Package leaflet: Information for the patient

Torisel 30 mg concentrate and solvent for solution for infusion

temsirolimus

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, pharmacist or nurse.
- 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 Torisel is and what it is used for
2. What you need to know before you receive Torisel
3. How Torisel is given
4. Possible side effects
5. How to store Torisel
6. Contents of the pack and other information

1. What Torisel is and what it is used for

Torisel contains the active substance temsirolimus.

Temsirolimus is a selective inhibitor of the enzyme mTOR (mammalian target of rapamycin) that blocks tumour cell growth and division.

Torisel is used to treat the following types of cancer in adults:
- Advanced cancer of the kidney (renal cancer).
- Previously treated mantle cell lymphoma, a type of cancer affecting the lymph nodes.

2. What you need to know before you receive Torisel

Do not use Torisel

- if you are allergic to temsirolimus, to polysorbate 80 or to any of the other ingredients listed in section 6.
- if you are allergic to sirolimus (used to prevent the body from rejecting transplanted kidneys) since sirolimus is released from temsirolimus in the body.
- if you have mantle cell lymphoma and liver problems.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before receiving Torisel

- **if you are allergic to antihistamines or cannot use antihistamines** for other medical reasons. Antihistamines are given to help prevent an allergic reaction to Torisel, including some life-threatening and rare fatal allergic reactions. Discuss alternatives with your doctor.
- **if you have or have had tumours in your brain or spinal cord, bleeding problems or bruising, or if you are taking medicines which prevent your blood from clotting (such as warfarin and acenocoumarole)**. Torisel may lead to a higher risk of bleeding into your brain. Tell your doctor if you are taking blood thinning medicines or have any bleeding or bruising while you are on Torisel.
- **if you have shortness of breath, cough, and/or fever**. Torisel may weaken your immune system. You may be at risk of getting an infection of the blood, skin, upper respiratory tract (including pneumonia), and/or urinary tract while you are taking Torisel. Tell your doctor if you experience new or worsening symptoms, or if you are taking or have recently taken medicines that weaken your immune system.
- **if you have or have had inflammation of the lungs**. Torisel may cause non-specific interstitial pneumonitis. Some patients did not have symptoms or had minimal symptoms. For this reason, your doctor may recommend a lung assessment by computed tomography scan or chest x-ray before and during your Torisel treatment. Promptly tell your doctor of any new or worsening respiratory symptoms such as shortness of breath or difficulty breathing.
- **if you drink alcohol or are an alcoholic**. Torisel contains alcohol and can be harmful to those who drink alcohol or to those suffering from alcoholism. Tell your doctor if you have a drinking problem or consume alcohol (see section "Torisel contains ethanol [alcohol]").
- **if you have or have had kidney problems**. Your doctor will monitor your kidney function.
- **if you have or have had liver problems**. Tell your doctor if you develop any of the following signs and symptoms of liver problems during Torisel treatment: itching, yellow eyes or skin, dark urine, and pain or discomfort in the right upper stomach area. Your doctor will do blood tests to check your liver function and then may decide to lower the dose of Torisel.
- **if you have or have had high cholesterol levels.** Torisel may elevate triglycerides and/or cholesterol, and this may require treatment with lipid-lowering agents (medicines used to reduce cholesterol in the blood).
- **if you are going to have surgery or if you had an operation recently.** Torisel may increase the risk of problems with wound healing. You will usually be taken off Torisel if you are having an operation. Your doctor will decide when to start Torisel again.
- **if you are planning to have a vaccination during treatment with Torisel**. A vaccination may be less effective or the use of certain vaccinations should be avoided during treatment with Torisel.
- **if you are over 65 years of age.** You may be more likely to have certain side effects, including swelling of your face, diarrhoea, pneumonia, anxiety, depression, shortness of breath, decreased number of white cells in the blood, muscle pain, change in the sense of taste, upper respiratory infection, fluid around the lungs, sores and inflammation in the mouth and/or the digestive tract, runny nose, dizziness and infections.
- **Torisel may increase blood glucose levels and worsen diabetes mellitus.** This may result in the need for insulin and/or oral antidiabetic agent therapy. Tell your doctor if you experience any excessive thirst or increased frequency and quantity of urination.
- **Torisel can decrease the number of blood cells that help in clotting and resisting infection.** This may increase the risk of bleeding/bruising and infection (see section "Possible side effects").
- **if you have or have had eye problems like cataracts**. Your doctor may prescribe a visual examination before or during Torisel treatment.
- **if you are receiving Torisel,** you may be at increased risk of cancers such as skin cancers and lymph node cancers (lymphoma).
- **if you are receiving Torisel,** you may be at increased risk of heart attack. Tell your doctor if you experience symptoms such as pain or sensation of pressure in chest, arm, shoulders or jaw, shortness of breath, feeling sick (nausea), anxiety, sweating or dizziness.

