

TORISEL® (temsirolimus) injection
Worldwide Fact Sheet

PRODUCT DESCRIPTION	TORISEL® (temsirolimus) is an intravenous inhibitor of mammalian target of rapamycin (mTOR), an intracellular protein that has been implicated in multiple growth related cellular functions. ^{1,2,3}
INDICATIONS	<p>TORISEL is an inhibitor of mTOR approved in the European Union for the first-line treatment of patients with advanced renal cell carcinoma (RCC) who have at least three of six prognostic risk factors.</p> <p>TORISEL is approved in the United States for the treatment of advanced RCC.³</p> <p>TORISEL is approved for the treatment of relapsed and/or refractory mantle cell lymphoma (MCL) in the European Union and several other countries outside the U.S.</p>
MECHANISM OF ACTION	Based on preclinical studies, TORISEL inhibits the activity of mTOR, an intracellular protein implicated in multiple growth-related cellular functions including proliferation, growth and survival. ^{1,2,3} The inhibition of mTOR also reduces levels of certain growth factors, such as vascular endothelial growth factor (VEGF), which are overexpressed in solid tumors like kidney cancer and are thought to play a crucial role in angiogenesis, ^{4,5} the process by which tumors acquire blood vessels, nutrients and oxygen needed for growth. ⁶ The mTOR pathway also regulates translation of the cell-cycle regulating protein cyclin D1, ⁷ which is commonly overexpressed in mantle cell lymphoma (MCL). ⁸
KIDNEY CANCER CLINICAL STUDIES	<p>In a Phase 3, randomized, multi-center trial, comparing TORISEL, IFN-α, and TORISEL plus IFN-α as first-line therapy in 626 patients with treatment-naïve advanced kidney cancer who also had three or more of six pre-selected prognostic risk factors:⁹</p> <ul style="list-style-type: none"> • TORISEL demonstrated a statistically significant increase in median overall survival (OS) compared with IFN-α. <ul style="list-style-type: none"> ◦ 10.9 months vs. 7.3 months with IFN-α (95% CI: 8.6,12.7 months and 6.1, 8.8 months, respectively [Hazard Ratio = 0.73], P=0.0078*) • TORISEL demonstrated a significant increase in median progression-free survival (PFS) compared with IFN-α as assessed by IRB. <ul style="list-style-type: none"> ◦ 5.5 months vs. 3.1 months with IFN-α (95%CI: 3.9, 7.0 months and 2.2, 3.8 months, respectively [Hazard Ratio = 0.66], P=0.0001[§]) • TORISEL did not show a significant difference in overall response rate (ORR) compared with IFN-α. <ul style="list-style-type: none"> ◦ 8.6 percent vs. 4.8 percent with IFN-α (95% CI: 4.8,12.4 and 1.9, 7.8, respectively [P=0.1232^{§**a}]) • The median duration of treatment in the study was 17 weeks for patients treated with TORISEL and 8 weeks for those treated with IFN-α. • 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 OS when compared with IFN- α alone.^{1,3}
MANTLE CELL LYMPHOMA CLINICAL STUDIES (Approved in the E.U. and several other countries outside the U.S.)	<p>In a Phase 3, randomized, multi-center trial, comparing two different dosing regimens of temsirolimus with an investigator's choice of therapy in 162 patients with relapsed and/or refractory mantle cell lymphoma:¹⁰</p> <ul style="list-style-type: none"> • Temsirolimus (175/75mg arm) led to a statistically significant improvement in the primary endpoint of PFS (independently assessed), compared with investigator's choice in patients with relapsed and/or refractory mantle cell lymphoma. <ul style="list-style-type: none"> ◦ 4.8 months vs.1.9 months with investigators choice (97.5% CI: 3.1, 8.1 months and 1.6, 2.5 months, respectively [P=0.0009, Hazard Ratio = 0.44]) • Temsirolimus (175/75mg arm) was associated with statistically significant advantages over investigator's choice in the secondary endpoint of ORR.

*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 Cochran-Mantel-Haenszel test stratified by prior nephrectomy and region

