TORISEL® is a kinase inhibitor, and in the United States is indicated for the treatment of advanced renal cell carcinoma (RCC).¹

MECHANISM OF ACTION

Based on preclinical studies, TORISEL inhibits the activity of mTOR, an intracellular protein implicated in multiple growth-related cellular functions including proliferation, growth and survival.¹ ² The inhibition of mTOR also reduces levels of certain growth factors, such as vascular endothelial growth factor (VEGF), which are overexpressed in solid tumors like kidney cancer and are thought to play a crucial role in angiogenesis,³ ⁴ the process by which tumors acquire blood vessels, nutrients and oxygen needed for growth.³ Preclinical activity does not necessarily correlate with clinical outcomes.

KIDNEY CANCER CLINICAL STUDY (GLOBAL ARCC TRIAL)

TORISEL is the only treatment with pivotal data showing significant improvement in overall survival (OS) in a predominantly poor-risk patient population with advanced RCC. This was demonstrated in a Phase 3, randomized, multi-center trial that compared TORISEL, interferon-alpha (IFN-α), and TORISEL plus IFN-α as first-line therapy in 626 patients with treatment-naïve advanced kidney cancer. In the trial, 94% of the patients were poor risk based on three or more of six pre-selected prognostic risk factors:*

- TORISEL demonstrated a statistically significant increase in OS compared with IFN-α. (Hazard Ratio = 0.73, 95% CI: 0.58, 0.92; P=0.0078)
  - Median OS of 10.9 months vs. 7.3 months with IFN-α (95% CI: 8.6,12.7 months and 6.1, 8.8 months, respectively)
  - OS was the primary endpoint
- TORISEL demonstrated a significant increase in progression-free survival (PFS) compared with IFN-α as determined by independent assessment (Hazard Ratio = 0.66, 95% CI: 0.53, 0.81; P=0.0001)
  - Median PFS of 5.5 months vs. 3.1 months with IFN-α (95% CI: 3.9, 7.0 months and 2.2, 3.8 months, respectively)
  - PFS was a secondary endpoint
- TORISEL did not show a significant difference in overall response rate (ORR) compared with IFN-α
  - 8.6 percent vs. 4.8 percent with IFN-α (95% CI: 4.8, 12.4 and 1.9, 7.8, respectively [P=0.1232])
  - ORR was a secondary endpoint
- The median duration of treatment in the study was 17 weeks (1-126 weeks) for patients treated with TORISEL and 8 weeks (1-124 weeks) for those treated with IFN-α
- Treatment with the combination of TORISEL and IFN-α was associated with an increased incidence of multiple adverse reactions and did not result in a significant increase in OS when compared with IFN-α alone¹

*Prognostic risk factors included: <1 year from the initial RCC diagnosis to randomization, KPS of 60 or 70, hemoglobin <LLN, corrected calcium >10 mg/dL, lactate dehydrogenase >1.5 x ULN, and ≥2 sites of metastasis⁵

IMPORTANT SAFETY INFORMATION¹

TORISEL is contraindicated in patients with bilirubin >1.5 x ULN and should be used with caution when treating patients with mild hepatic impairment (bilirubin >1-1.5 x ULN or AST >ULN but bilirubin ≤ULN). IF TORISEL must be given to patients with mild hepatic impairment, reduce the dose of TORISEL to 15 mg/week. In a phase 1 study, the overall frequency of ≥grade 3 adverse reactions and deaths, including deaths due to progressive disease, was greater in patients with baseline bilirubin >1.5 x ULN.

Hypersensitivity/infusion reactions, including flushing, chest pain, dyspnea, hypotension, apnea, loss of consciousness, hypersensitivity, and anaphylaxis, may occur very early in the first infusion or with subsequent infusions. Pretreat with an H1 antihistamine. TORISEL infusion should be interrupted in patients with infusion reactions and appropriate therapy given.

Please see continued Important Safety Information on page two and accompanying full Prescribing Information.
Serum glucose, serum cholesterol, and triglycerides should be tested before and during TORISEL treatment. TORISEL is likely to result in hyperglycemia and hyperlipemia. This may result in the need for an increase in the dose of, or initiation of, insulin and/or oral hypoglycemic agent therapy and/or lipid-lowering agents, respectively.

