PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Oral – Bruton's Tyrosine Kinase Inhibitor) – Imbruvica Prior Authorization Policy
- Imbruvica® (ibrutinib tablets, capsules, and oral suspension – Pharmacyclics/Janssen)

REVIEW DATE: 06/11/2025; selected revision 06/18/2025

INSTRUCTIONS FOR USE

THE FOLLOWING COVERAGE POLICY APPLIES TO HEALTH BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. CERTAIN CIGNA COMPANIES AND/OR LINES OF BUSINESS ONLY PROVIDE UTILIZATION REVIEW SERVICES TO CLIENTS AND DO NOT MAKE COVERAGE DETERMINATIONS. REFERENCES TO STANDARD BENEFIT PLAN LANGUAGE AND COVERAGE DETERMINATIONS DO NOT APPLY TO THOSE CLIENTS. COVERAGE POLICIES ARE INTENDED TO PROVIDE GUIDANCE IN INTERPRETING CERTAIN STANDARD BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. PLEASE NOTE, THE TERMS OF A CUSTOMER'S PARTICULAR BENEFIT PLAN DOCUMENT [GROUP SERVICE AGREEMENT, EVIDENCE OF COVERAGE, CERTIFICATE OF COVERAGE, SUMMARY PLAN DESCRIPTION (SPD) OR SIMILAR PLAN DOCUMENT] MAY DIFFER SIGNIFICANTLY FROM THE STANDARD BENEFIT PLANS UPON WHICH THESE COVERAGE POLICIES ARE BASED. FOR EXAMPLE, A CUSTOMER'S BENEFIT PLAN DOCUMENT MAY CONTAIN A SPECIFIC EXCLUSION RELATED TO A TOPIC ADDRESSED IN A COVERAGE POLICY. IN THE EVENT OF A CONFLICT, A CUSTOMER'S BENEFIT PLAN DOCUMENT ALWAYS SUPERSEDES THE INFORMATION IN THE COVERAGE POLICIES. IN THE ABSENCE OF A CONTROLLING FEDERAL OR STATE COVERAGE MANDATE, BENEFITS ARE ULTIMATELY DETERMINED BY THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT. COVERAGE DETERMINATIONS IN EACH SPECIFIC INSTANCE REQUIRE CONSIDERATION OF 1) THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT IN EFFECT ON THE DATE OF SERVICE; 2) ANY APPLICABLE LAWS/REGULATIONS; 3) ANY RELEVANT COLLATERAL SOURCE MATERIALS INCLUDING COVERAGE POLICIES AND; 4) THE SPECIFIC FACTS OF THE PARTICULAR SITUATION. EACH COVERAGE REQUEST SHOULD BE REVIEWED ON ITS OWN MERITS. MEDICAL DIRECTORS ARE EXPECTED TO EXERCISE CLINICAL JUDGMENT WHERE APPROPRIATE AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. WHERE COVERAGE FOR CARE OR SERVICES DOES NOT DEPEND ON SPECIFIC CIRCUMSTANCES, REIMBURSEMENT WILL ONLY BE PROVIDED IF A REQUESTED SERVICE(S) IS SUBMITTED IN ACCORDANCE WITH THE RELEVANT CRITERIA OUTLINED IN THE APPLICABLE COVERAGE POLICY, INCLUDING COVERED DIAGNOSIS AND/OR PROCEDURE CODE(S). REIMBURSEMENT IS NOT ALLOWED FOR SERVICES WHEN BILLED FOR CONDITIONS OR DIAGNOSES THAT ARE NOT COVERED UNDER THIS COVERAGE POLICY (SEE "CODING INFORMATION" BELOW). WHEN BILLING, PROVIDERS MUST USE THE MOST APPROPRIATE CODES AS OF THE EFFECTIVE DATE OF THE SUBMISSION. CLAIMS SUBMITTED FOR SERVICES THAT ARE NOT ACCOMPANIED BY COVERED CODE(S) UNDER THE APPLICABLE COVERAGE POLICY WILL BE DENIED AS NOT COVERED. COVERAGE POLICIES RELATE EXCLUSIVELY TO THE ADMINISTRATION OF HEALTH BENEFIT PLANS. COVERAGE POLICIES ARE NOT RECOMMENDATIONS FOR TREATMENT AND SHOULD NEVER BE USED AS TREATMENT GUIDELINES. IN CERTAIN MARKETS, DELEGATED VENDOR GUIDELINES MAY BE USED TO SUPPORT MEDICAL NECESSITY AND OTHER COVERAGE DETERMINATIONS.

CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Imbruvica, a Bruton's tyrosine kinase (BTK) inhibitor, is indicated for the following uses:[1]

- **Chronic lymphocytic leukemia (CLL)** or **small lymphocytic lymphoma (SLL),** in adults.
- **CLL** or **SLL,** with 17p deletion, in adults.
- **Graft-versus-host disease, chronic**, after failure of one or more lines of systemic therapy in adults and pediatric patients ≥ 1 year old.
- **Waldenström macroglobulinemia,** in adults.

Guidelines

Imbruvica is discussed in guidelines from the National Comprehensive Cancer Network (NCCN):

- **B-Cell Lymphomas:** NCCN guidelines (version 2.2025 – February 10, 2025) address mantle cell lymphoma, marginal zone lymphoma, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, non-gastric MALT lymphoma, diffuse large B-cell lymphomas, Acquired Immune Deficiency Syndrome (AIDS)-related B-Cell lymphomas, and post-transplant lymphoproliferative disorders.[2] The NCCN compendium recommends Imbruvica as a second-line and subsequent therapy for diffuse large B-cell lymphomas, human immunodeficiency virus (HIV)-related B-Cell lymphomas, post-transplant lymphoproliferative disorders, and high-grade B-cell lymphoma (category 2A).[3]
    - **Mantle cell lymphoma**: Imbruvica + rituximab is recommended as pretreatment in order to limit the number of cycles of aggressive induction therapy with RHyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone) regimen (category 2A). Imbruvica ± rituximab is recommended as second-line and subsequent therapy as "other recommended regimen" and Imbruvica + Venclexta (venetoclax tablets) as "useful in certain circumstances" (both category 2A).[2] Imbruvica is recommended as a "preferred" aggressive induction therapy as a component of TRIANGLE regimen: alternating RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) + covalent BTK inhibitor (Imbruvica)/RDHA (rituximab, dexamethasone, and cytarabine) + platinum regimen (category 2A). Imbruvica + rituximab is recommended as maintenance therapy (category 2A).
    - **Marginal zone lymphoma**: Imbruvica is recommended as second-line and subsequent therapy as "other recommended regimens" (category 2A). NCCN panel continues to recommend Imbruvica for marginal zone lymphoma, although this indication was withdrawn from Imbruvica's labeling following results of phase III confirmatory studies. While the Panel acknowledged the change in the regulatory status of Imbruvica, the consensus of the Panel was to continue the listing of Imbruvica monotherapy as an option for second-line and subsequent therapy based on the efficacy results from earlier phase II multicenter study in relapsed or refractory marginal zone lymphoma.
- **Central Nervous System (CNS) Cancers**: NCCN guidelines (version 1.2025 – June 3, 2025) recommend Imbruvica as one of the options for patients with relapsed or refractory disease for primary CNS lymphoma as "other recommended regimens" (category 2A).[4] The guidelines also recommend Imbruvica for induction therapy as a single agent as "useful in certain circumstances" if the patient is unsuitable for or intolerant to high-dose methotrexate (category 2A).[4] Imbruvica is used with high-dose methotrexate and rituximab in some clinical scenarios (category 2A).[4] Imbruvica is also recommended as treatment for brain metastases in lymphoma (category 2A).
- **CLL/SLL:** NCCN guidelines (version 3.2025 – April 2, 2025) recommend Imbruvica as a treatment option in various scenarios (e.g., first-line therapy for patients with or without 17p deletion/TP53 mutation and as second-line and third therapy [category 1 recommendations for many scenarios]) as "other

recommended regimens".[5] Imbruvica plays a vital role in the management of CLL/SLL and many trials describe its efficacy.[5]

