SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Torisel 30 mg concentrate and diluent for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of concentrate for solution for infusion contains 30 mg temsirolimus.

After first dilution of the concentrate with 1.8 ml of withdrawn diluent, the concentration of temsirolimus is 10 mg/ml (see section 4.2).

Excipients with known effect:

Ethanol

- 1 vial of concentrate contains 474 mg of anhydrous ethanol which is equivalent to 394.6 mg/ml (39.46% w/v).
  1.8 ml of the diluent provided contains 358 mg anhydrous ethanol which is equivalent to 199.1 mg/ml (19.91% w/v).

Propylene glycol

- 1 vial of concentrate contains 604 mg of propylene glycol which is equivalent to 503.3 mg/ml (50.33% w/v).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate and diluent for solution for infusion (sterile concentrate).

The concentrate is a clear, colourless to light-yellow solution, free from visible particulates.

The diluent is a clear to slightly turbid, light-yellow to yellow solution, free from visible particulates.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Renal cell carcinoma

Torisel is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC) (see section 5.1).

Mantle cell lymphoma

Torisel is indicated for the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (MCL) (see section 5.1).

4.2 Posology and method of administration

Torisel must be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products.

The vial of Torisel concentrate must first be diluted with 1.8 ml of diluent withdrawn from the supplied vial to achieve a concentration of temsirolimus of 10 mg/ml. Withdraw the required amount of the temsirolimus-diluent mixture (10 mg/ml) and then inject rapidly into sodium chloride 9 mg/ml (0.9%) solution for injection.

For instructions on preparation and to help ensure correct dosing, see section 6.6.

Posology

Patients should be given intravenous diphenhydramine 25 mg to 50 mg (or similar antihistamine) approximately 30 minutes before the start of each dose of temsirolimus (see section 4.4).

Treatment with Torisel should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.

Renal cell carcinoma

The recommended dose of Torisel for advanced renal cell carcinoma administered intravenously is 25 mg infused over a 30 to 60 minute period once a week (see section 6.6 for instructions on dilution, administration and disposal).

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 by 5 mg/week decrements.

Mantle cell lymphoma

The recommended dosing regimen of Torisel for mantle cell lymphoma is 175 mg, infused over a 30 to 60 minute period once a week for 3 weeks followed by weekly doses of 75 mg, infused over a 30 to 60 minute period. The starting dose of 175 mg was associated with a significant incidence of adverse events and required dose reductions/delays in the majority of patients. The contribution of the initial 175 mg doses to the efficacy outcome is currently not known.

Management of suspected adverse reactions may require temporary interruption and/or dose reduction of temsirolimus therapy according to the guidelines in the following tables. If a suspected reaction is not manageable with dose delays and/or optimal medical therapy, then the dose of temsirolimus should be reduced according to the dose reduction table below.

Dose reduction levels

Dose reduction level	**Starting dose 175 mg**	**Continuing dose[a] 75 mg**
-1	75 mg	50 mg
-2	50 mg	25 mg

[a] In the MCL Clinical Trial, up to two dose level reductions were allowed per patient.

Temsirolimus dose modifications based on weekly ANC and platelet counts

ANC	Platelets	Dose of temsirolimus
≥1.0 x 10^9/l	≥50 x 10^9/l	100% of planned dose
<1.0 x 10^9/l	<50 x 10^9/l	Hold[a]

[a] Upon recovery to ANC ≥1.0 x 10^9/l (1000 cells/mm^3) and platelets to ≥50 x 10^9/l (50,000 cells/mm^3), the doses should be modified to the next lower dose level according to the table above. If the patient cannot maintain ANC >1.0 x 10^9/l and platelets >50 x 10^9/l on the new dose reduction level, then the next lower dose should be given once the counts have recovered.
Abbreviation: ANC = absolute neutrophil count.

Special populations

Elderly

No specific dose adjustment is necessary in elderly patients.
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Renal impairment

No dose adjustment of temsirolimus is recommended in patients with renal impairment. Temsirolimus should be used with caution in patients with severe renal impairment (see section 4.4).

Hepatic impairment

Temsirolimus should be used with caution in patients with hepatic impairment (see section 4.4).

No dose adjustment of temsirolimus is recommended for patients with advanced renal cell carcinoma (RCC) and mild to moderate hepatic impairment. For patients with RCC and severe hepatic impairment, the recommended dose for patients who have baseline platelets ≥ 100 x 10^9/l is 10 mg intravenous once a week infused over a 30to 60 minute period (see section 5.2).

No dose adjustment is recommended for patients with MCL and mild hepatic impairment. Temsirolimus should not be used in patients with MCL and moderate or severe hepatic impairment (see section 4.3).

Paediatric population

There is no relevant use of temsirolimus in the paediatric population for the indication: treatment of renal cell carcinoma and mantle cell lymphoma.
Temsirolimus should not be used in the paediatric population for the treatment of neuroblastoma, rhabdomyosarcoma or high-grade glioma, because of efficacy concerns based on the available data (see section 5.1).

Method of administration

Torisel must be administered by intravenous infusion.

For instructions on dilution and preparation of the medicinal product before administration, see section 6.6.

Renal cell carcinoma

The recommended dose of Torisel for advanced renal cell carcinoma administered intravenously is 25 mg infused over a 30- to 60-minute period once a week (see section 6.6 for instructions on dilution, administration and disposal).

Mantle cell lymphoma

The recommended dose of Torisel for mantle cell lymphoma is 175 mg, infused over a 30-60 minute period once a week for 3 weeks followed by weekly doses of 75 mg, infused over a 30-60 minute period (see section 6.6 for instructions on dilution, administration and disposal).

4.3 Contraindications

Hypersensitivity to temsirolimus, its metabolites (including sirolimus), polysorbate 80, or to any of the excipients listed in section 6.1.

Use of temsirolimus in patients with MCL with moderate or severe hepatic impairment.

4.4 Special warnings and precautions for use

The incidence and severity of adverse events is dose-dependent. Patients receiving the starting dose of 175 mg weekly for the treatment of MCL must be followed closely to decide on dose reductions/delays.

Paediatric population

Temsirolimus is not recommended for use in paediatric patients (see sections 4.2, 4.8 and 5.1).

Elderly

Based on the results of a Phase 3 study in RCC, elderly patients (≥ 65 years of age) may be more likely to experience certain adverse reactions, including oedema, diarrhoea, and pneumonia. Based on the results of a Phase 3 study in MCL, elderly patients (≥ 65 years of age) may be more likely to experience certain adverse reactions, including pleural effusion, anxiety, depression, insomnia, dyspnoea, leukopenia, lymphopenia, myalgia, arthralgia, taste loss, dizziness, upper respiratory infection, mucositis, and rhinitis.

Renal impairment/renal failure

Temsirolimus elimination by the kidneys is negligible; studies in patients with varying renal impairment have not been conducted (see sections 4.2 and 5.2). Temsirolimus has not been studied in patients undergoing haemodialysis.

Renal failure (including fatal outcomes) has been observed in patients receiving temsirolimus for advanced RCC and/or with pre-existing renal insufficiency (see section 4.8).

Hepatic impairment

Caution should be used when treating patients with hepatic impairment.

Temsirolimus is cleared predominantly by the liver. In an open-label, dose-escalation Phase 1study in 110 subjects with advanced malignancies and either normal or impaired hepatic function, concentrations of temsirolimus and its metabolite sirolimus were increased in patients with elevated aspartate aminotransferase (AST) or bilirubin levels. Assessment of AST and bilirubin levels is recommended before initiation of temsirolimus and periodically after. An increased rate of fatal events was observed in patients with moderate and severe hepatic impairment. The fatal events included those due to progression of disease; however a causal relationship cannot be excluded.

