PDL NEW DRUG REVIEW

Proprietary Name: Iclusig®
Common Name: ponatinib
PDL Category: Tyrosine Kinase Inhibitor

Comparable Products	Preferred Drug List Status
Bosulif	Non-Recommended
Gleevec	Recommended
Sprycel	Non-Recommended

Summary

Indications and Usage: Treatment of adults with chronic phase (CP), accelerated phase (AP), or blast phase (BP) chronic myeloid leukemia (CML) that is resistant or intolerant to prior tyrosine kinase inhibitor therapy or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) that is resistant or intolerant to prior tyrosine kinase inhibitor therapy. There are no studies verifying an improvement in disease-related symptoms or increased survival with Iclusig®. This is a pregnancy category D medication. The safety and efficacy of use in children under the age of 18 have not been established.

Drug Interactions: Ponatinib is a substrate of CYP3A4/5, and to a lesser extent CYP2C8 and CYP2D6, based on *in vitro* studies. It also inhibits P-glycoprotein (P-gp).

It is recommended that the starting dose of Iclusig® be reduced to 30mg daily if being used concomitantly with strong inhibitors of CYP3A4 (eg ketoconazole, indinavir, telithromycin). Please refer to the PI for a more exhaustive list of CYP3A4 inhibitors. While not evaluated in clinical trials, it is recommended that the concomitant use of Iclusig® with strong CYP3A4 inducers be avoided unless the benefit outweighs the potential risks, as a reduction of ponatinib is likely. While also not evaluated in clinical trials, it is recommended that the concomitant use of Iclusig® be avoided with those drugs that elevate the gastric pH (eg PPIs, H2 blockers, or antacids), unless the benefit outweighs the potential risks, as an elevated gastric pH may decrease the bioavailability of Iclusig®. The concomitant use of Iclusig® with substrates of P-gp has not been evaluated.

Dosage Forms: Film-coated Tablets: 15mg, 45mg

Recommended Dosage: Take 45mg orally once daily, and continue treatment as long as there is no evidence of disease progression or unacceptable toxicity. It may be taken without regards to meals. Dose modifications are required in those with myelosuppression (neutropenia and thrombocytopenia). Furthermore, dose modifications are recommended for serious non-hematologic adverse reactions, including but not limited to hepatic toxicity, pancreatitis, and elevation of lipase. Please refer to the PI for specific details regarding dose modifications in these situations. Lastly, as discussed above, the recommended Iclusig® dose is 30mg daily if given concomitantly with a strong CYP3A3 inhibitor.

Iclusig® has not been studied in those with renal impairment, and thus it is not known if a dose reduction is needed in this population. While Iclusig® has not been studied in those with hepatic impairment, it is known that a major route of excretion is via hepatic elimination. Thus, it is recommended that Iclusig® not be used in those with moderate to severe hepatic impairment, unless the benefit outweighs the potential risks.

Common Adverse Drug Reactions: *There was no placebo data available in the PI. The included adverse reaction data included those occurring in >10% of patients with any grade of chronic-phase chronic myeloid leukemia (CP CML).* These adverse events reported included hypertension (68%), arterial ischemia (13%), cardiac failure (6%),

abdominal pain (49%), constipation (37%), nausea (23%), diarrhea (16%), vomiting (13%), oral mucositis (10%), upper respiratory tract infection (11%), headache (39%), peripheral neuropathy (13%), dizziness (11%), cough (12%), dyspnea (11%), rash and related conditions (54%), dry skin (39%), arthralgia (26%), myalgia (22%), pain in extremity (17%), back pain (15%), muscle spasms (12%), bone pain (12%), fatigue/asthenia (39%), pyrexia (23%), and peripheral edema (13%). Please refer to the prescribing information for additional reported adverse events.

24% of those on Iclusig® experienced congestive heart failure (CHF) or left ventricular dysfunction, and there were 4 reported deaths. It is therefore recommended that all be monitored for signs and symptoms that are consistent with CHF and be treated as clinically needed. Furthermore, Iclusig® treatment should be interrupted and in those who develop serious CHF Iclusig® should be discontinued.

Pancreatitis occurred in 6% (N=28/449) of those treated with Iclusig®. Of those cases, the pancreatitis resolved in 22 of them within 2 weeks with dose interruption or reduction. Therefore, it is recommended that serum lipase be checked every 2 weeks for the first 2 months and then monthly thereafter or as clinically indicated. It may be considered to perform additional serum lipase monitoring in those with a history of pancreatitis or alcohol abuse.

Severe myelosuppression (grade 3 or 4) occurred in 48% of those treated with Iclusig®; therefore, it is recommended that a complete blood count be obtained every 2 weeks for the first 3 months and then monthly or as clinically indicated. Adjust the dose as recommended per the prescribing information.

Contraindications: There are currently no contraindications listed in the PI.

Manufacturer: ARIAD Pharmaceuticals, Inc.

Analysis: Ponatinib, the active ingredient of Iclusig®, is a kinase inhibitor, with *in vitro* tyrosine kinase activity of ABL and T315I mutant ABL, as well as members of the VEGFR, PDGFR, FGFR, EPH receptors and SCR families of kinases, and KIT, RET, TIE2, and FLT3. Iclusig® does have a box warning regarding the risk of arterial thrombosis with use. Cardiovascular, cerebrovascular, and peripheral vascular thrombosis, including fatal MI/stroke, have been reported with use, occurring in about 8% of the population. It is recommended that Iclusig® therapy be interrupted and discontinuation be considered in those who develop arterial thrombotic events. Iclusig® carries a second box warning regarding the potential for hepatotoxicity with use. Hepatotoxicity, liver failure, and death have all been reported with Iclusig® use. Therefore, it is recommended that hepatic function be monitored prior to and during treatment, and to interrupt and then reduce or discontinue treatment if hepatoxicity occurs.

A multicenter, single-arm, open-label trial (N=449) was performed to assess the safety and efficacy for those with CML and Ph+ ALL who were intolerant or resistant on prior tyrosine kinase inhibitor (TKI) therapy. The primary outcome in those with CP-CML was major cytogenetic response (MCyR), which included complete and partial cytogenetic responses (CCyR and PCyR). The primary endpoint in those with AP-CML, BP-CML, and Ph+ ALL was major hematologic response (MaHR), defined as either a complete hematologic response (CHR) or no evidence of leukemia (NEL). Results suggest that the overall MCyR rate with CP CML was 54% and the overall CCyR rate was 44%. The MaHR/CHR rates for the AP-CML, BP-CML, and Ph+ ALL cohorts were 52%/47%, 31%/21%, and 41%/34%, respectively.

It is recommended that Iclusig® be added to the Recommended Drug List as a non-recommended drug, as it is not intended as a first-line treatment option.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended**

References

[1] Iclusig® [package insert]. Cambridge, MA: ARIAD Pharmaceuticals, Inc; 2012.