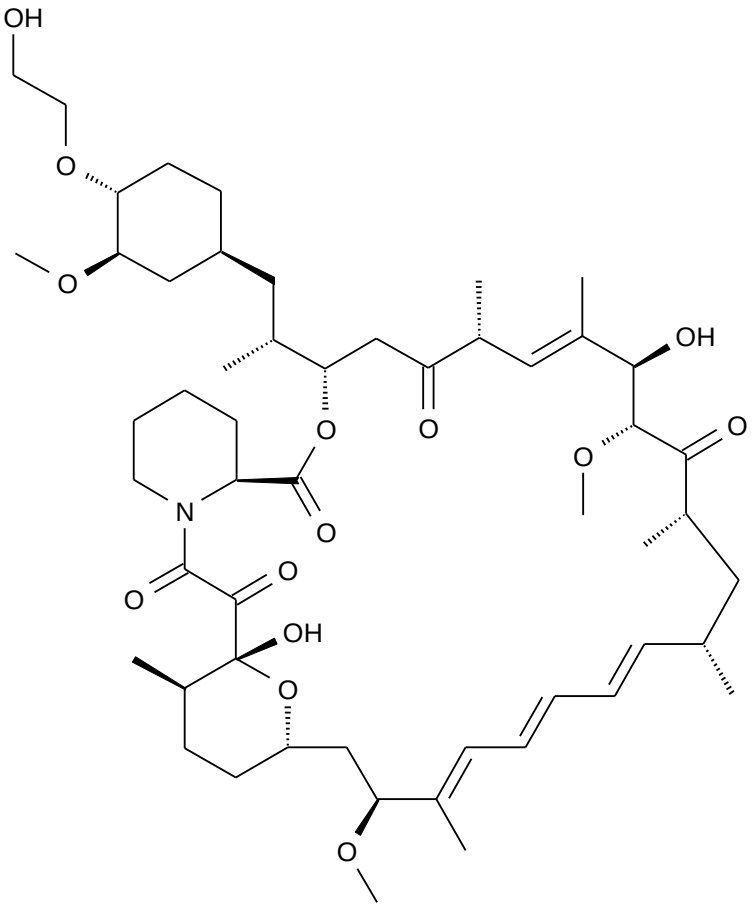
CERTICAN®
(everolimus)

NAME OF THE MEDICINE

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:



DESCRIPTION

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 signalling 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 G_1 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 post dose. 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 Cmax 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 (Vz/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. Tmax occurs at 1 to 2 h post dose. Cmax 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 (Vc/F) is 110 L (36% interpatient variation). Residual variability in blood concentrations is 31%. The elimination half-life is 28 ± 7h.

Hepatic impairment:

Relative to the AUC of everolimus in subjects with normal hepatic function, the average AUC in 6 patients with mild hepatic impairment (Child-Pugh Class A) was 1.6-fold higher; in two independently studied groups of 8 and 9 patients with moderate hepatic impairment (Child-Pugh Class B) the average AUC was 2.1-fold and 3.3-fold higher respectively; and in 6 patients with severe hepatic impairment (Child-Pugh Class C) the average AUC was 3.6-fold higher. For patients with mild hepatic impairment (Child-Pugh Class A), the dose should be reduced to two-thirds of the normal dose. For patients with moderate hepatic impairment (Child-Pugh Class B), the dose should be reduced to one half of the normal dose. For patients with severe hepatic impairment (Child-Pugh Class C) the dose should be reduced by at least one half the normal dose with strict attention to therapeutic drug monitoring. Further dose titration should be based on close therapeutic drug monitoring (see Precautions, Dosage and Administration).

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 m^2), and weight (11-77 kg). Steady-state CL/F was 10.2 ± 3.0 L/h/m^2 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/m^2 (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 renal and cardiac transplant patients (See Table 1 below). In hepatic transplant patients the relationship of everolimus trough concentrations and clinical events is less well defined, however, higher exposures do not correlate with an increase in adverse effects.

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

Renal transplantation (Study B251)					
Trough level (C0) (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 %
Cardiac transplantation (Study B253)					
Trough level (C0) (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 %
Hepatic transplantation (Study H2304)					
Trough level (C0) (ng/mL)	≤ 3	3-8			≤ 8
Freedom from treated BPAR	88%	98%			92%
Thrombocytopenia (≤ 75x10^9/L)	35%	13%			18%
Neutropenia (< 1.75x10^9/L)	70%	31%			44%

CLINICAL TRIALS

Renal 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). Mycofenolate 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 IIIb 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 ≥3ng/mL) in combination with reduced exposure to cyclosporin. 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/d, given twice a day, subsequently modified from Day 5 onwards to maintain target blood trough everolimus levels of 3 to 8 ng/mL and 6 to 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 Dosage and Administration).

