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

Please see Important Safety Information on pages 21 and 22. For additional information about TORISEL, please see the full Prescribing Information following this brochure.
Why TORISEL may be right for you

How TORISEL works
TORISEL is a type of treatment for advanced renal cell carcinoma. TORISEL blocks a specific part of cells, including normal cells and cancerous kidney cells, and helps stop them from growing and dividing. TORISEL may help stop the creation of new blood vessels that feed the advanced renal cell carcinoma cells.

Factors your health care provider (HCP) may consider
TORISEL is a treatment for advanced RCC. Your HCP may choose TORISEL therapy for you for a number of reasons—including those listed below:

• Your overall health status
• Certain medical issues you may have
• Other medicines you may be taking
• Your predicted outcome of disease
• Whether or not certain risks of TORISEL might be higher for you.

For example, some patients, such as those with moderate to severe liver damage, should not receive TORISEL.
How TORISEL can help

TORISEL has been proven to extend survival longer than interferon alpha (a type of immunotherapy) in patients with advanced RCC.

While TORISEL has been shown to extend survival, it is not a cure for advanced RCC.
What you may experience when receiving TORISEL

How TORISEL is given

• TORISEL is administered into the vein (intravenously)
• 30 minutes before you receive TORISEL, your health care provider (HCP) may give you an IV antihistamine to decrease the risk of an allergic reaction
  – Even after you receive an antihistamine, it is possible to have an allergic reaction or even a severe reaction called anaphylaxis, which may result in death
  – Tell your HCP if you are allergic to TORISEL or antihistamines or if you cannot take antihistamines for any other reasons
  – During treatment, tell your HCP if you have any swelling around your face, difficulty breathing, chest pain, flushing, hives, itching, wheezing, crampy abdominal pain, diarrhea, vomiting, irregular heartbeat, light-headedness, anxiety, or weakness in your muscles
• You will receive TORISEL once a week as an IV infusion lasting 30-60 minutes

Intravenously, also called IV, is a common way to give certain medicines. The medicine is in a bag or bottle. A thin tube connects the bag or bottle to a needle. The needle goes into a vein to supply the medicine directly to the bloodstream.

An antihistamine is a medication that can help lower the chance of an allergic reaction. Benadryl® is an example of a common antihistamine.

An allergic reaction occurs when the body reacts to an allergen, such as food or medicine. Some signs include a rash and trouble breathing.

Anaphylaxis is a severe allergic reaction. Common symptoms include abdominal cramps/pain, nausea, diarrhea, hives, itching, flushing, irregular heartbeat, chest discomfort, wheezing, difficulty breathing, light headedness, and anxiety. It may result in death.

Benadryl is a registered trademark of McNeil-PPC, Inc.

Please see Important Safety Information on pages 21 and 22.
For additional information about TORISEL, please see the full Prescribing Information following this brochure.
Where TORISEL is given

TORISEL is given to you by your HCP in a special room called an infusion suite. Infusion suites can be located at any of the following locations:

- Hospitals
- Your HCP’s office
- Clinics
- Infusion centers (facilities that specialize in giving people IV medications)

Infusion suites have comfortable chairs for you to sit in as you receive treatment. You may find that infusion time can provide an opportunity to do the following:

- Read
- Chat with friends or family members
- Take a nap

Connecting with your health care team during infusions

Your TORISEL infusion appointments will bring you into contact with members of your health care team on a weekly basis. This may provide you with regular opportunities to do the following:

- Learn more about RCC and management options
- Ask your health care team questions about your care

Please see Important Safety Information on pages 21 and 22. For additional information about TORISEL, please see the full Prescribing Information following this brochure.
What are some steps I should take before and during TORISEL treatment?

