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

Product Name	Indication	Dosage Form	Quantity Limit
ibrutinib (Imbruvica)	Chronic Graft versus Host Disease (refractory); Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; Waldenström Macroglobulinemia Chronic Graft versus Host Disease (refractory)	420 mg tablets	28 tablets/28 days
		70mg/mL suspension	216mL/35 days**
	Dose modification	280 mg tablets	56 tablets/28 days
	Dose modification	140 mg tablets	112 tablets/28 days
	Dose modification	140 mg capsules	120 capsules/30 days
	Dose modification	70 mg capsules	30 capsules/30 days

***Body surface area (BSA) dosing under 12 years of age: 240 mg/m²once daily; maximum dose: 420 mg/dose. Due to the unbreakable packaging, 216mL/35 days is the maximum dosing. Those 12 and older should use 420mg tablets.*

Initial Evaluation

I. **Ibrutinib (Imbruvica)** may be considered medically necessary when the following criteria below are met:
   A. Treatment is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   B. If the request is for the 140 mg tablets or 280 mg tablets, there is documentation that the member has tried and failed or has a contraindication to the 140 mg capsules; **OR**
      1. If the request is for the 70mg/mL suspension, the patient is under 12 years of age; **AND**
   C. Member has not experienced disease progression while on a BTK inhibitor [e.g., zanubrutinib (Brukinsa), acalabrutinib (Calquence)]; **AND**
   D. A diagnosis of one of the following:
      1. **Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL); AND**
         i. Member is 18 years of age or older; **AND**

ii. The member does not have a 17p deletion or TP53 mutation confirmed by testing; **AND**
   a. Ibrutinib (Imbruvica) will be used as monotherapy; **OR**
      i. The request is for use in combination with bendamustine and rituximab in the relapsed/refractory setting; **OR**

iii. The member has a 17p deletion or TP53 mutation confirmed by testing; **AND**
   a. Ibrutinib (Imbruvica) will be used as monotherapy; **OR**

2. **Waldenström Macroglobulinemia (WM); AND**
   i. Member is 18 years of age or older; **AND**
   ii. Ibrutinib (Imbruvica) will be used as monotherapy; **OR**
   iii. Ibrutinib (Imbruvica) will be used with rituximab; **OR**
3. **Chronic Graft versus Host Disease (cGVHD); AND**
   i. Member is one year of age or older; **AND**
   ii. Member has failed one or more lines of systemic therapy (e.g., corticosteroids, mycophenolate mofetil, calcineurin inhibitors, sirolimus)

II. Ibrutinib (Imbruvica) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Chronic lymphocytic leukemia/small lymphocytic lymphoma in combination with rituximab only
   B. Mantle cell lymphoma (new to therapy)
   C. Marginal zone lymphoma (new to therapy)

III. Ibrutinib (Imbruvica) is considered investigational when used for all other conditions, including but not limited to:
   A. Chronic lymphocytic leukemia/small lymphocytic lymphoma in the first line setting in combination with obinutuzumab
   B. Relapsed/refractory Hodgkin lymphoma
   C. Diffuse large B cell lymphoma
   D. Relapsed/refractory multiple myeloma
   E. Hairy cell leukemia
   F. Primary CNS lymphoma
   G. Esophagogastric carcinoma
   H. Glioblastoma
   I. Non-small-cell lung carcinoma
   J. T-cell lymphoma

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. If the request is for the 140 mg tablets or 280 mg tablets, the member has tried and failed or has a contraindication to the 140 mg capsules; **OR**
- If the request is for the 70mg/mL suspension, the member under the age of 12 years; **AND**

IV. The member has exhibited improvement of their condition defined as:
- **For GVHD:** The member has exhibited improvement or stability of symptoms [e.g., manifestations of disease to the skin, oral cavity, musculoskeletal system]; **OR**
- **For oncology indications:** The member has not experienced disease progression while on ibrutinib (Imbruvica); **OR**

V. Compelling clinical evidence of benefit is provided if therapy is to be continued after disease progression.

Supporting Evidence

I. NCCN guidelines note that acquired resistance to ibrutinib (Imbruvica) is mediated by BTK mutations, which have also been described in patients receiving other BTK inhibitors (e.g., acalabrutinib [Calquence], zanubrutinib [Brukinsa]).

