TORISEL®
(Temsirolimus)

NAME OF THE MEDICINE

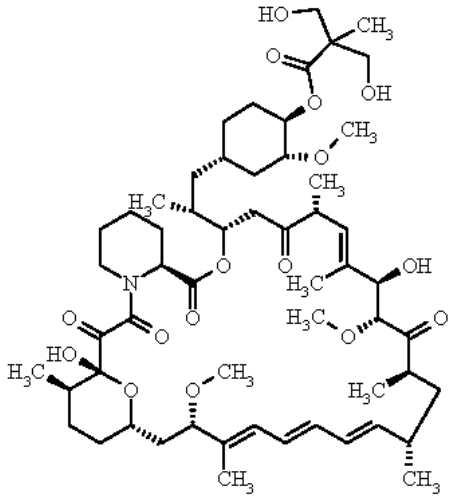
TORISEL (temsirolimus) 25 mg concentrate for injection and diluent.

TORISEL contains the active substance temsirolimus.

Temsirolimus is the 2,2-bis(hydroxymethyl) propionic acid ester of sirolimus, a macrocyclic lactone produced by *Streptomyces hygroscopicus*.

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

The structural formula of temsirolimus is shown below:



Molecular Formula: $C_{56}H_{87}NO_{16}$
Molecular Weight: 1030.3
CAS Registry Number: 162635-04-3

DESCRIPTION

Temsirolimus is a white to off-white powder. It is non-hygroscopic. Temsirolimus is insoluble in water and soluble in ethanol. It has no ionisable functional groups and its solubility is independent of pH.

The temsirolimus concentrate for injection vial contains temsirolimus. After 1.8 mL of the diluent is extracted and mixed with the contents of the TORISEL vial, only 2.5 mL of the resulting solution should be removed. This constituted solution contains 30 mg temsirolimus as a 10 mg/mL, non-aqueous solution. This is further diluted in saline prior to infusion (see directions in DOSAGE AND ADMINISTRATION).

PHARMACOLOGY

Pharmacodynamics

Mechanism of Action

Temsirolimus is a selective inhibitor of mTOR (mammalian target of rapamycin). In humans, sirolimus is a major metabolite of temsirolimus that was equipotent to temsirolimus at inhibiting mTOR phosphorylation, and at inhibiting cell proliferation or tumour cell growth both in tissue culture and in nude mouse xenograft models. Temsirolimus binds to an intracellular protein (FKBP-12), and the protein-drug complex binds and inhibits the activity of mTOR that controls cell proliferation. Inhibition of mTOR activity results in a G1 growth arrest in treated tumour cells resulting from selective disruption of translation of cell cycle regulatory proteins, such as D-type cyclins, c-myc, and ornithine decarboxylase. Temsirolimus exerts its effect by binding in a complex with FKBP-12 and mTOR. When mTOR is bound in this complex, its ability to phosphorylate, and thereby control the activity of protein translation factors (4E-BP1 and S6K, both downstream of mTOR in the PI3 kinase/AKT pathway) that control cell division, is blocked.

In addition to regulating cell cycle proteins, mTOR can regulate translation of the hypoxia-inducible factors, HIF-1 and HIF-2 alpha. These transcription factors regulate the ability of tumours to adapt to hypoxic microenvironments and to produce the angiogenic factor vascular endothelial growth factor (VEGF). The anti-tumour effect of temsirolimus, therefore, may also in part, stem from its ability to depress levels of HIF and VEGF in the tumour or tumour microenvironment, thereby impairing vessel development.

Concentration-Effect Relationship

The effect of temsirolimus intravenous treatment on the inhibition of phosphorylation of S6-ribosomal protein in circulating lymphocytes was examined in 30 healthy subjects. Data indicate that inhibition of protein phosphorylation was rapid and dose-dependent. Following a single 25 mg intravenous dose of temsirolimus, 20% and 50% of inhibition of S6-ribosomal protein was shown for at least 8 days and 3 days, respectively.

Pharmacokinetics

Absorption

Following administration of a single 25 mg intravenous dose of temsirolimus in patients with cancer, mean 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%).

Distribution

Temsirolimus exhibits a polyexponential decline in whole blood concentrations and distribution and is attributable by preferential binding to FKBP-12 in blood cells. The

mean (standard deviation, SD) dissociation constant (Kd) of binding was 5.1 (3.0) ng/mL, denoting the concentration at which 50% of binding sites in blood cells were occupied. Temsirolimus distribution is dose-dependent with mean (10^{th}, 90^{th} percentiles) maximal specific binding in blood cells of 1.4 mg (0.47 to 2.5 mg). Following a single 25 mg intravenous dose, mean steady-state volume of distribution in whole blood of patients with cancer was 172 litres. Plasma protein binding is approximately 89%.

Metabolism
Sirolimus, an equally potent metabolite to temsirolimus was observed as the principal metabolite in humans following intravenous treatment. During *in-vitro* temsirolimus metabolism studies, sirolimus, seco-temsirolimus and seco-sirolimus, were observed; additional metabolic pathways were hydroxylation, reduction and demethylation. Sirolimus and temsirolimus are metabolised predominantly by CYP3A4. 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.

Excretion
Following a single 25 mg intravenous dose of temsirolimus in patients with cancer, temsirolimus mean (CV) systemic clearance was 16.2 (22%) L/h. Mean half-lives of temsirolimus and sirolimus were 17.3 hr and 54.6 hr, respectively. Following administration of [^{14}C]-labelled temsirolimus, excretion was predominantly via the faeces (78%), with renal elimination of drug and metabolites accounting for 4.6% of the administered dose.

Special Populations
Elderly
In population pharmacokinetic-based data analyses, age did not have a significant effect on the disposition of temsirolimus or sirolimus metabolite.

Paediatric
There are no data available for paediatric patients.

Gender
In population pharmacokinetic-based data analyses, gender did not have a significant effect on the disposition of temsirolimus or sirolimus metabolite.

Patients with renal impairment
Temsirolimus elimination through kidneys is low. Since differences in creatinine clearance do not affect temsirolimus disposition, no change in temsirolimus intravenous treatment regimen is required for patients with renal impairment (see DOSAGE AND ADMINISTRATION).

Patients with hepatic insufficiency or hepatic impairment
Temsirolimus is cleared predominantly by the liver. No data are currently available regarding the influence of hepatic dysfunction and/or hepatic metastases on temsirolimus disposition.

Temsirolimus is contraindicated in patients with bilirubin >1.5 x ULN (see CONTRAINDICATIONS and PRECAUTIONS).

Effects of Food
The effect of food on exposure following an intravenous dose of temsirolimus was not examined.

CLINICAL TRIALS

Renal Cell Carcinoma
The safety and efficacy of TORISEL in the treatment of advanced renal cell carcinoma (RCC) were studied in the following two randomised clinical trials.

Study 1
Study 1 was a Phase 3, multi-centre, 3-arm, randomised, open-label study in previously untreated patients with advanced renal cell carcinoma (RCC) and with 3 or more of 6 pre-selected risk factors indicating a poor prognosis (less than 1 year from time of initial RCC diagnosis to randomisation, Karnofsky performance status of 60 or 70, haemoglobin 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 1 metastatic organ site). The primary study endpoint was overall survival (OS). Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), clinical benefit rate, time to treatment failure (TTF), and quality adjusted survival measurement. Patients were stratified for prior nephrectomy status within 3 geographic regions and were randomly assigned (1:1:1) to receive interferon alpha (IFN-α) alone (n=207), TORISEL alone (25 mg weekly; n=209), or the combination of IFN-α and TORISEL (n=210).

