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tisotumab vedotin-tftv
for injection 40 mg

Tivdak Required Eye Care

EYE CARE PROVIDER GUIDE

Indication

TIVDAK is indicated for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Important Safety Information

BOXED WARNING: OCULAR TOXICITY

TIVDAK caused changes in the corneal epithelium and conjunctiva resulting in changes in vision, including severe vision loss, and corneal ulceration. Conduct an ophthalmic exam at baseline, prior to each dose, and as clinically indicated. Adhere to premedication and required eye care before, during, and after infusion. Withhold TIVDAK until improvement and resume, reduce the dose, or permanently discontinue, based on severity.

Please see additional Important Safety Information on pages 2-4 and full prescribing information, including BOXED WARNING for TIVDAK.

Important Safety Information (continued)

Warnings and Precautions

Ocular adverse reactions occurred in 60% of patients with cervical cancer treated with TIVDAK across clinical trials. The most common were conjunctival adverse reactions (40%), dry eye (29%), corneal adverse reactions (21%), and blepharitis (8%). Grade 3 ocular adverse reactions occurred in 3.8% of patients, including severe ulcerative keratitis in 3.2% of patients. One patient experienced ulcerative keratitis with perforation requiring corneal transplantation. Cases of symblepharon were reported in patients with other tumor types treated with TIVDAK at the recommended dose.

In innovaTV 204, 4% of patients experienced visual acuity changes to 20/50 or worse including 1% of patients who experienced a visual acuity change to 20/200. Of the patients who experienced decreased visual acuity to 20/50 or worse, 75% resolved, including the patient who experienced decreased visual acuity to 20/200.

Refer patients to an eye care provider for an ophthalmic exam, including visual acuity and slit lamp exam, at baseline, prior to each dose, and as clinically indicated. Adhere to premedication and required eye care to reduce the risk of ocular adverse reactions. Promptly refer patients to an eye care provider for any new or worsening ocular signs and symptoms. Withhold dose, reduce the dose, or permanently discontinue TIVDAK based on the severity of the adverse reaction.

Peripheral neuropathy (PN) occurred in 42% of cervical cancer patients treated with TIVDAK across clinical trials; 8% of patients experienced Grade 3 PN. PN adverse reactions included peripheral neuropathy (20%), peripheral sensory neuropathy (11%), peripheral sensorimotor neuropathy (5%), motor neuropathy (3%), muscular weakness (3%), and demyelinating peripheral polyneuropathy (1%). One patient with another tumor type treated with TIVDAK at the recommended dose developed Guillain-Barre syndrome.

Monitor patients for signs and symptoms of neuropathy such as paresthesia, tingling or a burning sensation, neuropathic pain, muscle weakness, or dysesthesia. For new or worsening PN, withhold, then dose reduce, or permanently discontinue TIVDAK based on the severity of PN.

Hemorrhage occurred in 62% of cervical cancer patients treated with TIVDAK across clinical trials. The most common all grade hemorrhage adverse reactions were epistaxis (44%), hematuria (10%), and vaginal hemorrhage (10%). Grade 3 hemorrhage occurred in 5% of patients.

Important Safety Information (continued)

Monitor patients for signs and symptoms of hemorrhage. For patients experiencing pulmonary or central nervous system (CNS) hemorrhage, permanently discontinue TIVDAK. For Grade ≥2 hemorrhage in any other location, withhold until bleeding has resolved, blood hemoglobin is stable, there is no bleeding diathesis that could increase the risk of continuing therapy, and there is no anatomical or pathologic condition that can increase the risk of hemorrhage recurrence. After resolution, either resume treatment or permanently discontinue TIVDAK.

Pneumonitis: that is severe, life-threatening, or fatal can occur in patients treated with antibody-drug conjugates containing vedotin, including TIVDAK. Among patients with cervical cancer treated with TIVDAK across clinical trials, 2 patients (1.3%) experienced pneumonitis, including 1 patient who had a fatal outcome.

