WHEN PROGNOSTIC RISK IS HIGH—
LET EVIDENCE CHART THE COURSE

In the treatment of advanced RCC,
TORISEL® (temsirolimus) is indicated for the treatment of advanced renal cell carcinoma (RCC).

Please see Important Safety Information throughout and accompanying full Prescribing Information.
TORISEL® (temsirolimus)—powerful 1st-line evidence in poor-risk patients with advanced RCC

Most patients had poor prognostic risk in the TORISEL phase 3 Global ARCC study (N=626)

- 94% of patients were poor risk based on ≥3 of 6 preselected risk factors

TORISEL significantly extended OS in poor-risk patients

- Results from the phase 3 Global ARCC study, in which most patients had poor prognostic risk

Important Safety Information

- 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 bilirubin >1.5 x ULN.

- 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.

Important Safety Information (cont’d)

- 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 anemia (11%), dyspnea (9%), hemoglobin decreased (20%), lymphocytes decreased (16%), glucose increased (16%), phosphorus decreased (18%), and triglycerides increased (44%).

Please see Important Safety Information throughout and accompanying full Prescribing Information.
TORISEL® (temsirolimus)—established tolerability profile in poor-risk patients

- The majority of patients did not discontinue TORISEL due to adverse reactions (ARs)
- Additional reasons for discontinuation of TORISEL or IFN/H9251, respectively, included symptomatic deterioration (6.7% vs 14.0%), patient request (3.8% vs 3.0%), death (2.9% vs 5.0%), other (1.0% vs 2.0%), protocol violation (0.5% vs 1.0%), and disease progression (73.6% vs 57.5%).
- TORISEL has an established tolerability profile
  - The most common (incidence ≥30%) ARs observed with TORISEL are rash (47%), asthenia (51%), mucositis (41%), nausea (37%), edema (35%), and anemia (32%)
  - Most common grade 3/4 ARs and laboratory abnormalities included asthenia (11%), dyspnea (9%), hemoglobin decreased (20%), lymphocytes decreased (16%), glucose increased (16%), phosphorus decreased (18%), and triglycerides increased (44%).

Important Safety Information (cont’d)

- 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.
Attributes of administering IV therapy

**Ability to control and verify drug delivery**

TORISEL® (temsirolimus) typically reaches peak exposure and 100% bioavailability by the end of the infusion (30-60 minutes).

**Bioavailability is not affected by gastrointestinal function or food intake.**

**Opportunities for patient management and monitoring**

- Weekly infusion enables regular monitoring of dose adherence and ARs

**Important Safety Information (cont’d)**

- 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.
- Strong inducers of CYP3A4/5 (eg, dexamethasone, rifampin) and strong inhibitors of CYP3A4 (eg, ketoconazole, abacavir) may decrease and increase concentrations of the major metabolite of TORISEL, respectively. If alternatives cannot be used, dose modifications of TORISEL are recommended.
- 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.
- Elderly patients may be more likely to experience certain adverse reactions including diarrhea, edema, and pneumonia.

Support and information from Pfizer Oncology

**Pfizer RxPathways™**

Pfizer RxPathways connects patients with support services that may help them get access to the Pfizer medicines they need.

- **Reimbursement Support Services**—A Pfizer RxPathways counselor will help patients and their health care professionals understand coverage and reimbursement options. This includes benefit verification, in which the counselor will review a patient’s benefits to see how they are covered for the medicine they need. They will research and verify benefits, explain coverage options and policies, as well as investigate and explain the prior authorization process.
- **Patient Assistance**—Through the Pfizer RxPathways Patient Assistance program, uninsured patients may be able to get certain Pfizer medicines for free if they are unable to secure alternate funding. A Pfizer RxPathways counselor will work with the patient to research and apply for alternate insurance options. During that search, up to a 90-day supply of medicine will be provided by Pfizer RxPathways for free if the patient meets certain eligibility criteria.
- **Appeals Process Information**—If a claim is underpaid or denied, Pfizer RxPathways provides patients with information on the appeals process.

*Services vary by product and eligibility.

Pfizer RxPathways™ is a joint program of Pfizer Inc and the Pfizer Patient Assistance Foundation™.

