הודעה על החמרה (מידע בטיחות) בעלון לרופא

(מעודכן 3102.50)

תאריך: 06/11/2013

שם תכשיר באנגלית ומספר הרישום: Torisel 143 18 32044 00

שם בעל הרישום: NEOPHARM LTD

טופס זה מיועד לפרוט ההחמרות בלבד !

ההחמרות המבוקשות		
טקסט חדש	**טקסט נוכחי**	**פרק בעלון**
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 Pneumocystis jiroveci pneumonia (PCP) should be considered for patients who require concomitant use of corticosteroids or other immunosuppressive agents based upon current standard of care. . . . **Interstitial lung disease** There have been cases of non-specific interstitial pneumonitis, including fatal reports, occurring in patients who received weekly intravenous Torisel. Some patients were asymptomatic or had minimal symptoms with pneumonitis detected on computed tomography scan or chest radiograph. Others presented with symptoms such as dyspnoea, cough, and fever. Some patients required discontinuation of Torisel or treatment with corticosteroids and/or antibiotics, while some patients continued treatment	**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. . . . **Interstitial lung disease** There have been cases of non-specific interstitial pneumonitis, including fatal reports, occurring in patients who received weekly intravenous TORISEL. Some patients were asymptomatic or had minimal symptoms with pneumonitis detected on computed tomography scan or chest radiograph. Others presented with symptoms such as dyspnoea, cough, and	**Special Warnings and Special Precautions for Use**

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 Torisel 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, consider withholding Torisel administration 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.	fever. Some patients required discontinuation of TORISEL or treatment with corticosteroids and/or antibiotics, while some patients continued treatment without additional intervention. It is recommended that patients undergo baseline radiographic assessment by lung computed tomography scan or chest radiograph prior to the initiation of TORISEL 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, consider withholding TORISEL administration until after recovery of symptoms and improvement of radiographic findings related to pneumonitis. Empiric treatment with corticosteroids and/or antibiotics may 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, gout/cellulitis requiring hospitalisation) were observed in two out of three 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). . . **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,	**Interactions with drugs 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, but mean C_{max} concentrations of temsirolimus are 2.6 µM in MCL patients receiving the 175 mg IV dose of temsirolimus. Therefore, when temsirolimus is co-administered with medications which are P-gp substrates (e.g. digoxin, vincristine, colchicine, and paclitaxel) close monitoring for adverse events related to the co-administered drugs should be observed.	**Interaction with Other Medicinal products and Other Forms of Interaction**

dabigatran, lenalidomide, and paclitaxel) close monitoring for adverse events related to the co-administered medicinal products should be observed.		
Summary of the safety profile The most serious reactions observed with Torisel 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, intestinalperforation, wound healing complication, thrombocytopenia, neutropenia (including febrile neutropenia), pulmonary embolism. The adverse reactions (all grades) experienced by at least 20% of the patients in renal cell carcinoma and mantle cell lymphoma registration studies include anaemia, nausea, rash (including rash, pruritic rash, maculopapular rash, pustular rash), decreased appetite, oedema asthenia, fatigue, thrombocytopaenia, diarrhea, pyrexia, epistaxis, mucosal inflammation, stomatitis, vomiting, hyperglycemia, hypercholesterolemia, dysgeusia, pruritus, cough, infection, pneumonia, dyspnoea. Cataracts have been observed in some patients who received the combination of temsirolimus and interferon-α. Based on the results of the phase 3 studies, elderly patients may be more likely to experience certain adverse reactions, including face	Due to the different approved posology for RCC and MCL and the dose-dependency of the frequency and severity of undesirable effects, adverse drug reactions are listed separately. **Renal cell carcinoma** A total of 626 patients were randomly assigned in a phase 3, three-arm, randomised, open-label study of Interferon alfa (IFN-α) alone, TORISEL alone, and TORISEL and IFN-α. A total of 616 patients received treatment: 200 patients received IFN-α weekly; 208 received TORISEL 25 mg weekly, and 208 patients received a combination of IFN-α and TORISEL weekly. Based on the results of the phase 3 study, elderly patients may be more likely to experience certain adverse reactions, including face oedema and pneumonia. The most serious reactions observed with TORISEL are hypersensitivity/infusion reactions (including some life-threatening and rare fatal reactions), hyperglycaemia/glucose intolerance, infections, interstitial lung disease (pneumonitis), hyperlipaemia, intracerebral bleeding, renal failure, bowel perforation, and wound healing complication. The most common (≥30%) adverse reactions (all grades) observed with TORISEL include anaemia, nausea, rash (including rash, pruritic rash, maculopapular rash, pustular rash), anorexia, oedema (including facial oedema and peripheral oedema), and asthenia. Cataracts have been observed in some patients who received the combination of temsirolimus and interferon-α. See section 4.4 for additional information concerning serious adverse reactions, including appropriate actions to be taken if	**Undesirable effects**

