09-J2000-23

Original Effective Date: 12/15/14

Reviewed: 07/10/19

Revised: 08/15/19

Subject: Idelalisib (Zydelig®) Oral Tablet

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Idelalisib (Zydelig) was approved by the U.S. Food and Drug Administration (FDA) in July 2014 for the treatment of relapsed chronic lymphocytic leukemia (CLL), follicular B-cell non-Hodgkin lymphoma (FL), and small lymphocytic lymphoma (SLL). Prior to FDA approval, idelalisib was granted orphan drug designation by the FDA in 2013 for these same three indications. Idelalisib was also granted orphan drug designation, as sponsored by the innovator drug company, in 2013 for lymphoplasmacytic lymphoma with or without Waldenström's macroglobulinemia, as well as splenic, nodal, and extranodal marginal zone lymphomas. Idelalisib inhibits phosphatidylinositol 3-kinase (PI3K), which is expressed in both normal and malignant B-cells, to induce apoptosis and inhibit cell proliferation.

Idelalisib is indicated in combination with rituximab for the treatment of relapsed CLL in adults when rituximab alone is appropriate therapy due to other comorbidities. In a randomized study in patients with relapsed chronic lymphocytic leukemia unable to undergo chemotherapy (N=220), idelalisib plus rituximab compared with rituximab plus placebo significantly improved 24-week progression-free survival (93% vs 46%), 12-month overall survival (92% vs 80%), and overall response rate (81% vs 13%).

Accelerated approval for idelalisib was permitted for treatment of relapsed FL and SLL on the basis of overall response rate in a clinical study. Continued approval will depend on verification of clinical benefit in confirmatory studies. Idelalisib treatment resulted in an overall response rate of 57% (6% complete; 50% partial; 1% minor) in the open-label DELTA study (N=125) of patients with B-cell indolent non-Hodgkin lymphomas who had not responded or relapsed within 6 months of receipt of rituximab and an alkylating agent. Included in the study were 28 patients with small lymphocytic lymphoma. Treatment duration was 6.6 months. The median time to response was 1.9 months, and the duration of response

was 12.5 months. Median progression-free survival was 11 months, and median overall survival was 20.3 months.

The National Comprehensive Cancer Network (NCCN) Guidelines for Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma (CLL/SLL) (Version 5.2019) list idelalisib in combination with rituximab, as a category 1 recommendation, under "Preferred regimens", and idelalisib monotherapy, as a category 2A recommendation, under "Other recommended regimens" for the second-line or later treatment of relapsed or refractory CLL/SLL with or without del(17p) mutation. The NCCN Guidelines for B-Cell Lymphomas (Version 5.2019) list idelalisib monotherapy, as a category 2A recommendation, under "Other recommended regimens" for the treatment of follicular lymphoma, gastric and non-gastric mucosa associated lymphoid tissue (MALT) lymphoma, and nodal or splenic marginal zone lymphoma in patients that are relapsed or refractory after two prior therapies.

POSITION STATEMENT:

Comparative Effectiveness

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

The initiation of idelalisib (Zydelig) **meets the definition of medical necessity** when used for **ANY** of the following indications ("1" to "8"), the dosage does not exceed 150 mg twice daily (achieved using the few number of tablets possible), and all indication-specific criteria are met:

1. Chronic lymphocytic leukemia (CLL)
    a. Member's disease is relapsed or refractory to prior first-line systemic treatment
    b. Use is in combination with rituximab (Rituxan) or as monotherapy
2. Follicular lymphoma
    a. Member has relapsed or refractory disease
    b. Member has received at least two prior systemic therapies for their disease
    c. Use is as a single agent
3. Gastric mucosa-associated lymphoid tissue (MALT) lymphoma
    a. Member has relapsed or refractory disease
    b. Member has received at least two prior systemic therapies for their disease
    c. Use is as a single agent
4. Nodal marginal zone lymphoma
    a. Member has relapsed or refractory disease
    b. Member has received at least two prior systemic therapies for their disease
    c. Use is as a single agent
5. Non-gastric MALT lymphoma
    a. Member has relapsed or refractory disease

b. Member has received at least two prior systemic therapies for their disease

c. Use is as a single agent

6. Small lymphocytic lymphoma (SLL)
   a. Member's disease is relapsed or refractory to prior first-line systemic treatment
   b. Use is in combination with rituximab (Rituxan) or as monotherapy
7. Splenic marginal zone lymphoma
   a. Member has relapsed or refractory disease
   b. Member has received at least two prior systemic therapies for their disease
   c. Use is as a single agent
8. Other FDA-approved or NCCN supported diagnosis (not previously listed above) when **ONE** of the following is met ("a" or "b"):
   a. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)
   b. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation

