ibrutinib (Imbruvica®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO037

Description

Ibrutinib (Imbruvica) is an orally administered Bruton's tyrosine kinase (BTK) inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

ibrutinib (Imbruvica)	Indication	Quantity Limit	DDID
560 mg tablets	Mantle Cell Lymphoma, previously treated; Marginal Zone Lymphoma, relapsed/refractory	30 tablets/30 days	201835
420 mg tablets	Chronic Graft versus Host Disease (refractory); Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; Waldenström Macroglobulinemia	30 tablets/30 days	201834
280 mg tablet	Dose modification	30 tablets/30 days	201832
140 mg tablet	Dose modification	30 tablets/30 days	181820
140 mg capsule	Dose modification	60 capsules/30 days	201838
70 mg capsule	Dose modification	30 capsules/30 days	201831

Initial Evaluation

I. Ibrutinib (Imbruvica) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Treatment is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   C. If the 140 mg or 280 mg tablet have been prescribed, the member has tried and failed or has a contraindication to 140 mg capsules; **AND**
   D. A diagnosis of one of the following:
      1. **Mantle Cell Lymphoma (MCL)**; **AND**

i. Member has received one prior therapy (e.g., lenalidomide, rituximab, stem cell transplant, etc.); **OR**

2. **Marginal Zone Lymphoma (MZL)**; **AND**
   i. Member has received at least one prior anti-CD20-based therapy (e.g., rituximab, obinutuzumab, ofatumumab); **OR**
3. **Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Leukemia (SLL); AND**
   i. Used as a single agent; **AND**
      a. Ibrutinib (Imbruvia) is being used in the first-line setting or in the relapsed/refractory setting; **OR**
   ii. Ibrutinib (Imbruvica) is used in combination with rituximab plus bendamustine in the relapsed/refractory setting; **AND**
      a. Members are **without** 17p deletion or TP53 mutation and documentation of testing has been provided; **OR**
   iii. Ibrutinib (Imbruvica) is used in combination with obinutuzumab in the first line setting; **AND**
      a. Members are **without** 17p deletion or TP53 mutation and documentation of testing has been provided; **AND**
      b. Considered unsuitable for fludarabine-based chemoimmunotherapy due member age 65 years or greater or member younger than 65 years with significant comorbidity; **OR**
4. **Waldenström Macroglobulinemia (WM); AND**
   i. Ibrutinib (Imbruvica) will be used as monotherapy; **OR**
   ii. Ibrutinib (Imbruvica) will be used with rituximab; **OR**
5. **Chronic Graft versus Host Disease (cGVHD); AND**
   i. Member has failed one or more lines of systemic therapy (e.g., corticosteroids, mycophenolate mofetil, calcineurin inhibitors, sirolimus)

II. Ibrutinib (Imbruvica) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Relapsed/refractory Hodgkin lymphoma
   B. Mantle Cell Lymphoma, frontline
   C. Diffuse Large B Cell Lymphoma
   D. Relapsed/refractory Multiple Myeloma
   E. Hairy Cell Leukemia
   F. Mantle Cell Lymphoma, combination therapy
   G. Primary CNS lymphoma
   H. Esophagogastric carcinoma
   I. Gliobalastoma
   J. Non-small-cell lung carcinoma
   K. T-cell Lymphoma

Renewal Evaluation

I. Treatment is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
II. If the 140 mg or 280 mg tablet have been prescribed, the member has tried and failed or has a contraindication to 140 mg capsules; **AND**
III. Absence of unacceptable toxicity from the ibrutinib (Imbruivca); **AND**
IV. The patient has not experienced disease progression while on ibrutinib (Imbruvica); **OR**
V. Documentation of compelling clinical evidence of benefit is provided if therapy is to be continued after disease progression.