oedema, pneumonia, pleural effusion, anxiety, depression, insomnia, dyspnoea, leukopaenia, lymphopaenia, myalgia, arthralgia, ageusia, dizziness, upper respiratory infection, mucositis, and rhinitis.
Serious adverse reactions observed in clinical trials of temsirolimus for advanced renal cell carcinoma, but not in clinical trials of temsirolimus for mantle cell lymphoma include: anaphylaxis, impaired wound healing, renal failure with fatal outcomes, and pulmonary embolus.
Serious adverse reactions observed in clinical trials of temsirolimus for mantle cell lymphoma, but not in clinical trials of temsirolimus for advanced renal cell carcinoma 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 Torisel/week for MCL, e.g. grade 3 or 4 infections or thrombocytopaenia, is associated with a higher incidence than that observed with either 75 mg Torisel/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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Adverse reactions are listed according to the following categories:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)

specific reactions occur.

The following list contains adverse reactions seen in RCC Clinical Trial 1. Only events for which there is at least reasonable suspicion of a causal relationship to intravenous treatment with TORISEL are listed.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse reactions are listed according to the following categories:
Very common: ≥1/10
Common: ≥1/100 to <1/10
Uncommon: ≥1/1,000 to <1/100

Adverse Reactions in RCC Clinical Trial 1

System Organ Class	Frequency	Adverse Reactions	All Grades n (%)	Grade 3 & 4 n (%)
Infections and infestations	Very common	Bacterial and viral infections (including infection, cellulitis, herpes zoster, herpes simplex, bronchitis, sinusitis, abscess)*	42 (20)	6 (3)
	Very common	Urinary tract infection (including dysuria, haematuria, cystitis, urinary frequency, urinary tract infection)*	31 (15)	4 (2)
	Very common	Pharyngitis	25 (12)	0 (0)
	Very common	Rhinitis	20 (10)	0 (0)
	Common	Pneumonia	17 (8)	5 (2)
	Common	Upper respiratory tract infection	14 (7)	0 (0)
	Common	Folliculitis	4 (2)	0 (0)
Blood and lymphatic system disorders	Very common	Thrombocytopaenia	28 (14)	3 (1)
	Very common	Anaemia	94 (45)	41 (20)
	Common	Neutropaenia	15 (7)	6 (3)
	Common	Leukopoenia	13 (6)	1 (1)
	Common	Lymphopaenia	11 (5)	9 (4)
Immune system disorders	Common	Allergic/hypersensitivity reactions	18 (9)	0 (0)
Metabolism and nutrition	Very common	Hypokalaemia	20 (10)	7 (3)

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 (1.5)	5 (1.5)
		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	Neutropaenia	46 (14.3)	30 (9.3)
		Thrombocytopaenia**	97 (30.2)	56 (17.4)
		Anaemia	132(41.1)	48 (15)
	Common	Leukopoenia **	29 (9.0)	10 (3.1)
		Lymphopaenia	25 (7.8)	16 (5.0)
Immune system disorders	Common	Hypersensitivity reactions / drug hyperensitiviy	24 (7.5)	1 (0.3)
Metabolism and nutrition disorders	Very common	Hyperglycaemia	63 (19.6)	31 (9.7)
		Hypercholesterolaemia	60 (18.79)	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)
		Anxiety	28 (8.7)	0 (0.0)
Nervous system disorders	Very common	Dysgeusia	55 (17.1)	0 (0.0)
	Very common	Anorexia	66 (32)	6 (3)
	Very common	Hyperglycaemia/diabetes mellitus**	53 (26)	22 (11)
	Very common	Hypercholesterolaemia	51 (24)	1 (1)
	Very common	Hyperlipaemia	57 (27)	8 (4)
	Common	Hypophosphataemia	17 (8)	11 (5)
Psychiatric disorders	Very common	Insomnia	24 (12)	1 (1)
	Common	Anxiety	16 (8)	0 (0)
	Common	Depression	9 (4)	0 (0)
Nervous system disorders	Very common	Dysgeusia	31 (15)	0 (0)
	Common	Somnolence	14 (7)	3 (1)
	Common	Paresthaesia	13 (6)	1 (1)
	Common	Dizziness	19 (9)	1 (1)
	Common	Ageusia	11 (5)	0 (0)
	Uncommon	Intracerebral bleeding	1 (0.5)	1 (0.5)
Eye disorders	Common	Conjunctivitis (including conjunctivitis, lacrimation disorders)*	15 (7)	1 (1)
Cardiac disorders	Uncommon	Pericardial effusion (including haemodynamically significant pericardial effusions requiring intervention)	2 (1)	1 (1)
Vascular disorders	Common	Venous thromboembolism (including deep vein thrombosis, pulmonary embolus [including fatal outcomes], thrombosis)*	6 (3)	3 (1)
	Common	Hypertension	14 (7)	3 (1)
	Common	Thrombophlebitis	2 (1)	0 (0)
Respiratory, thoracic and mediastinal disorders	Very common	Dyspnoea	58 (28)	18 (9)
	Very common	Epistaxis	25 (12)	0 (0)
	Very common	Cough	54 (26)	2 (1)
	Common	Pneumonitis [including fatal pneumonitis] (see section 4.4)	4 (2)	1 (1)
	Common	Pleural effusion	8 (4)	5 (2)
Gastrointestinal disorders	Very common	Abdominal pain	44 (21)	9 (4)
	Very common	Vomiting	40 (19)	4 (2)
	Very common	Stomatitis*	42 (20)	3 (1)
	Very common	Diarrhoea	57 (27)	3 (1)
	Very common	Nausea	77 (37)	5 (2)
	Common	Abdominal distension	9 (4)	1 (1)
	Common	Oral pain	5 (2)	0 (0)