The combination arm did not exhibit a positive clinical benefit-risk ratio compared to IFN-α. Treatment with the combination of TORISEL 15 mg and IFN-α resulted in a statistically significant increase in the incidence of certain Grade 3-4 adverse events (weight loss, hyperlipidaemia, anaemia, neutropenia, thrombocytopenia and mucosal inflammation) when compared to the adverse events observed in the IFN-α or TORISEL 25 mg alone arms. The combination of TORISEL 15 mg and IFN-α did not result in a significant increase in OS when compared to IFN-α alone (median 8.4 vs. 7.3 months, hazard ratio = 0.96, p = 0.6965).

Information on the TORISEL 25 mg alone and IFN-α alone arms is described in this section. The demographic and disease characteristics of the study population are shown in Table 1. Baseline demographic and disease characteristics were well balanced across treatment arms.

TABLE 1: DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS FOR PATIENTS IN CLINICAL STUDY 1

Characteristic	TORISEL n (%)	IFN-α n (%)
Total patients in treatment arm	209	207
Age		
<65 years	145 (69.4)	142 (68.6)
>65 years	64 (30.6)	65 (31.4)
Sex		
Female	70 (33.5)	59 (28.5)

Characteristic	TORISEL n (%)	IFN-α n (%)
Male	139 (66.5)	148 (71.5)
Race		
White	186 (89.0)	191 (92.3)
Asian	6 (2.9)	4 (1.9)
Black	9 (4.3)	8 (3.9)
Other	8 (3.8)	4 (1.9)
Prior nephrectomy		
No	70 (33.5)	68 (32.9)
Yes	139 (66.5)	139 (67.1)
Stage of disease at baseline		
Stage IV	200 (95.7)	201 (97.1)
Recurrent Stage II	1 (0.5)	1 (0.5)
Recurrent Stage III	8 (3.8)	5 (2.4)
Primary cell type		
Clear	169 (82.0)	170 (82.5)
Indeterminate	24 (11.7)	23 (11.2)
Non-clear	13 (6.3)	13 (6.3)
Unknown	3	1

In Study 1, TORISEL was associated with a statistically significant advantage over IFN-α in the primary endpoint of OS (time from randomisation to death). The TORISEL arm showed a 49% increase in median OS compared with the IFN-α arm.

Figure 1 is a Kaplan-Meier plot of OS in Study 1. TORISEL was also associated with statistically significant advantages over IFN-α in the secondary endpoints of PFS (time from randomisation to disease progression or death, censored at the last tumour evaluation date); TTF (time from randomisation to disease progression, death, withdrawal from treatment due to an adverse event, withdrawal of voluntary consent, or loss to follow up) and clinical benefit rate (complete response, partial response, or stable disease for >24 weeks). The evaluations of PFS, ORR, and clinical benefit rate were based on blinded independent radiologic assessment of tumour response using Response Evaluation Criteria in Solid Tumors (RECIST)-based criteria. TTF utilised the investigator's assessment of progression. Efficacy results are summarised in Table 2.

FIGURE 1: KAPLAN-MEIER CURVES FOR OVERALL SURVIVAL - STUDY 1

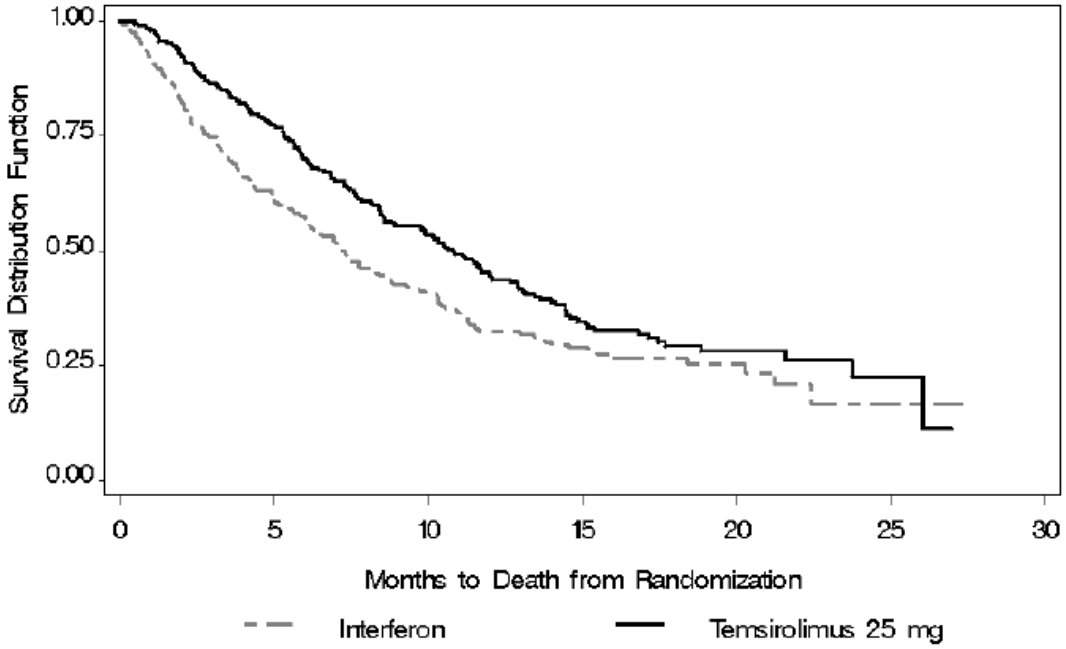


TABLE 2: SUMMARY OF EFFICACY RESULTS IN TORISEL CLINICAL STUDY 1

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
Median Time to Treatment Failure Months (95% CI)	3.8 (3.5, 3.9)	1.9 (1.7, 1.9)	<0.0001	0.61 (0.50, 0.74)
Clinical Benefit Rate % (95% CI)	32.1 (25.7, 38.4)	15.5 (10.5, 20.4)	<0.0001[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).

[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.

In clinical Study 1, 31% of patients treated with TORISEL were 65 years or older. In patients younger than 65, median OS for patients treated with TORISEL was 12 months (95% CI 9.9-14.5) with hazard ratio of 0.62 (95% CI 0.47-0.82), compared with IFN-α. In patients 65 years or older, median OS was 8.6 months (95% CI 6.4-11.5) with hazard ratio of 1.08 (95% CI 0.71-1.63) compared to those treated with

IFN-α.

Quality Adjusted Survival
Quality adjusted survival was compared across treatment groups using the quality-adjusted time without symptoms and toxicities (Q-TWiST) approach. Survival was value-weighted by the patient based on presence or absence of toxicity or progression by completing the EuroQoL 5D (EQ-5D) scale at baseline, Weeks 12 and 32, when a Grade 3 or 4 toxicity was reported, upon relapse or progression, or upon withdrawal from the study. TORISEL is associated with a statistically significant increase in quality adjusted survival (Q-TWiST) time of an estimated 1.3 months (7.0 vs. 5.7 months, 23%) as compared to IFN-α.

Study 2
Study 2 was a randomised, double-blind, multi-centre, outpatient trial to evaluate the efficacy, safety, and pharmacokinetics of three dose levels of TORISEL when administered to previously treated patients with advanced RCC. The primary efficacy endpoint was ORR. Clinical benefit rate, PFS, and OS were also evaluated. PFS was defined as time from the first dose of TORISEL to disease progression or death. One hundred eleven (111) patients were randomly assigned in a 1:1:1 ratio to receive 25 mg, 75 mg, or 250 mg TORISEL IV weekly. In the 25 mg arm, all patients had metastatic disease; 4 (11%) had no prior chemo- or immunotherapy; 17 (47%) had one prior treatment; and 15 (42%) had 2 or more prior treatments for RCC. Twenty-seven (27, 75%) had undergone a nephrectomy. Twenty-four (24, 67%) were Eastern Cooperative Oncology Group (ECOG) performance status (PS) = 1, and 12 (33%) were ECOG PS = 0.

