



NDA 22-088

Wyeth Pharmaceuticals
Attention: Patricia Johnson
Director, Regulatory Affairs
35 CambridgePark Drive
Cambridge, MA 02140

Dear Ms. Johnson:

Please refer to your new drug application (NDA) dated October 5, 2006, received October 5, 2006, submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act for TORISEL™ (temsirolimus) injection.

We acknowledge receipt of your submissions dated October 18, 2006; November 16, 21, and 22, 2006; December 5, and 13, 2006; January 19, and 26, 2007; February 20, 22, and 23, 2007; March 7, and 9, 2007; April 5, 12, 17, and 30, 2007, and May 4, 2007.

This new drug application provides for the use of TORISEL™ (temsirolimus) injection, for the treatment of advanced renal cell carcinoma.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/oc/datacouncil/spl.html>, that is identical in content to the enclosed labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission "SPL for approved NDA 22-088."

The final printed labeling (FPL) for immediate container and carton labels must be identical to the enclosed labeling. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 22-088**". Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated May 24, 2007.

These commitments are listed below.

1. Submit the completed report and data sets for the thorough QT prolongation evaluation for study entitled "A single-dose, single-blind, placebo and moxifloxacin controlled 2- period, randomized, crossover, 3rd-period sequential study of the effects of temsirolimus on cardiac repolarization in healthy subjects".

Protocol Submission: March 2006
Study Start: March 2006
Final Report Submission: September 2007

2. Submit the completed report and datasets for the hepatic impairment study (NCI study 6813 (3066K1-152-US))

Protocol Submission: November 2005
Study Start: January 2006
Final Report Submission: September 2008

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Commitment Protocol", "Postmarketing Study Commitment Final Report", or "Postmarketing Study Commitment Correspondence."**

We have the following comments and risk management statements regarding CMC.

1. As stated in the April 5, 2007 meeting, your proposed Chemistry, Manufacturing and Controls (CMC) Regulatory Agreement, submitted as part of the CMC Pilot program, was not reviewed and is not part of this approval action. Existing regulations and guidances should be followed, as appropriate, for all postapproval CMC changes. We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).
2. We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified during this process.

We remind you of our agreements that were made in the April 5, 2007 teleconference and in your submission dated April 12, 2007. These agreements are listed below:

1. You have agreed to investigate the use of a flag label, or a suitable alternative, in order to incorporate additional information in the container labels for both the diluent and active vials.
2. You have agreed to submit the developed strategy for the above agreement in a

Prior Approval supplement.

3. You have agreed to further discussions with the Agency regarding packaging technology options available, to ensure the physical connection of the two copackaged vials.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Carl Huntley, Regulatory Project Manager, at (301) 796-1372.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

Enclosure

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Richard Pazdur
5/30/2007 03:06:27 PM

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TORISEL™ safely and effectively. See full prescribing information for TORISEL.

TORISEL™ Kit (temsirolimus) injection, for intravenous infusion only
Initial U.S. approval: 2007

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

- The recommended dose of TORISEL is 25 mg infused over a 30-60 minute period once a week. Treat until disease progression or unacceptable toxicity. (2.1)
- Antihistamine pre-treatment is recommended. (2.2)
- 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. (3)

CONTRAINDICATIONS

- None. (4)

WARNINGS AND PRECAUTIONS

- To treat hypersensitivity reactions stop TORISEL and treat with an antihistamine. TORISEL may be restarted at physician discretion at a slower rate. (5.1)
- Hyperglycemia and hyperlipemia are likely and may require treatment. Monitor glucose and lipid profiles. (5.2, 5.5)
- Infections may result from immunosuppression. (5.3)

- Monitor for symptoms or radiographic changes of interstitial lung disease (ILD). If ILD is suspected, discontinue TORISEL, and consider use of corticosteroids and/or antibiotics. (5.4)
- Bowel perforation may occur. Evaluate fever, abdominal pain, bloody stools, and/or acute abdomen promptly. (5.6)
- Renal failure, sometimes fatal, has occurred. Monitor renal function at baseline and while on TORISEL. (5.7)
- Due to abnormal wound healing, use TORISEL with caution in the perioperative period. (5.8)
- Live vaccinations and close contact with those who received live vaccines should be avoided. (5.12)
- Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant. (5.13)

ADVERSE REACTIONS

The most common adverse reactions (incidence $\geq 30\%$) are rash, asthenia, mucositis, nausea, edema, and anorexia. The most common laboratory abnormalities (incidence $\geq 30\%$) 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.

Revision date: 5/2007

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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 *Hypersensitivity Reactions (5.1)*].