Monitor patients for pulmonary symptoms of pneumonitis. Symptoms may include hypoxia, cough, dyspnea or interstitial infiltrates on radiologic exams. Infectious, neoplastic, and other causes for symptoms should be excluded through appropriate investigations. Withhold TIVDAK for patients who develop persistent or recurrent Grade 2 pneumonitis and consider dose reduction. Permanently discontinue TIVDAK in all patients with Grade 3 or 4 pneumonitis.

Severe cutaneous adverse reactions, including events of fatal or life-threatening Stevens-Johnson syndrome (SJS), can occur in patients treated with TIVDAK.

Monitor patients for signs or symptoms of severe cutaneous adverse reactions, which include target lesions, worsening skin reactions, blistering or peeling of the skin, painful sores in mouth, nose, throat, or genital area, fever or flu-like symptoms, and swollen lymph nodes. If signs or symptoms of severe cutaneous adverse reactions occur, withhold TIVDAK until the etiology of the reaction has been determined. Early consultation with a specialist is recommended to ensure greater diagnostic accuracy and appropriate management. Permanently discontinue TIVDAK for confirmed Grade 3 or 4 severe cutaneous adverse reactions, including SJS.

Embryo-fetal toxicity: TIVDAK can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TIVDAK and for 2 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TIVDAK and for 4 months after the last dose.

Important Safety Information (continued)

Adverse Reactions

Serious adverse reactions occurred in 43% of patients; the most common (≥3%) were ileus (6%), hemorrhage (5%), pneumonia (4%), PN, sepsis, constipation, and pyrexia (each 3%). Fatal adverse reactions occurred in 4% of patients who received TIVDAK, including septic shock, pneumonitis, sudden death, and multisystem organ failure (each 1%).

Adverse reactions leading to permanent discontinuation occurred in 13% of patients receiving TIVDAK; the most common (≥3%) were PN (5%) and corneal adverse reactions (4%). Adverse reactions leading to dose interruption occurred in 47% of patients; the most common (≥3%) were PN (8%), conjunctival adverse reactions (4%), and hemorrhage (4%). Adverse reactions leading to dose reduction occurred in 23% of patients; the most common (≥3%) were conjunctival adverse reactions (9%) and corneal adverse reactions (8%).

The most common (≥25%) adverse reactions, including laboratory abnormalities, were hemoglobin decreased (52%), fatigue (50%), lymphocytes decreased (42%), nausea (41%), PN (39%), alopecia (39%), epistaxis (39%), conjunctival adverse reactions (37%), hemorrhage (32%), leukocytes decreased (30%), creatinine increased (29%), dry eye (29%), prothrombin international normalized ratio increased (26%), activated partial thromboplastin time prolonged (26%), diarrhea (25%), and rash (25%).

Drug Interactions

Strong CYP3A4 inhibitors: Concomitant use with strong CYP3A4 inhibitors may increase unconjugated monomethyl auristatin E (MMAE) exposure, which may increase the risk of TIVDAK adverse reactions. Closely monitor patients for TIVDAK adverse reactions.

Use in Specific Populations

Moderate or severe hepatic impairment: MMAE exposure and adverse reactions are increased. Avoid use.

Lactation: Advise lactating women not to breastfeed during TIVDAK treatment and for at least 3 weeks after the last dose.

Please see full prescribing information, including BOXED WARNING for TIVDAK.

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Overview[1,2]

Tivdak has a BOXED WARNING for ocular toxicity and caused changes in the corneal epithelium and conjunctiva resulting in changes in vision, including severe vision loss and corneal ulceration.

As an eye care provider, **you will play a pivotal role** in the ocular care of recurrent or metastatic cervical cancer patients being considered for or treated with Tivdak. It is important to partner closely with your patient's oncologist.