For patients treated weekly with 25 mg IV TORISEL, the median OS was 13.8 months (95% CI: 9.0, 18.7 months); median PFS was 6.3 months (95% CI: 3.6, 7.8 months); ORR was 5.6% (95% CI: 0.7, 18.7%), and clinical benefit rate was 52.8% (95% CI: 35.5, 69.6%).

Mantle Cell Lymphoma
The safety and efficacy of IV temsirolimus for the treatment of relapsed and/or refractory mantle cell lymphoma was studied in the following Phase 3 clinical study.

Study 3
Study 3 is a controlled, randomised, open-label, multicenter, outpatient study comparing 2 different dosing regimens of TORISEL with an investigator's choice of therapy in patients with relapsed and/or refractory mantle cell lymphoma. Subjects with mantle cell lymphoma that was confirmed by histology, immunophenotype, and cyclin D1 analysis who had received 2 to 7 prior therapies that included anthracyclines and alkylating agents, and rituximab (and could include haematopoietic stem cell transplant) and whose disease was relapsed and/or refractory were eligible for the study. Subjects were randomly assigned in a 1:1:1 ratio to receive TORISEL 175/75 - temsirolimus IV 175 mg (3 successive weekly doses) followed by 75 mg weekly (n=54), TORISEL 175/25 - temsirolimus IV 175 mg (3 successive weekly doses) followed by 25 mg weekly (n=54), or the investigator's choice of single-agent treatment (as specified in the protocol; n=54).

The primary endpoint of the study was PFS. Secondary endpoints included OS and

ORR. ORR was assessed using the International Workshop Modified Response Criteria for Non-Hodgkin's Lymphoma. PFS and ORR were assessed by blinded independent radiologists and oncologists.

Investigator's choice therapies included: gemcitabine (IV: 22 [41.5%]), fludarabine (IV: 12 [22.6%] or oral: 2 [3.8%]), chlorambucil (oral: 3 [5.7%]), cladribine (IV: 3 [5.7%]), etoposide (IV: 3 [5.7%]), cyclophosphamide (oral: 2 [3.8%]), thalidomide (oral: 2 [3.8%]), vinblastine (IV: 2 [3.8%]), alemtuzumab (IV: 1 [1.9%]), and lenalidomide (oral: 1 [1.9%]).

The median treatment time was 12 weeks for TORISEL 175/75, 14 weeks for TORISEL 175/25 and 5 weeks for investigator's choice. TORISEL 175/75 significantly increased tumour response and progression-free survival compared with investigator choice (see Table 3). TORISEL 175/25 did not differ significantly from investigator choice. The study was not powered to assess differences in OS.

TABLE 3: SUMMARY OF EFFICACY RESULTS IN TEMSIROLIMUS CONCENTRATE FOR INJECTION CLINICAL STUDY 3

	TORISEL 175/75 N=54	**TORISEL 175/25 N=54**	**Investigator Choice N=54**
Objective Response Rate [95% CI] Difference from Investigator Choice [95% CI] Fisher's Exact p value	22.2% [11.1%, 33.3%] 20.3% [8.75%, 32%] 0.0019	5.6% [0.0%, 11.7%] 3.7% [-3.4%, 10.8%] 0.6179	1.9%
Progression-Free Survival median months Hazard Ratio vs. Investigator Choice [97.5% CI][a] Log-Rank p value	4.8 0.44 [0.25, 0.78] 0.0009	3.4 0.65 [0.39, 1.10] 0.0618	1.9
Overall Survival median months Hazard Ratio vs. Investigator Choice [95% CI][a] Log-Rank p value	11.1 0.77 [0.46, 1.28] 0.3053	8.8 0.98 [0.60, 1.62] 0.9515	9.5

Abbreviations: CI = confidence interval.

[a] Compared with Investigator's Choice based on Cox proportional hazard model. In Study 3, there was no difference in efficacy in patients with respect to age, sex, race, geographic region, or baseline disease characteristics.

INDICATIONS

Renal Cell Carcinoma

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

Mantle Cell Lymphoma

TORISEL is indicated for the treatment of patients with relapsed and/or refractory mantle cell lymphoma.

CONTRAINDICATIONS

TORISEL is contraindicated in patients with a known hypersensitivity to temsirolimus or any component of this formulation.

TORISEL is contraindicated in patients with bilirubin >1.5 x ULN (see PRECAUTIONS: Hepatic Impairment).

PRECAUTIONS

Hypersensitivity/Infusion Reactions

Hypersensitivity/infusion reactions (including some life-threatening and rare fatal reactions), including but not limited to flushing, chest pain, dyspnoea, hypotension, apnoea, loss of consciousness, hypersensitivity and anaphylaxis, have been associated with the administration of temsirolimus. These reactions can occur very early in the first infusion, but may also occur with subsequent infusions. Patients should be monitored early during the infusion and appropriate supportive care should be available. Temsirolimus infusion should be interrupted in all patients with severe infusion reactions and appropriate medical therapy administered. A benefit-risk assessment should be done prior to the continuation of temsirolimus therapy in patients with severe or life-threatening reactions.

Sirolimus is the major metabolite of temsirolimus; therefore, TORISEL should be administered with caution in patients with a known hypersensitivity to sirolimus.

Because it is recommended that an H_1 antihistamine be administered to patients before the start of the intravenous TORISEL 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 despite the premedication, 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 H_1-receptor antagonist (such as diphenhydramine), if not previously administered, and/or an H_2-receptor antagonist (such as 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).

Hepatic Impairment

TORISEL was evaluated in a dose escalation Phase 1 study in 110 patients with normal or varying degrees of hepatic impairment as defined by AST and bilirubin levels and patients with liver transplant (Table 4). Patients with moderate and severe hepatic impairment had increased rates of adverse events and deaths, including deaths due to progressive disease, during the study.

TABLE 4 ADVERSE EVENTS IN PATIENTS WITH ADVANCED MALIGNANCIES PLUS NORMAL OR IMPAIRED HEPATIC FUNCTION

Hepatic Function	TORISEL dose range (mg)	Adverse Events Grade ≥3 n (%)**	Overall 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)

* Hepatic Function Groups: normal = bilirubin and AST ≤ ULN; mild = bilirubin >1 – 1.5 x ULN or AST >ULN but bilirubin ≤ ULN; moderate = bilirubin >1.5 – 3 x ULN; severe = bilirubin >3 x ULN; liver transplant = any bilirubin and AST.
** Common Terminology Criteria for Adverse Events, version 3.0, including all causality.
*** Includes deaths due to progression of underlying cancer and adverse reactions.

TORISEL is contraindicated in patients with bilirubin >1.5 x ULN due to increased risk of death, including deaths due to progression of underlying cancer (see CONTRAINDICATIONS).

Use caution when treating patients with mild hepatic impairment. Concentrations of temsirolimus and its metabolite sirolimus were increased in patients with elevated AST or bilirubin levels. Assessment of AST and bilirubin levels is recommended before initiation with temsirolimus and periodically thereafter.

Hyperglycaemia/Glucose Intolerance
The use of TORISEL in renal cell carcinoma patients was associated with increases in serum glucose. In Study 1, a Phase 3 clinical trial for renal cell carcinoma, 26% of patients reported hyperglycaemia as an adverse event. In Study 3, a Phase 3 clinical trial for mantle cell lymphoma, 11% of patients reported hyperglycaemia as an adverse event. This may result in the need for an increase in the dose of, or initiation of, insulin and/or oral hypoglycaemic agent therapy. Patients should be advised to report excessive thirst or any increase in the volume or frequency of urination.