• Before you begin treatment with TORISEL, it’s important that you tell your health care provider (HCP) about ALL MEDICINES you are taking, including:
  – Prescription medications, especially but not limited to: antibiotics, antiseizure medications, antidepressants, antifungals, antivirals, blood thinners, steroids such as dexamethasone, vaccines, and blood pressure medications
  – Nonprescription (over-the-counter) medications
  – Vitamins
  – Herbal supplements including, but not limited to, St. John’s Wort
  – Other cancer medications
• Tell your HCP if you are pregnant, plan to become pregnant, or if you have a partner of childbearing potential
• Tell your HCP if you are allergic to TORISEL or antihistamines
• Tell your HCP if you have any swelling around your face or difficulty breathing during or after treatment
• Avoid eating grapefruit or drinking grapefruit juice because it may change the amount of TORISEL in your body

Before treatment with TORISEL begins, you may want to ask your HCP:
• If it’s okay to eat before receiving TORISEL
• If you can receive TORISEL after taking other medications earlier in the day

Please see Important Safety Information on pages 21 and 22. For additional information about TORISEL, please see the full Prescribing Information following this brochure.
Avoid eating grapefruit or drinking grapefruit juice because it may change the amount of TORISEL in your body.

Please see Important Safety Information on pages 21 and 22. For additional information about TORISEL, please see the full Prescribing Information following this brochure.
Important safety considerations

Before starting TORISEL, you should be aware of potentially serious side effects and risks of therapy. Some of these side effects may be easy to notice. Others may be impossible to recognize without special tests that your health care provider (HCP) may require.

Liver function

You should not receive TORISEL if blood tests show that your liver function is moderately or severely decreased. TORISEL should be used with caution in patients whose liver function is mildly decreased and should be given at a reduced dose.

Increased blood sugar levels

Patients are likely to have raised blood sugar levels. This may require treatment with, or an increase in the dose of, a medicine that lowers blood sugar levels.

• Tell your HCP if you are thirstier than normal, urinating more than normal, feeling more hungry, losing weight, or feeling tired or irritated

Increased cholesterol and/or triglycerides

Patients are likely to have an increase in cholesterol and/or triglycerides.

• This may require treatment with, or an increase in the dose of, a medicine that lowers cholesterol and/or triglycerides

Triglycerides are a type of fat found in the blood.

Please see Important Safety Information on pages 21 and 22. For additional information about TORISEL, please see the full Prescribing Information following this brochure.
Important safety considerations (continued)

Problems with the immune system
TORISEL may keep your immune system from working normally. This means you may be at greater risk of getting an infection while receiving TORISEL. Your doctor will monitor you for signs of infection.

Lung infection
Some people may develop Pneumocystis jiroveci pneumonia (PJP). This is a type of fungal lung infection. And it can cause death. This fungal lung infection may be related to the use of TORISEL and corticosteroids or other medicines that suppress the immune system.

Lung damage
In some people, treatment with TORISEL has been associated with a lung disease that can lead to inflammation and scarring.

- In a clinical trial, 2% experienced this outcome, including rare fatalities
  - Tell your HCP right away if you have any trouble with breathing, coughing, or wheezing; feel pain in your chest; or develop a fever
  - Your doctor may perform tests before and during TORISEL therapy to make sure you don’t have or develop serious lung issues

Bowel perforation
Some people who received TORISEL developed tears in the walls of their intestines.

- Fatal cases have been reported (in a clinical trial, 1% of TORISEL patients experienced this outcome)
  - Tell your HCP right away if you have any new or worsening stomach pain, blood in your stool, chills, nausea, or vomiting

Your blood may be tested before you begin treatment and at other times over the course of therapy. Your HCP may tell you not to eat or drink before blood tests.

The immune system is the part of the body that fights infections. When the immune system is weak, the body is more likely to be infected by bacteria and viruses.
Important safety considerations (continued)

Abnormal wound healing
During treatment with TORISEL, wounds may not heal properly.

• Tell your health care provider (HCP) if you are recovering or still have an unhealed wound from surgery

• Tell your HCP if you plan to have surgery during treatment with TORISEL

Increased risk of bleeding in the brain
TORISEL may increase the risk of bleeding in the brain, which has, in some cases, been fatal. You may be at an increased risk if you have a central nervous system tumor (such as a brain tumor) or are taking medicine to keep your blood from clotting.

Kidney failure
Treatment with TORISEL may be associated with a risk of kidney failure, sometimes fatal.

The central nervous system includes the brain and spinal cord.

Clotting is the ability of the blood to thicken to help stop bleeding. However, if a blood clot in the body is too big, it could stop blood flow. Some people with blood clots or at high risk for forming blood clots take medicine to stop their blood from clotting.