Talk to your doctor, pharmacist, nurse if you have any concern.

Children and adolescents

This medicine is not for children and adolescents below 18 years of age because advanced cancer of the kidney and mantle cell lymphoma are not relevant for these patients, and it did not work in other cancers.

Other medicines and Torisel

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines.
Some medicines can interfere with the breakdown or metabolism of Torisel and therefore dose adjustment of Torisel may be required. In particular, you should inform your doctor or pharmacist if you are taking any of the following:

- protease inhibitors used in the treatment of Human Immunodeficiency Virus (HIV)
- antibiotics (including rifampicin) or antifungal medicines (including itraconazole, ketoconazole and voriconazole) used to treat infections
- nefazodone or selective serotonin re-uptake inhibitors used to treat depression
- anti-epileptic medicines, including carbamazepine, phenytoin and phenobarbital
- rifabutin used to treat infection in people with HIV and other diseases
- herbal medicines or natural remedies containing St. John's wort (*Hypericum perforatum*) used to treat mild depression
- angiotensin converting enzyme (ACE) inhibitors (such as enalapril, ramipril, lisinopril) or a calcium channel blocker (such as amlodipine) used to treat high blood pressure or other cardiovascular problems
- amphiphilic medicines used to treat heart arrhythmias (such as amiodarone), or statins used to treat high cholesterol
- sunitinib used to treat cancer of the kidney
- medicines which are P-gp substrates (such as digoxin, vincristine, colchicine, dabigatran, lenalidomide, paclitaxel)
- cannabidiol (uses amongst others include treatment of seizures)

Torisel with food and drink

Grapefruit and grapefruit juice may increase blood concentrations of Torisel and should be avoided.

Pregnancy and breast-feeding

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

Torisel has not been studied in pregnant women, and it must not be used during pregnancy, unless clearly necessary.

Women of childbearing potential must avoid pregnancy by using an effective method of birth control during treatment with Torisel. Men with partners of childbearing potential should use medically acceptable contraception while receiving Torisel.

Women should not breast-feed during treatment with Torisel, as this medicine may interfere with the growth and development of the baby.

Torisel contains alcohol (ethanol). If you are pregnant or breast-feeding your baby, you should talk to your doctor or pharmacist before taking this medicine.

Torisel contains propylene glycol. If you are pregnant, do not take this medicine unless recommended by your doctor (see section "Torisel contains propylene glycol"). Propylene glycol may pass into breast milk, if you are breast-feeding, do not take this medicine unless recommended by your doctor (see section "Torisel contains propylene glycol").

Driving and using machines

Torisel is unlikely to influence the ability to drive and use machines. However, feeling or being sick (nausea and vomiting) and difficulty in falling or staying asleep are very common side effects. If you feel sick (nausea and vomiting) or you have difficulty in falling or staying asleep, take special care when driving or using machines.

For patients receiving the higher dose of Torisel for the treatment of mantle cell lymphoma, the amount of alcohol in this medicine may impair your ability to drive or use machines (see section below "Torisel contains ethanol [alcohol]").

Torisel contains ethanol (alcohol)
This medicine contains ethanol (alcohol), equivalent to 18 ml beer or 7 ml wine per 25 mg dose. Patients receiving the higher dose of 175 mg of Torisel for the initial treatment of mantle cell lymphoma may receive a dose of ethanol equivalent to up to 122 ml beer or 49 ml wine per dose. It is harmful if you are suffering from alcoholism, and it is to be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease or epilepsy.

The amount of alcohol in this medicine is not likely to have an effect in adults and adolescents, and its effects in children are not likely to be noticeable. It may have some effects in babies and young children, for example feeling sleepy. If you are addicted to alcohol, talk to your doctor or pharmacist before taking this medicine.