**Important Safety Information (cont’d)**

- 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.
- Pleural effusion, hemodynamically significant pericardial effusions requiring intervention, rhabdomyolysis, Stevens-Johnson Syndrome, complex regional pain syndrome, and extravasations have been reported during postmarketing use.
- 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 Important Safety Information throughout and accompanying full Prescribing Information.
TORISEL—more than 7 years of experience since FDA approval

The total number of patients treated reflects an estimate based on the total number of TORISEL units sold from June 2007 to June 2013 (based on IMS MIDAS sales data). The number of unique patients is based on the average number of vials administered per patient per month, using an independent estimate conducted by IntrinsiQ, LLC from June 2007 to June 2013, and the average duration of treatment was derived from chart studies performed for Pfizer by Medimix International in 2011 and 2013.9

NCCN® recommendation for poor-risk patients with advanced RCC1

- Temsirolimus (TORISEL) has a category 1 recommendation specific to poor-risk patients in 1st-line treatment1

- Category 1: The recommendation is based on high-level evidence and there is uniform National Comprehensive Cancer Network® (NCCN®) consensus1


Important Safety Information (cont’d)

- 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%)

Please see Important Safety Information throughout and accompanying full Prescribing Information.
TORISEL® Kit (temsirolimus) injection

FULL PRESCRIBING INFORMATION: CONTENTS

1 INDICATIONS AND USAGE

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

2 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 for TORISEL. (3)
• To treat hypersensitivity reactions, stop TORISEL and treat with an antihistamine. (2.5)
• Dose modification guidelines (including some life-threatening and rare fatal reactions) can occur early in the first infusion of TORISEL. Patients should be monitored throughout the infusion. (5.1)
• To treat hypersensitivity reactions, stop TORISEL and treat with an antihistamine. TORISEL may be restarted at physician discretion at a slower rate. (5.1)
• Hepatic Impairment: Use caution when treating patients with mild hepatic impairment and reduce dose. (2.4, 5.2)

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

• Hypersensitivity/Infusion Reactions (including some life-threatening and rare fatal reactions) may occur early in the first infusion of TORISEL. Patients should be monitored throughout the infusion. (5.1)
• To treat hypersensitivity reactions, stop TORISEL and treat with an antihistamine. TORISEL may be restarted at physician discretion at a slower rate. (5.1)
• Hepatic Impairment: Use caution when treating patients with mild hepatic impairment and reduce dose. (2.4, 5.2)

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity/Infusion Reactions
• Hypersensitivity reactions may occur early in the first infusion of TORISEL. Patients should be monitored throughout the infusion. (5.1)
• To treat hypersensitivity reactions, stop TORISEL and treat with an antihistamine. TORISEL may be restarted at physician discretion at a slower rate. (5.1)
• Hepatic Impairment: Use caution when treating patients with mild hepatic impairment and reduce dose. (2.4, 5.2)

5.2 Hepatic Impairment
• Hyperglycemia and hyperlipemia are likely and may require treatment. Monitor glucose and lipid profiles. (5.3, 5.6)
• Infections may result from immunosuppression. (5.4)
• Monitor for symptoms or radiographic changes of interstitial lung disease (ILD). If ILD is suspected, discontinue TORISEL, and consider use of corticosteroids and/or antibiotics. (5.5)
• Bowel perforation may occur. Evaluate fever, abdominal pain, bloody stools, and/or acute abdomen promptly. (5.7)
• Renal failure, sometimes fatal, has occurred. Monitor renal function at baseline and while on TORISEL. (5.8)
• Due to abnormal wound healing, use TORISEL with caution in the perioperative period. (5.9)
• Live vaccinations and close contact with those who received live vaccines should be avoided. (5.13)
• Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant. (5.14)
• Elderly patients may be more likely to experience certain adverse reactions, including diarrhea, edema and pneumonia. (5.15)

6 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)

6.1 Clinical Trials Experience

6.2 Post-marketing and Other Clinical Experience

7 DRUG INTERACTIONS

7.1 Agents Inducing CYP3A4 Metabolism
• The concomitant use of strong CYP3A4 inhibitors should be avoided. (7.1, 7.2)

7.2 Agents Inhibiting CYP3A4 Metabolism
• The concomitant use of strong CYP3A4 inhibitors should be avoided. (7.1, 7.2)

7.3 Interactions with Drugs Metabolized by CYP2D6
• The concomitant use of strong CYP2D6 inhibitors should be avoided. (7.1, 7.2)

