UNSILENCE AN EXPRESSIVE INSTRUMENT

TAZVERIK®
(tazemetostat) tablets
200 mg

TAZVERIK® (tazemetostat): the first and only EZH2 inhibitor indicated for patients with relapsed or refractory (R/R) follicular lymphoma (FL)

TAZVERIK is indicated for the treatment of:

- Adult patients with relapsed or refractory follicular lymphoma 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.
- Adult patients with relapsed or refractory follicular lymphoma 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 these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).[1]

Important Safety Information

TAZVERIK increases the risk of developing secondary malignancies, including T-cell lymphoblastic lymphoma, myelodysplastic syndrome, and acute myeloid leukemia. Monitor patients long-term for the development of secondary malignancies.

TAZVERIK can cause fetal harm. Advise patients of potential risk to a fetus and to use effective non-hormonal contraception.

The most common (≥20%) adverse reactions are fatigue, upper respiratory tract infection, musculoskeletal pain, nausea, and abdominal pain.

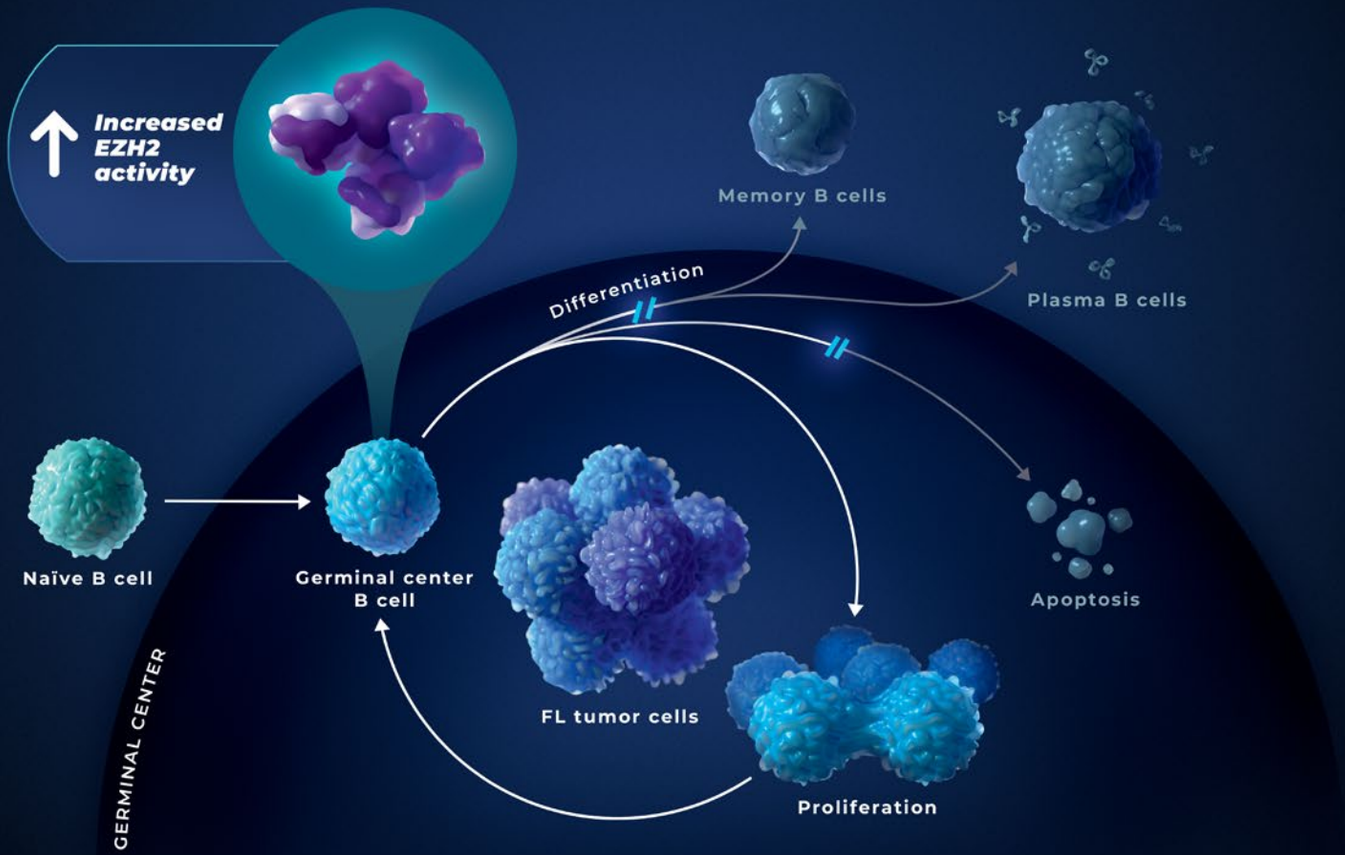
Please see additional Important Safety Information on the following pages and refer to the full Prescribing Information.

