PDL DRUG REVIEW

Proprietary Name: Tazverik®
Common Name: tazemetostat
PDL Category: Antineoplastics

Summary

Pharmacology/Usage: Tazemetostat, the active ingredient of Tazverik®, is an inhibitor of the methyltransferase, EZH2, and some EZH2 gain-of-function mutations. Tazemetostat also inhibited EZH1.

Indication: For:

- *Epithelioid Sarcoma*
  - The treatment of adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection.

- *Relapsed or Refractory Follicular Lymphoma*
  - The treatment of adults with relapsed or refractory follicular lymphoma (FL) whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies.
  - The treatment of adults with relapsed or refractory FL who have no satisfactory alternative treatment options.

These indications are approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

There is no pregnancy category for this medication; however, based on findings from animal studies and its mechanism of action, Tazverik® can cause fetal harm when administered to a pregnant woman. There are no available data on use in pregnant women to inform the drug associated risk. Advise pregnant women of the potential risk to a fetus. Verify the pregnancy status of females of reproductive potential prior to starting Tazverik® and advise this population to use effective non-hormonal contraception during treatment and for 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for at least 3 months after the final dose. The safety and efficacy of use in the pediatric population under the age of 16 years have not been established.

Dosage Form: Film-Coated Tablets: 200mg. Swallow tablets whole; do not cut, crush, or chew.

Recommended Dosage: Select patients with relapsed or refractory FL for treatment with Tazverik® based on the presence of EZH2 mutation of codons Y646, A682, or A692 in tumor specimens. Information on FDA-approved tests for the detection of EZH2 mutation in relapsed or refractory FL is available at http://www.fda.gov/CompanionDiagnostics.

Take 800mg PO BID with or without food until disease progression or unacceptable toxicity.

Dose modifications may be required for adverse reactions, such as neutropenia, thrombocytopenia, anemia, or others. Refer to the prescribing information for additional information. Dose adjustments are not required with renal impairment or mild hepatic impairment. Use has not been studied with moderate or severe hepatic impairment.

Drug Interactions: Avoid coadministration of moderate and strong CYP3A inducers with Tazverik®. Avoid concomitant use of Tazverik® with strong or moderate CYP3A inhibitors. If coadministration with a moderate CYP3A inhibitor cannot be avoided, reduce the Tazverik® dose.

Coadministration of Tazverik® with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and reduced efficacy of CYP3A substrates.

Box Warning: There is no box warning with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Tazverik®) for all grades in patients with epithelioid sarcoma. Please note that there was no placebo data to compare with.* The most frequently reported adverse events included pain (52%), fatigue (47%), nausea (36%), vomiting (24%), constipation (21%), diarrhea (16%), abdominal pain (13%), decreased appetite (26%), cough (18%), dyspnea (16%), hemorrhage (18%), headache (18%), and decreased weight (16%). Laboratory abnormalities include decreased hemoglobin (49%), decreased lymphocytes (36%), decreased white blood cell count (19%), increased triglycerides (36%), increased glucose (33%), decreased sodium (30%), decreased phosphate (28%), decreased albumin (23%), increased alkaline phosphatase (23%), decreased potassium (20%), increased aspartate aminotransferase (18%), decreased calcium (16%), decreased glucose (16%), increased partial thromboplastin time (15%), increased alanine aminotransferase (14%), increased creatinine (12%), and increased potassium (12%).

The risk of developing secondary malignancies is increased after treatment with Tazverik®. Across clinical trials of adults (N=729) who received Tazverik® 800mg BID, myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) occurred in 0.7% of patients. One pediatric patient developed T-cell lymphoblastic lymphoma (T-LBL). Monitor patients long-term for the development of secondary malignancies.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Epizyme, Inc.