7.4 Other Contraindications
• The concomitant use of strong CYP3A4 inhibitors should be avoided. (7.1, 7.2)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
• Use caution when treating patients with hepatic impairment. If TORESEL must be given in patients with mild hepatic impairment (bilirubin > 1.5 x ULN but bilirubin <ULN), reduce the dose of TORESEL to 15 mg/week. TORESEL is contraindicated in patients with bilirubin >1.5 x ULN. (see Contraindications (4), Warnings and Precautions (5.2) and Use in Specific Populations (8.7))

8.2 Nursing Mothers

8.3 Pediatric Use

8.4 Renal Impairment

8.5 Hepatic Impairment

10 OVERDOSE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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*Sections or subsections omitted from the full prescribing information are not listed

TORESEL® Kit (temsirolimus) injection

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. (2.1)

2.2 Premedication

Patients should receive prophylactic intravenous diphenhydramine 25 to 50 mg (or similar antihistamine) approximately 30 minutes before the start of each dose of TORISEL. (see Warnings and Precautions (5.1)).
be co-administered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, a TORISEL dose increase from 25 mg/wk should be considered. If patients must be co-administered a strong CYP3A4 inducer, based on pharmacokinetic studies, a TORISEL dose increase from 25 mg/wk 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 considered before restarting the dose used prior to initiation of the strong CYP3A4 inhibitor [see Warnings and Precautions (5.1) and Drug Interactions (7.2)].

Contraindications (4) TORISEL is contraindicated in patients with bilirubin >1.5 x ULN. Factors that may increase the risk of clinically significant respiratory symptoms include advanced interstitial lung disease, prior interstitial lung disease, and use of concomitant drugs (e.g., immunosuppressants, corticosteroids). Use TORISEL with caution in patients with known hypersensitivity to an ingredient of TORISEL, or to any other component (including the excipients) of TORISEL.

DILUTION

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, polyethylene, or polyethylene to avoid excessive loss of product and dyesthesis/hyphalplasia (DEHP) extraction. The administration materials should consist of 0.9% sodium chloride (PVC) tubing with appropriate filters. In the case when a PVC administration set has been used, it should not contain DEHP. An in-line polyethylene filter with a pore size of not greater than 5 microns is recommended for administration to avoid the sight of 10% dextrose in water (0.9% Sodium Chloride Injection, USP) and should be added at the set (i.e., an in-line filter). 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 in-line filter) before the admixture reaches the vein of the patient.

If patients must be co-administered a strong CYP3A4 inducer, based on pharmacokinetic studies, a TORISEL dose increase from 25 mg/wk 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 considered before restarting the dose used prior to initiation of the strong CYP3A4 inhibitor [see Warnings and Precautions (5.1) and Drug Interactions (7.2)].

Contraindications (4) TORISEL is contraindicated in patients with bilirubin >1.5 x ULN. Factors that may increase the risk of clinically significant respiratory symptoms include advanced interstitial lung disease, prior interstitial lung disease, and use of concomitant drugs (e.g., immunosuppressants, corticosteroids). Use TORISEL with caution in patients with known hypersensitivity to an ingredient of TORISEL, or to any other component (including the excipients) of TORISEL.

DILUTION

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, polyethylene, or polyethylene to avoid excessive loss of product and dyesthesis/hyphalplasia (DEHP) extraction. The administration materials should consist of 0.9% sodium chloride (PVC) tubing with appropriate filters. In the case when a PVC administration set has been used, it should not contain DEHP. An in-line polyethylene filter with a pore size of not greater than 5 microns is recommended for administration to avoid the sight of 10% dextrose in water (0.9% Sodium Chloride Injection, USP) and should be added at the set (i.e., an in-line filter). 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 in-line filter) before the admixture reaches the vein of the patient.

If patients must be co-administered a strong CYP3A4 inducer, based on pharmacokinetic studies, a TORISEL dose increase from 25 mg/wk 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 considered before restarting the dose used prior to initiation of the strong CYP3A4 inhibitor [see Warnings and Precautions (5.1) and Drug Interactions (7.2)].

Contraindications (4) TORISEL is contraindicated in patients with bilirubin >1.5 x ULN. Factors that may increase the risk of clinically significant respiratory symptoms include advanced interstitial lung disease, prior interstitial lung disease, and use of concomitant drugs (e.g., immunosuppressants, corticosteroids). Use TORISEL with caution in patients with known hypersensitivity to an ingredient of TORISEL, or to any other component (including the excipients) of TORISEL.
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 TT21a 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 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 throughout 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 Warnings and Precautions (5.7)].

