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)
- 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 ----------
- None. (4)

----------WARNINGS AND PRECAUTIONS ----------
- To treat hypersensitivity reactions stop TORISEL and treat with an antihistamine. TORISEL may be restarted at physician discretion at a slower rate. (5.1)
- Hyperglycemia and hyperlipemia are likely and may require treatment. Monitor glucose and lipid profiles. (5.2, 5.5)
- Infections may result from immunosuppression. (5.3)
- 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. (5.4)
- Bowel perforation may occur. Evaluate fever, abdominal pain, bloody stools, and/or acute abdomen promptly. (5.6)
- Renal failure, sometimes fatal, has occurred. Monitor renal function at baseline and while on TORISEL. (5.7)
- Due to abnormal wound healing, use TORISEL with caution in the perioperative period. (5.8)
- Live vaccinations and close contact with those who received live vaccines should be avoided. (5.12)
- Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant. (5.13)

----------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.
Revision date: 5/2007

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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 Hypersensitivity Reactions (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

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 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 Drug Interactions (7.1)*]

2.5 Instructions for Preparation and Administration

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.

Dilution:

In preparing the TORISEL administration solution, follow this two-step dilution process in an aseptic manner.

Step 1:

Inject 1.8 mL of DILUENT for TORISEL into the vial of TORISEL (temsirolimus) injection (25 mg/ml). The TORISEL (temsirolimus) vial contains an overfill of 0.2 mL (30 mg/1.2 mL). Due to the intentional overfill in the TORISEL injection vial, the drug concentration of the resulting solution will be 10 mg/mL. A total volume of 3 mL will be obtained including the overfill. Mix well by inversion of the vial. Allow sufficient time for air bubbles to subside. This 10 mg/mL drug solution/diluent mixture must be further diluted as described in Step 2 below.

The solution is clear to slightly turbid, colorless to yellow, and free from visual particulates. The 10 mg/mL drug solution/diluent mixture is stable for up to 24 hours at controlled room temperature.

Step 2:

Withdraw the required amount of temsirolimus from the 10 mg/mL drug solution/diluent mixture prepared in Step 1. Inject rapidly into a 250 mL container (glass, polyolefin, or polyethylene) of 0.9% sodium chloride injection. Mix the admixture by inversion of the bag or bottle. Avoid excessive shaking as this may cause foaming.

Administration:

- The sodium chloride injection container should be composed of non-DEHP containing materials, such as glass, polyolefin or polyethylene, and the administration set should consist of non-DEHP tubing to avoid extraction of di-(2-ethylhexyl) phthalate (DEHP). TORISEL contains polysorbate 80, which is known to increase the rate of di-(2-ethylhexyl) phthalate (DEHP) extraction from PVC.
- An in-line polyethersulfone filter with a pore size of not greater than 5 microns is recommended for administration.
- The final diluted solution of TORISEL is intravenously infused over a 30-60 minute period once a week. The use of an infusion pump is the preferred method of administration to ensure accurate delivery of the drug.

- Administration of the final diluted infusion solution should be completed within six hours from the time that the drug solution/diluent mixture is added to the sodium chloride injection.

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 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 includes an overfill of 0.2 mL.
- DILUENT for TORISEL. The DILUENT vial includes a deliverable volume of 1.8 mL.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnea, flushing, and chest pain have been observed with TORISEL.

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 hypersensitivity to an antihistamine, or patients who cannot receive an antihistamine for other medical reasons.

If a patient develops a hypersensitivity reaction during the TORISEL infusion, the infusion should be stopped and the patient should be observed for at least 30 to 60 minutes (depending on the severity of the reaction). At the discretion of the physician, treatment may be resumed with the administration of an H_1-receptor antagonist (such as diphenhydramine), if not previously administered [see *Dosage and Administration (2.2)*], and/or an H_2-receptor antagonist (such as intravenous famotidine 20 mg or intravenous ranitidine 50 mg) approximately 30 minutes before

restarting the TORISEL infusion. The infusion may then be resumed at a slower rate (up to 60 minutes).

5.2 Hyperglycemia/Glucose Intolerance

The use of TORISEL is likely to result in increases in serum glucose. In the phase 3 trial, 89% of patients receiving TORISEL had at least one elevated serum glucose while on treatment, and 26% of patients reported hyperglycemia as an adverse event. This may result in the need for an increase in the dose of, or initiation of, insulin and/or oral hypoglycemic agent therapy. Serum glucose should be tested before and during treatment with TORISEL. Patients should be advised to report excessive thirst or any increase in the volume or frequency of urination.

5.3 Infections

The use of TORISEL may result in immunosuppression. Patients should be carefully observed for the occurrence of infections, including opportunistic infections [*see Adverse Reactions (6.1)*].

5.4 Interstitial Lung Disease

Cases of interstitial lung disease, some resulting in death, occurred in patients who received TORISEL. Some patients were asymptomatic with infiltrates detected on computed tomography scan or chest radiograph. Others presented with symptoms such as dyspnea, cough, hypoxia, and fever. Some patients required discontinuation of TORISEL and/or treatment with corticosteroids and/or antibiotics, while some patients continued treatment without additional intervention. Patients should be advised to report promptly any new or worsening respiratory symptoms.

5.5 Hyperlipemia

The use of TORISEL is likely to result in increases in serum triglycerides and cholesterol. In the phase 3 trial, 87% of patients receiving TORISEL had at least one elevated serum cholesterol value and 83% had at least one elevated serum triglyceride value. This may require initiation, or increase in the dose, of lipid-lowering agents. Serum cholesterol and triglycerides should be tested before and during treatment with TORISEL.

5.6 Bowel Perforation

Cases of fatal bowel perforation occurred in patients who received TORISEL. These patients presented with fever, abdominal pain, metabolic acidosis, bloody stools, diarrhea, and/or acute abdomen. Patients should be advised to report promptly any new or worsening abdominal pain or blood in their stools.

5.7 Renal Failure

Cases of rapidly progressive and sometimes fatal acute renal failure not clearly related to disease progression occurred in patients who received TORISEL. Some of these cases were not responsive to dialysis.

5.8 Wound Healing Complications

Use of TORISEL has been associated with abnormal wound healing. Therefore, caution should be exercised with the use of TORISEL in the perioperative period.

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