2.3 Dosage Interruption/Adjustment

TORISEL should be held for absolute neutrophil count (ANC) $< 1,000/\text{mm}^3$, platelet count $< 75,000/\text{mm}^3$, or NCI CTCAE grade 3 or greater adverse reactions. Once toxicities have resolved to grade 2 or less, TORISEL may be restarted with the dose reduced by 5 mg/week to a dose no lower than 15 mg/week.

2.4 Dose Modification Guidelines

Concomitant Strong CYP3A4 Inhibitors: The concomitant use of strong CYP3A4 inhibitors should be avoided (e.g. ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole). Grapefruit juice may also increase plasma concentrations of sirolimus (a major metabolite of temsirolimus) and should be avoided. If patients must be co-administered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, a TORISEL dose reduction to 12.5 mg/week should be considered. This dose of TORISEL is predicted to adjust the AUC to the range observed without inhibitors. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inhibitors. If the strong inhibitor is discontinued, a washout period of approximately 1 week should be allowed before the TORISEL dose is adjusted back to the dose used prior to initiation of the strong CYP3A4 inhibitor. [see *Drug Interactions (7.2)*]

Concomitant Strong CYP3A4 Inducers: The use of concomitant strong CYP3A4 inducers should be avoided (e.g. dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifampacin, phenobarbital). If patients must be co-administered a strong CYP3A4 inducer, based on pharmacokinetic studies, a TORISEL dose increase from 25 mg/week up to 50 mg/week should be considered. This dose of TORISEL is predicted to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued the temsirolimus dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer. [see *Drug Interactions (7.1)*]

2.5 Instructions for Preparation and Administration

TORISEL must be stored under refrigeration at 2°-8°C (36°-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 (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final TORISEL dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

Dilution:

In preparing the TORISEL administration solution, follow this two-step dilution process in an aseptic manner.

Step 1:

Inject 1.8 mL of DILUENT for TORISEL into the vial of TORISEL (temsirolimus) injection (25 mg/mL). The TORISEL (temsirolimus) vial contains an overfill of 0.2 mL (30 mg/1.2 mL). Due to the intentional overfill in the TORISEL injection vial, the drug concentration of the resulting solution will be 10 mg/mL. A total volume of 3 mL will be obtained including the overfill. Mix well by inversion of the vial. Allow sufficient time for air bubbles to subside. This 10 mg/mL drug solution/diluent mixture must be further diluted as described in Step 2 below.

The solution is clear to slightly turbid, colorless to yellow, and free from visual particulates. The 10 mg/mL drug solution/diluent mixture is stable for up to 24 hours at controlled room temperature.

Step 2:

Withdraw the required amount of temsirolimus from the 10 mg/mL drug solution/diluent mixture prepared in Step 1. Inject rapidly into a 250 mL container (glass, polyolefin, or polyethylene) of 0.9% sodium chloride injection. Mix the admixture by inversion of the bag or bottle. Avoid excessive shaking as this may cause foaming.

Administration:

- The sodium chloride injection container should be composed of non-DEHP containing materials, such as glass, polyolefin or polyethylene, and the administration set should consist of non-DEHP tubing to avoid extraction of di-(2-ethylhexyl) phthalate (DEHP). TORISEL contains polysorbate 80, which is known to increase the rate of di-(2-ethylhexyl) phthalate (DEHP) extraction from PVC.
- An in-line polyethersulfone filter with a pore size of not greater than 5 microns is recommended for administration.
- The final diluted solution of TORISEL is intravenously infused over a 30-60 minute period once a week. The use of an infusion pump is the preferred method of administration to ensure accurate delivery of the drug.

- Administration of the final diluted infusion solution should be completed within six hours from the time that the drug solution/diluent mixture is added to the sodium chloride injection.

Compatibilities and Incompatibilities

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

3 DOSAGE FORMS AND STRENGTHS

TORISEL (temsirolimus) is supplied as a kit consisting of the following:

- TORISEL (temsirolimus) injection (25 mg/ml). The TORISEL vial includes an overfill of 0.2 mL.
- DILUENT for TORISEL. The DILUENT vial includes a deliverable volume of 1.8 mL.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

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

TORISEL should be used with caution in persons with known hypersensitivity to temsirolimus or its metabolites (including sirolimus), polysorbate 80, or to any other component (including the excipients) of TORISEL.

An H₁ antihistamine should be administered to patients before the start of the intravenous temsirolimus infusion. TORISEL should be used with caution in patients with known hypersensitivity to an antihistamine, or patients who cannot receive an antihistamine for other medical reasons.