Infections
Patients may be immunosuppressed and should be carefully observed for the occurrence of infections, including opportunistic infections. Cases of Pneumocystis jiroveci pneumonia (PJP), some with fatal outcomes, have been reported in patients who received temsirolimus, many of whom also received corticosteroids or other immunosuppressive agents. For patients who require concomitant use of corticosteroids or other immunosuppressive agents, prophylaxis of PJP may be considered.

Interstitial Lung Disease
There have been cases of non-specific interstitial pneumonitis, including fatal reports, occurring in patients who received weekly intravenous TORISEL. Some patients were asymptomatic or had minimal symptoms with pneumonitis detected on computed tomography scan or chest radiograph. Others presented with symptoms, such as dyspnoea, cough, and fever. Some patients required discontinuation of TORISEL or treatment with corticosteroids and/or antibiotics, while some patients continued treatment without additional intervention.

It is recommended that patients undergo baseline radiographic assessment by lung computed tomography scan or chest radiograph prior to the initiation of temsirolimus therapy. Follow such assessments periodically, even in the absence of clinical respiratory symptoms.

It is recommended that patients be followed closely for occurrence of clinical respiratory symptoms.

If clinically significant respiratory symptoms develop, consider withholding temsirolimus administration until after recovery of symptoms and improvement of radiographic findings related to pneumonitis. Opportunistic infections, such as PJP should be considered in the differential diagnosis. Empiric treatment with corticosteroids and/or antibiotics may be considered. For patients who require use of corticosteroids, prophylaxis of PJP may be considered.

Hyperlipidaemia
The use of TORISEL was associated with increases in serum triglycerides and cholesterol. In Study 1, hyperlipidaemia was reported as an adverse event (including elevated triglycerides and/or cholesterol) in 27% of patients. In Study 3, hyperlipaemia was reported as an adverse event in 9.3% of patients. 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.

Bowel Perforation
Cases of bowel perforation (including fatal outcomes) have occurred in patients who received TORISEL.

Wound Healing Complications
The use of TORISEL has been associated with abnormal wound healing. Therefore, caution should be exercised with the use of TORISEL in the peri-surgical period.

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

Renal Failure
Renal failure (including fatal outcomes) has been observed in patients receiving TORISEL for advanced renal cell cancer and/or with pre-existing renal insufficiency.

Thrombocytopenia and Neutropenia
Grades 3 and 4 thrombocytopenia and/or neutropenia have been observed in Study 3 (mantle cell lymphoma).

Cataracts
Cataracts have been observed in some patients who received the combination of TORISEL and IFN-α.

Vaccinations
The use of live vaccines should be avoided during treatment with TORISEL. Examples of live vaccines are: measles, mumps, rubella, oral polio, Bacillus Calmette-Guérin (BCG), yellow fever, varicella, and TY21a typhoid vaccines.

Effects on Fertility
In male rats, fertility was decreased at doses ≥0.5 mg/kg/day PO. Exposure (AUC; normalised for the frequency of administration) at this dose was below that expected at the maximum recommended human dose. Fertility was absent at 5 mg/kg/day. These effects on male fertility were accompanied by testicular tubular degeneration, decreased sperm concentration and motility, and decreased reproductive organ weights at dosages ≥0.5 mg/kg/day.

In female rats given temsirolimus for 2 weeks prior to mating until gestation day 6, there were increased incidences of pre- and post-implantation losses at dosages ≥0.7 mg/kg/day PO, resulting in decreased numbers of live foetuses which was considerably less than the maximum recommended dose on an AUC basis.

Use in Pregnancy
There are no adequate and well-controlled studies in pregnant women using TORISEL.

In oral developmental toxicity studies in rats, there was increased embryo/foetal mortality and decreased foetal growth at dosages ≥0.45 mg/kg/day. Exposure at this dose was considerably below that expected at the maximum recommended human dose on an AUC basis.

In oral developmental toxicity studies in rabbits, there was increased embryo/foetal mortality and decreased foetal growth at dosages ≥0.6 mg/kg/day. Exposure at this dose was considerably below that expected at the maximum recommended human dose on an AUC basis.

Women of childbearing age should use medically acceptable contraception during (and up to 12 weeks after) treatment.

TORISEL should not be used during pregnancy.

If a patient becomes pregnant during treatment with TORISEL, she and her treating physician should have a thorough discussion of the diagnosis, alternative options and the potential risks of TORISEL to the developing foetus.

In addition, men should be adequately counselled prior to starting treatment with TORISEL and need to understand the possible danger of taking a drug whose effects on the foetus or sperm are unknown. Men with partners of childbearing potential should use medically acceptable contraception throughout treatment and are recommended to continue this for 12 weeks after the last dose of TORISEL.

There is no information available for labour and delivery.

Use in Lactation

Lactation studies of intravenous TORISEL have not been conducted.

It is not known whether temsirolimus is excreted into human milk. Because many drugs are excreted in human milk, and because the effects of temsirolimus excretion in human milk have not been studied, women should be advised against breast-feeding while receiving TORISEL.

Paediatric Use
The safety and effectiveness of TORISEL in paediatric patients have not been established.

Use in the Elderly
Based on the results of a Phase 3 study for renal cell carcinoma, elderly patients may be more likely to experience certain adverse reactions, including oedema, diarrhoea, and pneumonia. Based on the results of a Phase 3 study for mantle cell lymphoma, elderly patients may be more likely to experience certain adverse reactions, including anxiety, depression, dyspnoea, leukopenia, myalgia, taste loss, and upper respiratory infection.

Overall survival in a subset of patients 65 years of age or older (n=64) treated with TORISEL was shorter than that observed with patients under 65 years of age and was not significantly different from INF-α (see CLINICAL TRIALS). The clinical relevance of this subgroup analysis is unclear.

No specific dose adjustment is recommended for elderly patients.

Genotoxicity
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.

Carcinogenicity
Carcinogenicity studies have not been conducted with temsirolimus. However, sirolimus, the major metabolite of temsirolimus in humans, was carcinogenic in mice and rats. Increased incidences of lymphoma, hepatocellular adenoma and carcinoma in mice, and testicular adenoma in rats were reported following oral dosing of sirolimus in carcinogenicity studies.

Effect on Laboratory Tests
Not applicable.

INTERACTIONS WITH OTHER MEDICINES

Temsirolimus and its active metabolite sirolimus are metabolised predominately by CYP3A4/5.

Agents Inducing CYP3A Metabolism
Agents such as carbamazepine, phenytoin, barbiturates, rifabutin, rifampicin, and St. John's Wort are strong inducers of CYP3A4/5 and may decrease composite

exposures of the active moieties, temsirolimus and its metabolite, sirolimus. Therefore, concomitant treatment with agents that have CYP3A4/5 induction potential should be avoided. If alternative treatment cannot be administered, a weekly intravenous dose up to 50 mg should be considered. For patients with mantle cell lymphoma, it is recommended that co-administration of CYP3A4/5 inducers should be avoided due to the higher dose of temsirolimus.

Co-administration of TORISEL with rifampin, a potent CYP3A4/5 inducer, had no significant effect on temsirolimus maximum concentration (C_{max}) and AUC, after intravenous administration, but decreased sirolimus C_{max} by 65% and AUC by 56%, and AUC_{sum} (composite of temsirolimus AUC plus sirolimus AUC) by 41% compared to TORISEL treatment alone.