Duration of approval: 6 months

Continuation of idelalisib (Zydelig) **meets the definition of medical necessity** when **ALL** of the following are met ("1", "2", and "3"):

1. Authorization or reauthorization for idelalisib (Zydelig) has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of CLL/SLL, follicular lymphoma, MALT lymphoma (gastric or non-gastric), nodal marginal cell lymphoma, splenic marginal zone lymphoma, or other FDA-approved or NCCN-supported diagnosis; **OR** the member previously met **ALL** indication-specific initiation criteria
2. The member has not experienced disease progression while receiving treatment with idelalisib
3. The member's dosage does not exceed 150 mg twice daily achieved using the few number of tablets possible

Duration of approval: 1 year

The use of idelalisib (Zydelig) **does NOT meet the definition of medical necessity** for the orphan indication of lymphoplasmacytic lymphoma with or without Waldenström's macroglobulinemia due to a reported high incidence of hepatoxicity and the availability of efficacious and better-studied alternative treatments.

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- In combination with rituximab, for the treatment of patients with relapsed chronic lymphocytic leukemia (CLL) for whom rituximab alone would be considered appropriate therapy due to other co-morbidities.
- Treatment of patients with relapsed follicular B-cell non-Hodgkin lymphoma (FL) who have received at least two prior systemic therapies.
- Treatment of patients with relapsed small lymphocytic lymphoma (SLL) who have received at least two prior systemic therapies.

The recommended dosage is 150 mg orally, twice daily. Continue treatment until disease progression or unacceptable toxicity. The optimal and safe dosing regimen for patients who receive treatment longer than several months is unknown. The package insert specifically states as a "Limitation of Use" that idelalisib is not indication and is not recommended for first line treatment of patients with CLL, FL, or SLL. For FL treatment there is an additional "Limitation of Use" stating that idelalisib is not indicated and is not recommended in combination with bendamustine and/or rituximab. For SLL and FL accelerated approval was granted based on Overall Response Rate. An improvement in patient survival or disease related symptoms has not been established. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.

Dose Adjustments

- Renal impairment: No dosage adjustment is necessary for patients with creatinine clearance (CrCl) ≥15 mL/min. No data is available for patients with a CrCl <15 mL/min.
- Hepatic impairment: Safety and efficacy data are not available in patients with baseline ALT or AST values greater than 2.5 × upper limit of normal (ULN) or bilirubin values greater than 1.5 × ULN, as these patients were excluded from clinical trials. The AUC of idelalisib increased up to 1.7-fold in subjects with ALT or AST or bilirubin greater than the ULN compared to healthy subjects with normal ALT or AST or bilirubin values.
- Adverse reactions: Refer to product label. Specific recommendations are given based on ALT/AST changes, bilirubin changes, diarrhea, neutropenia, thrombocytopenia, and infections. The dose may need to be withheld and reduced to 100 mg BID or treatment permanently discontinued. No dose modification is required for lymphocytosis, which has been observed in some patients taking idelalisib. This observed lymphocytosis is a pharmacodynamic effect and should NOT be considered progressive disease in the absence of other clinical findings.

Drug Availability

- Tablets: 100 mg and 150 mg

PRECAUTIONS:

Boxed Warning

- Fatal and/or serious hepatotoxicity occurred in 16 to 18% of idelalisib-treated patients. Monitor hepatic function prior to and during treatment. Interrupt and then reduce or discontinue idelalisib as recommended.
- Fatal and/or serious and severe diarrhea or colitis occurred in 14% to 20% of idelalisib -treated patients. Monitor for the development of severe diarrhea or colitis. Interrupt and then reduce or discontinue idelalisib as recommended.
- Fatal and/or serious pneumonitis occurred in 4% of idelalisib -treated patients. Monitor for pulmonary symptoms and bilateral interstitial infiltrates. Interrupt or discontinue idelalisib as recommended.