If a patient develops a hypersensitivity reaction during the TORISEL infusion, the infusion should be stopped and the patient should be observed for at least 30 to 60 minutes (depending on the severity of the reaction). At the discretion of the physician, treatment may be resumed with the administration of an H₁-receptor antagonist (such as diphenhydramine), if not previously administered [see *Dosage and Administration* (2.2)], and/or an H₂-receptor antagonist (such as intravenous famotidine 20 mg or intravenous ranitidine 50 mg) approximately 30 minutes before

restarting the TORISEL infusion. The infusion may then be resumed at a slower rate (up to 60 minutes).

5.2 Hyperglycemia/Glucose Intolerance

The use of TORISEL is likely to result in increases in serum glucose. In the phase 3 trial, 89% of patients receiving TORISEL had at least one elevated serum glucose 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.

5.3 Infections

The use of TORISEL may result in immunosuppression. Patients should be carefully observed for the occurrence of infections, including opportunistic infections [*see Adverse Reactions (6.1)*].

5.4 Interstitial Lung Disease

Cases of interstitial lung disease, some resulting in death, occurred in patients who received TORISEL. Some patients were asymptomatic with infiltrates detected on computed tomography scan or chest radiograph. Others presented with symptoms such as dyspnea, cough, hypoxia, and fever. Some patients required discontinuation of TORISEL and/or treatment with corticosteroids and/or antibiotics, while some patients continued treatment without additional intervention. Patients should be advised to report promptly any new or worsening respiratory symptoms.

5.5 Hyperlipemia

The use of TORISEL is likely to result in increases in serum triglycerides and cholesterol. In the phase 3 trial, 87% of patients receiving TORISEL had at least one elevated serum cholesterol value and 83% had at least one elevated serum triglyceride value. This may require initiation, or increase in the dose, of lipid-lowering agents. Serum cholesterol and triglycerides should be tested before and during treatment with TORISEL.

5.6 Bowel Perforation

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

5.7 Renal Failure

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

5.8 Wound Healing Complications

Use of TORISEL has been associated with abnormal wound healing. Therefore, caution should be exercised with the use of TORISEL in the perioperative period.

5.9 Intracerebral Hemorrhage

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

5.10 Co-administration with Inducers or Inhibitors of CYP3A Metabolism

Agents Inducing CYP3A Metabolism:

Strong inducers of CYP3A4/5 such as dexamethasone, carbamazepine, phenytoin, phenobarbital, rifampin, rifabutin, and rifampacin may decrease exposure of the active metabolite, sirolimus. If alternative treatment cannot be administered, a dose adjustment should be considered. St. John's Wort may decrease TORISEL plasma concentrations unpredictably. Patients receiving TORISEL should not take St. John's Wort concomitantly. [*see Dosage and Administration (2.4) and Drug Interactions (7.1)*].

Agents Inhibiting CYP3A Metabolism:

Strong CYP3A4 inhibitors such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, 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)*].

5.11 Concomitant use of TORISEL with sunitinib

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

5.12 Vaccinations

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

5.13 Pregnancy

Pregnancy Category D

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

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

dose of ≥ 7.2 mg/m²/day (approximately 0.12-fold the AUC in cancer patients at the recommended human dose).

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

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

5.14 Monitoring Laboratory Tests

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

6 ADVERSE REACTIONS

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

Hypersensitivity Reactions [see *Warnings and Precautions* (5.1)]

Hyperglycemia/Glucose Intolerance [see *Warnings and Precautions* (5.2)]

Interstitial Lung Disease [see *Warnings and Precautions* (5.4)]

Hyperlipemia [see *Warnings and Precautions* (5.5)]

Bowel Perforation [see *Warnings and Precautions* (5.6)]

Renal Failure (see *Warnings and Precautions* (5.7))

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

6.1 Clinical Trials Experience

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

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

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

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

Table 1 –Adverse Reactions Reported in at Least 10% of Patients Who Received 25 mg IV TORISEL or IFN-α in the Randomized Trial				
Adverse Reaction	TORISEL 25 mg n=208		IFN-α n=200	
	All Grades* n (%)	Grades 3&4* n (%)	All Grades* n (%)	Grades 3&4* n (%)
Any	208 (100)	139 (67)	199 (100)	155 (78)
General disorders				
Asthenia	106 (51)	23 (11)	127 (64)	52 (26)
Edema ^a	73 (35)	7 (3)	21 (11)	1 (1)
Pain	59 (28)	10 (5)	31 (16)	4 (2)
Pyrexia	50 (24)	1 (1)	99 (50)	7 (4)
Weight Loss	39 (19)	3 (1)	50 (25)	4 (2)
Headache	31 (15)	1 (1)	30 (15)	0 (0)
Chest Pain	34 (16)	2 (1)	18 (9)	2 (1)
Chills	17 (8)	1(1)	59 (30)	3 (2)
Gastrointestinal disorders				
Mucositis ^b	86 (41)	6 (3)	19 (10)	0 (0)
Anorexia	66 (32)	6 (3)	87 (44)	8 (4)
Nausea	77 (37)	5 (2)	82 (41)	9 (5)
Diarrhea	56 (27)	3 (1)	40 (20)	4 (2)
Abdominal Pain	44 (21)	9 (4)	34 (17)	3 (2)
Constipation	42 (20)	0 (0)	36 (18)	1 (1)
Vomiting	40 (19)	4 (2)	57 (29)	5 (3)
Infections				
Infections ^c	42 (20)	6 (3)	19 (10)	4 (2)
Urinary tract infection ^d	31 (15)	3 (1)	24 (12)	3 (2)
Pharyngitis	25 (12)	0 (0)	3 (2)	0 (0)
Rhinitis	20 (10)	0 (0)	4 (2)	0 (0)
Musculoskeletal and connective tissue disorders				
Back Pain	41 (20)	6 (3)	28 (14)	7 (4)
Arthralgia	37 (18)	2 (1)	29 (15)	2 (1)

