

TORISEL[®]
(temsirolimus) injection

Preparation and
Administration
Guide



**Please see Important Safety Information on pages 20 and 21,
and accompanying full Prescribing Information.**

Indication

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

Overall Survival Benefit Achieved as First-line Therapy

- 49% significant increase in median overall survival (OS) compared with IFN α ($P=.$ 0078^{*†}) (Hazard Ratio [95% CI][‡] = 0.73 [0.58, 0.92])[†]
 - 10.9 months [8.6, 12.7] vs 7.3 months [6.1, 8.8], respectively[†]
 - Median duration of treatment was 17 weeks (range 1-126 weeks) for TORISEL and 8 weeks (range 1-124 weeks) for IFN α [†]

In this reference guide you will find information regarding the dosage and administration of TORISEL, as well as Important Safety Information.

Contents

Topic	Page
Storage and Handling of TORISEL	4
Preparation of TORISEL for Infusion	6
Dosage and Administration of TORISEL	8
Contraindication and Information Regarding Patients With Hepatic Impairment.....	12
Drug Interactions With CYP3A Inhibitors and Inducers for TORISEL	14
Adverse Reactions	16
Important Safety Information	20

Important Safety Information

TORISEL is contraindicated in patients with bilirubin >1.5 x ULN and should be used with caution and at a reduced dose when treating patients with mild hepatic impairment. For additional information on this contraindication and other warnings and precautions, please see full Important Safety Information on pages 20 and 21.



Please see Important Safety Information on pages 20 and 21, and accompanying full Prescribing Information.



IFN α =interferon alpha. CI=confidence interval.

ULN=upper limit of normal.

*A comparison is considered statistically significant if the P -value is $<.0159$ (O'Brien-Fleming boundary at 446 deaths).

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

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

Storage and Handling of TORISEL

How Supplied

Each carton contains 1 vial of each of the following:

- TORISEL (temsirolimus) injection, 25 mg/mL, 1.2 mL (NDC 0008-1179-01)
- DILUENT for TORISEL (temsirolimus), 1.8 mL (deliverable volume) per vial (NDC 0008-1125-01)

These 2 vials are supplied as a kit in a single carton.



Storage

Both vials in the TORISEL Kit must be stored under refrigeration at 2° - 8°C (36° - 46°F) and protected from light.¹

Handling

During handling and preparation of admixtures, TORISEL should be protected from excessive room light and sunlight.¹

TORISEL should be inspected visually for particulate matter and discoloration prior to administration.¹



TORISEL[®]
(temsirolimus) injection

Please see Important Safety Information on pages 20 and 21, and accompanying full Prescribing Information.

Preparation of TORISEL for Infusion

Dilution

The TORISEL administration solution is prepared aseptically using a 2-step process.¹

Step 1:

- Inject 1.8 mL of diluent for TORISEL into the vial of TORISEL injection (25 mg/mL)¹
 - The TORISEL vial contains an intentional overfill of 0.2 mL
 - 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 inverting the vial¹
- Allow sufficient time for air bubbles to subside¹
- The solution is clear to slightly turbid, colorless to yellow, and free from visual particulates¹
- The 10 mg/mL drug solution/diluent mixture obtained in Step 1 is stable for up to 24 hours at controlled room temperature¹
- The 10 mg/mL drug solution/diluent mixture must be further diluted as described in Step 2

* A 1.2 mL volume of drug concentrate contains a total of 30 mg of drug product. When 1.2 mL of drug concentrate is combined with 1.8 mL of diluent, a total volume of 3 mL is obtained. The drug concentration will be 10 mg/mL.

