**Description**

Ponatinib is an oral tyrosine kinase inhibitor used to treat certain types of cancer. It works by blocking certain proteins that cancer cells need to grow.
Policy/Criteria

I. Most contracts require prior authorization approval of ponatinib prior to coverage. Ponatinib may be considered medically necessary in patients when criteria A or B below are met.

   A. Documentation of Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) when:
      1. There is documentation of a T315I mutation.
      OR
      2. All other tyrosine kinase inhibitors (TKIs) listed in Appendix 1 are ineffective, not tolerated, contraindicated, or not indicated.
      OR

   B. Documentation of Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) when:
      1. There is documentation of a T315I mutation.
      OR
      2. All other TKIs listed in Appendix 2 are ineffective, not tolerated, contraindicated, or not indicated.

II. Administration, Quantity Limitations, and Authorization Period

   A. OmedaRx considers ponatinib to be a self-administered medication.
   B. When prior authorization is approved, ponatinib may be authorized in quantities as follows:
      1. Ponatinib 15 mg tablets: up to 60 tablets per 30 days.
      2. Ponatinib 45 mg tablets: up to 30 tablets per 30 days.
   C. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

III. Ponatinib is considered investigational when used for all other conditions.

Position Statement

- Ponatinib is an oral tyrosine kinase inhibitor (TKI) approved for the treatment of chronic myelogenous leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL).
- The risks associated with ponatinib are much greater than those reported with other TKIs and include the risk of life-threatening vascular occlusive events.
- FDA labeling for ponatinib has been narrowed to include only patients with Ph+ CML or Ph+ ALL with a T315I mutation, or for whom no other TKI is indicated. A very small proportion of patients with CML have a mutation (T315I) that confers resistance to all other TKIs. Ponatinib may be an option in these patients.
- A new risk evaluation and mitigation strategy (REMS) and updated Medication Guide are also required to communicate these risks to patients and healthcare providers.
Ponatinib carries a boxed warning for increased risk of vascular occlusion, heart failure, and hepatotoxicity. These warning are not included in the package labeling for other TKI products used for CML.

The starting dose of ponatinib is 45 mg orally daily; however, the majority of patients require dose reductions during the course of therapy. Additional studies are now required to determine the optimal dose. The safety and efficacy of doses above 45 mg daily have not been demonstrated.

Ponatinib has not been shown to be safe and effective in Philadelphia chromosome-negative CML or ALL.

Clinical Efficacy

CHRONIC MYELOGENOUS LEUKEMIA (CML) AND PHILADELPHIA CHROMOSOME-POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA (PH+ ALL)

- One unreliable, uncontrolled, open-label trial studied ponatinib in subjects with CML (chronic, accelerated and blast phases) or Ph+ ALL who had resistance or intolerance to prior TKI therapy. [1]

* The study evaluated ponatinib at a dose of 45 mg once daily. The dose was decreased or interrupted for adverse effects.

* Cytogenetic response, a clinically relevant endpoint, was used as the primary outcome for patients with chronic phase CML. Major cytogenic response rates ranged from 49% to 70%. Complete cytogenetic responses ranged from 37% to 66%.

* Hematologic response rate was used as the primary outcome in patients with accelerated and blast phases of CML, and Ph+ ALL. Major hematologic response rates ranged from 31% to 52% in these populations while complete hematologic responses ranged from 21% to 43%. The highest response rates were reported in the cohort with accelerated CML, while the lowest rates were reported in patients with blast phase CML.

* Ponatinib had activity (based on improved cytogenetic response) in patients with chronic phase CML with the T315I mutation. This mutation confers resistance to all other available TKIs used in CML.

- There is no published evidence supporting the use of ponatinib as a front-line therapy in CML or Ph+ALL. Additionally, there is no evidence directly comparing it with any other therapy.

- Because of serious, life-threatening safety concerns (see safety section), the FDA-labeled indication was narrowed in December 2013 to include only patients with Ph+ CML or Ph+ALL who have the T315I mutation or for whom no other TKI therapy is indicated. [2]

- Ponatinib is recommended in the NCCN guidelines and compendia for the treatment T315I-positive Ph-positive ALL and Ph-positive ALL for whom no other TKI therapy is indicated. [3] In addition, ponatinib is listed in the NCCN guidelines and compendia for the treatment of T315I-positive Ph-positive CML and for whom CML has not responded to two or more TKI therapies. [6]
OmedaRx performs independent analyses of oncology medications. The OmedaRx analysis and coverage policy may differ from NCCN clinical practice guidelines.

**Safety**

- Risks associated with ponatinib are greater than for other TKIs used in the treatment of CML based on indirect safety comparisons and postmarketing studies.

- The manufacturer voluntarily suspended marketing of ponatinib in 2013 at the FDA’s request due to a safety investigation which revealed an increase in serious, life-threatening vascular events. [3] It was later brought back to market with a narrower indication and REMS communication plan to inform prescribers of the indications for ponatinib and the risk of vascular occlusion and thromboembolism.

