Ponatinib (Iclusig)

National Drug Monograph

October 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action	Ponatinib is a third-generation tyrosine kinase inhibitor specifically designed to avoid steric hindrance caused by the isoleucine residue at position 315 of the T315I mutation. In addition, ponatinib has activity against other BCR-ABL mutant forms.
Indication(s) Under Review	Treatment of adult patients with T315I-positive chronic myeloid leukemia (chronic, accelerated or blast phase) or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL). Treatment of adult patients with chronic (CP-CML), accelerated (AP-CML), blast phase (BP-CML) chronic myelogenous leukemia or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated. These indications are based upon response rate. There are no trials verifying an improvement in disease-related symptoms or increased survival with ponatinib.
Dosage Form(s) Under Review	Tablets: 15mg, 45 mg
REMS	☒ REMS ☐ No REMS *See Other Considerations for additional REMS information*
Pregnancy Rating	Category D

Executive Summary

Efficacy

- Ponatinib is the only tyrosine kinase inhibitor with activity against the T315I mutation.
- Evidence of efficacy was reported in the Ponatinib Ph-positive ALL and CML Evaluation (PACE), a phase 2 trial in heavily pretreated patients in all phases of CML as well as Ph+ ALL.
- Major Cytogenetic Responses (MCyR) were noted in CP-CML with resistance/intolerance to dasatinib and nilotinib as well as those with the T315I mutation.
- Major Hematologic Responses (MaHR) were achieved by those with AP-, BP-CML and ALL.

Safety

- Ponatinib marketing was voluntarily suspended soon after FDA-approval due to life-threatening blood clots and severe narrowing of blood vessels among treated patients in the phase 1 and 2 trials. Some of these events occurred within 2 weeks of therapy initiation. Marketing of ponatinib resumed once new safety measures were in place. These measures included a revised indication, changes to dosing recommendations, REMS and safety-related label changes.
- Boxed warnings highlight risk of vascular occlusion, heart failure and hepatotoxicity
- REMS program includes provider and patient education
- Optimal ponatinib dose has not been identified and may likely require need for dosage adjustments
- FDA labeling recommends discontinuation of therapy is response has not occurred within first 90 days.

Other Considerations

Effect Size	CP: MCyR 56%; 91% (51% R/I; 70% T315I+); MCyR 91% [95% CI, 85-95] ≥ 12 mos; OS 94% at 12 mos AP: MaHR 55%; 48% [95% CI, 32-63] ≥ 12 mos; OS 84% at 12 mos BP: MaHR 31%; 42% [95% CI, 19-63] ≥ 12 mos; OS 29% at 12 mos ALL: MaHR 41%; 8% [95% CI, 0.5-29] ≥ 12 mos; OS 40% at 12 mos

	Potential Harms (Grades 3, 4)	CP: HTN (39%), thrombocytopenia (36%), neutropenia (24%) AP, BP: HTN (26-36%), thrombocytopenia (47-57%), neutropenia (51-55%), lymphopenia (26-37%), anemia (26-55%) ALL: HTN (31%), febrile neutropenia (25%), sepsis (22%), thrombocytopenia (47%), neutropenia (63%), anemia (34%), lymphopenia (22%)
	Net Clinical Benefit	Moderate (high benefit with high risk of harm)
Potential Impact	• Ponatinib is the only TKI with activity against the T315I mutation. • Current evidence also supports consideration of use in patients who have not responded to two or more TKIs. • Education of safety profile is important for providers and patients; cautious patient selection with diligent monitoring is necessary for safe use • Oral formulation taken once daily allows for convenience, but frequent monitoring and close follow-up during therapy may prove to be inconvenient for some patients.	

Background

Purpose for review

FDA Drug Approval 2012

Issues to be determined:
Does ponatinib offer advantages to currently available alternatives?
What safety issues need to be considered?

Other therapeutic options

CML chronic myelogenous leukemia; Ph+ Philadelphia chromosome positive
CP chronic phase
AP accelerated phase
BC blast crisis
W/P warnings/precautions
BMS bone marrow suppression
R/I resistance/intolerance

(1) Treatment of adult patients with T315I-positive chronic myeloid leukemia (chronic, accelerated or blast phase) or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).

