PRODUCT MONOGRAPH

PrCERTICAN®

(everolimus)

0.25 mg 0.5 mg and 0.75 mg Tablets

Immunosuppressant

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Table of Contents

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	tablet 0.25 mg, 0.5 mg and 0.75 mg	butylated hydroxytoluene, lactose (monohydrate and anhydrous) as inactive ingredient. *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

PrCertican® (everolimus) is indicated for the prophylaxis of organ rejection in adult patients (18 years of age and over) at low to moderate immunologic risk receiving a renal transplant. Certican is to be administered with basiliximab induction concurrently with reduced doses of cyclosporine and corticosteroids. Therapeutic drug monitoring of everolimus and cyclosporine is recommended for all patients receiving these products.

CONTRAINDICATIONS

Certican is contraindicated in patients with known hypersensitivity to everolimus, sirolimus, or to components of the drug product or to any ingredient in the formulation or component of the container. For a complete listing, see the **Dosage Forms, Composition and Packaging** section of this Product Monograph.

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

- **Increased susceptibility to infection and the possible development of malignancies such as lymphoma and skin cancer may result from immunosuppression** (See Warnings and Precautions)
- **Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should use Certican. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.** (see Warnings and Precautions)
- **Increased nephrotoxicity can occur with standard doses of cyclosporine in combination with everolimus. Therefore reduced doses of cyclosporine should be used in combination with everolimus in order to reduce renal dysfunction. It is important to) monitor the cyclosporine and everolimus whole blood trough concentrations** (see Dosage and Administration, Warnings and Precautions and Clinical Pharmacology)
- **A risk of kidney arterial and venous thrombosis resulting in graft loss, was reported mostly within the first 30 days post-transplantation** (see Warnings and Precautions)

General

Certican is intended for oral administration only. Regular monitoring of renal function is recommended in all patients. Appropriate adjustment of the immunosuppressive regimen, in particular reduction of the cyclosporine dose should be considered in patients with elevated serum creatinine levels. Caution should be exercised when co-administering other medicinal products that are known to have a deleterious effect on renal function.

Certican has not been studied in patients with severe hepatic impairment. Close monitoring of everolimus whole blood trough levels (C0) in patients with impaired hepatic function is therefore recommended.

Patients administered Certican with an HMG-CoA reductase inhibitor and/or fibrate should be monitored for the possible development of adverse effects as described in the Dosage and Administration section (see also **Drug-Drug Interactions**).

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Certican, as this may result in diarrhea and malabsorption.

Carcinogenesis and Mutagenesis

Patients receiving immunosuppressants, including everolimus, are at increased risk of developing lymphomas and other malignancies, particularly of the skin (See **Warnings and Precautions,**

Boxed Warning). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent.

As usual for patients with increased risk for skin cancer, exposure to sunlight and ultraviolet light should be limited by wearing protective clothing and using a sunscreen with a high protection factor (see **Adverse Reactions**).

Serious Infections

Patients receiving immunosuppressants, including everolimus, are at increased risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections. These infections may lead to serious, including fatal, outcomes. Because of the danger of over immunosuppression of the immune system which can cause increased susceptibility to infection, combination immunosuppressant therapy should be used with caution.

Endocrine and Metabolism

Hyperlipidemia

Increased serum cholesterol and triglycerides, requiring the need for anti-lipid therapy, have been reported to occur following initiation of everolimus and the risk of hyperlipidemia is increased with higher everolimus whole blood trough concentrations (see **Adverse Events**). Use of anti-lipid therapy may not normalize lipid levels in patients receiving Certican.

Any patient who is administered everolimus should be monitored for hyperlipidemia. If detected, interventions, such as diet, exercise, and lipid-lowering agents should be initiated as outlined by the National Cholesterol Education Program guidelines. The risk/benefit should be considered in patients with established hyperlipidemia before initiating an immunosuppressive regimen containing everolimus. Similarly, the risk/benefit of continued everolimus therapy should be re-evaluated in patients with severe refractory hyperlipidemia. Everolimus has not been studied in patients with baseline cholesterol levels >350 mg/dL.

Due to an interaction with cyclosporine, clinical trials of everolimus and cyclosporine in kidney transplant patients strongly discouraged patients from receiving the HMG-CoA reductase inhibitors simvastatin and lovastatin. During everolimus therapy with cyclosporine, patients administered an HMG-CoA reductase inhibitor and/or fibrate should be monitored for the possible development of rhabdomyolysis and other adverse effects, as described in the respective labeling for these agents (See **Drug-Drug Interactions**).

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.

Hematologic

Increased Risk of Hemolytic Uremic Syndrome/Thrombotic Thrombocytopenic Purpura/ Thrombotic Microangiopathy (HUS/TTP/TMA):

The concomitant use of Certican with a calcineurin inhibitor (CNI) may increase the risk of CNI-induced hemolytic uremic syndrome, thrombotic thrombocytopenic purpura and thrombotic microangiopathy (see **Adverse Reactions**).

