HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TAZVERIK™ safely and effectively. See full prescribing information for TAZVERIK.

TAZVERIK (tazemetostat) tablets, for oral use
Initial U.S. Approval: 2020

---------- INDICATIONS AND USAGE ----------
TAZVERIK is a methyltransferase inhibitor indicated for the treatment of adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection. 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)

----------DOSAGE AND ADMINISTRATION ----------
Recommended Dosage: 800 mg taken orally twice daily with or without food. (2.1)

---------- DOSAGE FORMS AND STRENGTHS ----------
Tablets: 200 mg (3)

---------- CONTRAINDICATIONS ----------
None. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Secondary Malignancies: TAZVERIK increases the risk of developing secondary malignancies, including T-cell lymphoblastic lymphoma, myelodysplastic syndrome, and acute myeloid leukemia. (5.1)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of potential risk to a fetus and to use effective non-hormonal contraception. (5.2)

---------- ADVERSE REACTIONS ----------
- The most common (≥20%) adverse reactions are pain, fatigue, nausea, decreased appetite, vomiting, and constipation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Epizyme at 1-866-4EPZMED or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------
- Strong and Moderate Cytochrome P450 (CYP)3A Inhibitors: Avoid coadministration of strong and moderate CYP3A inhibitors with TAZVERIK. Reduce the dose of TAZVERIK if coadministration of moderate CYP3A inhibitors cannot be avoided. (2.3, 7.1)
- Strong and Moderate CYP3A Inducers: Avoid coadministration with TAZVERIK. (7.1)

---------- USE IN SPECIFIC POPULATIONS ----------
- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 1/2020

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TAZVERIK is indicated for the treatment of adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection. This indication is approved under accelerated approval based on overall response rate and duration of response *[see Clinical Studies (14)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of TAZVERIK is 800 mg orally twice daily with or without food until disease progression or unacceptable toxicity.

Swallow tablets whole.

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

2.2 Dosage Modifications for Adverse Reactions

Table 1 summarizes the recommended dose reductions and Table 2 summarizes the recommended dosage modifications of TAZVERIK for adverse reactions.

Table 1. Recommended Dose Reductions of TAZVERIK for Adverse Reactions

Dose Reduction	Dosage
First	600 mg orally twice daily
Second	400 mg orally twice daily*

*Permanently discontinue TAZVERIK in patients who are unable to tolerate 400 mg orally twice daily.

Table 2. Recommended Dosage Modifications of TAZVERIK for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Neutropenia *[see Adverse Reactions (6.1)]*	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 *[see Adverse Reactions (6.1)]*	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 *[see Adverse Reactions (6.1)]*	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 *[see Adverse Reactions (6.1)]*	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.

2.3 Dosage Modifications for Drug Interactions

Strong and Moderate CYP3A Inhibitors

Avoid coadministration of TAZVERIK with strong or moderate CYP3A inhibitors. If coadministration with a moderate CYP3A inhibitor cannot be avoided, reduce the TAZVERIK dose as shown in Table 3 below. After discontinuation of the moderate CYP3A inhibitor for 3 elimination half-lives, resume the TAZVERIK dose that was taken prior to initiating the inhibitor *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

Table 3. Recommended Dose Reductions of TAZVERIK for Moderate CYP3A Inhibitors

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

3 DOSAGE FORMS AND STRENGTHS

Tablets: 200 mg film-coated, red, round, biconvex shape and debossed with “EZM 200” on one side and plain on the other.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Secondary Malignancies

The risk of developing secondary malignancies is increased following treatment with TAZVERIK. Across clinical trials of 668 adults who received TAZVERIK 800 mg twice daily, myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) occurred in 0.6% of patients. One pediatric patient developed T-cell lymphoblastic lymphoma (T-LBL).

5.2 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.

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 *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in labeling:

- Secondary Malignancies *[see Warnings and Precautions (5.1)]*.