The amount of alcohol in this medicine may alter the effects of other medicines. Talk to your doctor or pharmacist if you are taking other medicines. The amount of alcohol in this medicine may impair your ability to drive or alter the effects of other medicines (see sections "Warning and precautions" and "Driving and using machines").

Torisel contains propylene glycol
Torisel contains 503.3 mg propylene glycol in each 25 mg dose which is equivalent to 201.33 mg/ml diluted product. If your child is less than 5 years old, talk to your doctor or pharmacist before giving them this medicine, in particular if they are being given other medicines that contain propylene glycol or alcohol. If you are pregnant or breast-feeding, or if you suffer from liver or kidney disease, do not take this medicine unless recommended by your doctor. Your doctor may carry out extra checks while you are taking this medicine.

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3. How Torisel is given

Torisel will always be prepared and given to you by a doctor or another healthcare professional as an intravenous infusion (into your vein).

You should receive an injection of antihistamine (to try to prevent allergic reaction to Torisel) directly into your vein approximately 30 minutes before your dose of Torisel.

The Torisel concentrate must first be diluted with 1.8 ml of the supplied solvent to achieve a concentration of 10 mg/ml before administration in sodium chloride 9 mg/ml (0.9%) solution for injection (see dilution instructions at the end of the package leaflet).

For renal cancer, the recommended dose is 25 mg infused (as a drip) over a 30 to 60 minute period once weekly.

For mantle cell lymphoma, the recommended dose is 175 mg infused (as a drip) over a 30 to 60 minute period once weekly for 3 weeks followed by single weekly doses of 75 mg infused (as a drip) over a 30 to 60 minute period.

Treatment with Torisel should continue until you are no longer benefiting from therapy or until unacceptable side effects occur.

As this medicine is prepared and given by a healthcare professional, it is unlikely you will be given too much or that you will miss a dose.

If you are concerned about this, tell your doctor immediately.
If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

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

Side effects may be more pronounced with the higher dose of 175 mg per week during initial treatment for mantle cell lymphoma.

The most important side effects you may experience during the treatment with Torisel are listed below. If you experience any of them, seek medical advice immediately.

Allergic reactions
You should **tell your doctor or nurse immediately** if you have symptoms of angioedema, such as swollen face, tongue or pharynx, and difficulty in breathing.
If you experience any of these during the administration of Torisel, the doctor or nurse will stop the infusion.

Bleeding in the brain
You should **seek medical advice immediately** if you feel confused, unusually tired, have difficulty in speaking or in swallowing and your pupils have different sizes. These symptoms might be caused by a bleeding in the brain.

Intestinal puncture, tear or holes
You should **seek medical advice immediately** if you have acute abdominal pain, high fever, nausea and vomiting, or blood in the stools. These symptoms might be caused by a perforation in your gut.

Kidney failure
You should **seek medical advice immediately** if you suffer from general swelling, shortness of breath, tiredness. These symptoms might be caused by a sudden decrease of kidney function.

Embolism in the lung
You should **seek medical advice immediately** if you experience shortness of breath, chest pain, coughing up blood, fast heartbeat, nausea, fainting, sweating, wheezing, and clammy or bluish skin. These symptoms might be caused by a blood clot in your lung.

You should also tell your doctor straight away
- if you have cough, chest pain, difficulties in breathing. Your doctor may prescribe you an x-ray examination of your chest.
- if the number of white cells in your blood has decreased. This may increase the risk of getting fever and infections.
- if the number of platelet (a type of blood cell that helps to clot blood) has decreased. This may increase the risk of bleeding in your body.
- if your blood levels of cholesterol and triglycerides have increased.
- if you experience any excessive thirst or increased frequency and quantity of urination. Your doctor may prescribe you insulin and/or oral antidiabetic agent therapy.
- if you have recently undertaken a surgery. Your doctor may delay the administration of Torisel until the wound is fully recovered as this medicine could interfere with the healing processes of pre-existing wounds.