EZH2=enhancer of zeste homologue 2.

FOLLICULAR LYMPHOMA OCCURS WHEN B CELLS PROLIFERATE WITHOUT DIFFERENTIATING[2,3,5,6]

- **EZH2 is an epigenetic regulator of B-cell identity** in the germinal center[3]
  - EZH2 represses the expression of gene sets that allow for germinal center exit and terminal differentiation[3,4]
  - EZH2 activity plays a role in **both normal B-cell biology and in the pathogenesis of FL**[3]
- FL is caused by heterozygous combinations of oncogenic hits[4,5]

The degree to which FL relies on EZH2 activity depends on the complex interplay between multiple drivers of oncogenesis[3,4]



SELECTIVELY INHIBITING EZH2 MAY RESTORE EXPRESSION OF GENES THAT ALLOW FOR GERMINAL CENTER EXIT[1-3,5,6]

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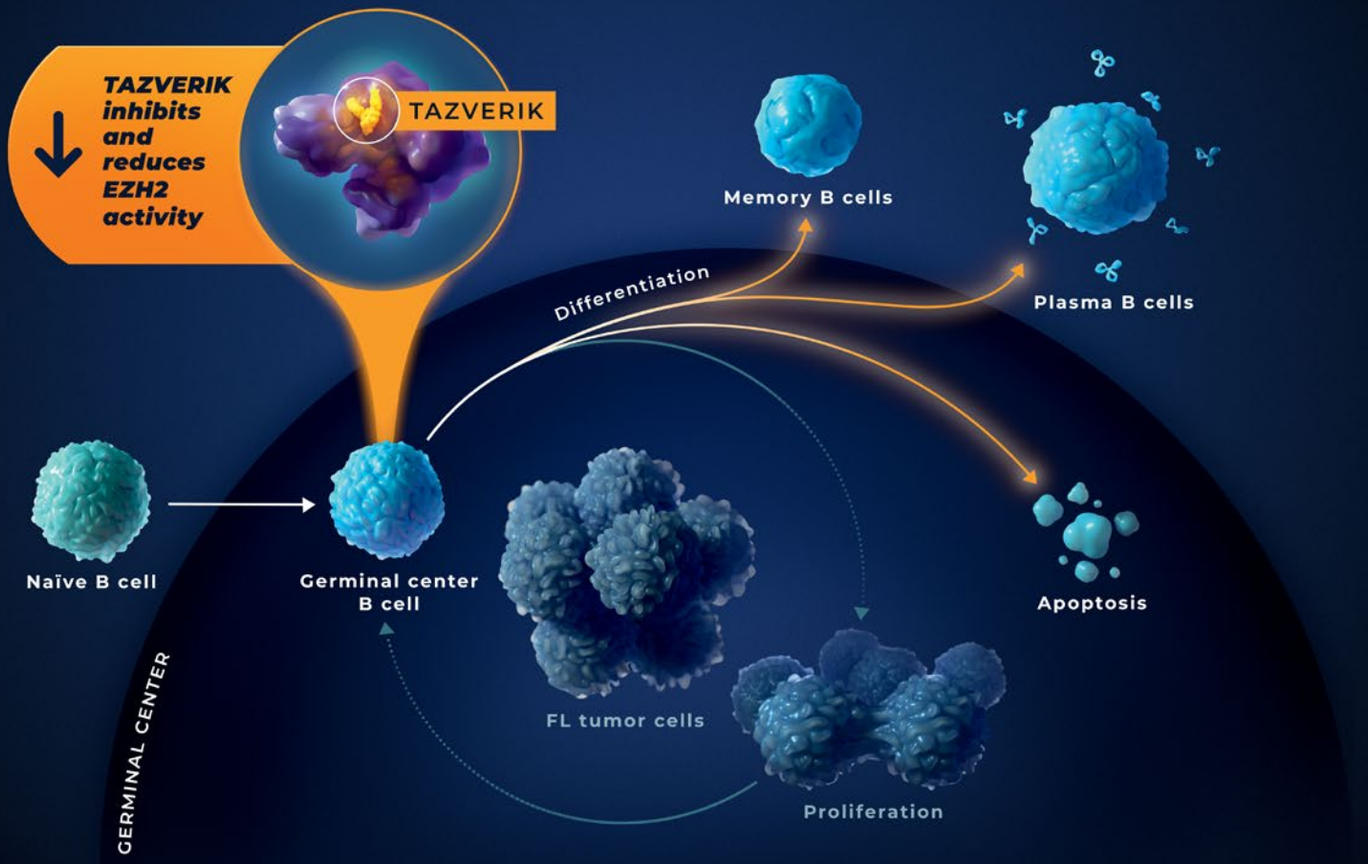

