Only for the use of a Registered Medical Practitioner or a Hospital or a Laboratory.

Biocon

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Temsirolimus Injection

GenXtor® जेनेक्सटोर

COMPOSITION
Each mL of Temsirolimus injection contains
Temsirolimus 25mg
Ethanol IP 40.0% w/v
Excipients q.s.

Each mL of diluent for Temsirolimus injection contains
Ethanol IP 20.0% w/v
Excipients q.s.

DESCRIPTION
Temsirolimus, an inhibitor of mTOR, is an antineoplastic agent.
Temsirolimus is a white to off-white powder with a molecular formula of $C_{56}H_{87}NO_{16}$ and a molecular weight of 1030.30. It is non-hygroscopic. Temsirolimus is practically insoluble in water and soluble in alcohol. It has no ionizable functional groups, and its solubility is independent of pH.

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

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

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

Metabolism - Cytochrome P450 3A4 is the major isozyme responsible for the formation of five Temsirolimus metabolites. Sirolimus, an active metabolite of Temsirolimus, is the principal metabolite in humans following intravenous treatment. The remainder of the metabolites account for less than 10% of radioactivity in the plasma. In human liver microsomes Temsirolimus was an inhibitor of CYP2D6 and 3A4. However, there was no effect observed *in vivo* when Temsirolimus was administered with Desipramine (a CYP2D6 substrate), and no effect is anticipated with substrates of CYP3A4 metabolism.

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

INDICATIONS AND USAGE
Temsirolimus injection is indicated for the treatment of advanced renal cell carcinoma.

DOSAGE AND ADMINISTRATION
Advanced Renal Cell Carcinoma
The recommended dose of Temsirolimus for advanced renal cell carcinoma is 25 mg infused over a 30-60 minute period once a week.
Treatment should continue until disease progression or unacceptable toxicity occurs.

Premedication
Patients should receive prophylactic intravenous diphenhydramine 25 to 50 mg (or similar antihistamine) approximately 30 minutes before the start of each dose of Temsirolimus

Dosage Interruption/Adjustment
Temsirolimus should be held for absolute neutrophil count (ANC) < 1,000/mm^3, platelet count < 75,000/mm^3, or National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade 3 or greater adverse reactions. Once toxicities have resolved to grade 2 or less, Temsirolimus may be restarted with the dose reduced by 5 mg/week to a dose no lower than 15 mg/week.

Dose Modification Guidelines
Hepatic Impairment: Use caution when treating patients with hepatic impairment. If Temsirolimus must be given in patients with mild hepatic impairment (bilirubin > 1 – 1.5 x ULN or AST >ULN but bilirubin ≤ ULN), reduce the dose of Temsirolimus to 15 mg/week. Temsirolimus is contraindicated in patients with bilirubin >1.5 x ULN .

Concomitant Strong CYP3A4 Inhibitors: The concomitant use of strong CYP3A4 inhibitors should be avoided (e.g. Ketoconazole, Itraconazole, Clarithromycin, Atazanavir, Indinavir, Nefazodone, Nelfinavir, Ritonavir, Saquinavir, Telithromycin, and Voriconazole). Grapefruit juice may also increase plasma concentrations of Sirolimus (a major metabolite of Temsirolimus) and should be avoided. If patients must be co-administered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, a Temsirolimus dose reduction to 12.5 mg/week should be considered. This dose of Temsirolimus is predicted to adjust the AUC to the range observed without inhibitors. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inhibitors. If the strong inhibitor is discontinued, a washout period of approximately 1 week should be allowed before the Temsirolimus dose is adjusted back to the dose used prior to initiation of the strong CYP3A4 inhibitor .

Concomitant Strong CYP3A4 Inducers: The use of concomitant strong CYP3A4 inducers should be avoided (e.g. Dexamethasone, Phenytoin, Carbamazepine, Rifampin, Rifabutin, Rifampacin, Phenobarbital). If patients must be co-administered a strong CYP3A4 inducer, based on pharmacokinetic studies, a Temsirolimus dose increase from 25 mg/week up to 50 mg/week should be considered. This dose of Temsirolimus is predicted to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued the Temsirolimus dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer

Instructions for Preparation
Temsirolimus must be stored under refrigeration at 2°-8°C and protected from light. During handling and preparation of admixtures, Temsirolimus should be protected from excessive room light and sunlight. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

In order to minimize the patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final Temsirolimus dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

Temsirolimus 25 mg/mL injection must be diluted with the supplied diluent before further dilution in 0.9% Sodium Chloride Injection IP. Please note that both the Temsirolimus injection and diluent vials contain an overfill to ensure the recommended volume can be withdrawn.

