PONATINIB

Generic	Brand	HICL	GCN	Exception/Other
PONATINIB HCL	ICLUSIG	39859		

This drug requires a written request for prior authorization.

GUIDELINES FOR USE

1. Does the patient have a diagnosis of T315I-positive chronic myeloid leukemia (CML), or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL)?

   If yes, **approve for 12 fills by GPID as requested with the following quantity limits:**
   - **45mg: #30 tablets per 30 days;**
   - **15mg: #60 tablets per 30 days.**

   APPROVAL TEXT: Please note that this drug has an important FDA safety warning. For more information, please ask your doctor or pharmacist.
   If no, continue to #2.

2. Does the patient have a diagnosis of chronic myeloid leukemia (CML), or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL)?

   If yes, continue to #3.
   If no, do not approve.
   DENIAL TEXT: See the denial text at the end of the guideline.

3. Has the patient previously tried or does the patient have a contraindication to Gleevec, Sprycel, Tasigna, or Bosulif?

   If yes, **approve for 12 fills by GPID as requested with the following quantity limits:**
   - **45mg: #30 tablets per 30 days;**
   - **15mg: #60 tablets per 30 days.**

   APPROVAL TEXT: Please note that this drug has an important FDA safety warning. For more information, please ask your doctor or pharmacist.
   If no, do not approve.
   DENIAL TEXT: See the denial text at the end of the guideline.

DENIAL TEXT: Approval requires that one of the following conditions are met: 1) a diagnosis of T315I-positive chronic myeloid leukemia (CML), or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL); or 2) a diagnosis of chronic myeloid leukemia (CML), or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) with a previous trial of Gleevec, Sprycel, Tasigna, or Bosulif, which may also require prior authorization.

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PONATINIB

RATIONALE

Ensure appropriate utilization of ponatinib based on FDA approved indication and dosage. The recommended dosage is 45mg once daily with or without food. Tablets should be swallowed whole. Continue treatment as long as the patient does not show evidence of disease progression or unacceptable toxicity. Dose modifications to 30mg and then 15mg daily are recommended for neutropenia and thrombocytopenia unrelated to leukemia; hepatic toxicity; or pancreatitis and lipase elevation. The recommended dose should be reduced to 30 mg once daily when administering Iclusig with strong CYP3A inhibitors.

Iclusig (ponatinib) is the fifth tyrosine kinase inhibitor (TKI) approved for the treatment of CML. It blocks the activity of ABL (including the T315I mutation) to treat CML and Ph+ALL. Iclusig also inhibited the in vitro activity of additional kinases involved in the growth and development of cancer cells. These include members of the VEGFR, PDGFR, FGFR, EPH receptors, the SRC families of kinases, and KIT, RET, TIE2, and FLT3.

CML is a malignant clonal disorder that results in rapid growth of myeloid stem cells in the bone marrow. It is usually associated with a chromosomal abnormality that results from the fusion of the BCR and ABL1 genes, called the Philadelphia (Ph) chromosome. Normally, the ABL1 gene produces a protein with tyrosine kinase catalytic activity that is tightly regulated. The fused BCR-ABL1 gene in the Ph chromosome however, produces a protein with deregulated and constitutively active kinase activity that is fundamental to the pathogenesis of CML. The presence of the T315I “gatekeeper” mutation has been associated with resistance to currently approved TKIs including Gleevec, Sprycel, Tasigna, and Bosulif.

The mainstay of treatment in CML over the last decade has been inhibition of the enzymatic activity of those proteins, and thus the TKIs Gleevec, Sprycel, and Tasigna are designated as first line treatment of CML in the National Comprehensive Cancer Network clinical practice guidelines. NCCN recommends that Bosulif, another TKI, be considered as a second line treatment. It is currently being studied in the phase III open-label BELA trial versus Gleevec for patients with newly diagnosed CML. Synribo, a first-in-class cephalotaxine that inhibits protein synthesis independently of direct BCR-ABL1 binding, was also approved in 2012 for patients that fail, cannot tolerate, or are resistant to TKI therapy. NCCN recommends its use for patients who failed two or more TKIs or have a T315I mutation. EPIC is an ongoing randomized trial comparing Iclusig to Gleevec in patients with newly diagnosed CML. EPIC began in June 2012 and has an estimated study completion date of June 2021. Initially Iclusig will likely be used as a second line agent (similar to Bosulif) except for those patients with the T315I mutation where it may be considered as a first line therapy (similar to Synribo). Depending on the results of the EPIC trial, Iclusig may be considered a first line agent for all patients regardless of mutation type.