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of TAZVERIK was evaluated in a cohort (Cohort 5) of Study EZH-202 that enrolled patients with epithelioid sarcoma *[see Clinical Studies (14)]*. Patients received TAZVERIK 800 mg orally twice daily (n=62). Among patients receiving TAZVERIK, 44% were exposed for 6 months or longer and 24% were exposed for greater than one year.

Serious adverse reactions occurred in 37% of patients receiving TAZVERIK. Serious adverse reactions in ≥3% of patients who received TAZVERIK were hemorrhage, pleural effusion, skin infection, dyspnea, pain, and respiratory distress.

One patient (2%) permanently discontinued TAZVERIK due to an adverse reaction of altered mood.

Dosage interruptions due to an adverse reaction occurred in 34% of patients who received TAZVERIK. The most frequent adverse reactions requiring dosage interruptions in ≥3% were hemorrhage, increased alanine aminotransferase (ALT), and increased aspartate aminotransferase (AST).

Dose reduction due to an adverse reaction occurred in one (2%) patient who received TAZVERIK; the dose was reduced in this patient for decreased appetite.

The most common adverse reactions (≥20%) were pain, fatigue, nausea, decreased appetite, vomiting, and constipation.

Table 4 presents adverse reactions in Cohort 5 of Study EZH-202.

Table 4. Adverse Reactions (≥10%) in Patients Receiving TAZVERIK in Cohort 5 of Study EZH-202

Adverse Reaction	TAZVERIK N=62	
	All Grades (%)	Grade 3-4 (%)
General		
Pain[a]	52	7
Fatigue[b]	47	1.6
Gastrointestinal		
Nausea	36	0
Vomiting	24	0
Constipation	21	0
Diarrhea	16	0
Abdominal pain[c]	13	1.6
Metabolism and nutrition		
Decreased appetite	26	4.8
Respiratory, thoracic and mediastinal		
Cough	18	0
Dyspnea[d]	16	4.8
Vascular		
Hemorrhage[e]	18	4.8
Nervous system		
Headache	18	0
Blood and lymphatic system		
Anemia	16	13
Investigations		
Weight decreased	16	7

a Includes tumor pain, pain in extremity, non-cardiac chest pain, flank pain, back pain, arthralgia, bone pain, cancer pain, musculoskeletal pain, myalgia, neck pain
b Includes fatigue and asthenia
c Includes abdominal pain, gastrointestinal pain, abdominal pain lower
d Includes dyspnea and dyspnea exertional
e Includes wound hemorrhage, rectal hemorrhage, pulmonary hemorrhage, hemorrhage intracranial, cerebral hemorrhage, hemoptysis

Table 5 summarizes select laboratory abnormalities in Cohort 5 of Study EZH-202.

Table 5. Select Laboratory Abnormalities (≥ 10%) Worsening from Baseline in Patients Receiving TAZVERIK in Cohort 5 of Study EZH-202

	TAZVERIK*	
Laboratory Abnormality	**All Grades (%)**	**Grade ≥ 3 (%)**
Hematology		
Decreased hemoglobin	49	15
Decreased lymphocytes	36	13
Decreased white blood cell count	19	0
Chemistry		
Increased triglycerides	36	3.3
Increased glucose	33	1.6
Decreased sodium	30	1.7
Decreased phosphate	28	1.7
Decreased albumin	23	0
Increased alkaline phosphatase	23	1.7
Decreased potassium	20	1.7
Increased aspartate aminotransferase	18	3.5
Decreased calcium	16	0
Decreased glucose	16	0
Increased partial thromboplastin time	15	5
Increased alanine aminotransferase	14	3.4
Increased creatinine	12	0
Increased potassium	12	0

*The denominator used to calculate the rate varied from 39 to 61 based on the number of patients with a baseline value and at least one post-treatment value.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on TAZVERIK

Strong and Moderate CYP3A Inhibitors

Coadministration of TAZVERIK with a strong or moderate CYP3A inhibitor increases tazemetostat plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may increase the frequency or severity of adverse reactions. Avoid coadministration of strong or moderate CYP3A inhibitors with TAZVERIK. If coadministration of moderate CYP3A inhibitors cannot be avoided, reduce TAZVERIK dose *[see Dosage and Administration (2.3)]*.

