Therapy With TORISEL

Information about treatment and useful resources

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

How TORISEL works
TORISEL is indicated for the treatment of 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

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.
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.

Important Safety Information

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.
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

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

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

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

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

Please see additional Important Safety Information on pages 21 and 22. For additional information about TORISEL, please see the full Prescribing Information accompanying 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 additional Important Safety Information on pages 21 and 22. For additional information about TORISEL, please see the full Prescribing Information accompanying 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.
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 buildup of too much fluid in the body. Edema can result in swelling.

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

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 accompanying 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

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

Please see Important Safety Information on pages 21 and 22. For additional information about TORISEL, please see the full Prescribing Information accompanying this brochure.
Please see Important Safety Information on pages 21 and 22. For additional information about TORISEL, please see the full Prescribing Information accompanying 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: __________________________
TORISEL® is a kinase inhibitor indicated for the treatment of advanced renal cell carcinoma. (1)

The recommended dose of TORISEL is 25 mg infused over a 30-60 minute period once a week. Treat until disease progression or unacceptable toxicity. (2.1)

- Antihistamine pre-treatment is recommended. (2.2)
- Dose reduction is required in patients with mild hepatic impairment. (2.4)
- TORISEL (temsirolimus) injection vial contents must first be diluted with the enclosed diluent before diluting the resultant solution with 250 mL of 0.9% Sodium Chloride Injection. (2.5)

Dosage Forms and Strengths

TORISEL injection, 25 mg/mL supplied with DILUENT for TORISEL®. (5)

Contraindications

TORISEL is contraindicated in patients with bilirubin > 1.5×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)
- Hyperglycemia and hyperlipemia are likely and may require treatment. Monitor glucose and lipid profiles. (5.3, 5.6)

ADVERSE REACTIONS

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)
- The concomitant use of strong CYP3A4 inhibitors 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: 7/2016
TORISEL is contraindicated in patients with bilirubin >1.5xULN (see Warnings and Precautions (5.1)) and Drug Interactions (7.1)).

2.5 Instructions for Preparation
TORISEL must be stored under refrigeration at 2°C to 8°C (36° to 46°F) and protected from light. During handling and preparation of admixtures, TORISEL should be protected from excessive room light and sunlight. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

In order to minimize the patient exposure to the plasticizer DEHP (2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final TORISEL dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

TORISEL 25 mg/mL injection must be diluted with the supplied diluent before further dilution in 0.9% Sodium Chloride Injection, USP.

Please note that both the TORISEL injection and diluent vials contain an overfill to ensure that the recommended volume can be withdrawn.

Follow this two-step dilution process in an aseptic manner.

Step 1:
DILUTION OF TORISEL INJECTION 25 MG/ML WITH SUPPLIED DILUENT
- Each Vial of Torisel (temsirolimus) must first be mixed with 1.8 mL of the enclosed diluent. The resultant solution contains 30 mg/mL (10 mg/mL).
- Mix well by inversion of the vial. Allow sufficient time for the air bubbles to subside. The solution should be clear to slightly turbid, colorless to light-yellow solution, essentially free from visual particulates.

The concentrate-diluent mixture is stable below 25°C for up to 24 hours.

Step 2:
DILUTION OF CONCENTRATE-DILUENT MIXTURE WITH 0.9% SODIUM CHLORIDE INJECTION, USP
- Withdraw precisely the required amount of concentrate-diluent mixture containing temsirolimus 10 mg/mL as prepared in Step 1 from the vial (i.e., 2.5 mL for a temsirolimus dose of 25 mg) and further dilute into an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, USP.
- Mix by inversion of the bag or bottle, avoiding excessive shaking, as this may cause foaming. The resulting solution should be inspected visually for particulate matter and discoloration prior to administration. The admixture of TORISEL in 0.9% Sodium Chloride Injection, USP should be protected from excessive room light and sunlight.