Follow this two-step dilution process in an aseptic manner.
Step 1:
DILUTION OF TEMSIROLIMUS INJECTION 25 MG/ML WITH SUPPLIED DILUENT
- Each Vial of Temsirolimus (Temsirolimus) must first be mixed with 1.8 mL of the enclosed diluent. The temsirolimus vial contains an overfill of 0.2 mL (30mg/1.2mL). The resultant solution contains 30 mg/3 mL (10 mg/mL)
- Mix well by inversion of the vial. Allow sufficient time for the air bubbles to subside. The solution should be clear to slightly turbid, colorless to light-yellow solution, essentially free from visual particulates.

The concentrate-diluent mixture is stable below 25ºC for up to 24 hours.

Step 2:
DILUTION OF CONCENTRATE-DILUENT MIXTURE WITH 0.9% SODIUM CHLORIDE INJECTION IP
- Withdraw precisely the required amount of concentrate-diluent mixture containing Temsirolimus 10 mg/mL as prepared in Step 1 from the vial (i.e., 2.5 mL for a Temsirolimus dose of 25 mg) and further dilute into an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection IP
- Mix by inversion of the bag or bottle, avoiding excessive shaking, as this may cause foaming.

The resulting solution should be inspected visually for particulate matter and discoloration prior to administration. The admixture of Temsirolimus in 0.9% Sodium Chloride Injection IP should be protected from excessive room light and sunlight.

Administration
- Administration of the final diluted solution should be completed within six hours from the time that Temsirolimus is first added to 0.9% Sodium Chloride Injection IP.
- Temsirolimus is infused over a 30 to 60-minute period once weekly. The use of an infusion pump is the preferred method of administration to ensure accurate delivery of the product.
- Appropriate administration materials should be composed of glass, polyolefin, or polyethylene to avoid excessive loss of product and diethylhexylpthalate (DEHP) extraction. The administration materials should consist of non-DEHP, non-polyvinylchloride (PVC) tubing with appropriate filter. In the case when a PVC administration set has to be used, it should not contain DEHP. 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 polyethersulfone filter should be added at 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.
- Temsirolimus, when diluted, contains polysorbate 80, which is known to increase the rate of DEHP extraction from PVC. This should be considered during the preparation and administration of Temsirolimus, including storage time elapsed when in direct contact with PVC following constitution.

CLINICAL STUDIES
A phase 3, multi-center, three-arm, randomized, open-label study was conducted in previously untreated patients with advanced renal cell carcinoma (clear cell and non-clear cell histologies).
The objectives were to compare Overall Survival (OS), Progression-Free Survival (PFS), Objective Response Rate (ORR), and safety in patients receiving IFN- α to those receiving Temsirolimus or Temsirolimus plus IFN- α Patients in this study had 3 or more of 6 pre-selected prognostic risk factors (less than one year from time of initial RCC diagnosis to randomization, Karnofsky performance status of 60 or 70, hemoglobin less than the lower limit of normal, corrected calcium of greater than 10 mg/dL, lactate dehydrogenase > 1.5 times the upper limit of normal, more than one metastatic organ site). Patients were stratified for prior nephrectomy status within three geographic regions and were randomly assigned (1:1:1) to receive IFN- α alone (n=207), Temsirolimus alone (25 mg weekly; n=209), or the combination arm (n=210).

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

The median duration of treatment in the Temsirolimus arm was 17 weeks (range 1-126 weeks). The median duration of treatment on the IFN arm was 8 weeks (range 1-124 weeks). There was a statistically significant improvement in OS (time from randomization to death) in the Temsirolimus 25 mg arm compared to IFN- α .The combination of Temsirolimus 15 mg and IFN- α did not result in a significant increase in overall survival when compared with IFN- α alone. Figure 1 is a Kaplan-Meier plot of OS in this study. The evaluations of PFS (time from randomization to disease progression or death) and ORR, were based on blinded independent radiologic assessment of tumor response. Efficacy results are summarized in Table 1.

