ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Tivdak 40 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of powder for concentrate for solution for infusion contains 40 mg tisotumab vedotin.

After reconstitution, each mL of solution for infusion contains 10 mg of tisotumab vedotin.

Tisotumab vedotin is comprised of a fully human IgG1-kappa antibody conjugated to the monomethyl auristatin E (MMAE) via a protease-cleavable vc (valine citrulline) linker.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White to off-white lyophilised cake or powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tivdak as monotherapy is indicated for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after systemic therapy (see section 5.1).

4.2 Posology and method of administration

Treatment with Tivdak should be initiated and supervised by a physician experienced in the use of anti-cancer therapies. Prior to the first infusion and as clinically indicated, an eye care professional should conduct an ophthalmic exam, including visual acuity and slit lamp exam (see "Eye care" at the end of this section and section 4.4).

Posology

The recommended dose of Tivdak is 2 mg/kg (up to a maximum of 200 mg for patients ≥ 100 kg) every 3 weeks until disease progression or unacceptable toxicity.

Dose modifications

The recommended Tivdak dose reduction schedule is provided in Table 1. Tivdak should be permanently discontinued in patients who cannot tolerate 0.9 mg/kg.

Table 1: Dose reduction schedule

	Dose level
Starting dose	2 mg/kg (up to maximum of 200 mg)
First dose reduction	1.3 mg/kg (up to maximum of 130 mg)
Second dose reduction	0.9 mg/kg (up to maximum of 90 mg)

The recommended dose modifications for adverse reactions are provided in Table 2. Patients should be referred to an eye care professional as soon as possible for an assessment of new or worsening ocular symptoms (see section 4.4).

Table 2: Dose modifications

Adverse reaction	**Severity***	**Occurrence**	**Dose modification**
Keratitis	Grade 1	Any	Withhold dose until clinically stable, then resume treatment at the same dose.
	Grade 2	First occurrence	Withhold dose until Grade ≤ 1, then resume treatment at the next lower dose level.
		Second occurrence	Withhold dose until Grade ≤ 1, then resume treatment at the next lower dose level. If no resolution to Grade ≤ 1, permanently discontinue.
		Third occurrence	Permanently discontinue.
	Grade 3 or 4	Any	Permanently discontinue.
Conjunctival ulceration	Grade 1 or 2	First occurrence	Withhold dose until clinically stable, then resume treatment at the next lower dose level.
		Second occurrence or more	Withhold dose until clinically stable, then resume treatment at the next lower dose level. If no stabilisation or improvement, permanently discontinue.
	Grade 3 or 4	Any	Permanently discontinue.
Conjunctival or corneal scarring or symblepharon	Any grade	Any	Permanently discontinue.
Conjunctivitis and other ocular reactions	Grade 1	Any	Withhold dose until clinically stable, then resume treatment at the same dose.
	Grade 2	First occurrence	Withhold dose until Grade ≤ 1, then resume treatment at the same dose.
		Second occurrence	Withhold dose until Grade ≤ 1, then resume treatment at the next lower dose level. If no resolution to Grade ≤ 1, permanently discontinue.
		Third occurrence	Permanently discontinue.
	Grade 3 or 4	Any	Permanently discontinue.

Adverse reaction	Severity*	Occurrence	Dose modification
Peripheral neuropathy	Grade 2 or 3	Any (initial or worsening of pre-existing condition)	Withhold dose until Grade ≤ 1, then resume treatment at the next lower dose level.
	Grade 4	Any	Permanently discontinue.
Severe cutaneous adverse reactions (including Stevens-Johnson syndrome (SJS))	Suspected (any grade)	Any	Immediately withhold dose and consult a specialist to confirm the diagnosis.
	Confirmed Grade 3 or 4	Any	Permanently discontinue.

*Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0) where Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, and Grade 4 is life-threatening

Missed doses

If a planned dose of Tivdak is missed, it should be administered as soon as possible. The scheduling of administration should be adjusted to maintain the appropriate interval between doses.

Eye care

Patients should adhere to the following recommendations to reduce the risk of ocular adverse reactions (see section 4.4).

Ocular evaluation by treating healthcare provider
Prior to each infusion, the treating healthcare provider should inspect the patient's eyes, including control of normal eye movement, and ask about any ocular signs or symptoms. The patient should be referred to an eye care professional for any ocular signs or symptoms (see section 4.4).

Topical preservative-free corticosteroid eye drops (e.g., dexamethasone 0.1% 3 times a day or the equivalent as prescribed)
Patients should be instructed to administer 1 drop in each eye 3 times daily starting 1 day prior to each infusion and to continue to administer as prescribed for 3 days after each infusion.

Topical preservative-free ocular vasoconstrictor drops (e.g., brimonidine tartrate 0.2% 3 drops per eye or the equivalent as prescribed)
Drops should be administered in each eye immediately prior to each infusion.

Cold packs
Following administration of eye drops, cooling eye pads should be applied prior to the start of the infusion and used during and for 30 minutes after the infusion.

Topical preservative-free lubricating eye drops
Patients should be instructed to administer lubricating eye drops multiple times every day throughout treatment and for 30 days after the last dose of Tivdak.

Contact lenses
Patients should be advised to avoid wearing contact lenses for the entire duration of therapy unless advised by their eye care professional.

Special populations

Elderly
No dose adjustment is required in patients aged ≥ 65 years (see section 5.2).

Renal impairment
No dose adjustment is required in patients with mild renal impairment [creatinine clearance (CrCL) > 60-90 mL/min], moderate (CrCL 30-60 mL/min). Tisotumab vedotin has not been studied in patients with severe renal impairment (CrCL 15-< 30 mL/min) or end-stage renal disease (CrCL < 15 mL/min) (see section 5.2).

Hepatic impairment
No dose adjustment is required in patients with mild hepatic impairment (total bilirubin of > 1 to 1.5 × upper limit of normal (ULN) and any aspartate aminotransferase (AST), or total bilirubin ≤ ULN and AST > ULN, as defined using the National Cancer Institute criteria for hepatic impairment). However, as the exposure is expected to increase in patients with mild hepatic impairment, caution is advised when treating patients with mild hepatic impairment. Tisotumab vedotin has not been studied in patients with moderate or severe hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of Tivdak in children and adolescents below the age of 18 years have not been established. No data are available.

Method of administration

Tivdak is for intravenous use. The recommended dose must be administered by intravenous infusion over 30 minutes. Tisotumab vedotin must not be administered as an intravenous push or bolus injection.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Ocular adverse reactions

Ocular adverse reactions occurred in patients treated with tisotumab vedotin across clinical studies in cervical cancer patients (see section 4.8). The most common ocular adverse reactions were conjunctivitis, dry eye, keratitis and blepharitis.