- Inhibition of EZH2 activity may allow for the expression of gene sets that lead to terminal differentiation decisions and germinal center exit[3]
- Regardless of oncogenic mutation, FL tumors have a critical dependence on EZH2 for growth and survival[1,3]

MOA=mechanism of action;
MOD=mechanism of disease.

Important Safety Information *(continued)*

Warnings and Precautions

• Secondary Malignancies

The risk of developing secondary malignancies is increased following treatment with TAZVERIK. Across clinical trials of 729 adults who received TAZVERIK 800 mg twice daily, 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.

Please see additional Important Safety Information on the following pages and refer to the full Prescribing Information.

TAZVERIK® (tazemetostat) WAS STUDIED IN A HEAVILY PRETREATED FL PATIENT POPULATION

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TAZVERIK was studied in an open-label, single-arm, multicenter, phase 2 trial with 6 cohorts of patients, including 2 cohorts with histologically-confirmed R/R FL[1]

Enrolled 2 cohorts: *EZH2* MT (n=45) and WT (n=54) patients[1]

- *EZH2* mutations were identified prospectively by central testing using the cobas® *EZH2* Mutation Test
- Patients in the *EZH2* MT cohort had the following mutations: Y646X [S,H,C] (36%), Y646F (29%), Y646N (27%), A682G (11%), and A692V (2%)

BASELINE DISEASE CHARACTERISTICS[1,7,8]	MT EZH2 (n=45)	WT EZH2 (n=54)
ECOG PS 0 or 1, %	100	91
ECOG PS 2, %*	0	7
POD24, %	42	59
Median time from initial diagnosis, years	4.7	6.5
Median number of lines of prior systemic therapy (range)	2 (1 to 11)	3 (1 to 8)
Refractory to rituximab, %	49	59
Double refractory to rituximab and an alkylating agent, %	20	28
Refractory to last therapy, %	49	41
Prior stem cell transplant, %	9	39

ECOG PS=Eastern Cooperative Oncology Group Performance Status; MT=mutant type; POD24=early progression within 24 months following front-line therapy; WT=wild type.

*ECOG PS was missing for one WT patient.

STUDY DESIGN: A SINGLE-ARM, PHASE 2 TRIAL OF RELAPSED OR REFRACTORY FL PATIENTS

TAZVERIK® (tazemetostat) tablets 200 mg

R/R FL after ≥2 systemic therapies[1]

MT: Median age: 62 (38-80); 42% male[1]
WT: Median age: 61 (36-87); 63% male[1]

Selected exclusion criteria[7]:

- Noncutaneous malignancies other than B-cell lymphomas
- Leptomeningeal metastases or brain metastases or history of previously treated brain metastases
- Thrombocytopenia, neutropenia, or anemia of Grade ≥3 and any prior history of myeloid malignancies, including MDS

TAZVERIK® (tazemetostat) dosing was 800 mg (4 tablets X 200 mg) twice daily until confirmed disease progression or unacceptable toxicity[1]

Assessments by IRC every 8 weeks through 24 weeks, then every 12 weeks[1]

Median duration of follow up was 22 months (MT; range: 3 to 44) and 36 months (WT; range: 32 to 39)[1]

- **Primary endpoint:** Overall response rate (ORR)[1,7]
- **Selected secondary endpoint:** Median duration of response (DOR)[1,7]

IRC=independent review committee; MDS=myelodysplastic syndromes.