Strong and Moderate CYP3A Inducers

Coadministration of TAZVERIK with a strong or moderate CYP3A inducer may decrease tazemetostat plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may decrease the efficacy of TAZVERIK. Avoid coadministration of moderate and strong CYP3A inducers with TAZVERIK.

7.2 Effect of TAZVERIK on Other Drugs

CYP3A Substrates

Coadministration of TAZVERIK with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and reduced efficacy of CYP3A substrates *[see Use in Specific Populations (8.3), Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1)]*, 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 [$AUC_{0\text{-}45h}$] at the 800 mg twice daily dose *(see Data)*. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4%, and 15% to 20%, respectively.

Data

Animal Data

In pregnant rats, once daily oral administration of tazemetostat during the period of organogenesis from gestation day (GD) 7 through 17 resulted in no maternal adverse effects at doses up to 100 mg/kg/day (approximately 6 times the adult human exposure at 800 mg twice daily). Skeletal malformations and variations occurred in fetuses at doses of ≥50 mg/kg (approximately 2 times the adult human exposure at the 800 mg twice daily dose). At 200 mg/kg (approximately 14 times the adult human exposure at the 800 mg twice daily dose), major findings included increased post implantation loss, missing digits, fused vertebrae, domed heads and fused bones of the skull, and reduced fetal body weights.

In pregnant rabbits, no adverse maternal effects were observed after once daily oral administration of 400 mg/kg/day tazemetostat (approximately 7 times the adult human exposure at the 800 mg twice daily dose) from GD 7 through 19. Skeletal variations were present at doses ≥100 mg/kg/day (approximately 1.5 times the adult human exposure at the 800 mg twice daily dose), with skeletal malformations at ≥200 mg/kg/day (approximately 5.6 times the adult human exposure at the 800 mg twice daily dose). At 400 mg/kg (approximately 7 times the adult human exposure at the 800 mg twice daily dose), major findings included increased post implantation loss and cleft palate and snout.

8.2 Lactation

Risk Summary

There are no animal or human data on the presence of tazemetostat in human milk or on its effects on the breastfed child or milk production. 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.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating TAZVERIK *[see Use in Specific Populations (8.1)]*.

Risk Summary

TAZVERIK can cause fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*.

Contraception

Females

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with TAZVERIK and for 6 months after the final dose. TAZVERIK can render some hormonal contraceptives ineffective *[see Drug Interactions (7.2)]*.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for at least 3 months after the final dose.

8.4 Pediatric Use

The safety and effectiveness of TAZVERIK have been established in pediatric patients aged 16 years and older (adolescents) with metastatic or locally advanced epithelioid sarcoma. Use of TAZVERIK for this indication is supported by evidence from adequate and well-controlled studies in adults (including 3 adolescent patients aged 16 years) *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.1)]*.

The safety and effectiveness of TAZVERIK in pediatric patients aged less than 16 years have not been established.

Juvenile Animal Toxicity Data

In a 13-week juvenile rat toxicology study, animals were dosed daily from post-natal day 7 to day 97 (approximately equivalent to neonate to adulthood). Tazemetostat resulted in:

- T-LBL at doses ≥50 mg/kg (approximately 2.8 times the adult human exposure at the 800 mg twice daily dose)
- Increased trabecular bone at doses ≥100 mg/kg (approximately 10 times the adult human exposure at the 800 mg twice daily dose)
- Increased body weight at doses ≥50 mg/kg (approximately equal to the adult human exposure at the 800 mg twice daily dose)
- Distended testicles in males at doses ≥50 mg/kg (approximately equal to the adult human exposure at the 800 mg twice daily dose)

8.5 Geriatric Use

Clinical studies of TAZVERIK did not include sufficient numbers of patients with epithelioid sarcoma aged 65 and over to determine whether they respond differently from younger subjects.

