Cytochrome P450 3A4 (CYP3A4) is the major isozyme responsible for the formation of 5 temsirolimus metabolites. Sirolimus, an active metabolite of temsirolimus, is the principal metabolite in humans following intravenous treatment and is also known to be metabolized by the CYP3A4 isoenzymes. The following tables are not all-inclusive. Care should be exercised when drugs or other substances that affect CYP3A4 are administered concomitantly with temsirolimus.

**CYP3A4/5 Inducers**

Strong inducers of CYP3A4/5 may decrease exposure of the active metabolite, sirolimus. Therefore, concomitant treatment with agents that have strong CYP3A4/5 induction potential should be avoided. If alternative treatment cannot be administered, a TORISEL dose increase up to 50 mg per week should be considered.

<table>
<thead>
<tr>
<th>Example of CYP3A Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic</strong></td>
</tr>
<tr>
<td>Anticonvulsants</td>
</tr>
<tr>
<td>carbamazepine</td>
</tr>
<tr>
<td>phenobarbital</td>
</tr>
<tr>
<td>phenytoin</td>
</tr>
<tr>
<td>Antibiotics</td>
</tr>
<tr>
<td>rifampin/rifampicin</td>
</tr>
<tr>
<td>rifabutin</td>
</tr>
<tr>
<td>Other Agents</td>
</tr>
<tr>
<td>St. John’s Wort (Hypericum perforatum)</td>
</tr>
<tr>
<td>dexamethasone</td>
</tr>
</tbody>
</table>

Co-administration of TORISEL with rifampin, a potent CYP3A4/5 inducer, had no significant effect on temsirolimus $C_{\text{max}}$ (maximum concentration) and AUC (area under the concentration versus the time curve) after intravenous administration but decreased sirolimus $C_{\text{max}}$ by 65% and AUC by 56% compared to TORISEL alone.

TORISEL is a registered trademark of Wyeth Pharmaceuticals Inc. Other brands listed are the trademarks of their respective owners and are not trademarks of Wyeth Pharmaceuticals Inc.
CYP3A4 Inhibitors
Strong CYP3A4 inhibitors may increase blood concentrations of the active metabolite, sirolimus. Therefore, concomitant treatment with agents that have strong CYP3A4 inhibition potential should be avoided. If alternative treatment cannot be administered, a TORISEL dose reduction to 12.5 mg per week should be considered.1

<table>
<thead>
<tr>
<th>Examples of CYP3A Inhibitors1</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic</strong></td>
<td><strong>Brand Name</strong></td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td><strong>Antifungals</strong></td>
</tr>
<tr>
<td>nefazodone</td>
<td>Sporanox®</td>
</tr>
<tr>
<td><strong>Antivirals</strong></td>
<td><strong>Macrolide Antibiotics</strong></td>
</tr>
<tr>
<td>atazanavir</td>
<td>Biaxin®</td>
</tr>
<tr>
<td>indinavir</td>
<td>Ketek®</td>
</tr>
<tr>
<td>nelfinavir</td>
<td><strong>Other Agents</strong></td>
</tr>
<tr>
<td>ritonavir</td>
<td>Adj.®</td>
</tr>
<tr>
<td>saquinavir</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Antivirals</strong></td>
<td><strong>Macrolide Antibiotics</strong></td>
</tr>
<tr>
<td>clarithromycin</td>
<td><strong>Other Agents</strong></td>
</tr>
<tr>
<td>telithromycin</td>
<td>Grapefruit juice</td>
</tr>
</tbody>
</table>

Co-administration of TORISEL with ketoconazole, a potent CYP3A4 inhibitor, had no significant effect on temsirolimus $C_{\text{max}}$ or AUC; however, sirolimus AUC increased 3.1-fold, and $C_{\text{max}}$ increased 2.2-fold compared to TORISEL alone.1
TORISEL is indicated for the treatment of advanced renal cell carcinoma (RCC).

**Important Safety Information**

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

- Serum glucose, serum cholesterol, and triglycerides should be tested before and during treatment with TORISEL.
  - The use of 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.

- The use of TORISEL may result in immunosuppression. Patients should be carefully observed for the occurrence of infections, including opportunistic infections.