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PONATINIB

RATIONALE (CONTINUED)
The PACE trial (n=444) studied Iclusig in patients with CML and Ph+ALL whose disease was considered to be resistant or intolerant to prior tyrosine kinase inhibitor (TKI) therapy. This was a single-arm, open-label, international, multicenter trial. All patients were administered a starting dose of 45 mg of Iclusig once daily. Patients were assigned to one of six cohorts based on disease phase (chronic phase CML [CP-CML]; accelerated phase CML [AP-CML]; or blast phase CML [BP-CML]/Ph+ALL), resistance or intolerance (R/I) to prior TKI therapy, and the presence of the T315I mutation. All patients had previously been on at least one FDA approved or investigational TKI therapy: 7% had 1 TKI therapy, 37% had 2 TKI therapies, and 56% had 3 or more TKI therapies.

Resistance in CP-CML while on prior TKI therapy, was defined as failure to achieve either a complete hematologic response (by 3 months), a minor cytogenetic response (by 6 months), or a major cytogenetic response (by 12 months). Patients with CP-CML who experienced a loss of response or development of a kinase domain mutation in the absence of a complete cytogenetic response or progression to AP-CML or BP-CML at any time on prior TKI therapy were also considered resistant. Resistance in AP-CML, BP-CML, and Ph+ALL was defined as failure to achieve either a major hematologic response (by 3 months in AP-CML, and by 1 month in BP-CML and Ph+ALL), loss of major hematologic response (at any time), or development of a kinase domain mutation in the absence of a complete major hematologic response while on prior TKI therapy. Intolerance was defined as the discontinuation of prior TKI therapy due to toxicities despite optimal management in the absence of a complete cytogenetic response in patients with CP-CML or major hematologic response for patients with AP-CML, BP-CML, or Ph+ALL.

The primary endpoint of major cytogenetic response (which combines both complete (no detectable Ph+ cells) and partial (1% to 35% Ph+ cells in at least 20 metaphases) cytogenetic responses) for CP-CML was 54% overall and 70% in the T315I cohort. At the time of analysis, the median duration of Iclusig treatment was 281 days in patients with CP-CML and the median duration of major cytogenetic response was not reached.

The results of the primary endpoint of overall major hematologic response (which combines complete hematologic responses and no evidence of leukemia) for AP-CML, BP-CML, and Ph+ALL were 52%, 31% and 41%, respectively. At the time of analysis, the median duration of Iclusig treatment was 286 days in patients with AP-CML, 89 days in patients with BP-CML, and 81 days in patients with Ph+ALL. The median time to overall, major hematologic response in patients with AP-CML, BP-CML, and Ph+ALL was 21 days, 29 days, and 20 days, respectively. The median duration of overall major hematologic response for patients with AP-CML, BP-CML, and Ph+ALL was 9.5 months, 4.7 months, and 3.2 months, respectively.

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RATIONALE (CONTINUED)
Iclusig has a boxed warning for vascular occlusion, heart failure and hepatotoxicity. Patients should be monitored for signs and symptoms of congestive heart failure, hypertension, pancreatitis, hemorrhage, fluid retention, cardiac arrhythmias, myelosuppression, tumor lysis syndrome, gastrointestinal perforation, and compromised wound healing. The most common non-hematologic adverse reactions (≥ 20%) were hypertension, rash, abdominal pain, fatigue, headache, dry skin, constipation, arthralgia, nausea, and pyrexia. Hematologic adverse reactions included thrombocytopenia, anemia, neutropenia, lymphopenia, and leukopenia. Iclusig is pregnancy category D and can cause fetal harm.

FDA APPROVED INDICATIONS
Iclusig (ponatinib) is a kinase inhibitor indicated for the:
- Treatment of adult patients with T315I-positive chronic myeloid leukemia (CML) (chronic phase, accelerated phase, or blast phase) and 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.

These indications are based upon response rate [see Clinical Studies (14)]. There are no trials verifying an improvement in disease-related symptoms or increased survival with Iclusig.

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STANDARD COMMERCIAL DRUG FORMULARY
PRIOR AUTHORIZATION GUIDELINES

PONATINIB

Library	Commercial	NSA
Yes	Yes	No

Part D Effective: N/A
Commercial Effective: 04/01/14

Created: 01/13
Client Approval: 03/14

P&T Approval: 02/14

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