

NEW ZEALAND DATA SHEET

CERTICAN[®]

Everolimus

0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg Tablets

0.1 mg or 0.25 mg Dispersible Tablets

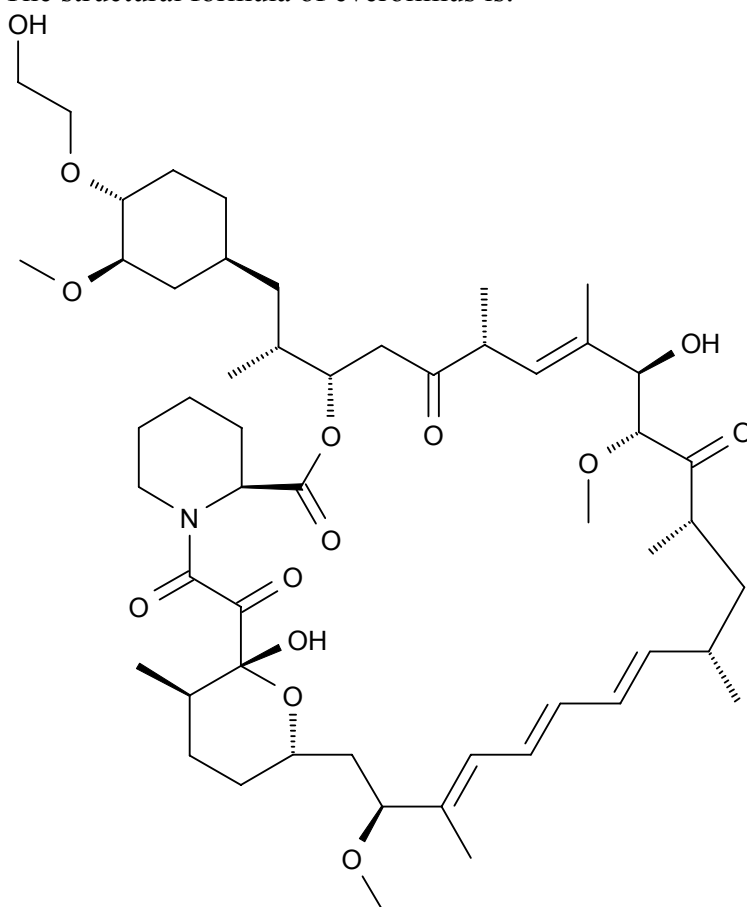
Description

The active ingredient of Certican is everolimus.

The chemical name is 40-O-(2-hydroxyethyl)-rapamycin or 40-O-(2-hydroxyethyl)-sirolimus. Its molecular formula is $C_{53}H_{83}NO_{14}$ and its molecular weight is 958.2.

CAS number: 159351-69-6

The structural formula of everolimus is:



Everolimus is a white to faintly yellow powder practically insoluble in water but soluble in organic solvents such as ethanol and methanol.

Excipients:

Tablets: Butylated hydroxytoluene, magnesium stearate, lactose monohydrate, hypromellose, crospovidone, lactose anhydrous.

Dispersible tablets: Butylated hydroxytoluene, magnesium stearate, lactose monohydrate, hypromellose, crospovidone, lactose anhydrous, colloidal anhydrous silica.

Pharmacology

Pharmacodynamics

Everolimus, a proliferation signal inhibitor, prevents allograft rejection in rodent and non-human primate models of allotransplantation. It exerts its immunosuppressive effect by inhibiting the proliferation, and thus clonal expansion, of antigen-activated T cells which is driven by T cell-specific interleukins, e.g. interleukin-2 and interleukin-15. Everolimus inhibits an intracellular signaling pathway which is triggered upon binding of these T cell growth factors to their respective receptors, and which normally leads to cell proliferation. The blockage of this signal by everolimus leads to an arrest of the cells at the G₁ stage of the cell cycle.

At the molecular level, everolimus forms a complex with the cytoplasmic protein FKBP-12. In the presence of everolimus the growth factor-stimulated phosphorylation of the p70 S6 kinase is inhibited. Since p70 S6 kinase phosphorylation is under the control of FRAP (also called m-TOR), this finding suggests that the everolimus-FKBP-12 complex binds to and thus interferes with the function of FRAP. FRAP is a key regulatory protein which governs cell metabolism, growth and proliferation; disabling FRAP function thus explains the cell cycle arrest caused by everolimus.

Everolimus, has a different mode of action than cyclosporin. In preclinical models of allotransplantation, the combination of everolimus and cyclosporin was more effective than either drug alone.

The effect of everolimus is not restricted to T cells. It inhibits in general, growth factor-stimulated proliferation of haematopoietic as well as non-haematopoietic cells, like, for instance, that of vascular smooth muscle cells. Growth factor-stimulated vascular smooth muscle cell proliferation, triggered by injury to endothelial cells and leading to neointima formation, plays a key role in the pathogenesis of chronic rejection. Preclinical studies with everolimus have shown inhibition of neointima formation in a rat aorta allotransplantation model.

Pharmacokinetics

Absorption: After oral dosing, peak everolimus concentrations occur 1 to 2 h postdose.

Everolimus blood concentrations are dose proportional over the dose range 0.25 to 15 mg in transplant patients. The relative bioavailability of the dispersible tablet compared with the tablet is 0.90 (90 % CI 0.76-1.07) based on the AUC-ratio.

Effects of Food: The C_{max} and AUC of everolimus are reduced by 60 % and 16 % when the tablet formulation is given with a high fat meal. To minimise variability, Certican should be taken consistently with or without food.

Distribution: The blood-to-plasma ratio of everolimus is concentration-dependent ranging from 17 % to 73 % over the range of 5 to 5000 ng/mL. Plasma protein binding is approximately 74 % in healthy subjects and patients with moderate hepatic impairment. The distribution volume associated with the terminal phase (V_z/F) in maintenance renal transplant patients is 342 ± 107 L.

Metabolism: Everolimus is a substrate of CYP3A4 and P-glycoprotein. The main metabolic pathways identified in man were mono-hydroxylations and O-dealkylations. Two main metabolites were formed by hydrolysis of the cyclic lactone. Everolimus was the main circulating component in blood. None of the main metabolites are likely to contribute significantly to the immunosuppressive activity of everolimus.