Prior to the first infusion and as clinically indicated, patients should be referred to an eye care professional for a full eye exam (including visual acuity and slit lamp exam). Prior to each infusion, the treating healthcare provider should inspect the patient's eyes, including control of normal eye movement, and ask about any ocular signs or symptoms. Patients should be monitored for new or worsening ocular signs and symptoms and referred as soon as possible to an eye care professional if warranted. Patients should be instructed to promptly report any new or worsening ocular signs or

symptoms. Tivdak should be withheld, dose reduced, or permanently discontinued based on the severity of the adverse reaction (see section 4.2).

Patients should adhere to recommendations in the "Eye care" subsection of section 4.2 to reduce the risk of ocular adverse reactions (see section 4.2).

Peripheral neuropathy

Peripheral neuropathy has occurred with tisotumab vedotin, including Grade 3 events (see section 4.8). Patients should be monitored for general symptoms of neuropathy, such as paraesthesia, tingling or a burning sensation, neuropathic pain, muscle weakness, or dysesthesia. Patients experiencing new or worsening peripheral neuropathy may require dose interruption, dose reduction, or permanent discontinuation of Tivdak (see section 4.2).

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions, including events of fatal or life-threatening SJS, can occur in patients treated with tisotumab vedotin. Patients should be monitored 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, Tivdak should be immediately withheld until the aetiology of the reaction has been determined. Early consultation with a specialist is recommended to ensure greater diagnostic accuracy and appropriate management. Tivdak should be permanently discontinued for confirmed Grade 3 or 4 severe cutaneous adverse reactions, including SJS (see section 4.2).

Embryo-foetal toxicity

Based on its mechanism of action and findings from animal studies, tisotumab vedotin can cause foetal harm when administered to a pregnant woman, including embryo-foetal toxicity and structural malformations (see sections 4.6 and 5.3). The pregnancy status of women of childbearing potential should be verified prior to initiating Tivdak treatment. Women of reproductive potential should be advised to use effective contraception during treatment with Tivdak and for 2 months after the last dose (see section 4.6).

Patients excluded from clinical studies

Patients with the following conditions were excluded from clinical studies: clinically significant active ocular surface disease, any prior episode of cicatricial conjunctivitis or ocular SJS, Grade ≥ 2 peripheral neuropathy, clinically significant bleeding issues or risks or cardiovascular risks (see section 5.1). In the absence of data, tisotumab vedotin should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

4.5 Interaction with other medicinal products and other forms of interaction

Formal drug-drug interaction studies with tisotumab vedotin have not been conducted.

CYP3A4 inhibitors, substrates, and inducers

Drug interaction studies

Clinical studies

Strong CYP3A4 inhibitors: ketoconazole (a strong CYP3A4 inhibitor) co-administered with another antibody-drug conjugate (ADC) that contains MMAE increased MMAE exposure, with no change in ADC exposure. The concomitant use of strong inhibitors of CYP3A4 with tisotumab vedotin would likely result in similar effects on unconjugated MMAE and ADC. Caution is advised in case of treatment with strong CYP3A4 inhibitors. Patients should be closely monitored for adverse reactions

when tisotumab vedotin is given concomitantly with strong CYP3A4 inhibitors (e.g., boceprevir, clarithromycin, cobicistat, indinavir, itraconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole).

Strong CYP3A4 inducers: rifampicin (a strong CYP3A4 inducer) co-administered with another ADC that contains MMAE decreased MMAE exposure, with no change in ADC exposure. The concomitant use of strong inducers of CYP3A4 with tisotumab vedotin would likely result in similar effects on unconjugated MMAE and ADC.

Sensitive CYP3A4 substrates: another ADC that contains MMAE co-administered with midazolam (a sensitive CYP3A4 substrate) did not affect the exposure of midazolam. Similarly, tisotumab vedotin is not expected to alter the exposure of drugs that are metabolised by CYP3A4 enzymes.

In vitro studies
Transporter systems: MMAE is a substrate of P-glycoprotein (P-gp), but not an inhibitor of P-gp.

4.6 Fertility, pregnancy, and lactation

Women of childbearing potential/Contraception in females and males

The pregnancy status of women of childbearing potential should be verified prior to initiating Tivdak treatment. Females of childbearing potential should be advised to use effective contraception during treatment and for at least 2 months after stopping treatment.

Males with female partners of reproductive potential should be advised to use effective contraception during treatment and for at least 4 months after the last dose of Tivdak.

Pregnancy

There are no available data from the use of tisotumab vedotin in pregnant women.

Based on its mechanism of action and findings from animal studies, tisotumab vedotin could cause embryo-foetal harm when administered to a pregnant woman, including embryo-foetal toxicity and structural malformations (see section 5.3).

Tivdak should not be used during pregnancy unless the clinical condition of the woman requires treatment with tisotumab vedotin.

Breast-feeding

It is unknown whether tisotumab vedotin is excreted in human milk. A risk to breast-fed children cannot be excluded. Breast-feeding should be discontinued during treatment with Tivdak and for at least 3 weeks after the last dose.

Fertility

Based on findings from animal studies, tisotumab vedotin may impair fertility in males and females (see section 5.3).

4.7 Effects on ability to drive and use machines

Tisotumab vedotin has moderate influence on the ability to drive and use machines. Because of potential adverse reactions such as ocular adverse reactions and peripheral neuropathy (see sections 4.4 and 4.8), patients should be advised to use caution when driving or operating machines until they are certain that Tivdak does not adversely affect them. The clinical status of the patient should be

considered when assessing the patient's ability to perform tasks that require judgement, motor, or cognitive skills.

4.8 Undesirable effects

Summary of the safety profile

Unless otherwise stated, the frequencies of adverse reactions are based on all-cause adverse event frequencies identified in 425 patients exposed to at least one dose of tisotumab vedotin 2 mg/kg intravenously during a median duration of 3.7 months in clinical studies.

The most common adverse reactions (≥ 25%) were peripheral neuropathy (39%), nausea (37%), epistaxis (33%), conjunctivitis (32%), alopecia (31%), anaemia (27%) and diarrhoea (25%).

Severe (Grade ≥ 3) adverse reactions occurred in 56% of patients. The most common severe adverse reactions (≥ 2%) were anaemia (10%), peripheral neuropathy (6%), fatigue (5%), abdominal pain (3%), neutropenia (3%), vomiting (2%), asthenia (2%) and diarrhoea (2%).

Serious adverse reactions occurred in 37% of patients. The most common serious adverse reactions (≥ 2%) were abdominal pain (2%), constipation (2%), pyrexia (2%), peripheral neuropathy (2%) and vomiting (2%). Fatal adverse reactions occurred in 2% of patients.

Adverse reactions leading to treatment discontinuation occurred in 15% of patients receiving tisotumab vedotin; the most common adverse reactions leading to treatment discontinuation (≥ 2%) were peripheral neuropathy (7%), conjunctivitis (2%) and keratitis (2%).