8.6 Renal Impairment

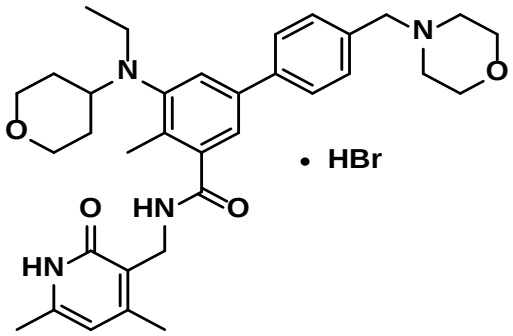
No dose adjustment of TAZVERIK is recommended for patients with mild to severe renal impairment or end stage renal disease *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No dose adjustment of TAZVERIK is recommended for patients with mild hepatic impairment (total bilirubin > 1 to 1.5 times upper limit of normal [ULN] or AST > ULN). TAZVERIK has not been studied in patients with moderate (total bilirubin > 1.5 to 3 times ULN) or severe (total bilirubin > 3 times ULN) hepatic impairment *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

Tazemetostat is a methyltransferase inhibitor. Tazemetostat hydrobromide has the following chemical name: [1,1'-Biphenyl]-3-carboxamide, *N*-[(1,2-dihydro-4,6-dimethyl-2-oxo-3-pyridinyl)methyl]-5-[ethyl(tetrahydro-2*H*-pyran-4-yl)amino]-4-methyl-4'-(4-morpholinylmethyl)-, hydrobromide (1:1). The molecular formula of tazemetostat hydrobromide is $C_{34}H_{44}N_4O_4 \cdot HBr$. Tazemetostat hydrobromide has a molecular weight of 653.66 g/mol and the following structural formula:



Tazemetostat hydrobromide is a white to off-white solid that is slightly soluble in water and has pKa values of 5.26, 6.88, and 12.62. A saturated aqueous solution of tazemetostat hydrobromide has a pH of approximately 5 at ambient conditions.

TAZVERIK (tazemetostat) tablets for oral use contain 200 mg tazemetostat, equivalent to 228 mg tazemetostat hydrobromide.

Each tablet is film-coated and contains the following inactive ingredients in the tablet core: hydroxypropyl cellulose, lactose monohydrate, low-substituted hydroxypropyl cellulose, magnesium stearate, and sodium starch glycolate. The film-coat contains hypromellose, polyethylene glycol, red iron oxide, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tazemetostat is an inhibitor of the methyltransferase, EZH2, and some EZH2 gain-of-function mutations including Y646X and A687V. Tazemetostat also inhibited EZH1 with a half-maximal inhibitory concentration (IC_{50}) of 392 nM, approximately 36 times higher than the IC_{50} for inhibition of EZH2.

The most well-characterized function of EZH2 is as the catalytic subunit of the polycomb repressive complex 2 (PRC2), catalyzing mono-, di-, and trimethylation of lysine 27 of histone H3. Trimethylation of histone H3 leads to transcriptional repression. SWItch/Sucrose Non-Fermentable (SWI/SNF) complexes can antagonize PRC2 function in the regulation of the expression of certain genes. Preclinical in vitro and in vivo models with the loss or dysfunction of certain SWI/SNF complex members (e.g., integrase interactor 1 [INI1/SNF5/SMARCB1/BAF47], SMARCA4 and SMARCA2) can lead to aberrant EZH2 activity or expression and a resulting oncogenic dependence on EZH2.

12.2 Pharmacodynamics

Tazemetostat exposure-response relationships and the time course of pharmacodynamic responses are unknown.

Cardiac Electrophysiology

The effect of orally administered TAZVERIK, at doses ranging from 100 mg to 1600 mg twice daily (0.125 to 2 times the approved recommended dosage) for 15 days, on the heart-rate corrected QT (QTc) interval was evaluated in a dose-finding study in 38 patients with advanced malignancies. Tazemetostat and its metabolite EPZ-6930 did not cause a large mean increase (i.e. >20 ms) on the QTc interval at the 800 mg twice daily dose. The largest mean increase (upper bound of 90% confidence interval) in QTc were 6.1 ms (8.5 ms) and 9.3 ms (12.5 ms) at a dose of 800 mg twice daily and 1600 mg twice daily, respectively.