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

Target cyclosporin C0 (ng/mL)	**Month 1**	**Months 2-3**	**Months 4-5**	**Months 6-12**
Certican groups	100-200	75-150	50-100	25-50
MPA* group	200-300	100-250	100-250	100-250

* MPA = sodium mycophenolate

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**	
Cyclosporin	*C0 level*	*C2 level*	*C0 level*	*C2 level*	*C0 level*	*C2 level*
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 C0 3-8)		(Target C0 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 C0 = trough-level, C2 = value 2 hours post-dose.

Source: App 1: Tables 4-3-1.5; 14.3-1.7c; 14.3-1.7c

* MPA = sodium mycophenolate

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 % *(Certican - MPA)*	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, 1^0 = primary, 2^0 = 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)
* MPA = sodium mycophenolate

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 were 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 C0 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 14. 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

	Certican 1.5 mg N=277	**Certican 3.0 mg N=279**	**MPA* 1.44 g N=277**
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

* MPA = sodium mycophenolate

Table 6 Study A2309: Urinary protein to creatinine ratio

		Category of proteinuria (mg/mmol)			
	Treatment	**normal %**(n) (<3.39)	**mild %**(n) (3.39-<33.9)	**sub-nephrotic %**(n) (33.9-<339)	**nephrotic %**(n) (>339)
Month 12 (TED)	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)

Cardiac transplantation:

In the Phase III cardiac 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 ≥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 ≥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.

In study (B253), cyclosporin doses were based on target trough levels of: weeks 1-4: 250-400 ng/mL, months 1-6: 200-350 ng/mL, months 7-24: 100-300 ng/mL.

Elevated serum creatinine was observed more frequently among subjects using Certican in combination with full dose cyclosporin microemulsion than in AZA patients. This effect suggests 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. Studies A2411 and A2310 have subsequently been carried out to investigate this.

Study A2411 was a randomised, 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 adult cardiac transplant patients. The study included a total of 174 patients. Certican (N=92) 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 (N=84) was initiated at a dosage of 1500 mg twice daily. Cyclosporin microemulsion doses were adjusted to target the trough levels (ng/mL) listed in Table 7.

Table 7. Study A2411: Target trough levels (ng/mL) of cyclosporin

	Month 1	**Month 2**	**Month 3-4**	**Month 5-6**	**Month 7-12**
Certican group	200-350	150-250	100-200	75-150	50-100
Mycophenolate mofetil group	200-350	200-350	200-300	150-250	100-250

Renal function in study A2411 did not meet the non-inferiority criteria (-6mL/mn) vs MMF. Mean creatinine clearance (Cockcroft-Gault formula) at 6 months: Certican: 65.4 v. MMF: 72.2 mL/mn (difference: -6.85 mL/mn, 95% CI: -14.9, 1.2) and at 12 months: Certican: 68.7 v. MMF: 71.8 mL/mn (Difference: -3.10 mL/mn 95% CI (-12.26, 6.06). The change from baseline was: Certican: -6.0mL/mn v. MMF: -4.2 mL/mn; p=0.697. Efficacy, expressed as the rate of biopsy-proven acute rejection episodes (ISHLT grade ≥3A), was maintained as comparable in the two groups at 12 months (Certican: 22.8% v. MMF: 29.8%).

Study A2310 is a phase III, multicentre, randomised, open-label study comparing the efficacy and safety of two Certican/reduced-dose cyclosporin regimens against a standard mycophenolate mofetil (MMF)/cyclosporin regimen over 24 months. The use of induction therapy was centre-specific, the options being no-induction or induction with either basiliximab or thymoglobulin. All patients received corticosteroids.

Starting doses in the two Certican groups were 1.5 mg/day and 3 mg/day, subsequently modified from Day 4 onwards to maintain target blood trough everolimus levels of 3-8 ng/ml and 6-12 ng/ml respectively. The MMF dose was 3 g/day. Cyclosporin dosages were adapted to maintain the same target blood trough level windows as in study A2411. Blood concentrations of everolimus and cyclosporin are shown in Table 8.

Recruitment to the experimental, upper-dosage Certican treatment arm was prematurely discontinued because of an increased rate of fatalities within this treatment group, due to infection and cardiovascular disorders, occurring within the first 90 days post-randomisation. The nature and pattern of the fatalities in this dosage arm did not suggest the difference to be linked to the presence or type of induction therapy.