Adverse reactions leading to dose interruption occurred in 37% of patients; the most common adverse reactions leading to dose interruption (≥ 2%) were conjunctivitis (6%), peripheral neuropathy (6%) and keratitis (3%).

Adverse reactions leading to dose reduction occurred in 25% of patients; the most common adverse reactions leading to dose reduction (≥ 2%) were peripheral neuropathy (6%), conjunctivitis (5%) and keratitis (3%).

Tabulated list of adverse reactions

Adverse reactions observed during clinical studies for tisotumab vedotin are listed by MedDRA System Organ Class and Preferred Term (see Table 3). Within each System Organ Class, adverse reactions are listed under frequency categories of: Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1 000 to < 1/100); Rare (≥ 1/10 000 to < 1/1 000); Very rare (< 1/10 000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing frequency.

Table 3: Adverse reactions

System organ class	Frequency category	Adverse reaction
Blood and lymphatic system disorders	Very common	anaemia
	Common	neutropenia
	Uncommon	febrile neutropenia
Metabolism and nutrition disorders	Very common	decreased appetite
Nervous system disorders	Very common	peripheral neuropathy[1]
Eye disorders	Very common	conjunctivitis, dry eye[2], keratitis
	Common	eye irritation[3], blepharitis, punctate keratitis, ulcerative keratitis, eye pruritus, ocular hyperaemia, conjunctival ulcer,

System organ class	Frequency category	Adverse reaction
		entropion, conjunctival hyperaemia, episcleritis, meibomianitis
	Uncommon	corneal erosion, trichiasis, vital dye staining cornea present, conjunctival scar, keratopathy, conjunctival disorder, conjunctival erosion, eyelid oedema, madarosis, meibomian gland dysfunction, periorbital oedema, symblepharon, chalazion, conjunctival abrasion, conjunctival oedema, corneal degeneration, corneal irritation, corneal opacity, corneal scar, corneal thinning, erythema of eyelid, eyelid margin crusting, noninfective conjunctivitis, swelling of eyelid
Respiratory, thoracic and mediastinal disorders	Very common	epistaxis
Gastrointestinal disorders	Very common	nausea[4], diarrhoea[5], constipation, abdominal pain[6], vomiting
Skin and subcutaneous tissue disorders	Very common	alopecia, rash[7], pruritus
	Uncommon	erythema multiforme, dermatitis bullous, Stevens-Johnson syndrome
General disorders and administration site conditions	Very common	fatigue, pyrexia, asthenia

[1]Peripheral neuropathy includes peripheral sensory neuropathy, neuropathy peripheral, paraesthesia, peripheral sensorimotor neuropathy, muscular weakness, peripheral motor neuropathy, hypoesthesia, gait disturbance, neuralgia, burning sensation, demyelinating polyneuropathy, neurotoxicity, polyneuropathy, sensory loss, and skin burning sensation
[2]Dry eye includes dry eye and lacrimation increased
[3]Eye irritation includes eye discharge, eye pain, eye irritation, and eye oedema
[4]Nausea includes nausea and retching
[5]Diarrhoea includes diarrhoea and gastroenteritis
[6]Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower and abdominal tenderness
[7]Rash includes rash, rash maculo-papular, erythema, eczema, rash macular, dermatitis acneiform, rash pustular, urticaria, dermatitis, dermatitis allergic, rash erythematous, skin irritation and skin toxicity

Description of selected adverse reactions

Ocular adverse reactions
Ocular adverse reactions occurred in 55% of the 425 patients with cervical cancer treated with tisotumab vedotin across clinical studies. The most common ocular adverse reactions were conjunctivitis (32%), dry eye (17%), keratitis (12%), and blepharitis (5%). Grade 3 ocular adverse reactions occurred in 3% of patients. Cases of Grade 3 ulcerative keratitis were reported in 1.2% of patients. Grade 4 ocular adverse reactions occurred in 0.2% of patients, including ulcerative keratitis.

The median time to onset for the first event of any grade ocular adverse reaction was 1.2 months (range: 0 to 17.1). Ocular adverse reactions led to treatment discontinuation in 6%, dose interruption in 13% and dose reduction in 12% of patients. Of the patients who experienced ocular adverse reactions, 59% had complete resolution and 31% had partial improvement at last follow-up. Of the patients with ongoing ocular adverse reactions at last follow-up, 28% of patients had maximum Grade 1, 10% had maximum Grade 2, and 3% had maximum Grade 3. For patients in whom events resolved, the median time to resolution was 0.59 months (range: 0 to 12.6) (see section 4.4).

Peripheral Neuropathy
Peripheral neuropathy occurred in 39% of the 425 patients with cervical cancer treated with tisotumab vedotin across clinical trials; 6% were Grade 3. The most common all grade peripheral neuropathy events were peripheral sensory neuropathy (23%), neuropathy peripheral (5%), paraesthesia (4%), peripheral sensorimotor neuropathy (3%) and muscular weakness (3%).

The median time to onset of the first event of any grade peripheral neuropathy was 2.4 months (range: 0 to 11.3). Of the patients who experienced peripheral neuropathy, 18% had complete resolution and 21% had partial improvement at last follow-up. Of the patients with ongoing peripheral neuropathy at last follow-up, 45% of patients had maximum Grade 1, 27% had maximum Grade 2, and 10% had maximum Grade 3. For patients in whom events resolved, the median time to resolution was 0.72 months (range: 0 to 20.7) (see section 4.4).

Severe cutaneous adverse reactions
Severe cutaneous adverse reactions occurred in 1.6% of the 425 patients with cervical cancer treated with tisotumab vedotin across clinical studies, including erythema multiforme (0.7%), bullous dermatitis (0.5%) and SJS (0.5%). Grade ≥ 3 severe cutaneous adverse reactions occurred in 0.5% of patients, including 1 patient who had a fatal outcome.

The median time to onset of the first event of severe cutaneous adverse reactions was 0.2 months (range: 0.1 to 0.9). Of the patients who experienced severe cutaneous adverse reactions, 43% had complete resolution at last follow-up. For patients in whom events resolved, the median time to resolution was 0.79 months (range: 0.5 to 2.3).

Gastrointestinal adverse reactions
Nausea, diarrhoea, constipation, abdominal pain, and vomiting were the most common all grade gastrointestinal disorders reported in the 425 patients with cervical cancer treated with tisotumab vedotin. Nausea occurred in 37% of patients and was Grade ≥ 3 in 1% patients. Diarrhoea occurred in 25% of patients and was Grade ≥ 3 in 2% of patients. Constipation occurred in 24% of patients and was Grade ≥ 3 in 1% of patients. Abdominal pain occurred in 22% of patients and was Grade ≥ 3 in 3% of patients. Vomiting occurred in 20% of patients and was Grade ≥ 3 in 2% of patients.