Other side effects with Torisel may include

Very common side effects (may affect more than 1 in 10 people)

General feeling of weakness, chills, swelling due to fluid retention, pain (including abdominal, back, chest and joint pain), feeling sick to the stomach (nausea and vomiting), diarrhoea, constipation, headache, fever, sores and inflammation in the mouth and/or the digestive tract, cough, pneumonia, nose bleed, rash, itching, dry skin, decreased appetite, shortness of breath, low levels of potassium in the blood (which may cause muscle weakness), low red blood cell count, decreased number of a type of white blood cells which is associated with an increased risk of infection, high blood sugar, high cholesterol, high triglycerides, abscess, infections (including eye infection, flu, viral infections, bronchitis), abnormal kidney function (including kidney failure), blood tests that show changes in the way the kidney is working, change in the sense of taste, difficulty falling asleep, low number of platelets which may cause bleeding and bruising.

Common side effects (may affect up to 1 in 10 people)

Runny nose, gum redness and swelling, mouth pain (including sores inside the mouth), stomach bloating, sore throat, high blood pressure, pink eye including watery eye disorder, taste loss, redness and swelling of the follicles in the skin, allergic reactions, severe scaling of the skin, increased blood clotting (including thrombosis of the veins), low levels of calcium in the blood, low levels of phosphates in the blood, upper respiratory infections, inflammation of the lung, fluid in the chest cavity, infection in the blood, dehydration, agitation, depression, numbness and tingling of the skin, dizziness, sleepiness, bleeding (from the lips, mouth, stomach or intestines), inflammation of the lining of the stomach, trouble with swallowing, skin bleeding (bruising), small pin-point haemorrage, nail disorder, acne, yeast infection, fungal infection, urinary tract infections, cystitis, blood tests that show changes in the way the liver is working, high blood fats other than triglycerides, diabetes, muscle pain.

Uncommon side effects (may affect up to 1 in 100 people)

Pericardial effusion (fluid around the heart that may require drainage and can affect the pumping of blood).
Bleeding into the brain in patients with brain tumours or who are on blood thinners, eye bleeding.
Embolism of the lung, perforation of the gut, problems with wound healing after surgery, inflammation and swelling of the voice box.

Rare side effects (may affect up to 1 in 1,000 people)

Lung infection caused by Pneumocystis jiroveci (*Pneumocystis jiroveci pneumonia*).

Side effects for which frequency is not known (cannot be estimated from available data)

Swelling of the face, lips, tongue, and throat, possibly causing difficulty breathing.
Serious reactions of the skin and/or mucous membranes which may include painful blisters and fever (*Stevens-Johnson syndrome*).
Unexplained muscle pain, tenderness or weakness which could indicate muscle damage *(rhabdomyolysis)*

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 at: 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 Torisel

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 vial label and carton. The expiry date refers to the last day of that month.
Store in a refrigerator (2°C - 8°C)
Do not freeze.

Keep the vials in the outer carton in order to protect from light.

After first dilution of the concentrate with 1.8 ml of the supplied solvent, the mixture may be stored for up to 24 hours below 25°C and protected from light prior to further dilution.

After further dilution of the concentrate-solvent mixture with sodium chloride 9 mg/ml (0.9%) solution for injection, the solution may be stored for up to 6 hours below 25°C and protected from light.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Torisel contains

- The active substance is temsirolimus.

  Each vial of concentrate contains 30 mg of temsirolimus.

  After first dilution of the concentrate with 1.8 ml of the supplied solvent, the concentration of temsirolimus is 10 mg/ml.

- The other ingredients in the concentrate are anhydrous ethanol, all-*rac*-α-tocopherol (E 307), propylene glycol (E 1520) and citric acid (E 330). The solvent contains polysorbate 80 (E 433), macrogol 400 and anhydrous ethanol (see section 2 “Torisel contains ethanol [alcohol]” and “Torisel contains propylene glycol).

What Torisel looks like and contents of the pack

Torisel is a concentrate and solvent for solution for infusion.
The concentrate is a clear, colourless to light-yellow solution. The solvent is a clear to slightly turbid, light-yellow to yellow solution. The solutions are essentially free from visible particulates.

Each pack of Torisel contains one glass vial of 1.2 ml of concentrate and one glass vial of 2.2 ml of solvent.

Marketing Authorisation Holder
Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
United Kingdom

Manufacturer
Wyeth Lederle S.r.l.
Via Franco Gorgone
Zona Industriale
95100 Catania
Italy

For any information about this medicine, please contact:
Medical Information, Pfizer Ltd, Walton Oaks, Dorking Road, Tadworth, Surrey, KT20 7NS.
Telephone 01304 616161.