	<ul style="list-style-type: none"> ○ 22 percent vs. 2 percent with investigators choice (95% CI: 1.1 percent, 33 percent and 0.0, 5.4 percent, respectively [P=0.0019]) • Temsirolimus (175/75mg arm) was not associated with a significantly longer OS, a secondary endpoint, compared to the investigator's choice arm. <ul style="list-style-type: none"> ○ 11.1 months vs. 9.5 months with investigators choice (95% CI: 8.2, 18.0 months and 5.3, 15.1 months, respectively [P= 0.3053, Hazard Ratio = 0.77])
SAFETY PROFILE	<p>Important Safety Information:¹</p> <p>Renal Cell Carcinoma The most serious reactions observed with TORISEL are hypersensitivity/infusion reactions (including some life-threatening and rare fatal reactions), hyperglycaemia/glucose intolerance, infections, interstitial lung disease (pneumonitis), hyperlipaemia, intracerebral bleeding, renal failure, bowel perforation, and wound healing complication.</p> <ul style="list-style-type: none"> • 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. <p>The most common (≥30%) adverse reactions (all grades) observed with TORISEL include anaemia, nausea, rash (including rash, pruritic rash, maculopapular rash, pustular rash), anorexia, oedema (including facial oedema and peripheral oedema), and asthenia.</p> <p>Cataracts have been observed in some patients who received the combination of temsirolimus and interferon-α.</p> <p>Mantle Cell Lymphoma The occurrence of undesirable effects following the dose of 175 mg TORISEL/week for MCL, e.g. grade 3 or 4 infections or thrombocytopenia, is associated with a higher incidence than that observed with either 75 mg TORISEL/week or conventional chemotherapy.</p> <p>The most serious reactions observed with TORISEL are thrombocytopenia, neutropenia, infections, interstitial lung disease (pneumonitis), bowel perforation, hypersensitivity reactions, and hyperglycaemia/glucose intolerance.</p> <p>The most common (>30%) adverse reactions (all grades) observed with TORISEL include thrombocytopenia, asthenia, anaemia, diarrhoea, bacterial and viral infections*, rash*, pyrexia, anorexia, epistaxis, mucositis, oedema*, and stomatitis*.</p> <p>Serious adverse reactions observed in clinical trials of temsirolimus for advanced renal cell carcinoma, but not in clinical trials of temsirolimus for mantle cell lymphoma include: anaphylaxis, impaired wound healing, renal failure with fatal outcomes, and pulmonary embolus.</p> <p>Use in Hepatic Impairment Caution should be used in treating patients with hepatic impairment. An increased rate of fatal events was observed in patients with moderate/severe hepatic impairment. The fatal events included those due to disease progression, however a causal relationship cannot be excluded. Use of TORISEL in patients with mantle cell lymphoma and moderate/severe hepatic impairment is</p>

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	<p>not recommended.</p> <p>Use in Elderly Based on the results of a phase 3 study in renal cell carcinoma, elderly patients (≥ 65 years of age) may be more likely to experience certain adverse reactions, including oedema, diarrhoea, and pneumonia. Based on the results of a phase 3 study in mantle cell lymphoma, elderly patients (≥ 65 years of age) may be more likely to experience certain adverse reactions, including pleural effusion, anxiety, depression, insomnia, dyspnoea, leukopaenia, lymphopaenia, myalgia, arthralgia, taste loss, dizziness, upper respiratory infection, mucositis, and rhinitis.</p>
PATIENT ACCESS TO TORISEL	Pfizer's First Resource program offers patient assistance to eligible patients and reimbursement support services, including appeals process and alternate funding information, for Pfizer Oncology medicines, including TORISEL.
CONTACT & ADDITIONAL INFORMATION	<p>If you are interested in speaking with a Pfizer Oncology media representative, please contact Matti Ojanen at Matti.Ojanen@Pfizer.com or +44-7557-202394.</p> <p>For more information about clinical studies involving temsirolimus currently enrolling in their area, patients and their physicians may call the clinical trial information line at 1-877-369-9753 or visit www.pfizeroncology.com.</p>

¹ TORISEL® (temsirolimus) Summary of Product Characteristics, Pfizer Inc.

² Adjei AA, Hidalgo M. Intracellular signal transduction pathway proteins as targets for cancer therapy. *J Clin Oncol*. 2005;23:5386-5403.

³ TORISEL® (temsirolimus) Prescribing Information, Pfizer Inc.

⁴ Cho D et al. The Role of Mammalian Target of Rapamycin Inhibitors in the Treatment of Advanced Renal Cancer. *Clinical Cancer Research*. 2007; 13: 758S-763S.

⁵ Yang J et al. A Randomized Trial of Bevacizumab, an Anti-Vascular Endothelial Growth Factor Antibody, for Metastatic Renal Cancer. *The New England Journal of Medicine*. 2003; 349: 427-434.

⁶ National Cancer Institute. Dictionary of Cancer Terms: Angiogenesis. Available at: <http://www.cancer.gov/dictionary/?Cdrid=46529>. Accessed July 12, 2011.

⁷ Gera J et al. AKT Activity Determines Sensitivity to Mammalian Target of Rapamycin (mTOR) Inhibitors by Regulating Cyclin D1 and c-myc Expression. *The Journal of Biological Chemistry*. 2004; 279: 2737-2746.

⁸ Fu K et al. Cyclin D1-negative mantle cell lymphoma: a clinicopathologic study based on gene expression profiling. *BLOOD*. 2005; 106: 4315-4321.

⁹ Hudes G, Carducci M, Tomczak P, et al. Global ARCC Trial. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med*. 2007; 356: 2271-81.

¹⁰ Hess G, Herbrecht R, Romaguera J, et al. Phase III Study to Evaluate Temsirolimus Compared With Investigator's Choice Therapy for the Treatment of Relapsed or Refractory Mantle Cell Lymphoma. *J Clin Oncol*. 2009; 27: 3822 – 29.

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