Special populations

Elderly
Among 425 patients with cervical cancer treated with tisotumab vedotin across clinical studies, 60 (14%) were ≥ 65 years of age. Grade ≥ 3 adverse reactions occurred in 60% of patients ≥ 65 years and in 55% of patients < 65 years. Serious adverse reactions occurred in 35% patients ≥ 65 years and in 38% of patients < 65 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no known antidote for overdose with tisotumab vedotin. In case of overdose, the patient should be closely monitored for adverse reactions and supportive treatment should be administered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other monoclonal antibodies and antibody-drug conjugates, ATC code: L01FX23

Mechanism of action

Tisotumab vedotin is an antibody-drug conjugate (ADC) directed to tissue factor (TF), a cell surface protein expressed at elevated levels on a variety of solid tumours relative to normal tissue. The small molecule, MMAE, is a microtubule-disrupting agent, attached to the antibody via a protease-cleavable linker. Tisotumab vedotin binds to TF-expressing tumour cells, the ADC-TF complex is internalised, and local release of MMAE occurs via proteolytic cleavage. MMAE disrupts the microtubule network of actively dividing cells, leading to cell cycle arrest and apoptotic cell death.

Direct cytotoxicity in TF-expressing cells, bystander cytotoxicity, antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and immunogenic cell death has been demonstrated *in vitro* with tisotumab and/or tisotumab vedotin.

Immunogenicity

Anti-drug antibodies (ADA) were commonly detected (5% across clinical studies). No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed, however, data are still limited.

Cardiac electrophysiology

The effect of tisotumab vedotin (2 mg/kg every 3 weeks) on the QTc interval was evaluated in 153 patients. At the dose of 2 mg/kg every 3 weeks, tisotumab vedotin had no clinically meaningful effect on QTc prolongation.

Clinical efficacy and safety

Cervical cancer
SGNTV-003
The efficacy of tisotumab vedotin was evaluated in an open-label, multicentre, randomised phase 3 study (SGNTV-003) in 502 patients with recurrent or metastatic cervical cancer who had received one or two prior systemic therapy regimens that included doublet chemotherapy (patients without prior exposure to platinum were allowed) with or without bevacizumab and an anti-PD-1/PD-L1 agent if eligible and available. Patients were randomised 1:1 to receive either tisotumab vedotin 2 mg/kg intravenously every 3 weeks or investigator's choice of chemotherapy (topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed) until disease progression or unacceptable toxicity.

Randomisation was stratified by ECOG performance status (0 vs 1), prior bevacizumab administration (yes vs no), region (US, EU, Other), and prior anti-PD-1 or anti-PD-L1 administration (yes vs no). Tumour response assessments were performed every 6 weeks for the first 30 weeks and every 12 weeks thereafter.

Patients were excluded from the study if they had primary neuroendocrine, lymphoid, or sarcomatoid histologies, clinically significant active ocular surface disease, any prior episode of cicatricial conjunctivitis or ocular SJS, Grade ≥ 2 peripheral neuropathy, clinically significant bleeding issues or risks, including known coagulation defects, diffuse alveolar haemorrhage from vasculitis and known bleeding diathesis, or significant cardiovascular issues or risks.

The primary endpoint of the study was overall survival (OS). Key secondary endpoints were progression free survival (PFS) and confirmed objective response rate (ORR) as assessed by investigator using RECIST v1.1.

Of the 502 patients randomised, the median age was 50 years (range: 26 to 80); 49% were White, 36% were Asian, and 2% were Black. Seventeen percent of patients were ≥ 65 years. Twenty percent of patients were Hispanic or Latino. Sixty-three percent of patients had squamous cell carcinoma, 32% had adenocarcinoma, and 5% had adenosquamous histology. ECOG performance status was 0 (54%) or 1 (46%). Sixty-one percent of patients had received 1 prior line of systemic therapy, and 38% had 2 prior lines of systemic therapy. Six patients (1.2%) had not received and 496 patients (99%) had received prior treatment with platinum-containing chemotherapy in the recurrent or metastatic setting. Sixty-four percent of patients had received bevacizumab and 27% of patients had received an anti-PD-1 or anti-PD-L1 as part of their prior systemic therapy.

At a median duration of follow-up of 10.8 months (95% CI: 10.3 to 11.6), SGNTV-003 demonstrated statistically significant improvement in OS, PFS and ORR for patients treated with tisotumab vedotin compared to chemotherapy. Efficacy results are summarised in Table 4 and Figures 1 and 2.

Table 4. Efficacy Results in SGNTV-003

Endpoint	Tisotumab vedotin N=253	Chemotherapy N=249
Overall survival		
Number (%) of patients with events	123 (48.6)	140 (56.2)
Median in months (95% CI)	11.5 (9.8, 14.9)	9.5 (7.9, 10.7)
Hazard ratio (95% CI)	0.70 (0.54, 0.89)	
2-sided p-value	0.0038[1]	
Progression free survival[2]		
Number (%) of patients with events	198 (78.3)	194 (77.9)
Median in months (95% CI)	4.2 (4.0, 4.4)	2.9 (2.6, 3.1)
Hazard ratio (95% CI)	0.67 (0.54, 0.82)	
2-sided p-value	<0.0001[3]	
Confirmed objective response rate (CR + PR)[2]		
ORR (%) (95% CI)	17.8 (13.3, 23.1)	5.2 (2.8, 8.8)
Duration of response[4]		
Median in months (95% CI)	5.3 (4.2, 8.3)	5.7 (2.8, NR)

CI=confidence interval; CR=complete response; NR=not reached; ORR=objective response rate; PR=partial response.

[1]The threshold for statistical significance is 0.0226 (2-sided)

[2]evaluated by investigator assessment using RECIST v1.1

[3]The threshold for statistical significance is 0.0453 (2-sided)

[4]Based on patients with a best objective response as confirmed complete or partial response (n=45 for tisotumab vedotin, n=13 for chemotherapy)