II. 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, was a randomized, multicenter, open-label, phase 3 study of ibrutinib (Imbruvica) versus ofatumumab in patients with relapsed or refractory CLL/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 which 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.

- The HELIOS study was a randomized, double-blind, placebo-controlled, Phase 3 trial of ibrutinib (Imbruvica) in combination with bendamustine and rituximab in 578 patients with relapsed or refractory CLL/SLL. Patients with del17p were excluded. The primary efficacy endpoint was PFS. Ibrutinib (Imbruvica) in combination with bendamustine and rituximab had a median PFS that was not evaluable compared to 13.3 months for ibrutinib (Imbruvica) in combination with placebo. The HR was 0.20 (95% CI 0.15, 0.28) for PFS.
- 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, ibrutinib (Imbruvica) with rituximab and bendamustine, or ibrutinib (Imbruvica) with obinutuzumab in members with 17p deletion/TP53 mutation as a treatment option.

III. 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 (Imbruvica) 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).

IV. The safety and efficacy of ibrutinib (Imbruvica) in cGVHD was shown in two clinical trials. One being the confirmatory FDA approval trial for adults and the second was a safety trial for an age expansion in pediatrics.

- Ibrutinib (Imbruvica) was studied in an open-label, multi-center, single-arm trial of 42 adult (18 and over) patients with cGVHD after failure of first line corticosteroid therapy and requiring additional therapy; patients received 420mg of ibrutinib daily. Therapy with ibrutinib (Imbruvica) resulted 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 include, but are not limited to, mycophenolate mofetil, calcineurin inhibitors (e.g., cyclosporine, tacrolimus), and sirolimus.
- In 2022, ibrutinib (Imbruvica) was studied in an open-label, multi-center, single arm trial in pediatric patients aged between 1 year and 22 years with moderate to severe cGVHD. The trial enrolled 47 patients who required additional therapy after

failure of one or more prior lines of systemic therapy (e.g. cyclosporine, tacrolimus). Patients 12 and older were treated with 420mg once daily and those 1 year to under 12 were treated with 240mg/m^2 once daily, with a maximum dose of 420mg. The ORR through week 25 was 60%. Additionally, there were no new safety signals compared to the adult confirmatory trial.

V. For several indications and trials, the rate of discontinuation/dose reduction/dose interruption was greater than 20% of the population studied. The high rate of discontinuation meets the requirements for split-fill criteria.

Investigational or Not Medically Necessary Uses

I. Ibrutinib (Imbruvica) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below.

Not Medically Necessary Uses

A. Chronic lymphocytic leukemia/small lymphocytic leukemia, in combination with rituximab
   i. In the E1912 trial, ibrutinib (Imbruvica) in combination with rituximab, showed significant improvements in PFS compared to fludarabine, cyclophosphamide, and rituximab chemoimmunotherapy. The primary endpoint was PFS, and the HR for disease progression was 0.34 (95% CI 0.22, 0.52). The results of the Phase 3 Alliance North American Intergroup Study (A041202) comparing ibrutinib (Imbruvica) monotherapy to ibrutinib (Imbruvica) + rituximab found the estimate 2-year PFS rates were 87% and 88% (p=0.49), respectively. NCCN guidelines note that the addition of rituximab to ibrutinib has not yet demonstrated improvement in clinical outcomes compared to ibrutinib monotherapy in a randomized clinical trial. The consensus was that the longer PFS in combination trials was more the result of continuous and indefinite treatment with ibrutinib, rather than due to the contribution of rituximab. There is a consideration that improved outcomes with the addition of anti-CD20 monoclonal antibodies may more likely be seen with fixed-duration treatment with these regimens.