12.3 Pharmacokinetics

The systemic exposure of tazemetostat is approximately dose proportional over the dose range of 200 mg to 1600 mg twice daily of TAZVERIK (0.25 to 2 times the approved recommended dosage). Following TAZVERIK 800 mg orally twice daily, steady-state was reached by Day 15. The mean (coefficient of variation [CV]%) steady-state peak plasma concentration (C_{max}) was 829 (56%) ng/mL and AUC_{0-12h} was 3340 (49%) ng•h/mL. Tazemetostat exhibited time-dependent pharmacokinetics (PK). The mean accumulation ratio (measured by AUC) was 0.58.

Absorption

The mean absolute oral bioavailability of tazemetostat is approximately 33%. The median time to reach the peak plasma concentration of tazemetostat is 1 to 2 hours.

Effect of Food

A high-fat, high-calorie (approximately 800 to 1000 calories) meal does not have a significant effect on tazemetostat exposure.

Distribution

The mean (CV%) apparent volume of distribution at steady-state (V_{ss}/F) is 1230 L (46%). Tazemetostat is 88% bound to human plasma proteins in vitro. The blood-to-plasma ratio is 0.73.

Elimination

At steady-state, the estimated mean (CV%) terminal elimination half-life of tazemetostat is 3.1 hours (14%) and the apparent total clearance (CL_{ss}/F) is 274 L/h (49%).

Metabolism

In vitro, tazemetostat is metabolized by CYP3A to form the inactive major metabolites M5 (EPZ-6930) and M3 (EPZ006931). M5 undergoes further metabolism by CYP3A.

Excretion

Following a single oral dose of radiolabeled tazemetostat, 94% of the total radioactivity was recovered over 12 days, with 15% excreted into urine and 79% into feces.

Specific Populations

Age (16 to 91 years), sex, race (White, Black, Asian), body weight (37.3 to 173 kg), mild hepatic impairment (total bilirubin > 1 to 1.5 times ULN or AST > ULN) and renal impairment, including end stage renal disease, have no clinically meaningful effect on the pharmacokinetics of tazemetostat. The effect of moderate to severe hepatic impairment has not been studied.

Drug Interaction Studies

Clinical Studies

Effect of CYP3A Inhibitors on Tazemetostat:

Coadministration of fluconazole (a moderate CYP3A inhibitor) with TAZVERIK 400 mg twice daily in patients increased tazemetostat steady-state AUC_{0-8h} by 3.1-fold and C_{max} by 2.3-fold.

Effect of Gastric Acid Reducing Agents on Tazemetostat:

Coadministration of omeprazole (a proton pump inhibitor) with TAZVERIK 800 mg twice daily in patients increased tazemetostat steady-state AUC_{0-8h} by 26% and C_{max} by 25%, which is not expected to have clinically relevant impact.

Effect of Tazemetostat on CYP3A Substrate:

Coadministration of TAZVERIK 800 mg twice daily with oral midazolam (a sensitive CYP3A substrate) in patients decreased midazolam AUC_{0-12h} by 40% and C_{max} by 21%.

Effect of Tazemetostat on CYP2C8 and CYP2C19 Substrates:

Coadministration of TAZVERIK 800 mg twice daily with repaglinide (a sensitive CYP2C8 substrate) and omeprazole (a sensitive CYP2C19 substrate) in patients increased repaglinide $AUC_{0\text{-}8h}$ by 80% and C_{max} by 51%; and had no effect on the exposure of omeprazole.

In Vitro Studies

Metabolic Enzymes:

Tazemetostat does not inhibit CYP1A2, CYP2B6, CYP2C9, and CYP2D6 at clinically relevant concentrations.

Drug Transporters:

Tazemetostat is a substrate of p-glycoprotein (P-gp). Tazemetostat is not a substrate of breast cancer resistance protein (BCRP); renal transporters organic cation transporter 2 (OCT2), organic anion transporter 3 (OAT3), and multidrug and toxin extrusion transporter 1 (MATE1); or hepatic transporters organic anion transporting polypeptide 1B1 (OATP1B1) and organic anion transporting polypeptide 1B3 (OATP1B3).