disorders		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 (6.0)	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)	3 (0.9)
	Common	Pneumonitis [a]	7 (2.2)	2 (0.6)
		Interstitial lung disease	6 (1.9)	3 (0.9)
		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)
Skin and subcutaneous tissue disorders	Very common	Rash (including rash, pruritic rash, maculo-papular rash, rash, generalized 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)
	Common	Gingivitis	5 (2)	0 (0)
	Common	Aphthous stomatitis	8 (4)	1 (0)
	Uncommon	Bowel perforation	1 (0.5)	1 (0.5)
Skin and subcutaneous tissue disorders	Very common	Rash (including rash, pruritic rash, maculopapular rash, pustular rash)*	88 (42)	10 (5)
	Very common	Pruritus	40 (19)	1 (1)
	Very common	Acne	21 (10)	0 (0)
	Very common	Nail disorder	28 (14)	0 (0)
	Very common	Dry skin	22 (11)	1 (1)
	Common	Exfoliative dermatitis	16 (8)	0 (0)
Musculoskeletal and connective tissue disorders	Very common	Back pain	41 (20)	6 (3)
	Very common	Arthralgia	37 (18)	2 (1)
	Common	Myalgia (including myalgia, leg cramps)*	17 (8)	1 (1)
Renal and urinary disorders	Common	Renal failure [including fatal outcomes] (see section 4.4)	4 (2)	2 (1)
General disorders and administration site conditions	Very common	Oedema (including oedema, facial oedema, peripheral oedema)*	72 (35)	7 (3)
	Very common	Asthenia	106 (51)	23 (11)
	Very common	Pain	59 (28)	11 (5)
	Very common	Pyrexia	51 (24)	1 (1)
	Very common	Mucositis	39 (19)	2 (1)
	Very common	Chest pain	34 (16)	2 (1)
	Common	Chills	17 (8)	1 (1)
	Common	Impaired wound healing	3 (1)	0 (0)
Investigations	Very common	Blood creatinine increased	30 (14)	6 (3)
	Common	Increased aspartate aminotransferase	17 (8)	3 (1)
	Common	Increased alanine aminotransferase	12 (6)	1 (1)

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

**Patients should be advised that treatment with TORISEL may be associated with an increase in blood glucose levels in diabetic and non-diabetic patients.

Mantle cell lymphoma

		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 generalized 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 mantle cell lymphoma
** Most NCI-CTC all grades reactions observed in clinical trials of temsirolimus for mantle cell lymphoma
*** All NCI-CTC Grade 1 and 2 reactions observed in clinical trials of temsirolimus for mantle cell lymphoma

Adverse reactions that were reported in post-marketing experience are listed below (Table 2), by system organ class and frequency as follows:
Rare (≥1/10,000 to <1/1,000)
Not known (cannot be estimated from the available data).

