ICLUSIG™
(ponatinib) tablets
45 mg, 15 mg

FDA Required REMS Safety Information

Iclusig® (ponatinib)
- **Indications**
- **Safety information about risks of arterial occlusion and venous thromboembolism**
- **Dosing considerations**

INDICATIONS

The indications are limited to:
- Treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom 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 Ph+ ALL

Limitations of use:
Iclusig is not indicated and is not recommended for the treatment of patients with newly diagnosed chronic phase CML.

UPDATED RISKS OF ARTERIAL OCCLUSION AND VENOUS THROMBOEMBOLISM IN BOXED WARNING

- Arterial occlusion has occurred in at least **35%** of Iclusig treated patients. Some patients experienced more than 1 type of event. Events observed include:
  - Fatal myocardial infarction
  - Stroke
  - Stenosis of large arterial vessels of the brain
  - Severe peripheral vascular disease, and Need for urgent revascularization procedures
- Venous thromboembolism has occurred in 6% of Iclusig-treated patients

Arterial Occlusion

Iclusig can cause fatal and life-threatening arterial occlusion within 2 weeks of starting treatment, at dose levels as low as 15 mg per day. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events (see Table 1).

Table 1: 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)	

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.

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DOSING CONSIDERATIONS

Optimal dosing 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. 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.

Start dosing with 45 mg once daily. Consider reducing the dose of Iclusig for chronic phase CML (CP-CML) and accelerated phase CML (AP-CML) patients who have achieved a major cytogenetic response. Consider discontinuing Iclusig if response has not occurred by 3 months (90 days). Interrupt or discontinue Iclusig immediately for arterial occlusion.

Consider dose modification or discontinuation of Iclusig in patients who develop serious venous thromboembolism. 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.

OTHER SERIOUS RISKS INCLUDED IN THE BOXED WARNING

- **Heart failure**, including fatalities, occurred in 9% of Iclusig-treated patients. Monitor cardiac function. Interrupt or stop Iclusig for new or worsening heart failure
- **Hepatotoxicity**, liver failure and death have occurred in Iclusig-treated patients. Monitor hepatic function. Interrupt Iclusig if hepatotoxicity is suspected

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WHAT IS THE ICLUSIG REMS?

A REMS (**R**isk **E**valuation and **M**itigation **S**trategy) is a program required by the FDA to manage known or potential serious risks associated with a drug product. The purpose of the Iclusig REMS is to inform Healthcare Providers of new important safety information in the revised Iclusig label, including serious risks of Iclusig. This fact sheet is required by the FDA as part of the Iclusig REMS program.

Please visit www.iclusigREMS.com for further information.

This fact sheet does not contain the complete safety profile for Iclusig. Please see the Prescribing Information, including Boxed Warning and Medication Guide.

REPORTING ADVERSE EVENTS

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088. Healthcare Providers should report all suspected adverse events associated with Iclusig to the FDA or to ARIAD at 1-855-552-7423 or send the information to ARIAD at medinfo@ariad.com.

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