Statistical comparisons are limited to comparisons between the completed treatment arms. The drug blood concentration levels actually achieved are described in Table 8.

Table 8 Study A2310: Measured trough blood levels of cyclosporin (CsA) and everolimus

Visit Window	Certican 1.5mg/reduced-dose CsA N=279		MMF 3g/std-dose CsA N=268
	everolimus (C0 ng/mL)	cyclosporin (C0 ng/mL)	cyclosporin (C0 ng/mL)
Day 4	5.7 (4.6)	153 (103)	151 (101)
Month 1	5.2 (2.4)	247 (91)	269 (99)
Month 3	5.7 (2.3)	209 (86)	245 (90)
Month 6	5.5 (2.2)	151 (76)	202 (72)
Month 9	5.4 (2.0)	117 (77)	176 (64)
Month 12	5.6 (2.5)	102 (48)	167 (66)

Numbers are mean ± SD of measured values with C0=trough level

Source: PT-Table 14.3-1.5, PT-Table 14.3-1.7a

The primary efficacy endpoint was a composite failure variable, implying occurrence of any of the following: Biopsy Proven Acute Rejection (BPAR) episode of ISHLT grade >=3A, acute rejection (AR) episode associated with hemodynamic compromise (HDC), graft loss/re-transplant, death, or loss to follow-up. Efficacy outcome at 12 months is shown in Table 9.

Table 9 Study A2310: Incidence rates of efficacy endpoints by treatment group (ITT Population - 12 Month Analysis)

Efficacy endpoints	Certican 1.5mg N=279 n (%)	MMF N=271 n (%)
Primary: Composite efficacy failure	99 (35.1)	91 (33.6)
- AR associated With HDC	11 (3.9)	7 (2.6)
- BPAR of ISHLT grade >= 3A	63 (22.3)	67 (24.7)
- Death	22 (7.8)	13 (4.8)
- Graft loss/re-transplant	4 (1.4)	5 (1.8)
- Loss to follow-up*	9 (3.2)	10 (3.7)
Secondary:		
Graft loss/re-transplant, death or loss to follow-up**	33 (11.7)	24 (8.9)
- Loss to follow-up**	11 (3.9)	11 (4.1)
Acute rejection treated with antibody	13 (4.6)	9 (3.3)

Composite efficacy failure: Biopsy Proven Acute Rejection (BPAR) episodes of ISHLT grade >=3A, Acute rejection (AR) associated with Haemodynamic Compromise (HDC), Graft loss/Re-transplant, death, or loss to follow-up.

* Loss to follow-up for relevant (primary or secondary) endpoint.

Source: PT-Table 14.2-1.1a

The higher fatality rate in the Certican arm relative to the MMF arm was mainly the result of an increased rate of fatalities from infection in the first three months among Certican patients in the study sub-group of patients receiving thymoglobulin induction therapy. A notably higher 3-month incidence in severe infections in Certican than MMF patients in the thymoglobulin subgroup appears to reflect greater immunosuppressive potency. The imbalance in fatalities within the thymoglobulin subgroup being particularly evident among patients hospitalised prior to transplantation and with L-ventricular assistance devices, suggests greater vulnerability in such patients to the consequences of infectious complications.

Intravascular ultrasound (IVUS) studies were performed on a subset of patients to investigate changes post-transplantation (Month 12 value relative to a baseline value effected during the first three months post-transplant) in intimal thickness within a segment of the left anterior descending (LAD) coronary artery. The results of the measured change in maximum intimal thickness along with frequency of patients with cardiac allograft vasculopathy (defined as an increase in the maximal intimal thickness of 0.5mm or more) are described in Table 10.

Table 10 Change in average maximum intimal thickness (mm) from Baseline to Month 12 and incidence of cardiac allograft vasculopathy (CAV) by donor disease and treatment (IVUS Population – 12 Month Analysis)

	Certican 1.5mg N=88	**MMF N=101**	**p-value of t-test (Certican v. MMF)**
Change in average maximum intimal thickness (mm) from Baseline to Month 12			
Mean (SD)	0.03 (0.05)	0.07 (0.11)	<0.001
Median (range)	0.02 (-0.12, 0.19)	0.03 (-0.15, 0.56)	
Cardiac allograft vasculopathy (CAV) by donor disease and treatment			
Donor disease	n/M (%)	n/M (%)	p-value
-Total	11/88 (12.5)	27/101 (26.7)	0.018
Donor disease	10/42 (23.8)	24/54 (44.4)	0.052
No donor disease	1/46 (2.2)	3/47 (6.4)	0.617

Baseline IVUS assessment was performed up to Day 105.