TORISEL may result in immunosuppression. Patients should be carefully observed for the occurrence of infections, including opportunistic infections. Pneumocystis jiroveci pneumonia (PJP), including fatalities, has been reported with TORISEL. This may be associated with concomitant use of corticosteroids or other immunosuppressive agents. Prophylaxis of PJP should be considered in patients taking concomitant corticosteroids or other immunosuppressive agents.

Cases of interstitial lung disease, some resulting in death, have occurred. Some patients were asymptomatic or had minimal symptoms. Patients should undergo baseline radiography prior to TORISEL therapy and periodically thereafter, even in the absence of clinical respiratory symptoms. Follow patients closely and, if clinically significant respiratory symptoms develop, consider withholding TORISEL until recovery of symptoms and radiographic improvement of pneumonitis findings. Some patients required TORISEL discontinuation and/or treatment with corticosteroids and/or antibiotics. Opportunistic infections such as PJP should be considered in the differential diagnosis.

Cases of fatal bowel perforation occurred with TORISEL. These patients presented with fever, abdominal pain, metabolic acidosis, bloody stools, diarrhea, and/or acute abdomen.

Cases of rapidly progressive and sometimes fatal acute renal failure not clearly related to disease progression occurred in patients who received TORISEL.

Due to abnormal wound healing, use TORISEL with caution in the perioperative period.

Patients with central nervous system tumors (primary CNS tumor or metastases) and/or receiving anticoagulation therapy may be at an increased risk of developing intracerebral bleeding (including fatal outcomes) while receiving TORISEL.

Live vaccinations and close contact with those who received live vaccines should be avoided. TORISEL may cause fetal harm. Patients and their partners should be advised to avoid pregnancy throughout treatment and for 3 months after TORISEL therapy has stopped. Elderly patients may be more likely to experience certain adverse reactions including diarrhea, edema, and pneumonia.

The most common (incidence ≥30%) adverse reactions observed with TORISEL are rash (47%), asthenia (51%), mucositis (41%), nausea (37%), edema (35%), and anorexia (32%). The most common laboratory abnormalities (incidence ≥30%) are anemia (94%), hyperglycemia (89%), hyperlipemia (87%), hypertriglyceridemia (83%), elevated alkaline phosphatase (68%), elevated serum creatinine (57%), lymphopenia (53%), hypophosphatemia (49%), thrombocytopenia (40%), elevated AST (38%), and leukopenia (32%).

Most common grade 3/4 adverse reactions and laboratory abnormalities included asthenia (11%), dyspnea (9%), hemoglobin decreased (20%), lymphocytes decreased (16%), glucose increased (16%), phosphorus decreased (18%), and triglycerides increased (44%).

Pleural effusion, hemodynamically significant pericardial effusions requiring intervention, convulsions, rhabdomyolysis, Stevens-Johnson Syndrome, complex regional pain syndrome, pancreatitis, cholecystitis, cholelithiasis, and extravasations have been reported during postmarketing use.

Strong inducers of CYP3A4/5 (eg, dexamethasone, rifampin) and strong inhibitors of CYP3A4 (eg, ketoconazole, atazanavir) may decrease and increase concentrations of the major metabolite of TORISEL, respectively. If alternatives cannot be used, dose modifications of TORISEL are recommended.

Avoid St. John’s Wort which may decrease TORISEL plasma concentrations, and grapefruit juice which may increase plasma concentrations of the major metabolite of TORISEL.

The combination of TORISEL and sunitinib resulted in dose-limiting toxicity (grade 3/4 erythematous maculopapular rash, and gout/cellulitis requiring hospitalization).

Please see the accompanying full Prescribing Information for TORISEL.
PATIENT ACCESS TO TORISEL

Access to medicines is a cornerstone of Pfizer’s commitment to health care. For more than 25 years, Pfizer has offered an array of prescription assistance programs to help eligible patients get access to their Pfizer medicines. Today, this assistance is provided through Pfizer RxPathways™, which helps eligible patients get access to their Pfizer medicines by offering a range of support services, including insurance counseling, co-pay help, providing Pfizer medicines for free or at a savings, and more.