In order to **monitor eye health** and reduce the risk of ocular adverse reactions, you, the patient, and the oncologist will adhere to **Tivdak Premedication and Required Eye Care**, details of which are described in this brochure.

In the event of an ocular adverse reaction, your patient may need to **visit you for diagnosis of the condition, grading, and treatment of symptoms.**

This guide is designed to assist you and your staff.

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Prevalence of ocular adverse reactions[1]

- Ocular adverse reactions occurred in 60% of patients with cervical cancer treated with Tivdak across clinical trials[a]
- The most common ocular adverse reactions were conjunctival adverse reactions (40%), dry eye (29%), corneal adverse reactions (21%), and blepharitis (8%)[a]
- Grade 3 ocular adverse reactions occurred in 3.8% of patients, including severe ulcerative keratitis in 3.2% of patients[a]
- 1 patient experienced ulcerative keratitis with perforation requiring corneal transplantation[a]
- Cases of symblepharon were reported in patients with other tumor types treated with Tivdak at the recommended dose[a]
- In innovaTV 204, 4% of patients experienced visual acuity changes to 20/50 or worse, including 1% of patients who experienced a visual acuity change to 20/200. Of the patients who experienced decreased visual acuity to 20/50 or worse, 75% resolved, including the patient who experienced decreased visual acuity to 20/200[b]
- The median time to onset of the first ocular adverse reaction was 1.2 months (range: 0-6.5). Ocular adverse reactions led to discontinuation of Tivdak in 6% of patients with cervical cancer[a]
- The most common (≥3%) ocular adverse reactions leading to dose reduction were conjunctival adverse reactions (9%) and corneal adverse reactions (8%)[b]

[a]These data reflect exposure to Tivdak in 158 patients with recurrent or metastatic cervical cancer who received at least one dose of Tivdak at 2 mg/kg intravenously every 3 weeks in 4 clinical trials.
[b]These data reflect exposure to Tivdak in 101 patients with recurrent or metastatic cervical cancer who received 2 mg/kg intravenously every 3 weeks in the innovaTV 204 clinical trial.

Please see Important Safety Information on pages 1-4 and full prescribing information, including BOXED WARNING for TIVDAK.

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Resolution of ocular adverse reactions[1,a]

At last follow-up, patients who experienced ocular adverse reactions had either

COMPLETE RESOLUTION	OR	PARTIAL IMPROVEMENT
55%		30%

Partial improvement was defined as a decrease in severity by 1 or more grades from the worst grade.

Time to resolution of ocular adverse reactions[2,3,b]

Time to resolution of ocular adverse reactions was exploratory. Data are provided as supportive clinical information.

The **median time to resolution** of each ocular adverse reaction was **0.7 months** (IQR: 0.3 to 1.6 months)[c]

At the 30-day follow-up after the last dose of Tivdak, 118 out of 138 ocular adverse reactions were resolved (86%)

[a]These data reflect exposure to Tivdak in 158 patients with recurrent or metastatic cervical cancer who received at least one dose of Tivdak at 2 mg/kg intravenously every 3 weeks in 4 clinical trials.
[b]These data reflect exposure to Tivdak in 101 patients with recurrent or metastatic cervical cancer who received Tivdak 2 mg/kg intravenously every 3 weeks in the innovaTV 204 clinical trial.
[c]IQR=interquartile range.

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Required exams and reminders

CONDUCT AN OPHTHALMIC EXAM[1]

An oncologist will refer their Tivdak patient to you for an ophthalmic exam. This should occur prior to their first infusion of Tivdak, prior to each dose, and as clinically indicated. This exam should include but is not limited to:

Visual acuity exam

Slit lamp exam

AVOID CONTACT LENSES AND IRRITANTS[1,2]

- Advise patients to avoid wearing contact lenses throughout treatment unless otherwise specified
- Advise patients to avoid putting any irritants near their eyes throughout treatment

There are no contraindications for Tivdak. Patients were excluded from the pivotal trial (innovaTV 204) if they had active ocular surface disease, any prior episode of cicatricial conjunctivitis, or Stevens Johnson syndrome.[1]

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Topical eye drops[1,2]

Three different topical eye drops will need to be prescribed to the patient prior to starting Tivdak treatment. Coordinate with the patient's oncologist to manage the eye drop prescriptions.