The p-value for change from baseline should be compared to the two-sided 0.025 significance level.

n = number of patients with an event of CAV in the donor disease status; M = the total number of patients within that donor disease status.

Source: PT-Table 14.2-3.2a, PT-Table 14.2-3.7

The reduced increase in intimal coronary thickness in Certican relative to MMF patients was apparent regardless of age, gender, presence or absence of diabetes and maximum level of serum cholesterol observed by Month 12.

Renal function over the course of study A2310, assessed by estimated glomerular filtration rate (eGFR) using the MDRD formula, indicates a statistically significant difference of 5.5

mL/min/1.73m^2 (97.5% CI -10.9, -0.2; p=0.019) lower for the everolimus 1.5 mg group at Month 12. The decrease in mean GFR from baseline to Month 12 was: Certican -7.1 mL/mn vs MMF -2.9 mL/min, p=0.211.

Post-hoc data analyses suggest that the difference observed was mainly associated with the exposure to cyclosporin. This difference was reduced to -3.6 mL/min/1.73m^2 and not statistically significant (97.5% CI -8.9, 1.8) in centres where the mean cyclosporin levels were lower in patients receiving Certican than in patients randomised to the control arm, as recommended.

Additionally, the difference was mainly driven by a difference developed during the first month post-transplantation when patients are still in an unstable hemodynamic situation possibly confounding the analysis of renal function. Thereafter, the decrease in mean GFR from Month 1 to Month 12 was significantly smaller in the everolimus group than in the control group (-6.4 vs -13.7 mL/min, p=0.002).

Proteinuria, expressed as urinary protein: urinary creatinine levels measured in spot urine samples tended to be more elevated in the Certican-treated patients. Sub-nephrotic values were observed in 22% of the patients receiving Certican compared to MMF patients (8.6%). Nephrotic levels were also reported (0.8%), representing 2 patients in each treatment group.

The adverse reactions for everolimus 1.5 mg group in Study A2310 are consistent with adverse drug reactions presented in Table 13. A lower rate of viral infections was reported for Certican-treated patients resulting principally from a lower reporting rate for CMV infection compared to MMF (7.2% vs 19.4%).

Hepatic transplantation:

In the phase III adult hepatic transplant study (H2304), reduced exposure tacrolimus and Certican was administered to HCV+ and HCV- patients with the initial Certican dose (1.0 mg/day) starting approximately 4 weeks after transplantation and was investigated vs. standard exposure tacrolimus. Certican was dose adjusted to maintain target blood everolimus trough levels between 3-8 ng/mL for the Certican + Reduced tacrolimus arm. Mean everolimus trough levels were within the target ranges at all time points ranging from 3.4 to 6.3 ng/mL in the Certican + Reduced tacrolimus arm. Tacrolimus doses were subsequently adjusted to achieve target trough levels between 3-5 ng/mL through 12 months in the Certican + Reduced tacrolimus arm. A third arm in study H2304 with complete withdrawal of tacrolimus at 4 months post transplantation has been associated with an increased risk of acute rejections and was terminated early.

The primary endpoint of the study was to compare the efficacy failure rate, defined as the composite endpoint of treated biopsy proven acute rejection, graft loss or death with early tacrolimus minimisation, facilitated by introduction of Certican starting approximately 4 weeks after liver transplantation, to standard exposure tacrolimus, at 12 months.

Overall, in the 12 month analysis, the incidence of the composite endpoint (tBPAR, graft loss or death) was lower in Certican + Reduced tacrolimus arm (6.7%) compared to the tacrolimus control arm (9.7%) (Table 11). The difference in estimates between Certican+Reduced tacrolimus and

tacrolimus control was - 3.0% with 97.5% CI: (-8.7% to 2.6%). Regarding the rates of graft loss and fatal cases the Certican + reduced tacrolimus arm was non-inferior compare to the tacrolimus control arm indicating no increased mortality risk in this population. A statistically significantly lower rate of biopsy proven acute rejection was seen in the Certican + Reduced tacrolimus arm (4.1%) compared to tacrolimus control arm (10.7%) (Table 12). Results are similar between HCV+ and HCV- patients.