Pfizer’s patient assistance programs have helped millions of uninsured and underinsured patients gain access to the medications they need. For more information on Pfizer RxPathways, please visit www.PfizerRxPath.com.

CONTACT & ADDITIONAL INFORMATION

If you are interested in speaking with a Pfizer Oncology representative, please contact Sally Beatty at Sally.Beatty@pfizer.com or (212) 733-6566.

For more information about clinical studies involving temsirolimus currently enrolling in their area, patients and their physicians may call the clinical trial information line at 1-800-718-1021 or visit www.pfizercancertrials.com.

Please see Important Safety Information on pages one and two and accompanying full Prescribing Information.

REFERENCES

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®. (5)

**CONTRAINDICATIONS**

- 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 started 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)

**WARNINGS AND PRECAUTIONS**

- Patients should receive prophylactic intravenous diphenhydramine 25 to 50 mg (or similar antihistamine) approximately 30 minutes before the start of each dose of TORISEL®. (5.1)
- 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. (5.11)
- 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).

**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, hyperlipidemia, hypertriglyceridemia, elevated alkaline phosphatase, elevated serum creatinine, lymphopenia, hypophosphatemia, thrombocytopenia, elevated AST, and leukopenia. (6)

**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)


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**FULL PRESCRIBING INFORMATION**

1 INDICATIONS AND USAGE
TORISEL® is indicated for the treatment of advanced renal cell carcinoma. (1)

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 Predismedication
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/mm³, platelet count <75,000/mm³, 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.

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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 studies with this drug 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 study. Temsirolimus is contraindicated in patients with bilirubin > 1.5×ULN when treated with TORISEL.

2.5 Instructions for Preparation
TORISEL must be stored under refrigeration at 2°C–8°C (36°F–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 (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/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 25°C 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 diethylenephtalate (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, hypertension, asthma, dyspnea, or angioedema, 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), polyethylene 80, or to any other component (including the excipients) of TORISEL.

An H1 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 H1-receptor antagonist (such as diphenhydramine), if not previously administered [see Dosage and Administration (2.2)] and/or an H2-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). A benefit-risk assessment should be done prior to the continuation of temsirolimus therapy in patients with severe or life-threatening reactions.

5.2 Hepatic Impairment
The safety and pharmacokinetics of TORISEL were evaluated in a dose escalation phase 1 study in 110 patients with normal or varying degrees of hepatic impairment. Patients with baseline bilirubin >1.5×ULN experienced greater toxicity than patients with baseline bilirubin <1.5×ULN when treated with TORISEL. The overall frequency of grade 3 adverse reactions and deaths, including deaths due to progressive disease, were greater in patients with baseline bilirubin >1.5×ULN due to increased risk of death [see Contraindications (4)]. Use caution when treating patients with mild hepatic impairment. Concentrations of temsirolimus and its metabolite sirolimus were increased in patients with elevated AST or bilirubin levels. If TORISEL must be given in patients with mild hepatic impairment (bilirubin >1.5×ULN or AST >7×ULN but bilirubin <1.5×ULN), reduce the dose of TORISEL to 15 mg/week [see Dosage and Administration (2.4)].

5.3 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.

5.4 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)]. Pneumocystis jiroveci pneumonia (PJP), including fatalities, has been reported in patients who received temsirolimus. This may be associated with concomitant use of corticosteroids or other immunosuppressive agents. Prophylaxis of PJP should be considered when concomitant use of corticosteroids or other immunosuppressive agents are required.

5.5 Interstitial Lung Disease
Cases of interstitial lung disease, some resulting in death, occurred in patients who received TORISEL. Some patients were asymptomatic, or had minimal symptoms, 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.

It is recommended that patients undergo baseline radiographic assessment by lung computed tomography scan or chest radiograph prior to the initiation of TORISEL therapy. Follow such assessments periodically, even in the absence of clinical respiratory symptoms. It is recommended that patients be followed closely for occurrence of clinical respiratory symptoms. If clinically significant respiratory symptoms develop, consider withholding TORISEL administration and initiating corticosteroid therapy. The use of corticosteroids and other respiratory agents may be associated with concomitant use of corticosteroids or other immunosuppressive agents. Prophylaxis of PJP should be considered if concomitant use of corticosteroids or other immunosuppressive agents are required.

