tivdak™
tisotumab vedotin-tftv
for injection 40 mg

Dosing, Administration, and Eye Care Guide

FOR YOUR PRACTICE

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.

Select 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 2-3 and the accompanying 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. For new or worsening PN, withhold, 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.

Monitor patients for signs and symptoms of hemorrhage. For patients experiencing pulmonary or 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: Severe, life-threatening, or fatal pneumonitis 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. 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.

Important Safety Information (continued)

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.

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.

The Tivdak™ infusion

The recommended dose of Tivdak is
2 mg/kg
(up to a maximum of 200 mg for patients ≥100 kg)

Tivdak is administered as an
intravenous infusion
over 30 minutes
every 3 weeks
until disease progression or unacceptable toxicity

The Tivdak infusion appointment takes approximately **60 minutes**
including administration of eye drops, application of cold packs, and a 30-minute infusion

Dosage Forms & Storage

Tivdak 40 mg for injection is supplied as a white to off-white lyophilized cake or powder in a single-dose vial for reconstitution. Tivdak vials are available in the following packages:

- Carton of one 40 mg single-dose vial

Store Tivdak vials refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light.

- Do not freeze
- Do not shake

Reconstitution in single-dose vial

PREPARATION AND ADMINISTRATION

- Administer as an intravenous infusion only
- Tivdak is a hazardous drug. Follow applicable special handling and disposal procedures
- Do not mix Tivdak as an IV push or bolus
- Do not mix with, or administer as an infusion with, other medicinal products

CALCULATE

- Calculate the recommended dose based on the patient's weight to determine the number of vials needed

RECONSTITUTE

- Reconstitute each 40 mg vial with 4.0 mL of sterile water for injection, USP, resulting in 10 mg/mL Tivdak
- Slowly swirl each vial until the contents are completely dissolved. Allow the reconstituted vial(s) to settle

DO NOT SHAKE THE VIAL. Do not expose to direct sunlight

INSPECT

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The reconstituted solution should be clear to slightly opalescent, colorless to brownish-yellow and free of visible particles. Discard any vial with visible particles or discoloration

USE OR STORE

- Based upon the calculated dose amount, the reconstituted solution from the vial(s) should be added to the infusion bag immediately. This product does not contain a preservative. If not used immediately, reconstituted vials may be stored for up to 24 hours in refrigeration at 2°C to 8°C (36 °F to 46 °F) or at room temperature up to 25°C (77°F) for up to a maximum of 8 hours prior to dilution

DO NOT FREEZE. Do not expose to direct sunlight. Discard unused vials with reconstituted solution beyond the recommended storage time

Dilution in infusion bag

TRANSFER

- Withdraw the calculated dose amount of reconstituted solution from the vial(s) and transfer into an infusion bag

DILUTE

- Dilute Tivdak™ with one of the following: 5% Dextrose Injection, USP, 0.9% Sodium Chloride Injection, USP, or Lactated Ringer's Injection, USP. The infusion bag size should allow enough diluent to achieve a final concentration of 0.7 mg/mL to 2.4 mg/mL Tivdak
- Mix diluted solution by gentle inversion

i DO NOT SHAKE THE BAG. Do not expose to direct sunlight

INSPECT

- Visually inspect the infusion bag for any particulate matter or discoloration prior to use. The reconstituted solution should be clear to slightly opalescent, colorless to brownish-yellow and free of visible particles

i Discard the infusion bag if particulate matter or discoloration is observed

DISCARD

- Discard any unused portion left in the single-dose vials

Administration

EYE DROPS
- Confirm administration of corticosteroid and vasoconstrictor eye drops

COLD PACKS
- Apply cold packs fully over the eyes following administration of the vasoconstrictor eye drops and leave on during the infusion. Change cold packs as needed throughout infusion to ensure eye area remains cold

Additional information on Tivdak Required Eye Care, including eye drop and cold pack administration, can be found on pages 12-14

INFUSION
- Immediately administer the infusion over 30 minutes through an intravenous line containing a 0.2 µm in-line filter

DELAYED INFUSION HANDLING
- If the infusion is not administered immediately, store the diluted Tivdak solution in refrigeration as specified in the table below. Discard if storage time exceeds these limits