Supporting Evidence

I. In the setting of MCL, ibrutinib (Imbruvica) was studied in an open-label, multi-center, single-arm trial of 111 previously treated patients that received at least one prior therapy. The primary endpoint of overall response rate (ORR) was 65.8% with ibrutinib (Imbruvica) therapy.
II. In the setting of MZL, ibrutinib (Imbruvica) was studied in an open-label, multi-center, single-arm trial of 63 patients who received at least one prior therapy, including one anti-CD20-directed regimen. The primary endpoint of ORR was 46% with ibrutinib (Imbruvica) therapy.
III. The safety and efficacy of ibrutinib (Imbruvica) in patients with CLL/SLL were demonstrated in one uncontrolled trial and four randomized, controlled trials. The RESONATE study, a randomized, multicenter, open-label, phase 3 study of ibrutinib versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma was conducted in patients with previously treated CLL or SLL. With an overall follow-up of 63 months, the median PFS was 44.1 months [95% CI (38.5, 56.9)] in the ibrutinib (Imbruvica) arm and 8.1 months [95% CI (7.8, 8.3)] in the ofatumumab arm, respectively. RESONATE included 127 patients with del17p CLL/SLL, PFS at 63 months was 40.6 months [95% CI (25.4, 44.6)] in the ibrutinib (Imbruvica) arm and 6.2 months [95% CI (4.6, 8.1)] in the ofatumumab arm. The RESONATE-2 study, a randomized, multicenter, open-label, phase 3 study versus chlorambucil in patients 65 years or older with treatment-naive CLL/SLL (n=269) reported an overall survival analysis in the intention to treat patient population resulted in a statistically significant HR of 0.44 [95% CI (0.21, 0.92)] and 2-year survival rate estimates of 94.7% [95% CI (89.1, 97.4)] and 84.3% [95% CI (76.7, 89.6)] in the ibrutinib (Imbruvica) and chlorambucil arms, respectively. Additional studies assessed ibrutinib (Imbruvica) in combination with bendamustine and Rituximab (HELIOS) or with obinutuzumab (iLLUMINATE). In the HELIOS trial patients with del17p were excluded. In the iLLUMINATE trial, all patients included in the study were considered unsuitable for fludarabinebased chemoimmunotherapy because they were aged 65 years or older or younger than 65 years with at least one of the following coexisting conditions: cumulative illness rating scale score greater than 6, creatinine clearance of less than

70 mL/min, presence of del17p confirmed by FISH, or TP53 mutation. The majority of high risk patients included in iLLUMINATE had unmutated IGVH (65%) while only 16% of patients had a del17p or TP53 mutation. NCCN CLL/SLL guidelines recommend ibrutinib (Imbruvica) monotherapy as a Category 1 recommendation in in the relapsed/refractory setting in patients with or without 17p deletion/TP53 mutation. In the first-line setting monotherapy also carries a Category 1 recommendation in patients without 17p deletion/TP53 mutation, with a 2A recommendation in those with the deletion/mutation. NCCN guidelines do not list combination ibrutinib (Imbruvica) with rituximab and bendamustine or with obinutuzumab in members with 17p deletion/TP53 mutation as a treatment option. Both regimens carry 2B recommendations in CLL/SLL without del17p/TP53 mutation.

IV. The safety and efficacy of ibrutinib (Imbruvica) in patients with WM were demonstrated in two single-arm trials and one randomized, controlled trial. Study 1118, an open-label, multi-center, single-arm trial of 63 previously treated patients reported a response rate of 61.9%. The INNOVATE monotherapy arm included 31 patients with previously treated WM who failed prior rituximab-containing therapy and received single-agent ibrutinib (Imbruvica). The response rate observed in the INNOVATE monotherapy arm was 71%, with a median follow-up time on study of 34 months. The INNOVATE study, a randomized, double-blind, placebo-controlled, phase 3 study of ibrutinib or placebo in combination with rituximab in subjects with treatment naïve or previously treated WM. The primary endpoint of progression-free survival (PFS) was 82% with ibrutinib–rituximab versus 28% with placebo–rituximab (hazard ratio for progression or death, 0.20; P<0.001).

V. In the setting of cGVHD, ibrutinib (Imbruvica) was studied in an open-label, multi-center, single-arm trial of 42 patients with cGVHD after failure of first line corticosteroid therapy and requiring additional therapy. Therapy with ibrutinib (Imbruvica) results in an ORR of 67%. Corticosteroids are the mainstay of initial systemic treatment for patients with cGVHD. Alternatives to, or add-on therapy to corticosteroids includes but is not limited to: mycophenolate mofetil, calcineurin inhibitors (e.g., cyclosporine, tacrolimus), sirolimus.