(2) Treatment of adult patients with chronic (CP-CML), accelerated (AP-CML), blast phase (BP-CML) chronic myelogenous leukemia or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated.

Formulary Alternatives	Other Considerations
None	

Non-formulary Alternative	Other Considerations
Omacetaxine	SubQ injectable given twice daily; Effective against T315I mutation; approved in CP or AP CML with R/I to ≥ 2 TKIs W/P: BMS, hemorrhage, hyperglycemia

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to June 2015) using the search terms ponatinib and Iclusig. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy

A. Response Definitions

Table 2. Ponatinib Response Criteria

Response by Disease	Definitions
CP-CML	**Complete Hematologic Response (CHR)** • WBC < 10 x 10^9 /L • Basophils < 5% • No immature cells such as myelocytes, promyelocytes, myeloblasts in the differential • Platelet count < 450 x 10^9 /L • Spleen non-palpable
AP-CML, BP-CML, Ph+ ALL	**Major hematologic response (MaHR)** defined as either: **Complete Hematologic Response (CHR)** • WBC ≤ ULN • ANC ≥ 1000/mm^3 • Platelets ≥ 100,000/mm^3 • No blasts or promyelocytes on peripheral blood • Marrow blasts ≤ 5% • < 5% myelocytes + metamyelocytes in peripheral blood • Basophils < 5% in peripheral blood • No extramedullary involvement (no hepatomegaly or splenomegaly) **No Evidence of Leukemia (NEL)** • WBC ≤ ULN • No blasts or promyelocytes on peripheral blood • Marrow blasts ≤ 5% • < 5% myelocytes + metamyelocytes in peripheral blood • Basophils < 5% in peripheral blood • No extramedullary involvement (no hepatomegaly or splenomegaly) • At least one of the following: -Platelets 20-100,000/mm^3 -ANC 500-1000/mm^3
All phases CML, Ph+ALL	**Cytogenetic** Major (MCyR): 0-35% Ph+ metaphases (complete + partial) Complete (CCyR): No Ph+ metaphases Partial: 1-35% Ph+ metaphases
CP-CML, AP-CML	**Major Molecular Response (MMR)** ≤ 0.1% BCR-ABL transcripts on the International Scale (IS) **Molecular Response 4 (MR^4)** Either detectable transcripts ≤0.01% $BCR\text{-}ABL^{IS}$ or undetectable BCR-ABL transcripts in cDNA with ≥ 10,000 ABL transcripts, in peripheral blood as measured by reverse transcription quantitative polymerase chain reaction (RT-qPCR) **Molecular Response 4.5 ($MR^{4.5}$)** Either detectable transcripts ≤ 0.0032% $BCR\text{-}ABL^{IS}$ or undetectable BCR-ABL transcripts in cDNA with ≥ 32,000 ABL transcripts, in peripheral blood as measured by RT-qPCR

B. Summary of Evidence

Trial/design	Inclusion/Exclusion/Demo	Intervention	Results
Cortes, 2013 (PACE) P2, OL, multicenter trial 66 sites N=449 (safety pop'n) N=444 (efficacy pop'n) Key: DAS dasatinib NIL nilotinib PON ponatinib R resistance I intolerance	Inclusion Ph+ CML or Ph+ ALL with resistance to DAS or NIL, unacceptable toxicity from DAS or NIL, or T315I mutation after any TKI therapy; ECOG PS 0-2 Median age 53-62 yrs 37% rec'd 2 prior TKI 55% rec'd ≥ 3 prior TKI 23% cytarabine 34% interferon	PON 45 mg PO daily Six cohorts: 1. CP-CML + R/I (N=203) 2. CP-CML + T315I (N=64) 3. AP-CML + R/I (N=65) 4. AP-CML + T315I (N=18) 5. BP-CML or ALL + R/I (N=48) 6. BP-CML or ALL + T315I (N=46) Assessments CP-CML q 3 months AP, BP-CML, ALL q 28-days x 2, then q 2 months	Primary endpoints: CP-CML: MCyR within 12 months AP-CML: MaHR within 6 months BP-CML: MaHR within 6 months ALL: MaHR within 6 months CP-CML: MCyR 56% (51% R/I; 70% T315I) Time to MCyR 2.8 mos (CCyR 46%;MMR 34%) 91% sustained response x12 mos AP-CML: MaHR 55% (57% R/I; 50% T315I) Time to MaHR 3 weeks MCyR 39% (24% CCyR; 16% MMR) 48% sustained response x 12 mos BP-CML: MaHR 31% (32% R/I; 29% T315I) Time to MaHR 4 weeks MCyR 23% (CCyR 18%) Ph+ ALL: MaHR 41% (50% R/I; 36% T315I) Time to MHR 3 weeks MCyR 47% (CCyR 38%) Median duration PON: 12.8 mos Median RDI: 0.84 Dose-reductions in 55% Median time to reduction: 2.3 mos

