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, pharmacist or nurse. 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

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 after 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, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.
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 and Manufacturer

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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

<u>Reconstitution in single-dose vial</u>

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.