Hepatic/Biliary/Pancreatic

Liver function impairment

Everolimus whole blood trough levels (C0) are increased in patients with moderate impaired hepatic function. Therefore, the blood level should be closely monitored and everolimus dose should be adjusted based on blood concentration in the patients.

Interaction with Strong Inhibitors and Inducers of CYP3A4

Co-administration with strong CYP3A4-inhibitors (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir) and strong inducers (e.g., rifampicin, rifabutin) is not recommended without close monitoring of everolimus whole blood trough levels (see **Drug-Drug Interactions**).

Monitoring of whole blood trough levels (C0) of everolimus is recommended whenever inducers or inhibitors of CYP3A4 are co-administered or discontinued (see **Drug Interactions**).

Immune

Management of immunosuppression

In limited data with the complete elimination of CNI (calcineurin inhibition), there was an increased risk of acute rejection.

Serious and opportunistic infections:

Patients receiving immunosuppressants, including everolimus, are at increased risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections (see also **Adverse Reactions**). These infections may lead to serious, including fatal, outcomes. Because of the danger of over immunosuppression of the immune system which can cause increased susceptibility to infection, combination immunosuppressant therapy should be used with caution (see **Adverse Reactions*).***

Polyoma Virus Infections

Patients receiving immunosuppressants, including everolimus, are at increased risk for opportunistic infections, including BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML) [see **Boxed Warning**]."

BK virus-associated nephropathy (BKVAN) has been observed in patients receiving everolimus.

BKVAN is associated with serious outcomes; including deteriorating renal function and renal graft loss (See **Adverse Reactions**). Patient monitoring may help detect patients at risk for BK virus-associated nephropathy. Reductions in immunosuppression should be considered for patients who develop evidence of BK virus-associated nephropathy.

Vaccinations:

The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with Certican (see **Drug Interactions**).

Peri/Post -Operative Considerations

Wound Healing and Fluid Accumulation

Everolimus, like other m-TOR inhibitors, delays wound healing and increases the occurrence of wound-related complications like wound dehiscence, wound infection, incisional hernia, lymphocele and seroma. These wound-related complications may require more surgical intervention. Generalized fluid accumulation, including peripheral edema (e.g. lymphoedema) and other types of localized fluid collection, such as pericardial and pleural effusions and ascites have also been reported.

Renal Function /Nephrotoxicity

In renal and cardiac transplant, Everolimus with standard dose cyclosporine increases the risk of nephrotoxicity resulting in a lower glomerular filtration rate. Reduced doses of cyclosporine are required for use in combination with everolimus in order to reduce renal dysfunction. (see **Warnings and Precautions, Boxed Warning, Indications, Clinical Pharmacology**) Renal function should be monitored during the administration of everolimus in combination with cyclosporine. Consider switching to other immunosuppressive therapies if renal function does not improve after dose adjustments or if the dysfunction is thought to be drug related. Caution should be exercised when using other drugs which are known to impair renal function.

Proteinuria:

The use of Certican with calcineurin inhibitors (CNI) 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 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

A risk of kidney arterial and venous thrombosis, resulting in graft loss, has been reported, mostly within the first 30 days post-transplantation (See **Warnings and Precautions, Boxed Warning**).

Respiratory

Interstitial Lung Disease/ Non-Infectious Pneumonitis:

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. 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. Mostly, the condition resolves after discontinuation of Certican and/or addition of glucocorticoids. Fatal cases have been reported (see **Adverse Reactions***).*

Sexual Function/Reproduction

Male infertility

There is 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.

Skin

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

Vascular disorders

Leucocytoclastic vasculitis has been reported in patients treated with mTOR inhibitors, including patient receiving Certican. The condition resolved after discontinuation of the drug.

Special Populations

Pregnant Women:

Because everolimus is embryo/fetal toxic in animal studies, it may cause fetal harm when administered to pregnant women. In animal studies, embryo/fetal toxicity is manifested as mortality, malformation, and reduced fetal weights (see **Reproduction and Teratology section**).

There are no adequate and well-controlled studies of everolimus use in pregnant women. Consequently, use of everolimus during pregnancy should not be considered unless the potential benefit outweighs the potential risk to the embryo/fetus. Highly effective contraception must be

used before beginning everolimus therapy, during everolimus therapy and for 8 weeks after everolimus has been stopped.

Nursing Women:

It is not known whether everolimus is excreted in human milk. Everolimus and/or its metabolites readily transferred into milk of lactating rats at a concentration 3.5 times higher than in maternal serum. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from everolimus, women should avoid breast-feeding during treatment with Certican (see **Clinical Pharmacology**).

Pediatrics (< 18 years of age):

The safe and effective use of Certican in pediatric kidney transplant patients has not been established (see **Clinical Pharmacology: Special Populations**).