Table 1 –Adverse Reactions Reported in at Least 10% of Patients Who Received 25 mg IV TORISEL or IFN-α in the Randomized Trial				
Adverse Reaction	TORISEL 25 mg n=208		IFN-α n=200	
	All Grades* n (%)	Grades 3&4* n (%)	All Grades* n (%)	Grades 3&4* n (%)
Any	208 (100)	139 (67)	199 (100)	155 (78)
Myalgia	16 (8)	1 (1)	29 (15)	2 (1)
Respiratory, thoracic and mediastinal disorders				
Dyspnea	58 (28)	18 (9)	48 (24)	11 (6)
Cough	53 (26)	2 (1)	29 (15)	0 (0)
Epistaxis	25 (12)	0 (0)	7 (4)	0 (0)
Skin and subcutaneous tissue disorders				
Rash ^e	97 (47)	10 (5)	14 (7)	0(0)
Pruritus	40 (19)	1 (1)	16 (8)	0 (0)
Nail Disorder	28 (14)	0 (0)	1 (1)	0 (0)
Dry Skin	22 (11)	1 (1)	14 (7)	0 (0)
Acne	21 (10)	0 (0)	2 (1)	0 (0)
Nervous system disorders				
Dysgeusia ^f	41 (20)	0 (0)	17 (9)	0 (0)
Insomnia	24 (12)	1 (1)	30 (15)	0 (0)
Depression	9 (4)	0 (0)	27 (14)	4 (2)

* Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0.

^a Includes edema, facial edema, and peripheral edema

^b Includes aphthous stomatitis, glossitis, mouth ulceration, mucositis, and stomatitis

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

^d Includes cystitis, dysuria, hematuria, urinary frequency, and urinary tract infection

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

^f Includes taste loss and taste perversion

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

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

Eye Disorders - Conjunctivitis (including lacrimation disorder) occurred in 15 patients (7%).

Immune System - Allergic/Hypersensitivity reactions occurred in 18 patients (9%).

Angioneurotic edema-type reactions have been observed in some patients who received TORISEL and ACE inhibitors concomitantly.

Infections - Pneumonia occurred in 17 patients (8%); upper respiratory tract infection occurred in 14 patients (7%).

General Disorders and Administration Site Conditions - Impaired wound healing occurred in 3 patients (1%).

Respiratory, Thoracic and Mediastinal Disorders – Interstitial lung disease occurred in 5 patients (2%), including rare fatalities.

Vascular - Hypertension occurred in 14 patients (7%); venous thromboembolism (including deep vein thrombosis and pulmonary embolus) occurred in 5 patients (2%); thrombophlebitis occurred in 2 patients (1%).

Table 2 – Incidence of Selected Laboratory Abnormalities in Patients Who Received 25 mg IV TORISEL or IFN-α in the Randomized Trial				
Laboratory Abnormality	TORISEL 25 mg n=208		IFN-α n=200	
	All Grades* n (%)	Grades 3&4* n (%)	All Grades* n (%)	Grades 3&4* n (%)
Any	208 (100)	162 (78)	195 (98)	144 (72)
Hematology				
Hemoglobin Decreased	195 (94)	41 (20)	180 (90)	43 (22)
Lymphocytes Decreased**	110 (53)	33 (16)	106 (53)	48 (24)
Neutrophils Decreased**	39 (19)	10 (5)	58 (29)	19 (10)
Platelets Decreased	84 (40)	3 (1)	51 (26)	0 (0)
Leukocytes Decreased	67 (32)	1 (1)	93 (47)	11 (6)
Chemistry				
Alkaline Phosphatase Increased	141 (68)	7 (3)	111 (56)	13 (7)
AST Increased	79 (38)	5 (2)	103 (52)	14 (7)
Creatinine Increased	119 (57)	7 (3)	97 (49)	2 (1)
Glucose Increased	186 (89)	33 (16)	128 (64)	6 (3)
Phosphorus Decreased	102 (49)	38 (18)	61 (31)	17 (9)
Total Bilirubin Increased	16 (8)	2 (1)	25 (13)	4 (2)
Total Cholesterol Increased	181 (87)	5 (2)	95 (48)	2 (1)
Triglycerides Increased	173 (83)	92 (44)	144 (72)	69 (35)
Potassium Decreased	43 (21)	11 (5)	15 (8)	0 (0)