Based on the Phase 1study, no dose adjustment of temsirolimus is recommended for RCC patients with baseline platelet counts ≥ $100x10^9$/l and mild to moderate hepatic impairment (total bilirubin up to 3 times upper limit of normal [ULN] with any abnormality of AST, or as defined by Child-Pugh

Class A or B). For patients with RCC and severe hepatic impairment (total bilirubin > 3 times ULN with any abnormality of AST, or as defined by Child-Pugh Class C), the recommended dose for patients who have baseline platelets ≥ 100 x 10^9/l is 10 mg intravenous once a week infused over a 30 to 60 minute period (see section 4.2).

Intracerebral bleeding

Patients with central nervous system (CNS) 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 temsirolimus.

Thrombocytopenia neutropenia and anaemia

Grades 3 and 4 thrombocytopenia and/or neutropenia have been observed in the MCL clinical trial (see section 4.8). Patients on temsirolimus who develop thrombocytopenia may be at increased risk of bleeding events, including epistaxis (see section 4.8). Patients on temsirolimus with baseline neutropenia may be at risk of developing febrile neutropenia. Cases of anaemia have been reported in RCC and MCL (see section 4.8). Monitoring of complete blood count is recommended prior to initiating temsirolimus therapy and peridically thereafter.

Infections

Patients may be immunosuppressed and should be carefully observed for the occurrence of infections, including opportunistic infections. Among patients receiving 175 mg/week for the treatment of MCL, infections (including Grade 3 and 4 infections) were substantially increased compared to lower doses and compared to conventional chemotherapy. Cases of *pneumocystis jiroveci* pneumonia (PCP), some with fatal outcomes, have been reported in patients who received temsirolimus, many of whom also received corticosteroids or other immunosuppressive agents. Prophylaxis of PCP should be considered for patients who require concomitant use of corticosteroids or other immunosuppressive agents based upon current standard of care.

Cataracts

Cataracts have been observed in some patients who received the combination of temsirolimus and interferon-α (IFN-α).

Hypersensitivity/infusion reactions

Hypersensitivity/infusion reactions (including some life-threatening and rare fatal reactions), including and not limited to flushing, chest pain, dyspnoea, hypotension, apnoea, loss of consciousness, hypersensitivity and anaphylaxis, have been associated with the administration of temsirolimus (see section 4.8). 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. The 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.

If a patient develops a hypersensitivity reaction during the temsirolimus infusion, despite the premedication, the infusion must be stopped and the patient 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 after the administration of an H_1-receptor antagonist (diphenhydramine or similar antihistamine) and an H_2-receptor antagonist (intravenous famotidine 20 mg or intravenous ranitidine 50 mg) approximately 30 minutes before restarting the temsirolimus infusion. Administration of corticosteroids may be considered; however, the efficacy of corticosteroid treatment in this setting has

not been established. The infusion may then be resumed at a slower rate (up to 60 minutes) and should be completed within six hours from the time that temsirolimus is first added to sodium chloride 9 mg/ml (0.9%) solution for injection.

Because it is recommended that an H_1 antihistamine be administered to patients before the start of the intravenous temsirolimus infusion, temsirolimus should be used with caution in patients with known hypersensitivity to the antihistamine or in patients who cannot receive the antihistamine for other medical reasons.

Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, angioedema, exfoliative dermatitis and hypersensitivity vasculitis, have been associated with the oral administration of sirolimus.

Hyperglycaemia/glucose intolerance/diabetes mellitus

Patients should be advised that treatment with temsirolimus may be associated with an increase in blood glucose levels in diabetic and non-diabetic patients. In the RCC clinical trial, a Phase 3 clinical trial forRCC, 26% of patients reported hyperglycaemia as an adverse event. In the MCL clinical trial, 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 hypoglycaemic agent therapy. Patients should be advised to report excessive thirst or any increase in the volume or frequency of urination.

Interstitial lung disease

There have been cases of non-specific interstitial pneumonitis, including fatal reports, occurring in patients who received weekly intravenous temsirolimus. 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 temsirolimus 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. Periodical follow-up assessments may be considered. It is recommended that patients be followed closely for occurrence of clinical respiratory symptoms and patients should be advised to report promptly any new or worsening respiratory symptoms. If clinically significant respiratory symptoms develop, temsirolimus administration may be withheld until after recovery of symptoms and improvement of radiographic findings related to pneumonitis. Opportunistic infections such as PCP 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 PCP should be considered based upon current standard of care.

Hyperlipaemia

The use of temsirolimus was associated with increases in serum triglycerides and cholesterol. In the RCC clinical trial 1, hyperlipaemia was reported as an adverse event in 27% of patients. In the MCL clinical trial, 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 temsirolimus. The known association of temsirolimus with hyperlipaemia may predispose to myocardial infarction.

Wound healing complications

The use of temsirolimus has been associated with abnormal wound healing; therefore, caution should be exercised with the use of temsirolimus in the peri-surgical period.

Malignancies

The possible development of lymphoma and other malignancies, particularly of the skin, may result from immunosuppression. As usual for patients with increased risk for skin cancer, exposure to sunlight and ultraviolet (UV) light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

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, gout/cellulitis requiring hospitalisation) were observed in 2 out of 3 patients treated in the first cohort of a Phase 1 study at doses of temsirolimus 15 mg intravenous per week and sunitinib 25 mg oral per day (Days 1-28 followed by a 2-week rest) (see section 4.5).

Concomitant use of angiotensin-converting enzyme (ACE) inhibitors and/or calcium channel blockers

Caution should be exercised when temsirolimus is given concomitantly with ACE inhibitors (e.g. ramipril) and/or calcium channel blockers (e.g. amlodipine). An increased risk of angioneurotic oedema- (including delayed reactions occurring two months following initiation of therapy) is possible in patients who receive temsirolimus concomitantly with an ACE inhibitor and/or a calcium channel blocker(see sections 4.5 and 4.8).

Agents inducing CYP3A metabolism

Agents such as carbamazepine, phenobarbital, phenytoin, rifampicin, and St. John's wort are strong inducers of CYP3A4/5 and may decrease composite exposure of the active, drug substances temsirolimus and its metabolite, sirolimus. Therefore, for patients with RCC, continuous administration beyond 5-7 days with agents that have CYP3A4/5 induction potential should be avoided. For patients with MCL, it is recommended that coadministration of CYP3A4/5 inducers should be avoided due to the higher dose of temsirolimus (see section 4.5).

Agents inhibiting CYP3A metabolism

Agents such as protease inhibitors (nelfinavir, ritonavir), antifungals (e.g. itraconazole, ketoconazole, voriconazole), and nefazodone are strong CYP3A4 inhibitors and may increase blood concentrations of the active drug substances, temsirolimus and its metabolite, sirolimus. Therefore, concomitant treatment with agents that have strong CYP3A4 inhibition potential should be avoided. Concomitant treatment with moderate CYP3A4 inhibitors (e.g. aprepitant, erythromycin, fluconazole, verapamil, grapefruit juice) should only be administered with caution in patients receiving 25 mg and should be avoided in patients receiving temsirolimus doses higher than 25 mg (see section 4.5). Alternative treatments with agents that do not have CYP3A4 inhibition potential should be considered (see section 4.5).

