Pharmacy Policy Bulletin: J-0886 BTK Inhibitors – Commercial and Healthcare Reform	
Number: J-0886	**Category:** Prior Authorization
Line(s) of Business: ☒ Commercial ☒ Healthcare Reform ☐ Medicare	**Benefit(s):** **Commercial:** **Prior Authorization (1.):** **1.** Miscellaneous Specialty Drugs Oral = Yes with Prior Authorization **Quantity Limits (1., 2., 3., or 4.):** **1.** Rx Mgmt Quantity Limits = Safety/ Specialty **2.** Rx Mgmt Quantity Limits = Safety/Specialty + Dose Opt **3.** Rx Mgmt Quantity Limits = Safety/Specialty + Dose Opt + Watchful **4.** Quantity Limits = QPC = Yes **Healthcare Reform:** Not Applicable
Region(s): ☒ All ☐ Delaware ☐ New York ☐ Pennsylvania ☐ West Virginia	**Additional Restriction(s):** None
Version: J-0886-017	**Original Date:** 06/04/2003
Effective Date: 10/08/2025	**Review Date:** 09/17/2025

Drugs Product(s):	• Brukinsa (zanubrutinib) • Calquence (acalabrutinib) • Imbruvica (ibrutinib) • Jaypirca (pirtobrutinib) • Zydelig (idelalisib)
FDA-Approved Indication(s):	**Brukinsa (zanubrutinib)** • Treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. • Treatment of adult patients with Waldenström's macroglobulinemia (WM). • Treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one anti-CD20-based regimen. • Treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). • Treatment of adult patients with relapsed or refractory follicular lymphoma (FL), in combination with obinutuzumab after two or more lines of systemic therapy. **Calquence (acalabrutinib)**

	• Treatment of adult patients with previously untreated MCL who are ineligible for autologous hematopoietic stem cell transplantation (HSCT) in combination with bendamustine and rituximab. • Treatment of adult patients with MCL who have received at least one prior therapy. • Treatment of adult patients with CLL or SLL. **Imbruvica (ibrutinib)** • Treatment of adult patients with CLL or SLL • Treatment of adult patients with CLL/SLL with 17p deletion. • Treatment of adult patients with WM. • Adult and pediatric patients 1 year of age and older with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy. **Jaypirca (pirtobrutinib)** • Treatment of adult patients with relapsed or refractory mantle cell lymphoma (RR MCL) after at least two lines of systemic therapy, including a BTK inhibitor. • Treatment of adult patients with CLL or SLL who have received at least two prior lines of therapy, including a BTK inhibitor and a BCL-2 inhibitor. **Zydelig (idelalisib)** • Relapsed CLL, in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities

Background:	• Brukinsa is a small molecular inhibitor of Bruton's tyrosine kinase (BTK). In malignant B-cells, inhibition of BTK signaling resulted in reduced cell proliferation and tumor growth.
	  ○ In December 2023, the FDA approved a label update for Brukinsa that included superior progression-free survival (PFS) results from the Phase 3 ALPINE trial comparing Brukinsa to Imbruvica (ibrutinib) in previously treated patients with relapsed or refractory chronic lymphocytic leukemia (R/R CLL).
	  ○ Avoid concomitant use of moderate and strong CYP3A inducers with Brukinsa. If concomitant use with moderate CYP3A inducers cannot be avoided, increase the Brukinsa dose to 320 mg twice daily.
	• Per the NCCN B-Cell Lymphoma guidelines, first-line therapy for follicular lymphoma is based on age, tumor burden, comorbidities, and future treatment possibilities; therefore, treatment selection is highly individualized. Preferred first-line regimens include, but are not limited to: bendamustine + obinutuzumab or rituximab; cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) + obinutuzumab or rituximab; lenalidomide + rituximab; cyclophosphamide, vincristine, prednisone (CVP) + obinutuzumab or rituximab; and rituximab monotherapy. Preferred second-line therapies are similar, but in general, a first-line regimen is not repeated.
	• Calquence is an active metabolite, ACP-5862, that forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a signaling molecule of the B cell antigen receptor (BCR) and cytokine receptor pathways. In B cells, BTK signaling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion.
	  ○ It is recommended to avoid use of concomitant CYP3A4 inducers, such as rifampin, rifabutin, rifapentine, phenytoin, carbamazepine, phenobarbital, or St. John's Wort with Calquence. If concomitant use cannot be avoided, the dose of Calquence should be increased to 200 mg twice daily.
	• Imbruvica is a small-molecule inhibitor of BTK inhibitor. Imbruvica forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition

of BTK enzymatic activity. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion. Nonclinical studies show that Imbruvica inhibits malignant B-cell proliferation and survival in vivo as well as cell migration and substrate adhesion in vitro.