Agents Inhibiting CYP3A Metabolism
Agents such as protease inhibitors (such as atazanavir, indinavir nelfinavir, ritonavir and saquinavir), anti-fungals (such as itraconazole and ketoconazole), and macrolide antibiotics (such as clarithromycin and telithromycin) are strong CYP3A4 inhibitors and may increase blood concentrations of the active moieties, temsirolimus and its metabolite, sirolimus. Therefore, concomitant treatment with agents that have CYP3A4 inhibition potential should be avoided. Concomitant treatment with moderate CYP3A4 inhibitors should only be administered with caution in patients receiving 25 mg and should be avoided in patients receiving temsirolimus doses higher than 25 mg.

Alternative treatments with agents that do not have CYP3A4 inhibition potential should be considered.

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 AUC_{sum} increased 2.3-fold compared to TORISEL alone. Substances that are potent inhibitors of CYP3A4 activity increase sirolimus blood concentrations.

Interactions with Drugs Metabolised by CYP2D6
In 23 healthy subjects the concentration of desipramine, a CYP2D6 substrate, was unaffected when 25 mg of TORISEL was co-administered. In 36 patients with MCL, including 4 poor metabolisers, the effect of CYP2D6 inhibition after administration of a single dose of 175 mg and 75 mg temsirolimus was investigated. Population PK analysis based on sparse sampling indicated no clinically significant interaction effect on desipramine AUC and C_{max} in plasma. No clinically significant effect is anticipated when TORISEL is co-administered with agents that are metabolised by CYP2D6.

Interactions with Drugs Metabolised by CYP3A4/5
Patients with RCC
The effect of a 25 mg dose of temsirolimus on CYP3A4/5 substrates has not been studied. *In vitro* studies in human liver microsomes and simulation using physiologically-based PK modelling indicate that the blood concentrations achieved after 25 mg dose of temsirolimus may increase the AUC and C_{max} of midazolam, a CYP3A4/5 substrate, by 28% and 9% respectively. No clinically significant effect is anticipated when temsirolimus at a dose of 25 mg is co-administered with agents that

are metabolised by CYP3A4/5.

Patients with MCL
The effect of a 175 mg or 75 mg temsirolimus dose on CYP3A4/5 substrates has not been studied. However, *in vitro* studies in human liver microsomes and simulations using physiologically-based PK models indicate that the blood concentrations achieved after a 175 mg dose of temsirolimus may increase the AUC and C_{max} of midazolam by 182% and 40%, respectively. PK modelling at a 75 mg dose of temsirolimus was not studied. Therefore, caution is advised during concomitant administration of TORISEL to patients with MCL with medicinal products that are metabolised predominantly via CYP3A4/5 and that have a narrow therapeutic index.

Interactions with Drugs that are P-glycoprotein Substrates
In an *in vitro* study, temsirolimus inhibited the transport of digoxin, a P-glycoprotein (P-gp) substrate, with an IC_{50} value of 2 μM. Clinical implications related to concomitant administration of P-gp substrates are not known.

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, gout/cellulitis requiring hospitalisation) were observed in two out of three patients treated in the first cohort of a Phase I study at doses of TORISEL 15 mg intravenous per week and sunitinib 25 mg oral per day (days 1-28 followed by a 2-week rest).

Concomitant Use of Angiotensin-Converting Enzyme (ACE) Inhibitors
Angioneurotic oedema-type reactions (including delayed reactions occurring 2 months following initiation of therapy) have been observed in some patients who received TORISEL and ACE inhibitors concomitantly.

Concomitant Use of ACE Inhibitors and/or Calcium Channel Blockers
An increased risk of angioedema is possible in patients taking mTOR inhibitors in combination with ramipril and/or amlodipine. Caution should be used when temsirolimus is given concomitantly with an ACE inhibitor (e.g., ramipril) or a calcium channel blocker (e.g., amlodipine).

ADVERSE EFFECTS

The following serious adverse reactions have been associated with TORISEL in clinical trials and are discussed in greater detail in the PRECAUTIONS section.

Hypersensitivity/Infusion Reactions
Hepatic Impairment
Hyperglycaemia/Glucose Intolerance
Infections
Interstitial Lung Disease
Hyperlipidaemia
Bowel Perforation
Wound Healing Complications
Thrombocytopenia and Neutropenia
Renal Failure

The most common (≥30%) adverse reactions observed with TORISEL are rash, asthenia, mucositis, nausea, oedema, and anorexia. The most common (≥30%) laboratory abnormalities observed with TORISEL are anaemia, hyperglycaemia, hyperlipaemia, hypertriglyceridaemia, lymphopenia, elevated alkaline phosphatase, elevated serum creatinine, hypophosphataemia, thrombocytopenia, elevated AST, and leukopenia.

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.

Renal Cell Carcinoma
In the Phase 3 randomised, open-label study of interferon alpha (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 TRIALS).

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 5 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 6 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 5: ADVERSE REACTIONS REPORTED IN AT LEAST 10% OF PATIENTS WHO RECEIVED 25 IV TORISEL OR IFN-ALPHA IN THE RANDOMISED 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)
Oedema[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)

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 (%)
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)
Diarrhoea	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)
Myalgia	16 (8)	1 (1)	29 (15)	2 (1)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	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 Toxicity Criteria for Adverse Events (CTCAE), Version 3.0.

[a] Includes oedema, facial oedema, and peripheral oedema.

[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 (0.5%), abdominal distension (4.3%), dysphagia (3.4%), mouth pain (2.4%), gingivitis (2.4%), gastritis (1.0%), gastrointestinal haemorrhage (1.0%), haemorrhoidal haemorrhage (1.0%), lip haemorrhage (0.5%), mouth haemorrhage (0.5%), rectal haemorrhage (1.0%).

Eye Disorders - Conjunctivitis (including lacrimation disorder) (7.7%).

Immune System - Allergic/Hypersensitivity reactions (9%).

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

Infections - Rhinitis (9.6%), pneumonia (8%); upper respiratory tract infection occurred in 14 patients (7%), flu syndrome (3.4%), oral moniliasis (2.4%), sinusitis (1.9%), folliculitis (1.9%), wound infection/post-operative wound infection (1.0%), laryngitis (1.0%), fungal infection/fungal dermatitis (1.0%), sepsis (0.5%).

General Disorders and Administration Site Conditions - Diabetes mellitus (4.8%), dehydration (4.8%), impaired wound healing (1.4%), generalised oedema (0.5%).

Respiratory, Thoracic and Mediastinal Disorders - Pleural effusion (3.8%), interstitial lung disease (2.9%), including rare fatalities.

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

Nervous System Disorders - Dizziness (9.1%), anxiety (7.7%), somnolence (6.7%), paresthesia (6.3%), convulsion (0.5%).

TABLE 6: INCIDENCE OF SELECTED LABORATORY ABNORMALITIES IN PATIENTS WHO RECEIVED 25 MG IV TORISEL OR IFN-α IN THE RANDOMISED 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)
Haematology				
Haemoglobin 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)

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 (%)
Chemistry				
Alkaline Phosphatase Increased	141 (68)	7 (3)	111 (56)	13 (7)
AST Increased	79 (38)	5 (2)	103 (52)	14 (7)
Calcium Decreased	82 (39)	9 (4.3)	83 (42)	9 (5)
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.

Mantle Cell Lymphoma
Fifty-four patients were treated with TORISEL 175/75 in the initial treatment period in Study 3, a randomised, open-label trial comparing two TORISEL dosing regimens with an investigator's choice regimen (see CLINICAL TRIALS). During an additional 40 months of safety follow up, patients who had previously discontinued therapy or were receiving either investigator's choice regimen or TORISEL 175/25 were eligible to crossover to TORISEL 175/75 treatment. In this safety population TORISEL 175/75 n=57, TORISEL 175/25 n=56, and investigator's choice regimen n=54.