Figure 1. Kaplan Meier Plot of Overall Survival

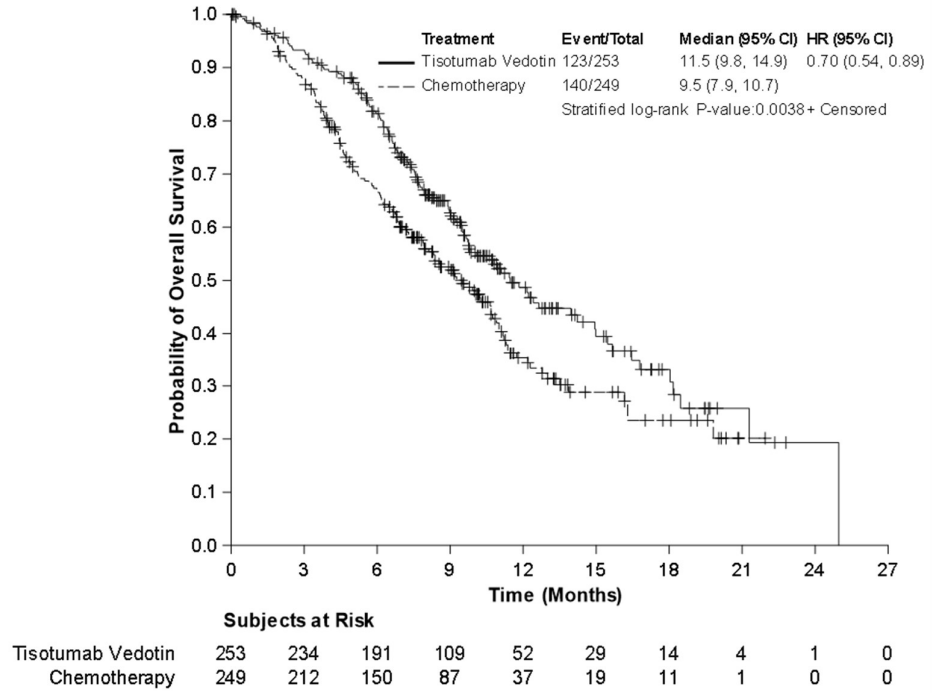
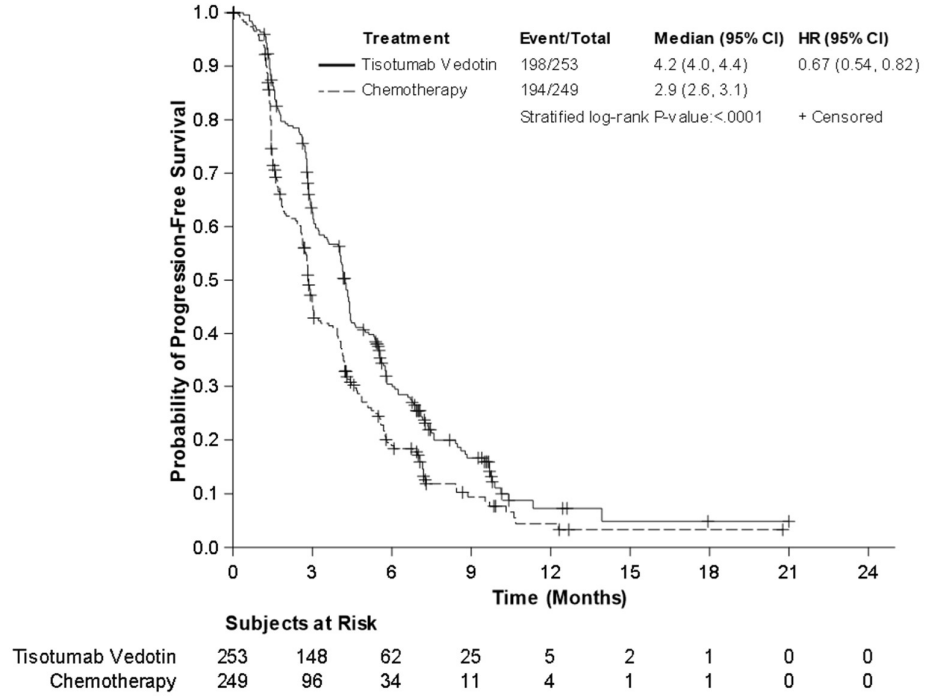


Figure 2. Kaplan Meier Plot of Progression Free Survival



Efficacy results for OS and PFS were generally consistent across prespecified patient subgroups.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Tivdak in all subsets of the paediatric population in cervical cancer (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Distribution

Based on population pharmacokinetic analysis tisotumab vedotin central volume of distribution was estimated to be 3.10 L.

In vitro, the binding of MMAE to human plasma proteins ranged from 68–82%.

Biotransformation

Tisotumab vedotin catabolism has not been studied in humans; however, it is expected to undergo catabolism to small peptides, amino acids, unconjugated MMAE, and unconjugated MMAE-related metabolites. Tisotumab vedotin releases MMAE via proteolytic cleavage, and MMAE is primarily metabolised by CYP3A4 *in vitro*. In vivo data in animals and humans suggest that only a small fraction of MMAE released from tisotumab vedotin is metabolised. The levels of MMAE metabolites have not been measured in human plasma.

Elimination

Based on population pharmacokinetic analysis, the median terminal half-life of tisotumab vedotin is approximately 4.04 days and the terminal half-life of MMAE is approximately 2.56 days. The linear clearance of tisotumab vedotin was estimated to be 1.42 L/day and following a 2 mg/kg dose approximately 60% of the dose was estimated to be eliminated by linear clearance (CL). Clearance of unconjugated MMAE was estimated to be 42.8 L/day. Elimination of MMAE appeared to be limited by its rate of release from tisotumab vedotin.

Excretion

The excretion of tisotumab vedotin is not fully characterised. Following a single dose of another ADC that contains MMAE, 17% of the total MMAE administered was recovered in faeces and 6% in urine over a 1-week period, primarily as unchanged drug. A similar excretion profile of MMAE is expected after tisotumab vedotin administration.

Specific populations

Elderly
Based on population pharmacokinetic analysis, age (21 to 81 years) does not have a clinically meaningful effect on the pharmacokinetics of tisotumab vedotin.

Gender
Based on population pharmacokinetic analysis, gender does not have a clinically meaningful effect on the pharmacokinetics of tisotumab vedotin.

Renal impairment
Based on population pharmacokinetic analysis, no clinically meaningful differences in exposures of tisotumab vedotin and MMAE were observed in patients with mild (creatinine clearance; CrCL > 60-90 mL/min, n=142) or moderate (CrCL 30-60 mL/min, n=42) renal impairment compared to patients with normal renal function. The effect of severe renal impairment or end-stage renal disease

with or without dialysis on tisotumab vedotin and unconjugated MMAE pharmacokinetics is unknown.

Hepatic impairment
Based on population pharmacokinetic analysis, no clinically meaningful differences in exposures of tisotumab vedotin were observed in patients with mild hepatic impairment (total bilirubin > 1 to 1.5 × ULN and any AST, or total bilirubin ≤ ULN and AST > ULN, n=58) compared to patients with normal hepatic function, while MMAE exposures were 37% higher in mild hepatic impairment as compared to normal hepatic function. The effect of moderate or severe hepatic impairment or liver transplantation on the pharmacokinetics of tisotumab vedotin or unconjugated MMAE is unknown.

Pharmacokinetic/pharmacodynamic relationships

In an exposure-response analysis at 2 mg/kg every 3 weeks, a higher tisotumab vedotin exposure was associated with higher incidence of some adverse reactions (e.g., Grade ≥ 2 ocular adverse reactions) and a lower exposure was associated with lower efficacy.