Tazemetostat is an inhibitor of MATE1 and multidrug and toxin extrusion transporter 2-K (MATE2-K). Tazemetostat does not inhibit P-gp, BCRP, OATP1B1, OATP1B3, organic cation transporter 1 (OCT1), OCT2, organic anion transporter 1 (OAT1), OAT3, or bile salt export pump (BSEP) at clinically relevant concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Dedicated carcinogenicity studies were not conducted with tazemetostat, but T-LBL, MDS, and AML have been reported clinically and T-LBL occurred in juvenile and adult rats after ~9 or more weeks of tazemetostat administration during 13-week toxicity studies. Based on nonclinical studies in rats, the risk of T-LBL appears to be greater with longer duration dosing.

Tazemetostat did not cause genetic damage in a standard battery of studies including a screening and pivotal bacterial reverse mutation (Ames) assay, an in vitro micronucleus assessment in human peripheral blood lymphocytes, and an in vivo micronucleus assessment in rats after oral administration.

Fertility and early embryonic development studies have not been conducted with tazemetostat; however, an assessment of male and female reproductive organs were included in 4- and 13-week repeat-dose toxicity studies in rats and Cynomolgus monkeys. Oral daily administration of tazemetostat did not result in any notable effects in the adult male and female reproductive organs *[see Use in Specific Populations (8.3)]*.

14 CLINICAL STUDIES

The efficacy of TAZVERIK was evaluated in an open-label, single-arm cohort (Cohort 5) of a multi-center study (Study EZH-202, NCT02601950) in patients with histologically confirmed, metastatic or locally advanced epithelioid sarcoma. Patients were required to have INI1 loss, detected using local tests, and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2. Patients received TAZVERIK 800 mg orally twice daily until disease progression or unacceptable toxicity. Tumor response assessments were performed every 8 weeks. The major efficacy outcome measures were confirmed overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as assessed by blinded independent central review (BICR) and duration of response (DOR). Median duration of follow-up was 14 months (range 0.4 to 31).

Among the 62 patients who received TAZVERIK, median age was 34 years (range 16 to 79); 63% were male, 76% were White, 11% were Asian, 44% had proximal disease, 92% had an ECOG PS of 0 or 1, and 8% had an ECOG PS of 2. Prior surgery occurred in 77% of patients; 61% received prior systemic chemotherapy.

Efficacy results are summarized in Table 6.

Table 6. Efficacy Results for the Epithelioid Sarcoma Cohort 5 of Study EZH-202

Efficacy Endpoints	**TAZVERIK N=62**
Overall Response Rate (95% CI)*	15% (7%, 26%)
Complete Response	1.6%
Partial Response	13%
Duration of Response	
% with duration ≥ 6 months	67%
Range in months	3.7, 24.5+

CI: Confidence Interval

* Time to response ranged from 2.4 to 18.4 months.

16 HOW SUPPLIED/STORAGE AND HANDLING

TAZVERIK 200 mg film-coated tablets are red, round, biconvex shape and debossed with “EZM 200” on one side and plain on the other. TAZVERIK is available in:

Bottles of 240 tablets with a desiccant; NDC 72607-100-00

Do not store above 30°C (86°F).

17 PATIENT COUNSELING INFORMATION

Instruct the patient to read the FDA-approved patient labeling (Medication Guide).

Secondary Malignancies

Advise patients of the increased risk of secondary malignancies, including AML, MDS, and T-LBL. Advise patients to inform their healthcare provider if they experience fatigue, easy bruising, fever, bone pain, or paleness *[see Warnings and Precautions (5.1)]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with TAZVERIK and for 6 months after the final dose *[see Use in Specific Populations (8.3)]*.

Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for 3 months after the final dose *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)]*.

Lactation

Advise women not to breastfeed during treatment with TAZVERIK and for 1 week after the final dose *[see Use in Special Populations (8.2)]*.

