DRUG INTERACTIONS WITH CYP3A INDUCERS AND INHIBITORS FOR TORISEL® (temsirolimus) injection

Cytochrome P450 3A4 (CYP3A4) is the major isozyme responsible for the formation of 5 temsirolimus metabolites.[1] Sirolimus, an active metabolite of temsirolimus, is the principal metabolite in humans following intravenous treatment and is also known to be metabolized by the CYP3A4 isoenzymes.[1] The following tables are not all-inclusive. Care should be exercised when drugs or other substances that affect CYP3A4 are administered concomitantly with temsirolimus.[1]

CYP3A4/5 Inducers

Strong inducers of CYP3A4/5 may decrease exposure of the active metabolite, sirolimus. **Therefore, concomitant treatment with agents that have strong CYP3A4/5 induction potential should be avoided.** If alternative treatment cannot be administered, a **TORISEL dose increase up to 50 mg** per week should be considered.[1]

Examples of CYP3A Inducers[1]

Generic	Brand Name
Anticonvulsants	
carbamazepine	Tegretol®
phenobarbital	N/A
phenytoin	Dilantin®
Antibiotics	
rifampin/rifampicin	Rifadin®
rifabutin	Mycobutin®
Other Agents	
St. John's Wort (*Hypericum perforatum*)	N/A
dexamethasone	Decadron®

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 alone.[1]

Please see inside for Important Safety Information.

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CYP3A4 Inhibitors

Strong CYP3A4 inhibitors may increase blood concentrations of the active metabolite, sirolimus. **Therefore, concomitant treatment with agents that have strong CYP3A4 inhibition potential should be avoided.** If alternative treatment cannot be administered, a **TORISEL dose reduction to 12.5 mg** per week should be considered.[1]

Examples of CYP3A Inhibitors[1]

Generic	Brand Name
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	N/A

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.[1]

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

Important Safety Information

- 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 ≥30%) adverse reactions observed with TORISEL are: rash (47%), asthenia (51%), mucositis (41%), nausea (37%), edema (35%), and anorexia (32%). The most common laboratory abnormalities (incidence ≥30%) are anemia (94%), hyperglycemia (89%), hyperlipemia (87%), hypertriglyceridemia (83%), elevated alkaline phosphatase (68%), elevated serum creatinine (57%), lymphopenia (53%), hypophosphatemia (49%), thrombocytopenia (40%), elevated AST (38%), and leukopenia (32%).
- In the randomized, phase 3 trial, complete blood counts (CBCs) were checked weekly, and chemistry panels were checked every 2 weeks. Laboratory monitoring for patients receiving TORISEL may need to be performed more or less frequently at the physician's discretion.
- Most common grades 3/4 adverse events 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).

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TORISEL is administered as a fixed, weekly 25 mg IV infusion

- The recommended dose of TORISEL for advanced RCC is 25 mg infused over a 30- to 60-minute period once a week[1]
- Treatment should continue until disease progression or unacceptable toxicity occurs[1]
- 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]
- If a patient develops a hypersensitivity reaction, stop the infusion and observe for at least 30 to 60 minutes. At the physician's discretion, treat with an H_1 antagonist, if not previously administered, and/or an H_2 antagonist. The infusion may then be resumed at a slower rate (up to 60 minutes)[1]
- TORISEL should be held for absolute neutrophil count (ANC) <1,000/mm^3, platelet count <75,000/mm^3, or NCI CTCAE Grade 3 or greater adverse reactions. Once toxicities have been 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]
- Consider a TORISEL dose reduction to 12.5 mg/week if a strong CYP3A4 inhibitor is to be administered. Consider a TORISEL dose increase up to 50 mg/week if a strong CYP3A4 inducer is to be administered[1]

- TORISEL must be stored under refrigeration at 2°C to 8°C (36°F to 46°F) and protected from light[1]
- TORISEL must be diluted twice before administration[1]

Please see inside for Important Safety Information.

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Reference: 1. TORISEL™ Kit (temsirolimus) Prescribing Information, Wyeth Pharmaceuticals Inc.

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