Excretion: After a single dose of radiolabeled everolimus to transplant patients receiving cyclosporin the majority (80%) of radioactivity was recovered from the faeces, and only a minor amount (5%) was excreted in urine. Parent drug was not detected in urine nor faeces.

Steady-state pharmacokinetics: Pharmacokinetics were comparable for kidney and heart transplant patients receiving everolimus twice daily simultaneously with cyclosporin. Steady-

state is reached by day 4 with an accumulation in blood levels of 2 to 3-fold compared with the exposure after the first dose. T_{max} occurs at 1 to 2 h postdose. C_{max} averages 11.1 ± 4.6 and 20.3 ± 8.0 ng/mL and AUC averages 75 ± 31 and 131 ± 59 ng.h/mL at 0.75 and 1.5 mg bid, respectively. Predose trough blood levels (C_{min}) average 4.1 ± 2.1 and 7.1 ± 4.6 ng/mL at 0.75 and 1.5 mg bid, respectively. Everolimus exposure remains stable over time in the first post-transplant year. C_{min} is significantly correlated with AUC yielding a correlation coefficient between 0.86 and 0.94. Based on a population pharmacokinetic analysis, oral clearance (CL/F) is 8.8 L/h (27% interpatient variation) and the central distribution volume (V_c/F) is 110 L (36% interpatient variation). Residual variability in blood concentrations is 31%. The elimination half-life is 28 ± 7h.

Hepatic impairment: Everolimus AUC was increased an average 2-fold in 8 patients with moderate hepatic impairment (Child-Pugh Class B) as compared with 8 healthy subjects. The AUC of everolimus tended to be greater than that of healthy subjects where bilirubin was >34 µmol/L, prothrombin time was >1.3 INR (> 4 sec prolongation), and/or albumin concentration was <35 g/L. The impact of severe hepatic impairment (Child-Pugh Class C) has not been assessed but the effect on everolimus AUC is likely to be as large or larger compared with moderate impairment.

Renal impairment: Post-transplant renal impairment (Cl_{crea} range, 11-107 mL/min) did not affect the pharmacokinetics of everolimus.

Paediatrics: Everolimus CL/F increased in a linear manner with patient age (1 to 16 years), body surface area (0.49-1.92 m²), and weight (11-77 kg). Steady-state CL/F was 10.2 ± 3.0 L/h/m² and elimination half-life was 30 ± 11 h. Nineteen paediatric *de novo* renal transplant patients (1 to 16 years) received Certican dispersible tablets at a dose of 0.8 mg/m² (maximum 1.5 mg) twice-daily with cyclosporin microemulsion. They achieved an everolimus AUC of 87 ± 27 ng.h/mL which is similar to adults receiving 0.75 mg twice daily. Steady-state trough levels were 4.4 ± 1.7 ng/mL.

Elderly: A limited reduction in everolimus oral CL of 0.33 % per year was estimated in adults (age range studied was 16-70 years). No dose adjustment is considered necessary.

Exposure-response relationships: The average everolimus trough concentration over the first 6 months post-transplant was related to the incidence of biopsy-confirmed acute rejection and with thrombocytopenia in kidney and heart transplant patients (See Table 1 below).

Table 1. Drug Exposure-Response Relationships (Studies B251/B253)

Kidney transplantation (Study B251)					
Trough level (ng/mL)	≤ 3.4	3.5 - 4.5	4.6 - 5.7	5.8 - 7.7	7.8 - 15.0
Freedom from rejection	68 %	81 %	86 %	81 %	91 %
Thrombocytopenia (<100 x 10 ⁹ /L)	10 %	9 %	7 %	14 %	17 %
Heart transplantation (Study B253)					
Trough level (ng/mL)	≤ 3.5	3.6 - 5.3	5.4 - 7.3	7.4 - 10.2	10.3 - 21.8
Freedom from rejection	65 %	69 %	80 %	85 %	85 %
Thrombocytopenia (<75 x 10 ⁹ /L)	5 %	5 %	6 %	8 %	9 %

Clinical trials

Kidney transplantation

Certican in fixed doses of 1.5 mg/day and 3 mg/day, in combination with standard doses of cyclosporin microemulsion and corticosteroids was investigated in two Phase III *de novo* renal transplant trials (Studies B201 and B251). Mycophenolate mofetil (MMF) 1 g twice a day was used as comparator. The co-primary composite endpoints were efficacy failure (biopsy-proven acute rejection, graft loss, death or loss to follow-up) at 6 months, and graft loss, death or loss to follow-up at 12 months. Certican was overall non-inferior to MMF in these trials. The incidence of biopsy-proven acute rejection at 6 months in the B201 study was 21.6 %, 18.2 %, and 23.5 % for the Certican 1.5 mg/day, Certican 3 mg/day and MMF groups, respectively. In the B251 study, the incidences were 17.1 %, 20.1 %, and 23.5 % for the Certican 1.5 mg/day, Certican 3 mg/day and MMF groups respectively.

Reduced allograft function with elevated serum creatinine was observed more frequently among subjects using Certican in combination with full dose cyclosporin microemulsion than in MMF patients. This effect is believed to be due to increased cyclosporin nephrotoxicity. Drug concentration-pharmacodynamic analysis showed that renal function could be improved with reduced exposure to cyclosporin while conserving efficacy for as long as blood trough everolimus concentration was maintained above 3ng/mL. This concept was subsequently confirmed in two further Phase III studies (A2306 and A2307, including 237 and 256 patients respectively) which evaluated efficacy and safety of Certican 1.5 and 3 mg per day (initial dosing, subsequent dosing based on target trough concentration ≥ 3 ng/mL) in combination with reduced exposure to cyclosporin microemulsion. In both studies, renal function was improved without compromising efficacy. In these studies however there was no non-Certican comparative arm.

A phase III, multicentre, randomised, open-label, controlled trial A2309, has been completed in which 833 *de-novo* renal transplant recipients were randomised to either one of two Certican regimens, differing by dosage, and combined with reduced-dose cyclosporin or a standard regimen of sodium mycophenolate (MPA) + cyclosporin and treated for 12 months. All patients received induction therapy with basiliximab pre-transplant and on Day 4 post-transplant. Steroids could be given as required post-transplant.