- Cases of interstitial lung disease, some resulting in death, have occurred. Some patients were asymptomatic and others presented with symptoms. Some patients required discontinuation of TORISEL and/or treatment with corticosteroids and/or antibiotics.

- 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.

- Patients and their partners should be advised to avoid pregnancy throughout treatment and for 3 months after TORISEL therapy has stopped.

- 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%).

- In the randomized, phase 3 trial, complete blood counts (CBCs) were checked weekly, and chemistry panels were checked every 2 weeks. Laboratory monitoring for patients receiving TORISEL may need to be performed more or less frequently at the physician’s discretion.

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

- 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.

- St. John’s Wort may decrease TORISEL plasma concentrations, and grapefruit juice may increase plasma concentrations of the major metabolite of TORISEL, and therefore both should be avoided.

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

Please see accompanying full Prescribing Information.
TORISEL is administered as a fixed, weekly 25 mg IV infusion

- The recommended dose of TORISEL for advanced RCC is 25 mg infused over a 30- to 60-minute period once a week\(^1\)
- Treatment should continue until disease progression or unacceptable toxicity occurs\(^1\)
- Patients should receive prophylactic intravenous diphenhydramine 25 to 50 mg (or similar antihistamine) approximately 30 minutes before the start of each dose of TORISEL\(^1\)
- If a patient develops a hypersensitivity reaction, stop the infusion and observe for at least 30 to 60 minutes. At the physician's discretion, treat with an \(H_1\) antagonist, if not previously administered, and/or an \(H_2\) antagonist. The infusion may then be resumed at a slower rate (up to 60 minutes).
- 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 been 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\(^1\)
- Consider a TORISEL dose reduction to 12.5 mg/week if a strong CYP3A4 inhibitor is to be administered. Consider a TORISEL dose increase up to 50 mg/week if a strong CYP3A4 inducer is to be administered\(^1\)
- TORISEL must be stored under refrigeration at 2°C to 8°C (36°F to 46°F) and protected from light\(^1\)
- TORISEL must be diluted twice before administration\(^1\)

Please see inside for Important Safety Information.

Please see accompanying full Prescribing Information.

Reference: 1. TORISEL® Kit (temsirolimus) Prescribing Information, Wyeth Pharmaceuticals Inc.
TORISEL® Kit (temsirolimus) injection

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

1 INDICATIONS AND USAGE
TORISEL® is a kinase inhibitor 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 is 25 mg infused over a 30-60 minute period once a week. Treat until disease progression or unacceptable toxicity. (2.1)

2.2 Premedication
Antihistamine pre-treatment is recommended. (2.2)

2.3 Dosage Interruption/Adjustment
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)

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

4 CONTRAINDICATIONS
None. (4)

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions
To treat hypersensitivity reactions stop TORISEL and treat with an antihistamine. TORISEL may be restarted at physician discretion at a slower rate. (5.1)

5.2 Hyperglycemia and hyperlipemia are likely and may require treatment. Monitor glucose and lipid profiles. (5.2, 5.5)

5.3 Infections may result from immunosuppression. (5.3)

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. (5.4)

5.5 Bowel perforation may occur. Evaluate fever, abdominal pain, bloody stools, and/or acute abdomen promptly. (5.6)

5.6 Renal failure, sometimes fatal, has occurred. Monitor renal function at baseline and while on TORISEL. (5.7)

5.7 Due to abnormal wound healing, use TORISEL with caution in the perioperative period. (5.8)

5.8 Live vaccinations and close contact with those who received live vaccines should be avoided. (5.12)

5.9 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.

Revised: 09/2008

FULL PRESCRIBING INFORMATION: CONTENTS*
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Advanced Renal Cell Carcinoma
2.2 Premedication
2.3 Dosage Interruption/Adjustment
2.4 Dose Modification Guidelines
2.5 Instructions for Preparation and Administration
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity Reactions
5.2 Hyperglycemia/Glucose Intolerance
5.3 Infections
5.4 Interstitial Lung Disease
5.5 Hyperlipemia
5.6 Bowel Perforation
5.7 Renal Failure
5.8 Wound Healing Complications
5.9 Intracerebral Hemorrhage
5.10 Co-administration with Inducers or Inhibitors of CYP3A Metabolism
5.11 Concomitant use of TORISEL with sunitinib
5.12 Vaccinations
5.13 Pregnancy
5.14 Monitoring Laboratory Tests
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
7 DRUG INTERACTIONS
7.1 Agents Inducing CYP3A Metabolism
7.2 Agents Inhibiting CYP3A Metabolism
7.3 Interactions with Drugs Metabolized by CYP2D6
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.
Concomitant Strong CYP3A4 Inducers: The concomitant use of strong CYP3A4 inhibitors should be avoided (e.g. ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, neflinavir, 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)]

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 inline 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 patients with known hypersensitivity to temsirolimus or its metabolites (including sirolimus), polysorbate 80, or to any other component (including the excipients) of TORISEL.