- **Hairy Cell Leukemia**: NCCN guidelines (version 1.2025 – September 26, 2024) recommend Imbruvica as one of the options for treatment of progressive disease after therapy for relapsed or refractory disease as "other recommended regimens" (category 2A).[6]
- **Graft-Versus-Host Disease:** NCCN guidelines for hematopoietic stem cell transplantation (version 2.2025 – June 3, 2025) recommend Imbruvica as a systemic agent for steroid-refractory chronic graft-versus-host disease after failure of one or more lines of systemic therapy in patients ≥ 1 years of age (category 2A).[7] The guidelines note that Imbruvica should be used with caution in patients with history of heart arrhythmias or heightened risk of bleeding.
- **Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphomas:** NCCN guidelines (version 3.2025 – February 6, 2025) recommend Imbruvica ± rituximab, as a primary therapy option or therapy for previously treated disease as a "preferred" regimen (category 1).[8] Imbruvica is also a "preferred" regimen for symptomatic management of Bing Neel Syndrome (category 2A).[8]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Imbruvica. All approvals are provided for the duration noted below.

- **Imbruvica® (ibrutinib tablets, capsules, and oral suspension - Pharmacyclics/Janssen)**

is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

FDA-Approved Indications

1. **Chronic Lymphocytic Leukemia.** Approve for 1 year if the patient is ≥ 18 years of age.

2. **Graft-Versus-Host Disease, Chronic:** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Patient is ≥ 1 year of age; AND
   B) Patient has tried at least one systemic medication for graft-versus-host disease.
   Note: Examples of systemic medications include: corticosteroids (methylprednisolone, prednisone), imatinib, low-dose methotrexate, sirolimus, mycophenolate mofetil, Jakafi (ruxolitinib tablets), Rezurock (belumosudil tablets), Niktimvo (axatilimab-csfr intravenous infusion), hydroxychloroquine, rituximab, pentostatin, interleukin-2 (e.g., Proleukin [aldesleukin intravenous infusion]), cyclosporine, tacrolimus, sirolimus, an etanercept product.

3. **Small Lymphocytic Lymphoma.** Approve for 1 year if the patient is ≥ 18 years of age.

4. **Waldenström Macroglobulinemia.** Approve for 1 year if the patient is ≥ 18 years of age.
   Note: This includes lymphoplasmacytic lymphoma and Bing-Neel syndrome.

Other Uses with Supportive Evidence

5. **B-Cell Lymphoma.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   Note: Examples of B-cell lymphomas include: diffuse large B-cell lymphomas, Human immunodeficiency virus (HIV)-related B-cell lymphomas, post-transplant lymphoproliferative disorders, and high-grade B-cell lymphoma.
   A) Patient is ≥ 18 years of age; AND
   B) Patient has tried at least one systemic regimen.
   Note: Examples of a systemic regimen include one or more of the following products: cisplatin, cytarabine, rituximab, oxaliplatin, gemcitabine, ifosfamide, carboplatin, etoposide, or rituximab.

6. **Hairy Cell Leukemia.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has tried at least two systemic regimens.
   Note: Examples of a systemic regimen include one or more of the following products: cladribine, pentostatin, rituximab, Pegasys (peginterferon alfa-2a subcutaneous injection), Mekinist (trametinib tablets or oral solution), Tafinlar (dabrafenib capsules or tablets for oral suspension), or Zelboraf (vemurafenib tablets).

7. **Mantle Cell Lymphoma.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient meets ONE of the following (i, ii, or iii):
      i. Patient is continuing therapy with Imbruvica and meets ONE of the following (a or b):
         a) Patient has tried at least one systemic regimen; OR
         Note: Examples of a systemic regimen include one or more of the following products: bendamustine, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, cytarabine, carboplatin, cisplatin, oxaliplatin, or lenalidomide.
         b) According to the prescriber, patient is not a candidate for a chemotherapy regimen; OR
      ii. Imbruvica is used in combination with rituximab prior to induction therapy; OR
      Note: Examples of induction therapy include: rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone.

iii. Imbruvica is used as induction or maintenance therapy in combination with chemotherapy.

8. Marginal Zone Lymphoma. Approve for 1 year if the patient meets ALL of the following (A, B and C):
Note: Marginal zone lymphoma includes gastric mucosa-associated lymphoid tissue (MALT) lymphoma, non-gastric MALT lymphoma, nodal marginal zone lymphoma, and splenic marginal zone lymphoma.
A) Patient is ≥ 18 years of age; AND
B) Patient is continuing therapy with Imbruvica; AND
C) Patient has tried at least one systemic regimen.
Note: Examples of a systemic regimen include one or more of the following products: bendamustine, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, or lenalidomide.