Table 11 Study H2304: Comparison between treatment groups for Kaplan-Meier (KM) incidence rates of primary efficacy endpoints (ITT population – 12 month analysis)

Statistic	**EVR+Reduced TAC n=245**	**TAC Control n=243**
Number of composite efficacy failure (tBPAR, graft loss or death) from randomisation till Month 12	16	23
KM estimate of incidence rate of composite efficacy failure (tBPAR, graft loss or death) at Month 12	6.7%	9.7%
Difference in KM estimates (vs. Control)	-3.0%	
97.5% CI for difference	(-8.7%, 2.6%)	
P-value of Z-test for (Reduced TAC - Control = 0) (No Difference Test)	0.230	
P-value* of Z-test for (Reduced TAC - Control ≥ 0.12) (Non-inferiority Test)	<0.001	

1. tBPAR = treated biopsy proven acute rejection. Local laboratory biopsy results are used to define tBPAR.
2. *Z-test p-value for non-inferiority test (non-inferiority margin = 12%) is for one-sided test and was compared to 0.0125 significance level.
3. In Kaplan-Meier estimate, the censoring day for patients without event is the last contact day.

Table 12 Study H2304: Comparison between treatment groups for incidence rates of secondary efficacy endpoints (ITT population – 12 month analysis)

Efficacy endpoints	**EVR/Reduced TAC N=245 n (%)**	**TAC Control N=243 n (%)**	**Risk Diff. (95% CI)**	**P-value**
Graft loss*	6 (2.4)	3 (1.2)	1.2 (-7.8, 10.2)	0.5038
Death*	9 (3.7)	6 (2.5)	1.2 (-7.8, 10.1)	0.6015
BPAR	10 (4.1)	26 (10.7)	-6.6 (-11.2, -2.0)	0.0052
tBPAR	7 (2.9)	17 (7.0)	-4.1 (-8.0, -0.3)	0.0345
Subclinical AR*	1 (0.4)	5 (2.1)	-1.6 (-10.6, 7.3)	0.1216

1. AR = Acute rejection; BPAR = biopsy proven acute rejection; tBPAR = treated biopsy proven acute rejection. Local laboratory biopsy results are used to define BPAR and tBPAR.

2. Loss to follow-up for 'graft loss, death or loss to follow-up' is defined as a patient who does not die, does not have graft loss, and whose last day of contact is prior to the lower limit of the Month 12 visit window.
3. * = exact confidence interval and two-sided Fisher exact test used for that variable. For others, asymptotic confidence interval and Pearson Chi-square test are used.
4. All p-values are for two-sided test and were compared to 0.05 significance level.

Comparison between treatment groups for change in eGFR (MDRD4) [mL/min/1.73 m^2] from time of randomisation (day 30) to Month 12 for the ITT population is presented in Table 13. The adjusted mean difference between the Certican+Reduced tacrolimus arm and the tacrolimus control arm in eGFR at Month 12 was 8.50 mL/min/1.73m2. (p<0.001; 97.5% CI: 3.74, 13.27). A higher eGFR was observed throughout the study and at 12 months for Certican+ Reduced tacrolimus (80.9 mL/min/1.73m^2) in comparison to the tacrolimus control (70.3 mL/min/1.73m^2).

Table 13 Study H2304: Comparison between treatment groups for eGFR (MDRD 4) at Month 12 (ITT population – 12 month analysis)

Difference vs Control						
Treatment	N	LS Mean (SE)	LSM Mean (SE)	97.5% CI	P value(1)	P value(2)
EVR+Reduced TAC	244	-2.23 (1.54)	8.50 (2.12)	(3.74, 13.27)	<0.001	<0.001
TAC Control	243	-10.73 (1.54)				

1. Least squares means, 97.5% confidence intervals, and p-values are from an ANCOVA model containing treatment and HCV status as factors, and baseline eGFR as a covariate.
2. Imputation rules of missing Month 12 eGFR (MDRD4) values: 1) use the last available value before randomisation for patients with no post-randomisation eGFR; 2) use the minimal value if the last value is observed between randomisation and Month 6; or 3) use the minimal value between Month 6 and Month 12 if the last value is observed at or after Month 6; and 4) use 15 mL/min/1.73m^2 if the patient was on dialysis after randomisation.
3. Pvalue (1): Non-inferiority test with NI margin = -6 mL/min/1.73m^2, at one-sided 0.0125 level.
4. Pvalue (2): Superiority test at two-sided 0.025 levels.

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 and in adult patients receiving an allogeneic hepatic transplant (see Precautions).

CONTRAINDICATIONS

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

PRECAUTIONS

The clinical development of Certican has involved use of specific combinations of medicines. In renal and cardiac transplantation, Certican should be used in combination with cyclosporine

microemulsion and corticosteroids. In hepatic transplantation, Certican should be used in combination with tacrolimus and corticosteroids. Information about other combinations is lacking.

