Authorization with Conditions for ICLUSIG™

02 April 2015

Dear Health Care Professional(s):

ARIAD Pharmaceuticals, Inc. is pleased to announce that Health Canada has issued a Notice of Compliance with Conditions (NOC/c) under the NOC/c policy for ICLUSIG™ (as ponatinib hydrochloride) 15 milligram (mg) and 45 mg tablets for the following indication:

> "ICLUSIG is indicated for the 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 other tyrosine kinase inhibitor (TKI) therapy is not appropriate, including CML or Ph+ALL that is T315I mutation positive or where there is prior TKI resistance or intolerance.
>
> Marketing authorization with conditions is based on response rate. There are no trials demonstrating increased survival or improvement in symptoms with ICLUSIG. In the pivotal trial, the majority of the hematological responses occurred within 1 month. Consider discontinuing ICLUSIG if a hematological response has not been achieved by 3 months (90 days).
>
> **ICLUSIG for this indication has been issued marketing authorization with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the conditional nature of the authorization.**"

Health Canada has issued a marketing authorization with conditions under the NOC/c policy for ICLUSIG to reflect the promising nature of the clinical data of ICLUSIG in patients with these serious diseases and the need for further follow-up to verify the clinical benefit. ICLUSIG is of high quality and possesses an acceptable safety profile based on the benefit/risk assessment. As part of the conditions under Health Canada's NOC/c policy, ARIAD has undertaken to provide Health Canada with data from the confirmatory studies as follows:

1. Final clinical study report (CSR) for pivotal study AP24534-10-201 (PACE): A Pivotal Phase 2 Trial of Ponatinib in Patients with Refractory Chronic Myeloid Leukemia and Ph+ Acute Lymphoblastic Leukemia. A starting dose of 45 mg oral ponatinib was administered in this trial.

2. Final CSR for confirmatory study AP24534-14-203: A Randomized, Open-label, Phase 2 Trial of Ponatinib in Patients with Resistant Chronic Phase CML (CP-CML) to Characterize the Efficacy and Safety of a Range of Doses. Starting doses of 15 mg, 30 mg, and 45 mg will be administered to CP-CML patients with and without the T315I mutation. The trial will also include pharmacokinetic sampling to provide exposure-toxicity and exposure-response data to identify appropriate dose ranges for patients who progressed after 2 or more tyrosine kinase inhibitors, with no other options.

Controlled Distribution Program

In order to prescribe ICLUSIG, Health Care Professionals are required to become certified through the ICLUSIG Controlled Distribution Program by doing the following:

- Successfully complete the online Prescriber Training Program at http://www.iclusigcdp.ca/ (hard copies of the text may be requested by calling 1-855-552-7423) and
- Complete the ICLUSIG Prescriber Registration Form

Once a passing score has been achieved, you will receive an acknowledgement of certification and become eligible to prescribe ICLUSIG.

ICLUSIG is only available through pharmacies that agree to follow the ICLUSIG Controlled Distribution Program requirements.

More specific details about prescriber certification and the ICLUSIG Controlled Distribution Program can be found at http://www.iclusigcdp.ca/.

Indications and Clinical Use

ICLUSIG has been issued market authorization with conditions for the following indication:

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Action and Clinical Pharmacology

Ponatinib is a potent pan-BCR-ABL inhibitor with structural elements, including a carbon-carbon triple-bond that enables high affinity binding to native BCR-ABL and mutant forms of the ABL kinase. Ponatinib inhibits the in vitro tyrosine kinase activity of ABL and T315I mutant ABL with IC50s values of 0.4 and 2.0 nM, respectively.

Ponatinib inhibits the *in vitro* activity of additional kinases with IC50s between 0.1 and 20, including members of the VEGFR, PDGFR, FGFR, EPH receptors and SRC families of kinases, and KIT, RET, TIE2, and FLT3.

For further information on Action and Clinical Pharmacology, please refer to the ICLUSIG Product Monograph.

Contraindications

ICLUSIG is not to be used in patients

- who are hypersensitive to ponatinib or to any ingredients in the formulation or component of the container.

- who have unmanaged cardiovascular risk factors, including uncontrolled hypertension. Hypertension may contribute to the risk of arterial thrombotic events. Blood pressure should be monitored and managed to avoid hypertension.

- who are not adequately hydrated and with uncorrected high uric acid levels.

For further information on Contraindications, please refer to the ICLUSIG Product Monograph.

Serious Warnings and Precautions

ICLUSIG should only be prescribed and monitored by a physician who has completed the certification with the **ICLUSIG Controlled Distribution Program** and who is experienced in the use of antineoplastic therapy and in the treatment of CML or Ph+ ALL.

ICLUSIG is associated with serious risks including:

- Vascular Occlusion (arterial and venous thrombosis and occlusions), occurred in 24% (129/530) of ICLUSIG-treated patients with and without cardiovascular risk factors (including patients less than 50 years old). In clinical trials, serious treatment-emergent arterial thrombosis (cardiovascular, cerebrovascular, and peripheral vascular) and occlusions were seen in 14% of the ICLUSIG-treated patients including fatal myocardial infarction, fatal cerebral infarction, stroke, disseminated intravascular coagulation, and arterial stenosis sometimes requiring urgent revascularization procedures. Some of these events occurred within 2 weeks of starting treatment

with ICLUSIG. Monitor for evidence of thromboembolism and vascular occlusion. Interrupt or consider discontinuation in patients who develop arterial thrombotic events.

- Heart Failure (in some cases, fatal), including left ventricular dysfunction and ejection fraction decreases, occurred in 8% of ICLUSIG-treated patients, 5% of which were serious.

