HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TORISEL® safely and effectively. See full prescribing information for TORISEL.

TORISEL Kit (temsirolimus) injection, for intravenous infusion only
Initial U.S. Approval: 2007

INDICATIONS AND USAGE

TORISEL® is a kinase inhibitor indicated for the treatment of advanced renal cell carcinoma. (1)

DOSAGE AND ADMINISTRATION

- The recommended dose of TORISEL is 25 mg infused over a 30-60 minute period once a week. Treat until disease progression or unacceptable toxicity. (2.1)
- Antihistamine pre-treatment is recommended. (2.2)
- Dose reduction is required in patients with mild hepatic impairment. (2.4)
- TORISEL (temsirolimus) injection vial contents must first be diluted with the enclosed diluent before diluting the resultant solution with 250 mL of 0.9% Sodium Chloride Injection. (2.5)

DOSAGE FORMS AND STRENGTHS

TORISEL injection, 25 mg/mL supplied with DILUENT for TORISEL®. (3)

CONTRAINDICATIONS

TORISEL is contraindicated in patients with bilirubin > 1.5×ULN. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity/Infusion Reactions (including some life-threatening and rare fatal reactions) can occur early in the first infusion of TORISEL. Patients should be monitored throughout the infusion. (5.1)
- To treat hypersensitivity reactions, stop TORISEL and treat with an antihistamine. TORISEL may be restarted at physician discretion at a slower rate. (5.1)
- Hepatic Impairment: Use caution when treating patients with mild hepatic impairment and reduce dose. (2.4, 5.2)
- Hyperglycemia and hyperlipemia are likely and may require treatment. Monitor glucose and lipid profiles. (5.3, 5.6)
- Infections may result from immunosuppression. (5.4)
- Monitor for symptoms or radiographic changes of interstitial lung disease (ILD). If ILD is suspected, discontinue TORISEL, and consider use of corticosteroids and/or antibiotics. (5.5)
- Bowel perforation may occur. Evaluate fever, abdominal pain, bloody stools, and/or acute abdomen promptly. (5.7)
- Renal failure, sometimes fatal, has occurred. Monitor renal function at baseline and while on TORISEL. (5.8)
- Due to abnormal wound healing, use TORISEL with caution in the perioperative period. (5.9)
- Live vaccinations and close contact with those who received live vaccines should be avoided. (5.13)
- Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant. (5.14)
- Elderly patients may be more likely to experience certain adverse reactions, including diarrhea, edema and pneumonia. (5.15)

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥30%) are rash, asthenia, mucositis, nausea, edema, and anorexia. The most common laboratory abnormalities (incidence ≥30%) are anemia, hyperglycemia, hyperlipemia, hypertriglyceridemia, elevated alkaline phosphatase, elevated serum creatinine, lymphopenia, hypophosphatemia, thrombocytopenia, elevated AST, and leukopenia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Wyeth Pharmaceuticals Inc. at 1-800-934-5556 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

Strong inducers of CYP3A4/5 and inhibitors of CYP3A4 may affect concentrations of the primary metabolite of TORISEL. If alternatives cannot be used, dose modifications of TORISEL are recommended. (7.1, 7.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 07/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TORISEL is indicated for the treatment of advanced renal cell carcinoma.

2 DOSAGE AND ADMINISTRATION

2.1 Advanced Renal Cell Carcinoma

The recommended dose of TORISEL for advanced renal cell carcinoma is 25 mg infused over a 30 – 60 minute period once a week.

Treatment should continue until disease progression or unacceptable toxicity occurs.

2.2 Premedication

Patients should receive prophylactic intravenous diphenhydramine 25 to 50 mg (or similar antihistamine) approximately 30 minutes before the start of each dose of TORISEL *[see Warnings and Precautions (5.1)]*.

2.3 Dosage Interruption/Adjustment

TORISEL should be held for absolute neutrophil count (ANC) <1,000/mm^3, platelet count <75,000/mm^3, or NCI CTCAE grade 3 or greater adverse reactions. Once toxicities have resolved to grade 2 or less, TORISEL may be restarted with the dose reduced by 5 mg/week to a dose no lower than 15 mg/week.

2.4 Dose Modification Guidelines

Hepatic Impairment: Use caution when treating patients with hepatic impairment. If TORISEL must be given in patients with mild hepatic impairment (bilirubin >1 – 1.5×ULN or AST >ULN but bilirubin ≤ULN), reduce the dose of TORISEL to 15 mg/week. TORISEL is contraindicated in patients with bilirubin >1.5×ULN *[see Contraindications (4), Warnings and Precautions (5.2) and Use in Specific Populations (8.7)]*.

Concomitant Strong CYP3A4 Inhibitors: The concomitant use of strong CYP3A4 inhibitors should be avoided (e.g. ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole). Grapefruit juice may also increase plasma concentrations of sirolimus (a major metabolite of temsirolimus) and should be avoided. If patients must be co-administered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, a TORISEL dose reduction to 12.5 mg/week should be considered. This dose of TORISEL is predicted to adjust the AUC to the range observed without inhibitors. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inhibitors. If the strong inhibitor is discontinued, a washout period of approximately 1 week should be allowed before the TORISEL dose is adjusted back to the dose used prior to initiation of the strong CYP3A4 inhibitor *[see Warnings and Precautions (5.11) and Drug Interactions (7.2)]*.