Table 1: Summary of efficacy results of Temsirolimus vs. IFN-α

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

CI = confidence interval; NA = not applicable
* A comparison is considered statistically significant if the p-value is < 0.0159 (O'Brien-Fleming boundary at 446 deaths).
** Not adjusted for multiple comparisons.
a. Based on log-rank test stratified by prior nephrectomy and region.
b. Based on Cox proportional hazard model stratified by prior nephrectomy and region.
c. Based on Cochran-Mantel-Haenszel test stratified by prior nephrectomy and region.

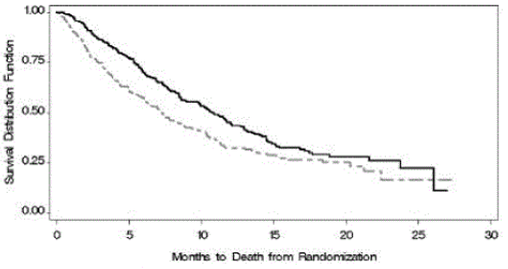

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Figure 1: Kaplan-Meier Curves for Overall Survival – Temsirolimus vs. IFN

SIDE EFFECTS
The following serious adverse reactions have been associated with Temsirolimus in clinical trials.
- Hypersensitivity Reactions
- Hyperglycemia/Glucose Intolerance
- Interstitial Lung Disease
- Hyperlipemia
- Bowel Perforation
- Renal Failure

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

Clinical Studies related to side effects
Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.
In the Phase 3 randomized, open-label study of interferon alfa (IFN- α)alone, Temsirolimus alone, and Temsirolimus and IFN- α a total of 616 patients were treated. Two hundred patients received IFN- α weekly, 208 received Temsirolimus 25 mg weekly, and 208 patients received a combination of Temsirolimus and IFN- α weekly.

Treatment with the combination of Temsirolimus 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 2 shows the percentage of patients experiencing treatment emergent adverse reactions. Reactions reported in at least 10% of patients who received Temsirolimus 25 mg alone or IFN- α alone are listed. Table 3 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 2: Adverse Reactions Reported in at Least 10% of Patients Who Received 25 mg IV Temsirolimus or IFN- α in the Randomized Trial

Adverse Reaction	Temsirolimus 25 mg n=208		IFN-a n=200	
	All Grades* n (%)	Grades 3&4* n (%)	All Grades* n (%)	Grades 3&4* n (%)
Any	208 (100)	139 (67)	199 (100)	155 (78)
GENERAL DISORDERS				
Asthenia	106 (51)	23 (11)	127 (64)	52 (26)
Edema [a]	73 (35)	7 (3)	21 (11)	1 (1)
Pain	59 (28)	10 (5)	31 (16)	4 (2)
Pyrexia	50 (24)	1 (1)	99 (50)	7 (4)
Weight Loss	39 (19)	3 (1)	50 (25)	4 (2)
Headache	31 (15)	1 (1)	30 (15)	0 (0)
Chest Pain	34 (16)	2 (1)	18 (9)	2 (1)
Chills	17 (8)	1 (1)	59 (30)	3 (2)
GASTROINTESTINAL DISORDERS				
Mucositis [b]	86 (41)	6 (3)	19 (10)	0 (0)
Anorexia	66 (32)	6 (3)	87 (44)	8 (4)
Nausea	77 (37)	5 (2)	82 (41)	9 (5)
Diarrhea	56 (27)	3 (1)	40 (20)	4 (2)
Abdominal Pain	44 (21)	9 (4)	34 (17)	3 (2)
Constipation	42 (20)	0 (0)	36 (18)	1 (1)
Vomiting	40 (19)	4 (2)	57 (29)	5 (3)
INFECTIONS				
Infections	42 (20)	6 (3)	19 (10)	4 (2)
Urinary tract infection [c]	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				
Dyspnea	58 (28)	18 (9)	48 (24)	11 (6)
Cough	53 (26)	2 (1)	29 (15)	0 (0)
Epistaxis	25 (12)	0 (0)	7 (4)	0 (0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Rash [f]	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 edema, facial edema, and peripheral edema
b Includes aphthous stomatitis, glossitis, mouth ulceration, mucositis, and stomatitis
c Includes infections not otherwise specified (NOS) and the following infections that occurred infrequently as distinct entities: abscess, bronchitis, cellulitis, herpes simplex, and herpes zoster
d Includes cystitis, dysuria, hematuria, urinary frequency, and urinary tract infection
e Includes eczema, exfoliative dermatitis, maculopapular rash, pruritic rash, pustular rash, rash (NOS), and vesiculobullous rash
f Includes taste loss and taste perversion

