ICLUSIG®
(ponatinib) tablets
45 mg, 15 mg

Iclusig® (ponatinib) REMS

FDA REQUIRED REMS SAFETY INFORMATION

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

<Date>

IMPORTANT SAFETY UPDATE

Dear Healthcare Provider:

In December 2013, the FDA required a REMS (Risk Evaluation Mitigation Strategy) for Iclusig to inform health care providers about the labeling updates that include revised indications, serious risks of vascular occlusion (comprising of arterial occlusion and venous thromboembolism) in the Boxed Warning, and new dosing considerations. A summary of the current prescribing information (November 2017) related to the indications and limitations of Iclusig use, risks of arterial occlusion, venous thromboembolism, and dosing are provided below:

- **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.
- **Safety information about 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
  - Venous thromboembolism has occurred in 6% of Iclusig-treated patients
- **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

Please see the non-promotional fact sheet, reviewed by the FDA, with more detailed safety information: Iclusig REMS Fact Sheet, enclosed. You may also visit www.iclusigREMS.com for more information.

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

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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 Takeda Pharmaceuticals, Co. Ltd. At 1-844-T-1POINT (1-844-817-6468).

Sincerely,

Howard Fingert, MD
Senior Medical Director, Oncology Clinical Research
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Takeda ONCOLOGY