*NCI CTC version 3.0

**Grade 1 toxicity may be under-reported for lymphocytes and neutrophils

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)].

7.2 Agents Inhibiting CYP3A Metabolism

Co-administration of TORISEL with ketoconazole, a potent CYP3A4 inhibitor, had no significant effect on temsirolimus $C_{\max}$ or AUC; however, sirolimus AUC increased 3.1-fold, and $C_{\max}$ increased 2.2-fold compared to TORISEL alone. If alternative treatment cannot be administered, a dose adjustment should be considered. [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 is 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* (5.13)].

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

No clinical studies were conducted with TORISEL in patients with decreased renal function. Less than 5% of total radioactivity was excreted in the urine following a 25 mg intravenous dose of [^{14}C]-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

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

10 OVERDOSAGE

There is no specific treatment for TORISEL intravenous overdose. TORISEL has been administered to patients with cancer in phase 1 and 2 trials with repeated intravenous doses as high as 220 mg/m². The risk of several serious adverse events, including thrombosis, bowel perforation, interstitial lung disease (ILD), seizure, and psychosis, is increased with doses of TORISEL greater than 25 mg.

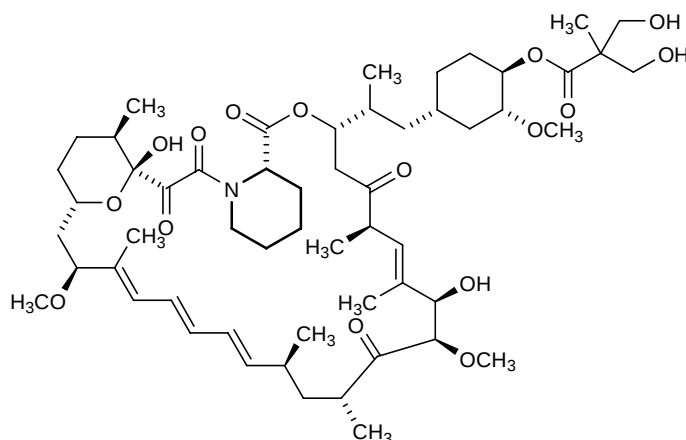
11 DESCRIPTION

Temsirolimus, an inhibitor of mTOR, is an antineoplastic 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

(3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34*aS*)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34*a*-Hexadecahydro-9,27-dihydroxy-3-[(1*R*)-2-[(1*S*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexameth3*H*-pyrido[2,1-*c*][1,4]oxaazacyclohentriacontine-1,5,11,28,29(4*H*,6*H*,31*H*)-pentone 4'-[2,2-bis(hydroxymethyl)propionate]; or Rapamycin, 42-[3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate].



TORISEL (temsirolimus) injection, 25 mg/mL, is a clear, colorless to light-yellow, non-aqueous, ethanolic, sterile solution. TORISEL (temsirolimus) injection requires two dilutions prior to intravenous infusion. TORISEL (temsirolimus) injection should be diluted only with the supplied DILUENT for TORISEL.

DILUENT for TORISEL is a sterile, non-aqueous solution that is supplied with TORISEL injection, as a kit.

TORISEL (temsirolimus) injection, 25 mg/mL:

Active ingredient: temsirolimus (25 mg/mL)

Inactive ingredients: dehydrated alcohol (39.5% w/v), *dl*-alpha-tocopherol (0.075% w/v), propylene glycol (50.3% w/v), and anhydrous citric acid (0.0025% w/v).

DILUENT for TORISEL

Inactive ingredients: polysorbate 80 (40.0% w/v), polyethylene glycol 400 (42.8% w/v), and dehydrated alcohol (19.9%w/v).

After the TORISEL (temsirolimus) injection vial has been diluted with DILUENT for TORISEL, in accordance with the instructions in section 2.5, the solution contains 35.2% alcohol.