Table 2: adverse reactions reported in post-marketing setting

A total of 54 patients were treated with 175/75 mg TORISEL in the MCL Clinical Trial, a phase 3, three-arm, randomised, open-label study of TORISEL comparing 2 different dosing regimens of temsirolimus with an investigator's choice of therapy in patients with relapsed and/or refractory mantle cell lymphoma. Based on the results of the phase 3 study, elderly patients (≥65 years) may be more likely to experience certain adverse reactions, including pleural effusion, anxiety, depression, insomnia, dyspnoea, leukopaenia, lymphopaenia, myalgia, arthralgia, taste loss, dizziness, upper respiratory infection, mucositis, and rhinitis.

The most serious reactions observed with TORISEL are thrombocytopaenia, neutropaenia, infections, interstitial lung disease (pneumonitis), bowel perforation, hypersensitivity reactions, and hyperglycaemia/glucose intolerance.

The most common (≥30%) adverse reactions (all grades) observed with TORISEL include thrombocytopaenia, asthenia, anaemia, diarrhoea, bacterial and viral infections*, rash*, pyrexia, anorexia, epistaxis, mucositis, oedema*, and stomatitis*.

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

*See table below for additional terms included with these adverse reactions.

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

The following list contains adverse reactions seen in the MCL

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

Post-marketing experience

Angioneurotic oedema-type reactions in some patients who received temsirolimus and ACE-inhibitors concomitantly.
Cases of Pneumocystis jiroveci pneumonia, some with fatal outcomes, have been reported (see section 4.4).

Clinical Trial. Only events for which there is at least reasonable suspicion of a causal relationship to intravenous treatment with TORISEL are listed.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse reactions are listed according to the following categories:
Very common: ≥1/10
Common: ≥1/100 to <1/10

Adverse Reactions in MCL Clinical Trial

System Organ Class	Frequency	Adverse Reactions	All Grades n (%)	Grade 3 & 4 n (%)
Infections and infestations	Very common	Bacterial and viral infections (including infection, cellulitis, bronchitis, sinusitis, herpes zoster, herpes simplex)*	23 (43)	8 (15)
	Very common	Pneumonia (including interstitial pneumonia)**	8 (15)	6 (11)
	Very common	Urinary tract infection (including dysuria, urinary frequency, urinary tract infection, urinary urgency)*	8 (15)	0 (0)
	Very common	Pharyngitis	4 (7)	0 (0)
	Very common	Upper respiratory tract infection	8 (15)	0 (0)
	Common	Sepsis (including sepsis, septic shock)*	3 (6)	3 (6)
	Common	Rhinitis	5 (9)	0 (0)
	Common	Folliculitis	1 (2)	0 (0)
Blood and lymphatic system disorders	Very common	Thrombocytopaenia**	39 (72)	32 (59)
	Very common	Anaemia	28 (52)	11 (20)
	Very common	Neutropaenia**	13 (24)	8 (15)
	Very common	Leukopaenia	8 (15)	4 (7)
	Very common	Lymphopaenia	6 (11)	4 (7)
Immune system disorders	Common	Allergic/hypersensitivity reactions	1 (2)	0 (0)
Metabolism	Very	Hypokalaemia	10 (19)	4 (7)

and nutrition disorders	common			
	Very common	Anorexia	20 (37)	1 (2)
	Very common	Hyperglycaemia***	6 (11)	6 (11)
	Very common	Hypercholesterolaemia	7 (13)	0 (0)
	Common	Dehydration	3 (6)	2 (4)
	Common	Hypophosphataemia	3 (6)	0 (0)
	Common	Hyperlipaemia	5 (9)	1 (2)
	Common	Hypocalcaemia	5 (9)	1 (2)
Psychiatric disorders	Very common	Insomnia	11 (20)	0 (0)
	Very common	Anxiety	8 (15)	0 (0)
	Common	Depression	5 (9)	0 (0)
Nervous system disorders	Very common	Dysgeusia	8 (15)	0 (0)
	Common	Paresthaesia	4 (7)	0 (0)
	Common	Dizziness	3 (6)	0 (0)
	Common	Ageusia	5 (9)	0 (0)
Eye disorders	Common	Conjunctivitis	4 (7)	0 (0)
	Common	Eye haemorrhage	2 (4)	0 (0)
Vascular disorders	Common	Thrombosis (including deep venous thrombosis, thrombosis)*	3 (6)	1 (2)
	Common	Hypertension	2 (4)	0 (0)
Respiratory, thoracic and mediastinal disorders	Very common	Dyspnoea	10 (19)	4 (7)
	Very common	Epistaxis	19 (35)	0 (0)
	Very common	Cough	14 (26)	0 (0)
	Common	Pneumonitis****	2 (4)	0 (0)
Gastrointestinal disorders	Very common	Abdominal pain	11 (20)	1 (2)
	Very common	Vomiting	9 (17)	0 (0)
	Very common	Stomatitis (including aphthous stomatitis, mouth ulceration, stomatitis, glossitis, oral pain)*	16 (30)	1 (2)
	Very common	Diarrhoea	24 (44)	4 (7)
	Very common	Nausea	14 (26)	0 (0)
	Common	Bowel perforation	1 (2)	1 (2)
	Common	Gastrointestinal haemorrhage (including gastrointestinal haemorrhage, rectal haemorrhage)*	6 (11)	2 (4)
	Common	Gingivitis	2 (4)	0 (0)
	Common	Gastritis	3 (6)	1 (2)
	Common	Dysphagia	4 (7)	0 (0)