Important Safety Information *(continued)*

Warnings and Precautions

• Embryo-Fetal Toxicity

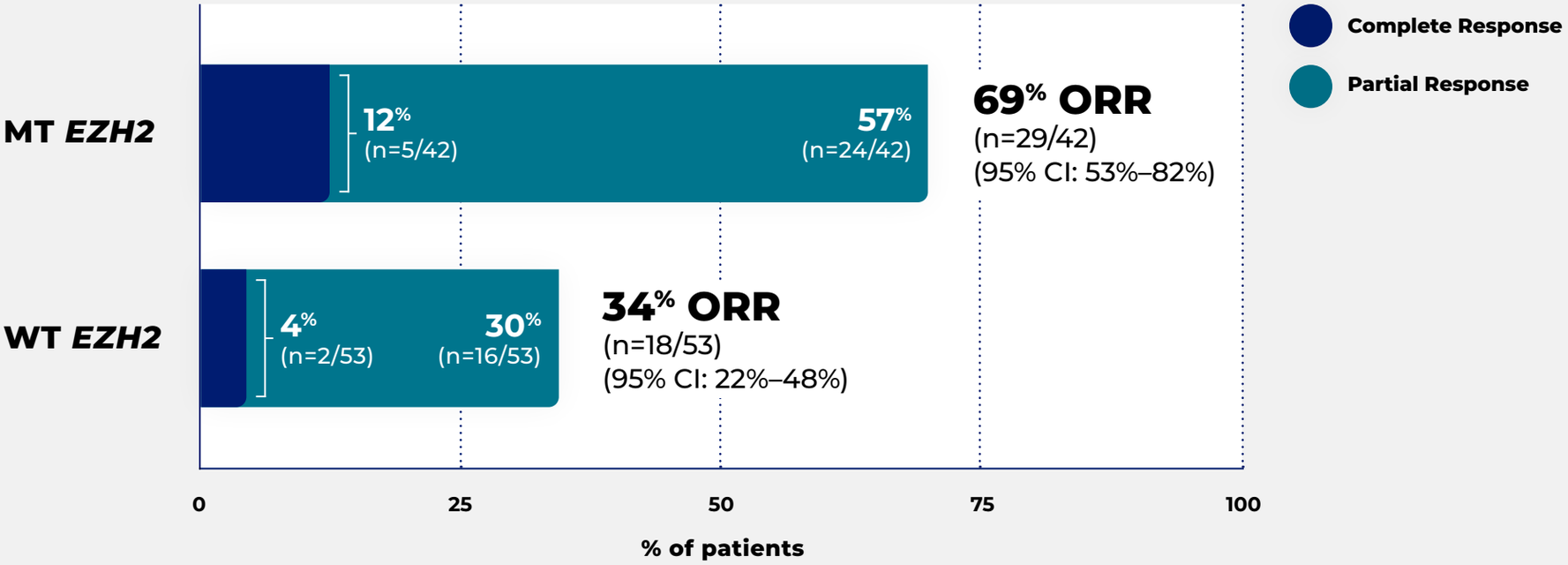
Based on findings from animal studies and its mechanism of action, TAZVERIK can cause fetal harm when administered to pregnant women. There are no available data on TAZVERIK use in pregnant women to inform the drug-associated risk. Administration of tazemetostat to pregnant rats and rabbits during organogenesis resulted in dose-dependent increases in skeletal developmental abnormalities in both species beginning at maternal exposures approximately 1.5 times the adult human exposure (area under the plasma concentration time curve [$AUC_{0\text{-}45h}$]) at the 800 mg twice daily dose.