Agents affecting P-glycoprotein

Concomitant use of mTOR inhibitors with inhibitors of P-glycoprotein (P-gp) may increase mTOR inhibitor blood levels. Caution should be observed when co-administering temsirolimus with drugs that inhibit P-glycoprotein. The clinical condition of the patient should be monitored closely. Dose adjustments of temsirolimus may be required (see section 4.5).

Vaccinations

Immunosuppressants may affect responses to vaccination. During treatment with temsirolimus, vaccination may be less effective. The use of live vaccines should be avoided during treatment with temsirolimus. Examples of live vaccines are: measles, mumps, rubella, oral polio, Bacillus Calmette-Guérin (BCG), yellow fever, varicella, and TY21a typhoid vaccines.

Excipient information

Ethanol

After first dilution the concentrate with 1.8 ml of the supplied diluent, the concentrate-diluent mixture contains 35% volume ethanol (alcohol), i.e., up to 0.693 g per 25 mg dose of temsirolimus, equivalent to 18 ml beer or 7 ml wine per dose. Patients administered the higher dose of 175 mg of temsirolimus for the initial treatment of MCL may receive up to 4.85 g of ethanol (equivalent to 122 ml beer or 49 ml wine per dose).

An example of ethanol exposure based on maximum single daily dose (see section 4.2) is as follows:

- Administration of the higher dose of 175 mg of temsirolimus for the initial treatment of MCL to an adult weighing 70 kg would result in exposure to 69.32 mg/kg of ethanol which may cause a rise in blood alcohol concentration (BAC) of about 11.5 mg/100 ml.

For comparison, for an adult drinking a glass of wine or 500 ml of beer, the BAC is likely to be about 50 mg/100 ml.

The amount of ethanol in this medicine is not likely to have an effect in adults and adolescents, and its effects in children are not likely to be noticeable. It may have some effects, such as somnolence, in neonates and young children.

The ethanol content in this medicinal product should be carefully considered in the following patient groups who may be at higher risk of ethanol-related adverse effects:

- Pregnant or breast-feeding women (see section 4.6)
- Patients suffering from alcoholism.

To be taken into account in pregnant or breast-feeding women, children and high-risk groups, such as patients with liver disease or epilepsy. The amount of alcohol in this medicinal product may alter the effects of other medicines.
Co-administration with medicines containing e.g. propylene glycol or ethanol may lead to accumulation of ethanol and induce adverse effects, particularly in young children with low or immature metabolic capacity.

The amount of alcohol in this medicinal product may impair the ability to drive or use machines (see section 4.7).

Propylene glycol
Torisel contains propylene glycol (see section 2). An example of propylene glycol exposure based on maximum single daily dose (see section 4.2) is as follows: Administration of the higher dose of 175 mg of temsirolimus for the initial treatment of MCL to an adult weighing 70 kg would result in a propylene glycol exposure of 50.33 mg/kg/day.

Medical monitoring, including measurement of the osmolar and/or anion gap, is required in patients with impaired renal and/or hepatic function who receive ≥50 mg/kg/day of propylene glycol. Various adverse effects attributed to propylene glycol have been reported, such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction.

Prolonged administration of propylene glycol-containing products, as well as co-administration with other substrates of alcohol dehydrogenase (e.g. ethanol), increase the risk of propylene glycol accumulation and toxicity, especially in patients with liver or kidney impairment.

Propylene glycol doses of ≥1 mg/kg/day may induce serious adverse effects in neonates, while doses of ≥50 mg/kg/day may induce adverse effects in children less than 5 years old and should only be administered on a case by case basis.

Administration of ≥50 mg/kg/day of propylene glycol to pregnant or lactating women should only be considered on a case by case basis (see section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

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, gout/cellulitis requiring hospitalisation) were observed in 2 out of 3 patients treated in the first cohort of a Phase 1 study at doses of temsirolimus 15 mg intravenous per week and sunitinib 25 mg oral per day (Days 1-28 followed by a 2-week rest) (see section 4.4).

Concomitant use of angiotensin-converting enzyme (ACE) inhibitors and/or calcium channel blockers

An increased incidence of angioneurotic oedema- (including delayed reactions occurring two months following initiation of therapy) has been observed in patients who received temsirolimus or other mTOR inhibitors in combination with an ACE inhibitor (e.g. ramipril) and/or a calcium channel blocker (e.g. amlodipine) (see sections 4.4 and 4.8).

Agents inducing CYP3A metabolism

Co-administration of temsirolimus with rifampicin, a potent CYP3A4/5 inducer, had no significant effect on temsirolimus maximum concentration ($C_{max)}$ and area under the concentration vs. time curve(AUC) after intravenous administration, but decreased sirolimus C_{max} by 65% and AUC by 56%, compared to temsirolimus treatment alone. Therefore, concomitant treatment with agents that have CYP3A4/5 induction potential should be avoided (e.g. carbamazepine, phenobarbital, phenytoin, rifampicin, and St. John's wort) (see section 4.4).

Agents inhibiting CYP3A metabolism

Co-administration of temsirolimus 5 mg 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} (temsirolimus + sirolimus) increased 2.3-fold compared to temsirolimus alone. The effect on the unbound concentrations of sirolimus has not been determined, but is expected to be larger than the effect on whole-blood concentrations due to the saturable binding to red blood cells. The effect may also be more pronounced at a 25 mg dose. Therefore, substances that are potent inhibitors of CYP3A4 activity (e.g. nelfinavir, ritonavir, itraconazole, ketoconazole, voriconazole, nefazodone) increase sirolimus blood concentrations. Concomitant treatment of temsirolimus with these agents should be avoided (see section 4.4).

Concomitant treatment with moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, clarithromycin, erythromycin, aprepitant, amiodarone) should only be administered with caution in patients receiving 25 mg and should be avoided in patients receiving temsirolimus doses higher than 25 mg.

Cannabidiol (P-gp inhibitor)

There have been reports of increased blood levels of other mTOR inhibitors during concomitant use with cannabidiol. Co-administration of cannabidiol with another orally administered mTOR inhibitor in a healthy volunteer study led to an increase in exposure to the mTOR inhibitor of approximately 2.5- fold for both C_{max} and AUC, due to inhibition of intestinal P-gp efflux by cannabidiol. Temsirolimus was demonstrated to be a substrate for P-gp *in vitro*. Caution should be used when cannabidiol and temsirolimus are co-administered, closely monitoring for side effects and adjusting the temsirolimus dose as needed (see sections 4.2 and 4 4).

Interaction with medicinal products metabolised by CYP2D6 or CYP3A4/5

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

The effect of a 175 or 75 mg temsirolimus dose on CYP3A4/5 substrates has not been studied. However, *in vitro* studies in human liver microsomes followed by physiologically-based pharmacokinetic modelling indicate that the blood concentrations achieved after a 175 mg dose of temsirolimus most likely leads to relevant inhibition of CYP3A4/5 (see section 5.2). Therefore, caution is advised during concomitant administration of temsirolimus at a dose of 175 mg with medicinal products that are metabolised predominantly via CYP3A4/5 and that have a narrow therapeutic index.