  - Imbruvica oral tablets and oral capsules should not be opened, broken, or chewed.
  - In April 2023, AbbVie withdrew from the US market the Imbruvica indication for mantle cell lymphoma (MCL) who have received at least one prior therapy. This indication was previously granted accelerated approval in November 2013 based on overall response rate data from a phase 2 study (NCT01236391). Data published in 2022 from the phase 3 SHINE (NCT01776840) study in previously untreated MCL met the primary endpoint of progression-free survival; however, the addition of Imbruvica to chemoimmunotherapy was associated with increased adverse reactions compared to the placebo-controlled arm.
  - In April 2023, AbbVie withdrew from the US market the Imbruvica indication marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy. This indication was previously granted accelerated approval in January 2017 based on ORR data from the phase 2 PCYC-1121 study (NCT01980628). Data from the Phase 3 SELENE study (NCT01974440) did not meet the primary endpoint of progression-free survival.

- Jaypirca is a small molecule, noncovalent inhibitor of BTK. BTK is a signaling protein of BCR and cytokine receptor pathways. In B-cells, BTK signaling results in the activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. Jaypirca inhibits BTK-mediated B-cell CD69 expression and inhibits malignant B-cell proliferation. Since Jaypirca is the first non-covalent or reversible BTKi, it targets a different bonding site on the BTK protein for its mechanism of action and can be used on patients who have failed a covalent BTKi.
  - Avoid concomitant use of strong CYP3A inhibitors with Jaypirca. If concomitant use of a strong CYP3A4 inhibitor is unavoidable, reduce the Jaypirca dose by 50 mg. If the current dosage is 50 mg once daily, interrupt Jaypirca treatment for the duration of strong CYP3A inhibitor use.
  - Avoid concomitant use of strong or moderate CYP3A inducers with Jaypirca. If concomitant use with moderate CYP3A inducers is unavoidable and the current dosage of Jaypirca is 200 mg once daily, increase the dose to 300 mg. If the current dosage is 50 mg or 100 mg once daily, increase the dose by 50 mg.
- Zydelig is an inhibitor of PI3Kδ kinase, which is expressed in normal and malignant B-cells. Idelalisib induced apoptosis and inhibited proliferation in cell lines derived from malignant B-cells and in primary tumor cells. Zydelig inhibits several cell signaling pathways, including B-cell receptor (BCR) signaling and the CXCR4 and CXCR5 signaling, which are involved in trafficking and homing of B-cells to the lymph nodes and bone marrow. Treatment of lymphoma cells with idelalisib resulted in inhibition of chemotaxis and adhesion, and reduced cell viability.
  - In February 2022, Gilead Sciences withdrew from the US market the B-cell non-Hodgkin lymphoma and small lymphocytic lymphoma (SLL) indication for Zydelig. These indications were previously granted accelerated approval by the FDA in 2014.
- Anti-CD20-based regimens utilized in the treatment of MZL may include bendamustine + obinutuzumab or rituximab, lenalidomide + rituximab, etc.

	• Prescribing Considerations: ○ Kinase inhibitors should be prescribed under the supervision of a hematologist/oncologist.

Approval Criteria

I. Initial Authorization

A. Brukinsa

1. Mantle Cell Lymphoma (MCL)

When a benefit, coverage of Brukinsa may be approved when all of the following criteria are met **(a., b., and c.)**:

a. The member is 18 years of age or older.
b. The member has a diagnosis of MCL (ICD-10 C83.1).
c. The member has received at least one (1) prior therapy.

2. Waldenström's Macroglobulinemia (WM)

When a benefit, coverage of Brukinsa may be approved when all of the following criteria are met **(a. and b.)**:

a. The member is 18 years of age or older.
b. The member has a diagnosis of WM (ICD-10 C88.0).