5.6 Hyperlipemia
The use of TORISEL is likely to result in increases in serum triglycerides and cholesterol. In the phase 3 trial, 67% of patients receiving TORISEL had at least one elevated serum cholesterol value and 85% 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.

5.7 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.

5.8 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.
5.9 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.

5.10 Intracerebral Hemorrhage
Patients with central nervous system tumors (primary CNS tumor or metastases) and/or receiving antiangiogenic therapy may be at an increased risk of developing intracerebral bleeding (including fatal outcomes) while receiving TORISEL.

5.11 Co-administration with Inducers or Inhibitors of CYP3A Metabolism
Agents Inducing CYP3A Metabolism:
Strong inducers of CYP3A4/5 such as dexamethasone, carbamazepine, phenytoin, phenobarbital, rifampin, rifabutin, and rifampicin may decrease exposure of the active metabolite, sirolimus. If alternative treatment cannot be administered, a dose adjustment should be considered. St. John's Wort may decrease TORISEL plasma concentrations unpredictably. Patients receiving TORISEL should not take St. John's Wort concomitantly [see Dosage and Administration (2.4) and Drug Interactions (7.1)].

Agents Inhibiting CYP3A Metabolism:
Strong CYP3A4 inhibitors such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, neflunin, ritonavir, saquinavir, and telithromycin may increase blood concentrations of the active metabolite sirolimus. If alternative treatments cannot be administered, a dose adjustment should be considered [see Dosage and Administration (2.4) and Drug Interactions (7.2)].

5.12 Concomitant use of TORISEL with sunbathing
The combination of TORISEL and sunbathing resulted in dose-limiting toxicity. Dose-limiting toxicities (Grade 3/4 erythematous maculopapular rash, and goitrous [cellulitis requiring hospitalization]) were observed in two out of three patients treated in the first cohort of a phase 1 study at doses of TORISEL 15 mg IV per week and sunbath 25 mg oral per day (Days 1-28 followed by a 2-week rest).

5.13 Vaccinations
The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with TORISEL. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

5.14 Use in Pregnancy
There are no adequate and well-controlled studies of TORISEL in pregnant women. However, based on its mechanism of action, TORISEL may cause fetal harm when administered to a pregnant woman. Temsirolimus administered daily as an oral formulation caused embryo-fetal and intrauterine toxicities in rats and rabbits at human sub-therapeutic exposures. If this drug is used during pregnancy or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant through treatment and for 3 months after TORISEL therapy has stopped [see Use in Specific Populations (8.1)].

Men should be counseled regarding the effects of TORISEL on the fetus and sperm prior to starting treatment [see Nonclinical Toxicology (13.1)]. Men with partners of childbearing potential should use reliable contraception throughout treatment and are recommended to continue this for 3 months after the last dose of TORISEL.

5.15 Elderly Patients
Based on the results of a phase 3 study, elderly patients may be more likely to experience certain adverse reactions including diarrhea, edema, and pneumonia [see Use in Specific Populations (8.5)].

5.16 Monitoring Laboratory Tests
In the randomized, phase 3 trial, complete blood counts (CBCs) were checked weekly, and chemistry panels were checked every two weeks. Laboratory monitoring for patients receiving TORISEL may need to be performed more or less frequently at the physician's discretion.

6 ADVERSE REACTIONS
The following serious adverse reactions have been associated with TORISEL in clinical trials and are discussed in greater detail in other sections of the label [see Warnings and Precautions (5)].

- Hypersensitivity/Infusion Reactions [see Warnings and Precautions (5.1)]
- Hepatic Impairment [see Warnings and Precautions (5.2)]
- Hyperglycemia/Glucose Intolerance [see Warnings and Precautions (5.3)]
- Infections [see Warnings and Precautions (5.4)]
- Intestinal Lung Disease [see Warnings and Precautions (5.5)]
- Hyperlipemia [see Warnings and Precautions (5.6)]
- Bowel Perforation [see Warnings and Precautions (5.7)]
- Renal Failure [see Warnings and Precautions (5.8)]
- Wound Healing Complications [see Warnings and Precautions (5.9)]
- Intracerebral Hemorrhage [see Warnings and Precautions (5.10)]

The most common (>30%) adverse reactions observed with TORISEL are rash, asthenia, mucositis, nausea, edema, and anorexia. The most common (>30%) laboratory abnormalities observed with TORISEL are anemia, hyperglycemia, hyperlipidemia, hypertriglyceridemia, lymphopenia, elevated alkaline phosphatase, elevated serum creatinine, hypophosphatemia, thrombocytopenia, elevated AST, and leukopenia.