Please see Important Safety Information on pages 21 and 22. For additional information about TORISEL, please see the full Prescribing Information following this brochure.
Important safety considerations (continued)

Vaccine issues
Some vaccines may be harmful or less effective when given during the course of treatment with TORISEL.
• You should avoid the use of live vaccines and close contact with those who have recently received live vaccines
  – Ask your HCP if you can receive a flu shot

Pregnancy concerns
TORISEL can harm an unborn baby.
• Both men and women should use a reliable form of birth control during treatment and for 3 months after the last dose of TORISEL

Tell your HCP before beginning treatment if you or your partner are pregnant or thinking of becoming pregnant.

Concerns for people 65 or older
If you are 65 or older, you may be more likely to experience certain issues during TORISEL therapy, including the following:
• Diarrhea
• Edema (swelling)
• Pneumonia

Please see Important Safety Information on pages 21 and 22. For additional information about TORISEL, please see the full Prescribing Information following this brochure.
Common side effects you may experience

The following pages list some side effects that commonly occur with TORISEL. Be sure to discuss any side effects with your health care provider (HCP) immediately.

Skin rash
Several types of skin rash have been experienced while taking TORISEL. Tell your HCP right away if you have any unusual skin irritation or pain.

Examples of rash courtesy of the Cleveland Clinic Taussig Cancer Institute.

Weakness or fatigue
Many cancer treatments, including TORISEL, can cause people to feel weak or fatigued (very tired).

Mouth sores
Mouth sores commonly occurred in people who took TORISEL. Your HCP may refer to mouth sores by the medical name mucositis. Mucositis can also refer to sores along your digestive tract.

Please see Important Safety Information on pages 21 and 22. For additional information about TORISEL, please see the full Prescribing Information following this brochure.
Common side effects you may experience (continued)

Nausea
Like many cancer treatments, TORISEL can cause you to have nausea or feel like you need to vomit.

Swelling or fluid retention
Edema can occur in people who take TORISEL. It’s very important to tell your HCP about swelling of any part of your body.

Loss of appetite
While on TORISEL, you may notice that you don’t feel hungry or may not feel as motivated to eat as you normally would.

Edema is a build-up of too much fluid in the body. Edema can result in swelling.

Please see Important Safety Information on pages 21 and 22. For additional information about TORISEL, please see the full Prescribing Information following this brochure.
Preparing for TORISEL treatment

Helpful tips

- Tell all of your health care providers (HCPs) you are receiving TORISEL
- Arrange for a friend or family member to drive you to and from your weekly appointments
  - Treatment with TORISEL may make you feel weak or sick
- Maintain good oral hygiene
  - Basic oral care may help reduce the severity of potential mouth sores
- Talk to your HCP about diet and exercise
- **Tell your HCP about any changes in the way you look or feel during treatment**
  - These may be signs of side effects or a change in your disease

Please see Important Safety Information on pages 21 and 22. For additional information about TORISEL, please see the full Prescribing Information following this brochure.
Resources from TORISEL.com

Resources are just a mouse-click away
As you continue treatment for advanced RCC, it’s important to take advantage of all the cancer-related information and tools available. At TORISEL.com, you have access to a number of helpful resources to help you stay informed as you continue therapy with TORISEL and make decisions about your care.

Additional TORISEL-related tools and information
The website provides useful tools and information about treatment with TORISEL, including:

• The clinical trial for TORISEL
• Safety considerations for TORISEL
• Side effects of TORISEL
• How TORISEL is given
• Customizable TORISEL guide—Allows you to select only the portions of TORISEL.com that are most useful to you, instantly creating a helpful guide that you can print out for your reference

Please see Important Safety Information on pages 21 and 22. For additional information about TORISEL, please see the full Prescribing Information following this brochure.
Support for coping

Although dealing with advanced RCC may seem quite overwhelming, there are many cancer support organizations listed on the website that are available to assist you.