Please see additional Important Safety Information on the following pages and refer to the full Prescribing Information.

TAZVERIK® (tazemetostat) ACHIEVED OVERALL RESPONSE RATES OF 69% IN PATIENTS WITH MT EZH2 AND 34% IN PATIENTS WITH WT EZH2

TAZVERIK® (tazemetostat) tablets 200 mg

*Overall Response Rate (ORR, primary endpoint)[1,7]**



Median time to response for patients with MT *EZH2* was 3.7 months (range: 1.6 to 10.9).
Median time to response for patients with WT *EZH2* was 3.9 months (range: 1.6 to 16.3).

CI=confidence interval.
*According to the International Working Group Non-Hodgkin Lymphoma (IWG-NHL) criteria as assessed by independent review committee.

Important Safety Information *(continued)*

Warnings and Precautions

• **Embryo-Fetal Toxicity** ***(continued)***

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAZVERIK and for 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for 3 months after the final dose.

Please see additional Important Safety Information on the following pages and refer to the full Prescribing Information.

TAZVERIK® (tazemetostat) DEMONSTRATED SUSTAINED EFFICACY IN A HEAVILY PRETREATED POPULATION, REGARDLESS OF EZH2 MUTATION

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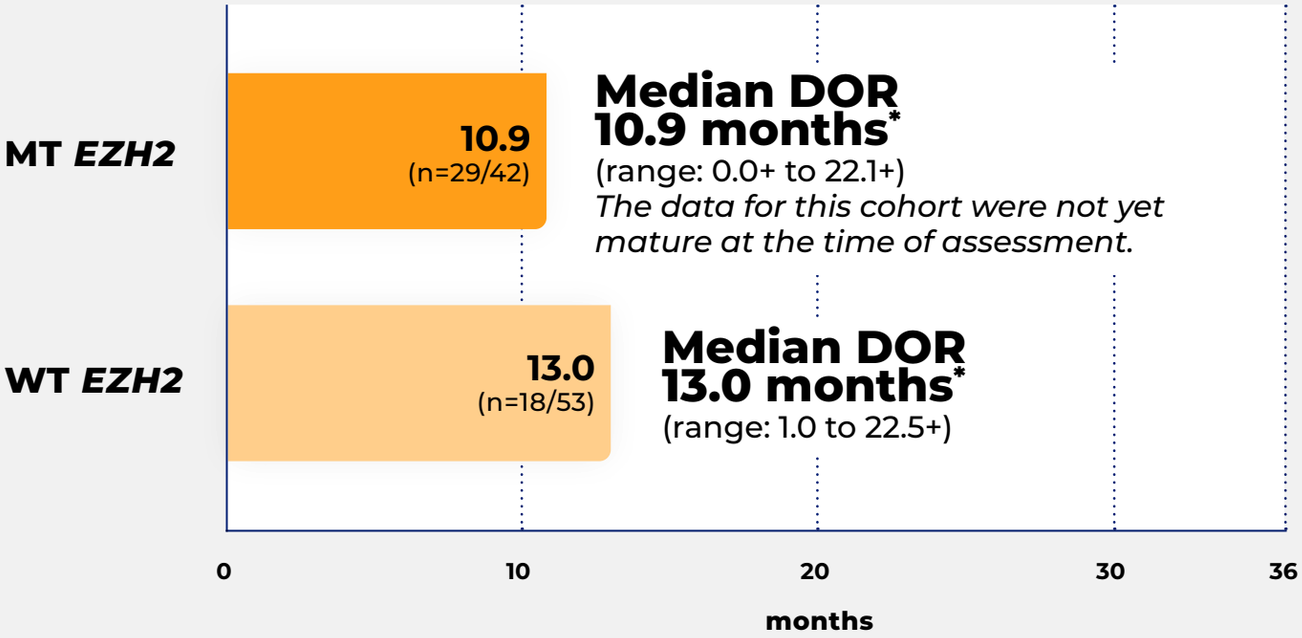
Duration of Response (DOR)[1,7]



Of those who responded†:

59% (n=17/29)	responded for ≥6 months
21% (n=6/29)	responded for ≥12 months
56% (n=10/18)	responded for ≥6 months
39% (n=7/18)	responded for ≥12 months

*95% CI for MT *EZH2*: 7.2–NE. 95% CI for WT *EZH2*: 5.6–NE.
†Percentages are based on the Intent-to-Treat subjects within each group that achieved CR or PR.
NE=not estimable.

