U.S. Food and Drug Administration
Protecting and Promoting Your Health

Drug Safety Communications

FDA Drug Safety Communication: FDA requires multiple new safety measures for leukemia drug Iclusig; company expected to resume marketing

This information is in follow-up to the FDA Drug Safety Communication: FDA asks manufacturer of the leukemia drug Iclusig (ponatinib) to suspend marketing and sales that was issued on October 31, 2013, and updated on November 5, 2013 http://www.fda.gov/Drugs/DrugSafety/ucm373040.htm.

[12-20-2013] The U.S. Food and Drug Administration (FDA) is requiring several new safety measures for the leukemia drug Iclusig (ponatinib) to address the risk of life-threatening blood clots and severe narrowing of blood vessels. Once these new safety measures are in place, the manufacturer of Iclusig is expected to resume marketing to appropriate patients. Health care professionals should review these additional safety measures and carefully consider them when evaluating the risks and benefits of Iclusig for each patient.

The required safety measures involve label changes to narrow the indication, provide additional warnings and precautions about the risk of blood clots and severe narrowing of blood vessels, revise recommendations about dosage and administration of Iclusig, and update the patient Medication Guide. We are also requiring a risk evaluation and mitigation strategy (REMS). In addition, the manufacturer of Iclusig, ARIAD Pharmaceuticals, must conduct postmarket investigations to further characterize the drug's safety and dosing.

On October 31, 2013, FDA requested and ARIAD agreed to voluntarily suspend marketing of Iclusig section of http://www.fda.gov/Drugs/DrugSafety/ucm373040.htm. FDA's request resulted from FDA's investigation, which revealed a steady increase in the number of serious vascular occlusion events identified through continued safety monitoring of the drug. This observation represented a significant change in the safety profile of Iclusig as the proportion of patients on the drug experiencing vascular occlusion events such as blood clots and severe narrowing of blood vessels was significantly greater than the proportion reported at the time of its approval in December 2012 (see Data Summary).

During the marketing suspension, Iclusig treatment has been available through single patient or emergency investigational new drug applications (INDs). Patients should continue to receive Iclusig under their authorized IND until marketing of Iclusig is resumed. FDA is working closely with ARIAD on the new safety measures and anticipates these will be in place by the end of January 2014. Once that process is complete, patients being treated under these INDs can be transitioned back to receiving the marketed Iclusig product.

In more detail, the new safety measures for Iclusig include the following:

- The indications for use are limited to:

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

- The *Warnings and Precautions* in the label are revised to describe the vascular occlusion events. This includes a description of the observed arterial and venous thrombosis and occlusions that have occurred in at least 27% — more than one in every four — of patients treated with Iclusig.

- The *Dosage and Administration* recommendations are revised to state that the optimal dose of Iclusig has not been identified. The recommended starting dose remains 45 mg administered orally once daily with or without food; however, additional information is included regarding dose decreases and discontinuations.

- The patient Medication Guide is revised to include additional safety information consistent with the safety information in the revised drug label.

- The Iclusig REMS will inform prescribers about the approved indications for use and the serious risk of vascular occlusion and thromboembolism associated with the drug. The REMS includes the following:
  - REMS letter to healthcare professionals who are known or likely to prescribe Iclusig
  - REMS letter for professional societies to be distributed to their members
  - REMS fact sheet for health care professionals
  - Public statement to be published quarterly for one year in several professional journals
  - Information to be prominently displayed at scientific meetings
  - Iclusig REMS Web site to provide access to all REMS materials for the duration of the REMS

- ARIAD's postmarket investigations will further evaluate dose selection, drug exposure, treatment response, and toxicity of Iclusig therapy.

We urge health care professionals and patients to report side effects involving Iclusig to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Additional Information for Patients and Caregivers

- Patients taking Iclusig should seek immediate medical attention if they experience symptoms suggesting a heart attack or symptoms of a stroke. Symptoms of a heart attack include chest pain or pressure; pain in the arms, back, neck, or jaw; and shortness of breath. Symptoms of stroke include numbness or weakness on one side of the body, trouble talking, severe headache, or dizziness.