Geriatrics (> 65 years of age):

There is limited clinical experience on the use of Certican in patients of age 65 or older. There is no evidence to suggest that elderly patients will require a different dosage recommendation from younger adult patients (see **Clinical Pharmacology: Special Populations).**

Monitoring and Laboratory Tests

Therapeutic Drug Monitoring - Everolimus

Routine everolimus whole blood therapeutic drug concentration monitoring is recommended for all patients using appropriate assay methodology. Based on exposure-efficacy and exposure-safety analysis, patients achieving everolimus whole blood trough levels (C0) ≥3.0 ng/mL have been found to have a lower incidence of biopsy-proven acute rejection in renal transplantation than patients whose trough levels (C0) are below 3.0 ng/mL. The recommended upper limit of the therapeutic range is 8 ng/mL. These recommended ranges for everolimus are based on chromatographic methods (see **Clinical Pharmacology**). Careful attention should be made to clinical signs and symptoms, tissue biopsies, and laboratory parameters.

It is especially important to monitor everolimus blood concentrations, in patients with hepatic impairment, during concomitant administration of CYP3A4 inducers or inhibitors, when switching cyclosporine formulations and/or when cyclosporine dosing is reduced according to recommended target concentrations (see **Clinical Pharmacology**).

Optimally, dose adjustments of everolimus should be based on trough concentrations (C_0)obtained 4 or 5 days after a previous dosing change. There is an interaction of cyclosporine with everolimus, and consequently, everolimus concentrations may decrease if cyclosporine exposure is reduced (see **Drug Interactions**).

Therapeutic Drug Monitoring- Cyclosporine

Both cyclosporine doses and the target range for whole blood trough concentrations should be reduced, when given in a regimen with everolimus, in order to reduce the risk of nephrotoxicity (see **Warnings and Precautions** and **Drug Interactions, Clinical Pharmacology**).

Renal transplantation: recommended target cyclosporine blood trough-level windows

Target cyclosporine 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

(See **Pharmacodynamics** for measured levels).

Cyclosporine, should be initiated as soon as possible – and no later than 48 hours - after reperfusion of the graft and dose adjusted to target concentrations from Day 5 onwards.

In renal transplantation, there are limited data regarding dosing everolimus with reduced cyclosporine trough concentrations of 25-50 ng/mL after 12 months. Prior to dose reduction of cyclosporine it should be ascertained that steady-state everolimus whole blood trough concentration is at least 3 ng/mL. There is an interaction of cyclosporine on everolimus, and consequently, everolimus concentrations may decrease if cyclosporine exposure is reduced (see **Drug-Drug Interactions**).

The median trough concentrations observed in the clinical trial are listed in Table 1 below:

Table 1 Study A2309: Measured trough blood levels of cyclosporine and everolimus

Trough levels (ng/mL)	Certican group (low dose cyclosporine)		MPA (standard cyclosporine)	
	Certican 1.5 mg		Myfortic* 1.44 g	
Cyclosporine	***C0 level***	***C2 level***	***C0 level***	***C2 level***
Day 7	195 ± 106	847 ± 412	239 ± 130	934 ± 438
Month 1	173 ± 84	770 ± 364	250 ± 119	992 ± 482
Month 3	122 ± 53	580 ± 322	182 ± 65	821 ± 273
Month 6	88 ± 55	408 ± 226	163 ± 103	751 ± 269
Month 9	55± 24	319 ± 172	149 ± 69	648 ± 265
Month 12	55 ± 38	291 ± 155	137 ± 55	587± 241
Everolimus	**(Target C0 3-8)**			
Day 7	4.5 ± 2.3		-	-
Month 1	5.3 ± 2.2		-	-
Month 3	6.0 ± 2.7		-	-
Month 6	5.3 ± 1.9		-	-
Month 9	5.3 ± 1.9		-	-
Month 12	5.3 ± 2.3		-	-
Numbers are mean ± SD of measured values with C0 = trough-level, C2 = value 2 hours post-dose.				

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The data described below reflect exposure to everolimus in an open-label, randomized trial of de novo kidney transplant patients of concentration-controlled everolimus at an initial starting dose of 1.5 mg per day (target trough concentrations 3 to 8 ng/mL with reduced doses of cyclosporine (n=274) compared to mycophenolic acid (n=273) with standard doses of cyclosporine. All patients received basiliximab induction therapy and corticosteroids. The population was between 18 and 70 years; more than 43% were 50 years of age or older. More than 63% of all recipients were male and more than 64% were Caucasian. Demographic characteristics were comparable between treatment groups. The most frequent diseases leading to transplantation were balanced between groups and included hypertension/nephrosclerosis, glomerulonephritis/glomerular disease and diabetes mellitus.

Adverse reactions were systematically collected in this trial.

In this clinical trial, significantly more patients discontinued everolimus 1.5mg/day treatment (83/277, 30.0%) than discontinued the control regimen (60/277, 21.7%). Of those patients who prematurely discontinued treatment, most discontinuations were due to adverse events: 18.1% in the everolimus group compared to 9.4% in the control group (p-value= 0.004). This difference was primarily driven by significant differences between treatment groups among female patients. In those patients discontinuing study medication adverse events were collected up to 7 days after study medication discontinuation and serious adverse events up to 30 days after study medication discontinuation.