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The following selected adverse reactions were reported less frequently (< 10%).
Gastrointestinal Disorders - Fatal bowel perforation occurred in 1 patient (1%).
Eye Disorders - Conjunctivitis (including lacrimation disorder) occurred in 15 patients (7%).
Immune System - Allergic/Hypersensitivity reactions occurred in 18 patients (9%). Angioneurotic edema-type reactions have been observed in some patients who received temsirolimus and ACE inhibitors concomitantly.
Infections - Pneumonia occurred in 17 patients (8%); upper respiratory tract infection occurred in 14 patients (7%).
General Disorders and Administration Site Conditions - Impaired wound healing occurred in 3 patients (1%).
Respiratory, Thoracic and Mediastinal Disorders - Interstitial lung disease occurred in 5 patients (2%), including rare fatalities.
Vascular - Hypertension occurred in 14 patients (7%); venous thromboembolism (including deep vein thrombosis and pulmonary embolus) occurred in 5 patients (2%); thrombophlebitis occurred in 2 patients (1%).

Table 3: Incidence of selected laboratory abnormalities in patients who received 25 mg IV Temsirolimus or IFN- α in the randomized trial

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

*NCI CTC version 3.0
**Grade 1 toxicity may be under-reported for lymphocytes and neutrophils

DRUG INTERACTIONS
Agents Inducing CYP3A Metabolism - Co-administration of Temsirolimus 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 Temsirolimus treatment alone. If alternative treatment cannot be administered, a dose adjustment should be considered.
Agents Inhibiting CYP3A Metabolism - Co-administration of Temsirolimus 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 Temsirolimus alone. If alternative treatment cannot be administered, a dose adjustment should be considered.
Interactions with Drugs Metabolized by CYP2D6 - The concentration of desipramine, a CYP2D6 substrate, was unaffected when 25 mg of Temsirolimus was co-administered. No clinically significant effect is anticipated when Temsirolimus is co-administered with agents that are metabolized by CYP2D6 or CYP3A4.