TORISEL (temsirolimus) injection and DILUENT for TORISEL are filled in clear glass vials with butyl rubber stoppers.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

Absorption

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

Distribution

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

Metabolism

Cytochrome P450 3A4 is the major isozyme responsible for the formation of five temsirolimus metabolites. Sirolimus, an active metabolite of temsirolimus, is the principal metabolite in humans following intravenous treatment. The remainder of the metabolites account for less than 10% of radioactivity in the plasma. In human liver microsomes temsirolimus was an inhibitor of

CYP2D6 and 3A4. However, there was no effect observed *in vivo* when temsirolimus was administered with desipramine (a CYP2D6 substrate), and no effect is anticipated with substrates of CYP3A4 metabolism.

Elimination

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

Effects of Age and Gender

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

In male rats, the following fertility effects were observed: decreased number of pregnancies, decreased sperm concentration and motility, decreased reproductive organ weights, and testicular tubular degeneration. These effects were observed at oral temsirolimus doses ≥ 3 mg/m²/day (approximately 0.2-fold the human recommended intravenous dose). Fertility was absent at 30 mg/m²/day.

In female rats, an increased incidence of pre- and post-implantation losses occurred at oral doses ≥ 4.2 mg/m²/day (approximately 0.3-fold the human recommended intravenous dose), resulting in decreased numbers of live fetuses.

14 CLINICAL STUDIES

A phase 3, multi-center, three-arm, randomized, open-label study was conducted in previously untreated patients with advanced renal cell carcinoma (clear cell and non-clear cell histologies). The objectives were to compare Overall Survival (OS), Progression-Free Survival (PFS), Objective Response Rate (ORR), and safety in patients receiving IFN- α to those receiving TORISEL or TORISEL plus IFN- α . Patients in this study had 3 or more of 6 pre-selected prognostic risk factors (less than one year from time of initial RCC diagnosis to randomization, Karnofsky performance status of 60 or 70, hemoglobin less than the lower limit of normal,

corrected calcium of greater than 10 mg/dL, lactate dehydrogenase > 1.5 times the upper limit of normal, more than one metastatic organ site). Patients were stratified for prior nephrectomy status within three geographic regions and were randomly assigned (1:1:1) to receive IFN- α alone (n=207), TORISEL alone (25 mg weekly; n=209), or the combination arm (n=210).

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

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

There was a statistically significant improvement in OS (time from randomization to death) in the TORISEL 25 mg arm compared to IFN- α . The combination of TORISEL 15 mg and IFN- α did not result in a significant increase in overall survival when compared with IFN- α alone. Figure 1 is a Kaplan-Meier plot of OS in this study. The evaluations of PFS (time from randomization to disease progression or death) and ORR, were based on blinded independent radiologic assessment of tumor response. Efficacy results are summarized in Table 3.

Table 3: Summary of Efficacy Results of TORISEL vs. IFN-α				
Parameter	TORISEL n = 209	IFN-α n = 207	P-value^a	Hazard Ratio (95% CI)^b
Median Overall Survival Months (95% CI)	10.9 (8.6, 12.7)	7.3 (6.1, 8.8)	0.0078*	0.73 (0.58, 0.92)
Median Progression-Free Survival Months (95% CI)	5.5 (3.9, 7.0)	3.1 (2.2, 3.8)	0.0001**	0.66 (0.53, 0.81)
Overall Response Rate % (95% CI)	8.6 (4.8, 12.4)	4.8 (1.9, 7.8)	0.1232** ^c	NA

CI = confidence interval; NA = not applicable

* A comparison is considered statistically significant if the p-value is <0.0159 (O'Brien-Fleming boundary at 446 deaths).

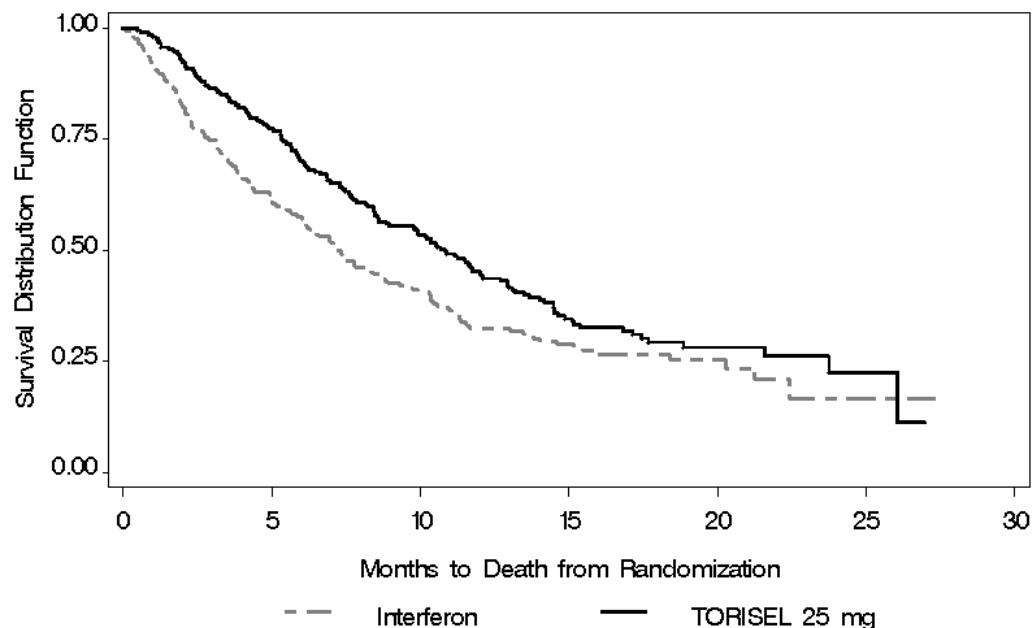
** Not adjusted for multiple comparisons.