- FDA-approval was granted based upon results of the Ponatinib in Ph-positive Acute Lymphocytic Leukemia and Chronic Myelogenous Leukemia Evaluation (PACE) trial. PACE was an open-label, multinational, phase 2 trial of heavily pretreated patients with CML or Ph+ ALL and with either resistance and/or intolerance to dasatinib or nilotinib or harbor the T315I nutation after prior TKI therapy.
- Among those with CP-CML (n=267), MCyR, the primary endpoint, was achieved by 56% overall and 91% maintained this response for ≥ 12 months; MCyR was achieved in 51% of the resistance/intolerance group and 70% of the T315I mutation group.
- Among the CP-CML population, a pre-specified subgroup analysis noted that those who received fewer prior TKIs, were younger, and had a shorter span of time between diagnosis and study enrollment, appeared to experience higher response rates. Similar findings were noted among the AP-CML population, those who received less prior TKI therapy tended to have higher response rates.
- MaHR was the primary endpoint in the advanced phase groups: 55% achieved MaHR in AP-CML; 31% achieved MaHR in BP-CML and 41% achieved MaHR in Ph+ALL.
- Overall, the median duration of ponatinib therapy was ~ 13 months.

Potential Off-Label Use

Research with ponatinib is ongoing in the following areas:

- Hyper-CVAD and Ponatinib in Ph-Positive and/or BCR-ABL Positive Acute Lymphoblastic Leukemia (ALL)
- Bevacizumab-Refractory Glioblastoma
- Advanced NSCLC w/ RET Translocations
- Front-line treatment of Ph+ ALL; metastatic gastrointestinal stromal tumor (GIST)
- Advanced medullary thyroid cancer
- FGFR mutation positive solid tumors (i.e. endometrial carcinoma)

Safety

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	• Risk of vascular occlusion: Arterial and venous thrombosis and occlusions have occurred in at least 27% of ponatinib-treated patients, including fatal myocardial infarction, stroke, stenosis 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 less than 50 years old, experienced these events. Monitor for evidence of thromboembolism and vascular occlusion. Interrupt or stop ponatinib immediately for vascular occlusion. • Risk of heart failure: Heart failure, including fatalities, occurred in 8% of ponatinib-treated patients. Monitor cardiac function. Interrupt or stop ponatinib for new or worsening heart failure. • Risk of Hepatotoxicity: Hepatotoxicity, liver failure and death have occurred in ponatinib-treated patients. Monitor hepatic function. Interrupt ponatinib if hepatotoxicity is suspected.
Contraindications	• None
Warnings/Precautions	• Vascular Occlusion. Arterial and venous thrombosis and occlusions and the need for urgent revascularization procedures have occurred in at least 27% of patients treated from the phase 1 and 2 trials. These events can occur within 2 weeks of initiating ponatinib treatment. Recurrent or multi-site vascular occlusion has also been reported. In the phase 1 trial, 48% (31/65) patients with CML or Ph+ ALL developed occlusive events. Median time to onset of first event was 5 months. These events can occur at doses as low as 15 mg daily. Events were noted regardless of pre-existing cardiovascular risk factors. The incidence of events increased with age and prior history of ischemia, HTN, diabetes or hyperlipidemia. • Arterial occlusion and thrombosis occurred in $\geq$ 20% (91/449) patients; some experienced more than one event. Revascularization procedures were necessary in some cases. • Cardiac vascular occlusion (including fatal and life-threatening MI and coronary artery occlusion has occurred in 12% (55/449). Heart failure has developed concurrent or subsequent to the MI events. • Cerebrovascular occlusion, including fatal stroke, is reported in 6% (27/449). Ponatinib can cause stenosis of multiple segments in major arterial vessels supplying the brain. • Peripheral arterial occlusive events (including fatal mesenteric artery occlusion and life-threatening peripheral arterial disease) have occurred in 8% (36/449) patients. Digital or distal extremity necrosis requiring amputations has occurred. • Venous thromboembolic events has been reported in 5% (23/449)