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 (5.3)].

Hypersensitivity/Infusion Reactions [see Warnings and Precautions (5.3)]

Hypoglycemia/Glucocone Intolerance [see Warnings and Precautions (5.3)]

Intestinal Lung Disease [see Warnings and Precautions (5.5)]

Hypertension [see Warnings and Precautions (5.6)]

Bowel Perforation [see Warnings and Precautions (5.7)]

Renal Failure [see Warnings and Precautions (5.8)]

The most common (≥ 30%) adverse reactions observed with TORISEL are rash, asthenia, mucositis, nausea, edema, and anemia. The most common (≥ 30%) laboratory abnormalities observed with TORISEL are anemia, hyperglycemia, 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 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 (14.3)].

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>Table 1 – Adverse Reactions Reported in at Least 10% of Patients Who Received 25 mg IV TORISEL or IFN-α in the Randomized Trial (continued)</th>
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<tbody>
<tr>
<td>Adverse Reaction</td>
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<td>TORISEL 25 mg n = 208</td>
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<td>General disorders</td>
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<td>Respiratory, Thoracic and Mediastinal disorders</td>
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<td>Musculoskeletal and connective tissue disorders</td>
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<td>Respiratory, mediastinal and pleural disorders</td>
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* Common Toxicity Criteria for Adverse Events (CTCAE), Version 3.0.

** Includes edema, facial edema, and peripheral edema

† Includes aphthous stomatitis, glossitis, mouth ulceration, mucositis, and stomatitis

‡ Includes infections not otherwise specified (NOS) and the following infections that occurred infrequently as distinct entities: abscess, bronchitis, cellulitis, herpes simplex, and herpes zoster

§ Includes cystitis, dysuria, hematuria, urinary frequency, and urinary tract infection

∥ Includes eczema, exfoliative dermatitis, maculopapular rash, pruritic rash, pustular rash, rash (NOS), and vesiculobullous rash

* Includes taste loss and taste perversion

The following selected adverse reactions were reported less frequently (<10%).

Gastrointestinal Disorders – Fatal bowel perforation (1%), gastrointestinal hemorrhage (1%), rectal hemorrhage (1%).

Eye Disorders – Conjunctivitis (including lacrimation disorder) (8%).

Immunologic System – Allergic/Hypersensitivity reactions (9%).

Anogenital 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%), impaired wound healing (1%).

Respiratory, Thoracic and Mediastinal Disorders – Pleural effusion (4%), interstitial lung disease/pneumonitis/alveolitis (3%) including fatalities.

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

Nervous System Disorders – Convulsion (1%).

6.2 Post-marketing and Other Clinical Experience
The following adverse reactions have been identified during post approval use of TORISEL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to readily estimate their frequency or establish a causal relationship to drug exposure.

The following adverse reactions have been observed in patients receiving temsirolimus: rhabdomyolysis, Stevens-Johnson Syndrome, and complex regional pain syndrome (reflex sympathetic dystrophy).

There are also post-marketing reports of temsirolimus extravasations resulting in swelling, pain, warmth, and erythema.

7 DRUG INTERACTIONS
7.1 Agents Inducing CYP3A Metabolism
Co-administration of TORISEL with ritonavir-boosted potent CYP3A4/5 inducer, had no significant effect on temsirolimus Cmax (maximum concentration) and AUC (area under the concentration versus the time curve) after intravenous administration, but decreased sirolimus Cmax by 65% and AUC by 56% compared to TORISEL treatment alone. If alternative treatment cannot be administered, a dose adjustment should be considered [see Dosage and Administration (2.4)].
TORISEL® Kit (temsirolimus) Injection

7.2 Agents Inhibiting CYP3A Metabolism CYP3A inhibition by TORISEL (temsirolimus) injection, a potent CYP3A4 inhibitor, had no significant effect on temsirolimus Cmax or AUC; however, sirolimus AUC increased 3.1-fold, and Cmax increased 2.2-fold compared to TORISEL alone. If alternative treatment cannot be administered, a dose adjustment should be considered (see Dosages and Administration (2.4)).