5.3 Preclinical safety data

Repeat-dose toxicity

Repeat-dose toxicity studies were performed with tisotumab vedotin at approximately 2.3-4.3 times the human area under the curve (AUC) at the recommended clinical dose. Skin lesions were noted in a repeat-dose study at ≥ 3 mg/kg in monkeys (13 weeks). The skin changes were fully reversible by the end of a 6-week recovery period. In both rats and cynomolgus monkeys, administration of MMAE and tisotumab vedotin (only monkeys dosed at ≥ 3 mg/kg) led to reversible bone marrow toxicity and associated peripheral blood cell effects. Reddened or swollen eyes and conjunctiva (with or without discharge), and/or conjunctivitis was observed following tisotumab vedotin treatment in monkeys at 5 mg/kg (13 weeks). These findings reversed following a 6-week recovery period.

Carcinogenicity

Carcinogenicity studies in animals have not been performed with tisotumab vedotin or MMAE.

Genotoxicity

MMAE was positive for genotoxicity in the in vivo rat bone marrow micronucleus study through an aneugenic mechanism.

Reproductive and developmental toxicity

Dedicated fertility studies in animals have not been performed with tisotumab vedotin or MMAE. However, results of repeat-dose toxicity studies indicate the potential for tisotumab vedotin to impair male and female fertility.

Results of a 13-week repeat-dose toxicity study in cynomolgus monkeys administered tisotumab vedotin demonstrated seminiferous tubular atrophy of the testes and absence of sperm, decreased sperm content, and epithelial vacuolation in the epididymides. The changes were associated with decreased testicular size, and reduced or total absence of sperm counts and sperm motility was observed at doses of 1, 3, and 5 mg/kg corresponding to approximately 0.5- to 4-fold the human systemic exposure (based on AUC) at the clinically recommended dose. There was partial recovery of the testes and epididymides findings at 3 and 5 mg/kg; and full recovery at 1 mg/kg after a 6-week postdose period.

Ovarian effects were observed in repeat-dose toxicity studies of other MMAE-containing ADCs. A mild to moderate decrease in, or absence of, secondary and tertiary ovarian follicles was observed in

young female cynomolgus monkeys at doses ≥ 3 mg/kg weekly for 4 weeks. These effects showed evidence of recovery 6 weeks after the end of dosing and no changes were observed in primordial follicles.

Animal reproduction studies have not been conducted with tisotumab vedotin to evaluate its effect on reproduction and foetal development. Based on its mechanism of action and findings from animal studies, tisotumab vedotin could cause embryo-foetal harm when administered to a pregnant woman. Intravenous administration of MMAE to pregnant rats during organogenesis (gestational Days 6 and 13) resulted in increased total resorptions, post implantation loss, early delivery, loss of viable foetuses, and teratogenic embryo-foetal toxicity at a dose of 0.2 mg/kg (approximately 0.5 times the human AUC at the recommended dose).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine
L-histidine hydrochloride monohydrate
Sucrose
D-mannitol

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial

5 years

Reconstituted solution in the vial

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for up to 24 hours at 2 °C to 8 °C or for up to 8 hours at 9 °C to 25 °C.

From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination, the reconstituted solution should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Diluted solution in the infusion bag

Chemical and physical in-use stability of the diluted solution has been demonstrated for the durations listed in Table 5.

From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the diluted solution should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Table 5: Diluted Tivdak solution refrigeration storage conditions

Solvent used to prepare solution for infusion	Diluted Tivdak solution storage conditions (including infusion time)
Sodium chloride 9 mg/mL (0.9%) injection	Up to 18 hours at 2 °C to 8 °C
Dextrose 50 mg/mL (5%) injection	Up to 24 hours at 2 °C to 8 °C
Lactated ringer's injection	Up to 12 hours at 2 °C to 8 °C

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10mL Type I glass vial with grey butyl rubber stopper, plug and top, 20 mm seal with silver coloured aluminium cap and garnet disc. Each carton contains 1 vial.

6.6 Special precautions for disposal and other handling

Reconstitution in single-dose vial

1. Follow procedures for proper handling and disposal of cytotoxic medicinal products.
2. Use appropriate aseptic technique for reconstitution and preparation of dosing solutions.
3. Calculate the recommended dose based on the patient's actual body weight to determine the number of vials needed.
4. Reconstitute each 40 mg vial with 4 mL of sterile water for injection, resulting in 10 mg/mL Tivdak.
5. 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.
6. Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. The reconstituted solution should be clear to slightly opalescent, colourless to brownish-yellow and free of visible particles. Discard any vial with visible particles or discolouration.
7. 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 refrigerated at 2 °C to 8 °C or at room temperature (9 °C to 25 °C) up to a maximum of 8 hours prior to dilution. Do not freeze. Discard unused vials with reconstituted solution beyond the recommended storage time.

Dilution in infusion bag

8. Withdraw the calculated dose amount of reconstituted solution from the vial(s) and transfer into an infusion bag.
9. Dilute Tivdak with one of the following: dextrose 50 mg/mL (5%), sodium chloride 9 mg/mL (0.9%), or Lactated Ringer's solution for injection. The infusion bag size should allow enough diluent to achieve a final concentration of 0.7 mg/mL to 2.4 mg/mL Tivdak.
10. Mix diluted solution by gentle inversion. Do not shake the bag. Do not expose to direct sunlight.
11. Visually inspect the infusion bag for any particulate matter or discolouration prior to use. The reconstituted solution should be clear to slightly opalescent, colourless to brownish-yellow and free of visible particles. Do not use the infusion bag if particulate matter or discolouration is observed.
12. Discard any unused portion left in the single-dose vials.

Administration

13. Confirm administration of steroid and vasoconstrictor eye drops (see section 4.2).
14. Apply cold packs fully over the eyes following administration of the vasoconstrictor eye drops, leave on during infusion and until 30 minutes after infusion. Change cold packs as needed throughout infusion to ensure eye area remains cold (see section 4.2).
15. Immediately administer the infusion over 30 minutes through an intravenous line containing a 0.2 µm in-line filter.
16. If the infusion is not administered immediately, store the diluted Tivdak solution in refrigeration as specified in Table 5 (see section 6.3). 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).

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1911/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Lonza AG
Lonzastrasse
3930 Visp
Switzerland

Name and address of the manufacturer responsible for batch release

Seagen B.V.
Evert van de Beekstraat 1-104
1118 CL Schiphol
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal. The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tivdak 40 mg powder for concentrate for solution for infusion
tisotumab vedotin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder for concentrate for solution for infusion contains 40 mg tisotumab vedotin. After reconstitution, each mL of solution contains 10 mg of tisotumab vedotin.