- Patients receiving Iclusig under single patient or emergency investigational new drug applications (INDs) should continue to receive the drug through this mechanism until marketing of Iclusig is resumed as anticipated in January 2014 and the drug is available without an IND.
- Discuss with your health care professional whether the benefits of Iclusig treatment are likely to exceed the risks of treatment.
- Carefully read the patient Medication Guide for the drug.
- Talk to your health care professional if you have any questions or concerns about Iclusig.
- Report side effects from Iclusig to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Additional Information for Health Care Professionals

- Arterial and venous thrombosis and occlusions have occurred in at least 27% of Iclusig-treated patients from the phase 1 and phase 2 trials. These adverse events have included fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures.
- Iclusig can cause fatal and life-threatening vascular occlusions within 2 weeks of starting treatment. Iclusig can also cause recurrent or multi-site vascular occlusions.
- Inform patients about the signs and symptoms of vascular occlusion events and advise them to seek immediate medical treatment if they experience symptoms suggesting a heart attack (such as chest pain or pressure, pain in their arms, back, neck or jaw, or shortness of breath), or symptoms of a stroke (such as numbness or weakness on one side of the body, trouble talking, severe headache, or dizziness).
- We expect that a REMS letter to healthcare professionals will be sent electronically or by mail to hematologists, oncologists, and other health care professionals known or likely to prescribe Iclusig by the end of January 2014. Prescribing Information and the Iclusig REMS fact sheet will accompany the letter.
- The Iclusig REMS Web site will contain information on the Iclusig REMS and will provide access to all the REMS materials and the U.S. Prescribing Information. The site will be available soon and for the duration of the REMS.
- Health care professionals should continue to work closely with FDA and ARIAD for patients currently receiving Iclusig under single patient or emergency INDs until the resumed marketing of Iclusig is complete as anticipated in January 2014 and the drug is available without an IND.
- ARIAD will send letters to all single patient IND (sIND) holders with an estimated time for transitioning these sINDs to commercial supply. The company will send a second communication at the time full commercial distribution resumes. Specialty pharmacies will provide outreach to sIND holders at the time of full marketing resumption to help facilitate this transition (refer to www.iclusig.com for further information).
- Encourage patients to read the patient Medication Guide for Iclusig.
- Adverse events involving Iclusig should be reported to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Data Summary

As a result of the postmarket safety monitoring of Iclusig (including through postmarket reports and ongoing trials), FDA identified a significant change in the safety profile of Iclusig. Arterial and venous thrombosis and occlusions have occurred in at least 27% of Iclusig-treated patients from the phase 1 and phase 2 trials. These adverse events have included fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures. We noted an increasing number of these serious vascular occlusion events as compared to those noted at the time of approval, which our analyses suggest are linked to the drug rather to than other factors.

We held multiple meetings with the sponsor, ARIAD Pharmaceuticals, to discuss these serious vascular occlusion events and recommended ARIAD review all cases of vascular occlusion events that occurred in patients treated with Iclusig. This review provided clarity with regard to the frequency and characterization of these events.

In addition, FDA conducted an independent data analysis of vascular occlusion events including heart attack, stroke, extremity necrosis, and pulmonary embolism to be serious events. These serious events occurred in those patients with and without established risk factors and in all age ranges. The cumulative number of vascular events was shown to increase with longer use of Iclusig. The rate of vascular occlusions also exceeded that of other drugs in the same class (e.g., imatinib, dasatinib, nilotinib, and bosutinib).

ARIAD announced termination of the EPIC (Evaluation of Ponatinib versus Imatinib in Chronic Myeloid Leukemia) trial on October 18, 2013. EPIC was a phase 3 trial comparing Iclusig to imatinib in the initial treatment of patients with chronic myeloid leukemia. The decision to terminate the trial was because of an excessive number of observed vascular occlusion events in patients treated with Iclusig. FDA agreed with the decision, in part, because of the availability of multiple alternative first-line treatments (imatinib, dasatinib, and nilotinib).

Previous reports of vascular occlusion events have tried to link events to either Iclusig or an underlying disease process. In its investigation, FDA included all vascular occlusion events, including those considered by investigator-led analyses as not related to the drug, in an effort to prevent the introduction of potential bias as these trials were unblinded and not randomized. The magnitude and timing of the vascular occlusion events, and the safety findings from the terminated EPIC trial, have provided increasing evidence of the relationship between Iclusig and arterial and venous vascular occlusion events.