The overall incidences of Serious Adverse Events were 56.6% in the everolimus group and 53.8 % in the Myfortic* group. Infections and infestations reported as SAEs had the highest incidence in both groups (19.7% in the everolimus group and 25.3% in the control group). The difference was mainly due to the higher incidence of viral infections in the myfortic group, mainly CMV and BK virus infections. Injury, poisoning and procedural complications reported as SAEs had the second highest incidence in both groups (14.2% in the everolimus group and 11.7% in the control group) followed by renal and urinary disorders (10.2% in the everolimus group and 13.2% in the control group) and vascular disorders (9.5% in the everolimus group and 7.3% in the control group).

A total of 13 patients died during the first 12 months of study; 7 (2.5%) in the everolimus group and 6 (2.2%) in the control group. The most common causes of death across the study groups were related to cardiac conditions and infections.

There were 12 (4.3%) graft losses in the everolimus group and 9 (3.2%) in the control group over the 12 month study period. Of the graft losses, 4 were due to renal artery and 2 due to renal vein thrombosis in the everolimus group (2.2%) compared to 2 renal artery thromboses in the control group (0.7%) (see **Warnings and Precautions**).

The most common (≥ 20%) adverse reactions observed in the everolimus group were: peripheral edema, constipation, hypertension, nausea, anemia, urinary tract infection, and hyperlipidemia.

Infections

The overall incidence of bacterial, fungal and viral infections reported as adverse events was higher in the control group (68%) compared to the everolimus group (64%) and was primarily due to an increased number of viral infections (21% in the control group and 10% in the everolimus group). The incidence of cytomegalovirus (CMV) infections reported as adverse events was 8.4% in the control group compared to 1.1% in the everolimus group; and 3% of the serious CMV infections in the control group versus 0% in the everolimus group (See **Warnings and Precautions**).

BK Virus

BK virus infections were lower in incidence in the everolimus group (2 patients, 0.7%) compared to the control group (11 patients, 4.0%). One of the two BK virus infections in the everolimus group and two of the 11 BK virus infections in the control group were also reported as SAEs. BK virus infections did not result in graft loss in any of the groups.

Wound Healing and Fluid Collections

Wound healing-related events were identified through a retrospective search and request for additional data. The overall incidence of wound-related events, including lymphocele, seroma, hematoma, dehiscence, incisional hernia, and infections was 35% in the everolimus group compared to 26% in the control group. More patients required intraoperative repair debridement or drainage of incisional wound complications and more required drainage of lymphoceles and seromas in the everolimus group compared to control.

Adverse events due to major fluid collections such as edema and other types of fluid collections was 45% in the everolimus group and 40% in the control group. (see **Warnings and Precautions**)

Neoplasms

Adverse events due to malignant and benign neoplasms were reported in 3.3% of patients in the everolimus group and 5.9 % in the control group. The most frequently reported neoplasms in the study were basal cell carcinoma, Squamous cell carcinoma, skin papilloma and seborrhoeic keratosis. One patient in the everolimus group who underwent a melanoma excision prior to transplantation died due to metastatic melanoma (see **Boxed Warning** and **Warnings and Precautions**).

New onset diabetes mellitus (NODM)

Although reported diabetes-related adverse events had similar incidences in the two groups, NODM based on adverse event reporting and random serum glucose values tended to be higher in the everolimus group than in the control group (9.1% v. 6.6%).

Endocrine Effects in Males

In the everolimus group, serum testosterone levels significantly decreased while the FSH levels significantly increased without significant changes being observed in the control group. In both the everolimus and the control groups mean testosterone and FSH levels remained within the normal range with the mean FSH level in the everolimus group being at the upper limit of the normal range (11.1 U/L). More patients were reported with erectile dysfunction in the everolimus treatment group compared to the control group (5.1% compared to 2.1% respectively).

Table 2 compares the incidence of treatment-emergent adverse events reported with an incidence of ≥ 10% for patients receiving everolimus with reduced dose cyclosporine or mycophenolic acid with standard dose cyclosporine, or the same incidence as for the comparator in case the event is known as an adverse drug reaction of the comparator. Within each MedDRA system organ class, the adverse reactions are presented in order of decreasing frequency.