Important Safety Information *(continued)*

Adverse Reactions

In 99 clinical study patients with relapsed or refractory follicular lymphoma receiving TAZVERIK 800 mg twice daily: Serious adverse reactions occurred in 30% of patients who received TAZVERIK. Serious adverse reactions occurring in ≥2% were general physical health deterioration, abdominal pain, pneumonia, sepsis, and anemia. The most common (≥20%) adverse reactions were fatigue (36%), upper respiratory tract infection (30%), musculoskeletal pain (22%), nausea (24%), and abdominal pain (20%).

Please see additional Important Safety Information on the following pages and refer to the full Prescribing Information.

SAFETY EVALUATED IN PATIENTS WITH RELAPSED OR REFRACTORY FL

TAZVERIK® (tazemetostat) tablets 200 mg

Adverse reactions (≥10%) in patients with relapsed or refractory FL who received TAZVERIK® (tazemetostat)[1]

ADVERSE REACTION	TAZVERIK N=99	
	ALL GRADES (%)	GRADE 3 OR 4 (%)
General		
Fatigue[a]	36	5
Pyrexia	10	0
Infections		
Upper respiratory tract infection[b]	30	0
Lower respiratory tract infection[c]	17	0
Urinary tract infection[d]	11	2
Gastrointestinal		
Nausea	24	1
Abdominal pain[e]	20	3
Diarrhea	18	0
Vomiting	12	1
Musculoskeletal and connective tissue		
Musculoskeletal pain[f]	22	1
Skin and subcutaneous tissue		
Alopecia	17	0
Rash[g]	15	0
Respiratory and mediastinal system		
Cough[h]	17	0
Nervous system		
Headache[i]	13	0

Fatigue was the only grade 3 or 4 adverse reaction reported in ≥5% of patients.[1]

30% of patients in the TAZVERIK clinical trial experienced serious adverse reactions. Serious adverse reactions occurring in ≥2% of patients taking TAZVERIK included:

- general physical health deterioration
- abodominal pain
- pneumonia
- sepsis
- anemia[1]

The most common (≥20%) adverse reactions were fatigue (36%), upper respiratory tract infection (30%), musculoskeletal pain (22%), nausea (24%), and abdominal pain (20%).[1]

[a]Includes fatigue and asthenia
[b]Includes laryngitis, nasopharyngitis, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, viral upper respiratory tract infection
[c]Includes bronchitis, lower respiratory tract infection, tracheobronchitis
[d]Includes cystitis, urinary tract infection, urinary tract infection staphylococcal
[e]Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper
[f]Includes back pain, limb discomfort, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, pain in jaw, spinal pain
[g]Includes erythema, rash, rash erythematous, rash generalized, rash maculo-papular, rash pruritic, rash pustular, skin exfoliation
[h]Includes cough and productive cough
[i]Includes headache, migraine, sinus headache

TAZVERIK® (tazemetostat) OFFERS ORAL, TWICE-DAILY DOSING

TAZVERIK® (tazemetostat) tablets 200 mg

How supplied: 240-count bottle

NDC number (10 digit): 72607-100-00
NDC number (11 digit): 72607-0100-00
CYP3A=Cytochrome P450 (CYP)3A
NDC=National Drug Code

Recommended dose of 800 mg (4 x 200 mg tablets) taken orally, twice daily, until disease progression or unacceptable toxicity.[1]

with or without food

1st dose 

2nd dose 

Tablets are not actual size.

Swallow tablets whole. Do not cut, crush, or chew tablets.

Do not take an additional dose if a dose is missed or vomiting occurs after taking TAZVERIK, but continue with the next scheduled dose.[1]

When selecting patients with an *EZH2* mutation, find information on FDA-approved tests at www.fda.gov/companiondiagnostics.[1]

TAZVERIK may also be used without mutation testing in adults with R/R FL who have no satisfactory treatment options available.[1]

Patient and product support is offered through EpizymeNOW to patients who qualify
To learn more, visit TAZVERIK.com or call 877-227-3405 (Monday through Friday, 9 am - 6 pm ET).