2.6 Administration
- Administration of the final diluted solution should be completed within six hours from the time that TORISEL is first added to 0.9% Solution Chloride Injection, USP.
- TORISEL is infused over a 30- to 60-minute period once weekly. The use of an infusion pump is the preferred method of administration to ensure accurate delivery of the product.
- Appropriate administration materials should be composed of glass, polyolefin, or polyethylene to avoid excessive loss of product and diethylenehexylphthalate (DEHP) extraction. The administration materials should consist of non-DEHP, non-polyvinylchloride (PVC) tubing with appropriate filter. In the case when a PVC administration set has to be used, it should not contain DEHP. An in-line polyethersulfone filter with a pore size of not greater than 5 microns is recommended for administration to avoid the possibility of particles bigger than 5 microns being infused. If the administration set available does not have an in-line filter incorporated, a polyethersulfone filter should be added at the set (i.e., an end-filter) before the admixture reaches the vein of the patient. Different end-filters can be used, ranging in filter pore size from 0.2 microns up to 5 microns. The use of both an in-line and end-filter is not recommended.
- TORISEL, when diluted, contains polysorbate 80, which is known to increase the rate of DEHP extraction from PVC. This should be considered during the preparation and administration of TORISEL, including storage time elapsed when in direct contact with PVC following constitution.

Compatibilities and Incompatibilities
Undiluted TORISEL injection should not be added directly to aqueous infusion solutions. Direct addition of TORISEL injection to aqueous solutions will result in precipitation of drug. Always combine TORISEL injection with DILUENT for TORISEL before adding to infusion solutions. It is recommended that TORISEL be administered in 0.9% Sodium Chloride Injection after combining with diluent. The stability of TORISEL in other infusion solutions has not been evaluated. Addition of other drugs or nutritional agents to admixtures of TORISEL in 0.9% Sodium Chloride Injection has not been evaluated and should be avoided. Temsirolimus is degraded by both acids and bases, and thus combinations of temsirolimus with agents capable of modifying solution pH should be avoided.

3 DOSAGE FORMS AND STRENGTHS
TORISEL® (temsirolimus) is supplied as a kit consisting of the following:
TORISEL (temsirolimus) injection (25 mg/mL). The TORISEL vial contains temsirolimus at a concentration of 25 mg/mL. The vial contains an overfill of 0.2 mL to ensure the ability to withdraw the recommended dose.
DILUENT for TORISEL®. The DILUENT vial includes a deliverable volume of 1.8 mL. This vial contains an overfill in order to ensure that the appropriate volume can be withdrawn.

4 CONTRAINDICATIONS
TORISEL is contraindicated in patients with bilirubin >1.5xULN (see Warnings and Precautions (5.2)).

5 WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity/Infusion Reactions
Hypersensitivity/infusion reactions, including but not limited to flushing, chest pain, dyspnea, hypotension, tachycardia, or signs of consciousness impairment, hypoglycemia, and anaphylaxis, have been associated with the administration of temsirolimus. These reactions can occur very early in the first infusion, but may also occur with subsequent infusions. Patients should be monitored throughout the infusion and appropriate supportive care should be available. Temsirolimus infusion should be interrupted in all patients with severe infusion reactions and appropriate medical therapy administered.
TORISEL should be used with caution in patients with known hypersensitivity to temsirolimus or its metabolites (including sirolimus), polysorbate 80, or to any other component (including the metabolites) of TORISEL.
An H1-antihistamine should be administered to patients before the start of the intravenous temsirolimus infusion. TORISEL should be used with caution in patients with known hypersensitivity to an antihistamine, or patients who cannot receive an antihistamine for other medical reasons.
If a patient develops a hypersensitivity reaction during the TORISEL infusion, the infusion should be stopped and the patient should be observed for at least 30 to 60 minutes (depending on the severity of the reaction). At the discretion of the physician, treatment may be resumed with the administration of an H1-receptor antagonist (such as diphenhydramine), if not previously administered (see Dosage and Administration (2.1)) and/or an H2-receptor antagonist (such as intravenous famotidine 20 mg or intravenous ranitidine 50 mg) approximately 30 minutes before restarting the TORISEL infusion. The infusion may then be resumed at a slower rate (up to 60 minutes).
A benefit-risk assessment should be done prior to the continuation of temsirolimus therapy in patients with severe or life-threatening reactions.