3. Marginal Zone Lymphoma (MZL)

When a benefit, coverage of Brukinsa may be approved when all of the following criteria are met **(a., b., and c.)**:

a. The member is 18 years of age or older.
b. The member has a diagnosis of relapsed or refractory MZL (ICD-10 C88).
c. The member has received at least one previous anti-CD20-based regimen.

4. Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL)

When a benefit, coverage of Brukinsa may be approved when all of the following criteria are met **(a. and b.):**

a. The member is 18 years of age or older.
b. The member has a diagnosis of CLL or SLL (No ICD-10 code).

5. Follicular Lymphoma (FL)

When a benefit, coverage of Brukinsa may be approved when all of the following criteria are met **(a. through d.)**:

a. The member is 18 years of age or older.
b. The member has a diagnosis of relapsed or refractory FL (ICD-10: C82).
c. The member will be using Brukinsa in combination with obinutuzumab (Gazyva).
d. The member has received at least two (2) prior lines of systemic therapy.

B. Calquence

1. Mantle Cell Lymphoma (MCL)

When a benefit, coverage of Calquence may be approved when all of the following criteria are met **(a. and b.):**

a. The member is 18 years of age or older.
b. The member has a diagnosis of MCL (ICD-10 C83.1) and meets one (1) of the following criteria **(i. or ii.):**
  i. The member has received at least one (1) prior therapy.
  ii. The member has not received prior therapy and meets all of the following criteria **(A) and B)):**
    A) The member is ineligible for autologous hematopoietic stem cell transplantation.

B) The member is using Calquence in combination with bendamustine and rituximab.

2. **Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL)**
When a benefit, coverage of Calquence may be approved when all of the following criteria are met **(a. and b.):**
   a. The member 18 years of age or older.
   b. The member has a diagnosis of CLL or SLL (No ICD-10 code).

C. Imbruvica
When a benefit, coverage of Imbruvica may be approved when all of the following criteria are met **(1., 2., and 3.)**:
1. The member meets one (1) of the following criteria **(a., b., or c.)**:

   a. Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia (CLL/SLL)
      i. The member is 18 years of age or older and has a diagnosis of CLL or SLL (No ICD-10 code).

   b. Waldenström's Macroglobulinemia (WM)
      i. The member is 18 years of age or older and has a diagnosis of WM (ICD-10 C88.0).

   c. Chronic Graft vs. Host Disease (cGVHD)
      i. The member is one (1) year of age or older and meets all of the following criteria **(A), B), and C))**:
         A) The member has a diagnosis of cGVHD (ICD-10 D89. 811).
         B) The member has received prior systemic therapy.
         C) If the request is for Imbruvica oral suspension, the member has an inability to swallow plan-preferred oral tablets or oral capsules.

2. If the request is for Imbruvica 140 mg tablets or 280 mg tablets, the member meets the following criterion **(a.)**:
   a. The member has experienced therapeutic failure or intolerance to plan-preferred Imbruvica 140 mg capsules.

3. If the request is for Imbruvica oral suspension, all of the following criteria are met **(a. and b.)**:
   a. The member has an inability to swallow oral tablets.
   b. The member has an inability to swallow oral capsules.

D. Jaypirca
1. **Mantle Cell Lymphoma (MCL)**
When a benefit, coverage of Jaypirca may be approved when all of the following criteria are met **(a., b., and c.):**
   a. The member is 18 years of age or older.
   b. The member has a diagnosis of relapsed or refractory MCL (ICD-10 C83.1).
   c. The member has received at least two (2) previous lines of systemic therapy, at least one (1) of which was a BTK inhibitor.

2. **Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia (CLL/SLL)**
When a benefit, coverage of Jaypirca may be approved when all of the following criteria are met **(a., b., and c.):**
   a. The member is 18 years of age or older.
   b. The member has a diagnosis of CLL or SLL (No ICD-10 code).
   c. The member has received at least two (2) prior lines of therapy, including at least one (1) from all of the following classes **(i. and ii.)**:

i. A BTK inhibitor
ii. A BCL-2 inhibitor [for example Venclexta (venetoclax)]

E. Zydelig

1. Chronic Lymphocytic Leukemia (CLL)
When a benefit, coverage of Zydelig may be approved when all of the following criteria are met **(a. through d.)**:
a. The member is 18 years of age or older.
b. The member has a diagnosis of relapsed CLL.
c. The prescriber provides documentation that idelalisib will be used in combination with rituximab.
d. The prescriber documents that the use of rituximab alone would be appropriate due to other comorbidities.