Step 2:

- Withdraw the required amount of TORISEL from the 10 mg/mL mixture prepared in Step 1¹
 - For example, for a 25 mg dose, withdraw 2.5 mL
- Inject the mixture rapidly into a **250 mL** container (glass, polyolefin, polyethylene) of 0.9% sodium chloride injection¹
 - Avoid using di-2-ethylhexyl phthalate (DEHP)-containing materials during the preparation and administration of TORISEL¹
- Mix the admixture by inverting the bag or bottle¹
 - **Avoid excessive shaking**, as this may cause foaming
- Administration of the final diluted infusion solution should be completed within 6 hours from the time that the drug solution/diluent mixture (obtained in Step 1) is added to the sodium chloride injection¹

Special Considerations Regarding Preparation

- Always combine TORISEL injection with diluent for TORISEL before adding to infusion solutions¹
- Do not add undiluted TORISEL injection directly to aqueous infusion solutions—this will result in precipitation of the drug¹
- During handling and preparation of admixtures, TORISEL should be protected from excessive room light and sunlight¹



 **TORISEL**[®]
(temsirolimus) injection

Please see Important Safety Information on pages 20 and 21, and accompanying full Prescribing Information.

Dosage and Administration of TORISEL

Premedication

Antihistamine pretreatment is recommended. Patients should receive prophylactic intravenous diphenhydramine 25 to 50 mg (or similar antihistamine) approximately 30 minutes before the start of each dose of TORISEL.¹

TORISEL should be used with caution in¹

- Patients with known hypersensitivity to an antihistamine
- Patients who cannot receive an antihistamine for other medical reasons
- See Hypersensitivity Information on page 11

Dosage

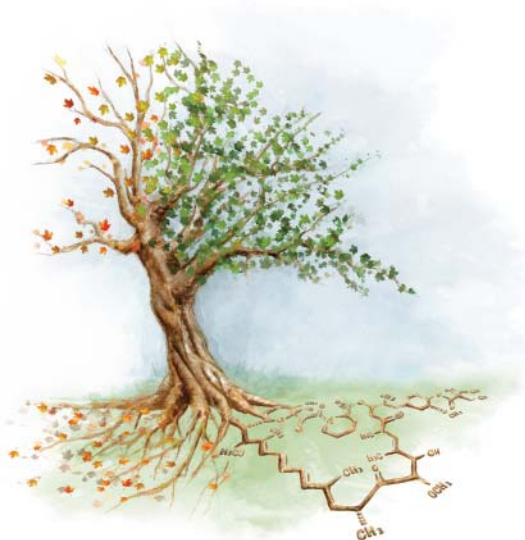
The recommended dose of TORISEL for advanced RCC is 25 mg infused intravenously over a 30- to 60-minute period once a week.¹

- Treatment should continue until disease progression or unacceptable toxicity occurs¹
- More information about dosage adjustment for specific circumstances or patient populations is included on the pages that follow

Administration

The final diluted solution of TORISEL should be infused over a 30- to 60-minute period.¹

- An infusion pump is the preferred method of administration to ensure accurate delivery of the drug¹
- An in-line polyethersulfone filter with a pore size of not greater than 5 microns is recommended for administration¹
- 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 DEHP. TORISEL contains polysorbate 80, which is known to increase the rate of DEHP extraction from PVC¹



 **TORISEL**[®]
(temsirolimus) injection

Please see Important Safety Information on pages 20 and 21, and accompanying full Prescribing Information.

Special Considerations Regarding the Dosage and Administration of TORISEL

- If TORISEL must be given to patients with mild hepatic impairment (bilirubin $>1 - 1.5 \times \text{ULN}$ or AST $>\text{ULN}$ but bilirubin $\leq\text{ULN}$), reduce the dose of TORISEL to 15 mg/week¹
 - See pages 12 and 13 for more information
- TORISEL administration should be held if the patient experiences at least 1 of the following toxicities¹:
 - Absolute neutrophil count (ANC) $<1,000/\text{mm}^3$
 - Platelet count $<75,000/\text{mm}^3$
 - 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.¹
- Strong inducers of CYP3A4/5 (eg, dexamethasone, rifampin) and strong inhibitors of CYP3A4 (eg, ketoconazole, atazanavir) may decrease and increase concentrations of the major metabolite of TORISEL, respectively. If alternatives cannot be used, dose modifications of TORISEL are recommended. See pages 14 and 15 for more information.

AST=aspartate aminotransferase.

National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE), version 3.0.