Investigational or Not Medically Necessary Uses

I. Relapsed/refractory Hodgkin lymphoma
   A. Subject of current ongoing trials.
II. Mantle cell lymphoma, frontline
   A. Ibrutinib is being investigated as a first-line treatment for patients with MCL in the phase III SHINE trial (NCT01776840), evaluating the safety and efficacy of ibrutinib plus bendamustine and rituximab (Rituxan) in older patients with newly-diagnosed MCL who are not eligible for stem cell transplant. SHINE has fully enrolled, but no data are available yet. The trial is expected to read out in 2021.
III. Diffuse large B cell lymphoma

A. Ibrutinib was studied in a phase 1/2 clinical trial that involved 80 subjects with relapsed or refractory DLBCL, ibrutinib produced complete or partial responses in 37% (14/38) of those with activated B cell–like (ABC) DLBCL, but in only 5% (1/20) of subjects with germinal center B cell–like (GCB) DLBCL (P = 0.0106). Additional studies are need and are currently underway, as ibrutinib is the subject of several ongoing phase 2 trials in the relapsed/refractory setting.

B. The addition of ibrutinib (Imbruivca) to standard R-CHOP chemotherapy regimen in the DLBCL first-line setting failed to meet its primary endpoint of improving event-free survival (EFS) when compared to R-CHOP alone in the phase III PHOENIX (NCT01855750) study. https://news.abbvie.com/news/abbvie-provides-update-on-phase-3-study-ibrutinib-imbruvica-in-blood-cancer-diffuse-large-b-cell-lymphoma-dlbcl-and-ongoing-ibrutinib-clinical-program.htm

IV. Relapsed/refractory multiple myeloma

A. Ibrutinib (Imbruvica) was studied in a phase 2 study that examined various doses of ibrutinib ± low-dose dexamethasone in patients who received ≥2 prior lines of therapy, including an immunomodulatory agent. The primary objective of clinical benefit rate (CBR; ≥minimal response) was the highest (CBR 28%) in Cohort 4 which consisted of ibrutinib + dexamethasone (n=43). Further evaluation is need to support use of ibrutinib (Imbruvica) in this setting.

V. Hairy cell leukemia

A. Ibrutinib (Imbruvica) was subject of a single arm phase two study (n=28) in patients with hairy cell leukemia stage 1. The primary overall of objective response rate, was seen in 46%, with objective responses more commonly seen in those patients with classical hairy cell leukemia (c-HCL). Additional studies are needed to further evaluate and support this use.

VI. Mantle cell lymphoma, combination therapy

A. A phase 2 study of ibrutinib plus venetoclax in relapsed or refractory MCL patients (n=23), found the primary endpoint of complete response rate at week 16 was 42%, which was higher than the historical control of 9% at this time point with ibrutinib monotherapy (P<0.001). Additional studies are needed to further evaluate and support this combination use.

VII. Primary CNS lymphoma

A. Ibrutinib (Imbruvica) was subject of a phase 1 trial in patients (n=13) with relapsed or refractory CNS lymphoma. Additional studies are needed to further evaluate and support this use.

VIII. Esophagogastric carcinoma

A. Ibrutinib (Imbruvica) is subject of ongoing trials in this setting.

IX. Gliobalastoma

A. Ibrutinib (Imbruvica) is subject of ongoing trials in this setting.

X. Non-small-cell lung carcinoma
   A. Ibrutinib (Imbruvica) is subject of ongoing trials in this setting.
XI. T-cell Lymphoma
   A. Ibrutinib (Imbruvica) is subject of ongoing trials in this setting.

References

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Policy Implementation/Update:

Date Created	February 2014
Date Effective	March 2014
Last Updated	March 2019
Last Reviewed	08/2014, 02/2015, 04/2015, 08/2017, 01/2018, 03/2019

Action and Summary of Changes	Date

Updated criteria to policy format, specified combination therapy in CLL/SLL patients to be used in members without 17p deletion/TP53 mutation, addition of trial and failure of 140mg capsules prior to use of 140 mg or 280 mg tablets. In MCL, marginal zone lymphoma, and graft versus host disease, added more detail on type of prior therapy required. For Waldenström macroglobulinemia added use to be as monotherapy or with rituximab.	03/2019
Updated formatting, extended initial approval from 3 months to 6 months.	01/2018