All treatment groups in the safety population experienced a high incidence of adverse events (over 95%). During the high dose part of TORISEL treatment (first three doses), approximately half the subjects had a dose reduction and two-thirds a dose delay. The dose delay was mostly 1-3 days. Table 7 lists the common events (incidence ≥10%) that were considerably more frequent with TORISEL 175/75 than investigator choice therapy. Of the common events, only neutropenia (41% vs. 26%), leukopenia (41% vs. 18%), oedema (13% vs. 5%), dyspnoea (30% vs. 23%), constipation (19% vs. 16%), lymphopenia (19% vs. 12%) and sweating (13% vs. 2%) were considerably more frequent in the investigator choice Group than the TORISEL 175/75 Group.

TABLE 7: INCIDENCE OF VERY COMMON (≥10%) ADVERSE EVENTS IN STUDY 3

System Organ Class Adverse Event*	TORISEL 175/75 N=57	Investigator Choice N=54
Body as a Whole		
Asthenia	39 (68)	15 (28)
Fever	25 (44)	18 (33)
Back pain	8 (14)	2 (4)
Chest pain	6 (11)	2 (4)

System Organ Class Adverse Event*	TORISEL 175/75 N=57	Investigator Choice N=54
Headache	10 (18)	5 (9)
Infection	19 (33)	5 (9)
Pain	19 (33)	2 (4)
Gastrointestinal		
Anorexia	23 (40)	8 (15)
Diarrhoea	27 (47)	6 (11)
Mucositis	21 (37)	0 (0)
Nausea	14 (25)	11 (20)
Rectal haemorrhage	6 (11)	1 (2)
Stomatitis	12 (21)	3 (6)
Vomiting	8 (14)	3 (6)
Haematological		
Thrombocytopenia	45 (79)	29 (54)
Anaemia	31 (54)	24 (44)
Metabolic		
Hypercholesteremia	11 (19)	0 (0)
Hyperglycemia	9 (16)	6 (11)
Hyperlipemia	7 (12)	0 (0)
Hypocalcemia	6 (11)	0 (0)
Hypokalaemia	14 (25)	1 (2)
Hypophosphatemia	7 (12)	0 (0)
Lactic dehydrogenase increased	6 (11)	1 (2)
Peripheral oedema	14 (25)	9 (17)
Weight loss	10 (18)	5 (9)
Musculoskeletal		
Arthralgia	12 (21)	1 (2)
Muscle cramp	7 (12)	1 (2)
Neurological		
Anxiety	9 (16)	3 (6)
Dizziness	4 (7)	1 (2)
Insomnia	12 (21)	4 (7)
Respiratory		
Epistaxis	26 (47)	3 (6)
Cough increased	20 (35)	6 (11)
Pneumonia	10 (18)	6 (11)
Rhinitis	6 (11)	3 (6)
Sinusitis	6 (11)	0 (0)
Upper respiratory infection	9 (165)	2 (4)
Skin		
Acne	6 (11)	0 (0)
Dry skin	7 (12)	1 (2)
Erythema	6 (11)	2 (4)
Herpes Simplex	6 (11)	4 (7)
Nail disorder	11 (19)	1 (2)
Pruritus	16 (28)	3 (6)
Rash	21 (37)	6 (11)

System Organ Class Adverse Event*	TORISEL 175/75 N=57	Investigator Choice N=54
Special Senses		
Taste perversion	9 (16)	1 (2)
Urogenital		
Unspecified	17 (30)	6 (11)

* coded for COSTART dictionary

In the safety population there was a higher incidence of severe (Grade 3-4) adverse events, serious adverse events, and deaths within 14 days of last dose in the TORISEL groups than in the investigator choice group. For severe adverse events, the incidences were 95%, 88% and 76% for TORISEL 175/75, TORISEL 175/25 and investigator choice respectively. For serious adverse events, the incidences were 60%, 61% and 28% and for deaths, 7%, 4% and 2%. Serious reactions with TORISEL were fever, diarrhoea, infection, general physical health deterioration, thrombocytopenia, neutropenia, infection, interstitial lung disease (pneumonitis), bowel perforation, hypersensitivity and hyperglycaemia/glucose intolerance.

Deaths due to adverse events occurred in two (4%) temsirolimus 175/75 patients and three (6%) temsirolimus 175/25 patients. There were no deaths due to adverse events in patients receiving investigator choice. Three deaths in the TORISEL groups were considered possibly related to the drug, one each due to duodenal perforation, sepsis and pneumonitis. The treatment and observation periods for temsirolimus were considerably longer than for investigator choice (median 12-14 weeks vs. 5 weeks for treatment), which would account for some of the difference in adverse event profiles.

The incidence of thrombocytopenia with TORISEL 175/75 was 79% compared with 54% with investigator choice. Both the drug and the underlying disease are likely to be contributing factors. The majority of cases of thrombocytopenia were severe. Minor bleeding, in particular epistaxis, was common and more frequent in this trial than in renal carcinoma patients.

Adverse events of higher incidence with TORISEL in this trial compared with previous experience in the lower dose renal carcinoma trial were thrombocytopenia, neutropenia, infection, diarrhoea, asthenia and pneumonitis.

Elderly patients (≥65 years) may be more likely to experience certain adverse reactions with TORISEL including anxiety, depression, dyspnoea, leukopenia, myalgia, taste loss and upper respiratory infection.

Table 8 contains the incidence of ADRs occurring at all frequencies and the incidence of Grade 3 & 4 ADRs for the TORISEL 175/75 mg treatment group in Study 3. The information in the table is based on the MedDRA dictionary. The frequency categories are Very common: ≥1/10 and Common: ≥1/100 to <1/10.

TABLE 8: ADVERSE REACTIONS REPORTED IN PATIENTS WHO RECEIVED TORISEL 175/75 MG IN STUDY 3 N=57

System Organ Class	Frequency	Adverse Reactions*	All Grades n (%)	Grade 3 & 4 n (%)

System Organ Class	Frequency	Adverse Reactions*	All Grades n (%)	Grade 3 & 4 n (%)
Infections and infestations	Very common	Bacterial and viral infections (including infection, viral infection, influenza, bacterial infection, cellulitis, bronchitis, sinusitis, herpes zoster, herpes simplex, herpes virus infection, oral herpes)[a]	25 (43.9)	10 (17.5)
		Pneumonia	10 (17.5)	6 (10.5)
		Upper respiratory tract infection	9 (15.8)	0 (0)
	Common	Pharyngitis	1 (1.8)	0 (0)
		Sepsis (including septic shock)[a]	3 (5.3)	3 (5.3)
		Sinusitis	5 (8.8)	0 (0)
		Candidiasis (including oral and anal candidiasis) and fungal skin infections	5 (8.8)	0 (0)
		Urinary tract infection	3 (5.3)	0 (0)
		Rhinitis	5 (9.3)	0 (0)
		Folliculitis	1 (1.8)	0 (0)
Blood and lymphatic system disorders	Very common	Thrombocytopaenia[b]	33 (57.9)	26 (45.6)
		Anaemia	25 (43.9)	8 (14.0)
		Neutropaenia[b]	15 (26.3)	10 (17.5)
		Leucopaenia	8 (14.0)	4 (7.0)
		Lymphopaenia	6 (11.1)	4 (7.0)
Immune system disorders	Common	Hypersensitivity reactions/drug hypersensitivity	3 (5.3)	0 (0)
Metabolism and nutrition disorders	Very common	Hypokalaemia	14 (24.6)	4 (7.0)
		Anorexia	23 (40.4)	2 (3.5)
		Hyperglycaemia[c]	9 (15.8)	6 (10.5)
		Hypercholesterolaemia	10 (17.5)	0 (0)
		Hypocalcaemia	6 (10.5)	1 (1.8)
	Common	Dehydration	3 (5.3)	2 (3.5)
		Hypophosphataemia	5 (8.8)	1 (1.8)
		Hyperlipaemia	5 (9.3)	1 (1.9)
		Hyperlipidaemia	1 (1.8)	0 (0)
		Hypotriglycerideamia	5 (8.8)	0 (0)
		Diabetes mellitus	2 (3.5)	1 (1.8)
Psychiatric disorders	Very common	Insomnia	13 (22.8)	0 (0)
		Anxiety	9 (15.8)	0 (0)
	Common	Depression	3 (5.3)	0 (0)
Nervous system disorders	Very common	Dysgeusia	11 (19.3)	0 (0)
		Headache	10 (17.5)	1 (1.8)