- Hemorrhage events (some fatal) including intracranial hemorrhage, hemorrhagic gastritis, (fatal), hemorrhagic cerebral infarction (fatal). Most hemorrhagic events, but not all, occurred in patients with grade 4 thrombocytopenia.

- Hepatotoxicity (including fatal acute hepatic failure) has been reported. Monitor hepatic function prior to and during treatment. Consider ICLUSIG dose interruption followed by dose reduction or discontinuation in patients with hepatotoxicity.

- Myelosuppression (thrombocytopenia, neutropenia, and anemia).

- Pancreatitis (7%) and elevations in amylase (2% grade 3 or greater) or lipase (12% grade 3 or greater) have been reported.

- ICLUSIG has not been studied in patients with renal impairment.

Adverse Reactions

The common hematologic and non-hematologic adverse reactions (≥ 10%) identified in a single-arm, open-label, international, multicenter trial in 449 CML and Ph+ALL patients who were resistant or intolerant to prior TKI therapy including those with a BCR-ABL T315I mutation were platelet count decreased (38%), rash (35%), dry skin (32%) and abdominal pain (23%), neutrophil count decreased (20%), headache (20%), lipase increased (19%), fatigue (18%), constipation (17%), myalgia (17%), arthralgia (16%), nausea (15%), anemia (14%), ALT increased (13%), hypertension (13%), AST increased (10%). At the time of primary analysis, 69% (310/449) of patients experienced a dose reduction of more than three days.

The most common adverse events (≥ 1%) that led to treatment discontinuation were platelet count decreased (5%) and neoplasm progression (3%). The most common adverse reactions (≥ 5%) that led to dose modification were platelet count decreased (29%), neutrophil count decreased (13%), lipase increased (11%), abdominal pain (9%), rash (8%), and pancreatitis (6%).

For further information on Adverse Reactions, please refer to the ICLUSIG Product Monograph.

Drug Interactions

Ponatinib is metabolized by esterases and/or amidases, and also by CYP3A4. Caution should be exercised and a reduction of the starting dose of ICLUSIG to 30 mg should be considered with concurrent use of ICLUSIG and strong CYP3A4 inhibitors (including food and herbal products containing strong CYP3A4 inhibitors).

Concomitant use of CYP3A inducers may decrease ponatinib serum concentrations. Co-administration of ICLUSIG with strong CYP3A inducers (such as carbamazepine, phenobarbital,

phenytoin, rifabutin, rifampicin, and St. John's Wort) should be avoided unless the benefit outweighs the possible risk of ICLUSIG underexposure.

ICLUSIG may be administered concurrently with proton pump inhibitors or other drugs that raise gastric pH without the need for adjustment of ICLUSIG dose or separation of administration.

In vitro, ponatinib is an inhibitor of P-gp and BCRP. Therefore, ponatinib may have the potential to increase plasma concentrations of co administered substrates of P-gp (for example, digoxin, dabigatran, colchicine, pravastatin) or BCRP (for example, methotrexate, rosuvastatin, sulfasalazine) and may increase their therapeutic effect and adverse reactions. Close clinical surveillance is recommended when ICLUSIG is administered with substrates of P-gp or BCRP.

For further information on Drug Interactions, please refer to the ICLUSIG Product Monograph.

Dosage and Administration

The recommended starting dose is 45 mg of ICLUSIG once daily. Consider reducing the dose of ICLUSIG from 45 mg once daily to 15 mg once daily for CP-CML patients who have achieved a MCyR. Consider discontinuing ICLUSIG if a hematological response has not been achieved by 3 months (90 days).

Before starting treatment with ICLUSIG, the cardiovascular status of the patient should be assessed and cardiovascular risk factors should be actively managed. An absolute distinction between patients at risk and patients not at risk of vascular occlusive events cannot be made. The optimal starting dose of ICLUSIG is not established. There are minimal data to support a 30 mg starting dose of ICLUSIG. Final data from a phase 2 randomized, dose-ranging study will help to clarify the optimal starting dose of ICLUSIG in adult patients with CML and Ph+ ALL.

Caution is recommended when administering ICLUSIG to patients with hepatic impairment. The recommended starting dose is 30 mg once daily in patients with hepatic impairment (Child-Pugh A, B, or C).

ICLUSIG may be administered with or without food.

For further information on Dosage and Administration, please refer to the ICLUSIG Product Monograph.

For any medical enquiries regarding ICLUSIG, please contact the ARIAD Pharmaceuticals, Inc. Medical Information Department at 1-855-552-7423.

Sincerely,

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ARIAD Pharmaceuticals, Inc.

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Canada Vigilance Program
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture
Address Locator: 0701C
Ottawa, Ontario
K1A 0K9

Telephone: 613-957-0337 or Fax: 613-957-0335
To report an Adverse Reaction, consumers and health professionals may call toll free:
Telephone: 1-866-234-2345
Fax: 1-866-678-6789
Email: CanadaVigilance@hc-sc.gc.ca

The Adverse Reaction Reporting Form and the Adverse Reaction Guidelines can be found on the Health Canada website (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) or in *The Canadian Compendium of Pharmaceuticals and Specialties* (http://www.pharmacists.ca/index.cfm/products-services/compendium-of-pharmaceuticals-and-specialties/).

For other inquiries related to this communication, please contact Health Canada at:
Bureau of Metabolism, Oncology and Reproductive Sciences (BMORS)
E-mail: bmors_enquiries@hc-sc.gc.ca
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