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 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 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 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.

5.3 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.

5.9 Intracerebral Hemorrhage
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.

5.10 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 rifampacin 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 exposure of the active metabolite, sirolimus. If alternative treatment cannot be administered, a dose adjustment should be considered. St. John's Wort may decrease exposure of the active metabolite, sirolimus. If alternative treatment cannot be administered, a dose adjustment should be considered.

Agents Inhibiting CYP3A Metabolism:
Strong CYP3A4 inhibitors such as atazanavir, clarithromycin, indinavir,itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin may increase exposure of the active metabolite sirolimus. If alternative treatments cannot be administered, a dose adjustment should be considered.

5.11 Concomitant use of TORISEL with sunitinib
The combination of TORISEL and sunitinib resulted in dose-limiting toxicity. Dose-limiting toxicities (Grade 3/4 erythematous maculopapular rash, and gout/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 sunitinib 25 mg oral per day (Days 1-28 followed by a 2-week rest).
TORISEL® Kit
(temsirolimus)
injection

5.12 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.

5.13 Pregnancy
Pregnancy Category D
Temsirolimus administered daily as an oral formulation caused embryo-fetal and intrauterine toxicities in rats and rabbits at human sub-therapeutic exposures. Embryo-fetal adverse effects in rats consisted of reduced fetal weight and reduced ossifications, and in rabbits included reduced fetal weight, omphalocele, bifurcated sternabrae, notched ribs, and incomplete ossifications.

In rats, the intrauterine and embryo-fetal adverse effects were observed at the oral dose of 2.7 mg/m²/day (approximately 0.04-fold the AUC in cancer patients at the human recommended dose). In rabbits, the intrauterine and embryo-fetal adverse effects were observed at the oral dose of ≥ 7.2 mg/m²/day (approximately 0.12-fold the AUC in cancer patients at the recommended human dose).

Women of childbearing potential should be advised to avoid becoming pregnant throughout treatment and for 3 months after TORISEL therapy has stopped. Temsirolimus can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. 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.

5.14 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 Reactions [see Warnings and Precautions (5.1)]
Hyperglycemia/Glucose Intolerance [see Warnings and Precautions (5.2)]
Interstitial Lung Disease [see Warnings and Precautions (5.4)]
Hyperlipemia [see Warnings and Precautions (5.5)]
Bowel Perforation [see Warnings and Precautions (5.6)]
Renal Failure [see Warnings and Precautions (5.7)]

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, hyperlipemia, 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)].

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 25 mg n=208</th>
<th>IFN-α n=200</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema</td>
<td>42 (20)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>77 (37)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>56 (27)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>44 (21)</td>
<td>9 (4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TORISEL 25 mg n=208</th>
<th>IFN-α n=200</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>40 (19)</td>
<td>4 (2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>IFN-α n=200</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murphy’s disease</td>
<td>28 (14)</td>
</tr>
<tr>
<td>Alopea</td>
<td>29 (15)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>29 (15)</td>
</tr>
</tbody>
</table>
Vascular - Hypertension occurred in 14 patients (7%); venous thromboembolism (including deep vein thrombosis and pulmonary embolus) occurred in 5 patients (2%); thrombophlebitis occurred in 2 patients (1%).

Immune System - Allergic/Hypersensitivity reactions occurred in 15 patients (7%).

Eye Disorders - Conjunctivitis (including lacrimation disorder) occurred in 1 patient (1%).

Gastrointestinal Disorders – Fatal bowel perforation occurred in 1 patient (1%).

8.1 Pregnancy

Pregnancy Category D [see Warnings and Precautions (5.13)].

