PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Zydelig® (idelalisib tablets – Gilead)

DATE REVIEWED: 06/03/2020

OVERVIEW

Zydelig, an inhibitor of phosphatidylinositol 3-kinase, is indicated for the treatment of patients with 1) relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other comorbidities; 2) relapsed follicular B-cell non-Hodgkin lymphoma in patients who have received at least two prior systemic therapies; and 3) relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies.[1] Accelerated approval was given for the relapsed follicular B-cell non-Hodgkin lymphoma and SLL indications based on overall response rate (ORR). Improvement in patient survival or disease-related symptoms has not been established. A limitation of use for all three indications is that Zydelig is not indicated and is not recommended for first-line treatment.

Disease Overview

CLL is one of the most prevalent adult leukemias in the Western world.[5] In 2019, an estimated 20,720 patients will be diagnosed with CLL in the US, and approximately 3,930 patients will die from the disease. The condition usually is diagnosed in older adults (≥ 70 years of age) and occurs more frequently in men. The leukemic cells appear as small, mature lymphocytes. CLL and SLL are different manifestations of the same condition and are managed similarly. In CLL, many of the abnormal lymphocytes are found in the blood, as well as in the bone marrow and lymphoid tissue. In SLL, there are few, if any, abnormal lymphocytes circulating in blood and most of the disease is in the lymph nodes, bone marrow, and other lymphoid tissue. The diagnosis requires the presence of at least 5 x 10^9/L monoclonal B-lymphocytes in the peripheral blood. SLL requires the presence of lymphadenopathy and/or splenomegaly with < 5 x 10^9/L B-lymphocytes found in the peripheral blood.

Follicular lymphoma is the most common subtype of indolent non-Hodgkin's lymphoma accounts for approximately 22% of all newly diagnosed cases of non-Hodgkin lymphoma.[8] Most cases (90%) of follicular lymphoma have a t(14;18) translocation, which results in the deregulated expression of BCL-2 protein. Pediatric type follicular lymphoma may occur, albeit rare.[8] Many patients with follicular lymphoma present with asymptomatic lymphadenopathy and bone marrow involvement is present. Some patients also have increased serum lactate dehydrogenase (LDH) is present. Patients with early stage disease generally receive radiation therapy as good responses have been achieved. Although further study is required, chemoimmunotherapy or systemic therapy plus radiation therapy may improve outcomes. Most patients present with advanced disease at diagnoses. Patients who are asymptomatic may not require immediate treatment. Rituximab, used with or without other therapies, has dramatically changed the course of treating follicular lymphoma, with noted improvement in survival. Autologous or allogeneic stem cell transplantations may be considered in some clinical scenarios but are generally reserved for patients with relapsed or refractory disease.

Guidelines

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines for CLL/SLL (version 4.2020 – December 20, 2019) address CLL. Zydelig is recommended with or without rituximab for relapsed or refractory therapy for CLL in various scenarios.[5] Many other agents have a more prominent role in the first-line management of CLL.[5,6] The guidelines note that CLL and SLL are different manifestations of the same condition and are treated similarly.

The NCCN clinical practice guidelines for B-cell Lymphomas (version 1.2020 – January 22, 2020) recommend Zydelig as second-line and subsequent therapy in patients with follicular lymphoma (grade 1-2) among patients refractory to two prior therapies.[8]

The NCCN clinical practice guidelines for B-Cell Lymphomas (version 1.2020 – January 22, 2020) recommend Zydelig as second-line and subsequent therapy for marginal zone lymphomas that are relapsed/refractory to two prior therapies.[8] Other regimens are recommended first line that are primarily rituximab-based.

Safety
Zydelig has a Boxed Warning regarding fatal and serious toxicities such as hepatotoxicity, fatal and/or serious and severe diarrhea or colitis, fatal and serious pneumonitis, fatal and/or serious infections, and fatal and serious intestinal perforation.[1] Zydelig was approved with a Risk Evaluation and Mitigation Strategy (REMS) program to highlight toxicities noted in the Boxed Warning.[2] The REMS program involves a communication plan. In March 2016, the FDA issued a healthcare professionals alert regarding studies with Zydelig which revealed an increased rate of adverse events (AEs), including deaths, in clinical trials when Zydelig was used in combination with other cancer medications.[3] The manufacturer is halting six clinical trials in patients with CLL, SLL and indolent non-Hodgkin lymphomas.