- **Listings of advanced RCC support resources**—Provides contact information for helpful cancer support organizations and explains the services they provide
  - Includes organizations that offer financial counseling and helpful programs for patients and caregivers
- **Guide to researching RCC**—This portion of the website lists a number of resources to help you inform yourself about advanced RCC and its treatment

Please see Important Safety Information on pages 21 and 22. For additional information about TORISEL, please see the full Prescribing Information following this brochure.
Resources from TORISEL.com (continued)

Getting the most from your health care team

Information is available on TORISEL.com to help you gain the most from your interactions with your health care team and improve discussions with your health care provider (HCP).

- **Guide for talking to your HCP**—Lists important questions to ask and suggestions for discussion topics during HCP visits

Help with paying for TORISEL

The website offers information to help simplify the reimbursement process and help you navigate your insurance plan.

- **Information to help you pay for TORISEL**—Pfizer RxPathways™ (which has replaced Pfizer First Resource®) helps eligible patients get access to their TORISEL by offering a range of prescription assistance services, including insurance counseling, co-pay help, providing Pfizer medicines for free or at a savings, and more

- **Explanation of how to gain coverage and reimbursement**—A Pfizer RxPathways counselor will help you and your health care professionals understand coverage and reimbursement options

- **Overview of how insurance works**—A brief explanation of the insurance industry, including information about the types of insurance plans available and the steps involved in the reimbursement process
Resources from TORISEL.com (continued)

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

Call 1-866-706-2400

Monday through Friday, 8 AM to 8 PM Eastern Time. English- and Spanish-speaking operators are available to speak with you.

Learn more about Pfizer RxPathways at TORISEL.com.
Working with your health care team

When making treatment decisions, it may help to discuss what kind of treatment may be best for you. You should talk with your cancer care team, including your doctor and nurse. Also, make sure your other health care providers (HCPs), including your primary care physician, are aware of your cancer treatment.

Remember, you should talk with your health care team at every step of your therapy about:

• Side effects that your treatment may cause
• Ways to manage side effects
• How they think you are responding to your treatment

Questions you may want to ask your HCP before or during RCC treatment

Q Has the cancer spread beyond the kidney?
A

Q What are my treatment choices?
A

Q What treatment do you think is best for me and why?
A

Q What results can I expect from treatment?
A

Q What side effects and/or risks are associated with my treatment?
A

Please see Important Safety Information on pages 21 and 22. For additional information about TORISEL, please see the full Prescribing Information following this brochure.
Working with your health care team (continued)

Q Will I need additional medications to control side effects?
A ________________________________

Q How long will my treatment last?
A ________________________________

Q Will I need to stay in the hospital?
A ________________________________

Q How much will the treatment cost?
A ________________________________

Q Does my insurance company cover my treatment?
A ________________________________

Q How will I feel during my treatment?
A ________________________________

Q What can I do to take care of myself during treatment?
A ________________________________

Q How does my treatment work and how can I tell if it is working?
A ________________________________

Q How will treatment affect my daily life?
A ________________________________

Q When will treatment begin/end?
A ________________________________

Please see Important Safety Information on pages 21 and 22. For additional information about TORISEL, please see the full Prescribing Information following this brochure.
Indication

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

Important Safety Information

• You should not receive TORISEL if certain tests show that your liver function is moderately or severely impaired. TORISEL should be used with caution in patients whose liver function is mildly impaired and should be given at a reduced dose.

• TORISEL can cause serious side effects. If you experience side effects that are too severe to tolerate, your health care professional may choose to delay your treatment, give you a lower dose of TORISEL, or discontinue treatment.

• Before you begin treatment with TORISEL, your doctor may give you an antihistamine. It is possible to have a serious (including a life-threatening or fatal) allergic reaction even after you receive an antihistamine. Tell your doctor or nurse if you are allergic to antihistamines or are unable to take antihistamines for any other medical reasons. Tell your doctor or nurse if you have any swelling around your face or trouble breathing during or after treatment with TORISEL.

• Patients are likely to experience increased blood sugar levels. This may require treatment with or an increase in the dose of a medicine that lowers blood sugar levels. Tell your doctor or nurse if you are thirstier than usual or urinate more often than usual.

• Patients are likely to experience an increase in cholesterol and/or triglycerides. This may require treatment with or an increase in the dose of a medicine that lowers cholesterol and/or triglycerides.