Hypersensitivity Information

- In the phase 3 study, all hypersensitivity reactions experienced by patients receiving TORISEL alone were of grade 1 or 2 severity²
 - 5% of patients experienced a hypersensitivity reaction(s) on the same day as dosing, despite receiving premedication with an antihistamine²
 - A total of 9% of patients experienced allergic or hypersensitivity reactions¹
- In post-marketing surveillance, hypersensitivity reactions include some life-threatening and rare fatal reactions, which can occur very early in the first infusion of TORISEL, but may also occur with subsequent infusions.² Patients should be monitored early during the infusion and appropriate supportive care should be available

Dosage and Administration Adjustments Following a Hypersensitivity Reaction

If a patient develops a hypersensitivity reaction during the TORISEL infusion¹

1. Stop the infusion
2. Observe the patient for at least 30 to 60 minutes (depending on the severity of the reaction)¹
3. At the discretion of the physician, treatment may be resumed with the administration of one or both of the following agents approximately 30 minutes before restarting the infusion:
 - H₁-receptor antagonist (such as diphenhydramine), if not previously administered
 - H₂-receptor antagonist (such as IV famotidine 20 mg or IV ranitidine 50 mg)
4. The infusion may then be resumed at a slower rate (up to 60 minutes)¹



TORISEL[®]
(temsirolimus) injection

Please see Important Safety Information on pages 20 and 21, and accompanying full Prescribing Information.

Contraindication and Information Regarding Patients With Hepatic Impairment

Contraindication

TORISEL is contraindicated in patients with bilirubin $>1.5 \times \text{ULN}$ due to increased risk of death.¹

TORISEL should be used with caution when treating patients with mild hepatic impairment, defined as:

- Bilirubin $>1 - 1.5 \times \text{ULN}$
or
- AST $>\text{ULN}$ but bilirubin $\leq \text{ULN}$

Dose Adjustment for Mild Hepatic Impairment

If TORISEL must be given to patients with mild hepatic impairment, reduce the dose to 15 mg/week.¹

Because there is a need for dosage adjustment based upon hepatic function, assessment of AST and bilirubin levels is recommended before initiation of TORISEL and periodically thereafter.¹

Phase 1 Study Results Regarding Hepatic Impairment

TORISEL was evaluated in a dose escalation phase 1 study in 110 patients with normal or varying degrees of hepatic impairment* and patients with liver transplant.¹

Patients with baseline bilirubin $>1.5 \times \text{ULN}$ experienced greater toxicity than patients with baseline bilirubin $\leq 1.5 \times \text{ULN}$ when treated with TORISEL. Concentrations of temsirolimus and its metabolite sirolimus were increased in patients with elevated AST or bilirubin levels.¹

The overall frequency of \geq grade 3 adverse reactions and deaths[†] were greater in patients with baseline bilirubin $>1.5 \times \text{ULN}$.¹

Adverse Reactions in Patients With Advanced Malignancies and Varying Hepatic Function			
Hepatic Function [‡]	TORISEL Dose Range (mg)	Adverse Reactions \geq Grade 3 [§] n (%)	Death [†] n (%)
Normal (n=25)	25–175	20 (80.0)	2 (8.0)
Mild (n=39)	10–25	32 (82.1)	5 (12.8)
Moderate (n=20)	10–25	19 (95.0)	8 (40.0)
Severe (n=24)	7.5–15	23 (95.8)	13 (54.2)
Liver Transplant (n=2)	10	1 (50.0)	0 (0)

* As defined by AST and bilirubin levels.

[†] Including deaths due to adverse reactions and progressive disease.

[‡] Hepatic Function Groups: normal = bilirubin and AST $\leq \text{ULN}$; mild = bilirubin $>1 - 1.5 \times \text{ULN}$ or AST $>\text{ULN}$ but bilirubin $\leq \text{ULN}$; moderate = bilirubin $>1.5 - 3 \times \text{ULN}$; severe = bilirubin $>3 \times \text{ULN}$; liver transplant = any bilirubin and AST.

[§] CTCAE, version 3.0, including all causality.



Please see Important Safety Information on pages 20 and 21, and accompanying full Prescribing Information.