Important Safety Information *(continued)*

Drug Interactions

Avoid coadministration of strong or moderate CYP3A inhibitors with TAZVERIK. If coadministration of moderate CYP3A inhibitors cannot be avoided, reduce TAZVERIK dose.

Avoid coadministration of moderate and strong CYP3A inducers with TAZVERIK, which may decrease the efficacy of TAZVERIK.

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

Please see additional Important Safety Information on the following pages and refer to the full Prescribing Information.

GUIDANCE FOR DOSE MODIFICATION AND REDUCTION

TAZVERIK® (tazemetostat) tablets 200 mg

Recommended dose reductions for adverse reactions[1]

DOSE REDUCTION	DOSAGE
First	600 mg twice daily
Second	400 mg twice daily*

DOSE ADJUSTMENTS NOT RECOMMENDED FOR PATIENTS WITH:
• mild to severe renal impairment, including end-stage renal disease.[1]
• mild hepatic impairment. TAZVERIK® (tazemetostat) has not been studied in patients with moderate or severe hepatic impairment.[1†]

*Permanently discontinue TAZVERIK in patients who are unable to tolerate 400 mg orally twice daily.[1]
†Mild=total bilirubin > 1 to 1.5 times ULN or AST > ULN; moderate=total bilirubin > 1.5 to 3 times ULN; severe=total bilirubin > 3 times ULN.[1]
AST=aspartate aminotransferase; ULN=upper limit of normal.

8% of patients permanently discontinued treatment due to an adverse reaction.

The adverse reaction resulting in permanent discontinuation in ≥2% of patients was second primary malignancy.[1]

9% of patients receiving TAZVERIK required dose reductions due to an adverse reaction.[1]

28% of patients receiving TAZVERIK required dose interruptions due to an adverse reaction.

Adverse reactions requiring dosage interruptions in ≥3% of patients were thrombocytopenia and fatigue.[1]

Important Safety Information *(continued)*

Lactation

Because of the potential risk for serious adverse reactions from TAZVERIK in the breastfed child, advise women not to breastfeed during treatment with TAZVERIK and for one week after the final dose.

Please see additional Important Safety Information on the following pages and refer to the full Prescribing Information.

GUIDANCE FOR DOSE MODIFICATION AND REDUCTION (continued)

TAZVERIK® (tazemetostat) tablets 200 mg

Recommended dosage modifications for adverse reactions[1]

ADVERSE REACTION	SEVERITY	DOSAGE MODIFICATION
Neutropenia	Neutrophil count less than 1 × 10^9/L	• Withhold until neutrophil count is greater than or equal to 1 × 10^9/L or baseline. • For first occurrence, resume at same dose. • For second and third occurrence, resume at reduced dose. • Permanently discontinue after fourth occurrence.
Thrombocytopenia	Platelet count less than 50 × 10^9/L	• Withhold until platelet count is greater than or equal to 75 × 10^9/L or baseline. • For first and second occurrence, resume at reduced dose. • Permanently discontinue after third occurrence.
Anemia	Hemoglobin less than 8 g/dL	• Withhold until improvement to at least Grade 1 or baseline, then resume at same or reduced dose.
Other adverse reactions	Grade 3	• Withhold until improvement to at least Grade 1 or baseline. • For first and second occurrence, resume at reduced dose. • Permanently discontinue after third occurrence.
	Grade 4	• Withhold until improvement to at least Grade 1 or baseline. • For first occurrence, resume at reduced dose. • Permanently discontinue after second occurrence.