patients and includes DVT (n=8), PE (n=6), superficial thrombophlebitis (n=3) and retinal vein thrombosis (n=2). Consider dose modification or discontinuation of ponatinib in patients who develop serious VTE.

- Benefits vs. risks of ponatinib should be considered for each patient. If an arterial thrombotic event is suspected, interrupt or stop ponatinib therapy. Again, address risk vs. benefit upon considering to restart therapy.

Incidence of Vascular Occlusion in Phase 2 Trial per Risk Categories

	Prior CV history	No CV history
Age < 49 yrs	18% (6/33)	12% (13/112)
Age 50-74 yrs	33% (50/152)	18% (20/114)
Age ≥ 75 yrs	56% (14/25)	46% (6/13)
All ages	33% (70/210)	16% (39/239)
Total	24% (109/449)	

- Heart Failure. Fatal and serious heart failure or left ventricular dysfunction occurred in 5% (n=22) of treated patients. Monitor patients for signs/symptoms of heart failure & treat as clinically indicated; interrupt ponatinib therapy. Consider discontinuation of ponatinib in situations of serious heart failure.
- Hepatotoxicity. Fulminant hepatic failure leading to death occurred in one patient within the first week of starting treatment. Other fatal cases of acute liver failure occurred in patients with blast phase CML or Ph+ ALL. Severe hepatotoxicity was noted in all disease cohorts. AST or ALT elevation was noted in 56% (all grades) and 8% (grades 3, 4). Reversal of AST or ALT elevations were not noted by date of last follow-up in 5% of patients. Monitor liver function tests at baseline, then at least monthly or as clinically indicated. Interrupt, dose-reduce or discontinue ponatinib as clinically indicated.
- Hypertension. Treatment-emergent HTN was noted in 67% (300/449) of patients. Eight patients (2%) experienced treatment-emergent symptomatic HTN as a serious adverse reaction and included hypertensive crisis.

  Baseline BP < 140/90 → 78% (220/282) had treatment-emergent HTN;
  49% (139/282) developed Stage 1 HTN;
  29% developed Stage 2 HTN
  Baseline Stage 1 HTN (n=131) → 61% (80/131) developed Stage 2 HTN

  Monitor and manage blood pressure elevations and treat HTN to normalize. Interrupt, dose-reduce or stop ponatinib if HTN is not medically controlled.
- Pancreatitis. Clinical pancreatitis occurred in 6% (28/449) patients; 5% experienced grade 3 severity. Treatment discontinuation or interruption was noted in 6% of patients (25/449). The majority of cases resolved within 2 weeks of dose interruption or reduction. Treatment-emergent lipase elevation was noted in 41%. Check serum lipase every 2 weeks for the first 2 months, then monthly thereafter or as clinically indicated. Consider additional monitoring in patients with a history of pancreatitis or alcohol abuse. If lipase elevations are accompanied by abdominal symptoms, interrupt ponatinib therapy and evaluate for pancreatitis. Do not restart

ponatinib until complete resolution of symptoms and lipase levels are less than 1.5 x ULN.