Drug Interactions With CYP3A Inhibitors and Inducers for TORISEL

CYP3A4 Inhibitors

Strong CYP3A4 inhibitors may increase blood concentrations of sirolimus, the active metabolite of TORISEL.¹

- Concomitant treatment with agents that have strong CYP3A4 inhibition potential should be avoided¹
- If alternative treatment cannot be administered, a TORISEL dose reduction to 12.5 mg/week should be considered¹

Examples of CYP3A Inhibitors ¹	
Class	Agents
Antidepressants	nefazodone (Serzone [®])
Antifungals	itraconazole (Sporanox [®]) ketoconazole (Nizoral [®]) voriconazole (Vfend [®])
Antivirals	atazanavir (Reyataz [®]) indinavir (Crixivan [®]) nelfinavir (Viracept [®]) ritonavir (Norvir [®]) saquinavir (Invirase [®])
Macrolide Antibiotics	clarithromycin (Biaxin [®]) telithromycin (Ketek [®])
Other Agents	grapefruit juice

CYP3A4 Inducers

Strong CYP3A4/5 inducers may decrease exposure of sirolimus, the active metabolite of TORISEL.¹

- Concomitant use of strong CYP3A4 inducers should be avoided¹
- If alternative treatment cannot be administered, a TORISEL dose increase up to 50 mg/week should be considered¹

Examples of CYP3A Inducers ¹	
Class	Agents
Anticonvulsants	carbamazepine (Tegretol [®]) phenobarbital phenytoin (Dilantin [®])
Antibiotics	rifampin/rifampicin (Rifadin [®]) rifabutin (Mycobutin [®])
Other Agents	St. John's Wort (<i>Hypericum perforatum</i>) dexamethasone (Decadron [®])

TORISEL is a registered trademark of Pfizer Inc. Other brands listed are the trademarks of their respective owners and are not trademarks of Pfizer Inc.

 **TORISEL**[®]
(temsirolimus) injection

Please see Important Safety Information on pages 20 and 21, and accompanying full Prescribing Information.

Adverse Reactions

Common Adverse Reactions

The following common adverse reactions of all grades* occurred with an incidence $\geq 30\%$ in patients receiving TORISEL.¹

Adverse Reaction	TORISEL (n=208)	
	All Grades	Grades 3&4
Asthenia	51%	11%
Rash [†]	47%	5%
Mucositis [‡]	41%	3%
Nausea	37%	2%
Edema [§]	35%	3%
Anorexia	32%	3%

* CTCAE, version 3.0.

[†] Includes eczema, exfoliative dermatitis, maculopapular rash, pruritic rash, pustular rash, rash not otherwise specified (NOS), and vesiculobullous rash.

[‡] Includes aphthous stomatitis, glossitis, mouth ulceration, mucositis, and stomatitis.

[§] Includes edema, facial edema, and peripheral edema.

Severe Adverse Reactions and Laboratory Abnormalities

The following severe (grade 3 or 4)* adverse reactions and laboratory abnormalities occurred with an incidence $\geq 10\%$ in patients receiving TORISEL.¹

Grade 3 or 4 Adverse Reaction or Lab Abnormality	TORISEL (n=208)
Hypertriglyceridemia	44%
Anemia	20%
Hypophosphatemia	18%
Lymphopenia [¶]	16%
Hyperglycemia	16%
Asthenia	11%

* CTCAE, version 3.0.

[¶] Grade 1 toxicity may be under-reported for lymphocytes.

Laboratory Abnormalities

Incidence of selected laboratory abnormalities in patients who received TORISEL.¹

Laboratory Abnormality	TORISEL (n=208)	
	All Grades*	Grades 3&4*
Any	100%	78%
Hematology (checked weekly)		
Hemoglobin decreased	94%	20%
Lymphocytes decreased [¶]	53%	16%
Platelets decreased	40%	1%
Leukocytes decreased	32%	1%
Neutrophils decreased [¶]	19%	5%
Chemistry (checked every 2 weeks)		
Glucose increased	89%	16%
Total cholesterol increased	87%	2%
Triglycerides increased	83%	44%
Alkaline phosphatase increased	68%	3%
Creatinine increased	57%	3%
Phosphorus decreased	49%	18%
AST increased	38%	2%
Potassium decreased	21%	5%
Total bilirubin increased	8%	1%

* CTCAE, version 3.0.

[¶] Grade 1 toxicity may be under-reported for lymphocytes and neutrophils.

