Imbruvica (ibrutinib)

Background
Imbruvica is a kinase inhibitor that is used to treat two types of lymphoma. Lymphoma is the most common blood cancer and occurs when lymphocytes, a form of white blood cell, grow and multiply uncontrollably. Imbruvica inhibits the enzyme needed by the cancer to multiply and spread (1).

Regulatory Status
FDA-approved indication: Imbruvica is a kinase inhibitor indicated for the treatment of patients with: (1)

1. Mantle cell lymphoma (MCL) who have received at least one prior therapy
2. Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)
3. Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) with 17p deletion
4. Waldenström’s macroglobulinemia/lymphoplasmacytic lymphoma
5. Marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy
6. Chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy

Off-label Uses: (2-4)

1. Follicular lymphoma
2. Diffuse large B-cell lymphoma
The B-cell antigen receptor (BCR) pathway is implicated in the pathogenesis of several B-cell malignancies, including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, mantle-cell lymphoma, and B-cell chronic lymphocytic leukemia (CLL). Bruton tyrosine kinase (BTK) is a critical signaling kinase in this pathway. Imbruvica is an irreversible inhibitor of the BTK in patients with B-cell malignancies (2).

Patients with MCL and CLL have a chance of Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, and hematuria). Imbruvica may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies. Consider the benefit-risk of withholding Imbruvica for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding (1).

Significant adverse reactions may occur with Imbruvica therapy including fatal and non-fatal infections, myelosuppression, renal toxicity, hepatic toxicity and primary malignancies including skin cancers. Patients should have the following monitored while on Imbruvica therapy: fever, infections, complete blood counts, creatinine levels, and hydration (1).

Advise women to avoid becoming pregnant while taking Imbruvica. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus (1).

The safety and effectiveness of Imbruvica in pediatric patients has not been established (1).

**Related policies**
Aliqopa, Arzerra, Bendeka, Brukinsa, Calquence, Copiktra, Gazyva, Revlimid, Rituxan, Treanda, Zydelig

**Policy**
This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Imbruvica may be considered **medically necessary** in patients who are 18 years of age or older with a confirmed diagnosis of mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), Waldenström’s macroglobulinemia/lymphoplasmacytic lymphoma, follicular lymphoma, diffuse large B-cell lymphoma, small lymphocytic lymphoma (SLL), marginal zone lymphoma (MZL), or chronic graft versus host disease (cGVHD) and if the conditions indicated below are met.

Imbruvica is considered **investigational** in patients who are less than 18 years of age and for all other indications.
Prior-Approval Requirements

Age 18 years of age and older

Diagnoses

Patient must have ONE of the following:

1. Mantle cell lymphoma (MCL)
   a. The patient has received at least one prior therapy
2. Chronic lymphocytic leukemia (CLL)
3. Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma
4. Follicular lymphoma
5. Diffuse large B-cell lymphoma
6. Small lymphocytic lymphoma (SLL)
7. Marginal zone lymphoma (MZL) who require systemic therapy
   a. The patient has received at least one prior anti-CD20-based therapy
8. Chronic graft versus host disease (cGVHD)
   a. The patient has received at least one prior systemic therapy

Prior – Approval Renewal Requirements

Age 18 years of age and older

Diagnoses

Patient must have ONE of the following:

1. Mantle cell lymphoma (MCL)
2. Chronic lymphocytic leukemia (CLL)
3. Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma
4. Follicular lymphoma
5. Diffuse large B-cell lymphoma
6. Small lymphocytic lymphoma (SLL)
7. Marginal zone lymphoma (MZL) who require systemic therapy
8. Chronic graft versus host disease (cGVHD)
Pre - PA Allowance
None

Prior - Approval Limits

<table>
<thead>
<tr>
<th>Quantity per 84 or 90 days</th>
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<tr>
<td>84 capsules per 84 days OR</td>
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<tr>
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<tr>
<td>84 tablets per 84 days OR</td>
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Maximum daily limit of any combination: 560 mg

Duration 12 months

Prior – Approval Renewal Limits
Same as above

Rationale

Summary
Imbruvica is an orally administered kinase inhibitor indicated for the treatment of patients with mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL) who have received at least one prior therapy or in patients with CLL and SLL. Imbruvica has also shown effectiveness in diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, marginal zone lymphoma (MZL) and chronic graft versus host disease (cGVHD). Current warnings include the possibility for hemorrhage, myelosuppression, renal toxicity, hepatic toxicity and primary malignancies including skin cancers. The safety and effectiveness of Imbruvica in pediatric patients has not been established (1-4).

Prior approval is required to ensure the safe, clinically appropriate and cost effective use of Imbruvica while maintaining optimal therapeutic outcomes.

References


**Policy History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>March 2014</td>
<td>New addition to PA</td>
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<tr>
<td>September 2014</td>
<td>Addition that the FDA indication of chronic lymphocytic leukemia (CLL) with 17p deletion does not require failure on prior therapy for CLL. Removal of the following criteria requirements: no baseline hepatic impairment, Physician agrees to monitor for: Hemorrhage, Myelosuppression with complete blood counts monthly, Renal toxicity by checking creatinine levels periodically, Second primary malignancies including skin cancers.</td>
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<tr>
<td>December 2014</td>
<td>Annual editorial review and reference update</td>
</tr>
<tr>
<td>February 2015</td>
<td>Addition of Waldenström’s macroglobulinemia, follicular lymphoma and diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td>June 2015</td>
<td>Annual editorial review and reference update</td>
</tr>
<tr>
<td>March 2016</td>
<td>Addition of Small lymphocytic lymphoma (SLL) and removal of who have received at least one prior therapy or in patients with chronic lymphocytic leukemia with 17p deletion Policy number change from 5.04.41 to 5.21.41</td>
</tr>
<tr>
<td>June 2016</td>
<td>Annual review</td>
</tr>
<tr>
<td>September 2016</td>
<td>Annual review</td>
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<tr>
<td>February 2017</td>
<td>Addition of marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy</td>
</tr>
<tr>
<td>June 2017</td>
<td>Annual editorial review</td>
</tr>
<tr>
<td>August 2017</td>
<td>Addition of age requirements to renewal criteria</td>
</tr>
<tr>
<td>September 2017</td>
<td>Addition of chronic graft versus host disease (cGVHD)</td>
</tr>
<tr>
<td>March 2018</td>
<td>Annual review</td>
</tr>
<tr>
<td>March 2019</td>
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<tr>
<td>September 2019</td>
<td>Addition of “maximum daily limit of any combination: 560 mg”</td>
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</table>
December 2019 Annual review and reference update

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 6, 2019 and is effective January 1, 2020.