Starting dosages in the two Certican groups were 1.5 mg/d and 3 mg, given b.i.d., subsequently modified from Day 5 onwards to maintain target blood trough everolimus levels of 3-8 ng/mL and 6-12 ng/mL respectively. Sodium mycophenolate dosage was 1.44 g/d. Cyclosporin dosages were adapted to maintain target blood trough-level windows as shown in table 2. The actual measured values for blood concentrations of everolimus and cyclosporin (C₀ and C₂) are shown in table 3.

Although the higher dosage Certican regimen was as effective as the lower-dosage regimen, the overall safety was worse and so the upper-dosage regimen is not recommended. The lower dosage regimen for Certican is that recommended (see section 4.2 Posology and method of administration).

Table 2 Study A2309: Target cyclosporin blood trough-level windows

Target cyclosporin C ₀ (ng/mL)	Mo 1	Mo 2-3	Mo 4-5	Mo 6-12
Certican groups	100-200	75-150	50-100	25-50
MPA group	200-300	100-250	100-250	100-250

Table 3 Study A2309: Measured trough blood levels of cyclosporin and everolimus

Trough levels (ng/mL)	Certican groups (low dose cyclosporin)				MPA (standard cyclosporin)	
	Certican 1.5 mg		Certican 3.0 mg		Myfortic 1.44 g	
	Co level	C2 level	Co level	C2 level	Co level	C2 level
Cyclosporin						
Day 7	195 ± 106	847 ± 412	192 ± 104	718 ± 319	239 ± 130	934 ± 438
Month 1	173 ± 84	770 ± 364	177 ± 99	762 ± 378	250 ± 119	992 ± 482
Month 3	122 ± 53	580 ± 322	123 ± 75	548 ± 272	182 ± 65	821 ± 273
Month 6	88 ± 55	408 ± 226	80 ± 40	426 ± 225	163 ± 103	751 ± 269
Month 9	55 ± 24	319 ± 172	51 ± 30	296 ± 183	149 ± 69	648 ± 265
Month 12	55 ± 38	291 ± 155	49 ± 27	281 ± 198	137 ± 55	587 ± 241
Everolimus	(Target Co 3-8)		(Target Co 6-12)			
Day 7	4.5 ± 2.3		8.3 ± 4.8			-
Month 1	5.3 ± 2.2		8.6 ± 3.9			-
Month 3	6.0 ± 2.7		8.8 ± 3.6			-
Month 6	5.3 ± 1.9		8.0 ± 3.1			-
Month 9	5.3 ± 1.9		7.7 ± 2.6			-
Month 12	5.3 ± 2.3		7.9 ± 3.5			-

Numbers are mean ± SD of measured values with Co = trough-level, C2 = value 2 hours post-dose.
Source: App 1: Tables 4-3-1.5; 14.3-1.7c; 14.3-1.7c

The primary efficacy endpoint was a composite failure variable (biopsy-proven acute rejection, graft loss, death or loss to follow-up). The outcome is shown in table 4.

Table 4 Study A2309: Composite and individual efficacy endpoints at 6 and 12 months (incidence in ITT population)

	Certican 1.5 mg N=277 % (n)		Certican 3.0 mg N=279 % (n)		MPA 1.44 g N=277 % (n)	
	6 mo	12 mo	6 mo	12 mo	6 mo	12 mo
Composite endpoint (1 ^o criterion)	19.1 (53)	25.3 (70)	16.8 (47)	21.5 (60)	18.8 (52)	24.2 (67)
Difference % (<i>Certican - MPA</i>)	0.4%	1.1%	-1.9%	-2.7%	-	-
95% CI	(-6.2, 6.9)	(-6.1, 8.3)	(-8.3, 4.4)	(-9.7, 4.3)	-	-
Individual endpoints (2 ^o criteria)						
Treated BPAR	10.8 (30)	16.2 (45)	10.0 (28)	13.3 (37)	13.7 (38)	17.0 (47)
Graft loss	4.0 (11)	4.3 (12)	3.9 (11)	4.7 (13)	2.9 (8)	3.2 (9)
Death	2.2 (6)	2.5 (7)	1.8 (5)	3.2 (9)	1.1 (3)	2.2 (6)
Loss to follow-up	3.6 (10)	4.3 (12)	2.5 (7)	2.5 (7)	1.8 (5)	3.2 (9)
Combined endpoints (2 ^o criteria)						
Graft loss / Death	5.8 (16)	6.5 (18)	5.7 (16)	7.5 (21)	4.0 (11)	5.4 (15)
Graft loss / Death / Loss to FU	9.4 (26)	10.8 (30)	8.2 (23)	10.0 (28)	5.8 (16)	8.7 (24)

mo = months, 1^o = primary, 2^o = secondary, CI = confidence interval, non-inferiority margin was 10%

Composite endpoint: treated biopsy proven acute rejection (BPAR), graft loss, death, or loss to follow-up (FU)

Changes in renal function, as shown by calculated glomerular filtration rate (GFR) using the MDRD formula are shown in table 5.

Proteinuria was assessed at scheduled visits by spot analysis of urinary protein/creatinine and categorized by levels of clinical relevance as represented in table 6. Few patients in any of the treatment groups reached the nephrotic threshold but a greater proportion of Certican patients was consistently in the sub-nephrotic category than was the case in the MPA group. A concentration effect was shown relating proteinuria levels to everolimus trough levels particularly at values of Cmin above 8 ng/mL.

Adverse events reported more frequently in the recommended (lower-dosage) Certican regimen than in the MPA control group have been included in Table 10 in the Adverse Reactions section. A lower frequency for viral infection was reported for Certican-treated

patients resulting principally from lower reporting rates for CMV infection (0.7% versus 5.95%) and BK virus infection (1.5% versus 4.8%).

Table 5 Study A2309: Renal function (MDRD calculated GFR) at 12 months (ITT population)

	Certican 1.5 mg N=277	Certican 3.0 mg N=279	MPA 1.44 g N=277
12-month mean GFR (mL/min/1.73 m ²)	54.6	51.3	52.2
Difference in mean (everolimus - MPA)	2.37	-0.89	-
95% CI	(-1.7, 6.4)	(-5.0, 3.2)	-

12-month GFR missing value imputation: graft-loss = 0; death or lost to follow up for renal function = LOCF1 (last-observation-carried-forward approach 1: End of Treatment (up to Month 12)).