Skin and subcutaneous tissue disorders	Very common	Rash (including rash, pruritic rash, maculopapular rash, pustular rash, eczema)*	22 (41)	4 (7)
	Very common	Pruritus	14 (26)	2 (4)
	Very common	Nail disorder	8 (15)	0 (0)
	Very common	Dry skin	7 (13)	0 (0)
	Common	Acne	4 (7)	0 (0)
	Common	Moniliasis (including moniliasis, oral moniliasis)*	2 (4)	0 (0)
	Common	Fungal dermatitis	1 (2)	0 (0)
	Common	Ecchymosis	4 (7)	0 (0)
Musculoskeletal, connective tissue and bone disorders	Very common	Back pain	7 (13)	0 (0)
	Very common	Arthralgia	11 (20)	1 (2)
	Very common	Myalgia (including muscle cramps, leg cramps, myalgia)*	9 (17)	0 (0)
General disorders and administration site conditions	Very common	Oedema (including oedema, facial oedema, peripheral oedema, scrotal oedema, genital oedema, generalised oedema)*	19 (35)	1 (2)
	Very common	Asthenia	34 (63)	7 (13)
	Very common	Pain	15 (28)	1 (2)
	Very common	Pyrexia	21 (39)	3 (6)
	Very common	Mucositis	19 (35)	3 (6)
	Very common	Chills	14 (26)	1 (2)
	Common	Chest pain	4 (7)	0 (0)
Investigations	Common	Blood creatinine increased	4 (7)	0 (0)
	Common	Increased aspartate aminotransferase	2 (4)	1 (2)
	Common	Increased alanine aminotransferase	1 (2)	1 (2)

*Body system totals are not necessarily the sum of the individual adverse events since a subject may report two or more different adverse events in the same body system.
**Grades 3 and 4 (thrombocytopaenia) are defined as 50,000-25,000 platelets/mm^3 and <25,000 platelets/mm^3, respectively. Grades 3 and 4 (neutropaenia) are defined as 1000-500 neutrophils/mm^3 and <500 neutrophils/mm^3, respectively.
***Patients should be advised that treatment with TORISEL may be associated with an increase in blood glucose levels in diabetic and non-diabetic patients.

	****One case of fatal pneumonitis was reported in a mantle cell lymphoma patient receiving 175/25 mg/week that is not included in this table. Serious adverse reactions observed in clinical trials of temsirolimus for advanced renal cell carcinoma, but not in clinical trials of temsirolimus for mantle cell lymphoma include: anaphylaxis, impaired wound healing, renal failure with fatal outcomes, and pulmonary embolus. **Adverse reactions for which frequency is undetermined** Angioneurotic oedema-type reactions in some patients who received temsirolimus and ACE-inhibitors concomitantly. <u>Post Marketing Experience</u> There have been reports of Stevens-Johnson syndrome in patients who received TORISEL. There have been reports of rhabdomyolysis in patients who received TORISEL.	
During handling and preparation of admixtures, Torisel should be protected from excessive room light and sunlight. Torisel, when diluted, contains polysorbate 80, which is known to increase the rate of di-(2-ethylhexyl) phthalate (DEHP) extraction from polyvinyl chloride (PVC). 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.	During handling and preparation of admixtures, TORISEL should be protected from excessive room light and sunlight. TORISEL, when diluted, contains polysorbate 80, which is known to increase the rate of di-(2-ethylhexyl) phthalate (DEHP) extraction from polyvinyl chloride (PVC). 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.	**Special precautions for disposal and other handling**

Do not use if particulates are present, or if discoloured. Use a new vial. **Dilution** **Torisel 30 mg concentrate must be diluted with the supplied diluent before administration in sodium chloride infusion.** Note: For mantle cell lymphoma, 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.**	**Dilution** **TORISEL 30 mg concentrate must be diluted with the supplied diluent before administration in sodium chloride infusion.** Note: For mantle cell lymphoma, 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).	