Iclusig® (ponatinib) REMS

Risk Evaluation and Mitigation Strategy

A REMS is a program required by the Food and Drug Administration (FDA) to manage known or potential serious risks associated with a drug product.

The purpose of the Iclusig REMS is to inform HealthCare Providers about the new safety information in the revised label including the serious risks of Iclusig. Safety updates include:

- Revised Indications
- New safety information about serious risk of vascular occlusion
- New dosing considerations

REVISED INDICATIONS

The Indications have been limited to:

- Treatment of adult patients with T315I-positive chronic myeloid leukemia (CML) (chronic phase, accelerated phase, or blastic phase) or T315I-positive Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL).
- Treatment of adult patients with chronic phase, accelerated phase, or blast phase CML, or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated.

UPDATED SERIOUS RISK OF VASCULAR OCCLUSION IN BOXED WARNING

Arterial and venous thromboembolic and occlusions have occurred in at least 27% of Iclusig clinical trial patients including:

- Focal myocardiopulmonary infection
- Severe peripheral vascular disease
- Stroke
- Need for urgent revascularization procedures
- Obstruction of the large arterial vessels of the brain

Iclusig can cause fatal and life-threatening vascular occlusion within 2 weeks of starting treatment. Patients with and without cardiovascular risk factors, including patients less than 30 years old, experienced these events.

<table>
<thead>
<tr>
<th>Table 1: Vascular Occlusion Incidence in Iclusig-Treated Patients in Phase 2 Trial According to Risk Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior History of Ischemia, Hypertension, Diabetes, or Hyperlipidemia</td>
</tr>
<tr>
<td>Age: 49 or younger</td>
</tr>
<tr>
<td>Age: 50 to 74 years</td>
</tr>
<tr>
<td>Age: 75 and older</td>
</tr>
<tr>
<td>All age groups</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

NEW DOSING CONSIDERATIONS

Optimal dosing has not yet been identified.

In clinical trials, the starting dose of Iclusig was 45 mg orally administered once daily. However, 50% of the patients required dose reductions to 30 mg or 15 mg once daily during the course of therapy.

Start dosing with 45 mg one daily. Consider reducing the dose of Iclusig for chronic phase CML, (CP-CML) and accelerated phase CML (AP-CML) patients who have uncontrolled major organ refractory response.

Consistent discontinuing Iclusig if response has not occurred by 3 months (36 days).

Do not start Iclusig in patients with arterial or venous occlusion unless the patient benefits outweigh the risk of recurrent arterial or venous occlusion and the patient has no other treatment options.

WARNING: VASCULAR OCCLUSION, HEART FAILURE, AND HEPARINOTHROMBOSIS

Vascular Occlusions:

- Arterial and venous thromboembolism and occlusions have occurred in at least 27% of Iclusig treated patients, including fatal myocardial infarction, stroke, occlusions 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 age 65 years or younger, experienced these events.

- Monitor for evidence of thromboembolism and vascular occlusions. Interrupt or stop Iclusig immediately for vascular occlusions. A benefit-risk consideration should guide a decision to restart Iclusig therapy.

Heart Failure:

- Heart failure, including fatalities, occurred in 8% of Iclusig-treated patients. Monitor cardiac function. Interrupt or stop Iclusig for new or worsening heart failure.

- Hypertension.

- Hypertensive episodes and death have occurred in Iclusig-treated patients. Monitor blood pressure. Interrupt Iclusig if hypertensive crisis is suspected.

This site is intended for US Healthcare Professionals.

Mylar is a registered trademark of Mylan Pharmaceuticals, Inc. © 2013 Mylan Pharmaceuticals, Inc. All rights reserved.

Reference ID: 3425762
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN T FARRELL
12/20/2013