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

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

5.4 Infections
The use of TORISEL may result in immunosuppression. Patients should be carefully observed for the occurrence of infections, including opportunistic infections (see Adverse Reactions (6.1)). Pneumocystis jiroveci pneumonia (PJP), including fatalities, has been reported in patients who received temsirolimus. This may be associated with concomitant use of corticosteroids or other immunosuppressive agents. Prophylaxis of PJP should be considered when concomitant use of corticosteroids or other immunosuppressive agents are required.

5.5 Interstitial Lung Disease
Cases of interstitial lung disease, some resulting in death, occurred in patients who received TORISEL. Some patients were asymptomatic, or had minimal symptoms, with infiltrates detected on computed tomography scan or chest radiograph. Others presented with symptoms such as dyspnea, cough, hypoxia, and fever. Some patients required discontinuation of TORISEL and/or treatment with corticosteroids and/or antibiotics, while some patients continued treatment without additional intervention. Patients should be advised to report promptly any new or worsening respiratory symptoms. It is recommended that patients undergo baseline radiographic assessment by lung computed tomography scan or chest radiograph prior to the initiation of TORISEL therapy. Follow such assessments periodically, even in the absence of clinical respiratory symptoms.
It is recommended that patients be followed closely for occurrence of clinical respiratory symptoms. If clinically significant respiratory symptoms develop, consider withholding TORISEL administration and/or treatment with corticosteroids and/or antibiotics and/or supportive care. 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, 67% of patients receiving TORISEL had at least one elevated serum cholesterol value and 85% had at least one elevated serum triglyceride value. This may require initiation, or increase in the dose of, lipid-lowering agents. Serum cholesterol and triglycerides should be tested before and during treatment with TORISEL.

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

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

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

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

Agents Inhibiting CYP3A Metabolism:
Strong CYP3A4 inhibitors such as azatadine, clarithromycin, indinavir, lataconazole, ketoconazole, nefazodone, neflavin, 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 sunlithin
The combination of TORISEL and sunlithin resulted in dose-limiting toxicity. Dose-limiting toxicities (Grade 3/4 erythematous maculopapular rash, and goitrous结节 requiring hospitalization) were observed in two out of three patients treated in the first cohort of a phase 1 study at doses of TORISEL 15 mg IV per week and sunlithin 25 mg oral per day (Days 1-28 followed by a 2-week rest).

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

5.14 Use in Pregnancy
There are no adequate and well-controlled studies of TORISEL in pregnant women. However, based on its mechanism of action, TORISEL may cause fetal harm when administered to a pregnant woman. Temsirolimus administered daily as an oral formulation caused embryo-fetal and intrauterine toxicities in rats and rabbits at human sub-therapeutic exposures. If this drug is used during pregnancy or if breastfeeding, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to discontinue breastfeeding prior to starting treatment with TORISEL.

5.15 Elderly Patients
Based on the results of a phase 3 study, elderly patients may be more likely to experience certain adverse reactions including diarrhea, edema, and pneumonia [see Use in Specific Populations (8.1)]. Men should be counseled regarding the effects of TORISEL on the sperm and testicles prior to starting treatment [see Nonclinical Toxicology (13.1)]. Men with partners of childbearing potential should be advised to discontinue potential contraception until the last dose of TORISEL.

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

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

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

The most common (≥30%) adverse reactions observed with TORISEL are rash, asthenia, mucositis, nausea, edema, and anorexia. The most common (≥30%) laboratory abnormalities observed with TORISEL are anaemia, hyperglycaemia, hyperlipidaemia, hyperglycaemia/dyslipidaemia, lymphopenia, elevated alkaline phosphatase, elevated serum creatinine, hypophosphatemia, thrombocytopenia, elevated AST, and leukopenia.