• Before you begin treatment with TORISEL, tell your doctor or nurse about ALL MEDICINES you are taking, including
  – Prescription medications, including but not limited to antibiotics, anticonvulsants, antidepressants, antifungals, antivirals, blood pressure medications, blood thinners, dexamethasone, vaccines
  – Nonprescription (over the counter) medications
  – Vitamins
  – Herbal supplements, including but not limited to St. John’s Wort

• Avoid eating grapefruit or drinking grapefruit juice during the course of your treatment with TORISEL, including the time between treatments, as they may change the amount of TORISEL in your body.

• Treatment with TORISEL may affect your immune system. You may be at greater risk of getting an infection while receiving TORISEL.

Please see Important Safety Information continued on page 22.
For additional information about TORISEL, please see the full Prescribing Information following this brochure.
Important Safety Information (continued)

• Patients may also be at risk for Pneumocystis jiroveci pneumonia (PJP), a fungal infection in the lungs. Fatal cases have been reported. This may be related to the use of TORISEL along with corticosteroids or other medications that suppress the immune system.

• Patients may get chronic inflammation of the lungs during treatment with TORISEL. Rare fatal cases have been reported. Tell your doctor or nurse right away if you have any trouble breathing, or develop a cough or fever.

• TORISEL may cause bowel perforation. Fatal cases have been reported. Tell your doctor or nurse right away if you have any new or worsening stomach pain or blood in your stool.

• Treatment with TORISEL may be associated with a risk of kidney failure, sometimes fatal.

• During treatment with TORISEL, wounds may not heal properly. Tell your doctor or nurse if you are recovering from surgery or have an unhealed wound. Tell your doctor or nurse if you plan to have surgery during treatment with TORISEL.

• TORISEL may increase the risk of bleeding in the brain, which has, in some cases, been fatal. You are at increased risk if
  – You have a central nervous system tumor, such as a brain tumor
  – You are taking medicine to keep your blood from clotting

• Some vaccines may be less effective when given during the course of treatment with TORISEL. You should avoid the use of live vaccines and close contact with people who have recently received live vaccines. Ask your doctor or nurse if you are eligible to receive a flu shot.

• Both men and women should use a reliable form of birth control during treatment and for 3 months after the last dose of TORISEL. TORISEL can harm an unborn baby. Tell your doctor or nurse before beginning treatment if you are pregnant or thinking of becoming pregnant.

• Elderly patients may be more likely to experience certain side effects, including diarrhea, edema, and pneumonia.

• The most common side effects are
  – Rash
  – Weakness/fatigue
  – Mouth sores
  – Nausea
  – Swelling/fluid retention
  – Loss of appetite

For additional information about TORISEL, please see the full Prescribing Information following this brochure.
Please see Important Safety Information on pages 21 and 22. For additional information about TORISEL, please see the full Prescribing Information following this brochure.
Talk to your health care provider (HCP) if you have any questions about treatment with TORISEL. To learn more about TORISEL, please visit TORISEL.com.

Doctor’s name: _____________________________________________

Nurse’s name: _______________________________________________

Phone number: __________________ Fax number: __________________

Emergency phone number: ___________________________________

Other information: ____________________________________________

Please see Important Safety Information on pages 21 and 22. For additional information about TORISEL, please see the full Prescribing Information following this brochure.
**INDICATIONS AND USAGE**

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

**DOSE 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. (2.6)
- Hepatic Impairment: Use caution when treating patients with mild hepatic impairment and reduce dose. (2.4, 5.2)

**DOSE FORMS AND STRENGTHS**

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

**CONTRAINDICATIONS**

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

**WARNINGS AND PRECAUTIONS**

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

**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: 5/2014

**FULL PRESCRIBING INFORMATION: CONTENTS**

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Advanced Renal Cell Carcinoma
2.2 Premedication
2.3 Dose Interruption/Adjustment
2.4 Dose Modification Guidelines
2.5 Instructions for Preparation
2.6 Administration
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity/Infusion Reactions
5.2 Hepatic Impairment
5.3 Hyperglycemia/Glucose Intolerance
5.4 Infections
5.5 Interstitial Lung Disease
5.6 Hyperlipemia
5.7 Bowel Perforation
5.8 Renal Failure
5.9 Wound Healing Complications
5.10 Intracerebral Hemorrhage
5.11 Co-administration with Inducers or Inhibitors of CYP3A Metabolism
5.12 Concomitant use of TORISEL with sunitinib
5.13 Vaccinations
5.14 Use in Pregnancy
5.15 Elderly Patients
5.16 Monitoring Laboratory Tests