- In the phase 3 clinical trial
 - Complete blood counts were checked weekly¹
 - Chemistry panels were checked every 2 weeks¹
 - Laboratory monitoring for patients receiving TORISEL may need to be performed more or less frequently at the physician's discretion¹
- Serum glucose, serum cholesterol, and triglycerides should be tested before and during treatment with TORISEL¹
- Because there is a need for dosage adjustment based upon hepatic function, assessment of AST and bilirubin levels is recommended before initiation of TORISEL and periodically thereafter¹



Please see Important Safety Information on pages 20 and 21, and accompanying full Prescribing Information.

Adverse reactions reported in at least 10% of patients who received TORISEL® (temsirolimus) or IFN α ¹

Adverse Reaction	All Grades*		Grades 3&4*	
	TORISEL 25 mg IV once weekly n=208 (%)	IFN α up to 18 MU 3x weekly n=200 (%)	TORISEL 25 mg IV once weekly n=208 (%)	IFN α up to 18 MU 3x weekly n=200 (%)
Any	100	100	67	78
General disorders				
Asthenia	51	64	11	26
Edema [†]	35	11	3	1
Pain	28	16	5	2
Pyrexia	24	50	1	4
Weight loss	19	25	1	2
Headache	15	15	1	0
Chest pain	16	9	1	1
Chills	8	30	1	2
Gastrointestinal disorders				
Mucositis [‡]	41	10	3	0
Anorexia	32	44	3	4
Nausea	37	41	2	5
Diarrhea	27	20	1	2
Abdominal pain	21	17	4	2
Constipation	20	18	0	1
Vomiting	19	29	2	3
Infections				
Infections [§]	20	10	3	2
Urinary tract infection	15	12	1	2
Pharyngitis	12	2	0	0
Rhinitis	10	2	0	0
Musculoskeletal and connective tissue disorders				
Back pain	20	14	3	4
Arthralgia	18	15	1	1
Myalgia	8	15	1	1
Respiratory, thoracic, and mediastinal disorders				
Dyspnea	28	24	9	6
Cough	26	15	1	0
Epistaxis	12	4	0	0
Skin and subcutaneous tissue disorders				
Rash [¶]	47	7	5	0
Pruritus	19	8	1	0
Nail disorder	14	1	0	0
Dry skin	11	7	1	0
Acne	10	1	0	0
Nervous system disorders				
Dysgeusia ^{**}	20	9	0	0
Insomnia	12	15	1	0
Depression	4	14	0	2

* CTCAE, version 3.0.

[†] Includes edema, facial edema, and peripheral edema.

[‡] Includes aphthous stomatitis, glossitis, mouth ulceration, mucositis, and stomatitis.

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

^{||} Includes cystitis, dysuria, hematuria, urinary frequency, and urinary tract infection.

[¶] Includes eczema, exfoliative dermatitis, maculopapular rash, pruritic rash, pustular rash, rash (NOS), and vesiculobullous rash.

^{**} Includes taste loss and taste perversion.

Please see Important Safety Information on pages 20 and 21, and accompanying full Prescribing Information.