- Neuropathy. Peripheral and cranial neuropathy has been reported. Peripheral neuropathy of any grade was noted in 13% (59/449) of ponatinib-treated patients (grade 3, 4 toxicity in 2%). Most common neuropathies reported were peripheral neuropathy (4%), paresthesia (4%), hypoesthesia (2%), hyperesthesia (1%). Cranial neuropathy developed in 1% (6/449) of patients. The onset of neuropathy occurred during the first month of treatment. Monitor patients for symptoms of neuropathy or weakness. Consider interrupting ponatinib therapy and evaluate if neuropathy is suspected.
- Ocular toxicity. Retinal toxicities including macular edema, retinal vein occlusion and retinal hemorrhage occurred in 3% of treated patients. Conjunctival or corneal irritation, dry eye or eye pain occurred in 13% of patients; visual blurring in 6%. Other toxicities include cataracts, glaucoma, iritis, iridocyclitis and ulcerative keratitis. Conduct comprehensive eye exams at baseline and periodically during treatment.
- Hemorrhage. Hemorrhage is reported in 25% of patients treated with ponatinib, with serious events (including fatalities) occurring in 5%. Severe events occurred with greater frequency among the AP-CML, BP-CML and Ph+ ALL patients. The most common reported bleeding events included cerebral hemorrhage and gastrointestinal hemorrhage. Most events occurred with grade 4 thrombocytopenia. Interrupt ponatinib therapy for serious or severe hemorrhage and evaluate.
- Fluid Retention. Fluid retention was reported in 23% of ponatinib-treated patients. Most common events included peripheral edema (16%), pleural effusion (7%) and pericardial effusion (3%). Serious events were reported in 3% (13/449) and included brain edema (1 fatality), pericardial effusion, pleural effusion and ascites. Monitor patients for fluid retention and manage patients as clinically indicated. Interrupt, reduce or discontinue ponatinib as indicated.
- Cardiac Arrhythmias. Ponatinib has been associated with bradycardia (1%) and supraventricular tachyarrhythmias (5%). Inform patients of the signs and symptoms of slow heart rate (fainting, dizziness or chest pain) and fast heart rate (palpitations, dizziness). Interrupt ponatinib therapy and evaluate.
- Myelosuppression. Bone marrow suppression (grade 3, 4) is reported in 48% of treated patients, with greater severity in AP-CML, BP-CML and Ph+ ALL. Obtain complete blood counts every 2 weeks for the first 3 months and then monthly or as clinically indicated; adjust dose as recommended.
- Tumor Lysis Syndrome. Hyperuricemia occurred in 7% of patients; < 1% developed serious tumor lysis syndrome. As the potential is greater in advanced disease, ensure adequate hydration and treat high uric acid levels prior to starting therapy with ponatinib.
- Compromised Wound Healing and Gastrointestinal Perforation. Based upon the mechanism of action, ponatinib could compromise wound healing. Interrupt therapy for at least 1 week prior to major surgery. Post-surgery, resume ponatinib when adequate wound healing has occurred.
- Embryo-Fetal Toxicity. Based upon animal studies and mechanism of action, fetal harm can be expected to result if given to a pregnant woman. Advise patients to avoid pregnancy while taking ponatinib

	due to the risk to the fetus and inform them of this risk if they become pregnant while taking the drug.

Safety Considerations

- In October 2013, the FDA requested the suspension and marketing of ponatinib due to life-threatening blood clots and severe narrowing of blood vessels among treated patients. Since the drug was approved in December 2012, approximately 24% of patients in the phase 2 trial (median treatment duration 1.3 years) and 48% of patients from the phase 1 trial (median treatment duration 2.7 years) experienced serious and fatal vascular events. Some of these events occurring within 2 weeks of therapy initiation. At the end of December 2013, the FDA announced that marketing of ponatinib will be allowed to resume once new safety measures are in place. These measures included a revised indication, changes to dosing recommendations, REMS and safety-related label changes.
- Patient selection, diligent monitoring and education of potential adverse reactions are essential for safe use of this drug. The incidence of vascular occlusion was increased in patients with prior history of cardiovascular risk factors, yet those without prior risk factors are still at risk.
- The FDA has limited approved indications and recommends that drug be discontinued if response has not occurred by 3 months (90 days).
- Independent of the thrombocytopenia caused by ponatinib, there is suggestion that it may cause platelet dysfunction as a result of inhibition of several kinases (SFK, LYN, FYN) that are involved in platelet activation. Support of this finding is evidenced by prolonged closure time with PFA 100 in 5 patients with CML. Others report their experiences with use of ponatinib in patients with a bleeding history or on anticoagulation and/or antiplatelet therapies as positive, with no bleeding episodes, suggesting that ponatinib can be safely used in such patients.