System Organ Class	Frequency	Adverse Reactions*	All Grades n (%)	Grade 3 & 4 n (%)
	Common	Paresthesia	4 (7.0)	0 (0)
		Dizziness	4 (7.0)	0 (0)
		Ageusia	3 (5.3)	0 (0)
Eye disorders	Common	Conjunctivitis	4 (7.0)	0 (0)
		Eye haemorrhage	2 (3.5)	0 (0)
Vascular disorders	Common	Venous thromboembolism (including deep vein thrombosis)	1 (1.8)	0 (0)
		Hypertension	2 (3.5)	0 (0)
Respiratory, thoracic and mediastinal disorders	Very common	Dyspnoea	13 (22.8)	5 (8.8)
		Epistaxis	26 (45.6)	1 (1.8)
		Cough	20 (35.1)	1 (1.8)
		Pleural effusion	6 (10.5)	2 (3.5)
	Common	Interstitial lung disease[d]	6 (10.5)	3 (5.3)
Gastrointestinal disorders	Very common	Abdominal pain	11 (19.3)	1 (1.8)
		Vomiting	8 (14.0)	0 (0)
		Stomatitis	14 (24.6)	1 (1.8)
		Diarrhoea	27 (47.4)	5 (8.8)
		Nausea	14 (24.6)	0 (0)
		Constipation	9 (15.8)	0 (0)
		Gastrointestinal haemorrhage (including rectal, anal and mouth haemorrhage)[a]	8 (14.0)	2 (3.6)
		Dysphagia	6 (10.5)	0 (0)
	Common	Duodenal perforation	1 (1.8)	1 (1.8)
		Gingivitis	2 (3.5)	0 (0)
		Gastritis	3 (5.3)	1 (1.8)
		Oral pain	3 (5.3)	1 (1.8)
		Aphthous stomatitis	3 (5.3)	0 (0)
		Abdominal distension	1 (1.8)	0 (0)
Skin and subcutaneous tissue disorders	Very common	Rash (including rash, pruritic rash, maculopapular rash, pustular rash, eczema)[a]	26 (45.6)	3 (5.3)
		Pruritus (including pruritis generalised)	16 (28.1)	3 (5.3)
		Dry skin	7 (12.3)	0 (0)
	Common	Acne	2 (3.5)	0 (0)
		Moniliasis (including moniliasis, oral moniliasis)[a]	2 (3.7)	0 (0)
		Dermatitis	2 (3.5)	0 (0)
		Nail disorder	5 (8.8)	0 (0)
		Ecchymosis	3 (5.3)	0 (0)
		Petechiae	3 (5.3)	0 (0)

System Organ Class	Frequency	Adverse Reactions*	All Grades n (%)	Grade 3 & 4 n (%)
Musculoskeletal, connective tissue and bone disorders	Very common	Back pain	8 (14.0)	0 (0)
		Arthralgia	11 (19.3)	1(1.9)
	Common	Myalgia	3 (5.3)	0 (0)
Renal and urinary disorders	Common	Renal failure	1 (1.8)	0 (0)
General disorders and administration site conditions	Very common	Oedema (including peripheral oedema, scrotal oedema, genital oedema)[a]	17 (29.8)	1 (1.8)
		Fatigue	26 (45.6)	4 (7.0)
		Asthenia	12 (21.1)	5 (8.8)
		Pain	7 (12.3)	1 (1.8)
		Pyrexia	23 (40.4)	3 (5.3)
		Mucosal inflammation	20 (35.1)	2 (3.5)
		Chills	15 (26.3)	1 (1.8)
	Common	Chest pain	5 (8.8)	0 (0)
Investigation	Common	Blood creatinine increased	5 (8.8)	0 (0)
		Increased aspartate aminotransferase	2 (3.5)	1 (1.8)
		Increased alanine aminotransferase	1 (1.8)	1 (1.8)

* coded for MedDRA dictionary

[a] Body system totals are not necessarily the sum of the individual adverse events since a subject may report two or more different adverse events in the same body system.

[b] Grades 3 and 4 (thrombocytopenia) are defined as 2550 platelets x 10^9/L and <25 platelets x 10^9/L, respectively. Grades 3 and 4 (neutropenia) are defined as 0.5 - 1.0 neutrophils x 10^9/L and <0.5 neutrophils x 10^9/L, respectively.

[c] Patients should be advised that treatment with TORISEL may be associated with an increase in blood glucose levels in patients with or without diabetes.

[d] Interstitial lung disease is defined by a cluster of related Preferred Terms: interstitial lung disease (n=1), pneumonitis (n=3), alveolitis allergic (n=1), pulmonary fibrosis (n=1). One case of fatal pneumonitis was reported in a mantle cell lymphoma patient receiving 175/25 mg/week that is not included in this table.

Serious adverse reactions observed in clinical trials of TORISEL for renal cell carcinoma but not in clinical trials of TORISEL for mantle cell lymphoma include: anaphylaxis, impaired wound healing, renal failure with fatal outcomes, pericardial effusion (including haemodynamically significant pericardial effusions requiring intervention), convulsions, and pulmonary embolus.

Post-Marketing Experience

Additional adverse events reported from worldwide marketing experience with TORISEL, occurring under circumstances where causal relationship with TORISEL is uncertain. The events are listed using the CIOMS frequency categories as follows:

Very common: ≥10%
Common: ≥1%
Uncommon: ≥0.1% and <1%
Rare: ≥0.01% and <0.1%

Very rare: <0.01%

Cardiac disorders
Uncommon: Pericardial effusion (including haemodynamically significant pericardial effusions requiring intervention).

Respiratory, thoracic and mediastinal disorders
Common: Pleural effusion.

Nervous system disorders
Uncommon: Convulsion.

Musculoskeletal and connective tissue disorders
Common: Myalgia (including myalgia, leg cramps).

Infections and infestations
Rare: Pneumocystis jiroveci pneumonia, some with fatal outcomes (see PRECAUTIONS).

The following adverse reactions have been observed in patients receiving temsirolimus: rhabdomyolysis, Stevens-Johnson syndrome, pancreatitis, cholecystitis, and cholelithiasis.

Angioneurotic oedema-type reactions have been reported in patients who received temsirolimus, including in some patients who received temsirolimus and ACE-inhibitors concomitantly.

DOSAGE AND ADMINISTRATION

Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. No special dosage modification is required for any of the populations that have been studied (e.g., gender, elderly).

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.

Management of suspected drug reactions may require temporary interruption and/or dose reduction of TORISEL therapy. If a suspected reaction is not manageable with dose delays, then Temsirolimus Concentrate for Injection may be reduced by 5 mg/week decrements.

Mantle Cell Lymphoma
The recommended dosing regimen of temsirolimus for mantle cell lymphoma is 175 mg, infused over a 30-60 minute period once weekly for 3 weeks followed by weekly doses of 75 mg, infused over a 30-60 minute period.