WARNINGS AND PRECAUTIONS
Hypersensitivity Reactions - Hypersensitivity/infusion reactions, including but not limited to flushing, chest pain, dyspnea, hypotension, apnea, 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 throughout 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.
Temsirolimus should be used with caution in persons with known hypersensitivity to temsirolimus or its metabolites (including Sirolimus), polysorbate 80, or to any other component (including the excipients) of Temsirolimus.
An H1 antihistamine should be administered to patients before the start of the intravenous temsirolimus infusion. Temsirolimus 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 Temsirolimus infusion, the infusion should be stopped and the patient should be observed for at least 30 to 60 minutes (depending on the severity of the reaction). At the discretion of the physician, treatment may be resumed with the administration of an H1-receptor antagonist (such as diphenhydramine), if not previously administered and/or an H2-receptor antagonist (such as intravenous famotidine 20 mg or intravenous ranitidine 50 mg) approximately 30 minutes before restarting the Temsirolimus infusion. The infusion may then be resumed at a slower rate (up to 60 minutes).
A benefit-risk assessment should be done prior to the continuation of Temsirolimus therapy in patients with severe or life-threatening reactions.
Hepatic Impairment - The safety and pharmacokinetics of Temsirolimus were evaluated in a dose escalation phase 1 study in 110 patients with normal or varying degrees of hepatic impairment. Patients with baseline bilirubin > 1.5 x ULN experienced greater toxicity than patients with baseline bilirubin ≤ 1 .x ULN when treated with Temsirolimus. The overall frequency of ≥ grade 3 adverse reactions and deaths, including deaths due to progressive disease, were greater in patients with baseline bilirubin > 1.5 x ULN. Temsirolimus is contraindicated in patients with bilirubin > 1.5 x ULN due to increased risk of death.
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. If Temsirolimus must be given in patients with mild hepatic impairment (bilirubin > 1 – 1.5 x ULN or AST > ULN but bilirubin ≤ ULN), reduce the dose of Temsirolimus to 15 mg/week.
Hyperglycemia/Glucose Intolerance - The use of Temsirolimus is likely to result in increases in serum glucose. In the phase 3 trial, 89% of patients receiving Temsirolimus had at least one elevated serum glucose while on treatment, and 26% of patients reported hyperglycemia as an adverse event. This may result in the need for an increase in the dose of or initiation of, insulin and/or oral hypoglycemic agent therapy. Serum glucose should be tested before and during treatment with Temsirolimus. Patients should be advised to report excessive thirst or any increase in the volume or frequency of urination.
Infections - The use of Temsirolimus may result in immunosuppression. Patients should be carefully observed for the occurrence of infections, including opportunistic infections.
Interstitial Lung Disease - Cases of interstitial lung disease, some resulting in death, occurred in patients who received Temsirolimus. Some patients were asymptomatic with infiltrates detected on computed tomography scan or chest radiograph. Others presented with symptoms such as dyspnea, cough, hypoxia, and fever. Some patients required discontinuation of Temsirolimus and/or treatment with corticosteroids and/or antibiotics, while some patients continued treatment without additional intervention. Patients should be advised to report promptly any new or worsening respiratory symptoms.
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. Empiric treatment with corticosteroids and/or antibiotics may be considered.
Hyperlipidemia - The use of Temsirolimus is likely to result in increases in serum triglycerides and cholesterol. In the phase 3 trial, 87% of patients receiving Temsirolimus had at least one elevated serum cholesterol value and 83% had at least one elevated serum triglyceride value. This may require initiation, or increase in the dose, of lipid-lowering agents. Serum cholesterol and triglycerides should be tested before and during treatment with Temsirolimus.
Bowel Perforation - Cases of fatal bowel perforation occurred in patients who received Temsirolimus. These patients presented with fever, abdominal pain, metabolic acidosis, bloody stools, diarrhea, and/or acute abdomen. Patients should be advised to report promptly any new or worsening abdominal pain or blood in their stools.
Renal Failure - Cases of rapidly progressive and sometimes fatal acute renal failure not clearly related to disease progression occurred in patients who received Temsirolimus. Some of these cases were not responsive to dialysis.
Wound Healing Complications - Use of Temsirolimus has been associated with abnormal wound healing. Therefore, caution should be exercised with the use of Temsirolimus in the perioperative period.
Intracerebral Hemorrhage - Patients with central nervous system tumors (primary CNS tumor or metastases) and/or receiving anticoagulation therapy may be at an increased risk of developing intracerebral bleeding (including fatal outcomes) while receiving Temsirolimus.

Co-administration with Inducers or Inhibitors of CYP3A Metabolism
Agents Inducing CYP3A Metabolism - Strong inducers of CYP3A4/5 such as Dexamethasone, Carbamazepine, Phenytoin, Phenobarbital, Rifampin, Rifabutin, and Rifampacin may decrease exposure of the active metabolite, Sirolimus. If alternative treatment cannot be administered, a dose adjustment should be considered. St. John's Wort may decrease Temsirolimus plasma concentrations unpredictably. Patients receiving Temsirolimus should not take St. John's Wort concomitantly.
Agents Inhibiting CYP3A Metabolism - Strong CYP3A4 inhibitors such as Atazanavir, Clarithromycin, Indinavir, Itraconazole, Ketoconazole, Nefazodone, Nelfinavir, Ritonavir, Saquinavir, and Telithromycin may increase blood concentrations of the active metabolite Sirolimus. If alternative treatments cannot be administered, a dose adjustment should be considered.
Concomitant use of Temsirolimus with Sunitinib - The combination of Temsirolimus and Sunitinib resulted in dose-limiting toxicity. Dose-limiting toxicities (Grade 3/4 erythematous maculopapular rash, and gout/cellulitis requiring hospitalization) were observed in two out of three patients treated in the first cohort of a phase 1 study at doses of Temsirolimus 15 mg IV per week and Sunitinib 25 mg oral per day (Days 1-28 followed by a 2-week rest).
Vaccinations - The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with Temsirolimus. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.
Pregnancy - There are no adequate and well-controlled studies of Temsirolimus in pregnant women. However, based on its mechanism of action, Temsirolimus may cause fetal harm when administered to a pregnant woman. Temsirolimus administered daily as an oral formulation caused embryo-fetal and intrauterine toxicities in rats and rabbits at human sub-therapeutic exposures. If this drug is used during pregnancy or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant throughout treatment and for 3 months after Temsirolimus therapy has stopped.
Men should be counseled regarding the effects of Temsirolimus on the fetus and sperm prior to starting treatment Men with partners of childbearing potential should use reliable contraception throughout treatment and are recommended to continue this for 3 months after the last dose of Temsirolimus.
Elderly patients - Based on the results of a phase 3 study, elderly patients are more likely to experience certain adverse reactions including diarrhea, edema and pneumonia.
Monitoring Laboratory Tests - In the randomized, phase 3 trial, complete blood counts (CBCs) were checked weekly, and chemistry panels were checked every two weeks. Laboratory monitoring for patients receiving Temsirolimus may need to be performed more or less frequently at the physician's discretion.