Adverse Reactions

Common adverse reactions	Incidence $\geq$ 20%: hypertension, rash, abdominal pain, fatigue, headache, dry skin, constipation, arthralgia, nausea, pyrexia Dose modifications due to adverse reactions in 74%; Common reasons to modify: thrombocytopenia 30%; neutropenia 13%, increased lipase 12%, rash 11%, abdominal pain 11%, pancreatitis 6%, ↑ LFTs 6%
Death/Serious adverse reactions	Myelosuppression was a common event in all patient populations with a higher frequency of grade 3 or 4 events in patients with AP-CML, BP-CML and Ph+ ALL. Grade 3 or 4 reactions occurring in $\geq$ 10%: hypertension (31-39%), arterial ischemia (0-11%), abdominal pain (6-10%), febrile neutropenia (<1-25%), sepsis (1-22%). Serious adverse reactions reported include the following: overall arterial ischemic events (11.8%), cardiovascular arterial ischemic events (6.2%), cerebrovascular events (4%), peripheral vascular (3.6%), hemorrhage (4.9%) includes CNS and GI bleeding, cardiac failure (4.9%), pancreatitis (5.1%), pneumonia (5.3%)
Discontinuations due to adverse reactions	CP-CML 13%, AP-CML 11%, BP-CML 15%, Ph+ ALL 9% Most common reasons to discontinue: thrombocytopenia 4% and infection 1%

Drug Interactions

Drug-Drug Interactions

- Recommended starting dose of ponatinib should be reduced to 30 mg once daily when co-administering with a strong CYP3A4 inhibitor (e.g. boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, etc.).
- Co-administration of ponatinib with strong CYP3A4 inducers (e.g. carbamazepine, phenytoin, rifampin, St. John's Wort) should be avoided as decreased ponatinib exposure may result.
- Co-administration with gastric pH-elevating medications does not significantly impact exposure to ponatinib.
- Ponatinib may effect drugs that are substrates of the P-gp or ABCG2 transporter systems. Refer to Prescribing Information for more detail.

Drug-food Interactions

- Recommended starting dose of ponatinib should be reduced to 30 mg once daily when co-administering with a strong CYP3A4 inhibitor (e.g. grapefruit juice).

Risk Evaluation

As of July 2015:

	Comments
Sentinel event advisories	• Sources: ISMP, FDA, TJC • ISMP Quarterly Action Agenda (April – June 2013) Notes name confusion with new cancer drugs PAZOPanib (VOTRIENT) and PONATinib (ICLUSIG), suggests tall man lettering to differentiate.
Look-alike/sound-alike error potentials	• LA/SA for Iclusig: • LA/SA for Ponatinib: pazopanib • Sources: As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List).