Concomitant Strong CYP3A4 Inducers: The use of concomitant strong CYP3A4 inducers should be avoided (e.g. dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifampacin, phenobarbital). If patients must be co-administered a strong CYP3A4 inducer, based on pharmacokinetic studies, a TORISEL dose increase from 25 mg/week up to 50 mg/week should be considered. This dose of TORISEL is predicted to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued the temsirolimus dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer *[see Warnings and Precautions (5.11) and Drug Interactions (7.1)]*.

2.5 Instructions for Preparation

TORISEL must be stored under refrigeration at 2°–8°C (36°–46°F) and protected from light. During handling and preparation of admixtures, TORISEL should be protected from excessive room light and sunlight. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

In order to minimize the patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final TORISEL dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

TORISEL 25 mg/mL injection must be diluted with the supplied diluent before further dilution in 0.9% Sodium Chloride Injection, USP.

Please note that both the TORISEL injection and diluent vials contain an overfill to ensure the recommended volume can be withdrawn.

Follow this two-step dilution process in an aseptic manner.

Step 1:

DILUTION OF TORISEL INJECTION 25 MG/ML WITH SUPPLIED DILUENT

- Each Vial of Torisel (temsirolimus) must first be mixed with 1.8 mL of the enclosed diluent. The resultant solution contains 30 mg/3 mL (10 mg/mL).
- Mix well by inversion of the vial. Allow sufficient time for the air bubbles to subside. The solution should be clear to slightly turbid, colorless to light-yellow solution, essentially free from visual particulates.

The concentrate-diluent mixture is stable below 25ºC for up to 24 hours.

Step 2:

DILUTION OF CONCENTRATE-DILUENT MIXTURE WITH 0.9% SODIUM CHLORIDE INJECTION, USP

- Withdraw precisely the required amount of concentrate-diluent mixture containing temsirolimus 10 mg/mL as prepared in Step 1 from the vial (i.e., 2.5 mL for a temsirolimus dose of 25 mg) and further dilute into an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, USP.

- Mix by inversion of the bag or bottle, avoiding excessive shaking, as this may cause foaming.

The resulting solution should be inspected visually for particulate matter and discoloration prior to administration. The admixture of TORISEL in 0.9% Sodium Chloride Injection, USP should be protected from excessive room light and sunlight.

2.6 Administration

- Administration of the final diluted solution should be completed within six hours from the time that TORISEL is first added to 0.9% Solution Chloride Injection, USP.

- TORISEL is infused over a 30- to 60-minute period once weekly. The use of an infusion pump is the preferred method of administration to ensure accurate delivery of the product.

- Appropriate administration materials should be composed of glass, polyolefin, or polyethylene to avoid excessive loss of product and diethylhexylpthalate (DEHP) extraction. The administration materials should consist of non-DEHP, non-polyvinylchloride (PVC) tubing with appropriate filter. In the case when a PVC administration set has to be used, it should not contain DEHP. 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 polyethersulfone filter should be added at 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, which is known to increase the rate of DEHP extraction from PVC. This should be considered during the preparation and administration of TORISEL, including storage time elapsed when in direct contact with PVC following constitution.

Compatibilities and Incompatibilities

Undiluted TORISEL injection should not be added directly to aqueous infusion solutions. Direct addition of TORISEL injection to aqueous solutions will result in precipitation of drug. Always combine TORISEL injection with DILUENT for TORISEL before adding to infusion solutions. It is recommended that TORISEL be administered in 0.9% Sodium Chloride Injection after combining with diluent. The stability of TORISEL in other infusion solutions has not been evaluated. Addition of other drugs or nutritional agents to admixtures of TORISEL in 0.9% Sodium Chloride Injection has not been evaluated and should be avoided. Temsirolimus is degraded by both acids and bases, and thus combinations of temsirolimus with agents capable of modifying solution pH should be avoided.

3 DOSAGE FORMS AND STRENGTHS

TORISEL® (temsirolimus) is supplied as a kit consisting of the following:

TORISEL (temsirolimus) injection (25 mg/mL). The TORISEL vial contains temsirolimus at a concentration of 25 mg/mL. The vial contains an overfill of 0.2 mL to ensure the ability to withdraw the recommended dose.

DILUENT for TORISEL®. The DILUENT vial includes a deliverable volume of 1.8 mL. This vial contains an overfill in order to ensure that the appropriate volume can be withdrawn.

4 CONTRAINDICATIONS

TORISEL is contraindicated in patients with bilirubin >1.5×ULN *[see Warnings and Precautions (5.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity/Infusion Reactions

Hypersensitivity/infusion reactions, including but not limited to flushing, chest pain, dyspnea, hypotension, apnea, loss of consciousness, hypersensitivity and anaphylaxis, have been associated with the administration of temsirolimus. These reactions can occur very early in the first infusion, but may also occur with subsequent infusions. Patients should be monitored throughout the infusion and appropriate supportive care should be available. Temsirolimus infusion should be interrupted in all patients with severe infusion reactions and appropriate medical therapy administered.

TORISEL should be used with caution in persons with known hypersensitivity to temsirolimus or its metabolites (including sirolimus), polysorbate 80, or to any other component (including the excipients) of TORISEL.

An H_1 antihistamine should be administered to patients before the start of the intravenous temsirolimus infusion. TORISEL should be used with caution in patients with known

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