3. LIST OF EXCIPIENTS

Also contains: D-mannitol, L-histidine, L-histidine hydrochloride monohydrate, Sucrose

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion.
1 vial.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous infusion after reconstitution.
Read the package leaflet before use.
Do not shake.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic: handle with caution.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1911/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Tivdak 40 mg powder for concentrate for solution for infusion
tisotumab vedotin
Intravenous use

2. METHOD OF ADMINISTRATION

For intravenous use only after reconstitution and dilution.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

40 mg

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Tivdak 40 mg powder for concentrate for solution for infusion
tisotumab vedotin

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tivdak is and what it is used for
2. What you need to know before you are given Tivdak
3. How Tivdak is given
4. Possible side effects
5. How to store Tivdak
6. Contents of the pack and other information

1. What Tivdak is and what it is used for

Tivdak is a cancer medicine that contains the active substance tisotumab vedotin.

It is used in adults to treat cervical cancer. People get Tivdak when their cancer has returned or has spread after a previous anti-cancer treatment.

The active substance in Tivdak is a monoclonal antibody (a type of protein that is designed to recognise and attach to a specific target) linked to MMAE, a substance intended to kill cancer cells. The monoclonal antibody attaches to a protein called tissue factor, which is found in high levels on the surface of many types of cancer cells and delivers MMAE inside the cancer cells. Once inside the cancer cells, MMAE kills the cancer cells by interfering with their ability to divide and grow. Tivdak also stimulates the immune system (the body's natural defences) to attack the cancer cells, and these actions combined are expected to slow down progression of the disease.

2. What you need to know before you are given Tivdak

You must not be given Tivdak
- if you are allergic to tisotumab vedotin or any of the other ingredients of this medicine (listed in section 6)

Before receiving Tivdak, tell your healthcare provider about all of your medical conditions, including if you:
- have a history of vision or eye problems
- have peripheral neuropathy (nerve damage, causing numbness or tingling in your hands or feet)
- have liver problems

Warnings and precautions

Eye problems

Tivdak can cause eye problems including dry eye, itchy eye, feeling like something is in your eye, eye redness, eye pain, excess of tears, difficulty opening your eye, discharge of crusting around your eye, eye irritation, burning or stinging sensation in the eye, decreased vision or abnormal sensitivity to light.

Before starting Tivdak, you will be referred to an eye care professional for an eye exam. Your doctor will check your eyes before you are given each infusion (drip) and ask if you have any signs or symptoms of eye problems. You may be referred to an eye care professional if you have any new or worsening signs and symptoms of eye problems. If you have eye problems, your doctor may pause treatment or reduce your dose until signs or symptoms have improved. If your eye problem worsens, your doctor may stop your treatment.

Your doctor will prescribe 3 different types of eyes drops before you start treatment with Tivdak.

Bring the eye drops with you every time you are given Tivdak and use them as instructed by your doctor to reduce your risk of eye problems:

- you should use 1 steroid drop in each eye 3 times a day starting 1 day before each infusion and continue as prescribed until 3 days after each infusion
- you should use vasoconstrictor eye drops in each eye right before each infusion
- you should use lubricating eye drops multiple times every day throughout treatment and for 30 days after your last dose of Tivdak

Cold packs will be placed on your eyes before the infusion and used during and for 30 minutes after the infusion.

Do not wear contact lenses throughout your treatment with Tivdak unless you are told to use them by your doctor.

Nerve problems

Tivdak can cause nerve problems (neuropathy) such as numbness, tingling or a burning sensation in your hands or feet or muscle weakness. Tell your doctor right away if you have symptoms of nerve problems. If this occurs, your doctor may pause treatment or reduce your dose until symptoms are improved. If your symptoms worsen, your doctor may stop your treatment.

Skin problems

Tivdak can cause severe skin problems like Stevens-Johnson syndrome (SJS), erythema multiforme (forming of red patches on the skin) and dermatitis bullous (blistering of the skin). Signs and symptoms include a rash that looks like rings (target lesions), skin blistering or peeling, painful sores or ulcers in your mouth, nose, throat or genital area, fever or flu-like symptoms, or swollen lymph nodes. Tell your doctor right away if you have any signs or symptoms of severe skin reactions. Your doctor may pause treatment until they determine the cause of these symptoms. If your skin reaction worsens and is confirmed, your doctor may stop your treatment.

Children and adolescents

This medicine should not be used in children and adolescents below 18 years of age.

Other medicines and Tivdak

Tell your doctor if you are taking, have recently taken or might take any other medicines.

Tell your doctor if you take medicines for fungal infections (e.g., ketoconazole, itraconazole, posaconazole, voriconazole) or viral infections (e.g., boceprevir, cobicistat, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir) as they can increase the amount of Tivdak in your blood. If you normally take these medicines, your doctor might change them and prescribe a different medicine for you during your treatment.

Tell your doctor if you take medicines for anti-bacterial infections (e.g., clarithromycin, telithromycin, rifampicin) as they can increase or decrease the amount of Tivdak in your blood. If you normally take these medicines, your doctor might change them and prescribe a different medicine for you during your treatment.

Pregnancy, breast-feeding and fertility

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before starting this medicine.

Tivdak may harm your unborn baby. You should not use this medicine if you are pregnant.

If you are a woman using Tivdak and you are able to become pregnant, you should use effective contraception (birth control) during treatment and for at least 2 months after stopping this medicine. If you are a man using Tivdak and your partner may become pregnant, you should use effective contraception during treatment and for at least 4 months you stop taking this medicine. Talk to your doctor to see which forms of contraception are right for you.

It is not known if this medicine passes into your breast milk and could harm your baby. Do not breast-feed during treatment and for at least 3 weeks after stopping Tivdak.

Driving and using machines
Do not drive or operate machines if you feel unwell during treatment.

3. How Tivdak is given

You will receive Tivdak in a hospital or clinic, under the supervision of a doctor experienced in giving such treatments.

How much Tivdak you will receive

The recommended dose of this medicine is 2 mg for every kilogram of body weight (up to a maximum of 200 mg for patients ≥ 100 kg) given once every 3 weeks. Your doctor will decide how many treatments you need.

How you will receive Tivdak

You will receive Tivdak by infusion (drip) into your vein over 30 minutes. Your doctor may decrease your dose, temporarily stop, or completely stop treatment with Tivdak if you have side effects. Cold packs will be placed on your eyes during the infusion and for 30 minutes after the infusion.

If you miss a dose of Tivdak

It is very important for you to keep all of your appointments to receive Tivdak. If you miss an appointment, contact your doctor as soon as possible to schedule your next dose.

If you stop receiving Tivdak

Do not stop treatment with Tivdak unless you have discussed this with your doctor. Stopping your treatment may stop the effect of the medicine.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some possible side effects may be serious:

Tell your doctor right away if you get any of the following serious side effects.