Management of immunosuppression

Certican has been administered in clinical trials concurrently with calcineurin inhibitors, 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/cyclosporin/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 cyclosporin at the blood concentration recommended for heart transplantation (higher than in kidney transplantation). This was associated with greater mortality among patients who were both hospitalised 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 with opportunistic pathogens (bacterial, fungal, viral, protozoal). Fatal infections and sepsis have been reported in patients treated with Certican. 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 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 jiroveci (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.

Liver function impairment

Close monitoring of everolimus whole blood trough levels (C0) and everolimus dose adjustment is recommended in patients with impaired hepatic function (see Dosage and Administration).

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 Medicines).

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

In transplant patients, concomitant use of Certican and cyclosporin microemulsion or tacrolimus 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.

Everolimus and calcineurin inhibitor-induced renal dysfunction

In renal and cardiac transplant 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. Appropriate adjustment of the immunosuppressive regimen, in particular reduction of the cyclosporin dose should be considered in patients with elevated serum creatinine levels.

In a liver transplant study Certican with reduced tacrolimus exposure has not been found to worsen renal function in comparison to standard exposure tacrolimus.

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 calcineurin inhibitors in 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

Certican, like other mTOR inhibitors, can impair healing increasing the occurrence of post-transplant complications such as wound dehiscence, fluid collections and wound infection which may require further surgical attention. Lymphocele is the most frequently reported such event in renal transplant recipients and tends to be more frequent in patients with higher body mass index. The frequency of pericardial and pleural effusion is increased in cardiac transplant recipients and the frequency of incisional hernias is increased in liver transplant recipients.

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 generally resolve on drug interruption with or without glucocorticoid therapy. However, fatal cases have also occurred.

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 MEDICINES

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 Cmax 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. However, everolimus may potentiate the renal toxicity of cyclosporin. Patients should be monitored for decrease in creatinine clearance.

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 Cmax by 58 % and AUC by 63 %. Combination with rifampicin is not recommended (see Precautions).

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.

Midazolam (CYP3A4A substrate): In a two-period, fixed-sequence, crossover drug interaction study, 25 healthy subjects received a single oral 4 mg dose of midazolam in period 1. In period 2, they received everolimus 10 mg once-daily for 5 days and a single 4 mg dose of midazolam with the last dose of everolimus. The Cmax of midazolam increased 1.25-fold (90% CI, 1.14 – 1.37) and the AUCinf increased 1.30-fold (1.22 – 1.39). The half-life of midazolam was unaltered. This study indicated that everolimus is a weak inhibitor of CYP3A4.

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, amprenavir **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, nevirapine.

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 EFFECTS

The frequency rates of the adverse drug reactions listed below are derived from analysis of the 12-month incidences of events reported in multicentre, randomised, controlled trials investigating Certican in combination with calcineurin inhibitors (CNI) and corticosteroids in transplant recipients. All but two of the trials (in renal transplant) included non-Certican, CNI-based standard-therapy arms. Certican combined with cyclosporin, was studied in five trials in renal transplant recipients totalling 2497 patients and three trials in heart transplant recipients totalling 1531 patients (ITT populations, see Clinical Trials).

Certican, combined with tacrolimus, was studied in one trial which included 719 liver transplant recipients (ITT population, see Pharmacodynamic properties).

The adverse reactions reported as possibly or probably related to Certican seen in the Phase III clinical trials are presented in Table 14. Unless noted otherwise, these disorders have been identified by an increased incidence in the phase III studies comparing patients on a Certican-treated patients with patients on a non-Certican standard-therapy regimen. Except where noted otherwise, the adverse reaction profile is relatively consistent across all transplant indications. It is compiled according to MeDRA standard organ classes:

Adverse reactions are listed according to their frequencies 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 14 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], pancytopenia[6, 8], anaemia[1], coagulopathy, thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome
	Uncommon	Haemolysis
Cardiac Disorder	Very Common	Pericardial effusion[2]
Endocrine disorders	Uncommon	Hypogonadism male (testosterone decreased, FSH and LH increased)
Gastrointestinal disorders	Very common	Abdominal pain[9]
	Common	Diarrhoea, nausea, pancreatitis, vomiting, stomatitis/ mouth ulceration, oropharyngeal pain
General disorders and administration site conditions	Very common	Peripheral oedema, incisional hernia[7]
	Common	Pain, impaired healing
Hepatobiliary disorders	Uncommon	Hepatitis, hepatic disorders, jaundice
Infections and infestations	Very common	Infections (viral, bacterial, fungal), upper respiratory tract infection
	Common	Sepsis, urinary tract infections, lower respiratory tract infection, wound infection
Metabolism and nutrition disorders	Very common	Hyperlipidemia (cholesterol and triglycerides), new onset diabetes mellitus[9]
Musculoskeletal and connective tissue disorders	Uncommon	Myalgia
Vascular disorders	Very common	Hypertension
	Common	Lymphocele[3], venous thromboembolism, graft thrombosis[3]
	Rare	Leukocytoclastic vasculitis[6]
Renal and urinary disorders	Common	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[5], acne, surgical wound complication
	Uncommon	Rash