7.3 Interactions with Drugs Metabolized by CYP2D6 The concentration of desipramine, a CYP2D6 substrate, was unaffected when 25 mg of TORISEL was co-administered. No clinically significant effect was anticipated when temsirolimus is co-administered with agents that are metabolized by CYP2D6 or CYP3A4.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Pregnancy Category D [see Warnings and Precautions (5.14)]. Women of childbearing potential should be advised to avoid becoming pregnant throughout treatment and for 6 months after the last dose of TORISEL therapy. 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.

Temsirolimus administered daily in the phase 1 study caused increased intrahepatic and intrahepatic 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, bicornary aortic arch, an omphalocele, and incomplete ossifications. In rats, the intrahepate and embryo-fetal adverse effects were observed at the oral dose of 2.7 mg/kg/day (approximately 0.04-fold the AUC in patients with cancer at the recommended dose). In rabbits, the intrahepate and embryo-fetal adverse effects were observed at the oral dose of 7.2 mg/kg/day (approximately 0.12-fold the AUC in patients with cancer at the recommended dose).

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 Limited data are available on the use of temsirolimus in pediatric patients. The effectiveness of temsirolimus in pediatric patients with cancer has not been established. TORISEL was studied in 71 patients (59 patients ages 1 to 17 years and 12 patients ages 18 to 21 years) with relapsed/refractory solid tumors in a phase 1-2 safety and exploratory pharmacodynamic study. In phase 1, 19 pediatric patients with advanced recurrent/refractory solid tumors received TORISEL at doses ranging from 10 mg/m² to 150 mg/m² as a 60-minute intravenous infusion once weekly in three-week cycles. In phase 2, 52 pediatric patients with recurrent/refractory neuroblastoma, rhabdomyosarcoma, or high grade glioma received TORISEL at a weekly dose of 75 mg/m². One of 19 patients with neuroblastoma achieved a partial response. There were no objective responses in pediatric patients with recurrent/refractory rhabdomyosarcoma or high grade glioma.

Adverse reactions associated with TORISEL were similar to those observed in adults. The most common adverse reactions ≥20% in pediatric patients receiving the 75 mg/m² dose included thrombocytopenia, infections, asthenia/fatigue, fever, pain, leukopenia, rash, anemia, hyperlipidemia, increased cough, stomatitis, anorexia, increased plasma levels of alanine aminotransferase and aspartate aminotransferase, hypercholesterolemia, abdominal pain, headache, hypotension, pyridostigmine, upper respiratory infection, nausea and vomiting, neutropenia, hypokalemia, and hypophosphatemia.

Pharmacokinetics: In phase 1 of the above mentioned pediatric trial, the single dose and multiple dose total systemic exposure (AUC) of temsirolimus and sirolimus were less than dose-proportional over the dose range of 10 to 150 mg/m². In the phase 2 portion, the multiple dose (Day 1, Cycle 2) pharmacokinetics of TORISEL 75 mg/m² were characterized in an additional 35 patients ages 28 days to 21 years (median age of 8 years). The geometric mean body surface adjusted clearance of temsirolimus and sirolimus was 9.45 L/h/m² and 9.26 L/h/m², respectively. The mean elimination half-life of temsirolimus and sirolimus was 31 hours and 44 hours, respectively.

The exposure (AUCs) to temsirolimus and sirolimus were approximately 6-fold and 2-fold higher, respectively than the exposure in adult patients receiving a 25 mg intravenous infusion.

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. 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 Warnings and Precautions (5.15)].

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 TORISEL was evaluated in a dose escalation phase 1 study in 110 patients with normal or varying degrees of hepatic impairment as defined by AST and bilirubin levels and patients with liver transplant (Table 3). Patients with moderate and severe hepatic impairment had increased rates of adverse reactions and deaths, including deaths due to progressive disease, during the study (Table 3).

<table>
<thead>
<tr>
<th>Hepatic Function*</th>
<th>TORISEL Dose Range</th>
<th>Adverse Reactions Grade ≥ 3* n (%)</th>
<th>Death** n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (n = 25)</td>
<td>25 – 175</td>
<td>20 (80.0)</td>
<td>2 (8.0)</td>
</tr>
<tr>
<td>Mild (n = 39)</td>
<td>10 – 25</td>
<td>32 (82.1)</td>
<td>5 (12.8)</td>
</tr>
<tr>
<td>Moderate (n = 20)</td>
<td>10 – 25</td>
<td>19 (95.0)</td>
<td>8 (40.0)</td>
</tr>
<tr>
<td>Severe (n = 24)</td>
<td>7.5 – 15</td>
<td>23 (95.8)</td>
<td>13 (54.2)</td>
</tr>
<tr>
<td>Liver Transplant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 2)</td>
<td></td>
<td>1 (50.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

