NEW DRUG APPROVAL

Brand Name	Tivdak™
Generic Name	tisotumab vedotin-tftv
Drug Manufacturer	Seagen Inc.

New Drug Approval

FDA Approval Date: September 20, 2021
Review Designation: N/A
Review Type: Biologic License Application (BLA): 761208
Dispensing Restrictions: Speciality Distribution

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Metastatic disease will develop in 15 to 61 percent women with cervical cancer, usually within the first two years of completing treatment. In the majority of cases, metastatic cervical cancer is not curable. However, for some patients who present with recurrent disease in the pelvis (locoregional recurrence) or with limited distant metastatic disease, surgical treatment is potentially curative.

Histologically, squamous cell carcinoma (SCC), adenocarcinoma, and adenosquamous carcinomas account for approximately 70, 25, and 3 to 5 percent of all cervical cancers, respectively. the estimated prevalence of organ site involvement by metastatic cervical cancer was:

- Pelvic or para-aortic nodes (75 and 62 percent, respectively)
- Lung (33 to 38 percent)
- Liver (33 percent)
- Peritoneum (5 to 27 percent)
- Adrenal gland (14 to 16 percent)
- Intestines (12 percent)
- Skin (10 percent)

An estimated 14,480 cases of invasive cervical cancer will be diagnosed in the United States in 2021, and about 4290 women will die from cervical cancer.

Approximately 4000 patients with recurrent or metastatic cervical cancer are treated with first-line therapies in the United States per year, and 2000 are treated with second-line therapies.

Efficacy

The efficacy of Tivdak™ was evaluated in innovaTV 204 (NCT03438396), an open-label, multicenter, singlearm trial that treated 101 patients with recurrent or metastatic cervical cancer who had received no more than two prior systemic regimens in the recurrent or metastatic setting, including at least one prior platinum-based chemotherapy regimen. Patients were excluded if they had active ocular surface disease, any prior episode of cicatricial conjunctivitis or Stevens Johnson syndrome, Grade ≥2 peripheral neuropathy or known coagulation defects leading to an increased risk of bleeding.

Patients received Tivdak™ 2 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity. Tumor response assessments were performed every 6 weeks for the first 30 weeks and every 12 weeks thereafter.

Sixty-eight percent of patients had squamous cell carcinoma, 27% Reference ID: 4859741 Reference ID: 4861281 had adenocarcinoma, and 5% had adenosquamous histology. ECOG performance status was 0 (58%) or 1 (42%). Seventy percent of patients had received 1 prior line of systemic therapy, and 30% had 2 prior lines of systemic therapy. Sixty-nine percent of patients previously received bevacizumab as part of their prior systemic therapy. Sixty-three percent received bevacizumab in combination with chemotherapy (paclitaxel and cisplatin or carboplatin, or paclitaxel and topotecan) as first-line therapy.

The major efficacy outcome measures were confirmed objective response rate (ORR) as assessed by an independent review committee (IRC) using RECIST v1.1 criteria and duration of response (DOR).

Table. Efficacy Results in innovaTV 204 by IRC

Endpoint	**N=101**
Confirmed ORR (95% CI)	24% (15.9, 33.3)
Complete response rate	7%
Partial response rate	17%
Duration of Response	
Median Duration of Response, months[1] (95% CI)	8.3 (4.2, NR)

Based on patients (n=24) with a response by IRC
CI: confidence interval
NR: not reached

Safety

ADVERSE EVENTS

The most common (≥25%) adverse reactions, including laboratory abnormalities, were hemoglobin decreased, fatigue, lymphocytes decreased, nausea, peripheral neuropathy, alopecia, epistaxis, conjunctival adverse reactions, hemorrhage, leukocytes decreased, creatinine increased, dry eye, prothrombin international normalized ratio increased, activated partial thromboplastin time prolonged, diarrhea, and rash.

WARNINGS & PRECAUTIONS

- Peripheral neuropathy: Monitor patients for new or worsening peripheral neuropathy. Withhold, reduce the dose, or permanently discontinue Tivdak™ based on severity.
- Hemorrhage: Monitor patients for signs and symptoms of hemorrhage. Withhold, reduce the dose, or permanently discontinue Tivdak™ based on severity.
- Pneumonitis: Severe, life-threatening, or fatal pneumonitis may occur. Withhold Tivdak™ for persistent or recurrent Grade 2 pneumonitis and consider dose reduction. Permanently discontinue Tivdak™ for Grade 3 or 4 pneumonitis.
- Embryo-fetal toxicity: Tivdak™ can cause fetal harm. Advise of the potential risk to a fetus and to use effective contraception.

CONTRAINDICATIONS

None

Clinical Pharmacology

MECHANISMS OF ACTION

Tisotumab vedotin-tftv is a tissue factor (TF)-directed antibody drug conjugate (ADC). The antibody is a human IgG1 directed against cell surface TF. TF is the primary initiator of the extrinsic blood coagulation cascade. The small molecule, MMAE, is a microtubule-disrupting agent, attached to the antibody via a protease-cleavable linker. Nonclinical data suggests that the anticancer activity of tisotumab vedotin-tftv is due to the binding of the ADC to TF expressing cancer cells, followed by internalization of the ADC-TF complex, and release of MMAE via proteolytic cleavage. MMAE disrupts the microtubule network of actively dividing cells, leading to cell cycle arrest and apoptotic cell death. In vitro, tisotumab vedotin-tftv also mediates antibody-dependent cellular phagocytosis and antibody-dependent cellular cytotoxicity.

Dose & Administration

ADULTS

- For intravenous infusion only. Do not administer Tivdak™ as an intravenous push or bolus. Do not mix with, or administer as an infusion with, other medicinal products.
- The recommended dose of Tivdak™ is 2 mg/kg (up to a maximum of 200 mg) given as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.

PEDIATRICS

Safety and effectiveness of Tivdak™ in pediatric patients have not been established.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

- Mild to moderate renal impairment (CrCl 30 to 89 mL/min): No dosage adjustment is recommended.
- Severe renal impairment (CrCl 15 to 29 mL/min) or end-stage renal disease (ESRD) with or without dialysis:

HEPATIC IMPAIRMENT

Avoid use of Tivdak™ in patients with moderate or severe hepatic impairment (total bilirubin > 1.5 × ULN).

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

For Injection: 40 mg as a lyophilized cake or powder in a single-dose vial for reconstitution.