B. Mantle cell lymphoma (MCL)
   i. Ibrutinib (Imbruvica) was previously FDA-approved under the accelerated approval pathway for the treatment of adult patients with MCL who have received at least one prior therapy. This indication approval was based on overall response rate and continued approval was contingent upon verification and description of clinical benefit in confirmatory trials. The confirmatory phase 3 trial (SHINE) met the primary endpoint of progression-free survival but failed to show significant overall survival benefit in patients treated with combination of ibrutinib

(Imbruvica), bendamustine, and rituximab compared to patients treated with combination of placebo, bendamustine, and rituximab. Overall survival at 7 years was 55% in the ibrutinib (Imbruvica) group and 56.8% in the placebo group. Moreover, the addition of ibrutinib (Imbruvica) to chemotherapy was associated with increased adverse reactions compared to placebo-controlled group. After discussion of the results with the FDA, AbbVie voluntarily withdrew the U.S. accelerated approval for patients with MCL as the confirmatory study was insufficient to support conversion to full approval. Requests for initiation of ibrutinib (Imbruvica) for the treatment of MCL are considered not medically necessary due to a failed confirmatory Phase 3 trial and lack of continued FDA approval. Patients currently receiving ibrutinib (Imbruvica) and experiencing benefit from therapy are eligible for renewal and continued use for the treatment of MCL.

ii. Ibrutinib (Imbruvica) was also studied against temsirolimus in one randomized, open-label, multi-center, Phase 3 trial in patients with relapsed or refractory MCL. Data is available for three years of follow up. Median progression free survival (PFS) was significantly longer for ibrutinib (Imbruvica) than temsirolimus (15.6 vs 6.2 months; HR 0.45 [95% CI 0.35–0.60]; P < 0.0001). Overall survival (OS) data was not statistically significant but favored ibrutinib (Imbruvica) numerically (30.3 vs 23.5 months, respectively; HR 0.74 [95% CI 0.54–1.02]; P = 0.0621).

<u>Ongoing studies of ibrutinib (Imbruvica) for the treatment of MCL:</u>

iii. Mantle cell lymphoma, frontline
    1. Ibrutinib (Imbruvica) is being investigated as a first-line treatment in patients up to 65 years of age in the European TRINANGLE trial (NCT02858258). The study evaluates the addition of ibrutinib (Imbruvica) in the induction phase and as maintenance, as well as if autologous stem cell transplant may be omitted. Three-year results have been reported at the 2022 American Society of Hematology Annual meeting, however, longer follow up is needed to confirm benefit.
    2. Ibrutinib (Imbruvica) is being investigated as a first line treatment in a Phase 2/3 trial (ENRICH) in patients over 60 years of age with MCL. The trial is comparing ibrutinib combined with rituximab, followed by rituximab maintenance against rituximab combined with chemotherapy, followed by rituximab maintenance. ENRICH is fully enrolled but there are no data available yet.

iv. Mantle cell lymphoma, combination therapy.
    1. Ibrutinib (Imbruvica) was studied in an open-label, single-arm, Phase 2 trial in combination with rituximab in patients with relapsed or refractory MCL and in patients over 65 years of age with newly-diagnosed,

untreated MCL. At a median follow-up of 16.5 months, 44 (88%, 95% CI 75.7-95.5) patients achieved an objective response. Additional studies are needed to further evaluate and support this combination use.

2. Combination of ibrutinib (Imbruvica), lenalidomide, and rituximab was studied in one open-label, single-arm, Phase 2 trial in patients with relapsed or refractory MCL who had previously been treated with at least one rituximab-containing regimen. The primary endpoint, ORR at 17.8 months was achieved in 38 (76%, 95% CI 63-86) patients. Additional studies are needed to further evaluate and support this combination use.
3. A Phase 2 study of ibrutinib (Imbruvica) 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 (Imbruvica) monotherapy (P<0.001). Additional studies are needed to further evaluate and support this combination use.

C. Marginal zone lymphoma (MZL)

i. In the setting of MZL, ibrutinib (Imbruvica) was FDA-approved under accelerated approval pathway based on an open-label, multi-center, single-arm trial (PCYC-1121) of 63 adult patients who received at least one prior therapy, including one anti-CD20-directed regimen. The confirmatory phase 3 study (SELENE; NCT01974440) in patients with relapsed/refractory follicular lymphoma or MZL did not meet its primary endpoint of progression-free survival in patients with R/R FL or MZL. The SELENE study results will be presented at a future scientific forum. After discussion of the results with the FDA, AbbVie voluntarily withdrew the U.S. accelerated approval for patients with MZL as the confirmatory study was insufficient to support conversion to full approval. Requests for initiation of ibrutinib (Imbruvica) for the treatment of MZL are considered not medically necessary due to a failed confirmatory Phase 3 trial and lack of continued FDA approval. Patients currently receiving ibrutinib (Imbruvica) and experiencing benefit from therapy are eligible for renewal and continued use for the treatment of MZL.