Corticosteroid eye drops

May address possible conjunctival inflammation. Patients will be referred to you for a slit lamp exam before the initial prescription and all renewals of any corticosteroid medication

Vasoconstrictor eye drops

May reduce blood flow to the eye area, thereby potentially decreasing off-tumor delivery of Tivdak

Lubricating eye drops

May add moisture to the eye, relieve dry eye discomfort, and reduce overall irritation

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The eye drop schedule[1,2]

With the help of a nurse, some of the topical eye drops will be applied during the infusion appointment. After and between infusions, the patient will self-administer some of the drops daily.

Day 1: Infusion Day

Pre-Infusion

Corticosteroid Eye Drops
1 drop per eye
Infusion nurse will administer 1 drop per eye prior to infusion or as prescribed

Vasoconstrictor Eye Drops
3 drops per eye
Infusion nurse will administer 3 drops per eye immediately prior to each infusion or as prescribed

Post-Infusion: Remainder of Day

Corticosteroid Eye Drops
1 drop per eye 2x/day
Patient will self-administer 1 drop per eye 2x throughout the remainder of the day or as prescribed

Days 2-3 (72 hours post-infusion)

After Infusion

Corticosteroid Eye Drops
1 drop per eye 3x/day
Patient will self-administer 1 drop per eye, 3x per day for Days 2-3 after infusion, or as prescribed

Throughout Treatment

Daily

Lubricating Eye Drops
Patient will self-administer for the duration of therapy, and for 30 days after the last dose of Tivdak

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Monitoring and assessing[1,2]

- Monitor patients for new or worsening ocular signs and symptoms
- In the event of an ocular adverse reaction, the oncologist may refer the patient to you for diagnosis of the condition, grading, and treatment of symptoms
- Depending on your assessment, the oncologist may maintain, withhold, reduce, or permanently discontinue Tivdak, based on recommended dosing modification guidelines found in the Tivdak USPI

In the event of an ocular adverse reaction 〉

EYE CARE PROVIDER		ONCOLOGIST
1 Eye exam	2 Ocular adverse reaction grading	3 Dosage modification

EYE SELF-CHECK[2]

- Encourage patients to monitor their eyes daily for any signs or symptoms of new or worsening ocular adverse reactions, including, but not limited to:
  - Dry eyes
  - Eye redness
  - Eye irritation
  - Light sensitivity
  - Blurred vision
  - Vision loss or impairment

Advise patients to call your office and their oncologist's office if they experience new or worsening ocular signs and symptoms.

Communicate with your patient's oncologist. The Tisotumab vedotin-tftv Eye Care Consult Form may help you relay any updates or concerns you have.

Contact your Tivdak sales representative for more information.

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Please see Important Safety Information on pages 1-4 and full prescribing information, including BOXED WARNING for TIVDAK.

References:

1. TIVDAK [Prescribing Information]. Bothell, WA: Seagen Inc. July 2023. **2.** Kim SK, Ursell P, Coleman RL, Monk BJ, Vergote I. Mitigation and management strategies for ocular events associated with tisotumab vedotin. *Gynecol Oncol*. 2022;165(2):385-392. **3.** Coleman RL, Lorusso D, Gennigens C, et al. Efficacy and safety of tisotumab vedotin in previously treated recurrent or metastatic cervical cancer (innovaTV 204/GOG-3023/ENGOT-cx6): a multicentre, open-label, single-arm, phase 2 study. *Lancet Oncol*. 2021;22(5):609-619.

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