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

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

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

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

<table>
<thead>
<tr>
<th>Table 1 – Adverse Reactions Reported in at Least 10% of Patients Who Received 25 mg IV TORISEL or IFN-α in the Randomized Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Reaction</strong></td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td><strong>General disorders</strong></td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Edema</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>Pyrexia</td>
</tr>
<tr>
<td>Weight Loss</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Chest Pain</td>
</tr>
<tr>
<td>Chills</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
</tr>
<tr>
<td>Mucositis</td>
</tr>
<tr>
<td>Anorexia</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Abdominal Pain</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
</tr>
<tr>
<td>Infections</td>
</tr>
<tr>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>Pharyngitis</td>
</tr>
<tr>
<td>Rhinitis</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
</tr>
<tr>
<td>Back Pain</td>
</tr>
<tr>
<td>Arthralgia</td>
</tr>
<tr>
<td>Myalgia</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
</tr>
<tr>
<td>Dyspnea</td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>Epistaxis</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Pruritus</td>
</tr>
<tr>
<td>Nail Disorder</td>
</tr>
<tr>
<td><strong>Acne</strong></td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Insomnia</td>
</tr>
<tr>
<td>Depression</td>
</tr>
</tbody>
</table>

Table 1 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 impetigo, exfoliative dermatitis, maculopapular rash, pruritic rash, purpuric rash, and NOS.
- Includes taste loss and taste perversion.

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

Gastrointestinal Disorders – Gastrointestinal hemorrhage (1%), rectal hemorrhage (1%).

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

Immune System – Angioedema edema-type reactions (including delayed reactions occurring two months following initiation of therapy) have been observed in some patients who received TORISEL and ACE inhibitors concomitantly.

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

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

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

Nervous System Disorders – Convulsion (1%).
Table 2 – Incidence of Selected Laboratory Abnormalities in Patients Who Received 25 mg IV TORISEL or IFN-α in the Randomized Trial

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TORISEL 25 mg</th>
<th>IFN-α</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades*</td>
<td>Grades 3 &amp; 4*</td>
</tr>
<tr>
<td>Any</td>
<td>208 (100)</td>
<td>162 (78)</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>59 (19)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Platelets Decreased</td>
<td>44 (20)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Leukocytes Decreased</td>
<td>67 (32)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Chemistry

<table>
<thead>
<tr>
<th></th>
<th>TORISEL Dose Range</th>
<th>Adverse Reactions 3***</th>
<th>Death***</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal(n = 25)</td>
<td>Mild(n = 39)</td>
<td>Moderate(n = 20)</td>
</tr>
<tr>
<td>Alkaline Phosphate</td>
<td>7.2 mg/m²/day</td>
<td>25 – 175</td>
<td>20 (80.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 – 25</td>
<td>32 (82.1)</td>
</tr>
<tr>
<td>Glucose</td>
<td>7.5 – 15 mg/m²/day</td>
<td>10 – 25</td>
<td>19 (95.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.5 – 15</td>
<td>23 (95.8)</td>
</tr>
</tbody>
</table>

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Nursing Use

8.3 Nutrition

8.4 Pediatric Use

11 DESCRIPTION

Temsirimus, an inhibitor of mTOR, is an antineoplastic agent. Temsirimus is a white to off-white powder with a molecular formula of C_{47}H_{33}N_{3}O_{12} and a molecular weight of 1030.30. It is non-hygroscopic. Temsirimus 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 temsirimus is

Temsirolimus is a substrate of the efflux transporter P-glycoprotein (Pgp) and the concentration of desipramine, a CYP2D6 substrate, was unaffected when 25 mg of temsirolimus was co-administered. No clinically significant effect is anticipated when 25 mg of temsirolimus is co-administered with agents that are metabolized by CYP2D6 or CYP3A.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Temsirolimus was not genotoxic in a battery of in vitro (bacterial reverse mutation in Salmonella typhimurium and Escherichia coli, forward mutation in mouse lymphoma cells, and chromosome aberrations in Chinese hamster ovary cells) and in vivo (mouse micronucleus) assays.

