment may result in increased plasma ponatinib concentrations *[see Use in Specific Populations (8.6)]*.

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 Use in Specific Populations (8.7)]*.

## 12.6 QT/QTc Prolongation

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 ms) from baseline were detected in the study. However, a small increase in the mean QTc interval (i.e., < 10 ms) cannot be excluded because of study design limitations.

# 13 NONCLINICAL TOXICOLOGY

## 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with ponatinib.

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 male and female fertility. Fertility studies using ponatinib were not conducted. However, ponatinib effects on male and female reproductive organs observed during general toxicology studies included degeneration of epithelium of the testes in rats and monkeys and follicular atresia in the monkey ovary with associated endometrial atrophy. Effects seen in rats were at exposures approximating the AUC in patients receiving the recommended dose of 45 mg/day and in monkeys were approximately 4 times the AUC in patients.

# 14 CLINICAL STUDIES

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. 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 [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 follow-up was 10 months (minimum of 6 months of follow-up for all ongoing patients). Baseline demographic characteristics are described in Table 8.

**Table 8: 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%) |

At the time of analysis, the median duration of Iclusig treatment was 281 days in patients with CP-CML, 286 days in patients with AP-CML, 89 days in patients with 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 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) | 54%<br>(48,60) | 49%<br>(42,56) | 70%<br>(58,81) |
| Complete (CCyR)<br>%<br>(95% CI) | 44%<br>(38,50) | 37%<br>(31,44) | 66%<br>(53,77) |

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

In patients with CP-CML patients who achieved MCyR, the median time to MCyR was 84 days (range: 49 to 334 days). At the time of analysis, the median durations of MCyR had not yet been reached.

**Table 10: 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) | 52%<br>(41,63) | 31%<br>(20,44) | 41%<br>(24,59) |
| Complete[b] (CHR)<br>%<br>(95% CI) | 47%<br>(33,55) | 21%<br>(12,33) | 34%<br>(19,53) |

[a] Primary endpoint for patients with AP-CML, BP-CML, and Ph+ALL was MaHR, 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 21 days (range: 12 to 176 days), 29 days (range 12 to 113 days), and 20 days (range: 11 to 168 days), respectively. The median duration of MaHR for patients with AP-CML, BP-CML, and Ph+ALL was 9.5 months (range: 1.1 to 17.7 months), 4.7 months (range: 1.8 to 14.1+ months), and 3.2 months (range: 1.8 to 8.8+ months), respectively.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Iclusig tablets are available in the following configurations:

| Strength | NDC Number | Description | Presentation |
|---|---|---|---|
| 15 mg | 76189-535-60 | round, white, film-coated tablets with debossed "A5" on one side and plain on the other side | 60 tablets in a wide-mouth white high density polyethylene (HDPE) bottle with child resistant closures that incorporate an induction heat seal liner |
| | 76189-535-80 | | 180 tablets in a wide-mouth white high density polyethylene (HDPE) bottle with child resistant closures that incorporate an induction heat seal liner |
| 45 mg | 76189-534-30 | round, white, film-coated tablets with debossed "AP4" on one side and plain on the other side | 30 tablets in a wide-mouth white high density polyethylene (HDPE) bottle with child resistant closures that incorporate an induction heat seal liner |
| | 76189-534-90 | | 90 tablets in a wide-mouth white high density polyethylene (HDPE) bottle with child resistant closures that incorporate an induction heat seal liner |

Iclusig tablets should be stored at 20° to 25°C (68° to 77°F); excursions permitted to 15°to 30° C (59° to 86° F) [see USP Controlled Room Temperature]. Keep away from children.

## 17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Medication Guide).

**Advise patients of the following and provide a copy of the Medication Guide:**

Thrombosis and Thromboembolism

Inform patients that serious arterial thromboses (including arterial stenosis sometimes requiring revascularization) and venous thromboembolism events have occurred. Advise patients to immediately contact their health care provider 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 (5.1)]*.

Hepatotoxicity

Inform patients of the possibility of developing liver function abnormalities and serious hepatic toxicity. Advise patients to immediately contact their health care provider if signs of liver failure occur, including yellowing of the eyes or skin, "tea"-colored urine, or drowsiness *[see Warnings and Precautions (5.2)]*.

Congestive Heart Failure and Cardiac Arrhythmias

Inform patients of the possibility of congestive heart failure, and abnormally slow or fast heart rates. Advise patients to contact their health care provide if they experience symptoms such as shortness of breath, chest pain, palpitations, dizziness, or fainting *[see Warnings and Precautions (5.3, 5.8)]*.

Hypertension

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 (5.4)]*.

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 *[see Warnings and Precautions (5.5)]*.

Hemorrhage

Inform patients of the possibility of serious bleeding and to immediately contact their health care provider with any signs or symptoms suggestive of hemorrhage such as unusual bleeding or easy bruising *[see Warnings and Precautions (5.6)]*.

Fluid Retention

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 *[see Warnings and Precautions (5.7)]*.

Myelosuppression

Inform patients of the possibility of developing low blood cell counts; inform patients to report immediately should fever develop, particularly in association with any suggestion of infection *[see Warnings and Precautions (5.9)]*.

Compromised Wound Healing and Gastrointestinal Perforation

Advise patients to inform their health care provider if they plan to undergo a surgical procedure or had recent surgery *[see Warnings and Precautions (5.11)]*.

Inform patients that cases of gastrointestinal perforation have been reported *[see Warnings and Precautions (5.12)]*.

Embryo-Fetal Toxicity

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 *[see Warnings and Precautions (5.12) and Use in Specific Populations (8.1)]*.

Instructions for Taking Iclusig

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. Iclusig may be taken with or without food. Iclusig tablets should be swallowed whole. Patients should not crush or dissolve the tablets.

Patients should not take two doses at the same time to make up for a missed dose.

Lactose

Inform patients that Iclusig contains 121 mg of lactose monohydrate in a 45 mg daily dose.

Manufactured for:

ARIAD Pharmaceuticals, Inc.

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