Reproductive system and breast disorders	Common	Erectile dysfunction
Investigations	Common	Hepatic enzyme abnormal [4, 8]

[1] A dose dependent effect was established or a significantly higher incidence was seen in patients receiving 3 mg/day

[2] In cardiac transplantation

[3] In renal transplantation

[4] γ-GT, AST, ALT elevated

[5]Predominantly in patients receiving concomitant ACE inhibitors

[6]Post-marketing finding

[7]In liver transplant

[8]In renal and cardiac transplantation uncommon

[9]In renal and cardiac transplantation uncommon

The relative rates of adverse effects between Certican and the comparators for the three main clinical trials, renal (A2309), cardiac (A2310) and hepatic (H2304) are included in Table 15 below.

Table 15: Incidence rates of most frequent (>= 20% in any of the three Certican treatment groups) adverse events / infections by primary system organ class, preferred term and treatment (Safety population A2309, A2310, and H2304 - 12 month analysis)

Primary System Organ Class Preferred Term	A2309 Cert. 1.5mg N=274 n (%)	A2310 Cert. 1.5mg N=279 n (%)	H2304 Cert. +Reduced tacrolimus N=245 n (%)
Any AE/Infection	271 (98.9)	279 (100.0)	232 (94.7)
Blood and lymphatic system disorders- Total	93 (33.9)	143 (51.3)	66 (26.9)
Anaemia	70 (25.5)	97 (34.8)	19 (7.8)
Cardiac disorders- Total			
Pericardial effusion	1 (0.4)	111 (39.8)	1 (0.4)
Gastrointestinal disorders- Total	197 (71.9)	175 (62.7)	136 (55.5)
Constipation			
Nausea	81 (29.6)	58 (20.8)	33 (13.5)

Primary System Organ Class Preferred Term	A2309 Cert. 1.5mg N=274 n (%)	A2310 Cert. 1.5mg N=279 n (%)	H2304 Cert. +Reduced tacrolimus N=245 n (%)
General disorders and administration site conditions- Total	182 (66.4)	180 (64.5)	94 (38.4)
Oedema peripheral	123 (44.9)	124 (44.4)	43 (17.6)
Infections and infestations- Total	173 (63.1)	173 (62.0)	123 (50.2)
Urinary tract infection	61 (22.3)	19 (6.8)	20 (8.2)
Metabolism and nutrition disorders- Total			
Hyperlipidaemia	57 (20.8)	14 (5.0)	18 (7.3)
Nervous system disorders- Total	94 (34.3)	145 (52.0)	89 (36.3)
Headache			
Psychiatric disorders- Total	90 (32.8)	128 (45.9)	39 (15.9)
Insomnia	47 (17.2)	75 (26.9)	14 (5.7)
Respiratory, thoracic and mediastinal disorders- Total	87 (31.8)	183 (65.6)	57 (23.3)
Cough	20 (7.3)	57 (20.4)	15 (6.1)
Pleural effusion	8 (2.9)	71 (25.4)	11 (4.5)
Vascular disorders- Total	124 (45.3)	172 (61.6)	56 (22.9)
Hypertension	82 (29.9)	122 (43.7)	42 (17.1)
Any AE/Infection	271 (98.9)	279 (100.0)	232 (94.7)
Blood and lymphatic system disorders- Total	93 (33.9)	143 (51.3)	66 (26.9)
Anaemia	70 (25.5)	97 (34.8)	19 (7.8)

Primary System Organ Class Preferred Term	A2309 Cert. 1.5mg N=274 n (%)	A2310 Cert. 1.5mg N=279 n (%)	H2304 Cert. +Reduced tacrolimus N=245 n (%)
Cardiac disorders- Total	43 (15.7)	189 (67.7)	19 (7.8)
Pericardial effusion			
Gastrointestinal disorders- Total	197 (71.9)	175 (62.7)	136 (55.5)
Constipation	106 (38.7)	69 (24.7)	16 (6.5)
Nausea			

1. MedDRA Version 12.0 (for A2309), 13.0(for A2310), 14.0 (for H2304) has been used for the reporting of adverse events/infections.

2. Primary system organ classes are presented alphabetically; preferred terms are sorted within the primary system organ class alphabetically.