In male rats, the following fertility effects were observed: decreased number of pregnancies, decreased sperm concentration and motility, decreased reproductive organ weights, and testicular tubular degeneration. These effects were observed at oral temsirolimus doses >3 mg/kg/day (approximately 0.2-fold the human recommended intravenous dose). Fertility was absent at 30 mg/kg/day.

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

14 CLINICAL STUDIES

A phase 3, multi-center, three-arm, randomized, open-label study was conducted in previously untreated patients with advanced renal cell carcinoma (clear cell and non-clear cell histologies). The objectives were to compare Overall Survival (OS), Progression-Free Survival (PFS), Objective Response Rate (ORR), and safety in patients receiving IFN-α to those receiving TORISEL or TORISEL plus IFN-α. Patients in this study had 3 or more of 6 pre-selected prognostic risk factors (less than one year from time of initial renal cell carcinoma diagnosis to randomization, Karnofsky performance status of 60 or 70, hemoglobin less than the lower limit of normal, corrected calcium of greater than 10 mg/dL, lactate dehydrogenase >1.5 times the upper limit of normal, more than one metastatic organ site). Patients were stratified for prior nephrectomy status within three geographic regions and were randomly assigned (1:1:1) to receive IFN-α alone (n = 207), TORISEL alone (25 mg weekly; n = 209), or the combination arm (n = 210).

The ITT population for this interim analysis included 626 patients. Demographics were comparable between the three treatment arms with regard to age, gender, and race. The mean age of all groups was 59 years (range 23–86). Sixty-nine percent were male and 31% were female. The racial distribution for all groups was 91% White, 4% Black, 2% Asian, and 3% other. Sixty-seven percent of patients had a history of prior nephrectomy.

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

There was a statistically significant improvement in OS (time from randomization to death) in the TORISEL 25 mg arm compared to IFN-α. The combination of TORISEL 15 mg and IFN-α did not result in a significant increase in OS when compared with IFN-α alone. Figure 1 is a Kaplan-Meier plot of OS in this study. The evaluations of PFS (time from randomization to disease progression or death) and ORR, were based on blinded independent radiologic assessment of tumor response. Efficacy results are summarized in Table 4.

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TORISEL n = 209</th>
<th>IFN-α n = 207</th>
<th>P-value</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Overall Survival (Months) (95% CI)</td>
<td>10.9 (8.5, 12.7)</td>
<td>7.3 (6.1, 8.8)</td>
<td>0.0008*</td>
<td>0.73 (0.58, 0.92)</td>
</tr>
<tr>
<td>Median Progression-Free Survival (Months) (95% CI)</td>
<td>5.5 (3.9, 7.0)</td>
<td>3.1 (2.2, 3.8)</td>
<td>0.0001**</td>
<td>0.66 (0.53, 0.81)</td>
</tr>
<tr>
<td>Overall Response Rate (%) (95% CI)</td>
<td>8.6 (4.8, 12.4)</td>
<td>4.8 (1.9, 7.8)</td>
<td>0.1232**</td>
<td>NA</td>
</tr>
</tbody>
</table>

CI = confidence interval; NA = not applicable

* A comparison is considered statistically significant if the p-value is <0.0159 (O’Brien-Fleming boundary at 466 deaths).

** Not adjusted for multiple comparisons.

Based on log-rank test stratified by prior nephrectomy and region.

Based on Cox proportional hazard model stratified by prior nephrectomy and region.

Based on Cochran-Mantel-Haenszel test stratified by prior nephrectomy and region.


16  HOW SUPPLIED/STORAGE AND HANDLING

NDC 0088-1179-01 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). Protect from light.

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 pretreatment 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 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 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, rifampin, rifabutin, nefazodone or selective serotonin re-uptake inhibitors used to treat depression, antibiotics or antifungal medicines used to treat infections [see Warnings and Precautions (5.11)].

• Vaccinations

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

• Pregnancy

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

• Elderly Patients

Elderly patients should be advised that they may be more likely to experience certain adverse reactions including diarrhea, edema, and pneumonia [see Warnings and Precautions (5.15)].

This product’s label may have been updated. For full prescribing information, please visit www.pfizer.com.

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