MDRD: modification of diet in renal disease

Table 6 Study A2309: Urinary protein to creatinine ratio

		Category of proteinuria (mg/mmol)			
		normal %(n) (<3.39)	mild %(n) (3.39-<33.9)	sub-nephrotic %(n) (33.9-<339)	nephrotic %(n) (>339)
Month 12 (TED)	Treatment				
	Certican 1.5 mg	0.4 (1)	64.2 (174)	32.5 (88)	3.0 (8)
	Certican 3 mg	0.7 (2)	59.2 (164)	33.9 (94)	5.8 (16)
	MPA 1.44 g	1.8 (5)	73.1 (198)	20.7 (56)	4.1 (11)

1 mg/mmol = 8.84 mg/g

TED: Treatment endpoint (Mo 12 value or last observation carried forward)

Heart transplantation

In the Phase III heart study (B253), both Certican 1.5 mg/day and 3 mg/day in combination with standard doses of cyclosporin microemulsion and corticosteroids, were investigated vs. azathioprine (AZA), 1-3 mg/kg/d. The primary endpoint was a composite of incidence of acute rejection \geq ISHLT grade 3A, acute rejection associated with haemodynamic compromise, graft loss, patient death or loss to follow-up at 6, 12 and 24 months. Both doses of Certican were superior to AZA at 6, 12 and 24 months. The incidence of biopsy proven acute rejection \geq ISHLT grade 3A at month 6 was 27.8 % for the 1.5 mg/d group, 19 % for the 3 mg/d group and 41.6% for the AZA group respectively ($p = 0.003$ for 1.5 mg vs control, < 0.001 for 3 mg vs control).

Based on coronary artery intravascular ultrasound data obtained from a subset of the study population, both Certican doses were statistically significantly more effective than AZA in preventing allograft vasculopathy (defined as an increase in maximum intimal thickness from baseline ≥ 0.5 mm in at least one matched slice of an automated pullback sequence), an important risk factor for long term graft loss.

Elevated serum creatinine was observed more frequently among subjects using Certican in combination with full dose cyclosporin microemulsion than in AZA patients. These results indicated that Certican increases the cyclosporin-induced nephrotoxicity. However, further analysis suggested that renal function could be improved with cyclosporin dose-reduction without loss of efficacy as long as everolimus blood values are maintained above a given threshold. Study A2411 was carried out to investigate this.

Study A2411 was a randomized, 12 month, open-label study comparing Certican in combination with reduced doses of cyclosporin microemulsion and corticosteroids to mycophenolic mofetil (MMF) and standard doses of cyclosporin microemulsion and corticosteroids in de-novo cardiac transplant patients. Certican was initiated at 1.5 mg/day and the dose was adjusted to maintain target blood everolimus trough levels between 3-8

ng/mL. MMF dosage was initiated at 1,500 mg bid. Cyclosporin microemulsion doses were adjusted to target the following trough levels (ng/mL):

Target cyclosporin C0	Mo 1	Mo 2	Mo 3-4	Mo 5-6	Mo 7-12
Certican group	200-350	150-250	100-200	75-150	50-100
MMF group	200-350	200-350	200-300	150-250	100-250

Actual blood levels measured are shown in table 7.

Table 7

A2411: Summary statistics for CsA blood levels* (mean \pm SD)

	Certican group (N=91)	MMF group (N=83)
Visit	C0	C0
Day 4	154 \pm 71 n=79	155 \pm 96 n=74
Mo 1	245 \pm 99 n=76	308 \pm 96 n=71
Mo 3	199 \pm 96 n=70	256 \pm 73 n=70
Mo 6	157 \pm 61 n=73	219 \pm 83 n=67
Mo 9	133 \pm 67 n=72	187 \pm 58 n=64
Mo 12	110 \pm 50 n=68	180 \pm 55 n=64

*:whole blood trough levels (C0)

Changes in renal function are shown in table 8. Efficacy outcome is shown in table 9.

Table 8

A2411: Changes in creatinine clearance during study (patients with paired values)

		Estimated Creatinine Clearance (Cockcroft-Gault)* mL/mn		
		Baseline Mean (\pm SD)	Value at timepoint Mean (\pm SD)	Difference between groups Mean (95% CI)
Month 1	Certican (n=87)	73.8 (\pm 27.8)	68.5 (\pm 31.5)	-7.3 (-18.1, 3.4)
	MMF (n=78)	77.4 (\pm 32.6)	79.4 (\pm 36.0)	
Month 6	Certican (n=83)	74.4 (\pm 28.2)	65.4 (\pm 24.7)	-5.0 (-13.6, 2.9)
	MMF (n=72)	76.0 (\pm 31.8)	72.4 (\pm 26.4)	
Month 12	Certican (n=71)	74.8 (\pm 28.3)	68.7 (\pm 27.7)	-1.8 (-11.2, 7.5)
	MMF (n=71)	76.2 (\pm 32.1)	71.9 (\pm 30.0)	

* includes patients with value at both baseline and visit

Table 9

A2411: Efficacy event rates (incidence in ITT population)

Efficacy endpoint	Certican n=92	MMF n=84	Difference in event rates Mean (95% CI)
At 6 months			
Biopsy-proven acute rejection \geq ISHLT grade 3A	18 (19.6%)	23 (27.4%)	-7.8 (-20.3, 4.7)
Composite efficacy failure *	26 (28.3%)	31 (36.9%)	-8.6 (-22.5, 5.2)
At 12 months			
Biopsy-proven acute rejection \geq ISHLT grade 3A	21 (22.8%)	25 (29.8%)	-6.9 (-19.9, 6.1)
Composite efficacy failure*	30 (32.6%)	35 (41.7%)	-9.1 (-23.3, 5.2)
Death or graft loss/retransplant	10 (10.9%)	10 (11.9%)	-

* Composite efficacy failure: any of the following-acute rejection \geq grade 3A, acute rejection with hemodynamic compromise, graft loss, death or loss to follow-up.

