RXADVANCE
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NEW DRUG APPROVAL

Brand Name	Tazveik™
Generic Name	tazemetostat
Drug Manufacturer	Epizyme Inc.

New Drug Approval

FDA Approval Date: June 19, 2020

Review Designation: Priority; Orphan

Type of Review: New Drug Application 213400

DISEASE DESCRIPTION & EPIDEMIOLOGY

Epithelioid sarcoma was first described by Enzinger in 1970 as a rare soft tissue sarcoma that mimics granulomatous disease, carcinoma, and synovial sarcoma. The tumor typically presents as a painless, slow-growing soft tissue swelling in the distal extremity of young adult males. It is locally invasive and frequently metastasizes to regional lymph nodes and distant sites, most commonly to the lungs. Complete surgical resection is curative in low-stage disease; however, a risk of recurrence and late metastasis remains. Epithelioid sarcomas are tumors of purportedly mesenchymal origin that show ultrastructural and immunophenotypic evidence of epithelial differentiation. The mixed differentiation of epithelioid sarcoma can make the differential diagnosis challenging from a histopathologic perspective. The differential diagnosis is narrowed by the somewhat unique epithelioid sarcoma immunophenotype expressing cytokeratin, epithelial membrane antigen, and CD34. Epithelioid sarcoma is one of only a few tumors that characteristically lacks INI-1/SMARCB1 expression.

Epithelioid sarcomas are rare, representing less than 1% of soft tissue sarcomas, and have a predilection for men (up to 2:1 male to female ratio). Most reported tumors occur in young males ranging in age from 10 to 45 years. The extremes of ages include ages 4 to 90, with a median age of 27 years.

In an analysis of a database on upper extremity sarcomas in the United States, the incidence of upper extremity epithelioid sarcoma was 0.1 cases per million per year. In a recent study it has been shown that the incidence has been increasing, with annual percentage change of 5.2% since 1973 and the incidence was reported as 0.4 case per million in 2005. It has been shown to be the second most common soft tissue sarcoma in the hand and the sixth most common soft tissue sarcoma in the upper extremity. This tumor is more common in males (1.8:1) and affects the young adult population. In a large retrospective study 74% of the patients presented between the ages of 10 and 39 and the average age of presentation was 27 years. Upper extremity sarcomas in general are more common in Caucasians but a review of tumors from different countries has shown no racial or geographical predisposition for epithelioid sarcoma. Although less common in females, epithelioid sarcoma has a more favorable prognosis in this population . The most common primary site for epithelioid sarcoma is distal upper extremities although cases of involvement of other parts of the body like vulva, penis and spine have been reported.

Efficacy

Tazverik's approval was based on the results of a clinical trial enrolling 62 patients with metastatic or locally advanced epithelioid sarcoma. During the clinical trial, patients received 800 milligrams (mg) of Tazverik twice a day until the disease progressed or the patient reached an unacceptable level of toxicity. Tumor response assessments were performed every eight weeks during the clinical trial. The trial measured how many patients experienced complete or partial shrinkage (by a certain amount) of their tumors during treatment (overall response rate). The overall response rate was 15%, with 1.6% of patients having a complete response and 13% having a partial response. Of the nine patients that had a response, six (67%) patients had a response lasting six months or longer.

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Safety

ADVERSE EVENTS

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

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

WARNINGS & PRECAUTIONS

Secondary Malignancies: TAZVERIK increases the risk of developing secondary malignancies, including T-cell lymphoblastic lymphoma, myelodysplastic syndrome, and acute myeloid leukemia.

Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of potential risk to a fetus and to use effective non-hormonal contraception.

CONTRAINDICATIONS

None

Clinical Pharmacology

MECHANISMS 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 (IC50) of 392 nM, approximately 36 times higher than the IC50 for inhibition of EZH2.

Dose & Administration

ADULTS

800 mg taken orally twice daily with or without food.

PEDIATRICS

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.

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

GERIATRICS

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.

RENAL IMPAIRMENT

No dose adjustment of TAZVERIK is recommended for patients with mild to severe renal impairment or end stage renal disease.

HEPATIC IMPAIRMENT

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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.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablets: 200 mg