<u>Ongoing studies of ibrutinib (Imbruvica) for the treatment of MZL:</u>

i. Marginal zone lymphoma, frontline

1. Ibrutinib (Imbruvica) has not been sufficiently studied in treatment naïve patients with MZL. A Phase 3, double-blind, placebo-controlled study evaluating ibrutinib (Imbruvica) in combination with rituximab in treatment naïve patients is currently underway with estimated completion date of June 30, 2024 (NCT04212013). Additionally, a Phase 2, single-arm, open-label trial (MALIBU) evaluating ibrutinib (Imbruvica)

in combination with rituximab is also underway with expected completion date of June 15, 2024 (NCT03697512).

Investigational

A. Chronic lymphocytic leukemia/small lymphocytic lymphoma in the first line setting in combination with obinutuzumab
    ii. The iLLUMINATE study was a randomized, open-label, active-controlled, multicenter, Phase 3 trial of ibrutinib (Imbruvica) in combination with obinutuzumab studied against chlorambucil in combination with obinutuzumab in 229 patients with treatment naïve CLL/SLL. Patients were either aged 65 years or older or younger than 65 years with coexisting conditions. The primary efficacy outcome was PFS. Ibrutinib (Imbruvica) in combination with obinutuzumab, had a median PFS that was not evaluable, compared to 19 months for chlorambucil in combination with obinutuzumab. The HR was 0.23 (95% CI 0.13, 0.37) for PFS. There have been no direct comparisons between ibrutinib (Imbruvica) monotherapy and ibrutinib (Imbruvica) in combination with obinutuzumab, therefore, it is not known if combination of the two agents will provide superior efficacy outcomes than ibrutinib (Imbruvica) monotherapy. Additionally, NCCN guidelines state that longer PFS may be the result of continuous and indefinite treatment with ibrutinib, rather than due to contribution of an anti-CD20 mAb during the first six months of treatment. There is a consideration that improved outcomes with the addition of anti-CD20 monoclonal antibodies may more likely be seen with fixed-duration treatment with these regimens.
    NCCN guidelines recommend ibrutinib (Imbruvica) + obinutuzumab (for frail patients with significant comorbidities and patients aged ≥65 years and younger patients with significant comorbidities) and ibrutinib + rituximab (for patients <65 years without significant comorbidities) as a 2B (other recommended regimens) recommendation.
B. Relapsed/refractory Hodgkin lymphoma
    iii. Subject of current ongoing trials.
C. Diffuse large B cell lymphoma
    iv. Ibrutinib (Imbruvica) was studied in a phase 1/2 clinical trial that involved 80 subjects with relapsed or refractory DLBCL, ibrutinib (Imbruvica) 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 (Imbruvica) is the subject of several ongoing phase 2 trials in the relapsed/refractory setting.

v. 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.

D. Relapsed/refractory multiple myeloma

vi. Ibrutinib (Imbruvica) was studied in a phase 2 study that examined various doses of ibrutinib (Imbruvica) ± 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 (Imbruvica) + dexamethasone (n=43). Further evaluation is needed to support use of ibrutinib (Imbruvica) in this setting.

E. Hairy cell leukemia

vii. 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.

F. Primary CNS lymphoma

viii. 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.

G. Esophagogastric carcinoma

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

H. Glioblastoma

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

I. Non-small-cell lung carcinoma

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

J. T-cell lymphoma

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

Related Policies

Policy Name	Disease state
ruxolitinib (Jakafi®)	Chronic Graft versus Host Disease
belumosudil (Rezurock™)	
acalabrutinib (Calquence ®)	Mantle cell lymphoma; CLL; SLL
lenalidomide (Revlimid®); pomalidomide (Pomalyst®); thalidomide (Thalomid®)	Mantle cell lymphoma; marginal zone lymphoma

zanubrutinib (Brukinsa™)	Mantle cell lymphoma; Waldenstrom's macroglobulinemia; marginal zone lymphoma' CLL, SLL