Indications

Certican is indicated for the prophylaxis of organ rejection in adult patients at mild to moderate immunological risk receiving an allogeneic renal or cardiac transplant.

Contraindications

Certican is contraindicated in patients with a known hypersensitivity to everolimus, sirolimus or to any of the excipients.

Precautions

Management of immunosuppression

Certican has been administered in clinical trials concurrently with cyclosporin microemulsion, basiliximab and corticosteroids. Certican in combination with immunosuppressive agents other than these has not been adequately investigated.

Certican has not been adequately studied in patients at high immunological risk.

Combination with thymoglobulin induction

Caution is advised with the use of thymoglobulin (rabbit anti-thymocyte globulin) induction and the Certican/ciclosporin/steroid regimen. In a clinical study in heart transplant recipients (Study A2310, see section 5.1 Pharmacodynamic properties), an increased incidence of serious infections was observed within the first three months after transplantation in the subgroup of patients who had received induction with rabbit anti-thymocyte globulin combined with Certican, steroid and ciclosporin at the blood concentration recommended for heart transplantation (higher than in kidney transplantation). This was associated with greater mortality among patients who were both hospitalized and required ventricular assistance device prior to transplantation suggesting that they may have been particularly vulnerable to increased immunosuppression.

Serious and opportunistic infections

Patients on a regimen of immunosuppressive medicinal products, including Certican, are at increased risk of developing infections especially infections with opportunistic pathogens (bacterial, fungal, viral, protozoal). Fatal infections and sepsis have been reported in patients treated with Certican (see section 4.8 Undesirable effects). Among opportunistic conditions to which immunosuppressed patients may be vulnerable are polyomavirus infections which include BK virus-associated nephropathy which can lead to kidney graft loss and the potentially fatal JC virus-associated progressive multiple leukoencephalopathy (PML). These infections, often related to total immunosuppressive burden, should be considered in the differential diagnosis of immunosuppressed patients with deteriorating kidney graft function or neurological symptoms.

In clinical trials with Certican, antimicrobial prophylaxis for *Pneumocystis jirovecii* (carinii) pneumonia was administered for the first 12 months following transplantation.

Cytomegalovirus (CMV) prophylaxis was recommended for 3 months after transplantation, particularly for patients at increased risk for CMV disease.

Severe liver function impairment

The pharmacokinetics of everolimus have not been studied in patients with severe hepatic impairment. It is recommended that everolimus whole blood trough levels be closely monitored in hepatically impaired patients.

Interaction with strong inhibitors, inducers of CYP3A4

Co-administration with strong 3A4-inhibitors (e.g. ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir) and inducers (e.g. rifampicin, rifabutin) is not recommended unless the benefit outweighs the risk. It is recommended that everolimus whole blood trough levels be monitored whenever inducers or inhibitors of CYP3A4 are concurrently administered and following their discontinuation (see Interactions with other drugs).

Lymphomas and other malignancies

Patients receiving a regimen of immunosuppressive drugs, including Certican, are at increased risk of developing lymphomas or other malignancies, particularly of the skin. The absolute risk seems related to the duration and intensity of immunosuppression rather than to the use of a specific agent. Patients should be monitored regularly for skin neoplasms and advised to minimise exposure to UV light, sunlight and use appropriate sunscreen.

Hyperlipidemia

The use of Certican with cyclosporin microemulsion in transplant patients has been associated with increased serum cholesterol and triglycerides that may require treatment. Patients receiving Certican should be monitored for hyperlipidemia and, if necessary, treated with lipid-lowering agents and appropriate dietary adjustments made. The risk/benefit should be considered in patients with established hyperlipidemia before initiating an immunosuppressive regimen including Certican. Similarly the risk/benefit of continued Certican therapy should be re-evaluated in patients with severe refractory hyperlipidemia. During Certican therapy with cyclosporin microemulsion, patients administered Certican in conjunction with an HMG-CoA reductase inhibitor and/or fibrates should be monitored for the development of rhabdomyolysis and other adverse effects associated with these agents.

Angioedema

Certican has been associated with the development of angioedema. In the majority of cases reported patients were receiving ACE inhibitors as co-medication.

Nephrotoxicity

Certican may potentiate the renal toxicity of cyclosporin. Certican with full-dose cyclosporin increases the risk of renal dysfunction. Reduced doses of cyclosporin are required for use in combination with Certican in order to avoid renal dysfunction. Regular monitoring of renal function is recommended in all patients. Appropriate adjustment of the immunosuppressive regimen, in particular reduction of cyclosporin dose, should be considered in patients with elevated serum creatinine levels. In patients receiving renal transplants, everolimus should not be used long-term together with full doses of cyclosporin (see Dosage and Administration). In patients receiving cardiac transplants, cyclosporin dose should be reduced as tolerated during the maintenance period, to prevent renal impairment. Caution should be exercised when co-administering other agents that are known to have a deleterious effect on renal function.

Proteinuria

The use of Certican with cyclosporin in *de-novo* renal transplant recipients has been associated with increased proteinuria. The risk increases with higher everolimus blood levels. In renal transplant patients with mild proteinuria while on maintenance immunosuppressive therapy including a calcineurin inhibitor (CNI) there have been reports of worsening proteinuria when the CNI is replaced by Certican. Reversibility has been observed with interruption of Certican and reintroduction of the CNI. The safety and efficacy of conversion from CNI to Certican in such patients have not been established.

Patients receiving Certican should be monitored for proteinuria.

Renal graft thrombosis

An increased risk of kidney arterial and venous thrombosis, resulting in graft loss, has been reported, mostly within the first 30 days post-transplantation.

Wound-healing complications

In clinical studies, the use of Certican has been associated with an increased frequency of surgical complications attributed to impaired wound-healing. Such complications include lymphocele, wound dehiscence, fluid collections, wound infections, and pleural and pericardial effusion in cardiac transplant recipients. There is evidence in the literature to suggest that such events may be more frequent in patients with elevated body mass index.

Thrombotic microangiopathy/Thrombotic thrombocytopenic purpura /Haemolytic uraemic syndrome

The concomitant administration of Certican with a calcineurin inhibitor (CNI) may increase the risk of CNI-induced haemolytic uraemic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy.