POLICY STATEMENT
Prior authorization is recommended for prescription benefit coverage of Zydelig. All approvals are provided for 3 years in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Zydelig is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Chronic Lymphocytic Leukemia (CLL).** Approve for 3 years if the patient has tried at least two prior therapies.
   Note: Examples include Imbruvica® (ibrutinib capsules and tablets); chlorambucil plus Gazyva® (obinutuzumab injection for intravenous use); chlorambucil plus rituximab; FCR (fludarabine, cyclophosphamide and rituximab); FR (fludarabine plus rituximab); PCR (pentostatin, cyclophosphamide, rituximab); Treanda® (bendamustine injection) with or without rituximab; high-dose methylprednisolone (HDMP) plus rituximab; Campath® (alemtuzumab injection for intravenous use) with or without rituximab; Venclexta® (venetoclax tablets) with or without rituximab; Calquence® (acalabrutinib capsules); Gazyva; rituximab; Arzerra® (ofatumumab injection for intravenous use); chlorambucil; Venclexta plus Gazyva; or Copiktra (duvelisib capsules).
2. **Follicular Lymphoma.** Approve for 3 years if the patient has tried at least two prior therapies.
   Note: Examples include Treanda® (bendamustine injection) plus rituximab; Treanda plus Gazyva® (obinutuzumab injection for intravenous use); CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) plus Gazyyva or rituximab; CVP (cyclophosphamide, vincristine, prednisone) plus Gazyva or rituximab; chlorambucil with or without rituximab;

cyclophosphamide with or without rituximab; Gazyva; Revlimid® (lenalidomide capsules); Copiktra™ (duvelisib capsules); or Aliqopa® (copanlisib injection for intravenous use).

3. **Small Lymphocytic Lymphoma (SLL).** Approve for 3 years if the patient has tried at least two prior therapies.
   Note: Examples include Imbruvica® (ibrutinib capsules or tablets); chlorambucil plus Gazyva® (obinutuzumab injection for intravenous use); chlorambucil plus rituximab; FCR (fludarabine, cyclophosphamide and rituximab); FR (fludarabine plus rituximab); PCR (pentostatin, cyclophosphamide, rituximab); Treanda® (bendamustine injection) with or without rituximab; high-dose methylprednisolone (HDMP) plus rituximab; Venclexta® (venetoclax tablets) with or without rituximab; Calquence® (acalabrutinib capsules); Gazyva; rituximab; Arzerra® (ofatumumab injection for intravenous use); chlorambucil; Venclexta plus Gazyva; or Copiktra (duvelisib capsules).

Other Uses with Supportive Evidence

4. **Marginal Zone Lymphoma.** Approve for 3 years if the patient has tried at least two other therapies.
   Note: Examples include rituximab; Treanda® (bendamustine injection for intravenous use) plus rituximab; RCHOP (rituximab, cyclophosphamide, vincristine, prednisone); RCVP (rituximab, cyclophosphamide, vincristine, prednisone); chlorambucil with or without rituximab; cyclophosphamide with or without rituximab; Imbruvica® (ibrutinib tablets and capsules); Copiktra™ (duvelisib capsules); Revlimid® (lenalidomide capsules) with or without rituximab; or Aliqopa® (copanlisib injection for intravenous use).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Zydelig has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Zydelig® tablets [prescribing information]. Foster City, CA: Gilead Sciences; October 2018.
2. Zydelig REMS program. Available at: http://www.zydeligrems.com/. Accessed on May 29, 2020.
3. U.S. Food and Drug Administration. FDA alerts healthcare professionals about clinical trials with Zydelig (idelalisib) in combination with other cancer medicines. Date: 03/14/2016. Available at: http://www.fda.gov/drugs/drugsafety/ucm490618.htm. Accessed on May 29, 2020.
4. Furman RR, Sharman JP, Coutry SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2014;370(11):997-1007. [and supplementary appendix]
5. The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Clinical Practice Guidelines in Oncology (Version 1.2020 – January 22, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 29, 2020.
6. Hallek M, Shanafelt TD, Eichhorst B. Chronic lymphocytic leukemia. *Lancet*. 2018;391:1524-1537.
7. Gopal AK, Kahl BS, de Vos S, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. *N Engl J Med*. 2014;370(11):1008-1018. [and supplementary appendix]
8. The NCCN B-cell Lymphomas Clinical Practice Guidelines in Oncology (Version 1.2020 – January 22, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed May 29, 2020.

9. Salles G, Schuster SJ, de Vos S, et al. Efficacy and safety of idelalisib in patients with relapsed, rituximab- and alkylating agent-refractory follicular lymphoma: a subgroup analysis of a phase 2 study. *Haematologica*. 2017;102(4):e156-e159.
10. Gopal AK, Kahl BS, Flowers CR, et al. Idelalisib is effective in patients with high-risk follicular lymphoma and early relapse after initial chemoimmunotherapy. *Blood*. 2017;129(22):3037-3039.