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

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

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

Figure 1: Kaplan—Meier Curves for Overall Survival — TORISEL vs. IFN



15 REFERENCES

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2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999.
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4. American Society of Health-System Pharmacists. (2006) ASHP Guidelines on Handling Hazardous Drugs.
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16 HOW SUPPLIED/STORAGE AND HANDLING

NDC 0008-1179-01 TORISEL (temsirolimus) injection, 25 mg/mL.

NDC 0008-1125-01 DILUENT for TORISEL, 1.8 mL (deliverable volume) per vial.

These two vials are supplied as a kit in a single carton, and must be stored at 2°-8°C (36°-46°F).
Protect from light.

U.S Patent No. 5,362,718

17 PATIENT COUNSELING INFORMATION

- **Allergic (Hypersensitivity) Reactions**

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

- **Increased Blood Glucose Levels**

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

- **Infections**

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

- **Interstitial Lung Disease**

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

- **Increased Blood Triglycerides and/or Cholesterol**

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

- **Bowel Perforation**

Patients should be warned of the possibility of bowel perforation. Patients should be directed to report promptly any new or worsening abdominal pain or blood in their stools [*see Warnings and Precautions (5.6)*].

- **Renal Failure**

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

- **Wound Healing Complications**

Patients should be advised of the possibility of abnormal wound healing if they have surgery within a few weeks of initiating therapy or during therapy [see *Warnings and Precautions* (5.8)].

- **Intracerebral Bleeding**

Patients with CNS tumors and/or receiving anticoagulants should be informed of the increased risk of developing intracerebral bleeding (including fatal outcomes) while on TORISEL [see *Warnings and Precautions* (5.9)].

- **Medications that can interfere with TORISEL**

Some medicines can interfere with the breakdown or metabolism of TORISEL. In particular, patients should be directed to inform their physician if they are taking any of the following: Protease inhibitors, anti-epileptic medicines including carbamazepine, phenytoin, and barbiturates, St. John's Wort, rifampicin, rifabutin, nefazodone or selective serotonin re-uptake inhibitors used to treat depression, antibiotics or antifungal medicines used to treat infections [see *Warnings and Precautions* (5.10)].

- **Vaccinations**

Patients should be advised that vaccinations may be less effective while being treated with TORISEL. In addition, the use of live vaccines, and close contact with those who have received live vaccines, while on TORISEL should be avoided. [see *Warnings and Precautions* (5.12)].

- **Pregnancy**

TORISEL can cause fetal harm. Women of childbearing potential should be advised to avoid becoming pregnant throughout treatment and for 3 months after TORISEL therapy has stopped. Men with 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* (5.13)]

Wyeth®

Wyeth Pharmaceuticals Inc.
Philadelphia, PA 19101

Manufactured for: Wyeth Pharmaceuticals Inc. Philadelphia, PA 19101

TORISEL (temsirolimus) injection is manufactured by: Pierre Fabre Medicament Production, Aquitaine Pharm International, Avenue du Bearn, F64320 Idron, France

DILUENT for TORISEL is manufactured by: Ben Venue Laboratories, Inc., Bedford, Ohio 44146-0568