Interstitial lung disease/non-infectious pneumonitis

A diagnosis of interstitial lung disease (ILD) should be considered in patients presenting with symptoms consistent with infectious pneumonia but not responding to antibiotic therapy and in whom infectious, neoplastic and other non-drug causes have been discounted through appropriate investigations. Cases of ILD have been reported with Certican which resolve on drug interruption with or without glucocorticoid therapy (see Adverse reactions).

New onset diabetes mellitus

Certican has been shown to increase the risk of new onset diabetes mellitus after transplant. Blood glucose concentrations should be monitored closely in patients treated with Certican.

Male infertility

There are literature reports of reversible azoospermia and oligospermia in patients treated with mTOR inhibitors. Preclinical toxicology studies having shown that everolimus can reduce spermatogenesis, male infertility must be considered a potential risk of prolonged Certican therapy.

Risk of intolerance to excipients

Patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Mutagenesis, carcinogenesis and impairment of fertility:

Everolimus did not show genotoxicity in in vitro tests for gene mutation (bacteria and mammalian cells), and in an in vitro test and in vivo mouse micronucleus assay for clastogenic activity. Long-term carcinogenicity studies have been carried out in mice and rats and no oncogenic responses were observed. Drug exposures (blood AUC) were up to 8-times the expected maximum human value in mice, but were less than the expected maximum human value in rats.

Everolimus completely impaired male rat fertility at an everolimus dose that resulted in a drug exposure (blood AUC) that was slightly above the expected maximum human value, and sperm number and motility were reduced. Testicular atrophy was observed in all animal species tested (mouse, rat, minipigs and monkey) at drug exposures similar to or slightly above the expected clinical exposure (blood AUC). There was evidence for partial recovery of fertility over a period approximately equivalent to the treatment period. Female rat fertility could not be assessed at dose resulting in an adequate drug exposure (blood AUC).

Use in pregnancy (Category C)

There are no adequate data from the use of Certican in pregnant women and the potential risk to the fetus is unknown. In a rat study in which oral treatment started before mating and continued to the end of the period of organogenesis, treatment resulted in increased pre- and post-implementation losses. There was a low incidence of fetal cleft sternum, the significance of which is uncertain because it occurred at a dose giving a high fetal resorption rate. Systemic drug exposures (blood AUC) with the doses used in this study were below the expected maximum human value. Treatment of pregnant rabbits during the period of organogenesis slightly increased late fetal resorptions but did not otherwise affect fetal development. The highest dose used in this study gave a systemic drug exposure (blood AUC) that was slightly below the expected maximum human value. Women of childbearing potential should be advised to use effective contraception methods while they are receiving everolimus and up to 8 weeks after treatment has been stopped.

Use in lactation

It is not known whether everolimus is excreted in human milk. In animal studies, everolimus and/or its metabolites were readily transferred into milk of lactating rats. Therefore, women who are taking Certican should not breast feed.

Interactions with Other Drugs

CYP3A4 is the main P450 enzyme involved in the microsomal metabolism of everolimus, and everolimus is a substrate for the multidrug efflux pump, p-glycoprotein (PgP). Therefore, absorption and subsequent elimination of systemically absorbed everolimus may be influenced by drugs that affect CYP3A4 and/or P-glycoprotein. Concurrent treatment with strong 3A4-inhibitors and inducers is not recommended unless the benefits outweigh the risk. Inhibitors of PgP may decrease the efflux of everolimus from intestinal cells and increase everolimus blood concentrations. *In vitro*, everolimus was a competitive inhibitor of CYP3A4 and of CYP2D6, potentially increasing the concentrations of drugs eliminated by these enzymes. Thus, caution should be exercised when co-administering everolimus with 3A4- and 2D6 substrates with a narrow therapeutic index. All *in vivo* interaction studies were conducted without concomitant cyclosporin.

Cyclosporin (CYP3A4/PgP inhibitor): The bioavailability of everolimus was significantly increased by co-administration of cyclosporin microemulsion. In a single-dose study in healthy subjects, cyclosporin increased everolimus AUC by 168 % (range, 46 % to 365 %) and C_{max} by 82 % (range, 25 % to 158 %) compared with administration of everolimus alone. Dose adjustment of everolimus may be necessary if the cyclosporin dose is altered. Certican had a clinically minor influence on cyclosporin pharmacokinetics in renal and heart transplant patients receiving cyclosporin microemulsion.

Rifampicin (CYP3A4 inducer): Pre-treatment of healthy subjects with multiple-dose rifampicin followed by a single dose of Certican increased everolimus clearance nearly 3-fold, and decreased C_{max} by 58 % and AUC by 63 %. Combination with rifampicin is not recommended (see Precautions)².

Atorvastatin (CYP3A4-substrate) **and pravastatin** (PgP-substrate): Single-dose administration of Certican with either atorvastatin or pravastatin to healthy subjects did not influence the pharmacokinetics of atorvastatin, pravastatin and everolimus, nor, to a clinically relevant extent, the total HMG-CoA reductase bioreactivity in plasma. These results cannot be extrapolated to other HMG-CoA reductase inhibitors. Patients should be monitored for the development of rhabdomyolysis and other adverse events as described in the Product Information of HMG-CoA reductase inhibitors.

Other possible interactions: Inhibitors of CYP3A4 and PgP may increase everolimus blood levels (e.g. **antifungal agents:** fluconazole, ketoconazole, itraconazole; **macrolide antibiotics:** clarithromycin, erythromycin, **calcium channel blockers:** verapamil, nicardipine, diltiazem **protease inhibitors:** nelfinavir, indinavir, amprenavir² **other substances:** cisapride, metoclopramide, bromocriptine, cimetidine, danazol,). Inducers of CYP3A4 may increase the metabolism of everolimus and decrease everolimus blood levels (e.g. St. John's wort (*Hypericum perforatum*), **anticonvulsants:** carbamazepine, phenobarbitone, phenytoin; **antibiotics:** rifabutin), **anti HIV drugs:** efavirenz, nevirapine². Grapefruit and grapefruit juice affect cytochrome P450 and PgP activity and should therefore be avoided.

