EXPRESS SCRIPTS®

PRIOR AUTHORIZATION POLICY

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

TAC APPROVAL DATE: 06/05/2019

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.

Guidelines

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines for CLL/SLL (version 5.2019 – May 23, 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 3.2019 – May 6, 2019) recommend Zydelig as second-line and subsequent therapy in patients with follicular lymphoma (grade 1-2) among patients refractory to an alkylator and rituximab.[8]

The NCCN clinical practice guidelines for B-Cell Lymphomas (version 3.2019 – May 6, 2019) recommend Zydelig as second-line and subsequent therapy for marginal zone lymphomas that are refractory to both an alkylator and rituximab.[8] Other regimens are recommended first line that are rituximab-based and often include an alkylator.

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 two prior therapies (e.g., Imbruvica® [ibrutinib capsules and tablets]; chlorambucil plus Gazyva® [obinutuzumab injection for intravenous use]; chlorambucil plus Arzerra® [ofatumumab 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; chlorambucil; Venclexta plus Gazyva; or Copiktra [duvelisib capsules]).

2. **Follicular Lymphoma.** Approve for 3 years if the patient has tried two prior therapies (e.g., 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 two prior therapies (e.g., Imbruvica® [ibrutinib capsules or tablets]; chlorambucil plus Gazyva® [obinutuzumab injection for intravenous use]; chlorambucil plus rituximab; chlorambucil plus Arzerra® [ofatumumab injection for intravenous use]; 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; 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 two other therapies (e.g., 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 31, 2019.
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 31, 2019.
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 5.2018 – March 26, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 16, 2018.
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 3.2019 – May 6, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed May 31, 2019.
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.

HISTORY

Type of Revision	Summary of Changes†	TAC Approval Date
Annual revision	Added Aliqopa® (copanlisib injection for intravenous use) as an alternative for patients with follicular B-cell non-Hodgkins lymphoma.	10/04/2017
Early annual revision	Alternatives for CLL revised (agents removed or added) based on NCCN guidelines. For Follicular B-Cell Non-Hodgkin Lymphoma changed the requirement that patients have tried two prior therapies instead of one therapy, to make it in-line with FDA-approved labeling; therapy alternatives were slightly revised based on NCCN guidelines. For SLL changed the requirement that patients have tried two prior therapies instead of one therapy to make it in-line with FDA-approved labeling; therapy alternatives were slightly revised based on NCCN guidelines. Criteria added regarding approval for marginal zone lymphoma if the patient had tried two other prior therapies based on NCCN guidelines.	05/16/2018
Annual revision	For clarity, the reference to Rituxan when listing previous required therapies was changed to "rituximab". The following changes were also made: 1. Chronic Lymphocytic Leukemia: The number of therapies required prior to approval of Zydelig was changed from one to two. Also, Venclexta plus Gazyva and Copiktra were added to the list of examples of agents that count toward this requirement. 2. Follicular Lymphoma: The wording "B-Cell Non-Hodgkin" was removed from the cited condition. The RCHOP regimen was removed from the listing of alternatives and the regimen that cited "CHOP plus Gazyva" was the changed to "CHOP plus Gazyva or rituximab". Likewise, the RCVP alternative was changed to state "CVP plus Gazyva or rituximab". Copiktra was also listed as an alternative that counts as the requirement to try two prior therapies. 3. Small Lymphocytic Lymphoma: Venclexta plus Gazyva and Copiktra were added to the list of examples of agents that count toward the requirement of a trial of two prior therapies. 4. Marginal Zone Lymphoma: Copiktra and Revlimid (with or without rituximab) were added as alternatives that count towards the requirement of two prior therapies.	06/05/2019

† For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx; TAC – Therapeutic Assessment Committee; CLL – Chronic lymphocytic leukemia; SLL – Small lymphocytic lymphoma; FDA – Food and Drug Administration; NCCN – National Comprehensive Cancer Network.