Analysis: The efficacy of Tazverik® was assessed in an open-label, single-arm cohort (Cohort 5) of a multicenter study that included patients with histologically confirmed, metastatic or locally advanced epithelioid sarcoma. Patients were required to have loss of INI1 expression detected using local tests, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. Among the 62 patients treated with Tazverik®, the median age was 34 years (range 16 to 79 years), while 63% were male, 76% were white, 44% had proximal disease, 92% had ECOG performance status of 0 or 1 and 8% had ECOG performance status (PS) of 2. Prior surgery occurred in 77% of patients, while 61% received prior systemic chemotherapy.

The main efficacy outcome measures included confirmed overall response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as assessed by blinded independent central review (BICR) and duration of response (DOR). The median duration of follow-up was 14 months (range 0.4 to 31). Note that the time to response for the overall response rate ranged from 1.4 to 18.4 months. Results can be seen in the table below, which was adapted from the prescribing information.

	Tazverik® (N=62)
Overall Response Rate	15%
Complete Response	1.6%
Partial Response	13%

	Tazverik® (N=62)
Duration of Response	
% with duration ≥6 months	67%
Range in months	3.7, 24.5+

The efficacy of Tazverik® was assessed in 2 open-label, single-arm cohorts (Cohorts 4 and 5) of a multicenter study that included patients with histologically confirmed follicular lymphoma after at least 2 prior systemic therapies. Patients were required to have ECOG PS of 0-2 and were enrolled based on EZH2 mutation status. There were 99 adults enrolled, including 45 whose tumors had one EZH2 mutations (mutant) and 54 whose tumors did not have one of the mutations (wild type). Of the 45 patients with EZH2 mutant FL, the median age was 62 years (range 38 to 80), 58% were female, 42% had early progression following front-line therapy (POD24), 82% were white (based on race being reported in 84% of patients), all had an ECOG PS of 0 or 1, and the median number of lines of prior systemic therapy was 2 (range 1 to 11). Among the 54 patients with EZH2 wild type FL, the median age was 61 years (range 36 to 87), 63% were male, 59% had POD24, 48% were white (based on race being reported in 57% of patients), 91% had an ECOG PS of 0 or 1, and the median number of lines of prior systemic therapy was 3 (range 1 to 8).

The main efficacy outcome measures were ORR and DOR per the International Working Group Non-Hodgkin Lymphoma (IWG-NHL) criteria as assessed by Independent Review Committee. Median duration of follow-up was 22 months for patients with EZH2 mutant positive tumors and 36 months for patients whose tumors did not have an EZH2 mutation detected.

The approval of Tazverik® was based upon the efficacy in 95 patients (42 EZH2 mutant, 53 EZH2 wild type) who had received at least 2 prior systemic therapies. Note that the median time to response for overall response rate for patients with EZH2 mutant FL was 3.7 months (range 1.6 to 10.9) and for patients with EZH2 wild type FL was 3.9 months (range 1.6 to 16.3). Results can be seen in the table below, which was adapted from the prescribing information.

	Tazverik® (N=95)	
	EZH2 Mutant FL (N=42)	EZH2 Wild-Type FL (N=53)
Overall Response Rate	69%	34%
Complete Response	12%	4%
Partial Response	57%	30%
Duration of Response		
Median in months	10.9	13.0
Range in months	0.0+, 22.1+	1, 22.5+

Place in Therapy: Tazverik® is an oral tablet indicated for the treatment of adults and pediatric patients 16 years of age and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection. It is also indicated for relapsed or refractory follicular lymphoma (for adults with relapsed or refractory FL whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies, and for adults with relapsed or refractory FL who have no satisfactory alternative treatment options). These indications are approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Tazverik® is the first and only FDA-approved EZH2 inhibitor, as well as the first and only FDA-approved treatment specifically for patients with epithelioid sarcoma. In a small open-label study that included patients with advanced epithelioid sarcoma, Tazverik® produced a 15% overall response rate. In addition, the overall response rate was 69% with Tazverik® in the EZH2 mutant FL cohort and 34% in the EZH2 wild type FL.

It is recommended that Tazverik® should be non-recommended with conditions in order to confirm the appropriate diagnosis and clinical parameters for its use.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended with Conditions**

References

[1]Tazverik [package insert]. Cambridge, MA: Epizyme, Inc; 2020.