3. A patient with multiple occurrences of an AE/infection is counted only once in the AE category.

4. A patient with multiple AEs/infections within a primary system organ class is counted only once in the Total row.

In controlled clinical trials in which a total of 3256 patients receiving Certican in combination with other immunosuppressants were monitored for at least 1 year, a total of 3.1% developed malignancies, with 1.0% developing skin malignancies and 0.6% developing lymphoma or lymphoproliferative disorder.

The occurrence of the adverse events may depend on the immunosuppressive regimen (i.e. degree and duration). In the studies, combining Certican with cyclosporin, elevated serum creatinine was observed more frequently in patients given Certican in combination with full dose cyclosporin microemulsion than in control patients. The overall incidence of adverse events was lower with reduced dose cyclosporin microemulsion (see Pharmacodynamics).

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 in renal and heart transplant recipients and BK virus in renal transplant recipients, has been shown with the currently-recommended Certican-based immunosuppressive regimen in renal transplant recipients (see Pharmacodynamics).

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. However, fatal cases have also occurred.

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 dose of 1.0 mg twice a day is recommended for the hepatic transplant population with the initial dose approximately 4 weeks after transplantation. A higher Certican dosage regimen (1.5 mg twice daily) was shown to be as effective as the recommended dosage regimen but the overall safety was worse. Therefore this higher-dosage regimen is not recommended. The daily dose of Certican should always be given orally in two divided doses, consistently either with or without food and at the same time as cyclosporin microemulsion or tacrolimus.

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*).

Paediatric Use

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 impaired hepatic function

Everolimus whole blood trough levels should be closely monitored in patients with impaired hepatic function. For patients with mild hepatic impairment (Child-Pugh Class A), the dose should be reduced to two-thirds of the normal dose. For patients with moderate hepatic impairment (Child-Pugh Class B), the dose should be reduced to one half of the normal dose. For patients with severe hepatic impairment (Child-Pugh Class C), the dose should be reduced by at least one half the normal dose with strict attention to therapeutic drug monitoring. Further dose titration should be based on close therapeutic drug monitoring (see pharmacokinetics).

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 ≥3.0 ng/mL have been found to have a lower incidence of biopsy-proven acute rejection in renal, cardiac and hepatic 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 >4-5 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 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 is improves renal function. Based on experience gained from study A2309, cyclosporin exposure reduction should be started immediately after initiation of Certican with the following 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

(Measured levels are shown in the Clinical Trials)

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 the dosing of Certican with cyclosporin trough concentrations below 50 ng/mL, or C2 levels below 350 ng/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 patients in the maintenance period could have their cyclosporin dose reduced beginning one month after transplantation, if Certican is used *de novo,* as tolerated, in order to improve kidney function. If impairment of renal function is progressive or if the calculated creatinine clearance is < 60 mL/min., the treatment regimen should be adjusted. For cardiac transplant patients, the cyclosporin dose should be guided by the experience in Study 2411 and confirmed in study 2310 in which Certican was administered with cyclosporin with recommended reduced target trough concentrations (C0) as follows:

Cardiac transplantation: recommended target cyclosporin blood trough-level windows

Target cyclosporin Co (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

(Measured levels are shown in the Clinical Trials)

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

Tacrolimus dose recommendation in hepatic transplantation

In liver transplantation, Certican should be used in combination with tacrolimus and corticosteroids. Hepatic transplant patients should have the tacrolimus exposure reduced to minimize calcineurin related renal toxicity. The tacrolimus dose should be reduced starting approximately 3 weeks after initiation of dosing in combination with Certican based on tacrolimus blood trough levels (C0) targeting 3-5 ng/mL. In a controlled clinical trial, complete withdrawal of tacrolimus has been associated with an increased risk of acute rejections, and is not recommended. Certican has not been evaluated with full dose tacrolimus in controlled clinical trials.

OVERDOSAGE

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. The Poisons Information Centre (telephone 13 11 26) is available for advice.

PRESENTATION AND STORAGE CONDITIONS

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

0.25mg (engraved with "C" on one side and "NVR" on the other): 60's; 0.50 mg (engraved with "CH" on one side and "NVR" on the other): 60's; 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

Not all presentations are marketed in Australia.

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

NAME AND ADDRESS OF THE SPONSOR

Novartis Pharmaceuticals Australia Pty Limited
(ABN No: 18 004 244 160)
54 Waterloo Road
NORTH RYDE NSW 2113

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POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (Schedule 4)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

17 March 2005

DATE OF MOST RECENT AMENDMENT

23 January 2013

For internal use only:

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