Nonclinical Toxicology
Carcinogenesis, Mutagenesis, Impairment of Fertility - Carcinogenicity studies have not been conducted with Temsirolimus. However, Sirolimus, the major metabolite of Temsirolimus in humans, was carcinogenic in mice and rats. The following effects were reported in mice and/or rats in the carcinogenicity studies conducted with Sirolimus: lymphoma, hepatocellular adenoma and carcinoma, and testicular adenoma.
Temsirolimus was not genotoxic in a battery of *in vitro* (bacterial reverse mutation in *Salmonella typhimurium* and *Escherichia coli*, forward mutation in mouse lymphoma cells, and chromosome aberrations in Chinese hamster ovary cells) and *in vivo* (mouse micronucleus) assays.
In male rats, the following fertility effects were observed: decreased number of pregnancies, decreased sperm concentration and motility, decreased reproductive organ weights, and testicular tubular degeneration. These effects were observed at oral Temsirolimus doses ≥ 3 mg/m²/day (approximately 0.2-fold the human recommended intravenous dose). Fertility was absent at 30 mg/m²/day.
In female rats, an increased incidence of pre- and post-implantation losses occurred at oral doses ≥ 4.2 mg/m²/day (approximately 0.3-fold the human recommended intravenous dose), resulting in decreased numbers of live fetuses.

Use in specific populations
Pregnancy - Pregnancy category D.
Women of childbearing potential should be advised to avoid becoming pregnant throughout treatment and for 3 months after Temsirolimus therapy has stopped. Temsirolimus can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.
Temsirolimus administered daily as an oral formulation caused embryo-fetal and intrauterine toxicities in rats and rabbits at human sub-therapeutic exposures. Embryo-fetal adverse effects in rats consisted of reduced fetal weight and reduced ossifications, and in rabbits included reduced fetal weight, omphalocele, bifurcated sternabrae, notched ribs, and incomplete ossifications.
In rats, the intrauterine and embryo-fetal adverse effects were observed at the oral dose of 2.7 mg/m²/day (approximately 0.04-fold the AUC in cancer patients at the human recommended dose). In rabbits, the intrauterine and embryo-fetal adverse effects were observed at the oral dose of ≥ 7.2mg/m²/day (approximately 0.12-fold the AUC in cancer patients at the recommended human dose).
Nursing mothers - It is not known whether Temsirolimus is excreted into human milk, and due to the potential for tumorigenicity shown for Sirolimus (active metabolite of Temsirolimus) in animal studies, a decision should be made whether to discontinue nursing or discontinue Temsirolimus, taking into account the importance of the drug to the mother.
Pediatric Use - The safety and effectiveness of Temsirolimus in pediatric patients have not been established.
Geriatric Use - Clinical studies of Temsirolimus did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. Based on the results of a phase 3 study, elderly patients may be more likely to experience certain adverse reactions including diarrhea, edema and pneumonia
Renal Impairment - No clinical studies were conducted with Temsirolimus in patients with decreased renal function. Less than 5% of total radioactivity was excreted in the urine following a 25 mg intravenous dose of [14C]-labeled Temsirolimus in healthy subjects. Renal impairment is not expected to markedly influence drug exposure, and no dosage adjustment of Temsirolimus is recommended in patients with renal impairment.
Temsirolimus has not been studied in patients undergoing hemodialysis.
Hepatic Impairment - Temsirolimus 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 reactions and deaths, including deaths due to progressive disease, during the study (Table 4).