Interactions with medicinal products that are P-glycoprotein substrates

In an *in vitro* study, temsirolimus inhibited the transport of P-glycoprotein (P-gp) substrates with an IC_{50} value of 2 µM. *In vivo*, the effect of P-gp inhibition has not been investigated in a clinical drug-drug interaction study **;**however**,**, recent preliminary data from a Phase 1 study of combined lenalidomide (dose of 25 mg) and temsirolimus (dose of 20 mg) seem to support the *in vitro* findings and suggest an increased risk of adverse events. Therefore, when temsirolimus is co-administered with medicinal products which are P-gp substrates (e.g. digoxin, vincristine, colchicine, dabigatran, lenalidomide, and paclitaxel) close monitoring for adverse events related to the co-administered medicinal products should be observed.

Amphiphilic agents

Temsirolimus has been associated with phospholipidosis in rats. Phospholipidosis has not been observed in mice or monkeys treated with temsirolimus, nor has it been documented in patients treated with temsirolimus. Although phospholipidosis has not been shown to be a risk for patients administered temsirolimus, it is possible that combined administration of temsirolimus with other amphiphilic agents such as amiodarone or statins could result in an increased risk of amphiphilic pulmonary toxicity.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Due to the unknown risk related to potential exposure during early pregnancy, women of childbearing potential must be advised not to become pregnant while using Torisel.

Men with partners of childbearing potential should use medically acceptable contraception while receiving Torisel (see section 5.3).

Pregnancy

There are no adequate data from the use of temsirolimus in pregnant women. Studies in animals have shown reproductive toxicity. In reproduction studies in animals, temsirolimus caused embryo/foetotoxicity that was manifested as mortality and reduced foetal weights (with associated delays in skeletal ossification) in rats and rabbits. Teratogenic effects (omphalocele) were seen in rabbits (see section 5.3).

The potential risk for humans is unknown. Torisel must not be used during pregnancy, unless the risk for the embryo is justified by the expected benefit for the mother. The ethanol content of this product should also be taken into account for pregnant women (see section 4.4).

Torisel contains propylene glycol (see section 4.4). Propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, however, it may reach the foetus. Administration of ≥50 mg/kg/day propylene glycol to pregnant women should only be considered on a case by case basis.

Breast-feeding

It is unknown whether temsirolimus is excreted in human breast milk. The excretion of temsirolimus in milk has not been studied in animals. However, sirolimus, the main metabolite of temsirolimus, is excreted in milk of lactating rats. Because of the potential for adverse reactions in breast-fed infants from temsirolimus, breast-feeding should be discontinued during therapy. The ethanol content of this product should be taken into account in women who are breast-feeding (see section 4.4).

Torisel contains propylene glycol (see section 4.4). Propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, however, it has been found in milk and may be orally absorbed by a nursing infant. Administration of ≥50 mg/kg/day propylene glycol to lactating women should only be considered on a case by case basis.

Fertility

In male rats, decreased fertility and partly reversible reductions in sperm counts were reported (see section 5.3).

4.7 Effects on ability to drive and use machines

Temsirolimus has no or negligible influence on the ability to drive and use machines based on the evidence available.

For patients receiving the higher dose of 175 mg intravenous of temsirolimus for the treatment of MCL, the amount of ethanol in this medicinal product may impair the ability to drive or use machines (see section 4.4).

4.8 Undesirable effects

Summary of the safety profile

The most serious reactions observed with temsirolimus in clinical trials are hypersensitivity/infusion reactions (including some life-threatening and rare fatal reactions), hyperglycaemia/glucose intolerance, infections, interstitial lung disease (pneumonitis), hyperlipaemia, intracranial haemorrhage, renal failure, intestinal perforation, wound healing complication, thrombocytopenia, neutropenia (including febrile neutropenia), pulmonary embolism.

The adverse reactions (all grades) experienced by at least 20% of the patients in RCC and MCL registration studies include anaemia, nausea, rash (including rash, pruritic rash, maculopapular rash, pustular rash), decreased appetite, oedema asthenia, fatigue, thrombocytopenia, diarrhoea, pyrexia, epistaxis, mucosal inflammation, stomatitis, vomiting, hyperglycaemia, hypercholesterolemia, dysgeusia, pruritus, cough, infection, pneumonia, dyspnoea.

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

Based on the results of the phase 3 studies, elderly patients may be more likely to experience certain adverse reactions, including face oedema, pneumonia, pleural effusion, anxiety, depression, insomnia, dyspnoea, leukopenia, lymphopenia, myalgia, arthralgia, ageusia, dizziness, upper respiratory infection, mucositis, and rhinitis.
Serious adverse reactions observed in clinical trials of temsirolimus for advanced RCC, but not in clinical trials of temsirolimus for MCL include: anaphylaxis, impaired wound healing, renal failure with fatal outcomes, and pulmonary embolism.
Serious adverse reactions observed in clinical trials of temsirolimus for MCL, but not in clinical trials of temsirolimus for advanced RCC include: thrombocytopenia, and neutropenia (including febrile neutropenia).

See section 4.4 for additional information concerning serious adverse reactions, including appropriate actions to be taken if specific reactions occur.

The occurrence of undesirable effects following the dose of 175 mg temsirolimus/week for MCL, e.g. Grade 3 or 4 infections or thrombocytopenia, is associated with a higher incidence than that observed with either 75 mg temsirolimus/week or conventional chemotherapy.

Tabulated list of adverse reactions

Adverse reactions that were reported in RCC and MCL patients in the phase 3 studies are listed below (Table 1), by system organ class, frequency and grade of severity (NCI-CTCAE). Frequencies are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data) Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions from clinical trials in RCC (study 3066K1-304) and in MCL (study 3066K1-305)

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, cellulitis, herpes zoster, oral herpes, influenza, herpes simplex, herpes zoster ophthalmic, herpes virus infection, bacterial infection, bronchitis*, abscess, wound infection, post-operative wound infections)	91 (28.3)	18 (5.6)
		Pneumonia[a] (including interstitial pneumonia)	35 (10.9)	16 (5.0)
	Common	Sepsis* (including septic shock)	5 (1.6)	5 (1.6)
		Candidiasis (including oral and anal candidiasis) and fungal infection/fungal skin infections	16 (5.0)	0 (0.0)
		Urinary tract infection (including cystitis)	29 (9.0)	6 (1.9)
		Upper respiratory tract infection	26 (8.1)	0 (0.0)
		Pharyngitis	6 (1.9)	0 (0.0)
		Sinusitis	10 (3.1)	0 (0.0)
		Rhinitis	7 (2.2)	0 (0.0)
		Folliculitis	4 (1.2)	0 (0.0)
	Uncommon	Laryngitis	1 (0.3)	0 (0.0)
Blood and lymphatic system disorders	Very common	Neutropenia	46 (14.3)	30 (9.3)
		Thrombocytopenia**	97 (30.2)	56 (17.4)
		Anaemia	132(41.1)	48 (15)
	Common	Leukopenia **	29 (9.0)	10 (3.1)
		Lymphopenia	25 (7.8)	16 (5.0)
Immune system disorders	Common	Hypersensitivity reactions / drug hypersensitivity	24 (7.5)	1 (0.3)
Metabolism and nutrition disorders	Very common	Hyperglycaemia	63 (19.6)	31 (9.7)
		Hypercholesterolaemia	60 (18.7)	1 (0.3)
		Hypertriglyceridaemia	56 (17.4)	8 (2.5)
		Decreased appetite	107 (33.3)	9 (2.8)
		Hypokalaemia	44 (13.7)	13 (4.0)
	Common	Diabetes mellitus	10 (3.1)	2 (0.6)
		Dehydration	17 (5.3)	8 (2.5)
		Hypocalcaemia	21 (6.5)	5 (1.6)
		Hypophosphataemia	26 (8.1)	14 (4.4)
		Hyperlipidaemia	4 (1.2)	0 (0.0)
Psychiatric disorders	Very common	Insomnia	45 (14.0)	1 (0.3)
	Common	Depression	16 (5.0)	0 (0.0)