DO NOT FREEZE. Once removed from refrigeration, complete administration of the diluted infusion solution of Tivdak within 4 hours (including infusion time)

Diluted Tivdak Solution Refrigeration Storage Conditions

Diluent Used to Prepare Solution for Infusion	Diluted Tivdak Solution Storage Conditions (Including Infusion Time)
0.9% Sodium Chloride Injection	Up to 18 hours at 2°C to 8°C (36°F to 46°F)
5% Dextrose Injection	Up to 24 hours at 2°C to 8°C (36°F to 46°F)
Lactated Ringer's Injection	Up to 12 hours at 2°C to 8°C (36°F to 46°F)

Please see information about dosage modification for Tivdak on pages 10-11.

Please see Important Safety Information on pages 1-3 and full prescribing information, including BOXED WARNING for TIVDAK.

Adverse reactions

FROM THE INNOVATV 204 CLINICAL TRIAL

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

Adverse Drug Reactions Reported in ≥10% of Patients Treated with Tivdak™ in innovaTV 204

Adverse Reaction	Tivdak (2 mg/kg) N=101	
	All Grades %	Grade 3-4 %
General		
Fatigue[a]	50	7
Pyrexia	16	1
Pruritus	13	1
Gastrointestinal disorders		
Nausea[b]	41	0
Diarrhea[c]	25	2
Constipation	23	2
Abdominal pain[d]	23	1
Vomiting	17	2
Nervous system disorders		
Peripheral neuropathy[e]	39	7
Skin and subcutaneous tissue disorders		
Alopecia	39	0
Rash[f]	25	0
Vascular disorders		
Epistaxis	39	0
Hemorrhage[g]	32	6
Eye disorders		
Conjunctival adverse reactions[h]	37	0
Dry eye[i]	29	0
Corneal adverse reactions[j]	21	3
Periorbital adverse reactions[k]	16	0
Musculoskeletal and connective tissue disorders		
Myalgia[l]	21	0
Arthralgia	16	0
Pain in extremity[m]	13	1
Metabolism and nutrition disorders		
Decreased appetite	16	1
Infections		
Urinary tract infection[n]	14	2
Investigations		
Weight decreased	12	0

[a]Fatigue includes fatigue and asthenia.

[b]Nausea includes nausea and retching.

[c]Diarrhea includes diarrhea, gastroenteritis, and colitis.

[d]Abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal distention, and abdominal discomfort.

[e]Peripheral neuropathy includes neuropathy peripheral, peripheral sensorimotor neuropathy, polyneuropathy, peripheral sensory neuropathy, paresthesia, hypoesthesia, burning sensation, neuralgia, sensory loss, peripheral motor neuropathy, muscular weakness, gait disturbance, and hyperesthesia.

[f]Rash includes rash, rash maculo-papular, rash macular, dermatitis acneiform, dermatitis allergic, and erythema.

[g]Hemorrhage includes vaginal hemorrhage, hematuria, rectal hemorrhage, cystitis hemorrhagic, lower gastrointestinal hemorrhage, urinary bladder hemorrhage, hematochezia, anal hemorrhage, gingival bleeding, post procedural hemorrhage, radiation associated with hemorrhage, metrorrhagia, large intestinal hemorrhage, paranasal sinus hemorrhage, and hemoptysis.

[h]Conjunctival adverse reactions includes conjunctivitis, conjunctival abrasion, conjunctival erosion, conjunctival hyperemia, conjunctival scar, noninfective conjunctivitis, ocular hyperemia, and conjunctival hemorrhage.

[i]Dry eye includes dry eye and lacrimation increased.

[j]Corneal adverse reactions includes keratitis, punctate keratitis, ulcerative keratitis, corneal erosion, corneal scar, keratopathy, and corneal bleeding.

[k]Periorbital adverse reactions includes blepharitis, meibomianitis, eye pruritus, entropion, trichiasis, chalazion, and meibomian gland dysfunction.

[l]Myalgia includes myalgia, musculoskeletal discomfort, and musculoskeletal pain.

[m]Pain in extremity includes pain in extremity and limb discomfort.

[n]Urinary tract infection includes urinary tract infection, urinary tract infection bacterial, and cystitis.