**TORISEL® Kit (temsirolimus) injection**

FULL PRESCRIBING INFORMATION

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

2 DOSAGE AND ADMINISTRATION
2.1 Advanced Renal Cell Carcinoma
The recommended dose of TORISEL for advanced renal cell carcinoma is 25 mg infused over a 30-60 minute period once a week. Treatment should continue until disease progression or unacceptable toxicity occurs.

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

- 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 diabetes, edema and pneumonia. (5.15)

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Post-marketing and Other Clinical 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
12.2 Pharmacodynamics
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*
be co-administered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, a TORisel dose reduction to 12.5 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 allowed. The results of this study (including the severity of the reaction). At the discretion of the physician, treatment may be resumed with the administration of an H2-receptor antagonist (such as cimetidine), if not previously administered [see Dosage and Administration (2.3.4)], similar to patients with severe renal impairment (40 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 commencement 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 $\geq 1.5 x$ U.LN or AST $\geq 1.5 x$ U.LN due to increased risk of death [see Adverse Reactions (6.1)]

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 to patients with mild hepatic impairment (bilirubin $\geq 1.5 x$ U.LN or bilirubin $\leq 1.5 x$ U.LN) but bilirubin $\geq 1.5 x$ U.LN, reduce the dose of TORisel to 15 mg/wk [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 periodically 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 serious infections (see Adverse Reactions (6.2)).

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 other immunosuppressive agents, 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 until recovery of symptoms and improvement of radiographic findings related to pneumonitis. Empiric treatment with corticosteroids and/or antibiotics may be considered. Opportunistic infections such as PJP should be considered in the differential diagnosis. For patients who require use of corticosteroids, prophylaxis of PJP may be considered.

5.6 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 63% 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 acute 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 periorbital period.

5.10 Intracerebral Hemorrhage

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

5.11 Co-administration with Inhibitors or Inducers of CYP3A Metabolism

Agents Inducing CYP3A Metabolism:

Strong inducers of CYP3A4s such as dexamethasone, carbamazepine, phenytoin, phenobarbital, rifampin, rifabutin, and rifampacin may increase decrease exposure of the active metabolite, sirolimus. If alternative treatments cannot be administered, a dose adjustment should be considered. St. John's Wort may decrease exposure and 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, nevirapine, 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 serotonin

The use of TORisel with serotonin antagonists (such as atypical antipsychotics) may result in increased risk of developing intracerebral bleeding (including fatal outcomes) while receiving TORisel.

5.13 Contraindications

TORisel is contraindicated in patients with bilirubin $\geq 1.5 x$ U.LN [see Warnings and Precautions (5.2)].

5.14 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity/Infusion Reactions

Hypersensitivity/infusion reactions, including but not limited to flushing, chest pain, dyspnea, hypotension, apnea, loss of consciousness, hypersensitivity and anaphylaxis, have been reported with 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 patients with known hypersensitivity to temsirolimus or its metabolites (including sirolimus), polystyrate 80, or to any other component (including the excipients) of TORisel.

TORISEL® (tezemetotide) Injection

An H2-antihistamine should be administered to patients before the start of the intravenous temsirolimus infusion. TORisel infusion should be interrupted in all patients with severe or life-threatening reactions. An H2-antihistamine should not be administered in 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 treated in accordance with established guidelines (including the severity of the reaction). At the discretion of the physician, treatment may be resumed with the administration of an H2-receptor antagonist (such as cimetidine), if not previously administered [see Dosage and Administration (2.3)].
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 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 throughout treatment and for 3 months after TORISEL therapy has stopped [see Use in Specific Populations (8.1)].

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)].