9. Primary Central Nervous System Lymphoma. Approve for 1 year if the patient meets BOTH of the following (A and B):
A) Patient ≥ 18 years of age; AND
B) Patient meets ONE of the following (i or ii):
i. According to the prescriber, the patient is not a candidate for or is intolerant to high-dose methotrexate; OR
ii. Patient has tried at least one therapy.
Note: Examples of therapies include methotrexate, rituximab, vincristine, procarbazine, cytarabine, thiotepa, carmustine, intrathecal methotrexate, cytarabine, or rituximab.

CONDITIONS NOT COVERED

- **Imbruvica® (ibrutinib tablets, capsules, and oral suspension - Pharmacyclics/Janssen)**

is(are) considered not medically necessary for ANY other use(s); criteria will be updated as new published data are available.

REFERENCES

1. Imbruvica® tablets, capsules, and oral solution [prescribing information]. Sunnyvale, CA and Horsham, PA: Pharmacyclics/Janssen; December 2024.
2. The NCCN B-Cell Lymphomas Guidelines in Oncology (version 2.2025 – February 10, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 9, 2025.
3. The NCCN Drugs and Biologics Compendium. © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 5, 2025. Search term: ibrutinib.
4. The NCCN Central Nervous System Cancers Guidelines in Oncology (version 1.2025 – June 3, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 9, 2025.
5. The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Clinical Practice Guidelines in Oncology (version 3.2025 – April 2, 2025). © 2025 National Comprehensive Cancer Network. Available at http://www.nccn.org. Accessed on June 5, 2025.

6. The NCCN Hairy Cell Leukemia Guidelines in Oncology (version 1.2025 – September 26, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 5, 2025.
7. The NCCN Hematopoietic Cell Transplantation (HCT) Guidelines in Oncology (version 2.2025 – June 3, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 5, 2025.
8. The NCCN Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma Clinical Practice Guidelines in Oncology (version 3.2025 – February 6, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 5, 2025.

HISTORY

Type of Revision	Summary of Change	Review Date
Annual Revision	**Mantle Cell Lymphoma**: The requirement that the patient is continuing therapy now only applies to a patient that has tried at least one systemic regimen or according to the prescriber, patient is not a candidate for a systemic regimen (i.e., an elderly person who is frail); previously this criteria only approved for patients continuing therapy. An alternative option of approval was added when Imbruvica is used as induction or maintenance therapy in combination with chemotherapy.	07/12/2023
Annual Revision	No criteria changes.	06/12/2024
Update	**04/08/2025**: The policy name was changed from "Oncology – Imbruvica PA Policy" to "Oncology (Oral - Bruton's Tyrosine Kinase Inhibitor) – Imbruvica PA Policy".	--
Annual Revision	**Graft-Versus-Host Disease, Chronic:** The requirement that the patient has tried at least "one conventional systemic treatment" for graft-versus-host disease was reworded to "one systemic medication for graft-versus-host disease". The following medications were added to the Note of examples of a systemic regime: Rezurock (belumosudil tablets), Niktimvo (axatilimab-csfr intravenous infusion), hydroxychloroquine, rituximab, pentostatin, interleukin-2 (e.g., Proleukin [aldesleukin intravenous infusion]), cyclosporine, tacrolimus, sirolimus, an etanercept product. **Hairy Cell Leukemia:** The following medications were added to the Note of examples of a systemic regimen: Mekinist (trametinib tablets or oral solution), Tafinlar (dabrafenib capsules or tablets for oral suspension), or Zelboraf (vemurafenib tablets). **Mantle Cell Lymphoma:** The wording of "systemic regimen" was reworded to "chemotherapy regimen" for the option of approval which previously stated "according to the prescriber, patient is not a candidate for a systemic regimen (i.e., an elderly person who is frail)."	06/11/2025
Selected Revision	**Mantle Cell Lymphoma:** The wording "i.e., an elderly patient who is frail" was removed from the requirement which previously stated, "according to the prescriber, patient is not a candidate for a chemotherapy regimen (i.e., an elderly patient who is frail)".	06/18/2025