Ocular adverse reactions

ACROSS CLINICAL TRIALS

PREVALENCE
- Ocular adverse reactions occurred in 60% of patients with cervical cancer treated with Tivdak across clinical trials.
- The most common ocular adverse reactions were conjunctival adverse reactions (40%), dry eye (29%), corneal adverse reactions (21%), and blepharitis (8%)

ONSET
- The median time to onset of the first any grade ocular adverse reaction was 1.2 months (range, 0-6.5)

RESOLUTION
- Of the patients who experienced ocular reactions, 55% had complete resolution and 30% had partial improvement at last follow-up.

MONITOR
- Monitor patients for new or worsening ocular signs and symptoms and promptly refer patients to an eye care provider if warranted

Peripheral neuropathy

ACROSS CLINICAL TRIALS

PREVALENCE
- Peripheral neuropathy occurred in 42% of patients with cervical cancer treated with Tivdak across clinical trials; 8% of patients experienced Grade 3 peripheral neuropathy.
- Peripheral neuropathy 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%)

ONSET
- The median time to onset of the first event of any grade peripheral neuropathy was 2.4 months (range, 0-11.3)

RESOLUTION
- Of the patients who experienced peripheral neuropathy, 17% had complete resolution and 17% had partial improvement at last follow up.

MONITOR
- Monitor patients for general signs and symptoms of neuropathy, such as paresthesia, tingling or a burning sensation, neuropathic pain, muscle weakness, or dysesthesia

Dosage Modification

Some patients may require dosage modifications or discontinuation of Tivdak™ to manage adverse reactions. The recommended dose modifications for adverse reactions are provided below. Refer patients to an eye care provider promptly for an assessment of new or worsening ocular signs and symptoms.

Dose Modification for Ocular Adverse Reactions[a]

Keratitis[b]	
Superficial punctate keratitis (SPK) (Any occurrence)	Monitor.
Confluent superficial keratitis (First occurrence)	Withhold dose until SPK or normal, then resume treatment at the next lower dose level.
Confluent superficial keratitis (Second occurrence)	Permanently discontinue.
Ulcerative keratitis or perforation (Any occurrence)	Permanently discontinue.
Conjunctival ulceration[b]	
Any ulceration (First occurrence)	Withhold dose until complete conjunctival re-epithelialization, then resume treatment at the next lower dose level.
Any ulceration (Second occurrence)	Permanently discontinue.
Conjunctival or corneal scarring or symblepharon	
Any scarring or symblepharon (Any occurrence)	Permanently discontinue.
Conjunctivitis and other ocular adverse reactions	
Grade 1 (Any occurrence)	Monitor.
Grade 2 (First occurrence)	Withhold dose until Grade ≤1, then resume treatment at the same dose.
Grade 2 (Second occurrence)	Withhold dose until Grade ≤1, then resume treatment at the next lower dose level. If no resolution to Grade ≤1, permanently discontinue.
Grade 2 (Third occurrence) or Grade 3 or 4 (Any occurrence)	Permanently discontinue.

[a]Please see the full prescribing information for more detail.

[b]Refer patients to an eye care provider promptly for an assessment of new or worsening ocular symptoms.

Dosage Modification (continued)

Dosage Modification for Peripheral Neuropathy[a]

Peripheral neuropathy	
Grade 2 Initial or worsening of pre-existing condition (Any occurrence)	Withhold dose until Grade ≤1, then resume treatment at the next lower dose level.
Grade 3 or 4 (Any occurrence)	Permanently discontinue.

Dosage Modification for Hemorrhage[a]

Hemorrhage	
Any grade pulmonary or CNS (Any occurrence)	Permanently discontinue.
Grade 2 in any other location (Any occurrence) or Grade 3 in any other location (First occurrence)	Withhold until resolved, then resume treatment at the same dose.
Grade 3 in any other location (Second occurrence) or Grade 4 in any other location (Any occurrence)	Permanently discontinue.

Dosage Modification for Pneumonitis[a]

Pneumonitis	
Grade 2 (Any occurrence)	Withhold dose until Grade ≤1 for persistent or recurrent pneumonitis, consider resuming treatment at next lower dose level.
Grade 3 or 4 (Any occurrence)	Permanently discontinue.

[a]Please see the full prescribing information for more detail.