II. Quantity Limits

A. Brukinsa
When a benefit, additional quantities of Brukinsa 80 mg capsules, up to 8 capsules per day, or Brukinsa 160 mg tablets, up to 4 tablets per day, may be approved when the following criterion is met **(1.)**:
1. The member is taking a moderate CYP3A inducer.

B. Calquence
When a benefit, additional quantities of Calquence 100 mg, up to 4 tablets or capsules per day, may be approved when the following criterion is met **(1.)**:
1. The member is taking a strong CYP3A4 inducer.

C. Jaypirca
When a benefit, additional quantities of Jaypirca 100 mg, up to 3 tablets per day, OR Jaypirca 50 mg, up to 3 tablets per day, may be approved when the following criterion is met **(1.)**:
1. The member is taking a moderate CYP3A4 inducer.

III. Reauthorization
When a benefit, reauthorization of a BTK inhibitor may be approved when the following criterion is met **(A.)**:
A. The prescriber attests that the member is tolerating therapy and has experienced a therapeutic response defined as one (1) of the following **(1. or 2.)**:
1. Disease improvement
2. Delayed disease progression

IV. An exception to some or all of the criteria above may be granted for select members and/or circumstances based on state and/or federal regulations.

V. Coverage of oncology medications listed in this policy may be approved on a case-by-case basis per indications supported in the most current NCCN guidelines.

Limitations of Coverage

I. Coverage of drug(s) addressed in this policy for disease states outside of the FDA-approved indications should be denied based on the lack of clinical data to support effectiveness and safety in other conditions unless otherwise noted in the approval criteria.
II. For Commercial or HCR members with a closed formulary, a non-formulary product will only be approved if the member meets the criteria for a formulary exception in addition to the criteria outlined within this policy.

Authorization Duration

- Commercial and HCR Plans: If approved, up to a 12 month authorization may be granted.

Automatic Approval Criteria

None

Refer to J-0699 and J-0652 for previous versions.

References:

1. Brukinsa [package insert]. San Mateo, California: BeiGene USA, Inc.; June 2025.
2. Calquence [package insert]. Wilmington, DE: AstraZeneca; January 2025.
3. Imbruvica [package insert]. Sunnyvale, CA: Pharmacyclics Inc.; December 2024.
4. Jaypirca [package insert]. Indianapolis, IN: Lilly USA, LLC; June 2024.
5. Zydelig [package insert]. Foster City, CA: Gilead Sciences, Inc.; February 2022.
6. AbbVie. Update on IMBRUVICA® (ibrutinib) U.S. Accelerated Approvals for Mantle Cell Lymphoma and Marginal Zone Lymphoma Indications. Published April 6, 2023. Available at: https://news.abbvie.com/news/press-releases/update-on-imbruvica-ibrutinib-us-accelerated-approvals-for-mantle-cell-lymphoma-and-marginal-zone-lymphoma-indications.htm. Accessed March 18, 2025.
7. Wang ML, Jurczak W, Jerkeman M, et al. Ibrutinib plus Bendamustine and Rituximab in Untreated Mantle-Cell Lymphoma. *N Engl J Med*. 2022 Jun 30;386(26):2482-2494.
8. ClinicalTrials.gov. A Study of PCI-32765 (Ibrutinib) in Combination With Either Bendamustine and Rituximab or Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Participants With Previously Treated Indolent Non-Hodgkin Lymphoma (SELENE). Available at: https://www.clinicaltrials.gov/ct2/show/NCT01974440. Accessed March 18, 2025.
9. National Comprehensive Cancer Network. NCCN Guidelines Version 2.2025 B-Cell Lymphomas. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed March 18, 2025.

Pharmacy policies do not constitute medical advice, nor are they intended to govern physicians' prescribing or the practice of medicine. They are intended to reflect the plan's coverage and reimbursement guidelines. Coverage may vary for individual members, based on the terms of the benefit contract.

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