- During postmarketing surveillance, arterial and venous thrombosis and occlusions were observed in at least 27% of patients treated with ponatinib. These events were observed as soon as 2 weeks after starting treatment. Recurrent or multi-site vascular occlusions were also reported. [2,3]

- Vascular events included fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures. [2,3]

- Ponatinib carries a boxed warning for vascular occlusion, heart failure, and hepatotoxicity. [2] This warning is not part of the labeling for other TKI products.

- Ocular toxicities leading to blindness or blurred vision have also been reported with ponatinib. [2]

- Commonly reported AEs (greater than 20% incidence) include hypertension, rash, abdominal pain, fatigue, headache, dry skin, constipation, arthralgia, nausea, and pyrexia. [2]

- Commonly reported hematologic effects (greater than 20% incidence) include thrombocytopenia, anemia, neutropenia, lymphopenia, and leukopenia. [2]

- Ponatinib carries the following warnings and precautions: hypertension, pancreatitis, neuropathy, ocular toxicity, hemorrhage, fluid retention, cardiac arrhythmias, myelosuppression, tumor lysis syndrome, compromised wound healing, gastrointestinal perforation, and embryo-fetal toxicity. [2]

**Dosing**

- The recommended starting dose for ponatinib is 45 mg orally daily with or without food; however, the majority of patients require dose reductions to 30 mg or 15 mg daily during the course of therapy. The optimal dose of ponatinib has not been determined. [2]

- Additional postmarketing studies will further evaluate dose selection and toxicity of ponatinib therapy. [3]

- Doses may be interrupted or decreased for non-hematologic and hematologic toxicity. Discontinuation of ponatinib should be considered if no response is seen in 3 months. [2]
### Appendix 1: Tyrosine Kinase Inhibitors (TKIs) Used in the Treatment of Chronic Myelogenous Leukemia (CML) [listed in alphabetical order]

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Bosutinib (Bosulif®)</strong></td>
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<tr>
<td><strong>Dasatinib (Sprycel®)</strong></td>
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</tr>
<tr>
<td><strong>Imatinib (Gleevec®)</strong></td>
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<tr>
<td><strong>Nilotinib (Tasigna®)</strong></td>
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<tr>
<td><strong>Ponatinib (Iclusig®)</strong></td>
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</table>

### Appendix 2: Tyrosine Kinase Inhibitors (TKIs) Used in the Treatment of Ph+ Acute Lymphoblastic Leukemia (ALL) [listed in alphabetical order]

<p>| | |</p>
<table>
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<tbody>
<tr>
<td><strong>Dasatinib (Sprycel®)</strong></td>
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<td><strong>Imatinib (Gleevec®)</strong></td>
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<tr>
<td><strong>Ponatinib (Iclusig®)</strong></td>
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### Appendix 3: Treatment Options Based on BCR-ABL KD Mutation Status [6]

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Treatment Recommendation a</th>
</tr>
</thead>
<tbody>
<tr>
<td>T315I</td>
<td>HSCT, clinical trial, ponatinib (Iclusig), or omacetaxine (Synribo)</td>
</tr>
<tr>
<td>V299L, T315A, F317L/V/I/C</td>
<td>nilotinib (Tasigna)</td>
</tr>
<tr>
<td>Y253H, E255K/V, F359V/C/I</td>
<td>dasatinib (Sprycel)</td>
</tr>
<tr>
<td>Any other mutation</td>
<td>High dose imatinib (Gleevec), dasatinib (Sprycel), nilotinib (Tasigna), or bosutinib (Bosulif)</td>
</tr>
</tbody>
</table>

a There are not suitable data on dose escalation available to indicate if mutations with lower IC50 values are sensitive to high-dose imatinib

### Cross References

- Bosulif®, bosutinib, Medication Policy Manual, Policy No. 285
- Gleevec®, imatinib, Medication Policy Manual, Policy No. 043
- Sprycel®, dasatinib, Medication Policy Manual, Policy No. 137
- Synribo®, omacetaxine, Medication Policy Manual, Policy No. 291
- Tasigna®, nilotinib, Medication Policy Manual, Policy No. 151
<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCPCS</td>
<td>J8999</td>
<td>Oral chemotherapeutic drug, not otherwise classified</td>
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<tr>
<td>ICD-9</td>
<td>205.10, 205.11, 205.12</td>
<td>Chronic myelogenous leukemia</td>
</tr>
<tr>
<td>ICD-9</td>
<td>204.00, 204.01, 204.02</td>
<td>Acute lymphoblastic leukemia</td>
</tr>
<tr>
<td>ICD-10</td>
<td>C92.10-C92.12</td>
<td>Chronic myelogenous leukemia</td>
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<td>ICD-10</td>
<td>C91.00-C91.02</td>
<td>Acute lymphoblastic leukemia</td>
</tr>
</tbody>
</table>

References

2. Iclusig® (ponatinib) [package insert]. ARIAD Pharmaceuticals, Inc.
4. Micromedex® Healthcare Series; Thomson Reuters. [updated periodically].

Revision Date | Revision Summary
--- | ---
01/08/2016 | No criteria changes