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)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TORISEL 25 mg n = 208</th>
<th>IFN-α n = 200</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades*</td>
<td>Grades 3&amp;4*</td>
<td>All Grades*</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>195 (94)</td>
<td>41 (20)</td>
</tr>
<tr>
<td>Lymphocytes Decreased**</td>
<td>110 (53)</td>
<td>33 (16)</td>
</tr>
<tr>
<td>Neutrophils Decreased**</td>
<td>39 (19)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Platelets Decreased</td>
<td>84 (40)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Leukocytes Decreased</td>
<td>67 (32)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkaline Phosphatase Increased</td>
<td>141 (68)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>AST Increased</td>
<td>79 (38)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Creatinine Increased</td>
<td>119 (57)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Glucose Increased</td>
<td>186 (89)</td>
<td>33 (16)</td>
</tr>
<tr>
<td>Phosphorus Decreased</td>
<td>102 (49)</td>
<td>38 (18)</td>
</tr>
<tr>
<td>Total Bilirubin Increased</td>
<td>16 (8)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Total Cholesterol Increased</td>
<td>181 (87)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Triglycerides Increased</td>
<td>173 (83)</td>
<td>92 (44)</td>
</tr>
<tr>
<td>Potassium Decreased</td>
<td>43 (21)</td>
<td>11 (5)</td>
</tr>
</tbody>
</table>
* NCI CTCAE version 3.0
** Grade 1 toxicity may be under-reported for lymphocytes and neutrophils

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.

7 DRUG INTERACTIONS
7.1 Agents Inducing CYP3A Metabolism
Co-administration of TORISEL with rifampin, a potent CYP3A4/5 inducer, had no significant effect on temsirolimus C_{max} (maximum concentration) and AUC (area under the concentration versus the time curve) after intravenous administration, but decreased sirolimus C_{max} 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 Clinical pharmacology of TORISEL was conducted in order to facilitate the formulation and administration of the drug. A potent CYP3A4 inhibitor, no significant effect on temsirolimus C_max or AUC; however, sirolimus AUC increased 3.1-fold, and C_min increased 2.2-fold compared to TORISEL alone. If alternative treatment cannot be administered, a dose adjustment should be recommended (see Dosage 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 1 month after treatment discontinuation. No data are available on the use of temsirolimus in pregnancy. Coadministration of temsirolimus may 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.

8.2 Lactation

It is not known whether TORISEL is excreted into human milk, and therefore, the potential for tumorigrernic effect on an infant is unknown. 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 whose tumors have 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 to six 3-week cycles. In phase 2, 52 pediatric patients with recurrent/refractory neuroblastoma, high grade glioma, 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 neuroblastosoma or high grade glioma.

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 (5.16)).

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 3 – Adverse Reactions in Patients with Advanced Malignancies Plus Normal or Impaired Hepatic Function

<table>
<thead>
<tr>
<th>Hepatic Function*</th>
<th>TORISEL Dose Range</th>
<th>Adverse Reactions Grade 3*</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 (n = 2)</td>
<td>1 (50)</td>
<td>0 (0.0)</td>
<td></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 – 5 x ULN; severe = bilirubin >5 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.

10.1 OVERDOSAGE

There is no specific treatment for TORISEL intravenous overdose. TORISEL has been administered to patients 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 antiangiogenic agent. Temsirolimus is a white to off-white powder with a molecular formula of C₅₆H₈₇NO₁₆ 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.

The chemical name of temsirolimus is (3S,6R,7R,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34S)-9,10,12,13,14,11,22,23,24,25,26,27,32,33,34,33a-Hexacosahexaenoyl-9,27-dihydroxy-3-[1R,7S]-13(R,14S,R)-4,8,12,16,20-pentacosapentaenoyl-21-(2,4-bis(2-hydroxyethyl)methylpropionate); or Ramipril, 42-[3-hydroxy-2-(hydroxymethyl)-2-methylpropionate].
1.3 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 chromosomal 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 time to 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 greater than normal, and magnesium less than normal). 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). Fifty-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-α arms was 5 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 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.

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 (5.4)).

- **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 increased 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 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, nelfinavir or selective serotonin reuptake 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.

- **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 (5.12)).

- **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.