Tivdak Required Eye Care

BEFORE STARTING THE TIVDAK INFUSION

PARTNER WITH AN EYE CARE PROVIDER

Refer your patient to an eye care provider for an ophthalmic exam, including visual acuity and slit lamp exam. This exam should occur prior to their first infusion to establish baseline eye health, prior to each treatment of Tivdak, and as clinically indicated.

PRESCRIBE TOPICAL EYE DROPS

Remind patients to bring all of their eye drops to their infusion appointment.

During and After Infusion

Day 1: Infusion Day (once every 3 weeks)

Pre-Infusion
(~10 min prior)

- **Vasoconstrictor Drops**
  3 drops per eye or as prescribed
- **Corticosteroid Drops**
  1 drop per eye or as prescribed
- **Cold Packs**
  Rotate as needed to keep eyes cool for 60 minutes total

During Infusion
(~30 min)

- **Infusion**
  2-mg/kg intravenous infusion
- **Cold Packs**
  Rotate as needed to keep eyes cool for 60 minutes total

After Infusion
(~20 min)

- **Cold Packs**
  Rotate as needed to keep eyes cool for 60 minutes total

Remainder of Day

- **Corticosteroid Drops**
  1 drop per eye, 2x throughout the remainder of the day or as prescribed
  (Patient to self-administer)

During and After Infusion (continued)

Post Infusion Day (patient-driven tasks)	DAY 2	DAY 3	ONGOING
Corticosteroid Drops[a] 1 drop per eye, 3x per day for Days 2-3 after infusion or as prescribed	S	S	
Lubricating Drops Instruct patients to administer for the duration of therapy and for 30 days after the last dose of Tivdak	L	L	L
Eye Self-Check Patients should monitor their eyes daily and call their eye care provider and/or your office in the event of an ocular adverse reaction			
Avoid Contact Lenses Advise patients to avoid wearing contact lenses throughout treatment unless directed to do so by an eye care provider			

[a] The initial prescription and all renewals of any corticosteroid medication should be made only after examination with a slit lamp.

Eye care checklist

A step-by-step checklist to help you adhere to Tivdak Required Eye Care

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DAY 1: INFUSION DAY

Prior to every infusion

- ☐ **Eye health check**
  Refer patients to an eye care provider for an ophthalmic exam, including visual acuity and slit lamp exam, prior to each treatment and as clinically indicated

Promptly refer patients to an eye care provider for any new or worsening signs and symptoms

- ☐ **Confirm patient has eye drops**

~10 minutes before infusion

- ☐ **Eye drops**
  - Administer 1 corticosteroid drop in each eye or as prescribed
  - Administer 3 vasoconstrictor drops in each eye or as prescribed
- ☐ **Cold packs**
  Place cold packs fully over eyes prior to each infusion

During infusion

- ☐ **Infusion (~30 min)**
  - Administer 2.0-mg/kg intravenous infusion of Tivdak (up to a maximum of 200 mg for patients ≥100 kg)
- ☐ **Rotate cold packs**
  - Rotate as needed to keep eyes cool for a total of 60 minutes

Remainder of day

- ☐ **Eye drops**
  Instruct patient to administer 1 corticosteroid drop in each eye 2x throughout the remainder of the day or as prescribed

Advise patients to avoid wearing contact lenses or applying any irritants on or near the eyes throughout treatment with Tivdak, including between infusions

AFTER INFUSION DAY

For Days 2-3 following infusion

- ☐ **Corticosteroid eye drops**
  1 drop per eye, 3x per day after infusion, or as prescribed

Ongoing

- ☐ **Lubricating eye drops**
  Instruct patients to administer for the duration of therapy and for 30 days after the last dose of Tivdak
- ☐ **Eye self-check**
  Patients should monitor their eyes daily and call their eye care provider and/or your office in the event of an ocular adverse reaction
- ☐ **Corticosteroid eye drop prescription renewal**
  Refer patients to an eye care provider for a slit lamp exam before the initial prescription and all renewals of any corticosteroid medication

Instruct patients to call your office or their eye care provider if they experience changes or discomfort with their eyes

Please see Important Safety Information and full prescribing information, including BOXED WARNING for TIVDAK.

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Reference: 1. TIVDAK [Prescribing Information]. Bothell, WA: Seagen Inc. September 2021.

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