- Fatal and/or serious infections occurred in 21% to 48% of idelalisib-treated patients. Monitor for signs and symptoms of infection. Interrupt idelalisib if infection is suspected.
- Fatal and serious intestinal perforation can occur in idelalisib-treated patients across clinical trials. Discontinue idelalisib for intestinal perforation.

Contraindications

- History of serious allergic reactions including anaphylaxis and toxic epidermal necrolysis

Precautions/Warnings

- **See Boxed Warnings**
- **Severe cutaneous reactions**: Fatal cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have occurred. Monitor patients for the development of severe cutaneous reactions and discontinue idelalisib
- **Anaphylaxi**s: Monitor patients for anaphylaxis and discontinue idelalisib.
- **Neutropenia**: Treatment-emergent Grade 3 or 4 neutropenia occurred in 25% of patients treated with monotherapy and 58% of patients treated in combination with rituximab or with unapproved combination therapies. Monitor blood counts at least every 2 weeks for the first 6 months of therapy, and at least weekly in patients while neutrophil counts are less than 1,000/mm^3.
- **Embryo-fetal toxicity**: May cause fetal harm. Advise women of potential risk to a fetus and to avoid pregnancy while taking idelalisib. If contraceptive methods are being considered, use effective contraception during treatment, and for at least 1 month after the last dose.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

C9399	Unclassified drugs or biologicals (Hospital Outpatient Use ONLY)
J8999	Prescription drug, oral, chemotherapeutic, Not Otherwise Specified

ICD-10 Diagnosis Codes That Support Medical Necessity

C82.00 – C82.09	Follicular lymphoma grade I
C82.10 – C82.19	Follicular lymphoma grade II
C82.20 – C82.29	Follicular lymphoma grade III, unspecified
C82.30 – C82.39	Follicular lymphoma grade IIIa
C82.40 – C82.49	Follicular lymphoma grade IIIb
C82.50 – C82.59	Diffuse follicle center lymphoma
C82.60 – C82.69	Cutaneous follicle center lymphoma
C82.80 – C82.89	Other types of follicular lymphoma
C82.90 – C82.99	Follicular lymphoma, unspecified
C83.00 – C83.09	Small cell B-cell lymphoma
C83.50 – C83.59	Lymphoblastic (diffuse) lymphoma
C83.80 - C83.89	Other non-follicular lymphoma
C85.80 – C85.89	Other specified types of non-Hodgkin lymphoma
C88.4	Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue [MALT-lymphoma]

C91.10	Chronic lymphocytic leukemia of B-cell type not having achieved remission
C91.12	Chronic lymphocytic leukemia of B-cell type in relapse

REIMBURSEMENT INFORMATION:

Refer to **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: BCBSF has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

None

RELATED GUIDELINES:

Allogeneic Bone Marrow and Stem Cell Transplantation, 02-38240-01

Autologous Bone Marrow and Stem Cell Transplantation, 02-38241-01

Bendamustine (Treanda), 09-J2000-40

Duvelisib (Copiktra), 09-J3000-14

Ibrutinib (Imbruvica), 09-J2000-09

Lenalidomide (Revlimid), 09-J0000-80

Obinutuzumab (Gazyva) Injection, 09-J2000-07

Procarbazine (Matulane), 09-J1000-59

Rituximab (Rituxan), 09-J0000-59

OTHER:

None

REFERENCES:

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 7/10/19.

GUIDELINE UPDATE INFORMATION:

12/15/14	New Medical Coverage Guideline.
12/15/15	Review and revision of guidelines consisting of updating the description, position statement, dosage/administration, precautions, billing/coding, related guidelines, and references.
12/15/16	Review and revision of guidelines consisting of updating the description, position statement, dosage/administration, precautions, billing/coding, and references.
02/15/17	Revision to guideline consisting of updating the description, position statement, and references based on an update to the NCCN guidelines for B-cell lymphomas.
12/15/17	Review and revision of guidelines consisting of updating the description, position statement, dosage/administration, billing/coding, and references.
08/15/18	Review and revision of guidelines consisting of updating the description section, position statement, dosage/administration, precautions, billing/coding, and references.
03/15/19	Revision to guideline consisting of updating the description section, position statement, and references based on updated NCCN B-Cell Lymphoma guidelines.
08/15/18	Review and revision of guidelines consisting of updating the description section and references.