Other Considerations

- Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterized by the Philadelphia chromosome (Ph), a translocation between chromosomes 9 and 22 that result in the production of the BCR-ABL fusion oncoprotein. This product, BCR-ABL, is a constitutively active tyrosine kinase. CML accounts for 10% of adult leukemias. The median age of onset is 64 years. An estimated 5980 new diagnoses and 810 deaths from CML were reported in the U.S. in 2014. Estimated number of unique patients within the VA with the diagnosis of CML ~ 4500.
- Response rates are high in the early stages of disease, also known as Chronic Phase (CP). Overall survival in the CP of CML ranges from 6-9 years. Patients in CP are at risk for progression into the advanced phases, also known as Accelerated Phase (AP) and Blast Phase (BP), which are more difficult to control and portend a poor survival rate.
- An estimated 25% of patients have disease that does not initially respond to front-line treatment with imatinib, or responds initially, then progresses. Secondary resistance is thought to be caused by the T315I mutation.
- The T315I mutation of BCR-ABL is present in up to 20% of patients with TKI-resistant disease; the presence of this mutation confers resistance to all other FDA-approved BCR-ABL tyrosine kinase inhibitors, except ponatinib.
- Ponatinib has activity in patients with the following BCR-ABL1 kinase domain mutations: E255K/V, F317L, F359V, G250E, M351T, T315I, V299L and Y253H. Mutations F317L and T315I are resistant to dasatinib; mutations Y253H, E255K/V, F359C/I/V and T315I are resistant to nilotinib; mutations V299L and T315I are resistant to bosutinib.
- In addition, ponatinib is a multikinase inhibitor and possesses activity against other tyrosine kinases such as KIT, PDFGRA, FGFR1 and FLT3.
- FDA granted accelerated approval to ponatinib in December 2012. In October 2013 the FDA requested the suspension and marketing of ponatinib due to life-threatening blood clots and severe narrowing of blood vessels among treated patients. At the end of December, 2013, the FDA announced that marketing of ponatinib will be allowed to resume once new safety measures are in place. These measures included a revised indication, changes to dosing recommendations, REMS and safety-related label changes.
- REMS includes provider education and a Medication Guide for patients.
- Ponatinib is available exclusively from Biologics Specialty Pharmacy. The Iclusig Prescription and Referral Form for VA must be completed and faxed to Biologics. They will provide the prescription to the end-user or VA pharmacy, depending on instructions provided.

Outcome in clinically significant area	CP: MCyR within 12 mos (R/I; T315I+) AP, BP, ALL: MaHR within 6 mos (R/I; T315I+) BP: MaHR 31% within 6 mos (R/I; T315I+) ALL: MaHR 41% within 6 mos (R/I; T315I+)
Effect Size	CP: MCyR 56% (51%; 70%); MCyR 91% [95% CI, 85-95] ≥ 12 mos; OS 94% at 12 mos AP: MaHR (57%; 50%); 48% [95% CI, 32-63] ≥ 12 mos; OS 84% at 12 mos BP: MaHR (32%; 29%); 42% [95% CI, 19-63] ≥ 12 mos; OS 29% at 12 mos ALL: MaHR (50%; 36%); 8% [95% CI, 0.5-29] ≥ 12 mos; OS 40% at 12 mos
Potential Harms (Grades 3, 4)	CP: HTN (39%), thrombocytopenia (36%), neutropenia (24%) AP, BP: HTN (26-36%), thrombocytopenia (47-57%), neutropenia (51-55%), lymphopenia (26-37%), anemia (26-55%) ALL: HTN (31%), febrile neutropenia (25%), sepsis (22%), thrombocytopenia (47%), neutropenia (63%), anemia (34%), lymphopenia (22%)
Net Clinical Benefit	Moderate (high benefit with high risk of harm)

Definitions

Outcome in clinically significant area: morbidity, mortality, symptom relief, emotional/physical functioning, or health-related quality of life

Effect Size: odds ratio, relative risk, NNT, absolute risk reduction, relative risk reduction, difference in size of outcomes between groups, hazard ratio

Potential Harms: Low risk (Grade 3 or 4 toxicity in <20%) versus High risk (Grade 3 or 4 toxicity in ≥20%)

Net Clinical Benefit: Substantial (high benefit with low risk of harm), moderate (high benefit with high risk of harm), minimal (low benefit with low risk of harm), negative (low benefit with high risk of harm)

Dosing and Administration

- The optimal dose of ponatinib has not been identified. In clinical trials, the starting dose was 45 mg administered orally once daily. However, 59% of patients required dose reductions to 30 mg or 15 mg once daily during the course of therapy.
- Start dosing with 45 mg once daily. Consider reducing the dose of ponatinib for chronic phase CML and accelerated phase CML patients who have achieved a major cytogenetic response. Additional studies are needed to determine if lower doses of ponatinib improve the safety profile without compromising efficacy.
- Some clinicians recommend that patients also receive aspirin while receiving ponatinib, although there is no prospective data that supports this practice.
- Consider discontinuing ponatinib if response has not occurred by 3 months (90 days).
- Ponatinib may be taken with or without food. Tablets should be swallowed whole.
- Refer to the prescribing information for dose modifications for myelosuppression, non-hematologic adverse reactions, concomitant therapy with strong CYP3A inhibitors or patients with hepatic impairment.