System organ class	Frequency	Adverse reactions	All grades n (%)	Grade 3 & 4 n (%)
		Anxiety	28 (8.7)	0 (0.0)
Nervous system disorders	Very common	Dysgeusia	55 (17.1)	0 (0.0)
		Headache	55 (17.1)	2 (0.6)
	Common	Dizziness	30 (9.3)	1 (0.3)
		Paresthaesia	21 (6.5)	1 (0.3)
		Somnolence	8 (2.5)	1 (0.3)
		Ageusia	6 (1.9)	0 (0.0)
	Uncommon	Intracranial haemorrhage	1 (0.3)	1 (0.3)
Eye disorders	Common	Conjunctivitis (including conjunctivitis, lacrimal disorder)	16 (5.0)	1 (0.3)
	Uncommon	Eye haemorrhage***	3 (0.9)	0 (0.0)
Cardiac disorders	Uncommon	Pericardial effusion	3 (0.9)	1 (0.3)
Vascular disorders	Common	Venous thromboembolism (including deep vein thrombosis, venous thrombosis)	7 (2.2)	4 (1.2)
		Thrombophlebitis	4 (1.2)	0 (0.0)
		Hypertension	20 (6.2)	3 (0.9)
Respiratory, thoracic and mediastinal disorders	Very common	Dyspnoea[a]	79 (24.6)	27 (8.4)
		Epistaxis **	69 (21.5)	1 (0.3)
		Cough	93 (29.0)	3 (0.9)
	Common	Interstitial lung disease[a]****	16 (5.0)	6(1.9)
		Pleural effusion[a,b]	19 (5.9)	9 (2.8)
	Uncommon	Pulmonary embolism [a]	2 (0.6)	1 (0.3)
Gastrointestinal disorders	Very common	Nausea	109 (34.0)	5 (1.6)
		Diarrhoea	109(34.0)	16 (5.0)
		Stomatitis	67 (20.9)	3 (0.9)
		Vomiting	57 (17.8)	4 (1.2)
		Constipation	56 (17.4)	0 (0.0)
		Abdominal pain	56 (17.4)	10 (3.1)
	Common	Gastrointestinal haemorrhage (including anal, rectal, haemorrhoidal, lip, and mouth haemorrhage, gingival bleeding)	16 (5.0)	4 (1.2)
		Gastritis **	7 (2.1)	2 (0.6)
		Dysphagia	13 (4.0)	0 (0.0)
		Abdominal distension	14 (4.4)	1 (0.3)
		Aphthous stomatitis	15 (4.7)	1 (0.3)
		Oral pain	9 (2.8)	1 (0.3)
		Gingivitis	6 (1.9)	0 (0.0)
	Uncommon	Intestinal[a]/duodenal perforation	2 (0.6)	1 (0.3)

System organ class	Frequency	Adverse reactions	All grades n (%)	Grade 3 & 4 n (%)
Skin and subcutaneous tissue disorders	Very common	Rash (including rash, pruritic rash, maculo-papular rash, rash, generalised rash, macular rash, papular rash)	138 (43.0)	16 (5.0)
		Pruritus (including pruritus generalised)	69 (21.5)	4 (1.2)
		Dry skin	32 (10.0)	1 (0.3)
	Common	Dermatitis	6 (1.9)	0 (0.0)
		Exfoliative rash	5 (1.6)	0 (0.0)
		Acne	15 (4.7)	0(0.0)
		Nail disorder	26 (8.1)	0 (0.0)
		Ecchymosis***	5 (1.6)	0 (0.0)
		Petechiae***	4 (1.2)	0 (0.0)
Musculoskeletal and connective tissue disorders	Very common	Arthralgia	50 (15.6)	2 (0.6)
		Back pain	53 (16.5)	8 (2.5)
	Common	Myalgia	19 (5.9)	0 (0.0)
Renal and urinary disorders	Common	Renal failure[a]	5 (1.6)	0 (0.0)
General disorders and administration site conditions	Very common	Fatigue	133 (41.4)	31 (9.7)
		Oedema (including generalised oedema, facial oedema, peripheral oedema, scrotal oedema, genital oedema)	122 (38.0)	11 (3.4)
		Asthenia[a]	67 (20.9)	16 (5.0)
		Mucosal inflammation	66 (20.6)	7 (2.2)
		Pyrexia	91 (28.3)	5 (1.6)
		Pain	36 (11.2)	7 (2.2)
		Chills	32 (10.0)	1 (0.3)
		Chest pain	32 (10.0)	1 (0.3)
	Uncommon	Impaired wound healing	2 (0.6)	0 (0.0)
Investigations	Very common	Blood creatinine increased	35 (10.9)	4 (1.2)
	Common	Increased aspartate aminotransferase	27 (8.4)	5 (1.6)
	Common	Increased alanine aminotransferase	17 (5.3)	2 (0.6)

[a] one fatal case .
[b] One pleural effusion fatal event occurred in the low-dose (175/25 mg) arm of the MCL study.
*Most NCI-CTC Grade 3 and above reactions observed in clinical trials of temsirolimus for MCL
** Most NCI-CTC all grades reactions observed in clinical trials of temsirolimus for MCL.
*** All NCI-CTC Grade 1 and 2 reactions observed in clinical trials of temsirolimus MCL.
****Interstitial lung disease is defined by a cluster of related Preferred Terms: interstitial lung disease (n = 6), pneumonitis[a] (n = 7), alveolitis (n = 1), alveolitis allergic (n = 1), pulmonary fibrosis (n = 1) and eosinophilic pneumonia (n = 0).

Adverse reactions that were reported in post-marketing experience are listed below (Table 2).

Table 2: Adverse reactions reported in post-marketing setting

System Organ class	Frequency	Adverse reactions

Infections and infestations	Rare	*Pneumocystis jiroveci* pneumonia
Immune system disorders	Not known	Angioneurotic oedema-type reactions
Skin and subcutaneous tissue disorders	Not known	Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders	Not known	Rhabdomyolysis

Description of selected adverse reactions

Post-marketing experience

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

Cases of PCP, some with fatal outcomes, have been reported (see section 4.4).

Paediatric population

In a Phase 1/2 study, 71 patients (59 patients, aged from 1 to 17 years old, and 12 patients, aged 18 to 21 years) were administered temsirolimus at doses ranging from 10 mg/m^2 to 150 mg/m^2 (see section 5.1).
The adverse reactions reported by the highest percentage of patients were haematologic (anaemia, leukopenia , neutropenia, and thrombocytopenia), metabolic (hypercholesterolemia, hyperlipaemia, hyperglycaemia, increase of serum aspartate amino transferase (AST) and serum alanine aminotransferase (ALT) plasma levels), and digestive (mucositis, stomatitis, nausea, and vomiting).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

(https://sideeffects.health.gov.il/

4.9 Overdose

There is no specific treatment for temsirolimus overdose. While temsirolimus has been safely administered to patients with renal cancer with repeated intravenous doses as high as 220 mg/m^2, in MCL, two administrations of 330 mg temsirolimus /week in one patient resulted in Grade 3 rectal bleeding and Grade 2 diarrhoea.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors; ATC code: L01E G01

Mechanism of action

Temsirolimus is a selective inhibitor of mTOR (mammalian target of rapamycin). Temsirolimus binds to an intracellular protein (FKBP-12), and the protein/temsirolimus complex binds and inhibits the activity of mTOR that controls cell division. *In vitro*, at high concentrations (10-20 μM), temsirolimus

can bind and inhibit mTOR in the absence of FKBP-12. Biphasic dose response of cell growth inhibition was observed. High concentrations resulted in complete cell growth inhibition *in vitro*, whereas inhibition mediated by FKBP-12/temsirolimus complex alone resulted in approximately 50% decrease in cell proliferation. Inhibition of mTOR activity results in a G1 growth delay at nanomolar concentrations and growth arrest at micromolar concentrations 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. When mTOR activity is inhibited, its ability to phosphorylate, and thereby control the activity of protein translation factors (4E-BP1 and S6K, both downstream of mTOR in the P13 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.