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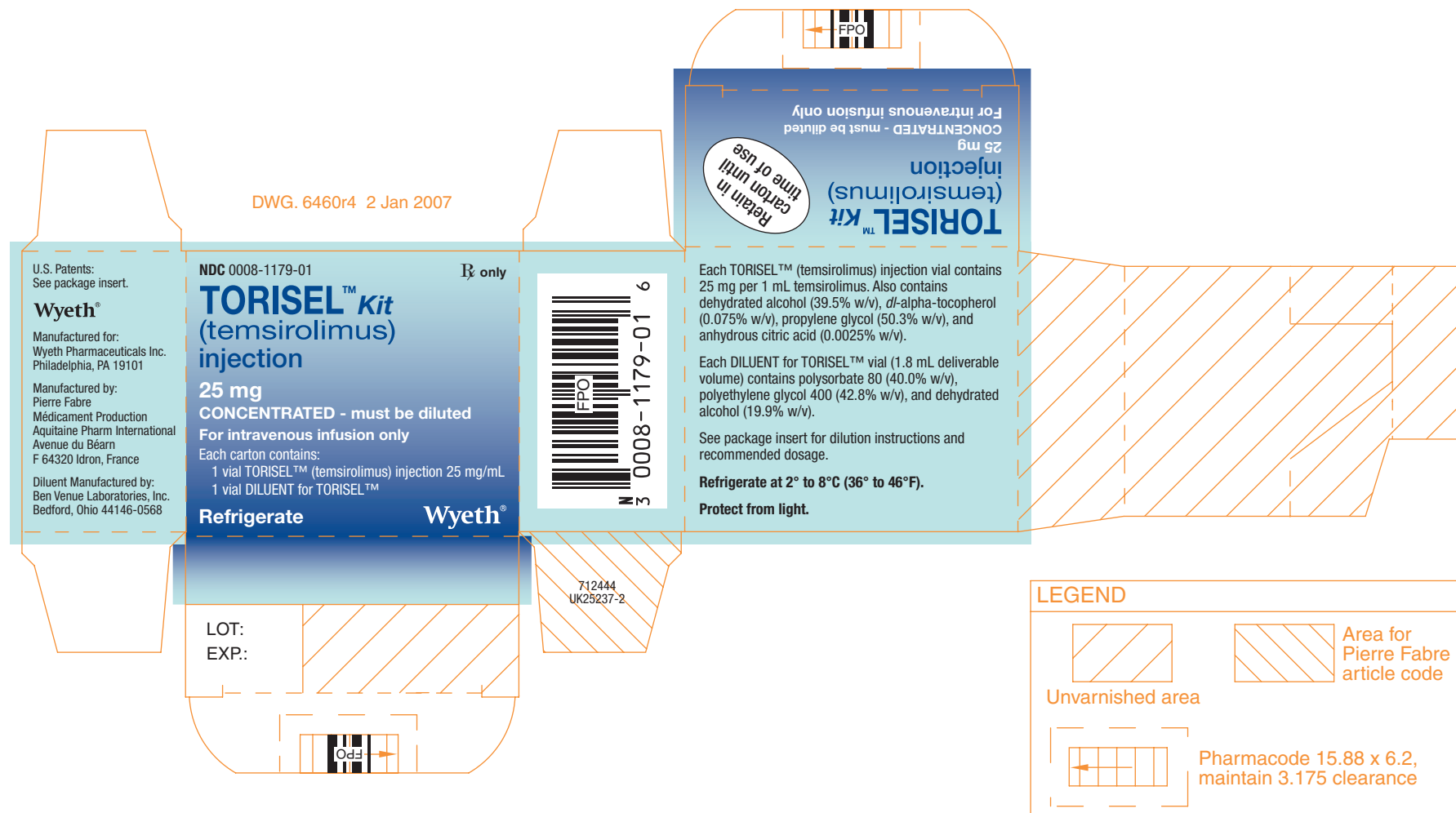
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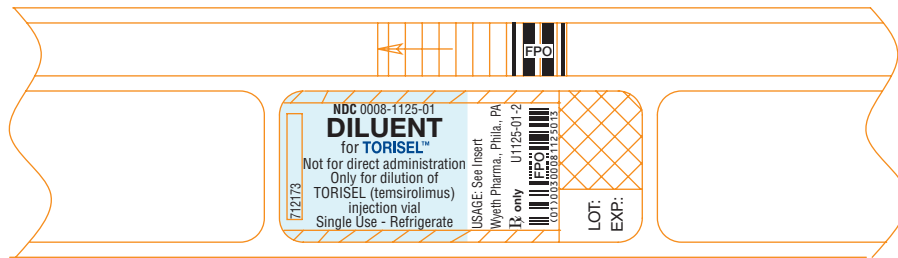
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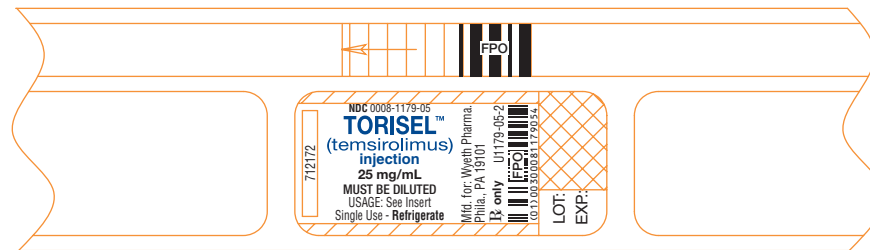
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