Table 2 Incidence Rates of Frequent (≥10% in Any Treatment Group) Adverse Events by Primary System Organ Class and Preferred Term

Primary System Organ Class Preferred Term	Certican (everolimus) 1.5 mg With reduced dose cyclosporine N=274 / n (%)	Myfortic* (mycophenolic acid) 1.44 g With standard dose cyclosporine N=273 / n (%)
Any Adverse Events*	271 (98.9)	270 (98.9)
Blood lymphatic system disorders	93 (33.9)	111 (40.7)
Anemia	70 (25.5)	68 (24.9)
Leukopenia	8 (2.9)	33 (12.1)
Gastrointestinal disorders	196 (71.5)	207 (75.8)
Constipation	105 (38.3)	117 (42.9)
Nausea	79 (28.8)	85 (31.1)
Diarrhea	51 (18.6)	54 (19.8)
Vomiting	40 (14.6)	60 (22.0)
Abdominal pain	36 (13.1)	42 (15.4)
Dyspepsia	12 (4.4)	31 (11.4)
Abdominal pain upper	9 (3.3)	30 (11.0)
General disorders and administrative site conditions	181 (66.1)	160 (58.6)
Edema peripheral	123 (44.9)	108 (39.6)
Pyrexia	51 (18.6)	40 (14.7)
Fatigue	25 (9.1)	28 (10.3)
Infections and Infestations	169 (61.7)	185 (67.8)
Urinary tract infection	60 (21.9)	63 (23.1)
Upper respiratory tract infection	44 (16.1)	49 (17.9)
Injury, poisoning and procedural complications	163 (59.5)	163 (59.7)
Incision site pain	45 (16.4)	47 (17.2)
Procedural pain	40 (14.6)	37 (13.6)
Investigations	137 (50.0)	133 (48.7)
Blood creatinine increased	48 (17.5)	59 (21.6)
Metabolism and Nutrition disorders	222 (81.0)	199 (72.9)
Hyperlipidemia	57 (20.8)	43 (15.8)
Hyperkalemia	49 (17.9)	48 (17.6)
Hypercholesterolemia	47 (17.2)	34 (12.5)
Dyslipidemia	41 (15.0)	24 (8.8)

Hypomagnesemia	37 (13.5)	40 (14.7)
Hypophosphatemia	35 (12.8)	35 (12.8)
Hyperglycemia	34 (12.4)	38 (13.9)
Hypokalemia	32 (11.7)	32 (11.7)
Musculoskeletal and connective tissue disorders	112 (40.9)	105 (38.5)
Pain in extremity	32 (11.7)	29 (10.6)
Back pain	30 (10.9)	28 (10.3)
Nervous system disorders	92 (33.6)	109 (39.9)
Headache	49 (17.9)	40 (14.7)
Psychiatric disorders	90 (32.8)	72 (26.4)
Insomnia	47 (17.2)	43 (15.8)
Renal and urinary disorders	112 (40.9)	124 (45.4)
Hematuria	33 (12.0)	33 (12.1)
Dysuria	29 (10.6)	28 (10.3)
Respiratory, thoracic and mediastinal disorders	86 (31.4)	93 (34.1)
Cough	20 (7.3)	30 (11.0)
Vascular disorders	122 (44.5)	124 (45.4)
Hypertension	81 (29.6)	82 (30.0)

*** As reported in the safety analysis population defined as all randomized patients who received at least one dose of treatment and had at least one post-baseline safety assessment.**

A third treatment group of everolimus 3.0 mg per day (1.5 mg twice daily; target trough concentrations 6 to 12 ng/mL) with reduced-dose cyclosporine was included in the study described above. Although as effective as the lower dose everolimus group, the overall safety was worse and consequently higher doses of everolimus cannot be recommended. Out of 279 patients, 95 (34.1%) discontinued the study medication with 57 (20.4%) doing so because of adverse events. The most frequent adverse events leading to discontinuation of everolimus when used at this higher dose were injury, poisoning and procedural complications (everolimus 1.5mg: 5.1%, everolimus 3.0mg: 7.2%, and control: 2.2%), infections (1.5%, 6.1%, and 2.9% respectively), renal and urinary disorders (4.0%, 6.5%, and 3.7% respectively) and gastro-intestinal disorders (1.1%, 2.5%, and 2.2%).

Adverse events reported in either of the everolimus groups notably more frequently (5% or more) than in the MPA control group included: anemia (everolimus 1.5mg: 25.5%, everolimus 3mg: 30.9%, control: 24.9%), acne (9.5%, 14.7% and 8.4% respectively), dyslipidemia (15.0%, 12.9%, and 8.8%), hypercholesterolemia (17.2%, 18.0% and 12.5%), hyperlipidemia (20.8%, 21.6%, and 15.8%), lymphocele (7.7%, 12.2% and 5.9%), peripheral edema (44.9%, 43.2% and 39.6%), proteinuria (9.1%, 12.9% and 7.3%), and stomatitis/mouth ulceration (8.4%, 7.9%, and 2.6%).