Table 4: Adverse reactions in patients with advanced malignancies plus normal or impaired hepatic function

Hepatic Function*	Temsirolimus Dose Range (mg)	Adverse Reactions 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)

*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 progressive disease and adverse reactions.

Temsirolimus is contraindicated in patients with bilirubin >1.5 x ULN . Use caution when treating patients with mild hepatic impairment. If Temsirolimus must be given in patients with mild hepatic impairment (bilirubin >1 – 1.5 x ULN or AST >ULN but bilirubin ≤ ULN), reduce the dose of Temsirolimus to 15 mg/week. Because there is a need for dosage adjustment based upon hepatic function, assessment of AST and bilirubin levels is recommended before initiation of Temsirolimus and periodically thereafter.

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

CONTRAINDICATIONS
Temsirolimus is contraindicated in patients with bilirubin > 1.5 x ULN.

PRESENTATION AND STORAGE:
Each carton contains
1 vial Temsirolimus injection 25 mg/ml, 1.2 mL, 1 vial diluent for Temsirolimus injection, 1.8 mL
Store in a refrigerator between 2°C to 8°C. Do not freeze. Protect from light.

PATIENT INFORMATION
Allergic (Hypersensitivity) Reactions - Patients should be informed of the possibility of serious allergic reactions, including anaphylaxis, despite premedication with antihistamines, and to immediately report any facial swelling or difficulty breathing.
Increased Blood Glucose Levels - Patients are likely to experience increased blood glucose levels while taking Temsirolimus. This may result in the need for initiation of, or increase in the dose of, insulin and/or hypoglycemic agents. Patients should be directed to report any excessive thirst or frequency of urination to their physician.
Infections - Patients should be informed that they may be more susceptible to infections while being treated with Temsirolimus.
Interstitial Lung Disease - Patients should be warned of the possibility of developing interstitial lung disease, a chronic inflammation of the lungs, which may rarely result in death. Patients should be directed to report promptly any new or worsening respiratory symptoms to their physician..
Increased Blood Triglycerides and/or Cholesterol - Patients are likely to experience elevated triglycerides and/or cholesterol during Temsirolimus treatment. This may require initiation of, or increase in the dose of, lipid-lowering agents.
Bowel Perforation - Patients should be warned of the possibility of bowel perforation. Patients should be directed to report promptly any new or worsening abdominal pain or blood in their stools.
Renal Failure - Patients should be informed of the risk of renal failure.
Wound Healing Complications - Patients should be advised of the possibility of abnormal wound healing if they have surgery within a few weeks of initiating therapy or during therapy.
Intracerebral Bleeding - Patients with CNS tumors and/or receiving anticoagulants should be informed of the increased risk of developing intracerebral bleeding (including fatal outcomes) while on Temsirolimus.
Medications that can interfere with Temsirolimus - Some medicines can interfere with the breakdown or metabolism of Temsirolimus. In particular, patients should be directed to inform their physician if they are taking any of the following: Protease inhibitors, anti-epileptic medicines including Carbamazepine, Phenytoin, and Barbiturates, St. John's Wort, Rifampicin, Rifabutin, Nefazodone or selective serotonin re-uptake inhibitors used to treat depression, antibiotics or antifungal medicines used to treat infections.
Vaccinations - Patients should be advised that vaccinations may be less effective while being treated with Temsirolimus. In addition, the use of live vaccines, and close contact with those who have received live vaccines, while on Temsirolimus should be avoided.
Pregnancy - Temsirolimus can cause fetal harm. Women of childbearing potential should be advised to avoid becoming pregnant throughout treatment and for 3 months after Temsirolimus therapy has stopped. Men with partners of childbearing potential should use reliable contraception throughout treatment and are recommended to continue this for 3 months after the last dose of Temsirolimus.
Elderly Patients - Elderly patients should be advised that they may be more likely to experience certain adverse reactions including diarrhea, edema and pneumonia.

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