Clinical efficacy and safety

Renal cell carcinoma

The safety and efficacy of temsirolimus in the treatment of advanced RCC were studied in the following two randomised clinical trials:

RCC clinical trial 1
RCC clinical trial 1 was a Phase 3, multi-centre, 3-arm, randomised, open-label study in previously untreated patients with advanced RCC and with 3 or more of 6 pre-selected prognostic risk factors (less than 1 year from time of initial renal cell carcinoma 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 IFN-α alone (n = 207), temsirolimus alone (25 mg weekly; n = 209), or the combination of IFN-α and temsirolimus (n = 210).

In RCC clinical trial 1, temsirolimus 25 mg was associated with a statistically significant advantage over IFN-α in the primary endpoint of OS at the 2nd pre-specified interim analysis (n = 446 events, p = 0.0078). The temsirolimus arm showed a 49% increase in median OS compared with the IFN-α arm. Temsirolimus also was associated with statistically significant advantages over IFN-α in the secondary endpoints of PFS, TTF, and clinical benefit rate.

The combination of temsirolimus 15 mg and IFN-α did not result in a significant increase in overall survival when compared to IFN-α alone at either the interim analysis (median 8.4 vs. 7.3 months, hazard ratio = 0.96, p = 0.6965) or final analysis (median 8.4 vs. 7.3 months, hazard ratio = 0.93, p = 0.4902). Treatment with the combination of temsirolimus and IFN-α resulted in a statistically significant increase in the incidence of certain Grade 3-4 adverse events (weight loss, anaemia, neutropenia, thrombocytopenia and mucosal inflammation) when compared to the adverse events observed in the IFN-α or temsirolimus-alone arms.

Summary of efficacy results in temsirolimus RCC clinical trial 1

Parameter	Temsirolimus n = 209	IFN-α n = 207	P-value[a]	Hazard ratio (95% CI)[b]
Pre-specified interim analysis				
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)
Final analysis				
Median overall survival, Months (95% CI)	10.9 (8.6, 12.7)	7.3 (6.1, 8.8)	0.0252	0.78 (0.63, 0.97)
Median progression-free survival by independent assessment Months (95% CI)	5.6 (3.9, 7.2)	3.2 (2.2, 4.0)	0.0042	0.74 (0.60, 0.91)
Median progression-free survival by investigator assessment Months (95% CI)	3.8 (3.6, 5.2)	1.9 (1.9, 2.2)	0.0028	0.74 (0.60, 0.90)
Overall response rate by independent assessment % (95% CI)	9.1 (5.2, 13.0)	5.3 (2.3, 8.4)	0.1361[c]	NA

CI = confidence interval; NA = not applicable.
[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 (95% CI are descriptive only).
[c] Based on Cochran-Mantel-Hansel test stratified by prior nephrectomy and region.

In RCC clinical trial 1, 31% of patients treated with temsirolimus were 65 or older. In patients younger than 65, median overall survival was 12 months (95% CI: 9.9, 14.2) with a hazard ratio of 0.67 (95% CI: 0.52, 0.87) compared with those treated with IFN-α. In patients 65 or older, median overall survival was 8.6 months (95% CI: 6.4, 11.5) with a hazard ratio of 1.15 (95% CI: 0.78, 1.68) compared with those treated with IFN-α.

RCC clinical trial 2
RCC clinical trial 2 was a randomised, double-blind, multi-centre, outpatient trial to evaluate the efficacy, safety, and pharmacokinetics of three dose levels of temsirolimus when administered to previously treated patients with advanced RCC. The primary efficacy endpoint was ORR, and OS was also evaluated. One hundred eleven (111) patients were randomly assigned in a 1:1:1 ratio to receive 25 mg, 75 mg, or 250 mg intravenous temsirolimus weekly. In the 25 mg arm (n = 36), 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 temsirolimus OS was 13.8 months (95% CI: 9.0, 18.7 months); ORR was 5.6% (95% CI: 0.7, 18.7%).

Mantle cell lymphoma

The safety and efficacy of intravenous temsirolimus for the treatment of relapsed and/or refractory MCL were studied in the following Phase 3 clinical study.

MCL clinical trial

MCL clinical trial is a controlled, randomised, open-label, multicentre, outpatient study comparing 2 different dosing regimens of temsirolimus with an investigator's choice of therapy in patients with relapsed and/or refractory MCL. Subjects with MCL (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 intravenous temsirolimus 175 mg (3 successive weekly doses) followed by 75 mg weekly (n = 54), intravenous temsirolimus 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). Investigator's choice therapies included: gemcitabine (intravenous: 22 [41.5%]), fludarabine (intravenous: 12 [22.6%] or oral: 2 [3.8%]), chlorambucil (oral: 3 [5.7%]), cladribine (intravenous: 3 [5.7%]), etoposide (intravenous: 3 [5.7%]), cyclophosphamide (oral: 2 [3.8%]), thalidomide (oral: 2 [3.8%]), vinblastine (intravenous: 2 [3.8%]), alemtuzumab (intravenous: 1 [1.9%]), and lenalidomide (oral: 1 [1.9%]). The primary endpoint of the study was PFS, as assessed by an independent radiologist and oncology review. Secondary efficacy endpoints included OS and ORR.

The results for the MCL clinical trial are summarized in the following table. Temsirolimus 175/75 (temsirolimus 175 mg weekly for 3 weeks followed by 75 mg weekly) led to an improvement in PFS compared with investigator's choice in patients with relapsed and/or refractory MCL that was statistically significant (hazard ratio = 0.44; p-value = 0.0009). Median PFS of the temsirolimus 175/75 mg group (4.8 months) was prolonged by 2.9 months compared to the investigator's choice group (1.9 months). OS was similar.

Temsirolimus also was associated with statistically significant advantages over investigator's choice in the secondary endpoint of ORR. The evaluations of PFS and ORR were based on blinded independent radiologic assessment of tumour response using the International Workshop Criteria.

Summary of efficacy results in temsirolimus MCL clinical trial

Parameter	**temsirolimus** 175/75 mg n = 54	**Investigator's Choice (inv choice)** n = 54	**P-value**	**Hazard ratio (97.5% CI)**[a]
Median progression-free survival[b] Months (97.5% CI)	4.8 (3.1, 8.1)	1.9 (1.6, 2.5)	0.0009[c]	0.44 (0.25, 0.78)
Objective response rate[b] % (95% CI)	22.2 (11.1, 33.3)	1.9 (0.0, 5.4)	0.0019[d]	NA
Overall survival Months (95% CI)	12.8 (8.6, 22.3)	10.3 (5.8, 15.8)	0.2970[c]	0.78 (0.49, 1.24)
One-year survival rate % (97.5% CI)	0.47 (0.31, 0.61)	0.46 (0.30, 0.60)		

[a] Compared with inv choice based on Cox proportional hazard model.
[b] Disease assessment is based on radiographic review by independent radiologists and review of clinical data by independent oncologists.
[c] Compared with inv choice based on log-rank test.
[d] Compared with inv choice alone based on Fisher's exact test.
Abbreviations: CI = confidence interval; NA = not applicable.