References

1. Imbruvica [package insert]. Horsham, PA: Janssen Biotech, Inc.; April, 2020; revised August 2022.
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guideline in Oncology. Chronic lymphocytic leukemia/Small lymphocytic lymphoma Version 4.2020. January 2, 2020.
3. Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2013;369(6):507-16.
4. Moreno C, Greil R, Demirkan F, et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20(1):43-56.
5. Dimopoulos MA, Tedeschi A, Trotman J, et al. Phase 3 Trial of Ibrutinib plus Rituximab in Waldenström's Macroglobulinemia. N Engl J Med. 2018;378(25):2399-2410.
6. National Comprehensive Cancer Network. NCCN Clinical Practice Guideline in Oncology. B-cell lymphomas. Version 5.2022. July 12, 2022.
7. Wilson WH, Young RM, Schmitz R, et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. Nat Med. 2015;21(8):922-6.
8. AbbVie Provides Update on Phase 3 Study of Ibrutinib (IMBRUVICA®) in Blood Cancer Diffuse Large B-Cell Lymphoma (DLBCL) and Ongoing Ibrutinib Clinical Program. Abbvie Press Release. July 2018. Available at: 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
9. Richardson PG, Bensinger WI, Huff CA, et al. Ibrutinib alone or with dexamethasone for relapsed or relapsed and refractory multiple myeloma: phase 2 trial results. Br J Haematol. 2018;180(6):821-830.
10. Jones, J., Andritsos, L., Kreitman, ert al. Efficacy and Safety of the Bruton Tyrosine Kinase Inhibitor Ibrutinib in Patients with Hairy Cell Leukemia: Stage 1 Results of a Phase 2 Study. Blood. 2016;128(22):1215.
11. Tam CS, Anderson MA, Pott C, et al. Ibrutinib plus Venetoclax for the Treatment of Mantle-Cell Lymphoma. N Engl J Med. 2018;378(13):1211-1223.
12. Grommes C, Pastore A, Palaskas N, et al. Ibrutinib Unmasks Critical Role of Bruton Tyrosine Kinase in Primary CNS Lymphoma. Cancer Discov. 2017;7(9):1018-1029.
13. Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib-Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia. N Engl J Med. 2019;381(5):432-443.
14. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. N Engl J Med. 2018;379(26):2517-2528.
15. Carpenter PA, Kang HJ, Yoo Kh, et al. Ibrutinib Treatment of Pediatric Chronic Graft-versus-Host Disease: Primary Results from the Phase 1/2 iMAGINE Study. Transplant Cell Ther. 2022 Aug 28:S2666-6367(22)01589-5. doi: 10.1016/j.jtct.2022.08.021.

Policy Implementation/Update:

Action and Summary of Changes	Date
Removed specialist requirement from renewal criteria	02/2025
Updated QL table to allow coverage of suspension in all indications	02/2024
Following withdrawal of FDA approval: removed mantle cell lymphoma (MCL) from covered indications, added MCL in the not medically necessary uses section, removed marginal zone lymphoma (MZL) from	04/2023

experimental and investigational uses section, added marginal zone lymphoma (MZL) in the not medically necessary uses section, updated renewal section with standard policy renewal language requirements, updated supporting evidence, changed quantity limits for 140 mg tablets and capsules and 280 mg tablets to allow for MCL and MZL dosing, removed MCL and MZL from quantity limits table, removed 560 mg tablet formulation, changed initial authorization length from three to six months.	
Updated cGVHD for the age expansion for those aged 1 year or older. Added criteria for the new formulation approved (70mg/ml suspension) for use in pediatric patients. Added in related policy table.	10/2022
Removed initial criteria and moved MZL indication to investigational or not medically necessary uses section. Added supporting evidence for MCL indication and updated MCL investigational or not medically necessary uses section. Moved ibrutinib (Imbruvica) in combination with obinutuzumab in the setting of treatment naïve CLL/SLL to investigational or not medically necessary uses section.	01/2022
Addition of split-fill requirement. Included requirement the member has not progressed on a previous BTK inhibitor. Updated policy based on new indication in combination with rituximab for CLL/SLL as not medically necessary. Criteria for CLL/SLL updated to focus on diagnosis and mutation status over use in combination with other agents. Updated criteria for MCL and MZL to only be used as monotherapy. Removed toxicity renewal requirement and added disease stability renewal examples for GVHD patients.	06/2020
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
Previous updates	08/2014 02/2015 04/2015 08/2017
Criteria created	02/2014