Less common adverse events (* indicates evidence to suggest a possible or probable link to treatment, i.e. may be adverse reactions), occurring in ≥1% to <10% of patients treated with everolimus include:

Blood and Lymphatic System Disorders: leukocytosis, leucopenia, lymphadenopathy, thrombocythemia, thrombocytopenia,*coagulopathy*, Thrombotic Microangiopathy (TMA), Thrombotic Thrombocytopenic Purpura (TTP), and Hemolytic Uremic Syndrome (HUS)*

Cardiac and Vascular Disorders: angina pectoris, atrial fibrillation, cardiac failure congestive, palpitations, tachycardia, hypertension including hypertensive crisis*, hypotension, venous thrombosis including deep vein thrombosis*, graft thrombosis*, epistaxis,lymphocele

Endocrine Disorders: Cushingoid, hyperparathyroidism

Eye Disorders: cataract, vision blurred

Gastrointestinal Disorders: abdominal pain*, abdominal distention, dyspepsia, dysphagia, epigastric discomfort, gastroesophageal reflux disease, gingival hypertrophy, hematemesis, hemorrhoids, ileus, mouth ulceration, oropharyngeal pain, peritonitis, stomatitis*, pancreatitis*

General Disorders and Administrative Site Conditions: chest discomfort, chest pain, chills, fatigue, malaise, edema including generalized edema*, impaired healing*, pain

Hepatobiliary Disorders: hepatic enzyme increased, bilirubin increased*

Infections and Infestations: Viral, bacterial and fungal infections*, including: pneumonia, sepsisurinary tract infection, BK virus infection , bacteremia, bronchitis, candidiasis, cellulitis, folliculitis, gastroenteritis, influenza, nasopharyngitis, onychomycosis, oral candidiasis, osteomyelitis, pneumonia, sinusitis, tinea pedis, urethritis, urinary tract infection, wound infection, herpes infections, conjunctivitis

Injury Poisoning and Procedural Complications: incision site complications including infections*, perinephric collection*, seroma*, wound dehiscence*, incisional hernia, perinephric hematoma, localized intraabdominal fluid collection*, lymophocele*, lymphorrhea*

Metabolism and Nutrition Disorders: blood urea increased, acidosis, anorexia, dehydration, diabetes mellitus*, fluid retention, gout, hypercalcemia, hypercholesterolemia*, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypocalcemia, hypoglycemia, hyponatremia, iron deficiency, vitamin B12 deficiency

Musculoskeletal and Connective Tissues Disorders: arthralgia, joint swelling, muscle spasms, muscular weakness, musculoskeletal pain, myalgia*, osteonecrosis, osteopenia, osteoporosis, spondylitis

Nervous System Disorders: dizziness, hemiparesis, hypoaesthesia, paresthesia, somnolence, syncope, tremor*

Psychiatric Disorders: agitation, anxiety, depression, hallucination

Renal and Urinary Disorders: bladder spasm, hydronephrosis, micturation urgency, nephritis interstitial, pollakiuria, polyuria, proteinuria*, pyuria, renal artery thrombosis, acute renal failure, renal impairment, urinary retention, renal tubule necrosis*

Reproductive System and Breast Disorders: erectile dysfunction*, ovarian cyst, scrotal edema

Respiratory, Thoracic, Mediastinal Disorders: atelectasis, cough, dyspnea, nasal congestion, pleural effusions*, pulmonary edema, rhinorrhea, sinus congestion, wheezing

Skin and Subcutaneous Tissue Disorders: alopecia, dermatitis acneiform, hirsutism, hyperhydrosis, hypertrichosis, skin neoplasm (malignant and unspecified), night sweats, pruritus, rash* angioneurotic edema*

Less common, serious adverse events (<1%) include:
• hemolysis*
• pancytopenia*
• male hypogonadism
• hepatic disporders*, hepatitis*, jaundice*
• Interstitial lung disease/Non-infectious Pneumonitis*, pulmonary alveolar proteinosis*
• Leukoclastic vasculitis*

The combination of fixed dose everolimus and standard doses cyclosporine in previous clinical trials resulted in frequent elevations of serum creatinine with higher mean and median serum creatinine values was observed than in the current study with reduced doses of cyclosporine. These results indicate that everolimus increases the cyclosporine-induced nephrotoxicity; and therefore should only be used in a concentration-controlled regimen with reduced doses of cyclosporine.

Post Marketing Adverse Drug Reactions

Reporting rates determined on the basis of spontaneously reported post marketing adverse drug events are generally presumed to underestimate the risks associated with drug treatment. Following adverse events have been reported spontaneously during post marketing period of Certican. The causal relationship to Certican can not be excluded for spontaneously reported events. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.
The events reported here include events observed in non-renal transplant recipients (heart or liver transplantation), and events labeled for everolimus in oncology indications.

Cardiac disorders: Pericardial effusion (specifically reported after heart transplantation)

Vascular disorders: Leukocytoclastic vasculitits

Respiratory, thoracic and mediastinal disorders: Pulmonary alveolar proteinosis

Skin and subcutaneous disorders: Erythroderma

DRUG INTERACTIONS

Overview

Everolimus is mainly metabolized by CYP3A4 in the liver and to some extent in the intestinal wall and is a substrate for the multidrug efflux pump, P-glycoprotein. Therefore, absorption and subsequent elimination of systemically absorbed everolimus may be influenced by medicinal products that affect CYP3A4 and/or P-glycoprotein. Concurrent treatment with strong inhibitors (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir) and inducers (e.g., rifampicin, rifabutin) of CYP3A4 is not recommended. Inhibitors of P-glycoprotein (e.g., digoxin, cyclosporine) 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 medicinal products eliminated by these enzymes. Thus, caution should be exercised when co-administering everolimus with CYP3A4 and CYP2D6 substrates with a narrow therapeutic index (See **Therapeutic Drug Monitoring**).