8.3 Nursing Mothers
It is not known whether TORISEL is excreted into human milk, and due to the potential for tumorigenicity shown for sirolimus (active metabolite of TORISEL) in animal studies, a decision should be made whether to discontinue nursing or discontinue TORISEL, taking into account the importance of the drug to the mother.

8.4 Pediatric Use
The safety and effectiveness of TORISEL in pediatric patients have not been established.

8.5 Geriatric Use
Clinical studies of TORISEL did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects.

8.6 Renal Impairment
No clinical studies were conducted with TORISEL in patients with decreased renal function. Less than 5% of total radioactivity was excreted in the urine following a 25 mg intravenous dose of [14C]-labeled temsirolimus in healthy subjects. Renal impairment is not expected to markedly influence drug exposure, and no dosage adjustment of TORISEL is recommended in patients with renal impairment. TORISEL has not been studied in patients undergoing hemodialysis.

8.7 Hepatic Impairment
Temsiriolimus is cleared predominantly by the liver. No data are currently available regarding the influence of hepatic dysfunction on temsirolimus disposition.

10 OVERDOSAGE
There is no specific treatment for TORISEL intravenous overdose. TORISEL has been administered to patients with cancer in phase 1 and 2 trials with repeated intravenous doses as high as 220 mg/m2. The risk of several serious adverse events, including thrombosis, bowel perforation, cancer in phase 1 and 2 trials with repeated intravenous overdoses, was increased with doses of TORISEL greater than 25 mg.

There is no specific treatment for TORISEL intravenous overdose. After the TORISEL (temsirolimus) injection vial has been diluted with DILUENT for TORISEL®, in accordance with the instructions in section 2.5, the solution contains 35.2% alcohol.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Temsiriolimus is an inhibitor of mTOR (mammalian target of rapamycin). Temsirolimus binds to an intracellular protein (FKBP-12), and the protein-drug complex inhibits the activity of mTOR that controls cell division. Inhibition of mTOR activity resulted in a G1 growth arrest in treated tumor cells. When mTOR was inhibited, its ability to phosphorylate p70S6k and S6 ribosomal protein, which are downstream of mTOR in the PI3 kinase/AKT pathway was blocked. In in vitro studies using renal cell carcinoma cell lines, temsirolimus inhibited the activity of mTOR and resulted in reduced levels of the hypoxia-inducible factors HIF-1 and HIF-2 alpha, and the vascular endothelial growth factor.

12.3 Pharmacokinetics
Absorption
Following administration of a single 25 mg dose of TORISEL in patients with cancer, mean temsirolimus C_{max} in whole blood was 585 ng/mL (coefficient of variation, CV =14%), and mean AUC in blood was 1627 ng·h/mL (CV=26%). Typically C_{max} occurred at the end of infusion. Over the dose range of 1 mg to 25 mg, temsirolimus exposure increased in a less than dose proportional manner while sirolimus exposure increased proportionally with dose. Following a single 25 mg intravenous dose in patients with cancer, sirolimus AUC was 2.7-fold that of temsirolimus AUC, due principally to the longer half-life of sirolimus.

Distribution
Following a single 25 mg intravenous dose, mean steady-state volume of distribution of temsirolimus in whole blood of patients with cancer was 172 liters. Both temsirolimus and sirolimus are extensively partitioned into formed blood elements.

Metabolism
Cytochrome P450 3A4 is the major isozyme responsible for the formation of five temsirolimus metabolites. Sirolimus, an active metabolite of temsirolimus, is the principal metabolite in humans following intravenous treatment. The remainder of the
metabolites account for less than 10% of radioactivity in the plasma. In human liver microsomes temsirolimus was an inhibitor of CYP2D6 and 3A4. However, there was no effect observed in vivo when temsirolimus was administered with desipramine (a CYP2D6 substrate), and no effect is anticipated with substrates of CYP3A4 metabolism.

Elimination
Elimination is primarily via the feces. After a single IV dose of 

\[ ^{14}C \] -temsirolimus approximately 82% of total radioactivity was eliminated within 14 days, with 4.6% and 78% of the administered radioactivity recovered in the urine and feces, respectively. Following a single 25 mg dose of TORISEL in patients with cancer, temsirolimus mean (CV) systemic clearance was 16.2 (22%) L/h. Temsirolimus exhibits a bi-exponential decline in whole blood concentrations and the mean half-lives of temsirolimus and sirolimus were 17.3 hr and 54.6 hr, respectively.