*Hepatic Function Groups: normal = bilirubin and AST <ULN; mild = bilirubin >1 – 1.5 x ULN or AST >ULN but bilirubin <ULN; moderate = bilirubin >1.5 – 3 x ULN or severe; bilirubin >3 x ULN; liver transplant = any bilirubin and AST.
**Common Terminology Criteria for Adverse Events, version 3.0, including all causality.
***Includes deaths due to progressive disease and adverse reactions.

TORISEL is contraindicated in patients with bilirubin >1.5 x ULN [see Contraindications (4)], and Warnings and Precautions (5.2)]. Use caution when treating patients with mild hepatic impairment. If TORISEL must be given in patients with mild hepatic impairment (bilirubin >1 – 1.5 x ULN or AST >ULN but bilirubin <ULN), reduce the dose of TORISEL to 15 mg/week [see Dosage and Administration (2.4)]. Because there is a need for dosage adjustment based upon hepatic function, assessment of AST and bilirubin levels is recommended before initiation of TORISEL and periodically thereafter.

10 OVERDOSE There is no specific treatment for TORISEL intravenous overdose. TORISEL has been administered to patients in multiple doses 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, interstitial lung disease (ILD), seizure, and psychosis, is increased with doses of TORISEL greater than 25 mg.

11 DESCRIPTION Temsirolimus, an inhibitor of mTOR, is an antiepithelial agent. Temsirolimus is a white to off-white powder with a molecular formula of C32H30N6O11 and a molecular weight of 1030.30. It is non-hygroscopic. Temsirolimus is practically insoluble in water and soluble in alcohol. It has no ionizable functional groups, and its solubility is independent of pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action Temsirolimus is an inhibitor of mTOR (mammalian target of rapamycin). Temsirolimus binds to the intracellular protein (FK BP-12), and the protein-drug complex inhibits the activity of mTOR that controls the expression of HIF-1 and HIF-2 alpha, and the vascular endothelial growth factor.

12.2 Pharmacodynamics Effects on Electrocardiogram: There were no clinically relevant QT changes observed at the recommended dose for TORISEL. In a randomized, single-blinded, crossover study, 58 healthy subjects received TORISEL 25 mg, placebo, and a single oral dose of mof洛xacin 400 mg. A supratherapeutic TORISEL dose was not studied in this randomized QT trial. The largest difference between the upper bound 2-sided 90% CI for the mean difference between TORISEL and placebo-corrected QT interval was less than 10 ms. In a different trial in 69 patients with a hematologic malignancy, TORISEL doses up to 175 mg were studied. No patient with a normal QTc at baseline had an increase in QTcF >40 ms. Additionally, there were no patients with a QTcF interval greater than 500 ms.

12.3 Pharmacokinetics Absorption Following administration of a single 25 mg dose of TORISEL in patients with cancer, mean temsirolimus Cmax 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 Cmax 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 infusion treatment. The remainder of the metabolism accounts 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.
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 total of 626 patients (21.9% of whom were black) were enrolled in this study. The median treatment duration of the TORISEL arm was 17 weeks (range 1–126 weeks). The median duration of treatment on the IFN arm was 12 weeks (range 1–124 weeks).

There was a statistically significant improvement in OS 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 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.

15 REFERENCEs

16 HOW SUPPLIED/STORAGE AND HANDLING
NDC 0008-1179-01 TORISEL® (temsirolimus) injection, 25 mg/mL. Each kit is supplied in a single carton containing one single-use vial of 25 mg/mL of temsirolimus and one DILUENT vial which includes a deliverable volume of 1.8 mL, and must be stored at 2º–8º C (36º–46º F).

17 PATIENT COUNSELING INFORMATION

• Allergic (Hypersensitivity/Infusion) Reactions
Patients should be informed of the possibility of serious allergic reactions, including anaphylaxis (including life threatening and fatal reactions), 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 [5.3]).

• Infections
Patients should be informed that they may be more susceptible to infections while being treated with TORISEL (see Warnings and Precautions [4.4]).

• 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 [5.5]). Patients, 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.

• 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 [5.6]).

• 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 medications 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, nelfinavir 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.