Recommended dose reductions of TAZVERIK® (tazemetostat) for moderate CYP3A inhibitors[1]

CURRENT DOSAGE	ADJUSTED DOSAGE
800 mg orally twice daily	400 mg orally twice daily
600 mg orally twice daily	400 mg for first dose and 200 mg for second dose
400 mg orally twice daily	200 mg orally twice daily

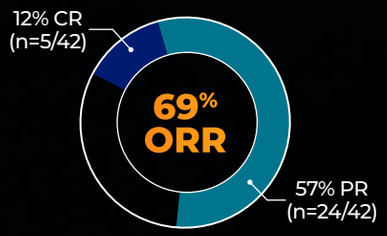
References: 1. TAZVERIK (tazemetostat) Prescribing Information. Cambridge, MA: Epizyme, Inc., July, 2020. **2.** Mamessier E, Broussais-Guillaumot F, Chetaille B, et al. Nature and importance of follicular lymphoma precursors. *Haematologica.* 2014;9(5):802-810. **3.** Béguelin W, Popovic R, Teater M, et al. EZH2 is required for germinal center formation and somatic EZH2 mutations promote lymphoid transformation. *Cancer Cell.* 2013;23:677-692. **4.** Huet S, Sujobert P, Salles G. From genetics to the clinic: A translational perspective on follicular lymphoma. *Nat Rev Cancer.* 2018;18:224-239. **5.** Lackraj T, Goswami R, Kridel R. Pathogenesis of follicular lymphoma. *Best Pract Res Cl Ha.* 2018;31:2-14. **6.** Naradikian MS, Scholz JL, Oropallo MA, Cancro MP. Understanding B cell biology. In: Bosch X, Ramos-Casals M, Khamashta MA (eds.). *Drugs Targeting B-Cells in Autoimmune Diseases.* Springer;2014. **7.** Data on file. **8.** Morschhauser F, Tilly H, Chaidos A, et al. Interim update from a phase 2 multicenter study of tazemetostat, an EZH2 inhibitor, in patients with relapsed or refractory follicular lymphoma. *The International Conference on Malignant Lymphoma (ICML).* 2019.

TAZVERIK® (tazemetostat): THE FIRST AND ONLY EZH2 INHIBITOR APPROVED FOR THE TREATMENT OF RELAPSED OR REFRACTORY FOLLICULAR LYMPHOMA FOLLOWING ≥2 PRIOR LINES OF THERAPY

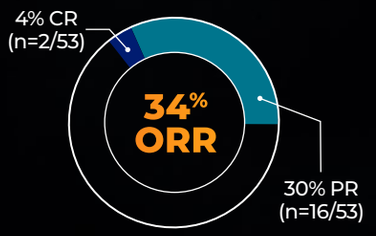
TAZVERIK® (tazemetostat) tablets 200 mg

This indication is 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).[1]

- Efficacy demonstrated in heavily pretreated FL patients[1,7]



in patients
with mutant-type (MT) *EZH2*
(n=29/42; 95% CI: 53%–82%)



in patients
with wild-type (WT) *EZH2*
(n=18/53; 95% CI: 22%–48%)

- Sustained response demonstrated in patients with both MT and WT *EZH2*[1,7]*

(range: 0.0+ to 22.1+)
in patients with MT *EZH2*
(n=29/42; 95% CI: 7.2–NE)

(range: 1.0 to 22.5+)
in patients with WT *EZH2*
(n=18/53; 95% CI: 5.6–NE)

- **Secondary malignancies:** TAZVERIK increases the risk of developing secondary malignancies, including T-cell lymphoblastic lymphoma, myelodysplastic syndrome, and acute myeloid leukemia. Monitor patients long-term for the development of secondary malignancies.
- **Embryo-fetal toxicity:** TAZVERIK can cause fetal harm. Advise patients of potential risk to a fetus and to use effective non-hormonal contraception.

NCCN recommended

Tazemetostat (TAZVERIK®) is recommended in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) as an option for appropriate patients with relapsed or refractory follicular lymphoma.†

*Duration of response data for the MT ***EZH2*** subgroup are not yet mature.

†Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-cell Lymphomas V.4.2020. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed August 17, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

CI=confidence interval; CR=complete response; DOR=duration of response; EZH2=enhancer of zeste homologue 2; NCCN=National Comprehensive Cancer Network; NE=not estimable; ORR=overall response rate; PR=partial response.

Please see Important Safety Information throughout this piece and refer to the full Prescribing Information.

Epizyme™

TZ-FL-BR-20-0050