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

In the phase 3 randomized, open-label study of interferon alfa (IFN-α) alone, TORISEL alone, and TORISEL and IFN-α, a total of 616 patients were treated. Two hundred patients received IFN-α weekly, 208 received TORISEL 25 mg weekly, and 208 patients received a combination of TORISEL and IFN-α weekly [see Clinical Studies (14)].

The following selected adverse reactions were reported less frequently (<10%).
Gastrointestinal Disorders – Gastrointestinal hemorrhage (1%), rectal hemorrhage (1%).
Eye Disorders – Conjunctivitis (including lacrimation disorder) (8%).
Immune System – Angioinoceratic edema-type reactions (including delayed reactions occurring two months following initiation of therapy) have been observed in some patients who received TORISEL and ACE inhibitors concomitantly.

Infections – Pneumonia (8%), upper respiratory tract infection (7%), wound infection/post-operative wound infection (1%), sepsis (1%).

General Disorders and Administration Site Conditions – Diabetes mellitus (5%), Respiratory, Thoracic and Mediastinal Disorders – Pleural effusion (4%).

Vascular – Hypertension (7%), venous thromboembolism (including deep vein thrombosis and pulmonary emboli [including fatal outcomes]) (2%), thrombophlebitis (1%), pericardial effusion (1%).

Nervous System Disorders – Convulsion (1%).

Treatment with the combination of TORISEL 15 mg and IFN-α was associated with an increased incidence of multiple adverse reactions and did not result in a significant increase in overall survival when compared with IFN-α alone.

Table 1 shows the percentage of patients experiencing treatment emergent adverse reactions. Reactions reported in at least 10% of patients who received TORISEL 25 mg alone or IFN-α alone are listed. Table 2 shows the percentage of patients experiencing selected laboratory abnormalities. Data for the same adverse reactions and laboratory abnormalities in the IFN-α alone arm are shown for comparison:

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TORISEL</th>
<th>IFN-α</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>106 (51)</td>
<td>23 (11)</td>
</tr>
<tr>
<td>Edema&lt;sup&gt;a&lt;/sup&gt;</td>
<td>73 (35)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Pain</td>
<td>59 (28)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>52 (24)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>39 (19)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Headache</td>
<td>31 (15)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Chemotherapeutic</td>
<td>34 (16)</td>
<td>2 (1)</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucositis&lt;sup&gt;b&lt;/sup&gt;</td>
<td>86 (41)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>68 (32)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>77 (32)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>56 (27)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>44 (22)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Constipation</td>
<td>42 (20)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>40 (19)</td>
<td>4 (2)</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back Pain</td>
<td>41 (20)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>37 (18)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>16 (8)</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>58 (28)</td>
<td>18 (9)</td>
</tr>
<tr>
<td>Cough</td>
<td>53 (25)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>25 (12)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>97 (47)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>40 (19)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Dry Skin</td>
<td>28 (14)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysgeusia&lt;sup&gt;c&lt;/sup&gt;</td>
<td>41 (20)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>24 (12)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Depression</td>
<td>9 (4)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Includes edema, facial edema, and peripheral edema.

<sup>b</sup> Includes aphthous stomatitis, glossitis, mouth ulceration, mucositis, and stomatitis.

<sup>c</sup> Includes infections not otherwise specified (NOS) and the following infections that occurred infrequently as distinct entities: abscess, bronchitis, cellulitis, herpes simplex, and herpes zoster.

<sup>d</sup> Includes cystitis, dysuria, hematuria, urinary frequency, and urinary tract infection.

<sup>e</sup> Includes eczema, exfoliative dermatitis, maculopapular rash, pruritic rash, postular rash, rash (NOS), and vesiculobullous rash.