All *in vivo* interaction studies were conducted without concomitant cyclosporine. Pharmacokinetic interactions between everolimus and concomitantly administered drugs are discussed below. Drug interaction studies have not been conducted with drugs other than those described below.

Drug-Drug Interactions

Cyclosporine (CYP3A4/P-gp inhibitor and CYP3A4 substrate)

The steady-state C_{max} and AUC estimates of everolimus were significantly increased by co-administration of single dose cyclosporine (see **Clinical Pharmacology**). Dose adjustment of everolimus might be needed if the cyclosporine dose is altered. (see Dosage and Administration). Everolimus had a clinically minor influence on cyclosporine pharmacokinetics in transplant patients receiving cyclosporine (Neoral*****).

Rifampicin (Strong CYP3A4) Inducers

Pre-treatment of healthy subjects with multiple-dose rifampin followed by a single dose of everolimus increased everolimus clearance nearly 3-fold and decreased the everolimus C_{max} by 58% and AUC estimates. Combination with rifampin is not recommended (see **Warnings and Precautions** and **Clinical Pharmacology**).

Ketoconazole

Multiple-dose ketoconazole administration to healthy volunteers significantly increased single dose estimates of everolimus C_{max}, AUC, and half-life. It is recommended that strong inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin,

ritonavir) not be coadministered with everolimus (see **Warnings and Precautions** and **Clinical Pharmacology**).

Erythromycin

Multiple-dose erythromycin administration to healthy volunteers significantly increased single dose estimates of everolimus C_{max}, AUC, and half-life. If erythromycin is coadministered, everolimus blood concentrations should be monitored and a dose adjustment made as necessary (see **Clinical Pharmacology**).

Verapamil (CYP3A4 and P-gp Substrate)

Multiple-dose verapamil administration to healthy volunteers significantly increased single dose estimates of everolimus C_{max} and AUC. Everolimus half-life was not changed. If verapamil is coadministered, everolimus blood concentrations should be monitored and a dose adjustment made as necessary (see **Clinical Pharmacology**).

Atorvastatin (CYP3A4 substrate) and **pravastatin** (P-gp substrate)

Single-dose administration of everolimus with either atorvastatin or pravastatin to healthy subjects did not influence the pharmacokinetics of atorvastatin, pravastatin and everolimus, as well as total HMG-CoA reductase bioreactivity in plasma to a clinically relevant extent. However, 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 respective labeling for these products.

Simvastatin and Lovastatin

Due to an interaction with cyclosporine, clinical studies of everolimus with cyclosporine conducted in kidney transplant patients strongly discouraged patients with receiving HMG-CoA reductase inhibitors such as simvastatin and lovastatin (See **Warnings and Precautions**).

Midazolam (CYP3A4 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 C_{max} of midazolam increased 1.25-fold (90% CI, 1.14 – 1.37) and the AUC_{inf} 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.

Octreotide

Coadministration of everolimus with depot octreotide increased octreotide Cmin with a geometric mean ratio (everolimus/placebo) of 1.47-fold.

Other Possible Interactions

Moderate inhibitors of CYP3A4 and P-gp may increase everolimus blood concentrations (e.g., fluconazole; macrolide antibiotics; nicardipine, diltiazem; nelfinavir, indinavir, amprenavir). Inducers of CYP3A4 may increase the metabolism of everolimus and decrease everolimus blood concentrations (e.g., St. John's Wort (*Hypericum perforatum*); anticonvulsants: carbamazepine, phenobarbital, phenytoin; efavirenz, nevirapine.

Vaccination

Immunosuppressants may affect the response to vaccination and vaccination during treatment with Certican may therefore be less effective (see **Warnings and Precautions**). The use of live vaccines should be avoided; examples include (not limited to) the following: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

Drug-Food Interactions

Grapefruit and grapefruit juice inhibit cytochrome P450 3A4 and P-gp activity and should therefore be avoided with concomitant use of everolimus and cyclosporine (see **Clinical Pharmacology**).

Drug-Herb Interactions

St. John's Wort (*Hypericum perforatum*) induces CYP3A4 and P-glycoprotein. Since everolimus is a substrate for both cytochrome CYP3A4 and P-glycoprotein, there is the potential that the use of St. John's Wort in patients receiving Certican could result in reduced whole blood everolimus concentrations.

Drug-Laboratory Interactions

There are no available studies on the potential for interactions of everolimus, cyclosporine and routine laboratory tests.

Drug-Lifestyle Interactions

As with other immunosuppressive agents, owing to potential risk of malignant skin changes, exposure to sunlight and ultraviolet light (UV) should be limited by wearing protective clothing and using sunscreen with a high protection factor.

DOSAGE AND ADMINISTRATION

Certican is for oral use only.