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/m²/day (approximately 0.2-fold the human recommended intravenous dose). Fertility was absent at 30 mg/m²/day. In female rats, an increased incidence of pre- and post-implantation losses occurred at oral doses ≥ 4.2 mg/m²/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 RCC 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, 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=207), 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 25 mg arm compared to IFN-α. The combination of TORISEL 15 mg and IFN-α did not result in a significant increase in overall survival 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 3.

<table>
<thead>
<tr>
<th>Table 3: Summary of Efficacy Results of TORISEL vs. IFN-α</th>
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<tbody>
<tr>
<td>Parameter</td>
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<tr>
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</tr>
<tr>
<td>Median Overall Survival Months (95% CI)</td>
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<tr>
<td>Median Progression-Free Survival Months (95% CI)</td>
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<tr>
<td>Overall Response Rate % (95% CI)</td>
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</tbody>
</table>

CI = confidence interval; NA = not applicable
* A comparison is considered statistically significant if the p-value is <0.0159 (O’Brien-Fleming boundary at 446 deaths).
** Not adjusted for multiple comparisons.
a Based on log-rank test stratified by prior nephrectomy and region.
b Based on Cox proportional hazard model stratified by prior nephrectomy and region.
c Based on Cochran-Mantel-Haenszel test stratified by prior nephrectomy and region.

Figure 1: Kaplan–Meier Curves for Overall Survival – TORISEL vs. IFN
TORISEL® Kit
(temsirolimus) injection

15 REFERENCES
http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html

16 HOW SUPPLIED/STORAGE AND HANDLING
NDC 0008-1179-01 TORISEL® (temsirolimus) injection, 25 mg/mL NDC 0008-1125-01 DILUENT for TORISEL®, 1.8 mL (deliverable volume) per vial.
These two vials are supplied as a kit in a single carton, and must be stored at 2°-8°C (36°-46°F). Protect from light. U.S. Patent No. 5,362,718

17 PATIENT COUNSELING INFORMATION

• Allergic (Hypersensitivity) Reactions
Patients should be informed of the possibility of serious allergic reactions, including anaphylaxis, despite premedication with antihistamines, and to immediately report any facial swelling or difficulty breathing [see Warnings and Precautions (5.1)].

• Increased Blood Glucose Levels
Patients are likely to experience increased blood glucose levels while taking TORISEL. This may result in the need for initiation of, or increase in the dose of, insulin and/or hypoglycemic agents. Patients should be directed to report any excessive thirst or frequency of urination to their physician [see Warnings and Precautions (5.2)].

• Infections
Patients should be informed that they may be more susceptible to infections while being treated with TORISEL [see Warnings and Precautions (5.3)].

• Interstitial Lung Disease
Patients should be warned of the possibility of developing interstitial lung disease, a chronic inflammation of the lungs, which may rarely result in death [see Warnings and Precautions (5.4)]. Patients should be directed to report promptly any new or worsening respiratory symptoms to their physician.

• Increased Blood Triglycerides and/or Cholesterol
Patients are likely to experience elevated triglycerides and/or cholesterol during TORISEL treatment. This may require initiation of, or increase in the dose of, lipid-lowering agents [see Warnings and Precautions (5.5)].

• 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 (5.6)].

• Renal Failure
Patients should be informed of the risk of renal failure [see Warnings and Precautions (5.7)].

• 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 (5.8)].

• 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 (5.9)].

• 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, nefazodone or selective serotonin re-uptake inhibitors used to treat depression, antibiotics or antifungal medicines used to treat infections [see Warnings and Precautions (5.10)].

• 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 (5.12)].

• 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 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 (5.13)].

Wyeth®
Wyeth Pharmaceuticals Inc.
Philadelphia, PA 19101
Manufactured for: Wyeth Pharmaceuticals Inc. Philadelphia, PA 19101
TORISEL® (temsirolimus) injection is manufactured by: Pierre Fabre Medicament Production, Aquitaine Pharm International, Avenue du Bearn, F64320 Idron, France
DILUENT for TORISEL® is manufactured by: Ben Venue Laboratories, Inc., Bedford, Ohio 44146-0588

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