Important Safety Information

- TORISEL is contraindicated in patients with bilirubin $>1.5 \times \text{ULN}$ and should be used with caution when treating patients with mild hepatic impairment (bilirubin $>1 - 1.5 \times \text{ULN}$ or AST $>\text{ULN}$ but bilirubin $\leq\text{ULN}$). If TORISEL must be given to patients with mild hepatic impairment, reduce the dose of TORISEL to 15 mg/week. In a phase 1 study, the overall frequency of \geq grade 3 adverse reactions and deaths, including deaths due to progressive disease, was greater in patients with baseline bilirubin $>1.5 \times \text{ULN}$.
- Hypersensitivity reactions manifested by symptoms, including, but not limited to anaphylaxis, dyspnea, flushing, and chest pain have been observed with TORISEL.
- Serum glucose, serum cholesterol, and triglycerides should be tested before and during treatment with TORISEL.
 - The use of TORISEL is likely to result in hyperglycemia and hyperlipemia. This may result in the need for an increase in the dose of, or initiation of, insulin and/or oral hypoglycemic agent therapy and/or lipid-lowering agents, respectively.
- The use of TORISEL may result in immunosuppression. Patients should be carefully observed for the occurrence of infections, including opportunistic infections.
- Cases of interstitial lung disease, some resulting in death, have occurred. Some patients were asymptomatic and others presented with symptoms. Some patients required discontinuation of TORISEL and/or treatment with corticosteroids and/or antibiotics.
- Cases of fatal bowel perforation occurred with TORISEL. These patients presented with fever, abdominal pain, metabolic acidosis, bloody stools, diarrhea, and/or acute abdomen.
- Cases of rapidly progressive and sometimes fatal acute renal failure not clearly related to disease progression occurred in patients who received TORISEL.
- Due to abnormal wound healing, use TORISEL with caution in the perioperative period.
- Patients with central nervous system tumors (primary CNS tumor or metastases) and/or receiving anticoagulation therapy may be at an increased risk of developing intracerebral bleeding (including fatal outcomes) while receiving TORISEL.
- Live vaccinations and close contact with those who received live vaccines should be avoided.
- Patients and their partners should be advised to avoid pregnancy throughout treatment and for 3 months after TORISEL therapy has stopped.
- The most common (incidence $\geq 30\%$) adverse reactions observed with TORISEL are: rash (47%), asthenia (51%), mucositis (41%), nausea (37%), edema (35%), and anorexia (32%). The most common laboratory abnormalities (incidence $\geq 30\%$) are anemia (94%), hyperglycemia (89%), hyperlipemia (87%), hypertriglyceridemia (83%), elevated alkaline phosphatase (68%), elevated serum creatinine (57%), lymphopenia (53%), hypophosphatemia (49%), thrombocytopenia (40%), elevated AST (38%), and leukopenia (32%).
- Most common grades 3/4 adverse events and laboratory abnormalities included asthenia (11%), dyspnea (9%), hemoglobin decreased (20%), lymphocytes decreased (16%), glucose increased (16%), phosphorus decreased (18%), and triglycerides increased (44%).
- Strong inducers of CYP3A4/5 (eg, dexamethasone, rifampin) and strong inhibitors of CYP3A4 (eg, ketoconazole, atazanavir) may decrease and increase concentrations of the major metabolite of TORISEL, respectively. If alternatives cannot be used, dose modifications of TORISEL are recommended.
- St. John's Wort may decrease TORISEL plasma concentrations, and grapefruit juice may increase plasma concentrations of the major metabolite of TORISEL, and therefore both should be avoided.
- The combination of TORISEL and sunitinib resulted in dose-limiting toxicity (Grade 3/4 erythematous maculopapular rash, and gout/cellulitis requiring hospitalization).

References: 1. TORISEL® Kit (temsirrolimus) Prescribing Information, Wyeth Pharmaceuticals Inc.
2. Data on file, Pfizer Inc.



Please see accompanying full Prescribing Information.

Dosage and Administration: Quick Reference Guide

- The recommended dose of TORISEL for advanced RCC is 25 mg infused over a 30- to 60-minute period once a week¹
- **NOTE:** If TORISEL must be given to patients with mild hepatic impairment (bilirubin >1 - 1.5 x ULN or AST >ULN but bilirubin ≤ULN), they should receive a 15 mg dose¹
- Strong inducers of CYP3A4/5 (eg, dexamethasone, rifampin) and strong inhibitors of CYP3A4 (eg, ketoconazole, atazanavir) may decrease and increase concentrations of the major metabolite of TORISEL, respectively. If alternatives cannot be used, dose modifications of TORISEL are recommended¹
- Treatment should continue until disease progression or unacceptable toxicity occurs¹
- Patients should receive prophylactic intravenous diphenhydramine 25 to 50 mg (or similar antihistamine) approximately 30 minutes before the start of each dose of TORISEL¹
- Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnea, flushing, and chest pain have been observed with TORISEL¹
- TORISEL administration should be held if the patient experiences at least 1 of the following toxicities¹:
 - Absolute neutrophil count (ANC) <1,000/mm³
 - Platelet count <75,000/mm³
 - 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/week¹



Please see Important Safety
Information on pages 20 and 21,
and accompanying full
Prescribing Information.

 **TORISEL**[®]
(temsirolimus) injection
www.TORISEL.com