The temsirolimus 175 mg (3 successive weekly doses) followed by 25 mg weekly treatment arm did not result in a significant increase in PFS when compared with investigator's choice (median 3.4 vs. 1.9 months, hazard ratio = 0.65, CI = 0.39, 1.10, p = 0.0618).

In the MCL clinical trial, there was no difference in efficacy in patients with respect to age, sex, race, geographic region, or baseline disease characteristics.

Paediatric population

In a Phase 1/2 safety and exploratory efficacy study, 71 patients (59 patients, aged from 1 to 17 years, and 12 patients, aged from 18 to 21 years) received temsirolimus as a 60-minute intravenous infusion once weekly in three-week cycles. In Part 1, 14 patients aged from 1 to 17 years with advanced recurrent/refractory solid tumours received temsirolimus at doses ranging from 10 mg/m^2 to 150 mg/m^2. In Part 2, 45 patients aged from 1 to 17 years with recurrent/relapsed rhabdomyosarcoma, neuroblastoma, or high- grade glioma were administered temsirolimus at a weekly dose of 75 mg/m^2. Adverse events were generally similar to those observed in adults (see section 4.8).

Temsirolimus was found to be ineffective in paediatric patients with neuroblastoma, rhabdomyosarcoma, and high-grade glioma (n = 52). For subjects with neuroblastoma, the objective response rate was 5.3% (95% CI: 0.1%, 26.0%). After 12 weeks of treatment, no response was observed in subjects with rhabdomyosarcoma or high-grade glioma. None of the 3 cohorts met the criterion for advancing to the second stage of the Simon 2-stage design.

The European Medicines Agency has waived the obligation to submit the results of studies with Torisel in all subsets of the paediatric population in MCL (see section 4.2 on paediatric use).

5.2 Pharmacokinetic properties

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%). For patients receiving 175 mg weekly for 3 weeks followed by 75 mg weekly, estimated C_{max} in whole blood at end of infusion was 2457 ng/ml during Week 1, and 2574 ng/ml during Week 3.

Distribution

Temsirolimus exhibits a polyexponential decline in whole blood concentrations, and distribution is attributable to preferential binding to FKBP-12 in blood cells. The mean ±standard deviation (SD) dissociation constant (K_d) 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 (10th, 90th percentiles) maximal specific binding in blood cells of 1.4 mg (0.47 to 2.5 mg). Following a single 25 mg temsirolimus intravenous dose, mean steady-state volume of distribution in whole blood of patients with cancer was 172 liters.

Biotransformation

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. 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.

Elimination

Following a single 25 mg intravenous dose of temsirolimus, temsirolimus mean ± SD systemic clearance from whole blood was 11.4 ± 2.4 l/h. Mean half-lives of temsirolimus and sirolimus were 17.7 hours and 73.3 hours, respectively. Following administration of [^{14}C] temsirolimus, excretion was predominantly via the faeces (78%), with renal elimination of active substance and metabolites accounting for 4.6% of the administered dose. Sulfate or glucuronide conjugates were not detected in the human faecal samples, suggesting that sulfation and glucuronidation do not appear to be major pathways involved in the excretion of temsirolimus. Therefore, inhibitors of these metabolic pathways are not expected to affect the elimination of temsirolimus.

Model-predicted values for clearance from plasma, after applying a 175 mg dose for 3 weeks, and subsequently 75 mg for 3 weeks, indicate temsirolimus and sirolimus metabolite trough concentrations of approximately 1.2 ng/ml and 10.7 ng/ml, respectively.

Temsirolimus and sirolimus were demonstrated to be substrates for P-gp *in vitro*.

Pharmacokinetic/pharmacodynamic relationship(s)

Inhibition of CYP isoforms

In *in vitro* studies in human liver microsomes, temsirolimus inhibited CYP3A4/5, CYP2D6, CYP2C9 and CYP2C8 catalytic activity with Ki values of 3.1, 1.5, 14 and 27 μM, respectively.

IC_{50} values for inhibition of CYP2B6 and CYP2E1 by temsirolimus were 48 and 100 μM, respectively. Based on a whole blood mean C_{max} concentration of 2.6 μM for temsirolimus in MCL patients receiving the 175 mg dose there is a potential for interactions with concomitantly administered medicinal products that are substrates of CYP3A4/5 in patients treated with the 175 mg dose of temsirolimus (see section 4.5). Physiologically-based pharmacokinetic modelling has shown that after four weeks treatment with temsirolimus, the AUC of midazolam can be increased 3-to 4-fold and C_{max} around 1.5-fold when midazolam is taken within a few hours after the start of the temsirolimus infusion. However, it is unlikely that whole blood concentrations of temsirolimus after intravenous administration of temsirolimus will inhibit the metabolic clearance of concomitant medicinal products that are substrates of CYP2C9, CYP2C8, CYP2B6 or CYP2E1.

Special populations

Hepatic impairment
Temsirolimus should be used with caution when treating patients with hepatic impairment.

Temsirolimus is cleared predominantly by the liver.

Temsirolimus and sirolimus pharmacokinetics have been investigated in an open-label, dose-escalation study in 110 patients with advanced malignancies and either normal or impaired hepatic function. For 7 patients with severe hepatic impairment (ODWG, group D) receiving the 10 mg dose of temsirolimus, the mean AUC of temsirolimus was ~1.7-fold higher compared to 7 patients with mild hepatic impairment (ODWG, group B). For patients with severe hepatic impairment, a reduction of the temsirolimus dose to 10 mg is recommended to provide temsirolimus plus sirolimus exposures in

blood (mean AUC_{sum} approximately 6510 ng·h/ml; n=7), which approximate to those following the 25 mg dose (mean AUC_{sum} approximately 6580 ng·h/ml; n=6) in patients with normal liver function (see sections 4.2 and 4.4).

The AUC_{sum} of temsirolimus and sirolimus on day 8 in patients with mild and moderate hepatic impairment receiving 25 mg temsirolimus was similar to that observed in patients without hepatic impairment receiving 75 mg (mean AUC_{sum} mild: approximately 9770 ng*h/ml, n=13; moderate: approximately 12380 ng*h/ml**,** n=6; normal approximately 10580 ng*h/ml, n=4).

Gender, weight, race, age
Temsirolimus and sirolimus pharmacokinetics are not significantly affected by gender. No relevant differences in exposure were apparent when data from the Caucasian population was compared with either the Japanese or Black population.

In population pharmacokinetic-based data analysis, increased body weight (between 38.6 and 158.9 kg) was associated with a two-fold range of trough concentration of sirolimus in whole blood.

Pharmacokinetic data on temsirolimus and sirolimus are available in patients up to age 79 years. Age does not appear to affect temsirolimus and sirolimus pharmacokinetics significantly.

Paediatric population
In the paediatric population, clearance of temsirolimus was lower and exposure (AUC) was higher than in adults. In contrast, exposure to sirolimus was commensurately reduced in paediatric patients, such that the net exposure as measured by the sum of temsirolimus and sirolimus AUCs (AUC_{sum}) was comparable to that for adults.