Vaccination: Immunosuppressants may affect response to vaccination and vaccination during treatment with Certican may be less effective. The use of live vaccines should be avoided.

Adverse reactions

The frequency of adverse reactions listed below represent those observed in patients being treated with a regimen of Certican combined with cyclosporin and corticosteroids in multi-centre, randomised, controlled studies. These include five studies in de-novo renal transplant

recipients (2497 patients), and two studies in de-novo heart transplant recipients (810 patients).

The adverse reactions reported as possibly or probably related to Certican seen in the Phase III clinical trials (renal and heart transplantation) are presented in Table 6. Unless noted otherwise, these disorders have been identified by an increased incidence in the phase III studies comparing patients on a Certican + cyclosporin regimen with patients on a non-Certican, cyclosporin-based regimen. It is compiled according to MedDRA standard organ classes:

Adverse reactions are listed according to their frequency which are defined as: very common > 1/10, common > 1/100 and < 1/10, uncommon > 1/1'000 and < 1/100, rare > 1/10'000 and < 1/1'000, very rare < 1/10'000.

Table 10. Adverse Reactions Possibly or Probably Related to Certican

Body system	Incidence	Adverse reaction
Blood and lymphatic system disorders	Very common	Leucopenia ¹
	Common	Thrombocytopenia ¹ , anaemia ¹ , coagulopathy, thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome
	Uncommon	Hemolysis, pancytopenia ⁵
Cardiac Disorder	Very Common	Pericardial effusion ²
Endocrine disorders	Uncommon	Hypogonadism male (testosterone decreased, FSH and LH increased)
Gastrointestinal disorders	Common	Abdominal pain, diarrhea, nausea, pancreatitis, vomiting, stomatitis/ mouth ulceration
General disorders and administration site conditions	Common	Oedema, pain, impaired healing
Hepatobiliary disorders¹	Uncommon	Hepatitis, hepatic dysfunction, jaundice, elevated γ -GT, AST, ALT
Infections and infestations	Common	Viral, bacterial and fungal infections, pneumonia, sepsis, urinary tract infection
	Uncommon	Wound infection
Metabolism and nutrition disorders	Very common	Hypercholesterolemia, hyperlipidemia
	Common	Hypertriglyceridemia, new onset diabetes mellitus
Musculoskeletal and connective tissue disorders	Uncommon	Myalgia
Vascular disorders	Common	Hypertension, lymphocele ³ , venous thromboembolism, raft thrombosis
	Rare	Leukocytoclastic vasculitis ⁵
Renal and urinary disorders		Proteinuria
	Uncommon	Renal tubular necrosis ³ , pyelonephritis
Respiratory, thoracic and mediastinal disorders	Very Common	Pleural effusion ²
	Uncommon	Interstitial lung disease
	Rare	Pulmonary alveolar proteinosis
Skin and subcutaneous tissue disorders	Common	Angioneurotic oedema ⁴ , acne, surgical wound complication
	Uncommon	Rash

Reproductive system and breast disorders	Common	Erectile dysfunction
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¹A dose dependent effect was established or a significantly higher incidence was seen in patients receiving 3 mg/day

²In cardiac transplantation

³In renal transplantation

⁴Predominantly in patients receiving concomitant ACE inhibitors

⁵Post-marketing finding

In controlled clinical trials in which a total of 2335 patients receiving Certican (1.5mg or 3.0mg/day) in combination with other immunosuppressants were monitored for at least 1 year, a total of 2.6% developed malignancies, with 1.0% developing skin malignancies and 0.43% developing lymphoma or lymphoproliferative disease.

The occurrence of the adverse events may depend on the immunosuppressive regimen (i.e. degree and duration). Elevations in serum creatinine were observed in the pivotal studies more frequently in patients dosed with Certican in combination with full dose cyclosporin microemulsion than in control patients. The overall incidence of adverse events was lower with reduced dose cyclosporin.

The safety profile of Certican in the trials in which it was administered with reduced-dose cyclosporin was similar to that described in the 3 pivotal studies in which full dose of cyclosporin was administered, except that elevation of serum creatinine was less frequent, and mean and median serum creatinine values were lower, than in the other phase III studies. A lower rate of viral infections, primarily due to CMV and BK virus, has been shown with the currently-recommended Certican-based immunosuppressive regimen in renal transplant recipients.

Cases of interstitial lung disease, implying lung intraparenchymal inflammation (pneumonitis) and/or fibrosis of non-infectious etiology, some fatal, have occurred in patients receiving rapamycins and their derivatives, including Certican. Mostly, the condition resolves after discontinuation of Certican and/or addition of glucocorticoids.

Dosage and administration

Treatment with Certican should only be initiated and maintained by physicians who are experienced in immunosuppressive therapy following organ transplantation. Everolimus should be used in combination with cyclosporin microemulsion and corticosteroids with cyclosporin exposure reduced over time post-transplantation (see *Therapeutic Drug Monitoring*).

An initial dose regimen of 0.75 mg twice a day is recommended for the general kidney and heart transplant population, administered as soon as possible after transplantation. The daily dose of Certican should always be given orally in two divided doses, consistently either with or without food.

Certican tablets should be taken whole and not crushed before use. For patients unable to swallow whole tablets, Certican dispersible tablets may be used as follows:

Administration in a 10mL oral syringe

The maximum amount of Certican that can be dispersed in a 10 mL syringe is 1.25 mg. Place the tablets into the syringe and add water to the 5 mL mark. Shake gently for 90 seconds. After dispersion administer orally directly from the syringe. Rinse the syringe with 5mL water and administer orally directly from the syringe. If required, a further 10 to 100 mL of water or flavoured drink can be administered.

Administration with a plastic cup

Place the Certican dispersible tablets in a plastic cup in approximately 25 mL of water. The maximum amount of Certican that can be dispersed in 25mL of water is 1.5mg. Allow the tablets to dissolve for approximately 2 minutes. Swirl gently before drinking and immediately rinse the cup with 25 mL of water and drink completely.