Drug Interactions

Advise patients and caregivers to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Inform patients to avoid St. John’s wort, grapefruit, and grapefruit juice while taking TAZVERIK *[see Drug Interactions (7.1)]*.

Manufactured for:
Epizyme, Inc.
400 Technology Square
Cambridge, MA 02139

MEDICATION GUIDE
TAZVERIK™ (taz vayr′ ik)
(tazemetostat)
tablets

What is the most important information I should know about TAZVERIK?
TAZVERIK can cause serious side effects, including:

- **Risk of new cancers.** An increase in new (second) cancers has happened in people who were treated with TAZVERIK. Talk with your healthcare provider about your risk of developing new cancers. Tell your healthcare provider if you are more tired than usual, or have easy bruising, fever, bone pain, or paleness.

See "**What are the possible side effects of TAZVERIK**" for more information about side effects.

What is TAZVERIK?
TAZVERIK is a prescription medicine used to treat adults and children aged 16 years and older with epithelioid sarcoma that has spread or grown and cannot be removed by surgery.
It is not known if TAZVERIK is safe and effective in children less than 16 years of age.

Before taking TAZVERIK tell your healthcare provider about all of your medical conditions, including if:

- You are pregnant or plan to become pregnant. TAZVERIK can harm your unborn baby. Your healthcare provider will give you a pregnancy test before you start treatment with TAZVERIK. Tell your healthcare provider right away if you become pregnant or think you may be pregnant.
  - **Females** who are able to become pregnant should use effective non-hormonal birth control (such as condoms) during treatment and for 6 months after the final dose of TAZVERIK. Birth control pills (oral contraceptives) and other hormonal forms of birth control may not be effective if used during treatment with TAZVERIK. Talk to your healthcare provider about birth control options that are right for you.
  - **Males** with female partners who are able to become pregnant should use effective birth control during treatment and for 3 months after the final dose of TAZVERIK.
- You are breastfeeding or plan to breastfeed. It is not known if TAZVERIK passes into your breast milk. Do not breastfeed during treatment and for 1 week after the final dose of TAZVERIK.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. TAZVERIK may affect the way other medicines work and other medicines may affect how TAZVERIK works.

How should I take TAZVERIK?

- Take TAZVERIK exactly as your healthcare provider tells you.
- Take TAZVERIK 2 times each day.
- Your healthcare provider may change your dose, temporarily stop, or completely stop treatment with TAZVERIK if you get certain side effects.
- Take TAZVERIK with or without food.
- Swallow TAZVERIK tablets whole.
- If you miss a dose or vomit after taking your dose, just skip that dose and take the next dose at your regular time.

What should I avoid while taking TAZVERIK?

- Avoid eating grapefruit or drinking grapefruit juice during treatment with TAZVERIK.
- Avoid taking St. John's wort during treatment with TAZVERIK.

What are the possible side effects of TAZVERIK?

TAZVERIK can cause serious side effects. See "What is the most important information I should know about TAZVERIK?"

The most common side effects of TAZVERIK include:

- pain
- nausea
- vomiting
- tiredness
- decreased appetite
- constipation

These are not all the possible side effects of TAZVERIK.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TAZVERIK?
Do not store TAZVERIK tablets above 86°F (30°C).
Keep TAZVERIK and all medicines out of the reach of children.

General information about the safe and effective use of TAZVERIK.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use TAZVERIK for a condition for which it was not prescribed. Do not give TAZVERIK to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about TAZVERIK that is written for health professionals.

What are the ingredients in TAZVERIK?
Active Ingredient: tazemetostat.

Inactive Ingredients: Tablet core: hydroxypropyl cellulose, lactose monohydrate, low-substituted hydroxypropyl cellulose, magnesium stearate, and sodium starch glycolate. Film-coating: hypromellose, polyethylene glycol, red iron oxide, talc, and titanium dioxide.

Manufactured for: Epizyme, Inc. 400 Technology Square, Cambridge, MA 02139
For more information, contact Epizyme at 1-866-4EPZMED.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued: 1/2020