Very common (may affect more than 1 in 10 people):
- Inflammation of the thin membrane covering the front of your eye (conjunctivitis) or the clear layer that covers your pupil and iris (keratitis).
- Nerve problems. Tell your doctor right away if you get numbness, tingling or a burning sensation in your hands or feet or muscle weakness.

Common (may affect up to 1 in 10 people):
- Damage or ulceration of the clear layer that covers your pupil and iris (punctate keratitis, ulcerative keratitis) or the thin membrane covering the front of your eye (conjunctival ulcer).
- Inward turning of your eyelid (entropion).

Uncommon (may affect up to 1 in 100 people):
- Severe skin reactions. This medicine may cause skin reactions like Stevens-Johnson syndrome (SJS), erythema multiforme (forming of red patches on the skin) and dermatitis bullous (blistering of the skin). Tell your doctor right away if you have any of these signs or symptoms of a severe skin reaction: skin reactions that look like rings (target lesions), rash or itching that continues to get worse, blistering or peeling of the skin, painful sores or ulcers in your mouth, nose throat or genital area, fever or flu-like symptoms, or swollen lymph nodes.
- Scarring or changes of the clear layer that covers your pupil and iris (corneal scar, corneal degeneration) or the thin membrane covering the front of your eye (conjunctival scar).
- Inflammation of the eye that causes your eyelid to stick to your eyeball (symblepharon).

Other possible side effects

Other side effects are listed below. Tell your doctor or nurse if you get any of these side effects.

Very common (may affect more than 1 in 10 people):
- Feeling sick (nausea)
- Nose bleeds (epistaxis)
- Hair loss (alopecia)
- Low red blood cell count (anaemia)
- Diarrhoea
- Constipation
- Decreased appetite
- Tiredness (fatigue)
- Belly (abdominal) pain
- Rash
- Dry eye
- Vomiting

- Fever (pyrexia)
- Lack of energy (asthenia)
- Dry or itchy skin (pruritus)

Common (may affect up to 1 in 10 people):
- Eye irritation
- Low white blood cell count (neutropenia)
- Inflammation of the eyelid (blepharitis) or the glands of the eyelid (meibomianitis)
- Itchy eye (eye pruritus)
- Redness of the eye (ocular hyperaemia) or the thin membrane covering the front of the eye (conjunctival hyperaemia)
- Inflammation of the tissue between the inside of the eyelid and the white part of the eye (episcleritis)

Uncommon (may affect up to 1 in 100 people):
- Damage, irritation, cloudiness or thinning of the clear layer that covers the pupil and iris (corneal erosion, vital eye staining cornea present, keratopathy, corneal irritation, corneal opacity, corneal thinning)
- Eyelashes growing back toward the eye (trichiasis)
- Fever with low white blood cell count (febrile neutropenia)
- Damage, swelling, or inflammation of the thin membrane covering the front of the eye (conjunctival disorder, conjunctival erosion, conjunctival abrasion, conjunctival oedema, noninfective conjunctivitis)
- Swelling, redness, or crusting of the eyelid (eyelid oedema, swelling of eyelid, erythema of eyelid, eyelid margin crusting)
- Eyelashes falling out (madarosis)
- Dysfunction of the glands of the eyelid (meibomian gland dysfunction)
- Swelling around the eye (periorbital oedema)
- Lump on the eyelid (chalazion)

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tivdak

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 ºC to 8 ºC). Do not freeze.

Do not store any unused portion of the infusion solution for reuse. Any unused medicine or waste material should be disposed of in accordance with local requirements.

6. Contents of the pack and other information

What Tivdak contains

- The active substance is tisotumab vedotin.
- One vial of powder for concentrate for solution for infusion contains 40 mg tisotumab vedotin.
- After reconstitution, each mL of solution contains 10 mg of tisotumab vedotin.

The other ingredients are L-histidine, L-histidine hydrochloride monohydrate, Sucrose, and D-mannitol.

What Tivdak looks like and contents of the pack

Tivdak powder for concentrate for solution for infusion is a white to off-white lyophilised cake or powder.

Tivdak is supplied in a box containing 1 glass vial.

Marketing Authorisation Holder

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

Manufacturer

Seagen B.V.
Evert van de Beekstraat 1-104
1118 CL Schiphol
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

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The following information is intended for healthcare professionals only:

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Instructions for preparation and administration

Reconstitution in single-dose vial

1. Follow procedures for proper handling and disposal of cytotoxic medicinal products.
2. Use appropriate aseptic technique for reconstitution and preparation of dosing solutions.
3. Calculate the recommended dose based on the patient's actual body weight to determine the number of vials needed.
4. Reconstitute each 40 mg vial with 4 mL of sterile water for injection, resulting in 10 mg/mL Tivdak.

5. 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.
6. Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. The reconstituted solution should be clear to slightly opalescent, colourless to brownish-yellow and free of visible particles. Discard any vial with visible particles or discolouration.
7. 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 refrigerated at 2 °C to 8 °C or at room temperature (9 °C to 25 °C) up to a maximum of 8 hours prior to dilution. Do not freeze. Discard unused vials with reconstituted solution beyond the recommended storage time.

Dilution in infusion bag

8. Withdraw the calculated dose amount of reconstituted solution from the vial(s) and transfer into an infusion bag.
9. Dilute Tivdak with one of the following: dextrose 50 mg/mL (5%), sodium chloride 9 mg/mL (0.9%), or Lactated Ringer's solution for injection. The infusion bag size should allow enough diluent to achieve a final concentration of 0.7 mg/mL to 2.4 mg/mL Tivdak.
10. Mix diluted solution by gentle inversion. Do not shake the bag. Do not expose to direct sunlight.
11. Visually inspect the infusion bag for any particulate matter or discolouration prior to use. The reconstituted solution should be clear to slightly opalescent, colourless to brownish-yellow and free of visible particles. Do not use the infusion bag if particulate matter or discolouration is observed.
12. Discard any unused portion left in the single-dose vials.

Administration

13. Confirm administration of steroid and vasoconstrictor eye drops (see section 4.2).
14. Apply cold packs fully over the eyes following administration of the vasoconstrictor eye drops, leave on during infusion and until 30 minutes after infusion. Change cold packs as needed throughout infusion to ensure eye area remains cold (see section 4.2).
15. Immediately administer the infusion over 30 minutes through an intravenous line containing a 0.2 µm in-line filter.
16. If the infusion is not administered immediately, store the diluted Tivdak solution in refrigeration as specified in Table 1. 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).

Table 1: Diluted Tivdak solution refrigeration storage conditions

Solvent used to prepare solution for infusion	**Diluted Tivdak solution storage conditions (including infusion time)**
Sodium chloride 9 mg/mL (0.9%) injection	Up to 18 hours at 2 °C to 8 °C
Dextrose 50 mg/mL (5%) injection	Up to 24 hours at 2 °C to 8 °C
Lactated ringer's injection	Up to 12 hours at 2 °C to 8 °C

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.