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The following information is intended for healthcare professionals only

During handling and preparation of admixtures, Torisel should be protected from excessive room light and sunlight.

Bags/containers that come in contact with Torisel must be made of glass, polyolefin, or polyethylene.

Polyvinyl chloride (PVC) bags and medical devices must not be used for the administration of preparations containing polysorbate 80, because polysorbate 80 leaches di-2-ethylhexylphthalate (DEHP) from PVC.
Torisel concentrate and solvent should be inspected visually for particulate matter and discolouration prior to administration.
Do not use if particulates are present, or if discoloured. Use a new vial.

Dilution

The concentrate for solution for infusion must be diluted with the supplied solvent before administration in sodium chloride 9 mg/ml (0.9%) solution for injection.

Note: For mantle cell lymphoma, multiple vials will be required for each dose over 25 mg. Each vial of Torisel must be diluted according to the instructions below. The required amount of concentrate-solvent mixture from each vial must be combined in one syringe for rapid injection into 250 ml of sodium chloride 9 mg/ml (0.9%) solution for injection.

The concentrate-solvent mixture should be inspected visually for particulate matter and discolouration.
Do not use if particulates are present, or if discoloured.

In preparing the solution, the following two-step process must be carried out in an aseptic manner according to local standards for handling cytotoxic/cytostatic medicines:

STEP 1: DILUTION OF THE CONCENTRATE FOR SOLUTION FOR INFUSION WITH THE SUPPLIED SOLVENT

- Withdraw 1.8 ml of the supplied solvent.
- Inject the 1.8 ml of solvent into the vial of Torisel 30 mg concentrate.
- Mix the solvent and the concentrate well by inversion of the vial. Sufficient time should be allowed for air bubbles to subside. The solution should be a clear to slightly turbid, colourless to light-yellow to yellow solution, essentially free from visual particulates.

One vial of Torisel concentrate contains 30 mg of temsirolimus: when the 1.2 ml concentrate is combined with 1.8 ml of the supplied solvent, a total volume of 3.0 ml is obtained and the concentration of temsirolimus will be 10 mg/ml. The concentrate-solvent mixture is stable below 25°C for up to 24 hours.
STEP 2: ADMINISTRATION OF CONCENTRATE FOR SOLUTION FOR INFUSION SOLVENT MIXTURE IN SODIUM CHLORIDE 9 MG/ML (0.9%) SOLUTION FOR INJECTION

- Withdraw the required amount of concentrate-solvent mixture (containing temsirolimus 10 mg/ml) from the vial; i.e., 2.5 ml for a temsirolimus dose of 25 mg.
- Inject the withdrawn volume rapidly into 250 ml of sodium chloride 9 mg/ml (0.9%) solution for injection to ensure adequate mixing.

The admixture should be mixed by inversion of the bag or bottle, avoiding excessive shaking, as this may cause foaming.

The final diluted solution in the bag or bottle should be inspected visually for particulate matter and discolouration prior to administration. The admixture of Torisel in sodium chloride 9 mg/ml (0.9%) solution for injection should be protected from excessive room light and sunlight.

For mantle cell lymphoma, multiple vials will be required for each dose over 25 mg.

Administration

• Administration of the final diluted solution should be completed within six hours from the time that the Torisel is first added to sodium chloride 9 mg/ml (0.9%) solution for injection.
• Torisel is infused over a 30 to 60 minute period once a week. The use of an infusion pump is the preferred method of administration to ensure accurate delivery of the medicinal product.
• Appropriate administration materials must be used to avoid excessive loss of medicinal product and to decrease the rate of DEHP extraction. The administration materials must consist of non-DEHP, non-PVC tubing with appropriate filter. An in-line polyethersulfone filter with a pore size of not greater than 5 microns is recommended for administration to avoid the possibility of particles bigger than 5 microns being infused. If the administration set available does not have an in-line filter incorporated, a filter should be added at the end of the set (i.e., an end-filter) before the admixture reaches the vein of the patient. Different end-filters can be used ranging in filter pore size from 0.2 microns up to 5 microns. The use of both an in-line and end-filter is not recommended.
• Torisel, when diluted, contains polysorbate 80, and therefore appropriate administration materials must be used. It is important that the recommendations in sections 4.2 and 6.6 in the SmPC be followed closely.

Disposal

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

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