Management of suspected adverse reactions may require temporary interruption and/or dose reduction of temsirolimus therapy. If a suspected reaction is not manageable with dose delays, then temsirolimus may be reduced as follows - if the

reaction occurs during the 175 mg dosing, the 175 mg weekly dose should be reduced to 75 mg weekly. Thereafter, the dose may be reduced by 25 mg/week decrements, to a minimum of 25 mg weekly.

Instructions for Intravenous Administration
TORISEL and diluent must be stored under refrigeration at 2°C - 8°C and protected from light. During handling and preparation of admixtures, TORISEL should be protected from excessive room light and sunlight.

TORISEL and diluent should be inspected visually for particulate matter and discolouration prior to administration. Bags/containers that come in contact with TORISEL must be made of glass, polyolefin, or polyethylene.

DO NOT USE IF PARTICULATES ARE PRESENT. USE A NEW VIAL.

Premedication
Patients should receive prophylactic medication of an intravenous antihistamine approximately 30 minutes before the start of each dose of TORISEL infusion. If a hypersensitivity/infusion reaction develops during the TORISEL infusion, the infusion should be stopped.

Upon adequate resolution, and at the discretion of the physician, treatment may be resumed with the administration of an H_1-receptor antagonist (or equivalent), if not previously administered, and/or an H_2-receptor antagonist (such as 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).

Dilution
Note: For mantle cell lymphoma, multiple vials will be required for each dose over 25 mg. Each vial of TORISEL should be diluted according to the instructions below. The required contents from each vial should be combined in one syringe for injection into 250 mL of 0.9% sodium chloride injection.

The diluted solution (concentrate and diluent) should be inspected visually for particulate matter and discolouration.

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

Step 1: Inject 1.8 mL of supplied diluent into the vial of TORISEL Concentrate for Injection. Mix well by inversion of the vial. One vial of TORISEL Concentrate contains 30 mg of temsirolimus. When the 1.2 mL vial of concentrate is combined with 1.8 mL of diluent, a total volume of 3.0 mL is obtained, and the concentration of temsirolimus is 10 mg/mL.

Allow sufficient time for air bubbles to subside from the TORISEL concentrate-diluent mixture. The resulting solution is clear to slightly turbid, colourless to light-yellow to yellow, essentially free from visual particulates. **Only 2.5 mL of solution, containing 25 mg temsirolimus, should be extracted from the vial.**

The TORISEL concentrate-diluent mixture is chemically stable when stored at controlled room temperature 20ºC to 25ºC for up to 24 hours. However, to reduce microbiological hazard the mixture should be used as soon as possible after preparation.

Step 2: Withdraw the required amount of TORISEL Concentrate for Injection/Diluent mixture from step 1 (10 mg/mL) and inject rapidly into 250 mL of 0.9% sodium chloride injection to ensure adequate mixing. Mix the admixture by inversion of the bag or bottle. Avoid excessive shaking as this may cause foaming.

The final diluted solution in the bag or bottle should be inspected visually for particulate matter.

Administration
Administration of the final diluted infusion solution should be completed within 6 hours from the time that the concentrate diluent mixture is added to the sodium chloride injection.

The use of an infusion pump is the preferred method of administration to ensure accurate delivery of the drug.

Appropriate administration materials must be composed of glass, polyolefin, or polyethylene to avoid excessive loss of drug and to decrease the rate of di-(2-ethylhexyl)phthalate (DEHP) extraction. The administration materials must consist of non-DEHP non-polyvinyl chloride (PVC) tubing with the appropriate filter. It is important that the recommendations in this section be followed closely.

An in-line polyethersulfone filter with a pore size of not greater than 5 microns is recommended for administration to avoid the possibility of particles bigger than 5 microns being infused. If the administration set available does not have an in-line filter incorporated, a filter should be added at the end of the set (i.e., an end-filter) before the admixture reaches the vein of the patient. Different end-filters can be used ranging in filter pore size from 0.2 microns up to 5 microns. The use of both an in-line and end-filter is not recommended.

TORISEL, when constituted, contains polysorbate 80, which is known to increase the rate of di-(2-ethylhexyl)phthalate (DEHP) extraction from polyvinyl chloride (PVC). This should be considered during the preparation and administration of TORISEL, including storage time elapsed in a PVC container following constitution.

Infusion sets and bags made of soft plastic such as ethylene vinyl acetate should not be used due to the potential to lose drug over time.

It is important that the recommendations in the DOSAGE AND ADMINISTRATION section are followed closely.

Use in Patients with Renal Impairment
Following a 25 mg intravenous dose of [^{14}C]-labelled temsirolimus in healthy subjects, renal elimination of total radioactivity was 4.6% of the administered dose.

Renal elimination is a minor pathway; therefore, renal impairment is not expected to markedly influence drug exposure, and no dosage adjustment of TORISEL is required in patients with renal impairment. Studies in patients with varying renal impairment have not been conducted.

TORISEL has not been studied in patients undergoing haemodialysis.

Use in Patients with Hepatic Impairment
Temsirolimus is contraindicated in patients with bilirubin >1.5 x ULN due to increased risk of death, including deaths due to progression of underlying cancer (see CONTRAINDICATIONS).

Use caution when treating patients with mild hepatic impairment. Concentrations of temsirolimus and its metabolite sirolimus were increased in patients with elevated AST or bilirubin levels. Assessment of AST and bilirubin levels is recommended before initiation of temsirolimus and periodically thereafter.

Use in Children
The safety and effectiveness of TORISEL in paediatric patients have not been established.

Use in Elderly Patients
No specific dose adjustment is recommended for elderly patients (see PRECAUTIONS: Use in the Elderly).

Compatibilities, Incompatibilities
TORISEL Concentrate for Injection should not be added directly to aqueous infusion solutions. Direct addition of TORISEL Concentrate for Injection to aqueous solutions will result in precipitation of drug. Always combine TORISEL Concentrate for Injection with diluent for TORISEL Concentrate for Injection 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 temsirolimus in other infusion solutions has not been evaluated. Addition of other drugs or nutritional agents to admixtures of temsirolimus 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.

OVERDOSAGE

There is no specific treatment for temsirolimus overdose; however, temsirolimus has been safely administered to patients with cancer with repeated intravenous doses as high as 220 mg/m^2.

PRESENTATION AND STORAGE CONDITIONS

TORISEL (temsirolimus) injection, 25 mg/mL.

DILUENT for TORISEL, 1.8 mL (deliverable volume) per vial.

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

Storage and Handling

Components

TORISEL Concentrate for Injection and diluent should be protected from excessive room light and sunlight during handling and preparation of admixtures. TORISEL Concentrate for Injection should be inspected visually for particulate matter and discolouration following reconstitution and prior to administration. Bags/containers that come in contact with TORISEL Concentrate for Injection must be made of glass, polyolefin, or polyethylene.

TORISEL Concentrate for Injection must be refrigerated (2°C to 8°C) and protected from light. TORISEL Concentrate for Injection is stable for 36 months under these storage conditions.

Diluent for TORISEL Concentrate for Injection is stable for 36 months when stored below 25°C. The diluent may be stored at controlled room temperature until packaged with product, at which time it is refrigerated and protected from light.

The drug concentrate-diluent mixture is stable for up to 24 hours at controlled room temperature 20ºC to 25ºC.

Admixtures

Once the concentrate is combined with the provided diluent, inject the mixture rapidly into 0.9% sodium chloride injection. To reduce microbiological hazard, use as soon as practical after preparation. 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. If storage is necessary, store at room temperature and protect from excessive light and sunlight.

TORISEL is for single use in one patient only. Discard any residue.

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Hong Kong