Special Populations (Adults)

	Comments
Elderly	• 35% (155/449) of clinical trial patients were ≥ 65 years • CP-CMP patients aged ≥ 65 years had a lower major cytogenetic response rate (38%) compared to < 65 years (64%) • AP-CML, BP-CML and Ph+ ALL patients aged ≥ 65 years had higher major hematologic response rate (47%) compared to < 65 years (40%) • 46% of patients ≥ 65 years had vascular occlusion events • Age ≥ 65 years associated with more adverse reactions therefore dose selection should be cautious, reflecting greater frequency of reduced hepatic, renal or cardiac function and concomitant diseases or other drug therapies
Pregnancy	• Category D. Based upon animal studies, ponatinib can cause fetal harm when given to a pregnant woman. Advise women to avoid becoming pregnant while taking ponatinib. If used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise patient of the potential hazard to a fetus.
Lactation	• It is likely that ponatinib is excreted in human milk, therefore a decision to discontinue nursing or discontinue therapy should be made, taking into account the importance of drug to the mother.
Renal Impairment	• No data identified
Hepatic Impairment	• The recommended starting dose is 30 mg once daily in patients with hepatic impairment (Child-Pugh A, B or C). • Increased risk of adverse reactions noted in patients with hepatic impairment
Pharmacogenetics/genomics	• No data identified

Projected Place in Therapy

- Approved indications have been limited due to safety profile. FDA-approved uses include: patients with evidence of T315I mutation and treatment of patients in CP, AP, BP-CML or Ph+ ALL for whom no other TKI is indicated.
- NCCN Guidelines, Version 1.2015, give ponatinib a Category 2A recommendation for those patients with the T315I mutation or patients who have not responded to 2 or more TKIs.
- European LeukemiaNet (ELN) recommendations for management of CML
  First-line: imatinib, nilotinib or dasatinib
  Second-line: This line of therapy is guided by patient characteristics (age, comorbidities), adverse effects from prior TKI, BCR-ABL1 point mutations, drug availability, cost and provider experience.
  Imatinib → dasatinib, nilotinib, bosutinib or ponatinib
  Nilotinib → dasatinib, bosutinib, ponatinib
  Dasatinib → nilotinib, bosutinib, ponatinib

References

Iclusig (ponatinib) Prescribing Information. Cambridge, MA: ARIAD Pharmaceuticals, Inc. September, 2014.

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Appendix 1: Approval Endpoints

Table 1. A Comparison of Important Cancer Approval Endpoints

Endpoint	Regulatory Evidence	Study Design	Advantages	Disadvantages
Overall Survival	Clinical benefit for regular approval	• Randomized studies essential • Blinding not essential	• Universally accepted direct measure of benefit • Easily measured • Precisely measured	• May involve larger studies • May be affected by crossover therapy and sequential therapy • Includes noncancer deaths
Symptom Endpoints (patient-reported outcomes)	Clinical benefit for regular approval	• Randomized blinded studies	• Patient perspective of direct clinical benefit	• Blinding is often difficult • Data are frequently missing or incomplete • Clinical significance of small changes is unknown • Multiple analyses • Lack of validated instruments
Disease-Free Survival	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias, particularly in open-label studies • Definitions vary among studies
Objective Response Rate	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Assessed earlier and in smaller studies compared with survival studies • Effect attributable to drug, not natural history	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Only a subset of patients with benefit
Complete Response	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Durable complete responses can represent clinical benefit • Assessed earlier and in smaller studies compared with survival studies	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Small subset of patients with benefit
Progression- Free Survival (includes all deaths) or Time to Progression (deaths before progression censored)	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies • Measurement of stable disease included • Not affected by crossover or subsequent therapies • Generally based on objective and quantitative assessment	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias particularly in open-label studies • Definitions vary among studies • Frequent radiological or other assessments • Involves balanced timing of assessments among treatment arms

*Adequacy as a surrogate endpoint for accelerated approval or regular approval is highly dependent upon other factors such as effect size, effect duration, and benefits of other available therapy. See text for details.

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