<sup>f</sup> Includes taste loss and taste perversion.
Temsirolimus is an inhibitor of mTOR, an antineoplastic agent.

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Temsirolimus is a white to off-white powder with a molecular formula of C\textsubscript{38}H\textsubscript{44}N\textsubscript{4}O\textsubscript{21}. It has no ionizable functional groups, and its solubility is independent of pH.

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Temsirolimus, an inhibitor of mTOR, is an antineoplastic agent.
Drug-Transport Systems - P-glycoprotein

Temsirolimus is a substrate of the efflux transporter P-glycoprotein (Pgp) in vitro. If TORISEL is administered with drugs that inhibit Pgp, increased concentrations of temsirolimus are likely and caution should be exercised. In vitro, temsirolimus inhibited human Pgp (IC50 value of 2 μM). If TORISEL is administered with drugs that are substrates of Pgp, increased concentrations of the substrate drug are likely and caution should be exercised.

Effects of Age and Gender

In population pharmacokinetic-based data analyses, no relationship was apparent between drug exposure and patient age or gender.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with temsirolimus. However, sirolimus, the major metabolite of temsirolimus in humans, was carcinogenic in mice and rats. The following effects were reported in mice and/or rats in the carcinogenicity studies conducted with sirolimus: lymphoma, hepatocellular adenoma and carcinoma, and testicular adenoma.

Temsirolimus was not genotoxic in a battery of in vitro (bacterial reverse mutation in Salmonella typhimurium and Escherichia coli, forward mutation in mouse lymphoma cells, and chromosome aberrations in Chinese hamster ovary cells) and in vivo (mouse micronucleus) assays. In male rats, the following fertility effects were observed: decreased number of pregnancies, decreased sperm concentration and motility, decreased reproductive organ weights, and testicular tubular degeneration. These effects were observed at oral temsirolimus doses >3 mg/kg/day (approximately 0.2-fold the human recommended intravenous dose). Fertility was absent at 30 mg/kg/day.

In female rats, an increased incidence of pre- and post-implantation losses occurred at oral doses >4.2 mg/kg/day (approximately 0.3-fold the human recommended intravenous dose), resulting in decreased numbers of live fetuses.

14 CLINICAL STUDIES

A phase 3, multi-center, three-arm, randomized, open-label study was conducted in previously untreated patients with advanced renal cell carcinoma (clear cell and non-clear cell histologies). The objectives were to compare Overall Survival (OS), Progression-Free Survival (PFS), Objective Response Rate (ORR), and safety in patients receiving IFN-α to those receiving TORISEL or TORISEL plus IFN-α. Patients in this study had 3 or more of 6 pre-selected prognostic risk factors (less than one year from time of initial renal cell carcinoma diagnosis to randomization, Karnofsky performance status of 60 or 70, hemoglobin less than the lower limit of normal, corrected calcium of greater than 10 mg/dL, lactate dehydrogenase >1.5 times the upper limit of normal, and more than one metastatic organ site). Patients were stratified for prior nephrectomy status within three geographic regions and were randomly assigned (1:1:1) to receive IFN-α alone (n = 267), TORISEL alone (25 mg weekly; n = 209), or the combination arm (n = 210). The ITT population for this interim analysis included 626 patients. Demographics were comparable between the three treatment arms with regard to age, gender, and race. The mean age of all groups was 59 years (range 23–86). Sixty-nine percent were male and 31% were female. The racial distribution for all groups was 91% White, 4% Black, 2% Asian, and 3% other. Sixty-seven percent of patients had a history of prior nephrectomy.

The median duration of treatment in the TORISEL arm was 17 weeks (range 1–126 weeks). The median duration of treatment on the IFN arm was 8 weeks (range 1–124 weeks).

There was a statistically significant improvement in OS (time from randomization to death) in the TORISEL arm compared to IFN-α (P = 0.0001) and to the combination arm (P = 0.0002). The combination of TORISEL 15 mg and IFN-α did not result in a significant increase in OS when compared with IFN-α alone. Figure 1 is a Kaplan-Meier plot of OS in this study. The evaluations of PFS (time from randomization to disease progression or death) and ORR, were based on blinded independent radiologic assessment of tumor response. Efficacy results are summarized in Table 4.