5.3 Preclinical safety data

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to or even lower than clinical exposure levels and with possible relevance to clinical use, were as follows: pancreatic islet cell vacuolation (rat), testicular tubular degeneration (mouse, rat and monkey), lymphoid atrophy (mouse, rat and monkey), mixed cell inflammation of the colon/caecum (monkey), and pulmonary phospholipidosis (rat).

Diarrhoea with mixed cell inflammation of the caecum or colon was observed in monkeys and was associated with an inflammatory response, and may have been due to a disruption of the normal intestinal flora.

General inflammatory responses, as indicated by increased fibrinogen and neutrophils, and/or changes in serum protein, were observed in mice, rats, and monkeys, although in some cases these clinical pathology changes were attributed to skin or intestinal inflammation as noted above. For some animals, there were no specific clinical observations or histological changes that suggested inflammation.

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 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: granulocytic leukaemia, lymphoma, hepatocellular adenoma and carcinoma, and testicular adenoma.

Reductions in testicular weights and/or histological lesions (e.g., tubular atrophy and tubular giant cells) were observed in mice, rats, and monkeys. In rats, these changes were accompanied by a decreased weight of accessory sex organs (epididymides, prostate, seminal vesicles). In reproduction toxicity studies in animals, decreased fertility and partly reversible reductions in sperm counts were

reported in male rats. Exposures in animals were lower than those seen in humans receiving clinically relevant doses of temsirolimus.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Concentrate
Dehydrated alcohol (ethanol, anhydrous)
dl-alpha tocopherol (Vitamin E)
Propylene glycol
Anhydrous citric acid

Polysorbate 80
Polyethylene glycol 400 (Macrogol 400)
Dehydrated alcohol (ethanol, anhydrous)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products, except those mentioned in section 6.6.

Torisel 30 mg concentrate must not be added directly to aqueous infusion solutions. Direct addition of Torisel 30 mg concentrate to aqueous solutions will result in precipitation of medicinal product.

Always dilute Torisel 30 mg concentrate with 1.8 ml of the supplied diluent before adding to the infusion solution. The concentrate-diluent mixture may only be administered in sodium chloride 9 mg/ml (0.9%) solution for injection.

Torisel, when diluted, contains polysorbate 80, which is known to increase the rate of di-(2-ethylhexyl) phthalate extraction (DEHP) from polyvinyl chloride (PVC). This incompatibility has to be considered during the preparation and administration of Torisel. It is important that the recommendations in sections 4.2 and 6.6 be followed closely.

PVC bags and medical devices must not be used for the administration of preparations containing polysorbate 80, because polysorbate 80 leaches DEHP from PVC.

6.3 Shelf life

Unopened vial
The expiry date of the product is indicated on the packaging materials.
After first dilution of Torisel 30 mg concentrate with 1.8 ml of the supplied diluent
24 hours when stored below 25°C and protected from light.

After further dilution of the concentrate-diluent mixture with sodium chloride 9 mg/ml (0.9%) solution for injection
6 hours when stored below 25°C and protected from light.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C)

Do not freeze.

Keep the vials in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Concentrate
Clear glass vial (type 1) with butyl rubber stopper and a plastic flip-top closure sealed with aluminum containing 1.2 ml of concentrate

Diluent
Clear glass vial (type 1) with butyl rubber stopper and a plastic flip-top closure sealed with aluminum containing 2.2 ml of diluent

Pack size: 1 vial of concentrate and 1 vial of diluent

6.6 Special precautions for disposal and other handling

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

Torisel, when diluted, contains polysorbate 80 and therefore appropriate administration materials must be used,
Therefore, PVC bags and medical devices must not be used for the preparation, storage and administration of Torisel solutions for infusions.

Bags/containers that come in contact with Torisel must be made of glass, polyolefin, or polyethylene.

Torisel concentrate and diluent should be inspected visually for particulate matter and discolouration prior to administration.
Do not use if particulates are present, or if discoloured. Use a new vial.

Dilution

The concentrate for solution for infusion must be diluted with the supplied diluent before administration in sodium chloride 9 mg/ml (0.9%) solution for injection.

Note: For MCL , multiple vials will be required for each dose over 25 mg. Each vial of Torisel must be diluted according to the instructions below. The required amount of concentrate-diluent mixture from each vial must be combined in one syringe for rapid injection into 250 ml of sodium chloride 9 mg/ml (0.9%) solution for injection (see section 4.2).

The concentrate-diluent mixture should be inspected visually for particulate matter and discolouration.

Do not use if particulates are present, or if discoloured.

In preparing the solution, the following two-step process must be carried out in an aseptic manner according to local standards for handling cytotoxic/cytostatic medicinal products:

STEP 1: DILUTION OF THE CONCENTRATE FOR SOLUTION FOR INFUSION WITH THE SUPPLIED DILUENT

- Withdraw 1.8 ml of the supplied diluent.
- Inject the 1.8 ml of diluent into the vial of Torisel 30 mg concentrate.
- Mix the diluent and the concentrate well by inversion of the vial. Sufficient time should be allowed for air bubbles to subside. The solution should be a clear to slightly turbid, colourless to light-yellow to yellow solution, essentially free from visual particulates.

One vial of Torisel concentrate contains 30 mg of temsirolimus: when the 1.2 ml concentrate is combined with 1.8 ml of the supplied diluent, a total volume of 3.0 ml is obtained, and the concentration of temsirolimus will be 10 mg/ml. The concentrate-diluent mixture is stable below 25°C for up to 24 hours.

STEP 2: ADMINISTRATION OF CONCENTRATE FOR SOLUTION FOR INFUSION--DILUENT MIXTURE IN SODIUM CHLORIDE 9MG/ML (0.9%) SOLUTION FOR INJECTION

- Withdraw the required amount of concentrate-diluent mixture (containing temsirolimus 10 mg/ml) from the vial; i.e., 2.5 ml for a temsirolimus dose of 25 mg.
- Inject the withdrawn volume rapidly into 250 ml of sodium chloride 9 mg/ml (0.9%) solution for injection to ensure adequate mixing.

The admixture should be mixed by inversion of the bag or bottle, avoiding excessive shaking, as this may cause foaming.

The final diluted solution in the bag or bottle should be inspected visually for particulate matter and discolouration prior to administration. The admixture of Torisel in sodium chloride 9 mg/ml (0.9%) solution for injection should be protected from excessive room light and sunlight.

For MCL, multiple vials will be required for each dose over 25 mg.

Administration

- Administration of the final diluted solution should be completed within six hours from the time that Torisel is first added to sodium chloride 9 mg/ml (0.9%) solution for injection.

- Torisel is infused over a 30- to 60-minute period once a week. The use of an infusion pump is the preferred method of administration to ensure accurate delivery of the medicinal product.

- Appropriate administration materials must be used to avoid excessive loss of medicinal product and to decrease the rate of DEHP extraction. The administration materials must consist of non-DEHP, non-PVC tubing with appropriate filter. 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 (see sections 6.1 and 6.2).

- Torisel, when diluted, contains polysorbate 80 ,and therefore appropriate administration materials must be used (see sections 6.1 and 6.2),. It is important that the recommendations in section 4.2 be followed closely.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. LICENSE HOLDER

Pfizer Pharmaceuticals Israel Ltd. 9 Shenkar St., Herzliya Pituach, 46725

8.MARKETING AUTHORISATION NUMBER(S)

143-18-32044-00

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