Administration via nasogastric tube

Place the Certican dispersible tablets in a small plastic beaker in 10mL of water. The maximum amount of Certican that can be dispersed in 10mL of water is 1.25mg. Allow the tablets to dissolve for approximately 90 seconds and swirl gently. Place the dispersion into a syringe and inject slowly (within 40 seconds) into the nasogastric tube. Rinse the beaker (and the syringe) 3 times with 5 mL water and inject into the tube. Flush the tube with 10mL water. The nasogastric tube should be clamped for a minimum of 30 minutes after Certican administration. When cyclosporin microemulsion is administered via nasogastric tube, it should be administered before Certican. The two medicines should not be mixed.

The relative bioavailability of the dispersible tablet compared with the tablet is 0.90 based on the AUC-ratio of the two forms. Therefore in the case of a switch from one pharmaceutical form to another, it is recommended to monitor everolimus blood concentrations and to adjust dosages as necessary to achieve the desired target concentration (see *Therapeutic drug monitoring*).

There is insufficient experience to recommend the use of Certican in children and adolescents. Limited information is available in renal transplant paediatric patients.

Patients with renal impairment

No dosage adjustment is required.

Patients with mild or moderate hepatic impairment

Everolimus whole blood trough levels should be closely monitored in patients with impaired hepatic function. For patients with mild or moderate hepatic impairment (Child-Pugh Class A or B), the dose should be reduced to one half of the normal dose if two of the following apply: bilirubin $>34 \mu\text{mol/L}$ ($>2\text{mg/dl}$), albumin $<35\text{g/L}$ ($<3.5\text{g/dl}$), INR time >1.3 prothrombin ($>4\text{sec}$ prolongation). Further dose titration should be based on therapeutic drug monitoring. Everolimus pharmacokinetics have not been evaluated in patients with severe hepatic impairment (Child-Pugh Class C).

Therapeutic Drug Monitoring

Routine everolimus whole blood therapeutic drug level monitoring is recommended. Based on exposure-efficacy and exposure-safety analysis, patients achieving everolimus whole blood trough levels $\geq 3.0 \text{ ng/mL}$ have been found to have a lower incidence of biopsy-proven acute rejection in both renal and cardiac transplantation compared with the patients whose trough levels are below 3.0 ng/mL . The upper limit to the therapeutic range is recommended at 8 ng/mL . Exposure above 12 ng/mL has not been studied. These recommended ranges for everolimus are based on chromatographic methods.

It is especially important to monitor everolimus blood concentrations, in patients with hepatic impairment, during concomitant administration of strong CYP3A4 inducers and inhibitors, when switching formulation and/or if cyclosporin microemulsion dosing is markedly reduced. Everolimus concentrations may be slightly lower following the dispersible tablet administration.

Optimally, dose adjustments of Certican should be based on trough levels obtained $>4\text{-}5$ days after the previous dosing change. There is an interaction of cyclosporin on everolimus, and consequently, everolimus levels may decrease if cyclosporin exposure is markedly reduced (i.e. trough concentration $<50 \text{ ng/mL}$).

Cyclosporin dose recommendation in renal transplantation

Certican should not be used long-term together with full doses of cyclosporin. Reduced exposure to cyclosporin in Certican-treated renal transplant patients improves renal function. Based on experience gained from study A2309, cyclosporin exposure reduction should be started immediately after transplantation with the following recommended whole blood trough level windows:

Renal transplantation: recommended target cyclosporin blood trough-level windows

Target cyclosporin C ₀ (ng/mL)	Month 1	Months 2-3	Months 4-5	Months 6-12
Certican groups	100-200	75-150	50-100	25-50

Prior to dose reduction of cyclosporin it should be ascertained that steady state everolimus whole blood trough concentrations (C₀) are equal to or above 3ng/mL.

There are limited data regarding dosing Certican with cyclosporin trough concentrations below 50ng/mL, or C₂ levels below 350ng/mL, in the maintenance phase. If the patient cannot tolerate reduction of cyclosporin exposure, the continued use of everolimus should be reconsidered.

Cyclosporin dose recommendation in cardiac transplantation

Cardiac transplant patients in the maintenance phase should have their cyclosporin microemulsion dose reduced beginning one month after transplantation as tolerated, in order to improve kidney function. If impairment of renal function is progressive or if the calculated creatinine clearance is <60mL/min., the treatment regimen should be adjusted. The cyclosporin dose should be guided by the experience in study 2411 in which Certican was administered with cyclosporin with reduced target trough concentrations (C₀) as follows:

Cardiac transplantation: recommended target cyclosporin blood trough-level windows

Target cyclosporin C ₀ (ng/mL)	Month 1	Month 2	Months 3-4	Months 5-6	Months 7-12
Certican group	200-350	150-250	100-200	75-150	50-100

Prior to dose reduction of cyclosporin it should be ascertained that steady state everolimus whole blood trough concentrations are equal to or above 3 ng/mL.

There are limited data regarding dosing everolimus with cyclosporin trough concentrations below 50-100 ng/mL after 12 months in cardiac transplantation. If the patient cannot tolerate reduction of cyclosporin exposure, the continued use of everolimus should be reconsidered.

Overdose

In animal studies, everolimus showed a low acute toxic potential. No lethality or severe toxicity was observed after single oral doses of 2000 mg/kg (limit test) in either mice or rats. Reported experience with overdose in humans is very limited. There is a single case of an accidental ingestion of 1.5 mg everolimus in a 2-year old child where no adverse events were observed. Single doses up to 25 mg have been administered to transplant patients with acceptable acute tolerability.

General supportive measures should be initiated in all cases of overdose.

Presentation

Certican tablets (white to yellowish, marbled, round, flat with bevelled edge)

0.25mg (engraved with "C" on one side and "NVR" on the other); 0.50 mg (engraved with "CH" on one side and "NVR" on the other); 0.75 mg (engraved with "CL" on one side and "NVR" on the other): 60's; 1.0 mg * (engraved with "CU" on one side and "NVR" on the other): 50's, 60's, 100's, 120's.

Certican dispersible tablets (white to yellowish, marbled, round, flat with bevelled edge)

0.10mg (engraved with "I" on one side and "NVR" on the other): 0.25mg (engraved with "JO" on one side and "NVR" on the other): 50's, 60's, 100's, 120's

Storage

Store below 30°C in the original packaging. Protect from light and moisture.

Medicine classification

Prescription Medicine

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