Table 4 - Summary of Efficacy Results of TORISEL vs. IFN-α

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TORISEL n = 209</th>
<th>IFN-α n = 207</th>
<th>P-value*</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Overall Survival</td>
<td>10.9 (8.6, 12.7)</td>
<td>7.3 (6.1, 8.8)</td>
<td>0.0078*</td>
<td>0.73 (0.58, 0.92)</td>
</tr>
<tr>
<td>(Months (95% CI))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Progression-Free</td>
<td>5.5 (3.9, 7.0)</td>
<td>3.1 (2.2, 3.8)</td>
<td>0.0001**</td>
<td>0.66 (0.53, 0.81)</td>
</tr>
<tr>
<td>Survival (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Response Rate</td>
<td>8.6 (4.8, 12.4)</td>
<td>4.8 (1.9, 7.8)</td>
<td>0.1232**</td>
<td>NA</td>
</tr>
<tr>
<td>(% (95% CI))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cr = confidence interval; NA = not applicable
* A comparison is considered statistically significant if the p-value is <0.0159 (O’Brien-Renier boundary at 466 deaths).
** Not adjusted for multiple comparisons.
* Based on log-rank test stratified by prior nephrectomy and region.
** Based on Cox proportional hazard model stratified by prior nephrectomy and region.
† Based on Cochran-Mantel-Haenszel test stratified by prior nephrectomy and region.

Figure 1: Kaplan-Meier Curves for Overall Survival – TORISEL vs. IFN
This may require initiation of, or increase in the dose of, lipid-lowering agents. Patients are likely to experience elevated triglycerides and/or cholesterol during TORISEL treatment. Patients should be directed to report promptly any new or worsening respiratory symptoms to their physician. Including those who are taking or have taken corticosteroids or immunosuppressive agents, should be directed to report promptly any new or worsening respiratory symptoms to their physician.

15 RECOMMENDATIONS

• Increased Blood Triglycerides and/or Cholesterol

Patients are likely to experience increased blood triglyceride and/or cholesterol levels during TORISEL treatment. This may require initiation of, or increase in the dose of, lipid-lowering agents.[see Warnings and Precautions (5.6)].

• Bowel Perforation

Patients should be warned of the possibility of bowel perforation. Patients should be directed to report promptly any new or worsening abdominal pain or blood in their stools.[see Warnings and Precautions (5.7)].

• Renal Failure

Patients should be informed of the risk of renal failure.[see Warnings and Precautions (5.8)].

• Wound Healing Complications

Patients should be advised of the possibility of abnormal wound healing if they have surgery within a few weeks of initiating therapy or during therapy.[see Warnings and Precautions (5.9)].

• Intracerebral Bleeding

Patients with CNS tumors and/or receiving anticoagulants should be informed of the increased risk of developing intracerebral bleeding (including fatal outcomes) while on TORISEL.[see Warnings and Precautions (5.10)].

• Medications that can interfere with TORISEL

Some medicines can interfere with the breakdown or metabolism of TORISEL. In particular, patients should be directed to inform their physician if they are taking any of the following: Protease inhibitors, anti-epileptic medicines including carbamazepine, phenytoin, and barbiturates, St. John’s Wort, rifampicin, rifabutin, netazodon or selective serotonin re-uptake inhibitors used to treat depression, antibiotics or antifungal medicines used to treat infections.[see Warnings and Precautions (5.11)].

• Vaccinations

Patients should be advised that vaccinations may be less effective while being treated with TORISEL. In addition, the use of live vaccines, and close contact with those who have received live vaccines, while on TORISEL should be avoided.[see Warnings and Precautions (5.13)].

• Pregnancy

TORISEL can cause fetal harm. Women of childbearing potential should be advised to avoid becoming pregnant throughout treatment and for 3 months after TORISEL therapy has stopped. Men with partners of childbearing potential should use reliable contraception throughout treatment and are recommended to continue this for 3 months after the last dose of TORISEL.[see Warnings and Precautions (5.14)].

• Elderly Patients

Elderly patients should be advised that they may be more likely to experience certain adverse reactions including diarrhea, edema, and pneumonia [see Warnings and Precautions (5.15)]. This product’s label may have been updated. For full prescribing information, please visit www.pfizer.com.

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