Treatment with Certican should only be initiated and maintained by physicians who are experienced in immunosuppressive therapy following organ transplantation and who have access to everolimus whole blood levels monitoring.

Administration

Adult Kidney Transplant Patients

Dosage:

An initial everolimus dose of 0.75 mg orally twice daily 12 hours apart (1.5mg /day) is recommended for adult kidney transplant patients in combination with reduced dose cyclosporine and corticosteroid. Adjust maintenance dose to achieve everolimus trough concentrations within the 3-8 ng/mL target range.

Administration:

Certican and cyclosporine should be administered as soon as possible after transplantation (see **Therapeutic Drug Monitoring and Clinical Trials**).

Certican tablets should be swallowed whole with a glass of water and not crushed before use.

Certican should be administered consistently with or without food at the same time as cyclosporine

Patients receiving everolimus may require dose adjustments based on everolimus blood concentrations achieved, tolerability, individual response, change in concomitant medications and the clinical situation. Dose adjustments can be made at 4-5 day intervals. (see **Therapeutic Drug Monitoring**). Oral prednisone should be initiated once oral medication is tolerated. Steroid doses may be further tapered on an individualized basis depending on the clinical status of patient and function of graft.

Dosing Considerations (see also above).

Pediatric Patients

There are no adequate data of the use of Certican in children and adolescents to support its use in patients in these age groups.

Elderly patients (≥ 65 years)

Clinical experience is limited in patients ≥ 65 years of age. A limited reduction in everolimus oral CL of 0.33% per year was estimated in adults (age range studied was 16-70 years. There are no apparent differences in the pharmacokinetics of everolimus in patients ≥ 65-70 years of age as compared with younger adults. There is no evidence to suggest that elderly patients will require a different dosage recommendation from younger adult patients.

Patients with Renal Impairment

No dosage adjustment is required (**see Pharmacokinetics**).

Patients with Hepatic Impairment

For patients with mild hepatic impairment (Child-Pugh Class A), the dose should be reduced to approximately two-thirds of the normal dose. For patients with moderate hepatic impairment (Child-Pugh Class B), the dose should be reduced to approximately one half of the normal dose. For patients with severe hepatic impairment (Child-Pugh C) the dose should be reduced to at least one half of the normal dose. These recommended dose reductions are based on a single dose PK study. The efficacy and safety have not been established in these patient populations.

Everolimus whole blood trough levels (C0) should be closely monitored and everolimus dose should be adjusted based on blood concentration in patients with impaired hepatic function.

Recommended Dose and Dosage Adjustment

see above

Missed Dose

Patients should be advised that to take a missed as soon as possible, and to take the next dose at its regular time. If it is almost time for their next dose, they should be advised to skip the missed dose, and never to take 2 doses at the same time.

OVERDOSAGE

For management of suspected drug overdose, contact your regional Poison Control Centre

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. Single doses up to 70 mg (without cyclosporine) have been given with acceptable acute tolerability.

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

Everolimus is not considered dialyzable to any relevant degree (<10% of everolimus removed within 6 hours of hemodialysis). 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The immunosuppressive activity of everolimus results from its ability to inhibit the interleukin-stimulated proliferation and clonal expansion of antigen-activated T and B lymphocytes.
In cells, everolimus binds to a cytoplasmic protein, the FK506 Binding Protein-12 (FKBP-12), to form the active immunosuppressive principle. That is, the everolimus: FKBP-12 complex binds to and inhibits the mammalian Target Of Rapamycin (mTOR), a key regulatory kinase and central controller of cell growth and proliferation. In the presence of everolimus phosphorylation of p70 S6 ribosomal protein kinase (p70S6K), a substrate of mTOR, is inhibited. Consequently, phosphorylation of the ribosomal S6 protein and subsequent protein synthesis are prevented which results in cell cycle arrest and inhibition of cell proliferation. The everolimus: FKBP-12 complex has no effect on calcineurin activity.

Pharmacodynamics

Preclinical Pharmacology

Everolimus inhibits antigenic and interleukin (IL-2 and IL-15) stimulated activation and proliferation of T and B lymphocytes.

In animal models, including non-human primate models, everolimus effectively prevents allograft rejection resulting in prolonged graft survival (orthotopic kidney, heterotopic heart, and unilateral lung allotransplantation in the rat; orthotopic kidney and unilateral lung allotransplantation in cynomolgus monkeys). It is also able to reverse ongoing allograft rejection as shown in rat unilateral lung allotransplantation. *In vitro* experiments and rat transplantation studies indicate synergistic immunosuppressive activity of everolimus and cyclosporine. The combination of everolimus and cyclosporine has also been demonstrated to be considerably more effective in cynomolgus monkey models of unilateral lung allotransplantation than either compound alone.

Everolimus has further the ability to inhibit growth factor-stimulated proliferation of vascular smooth muscle cells. Growth factor-stimulated vascular smooth muscle cell proliferation, which is triggered by injury to endothelial cells and leads to neointima formation, plays a key role in the pathogenesis of chronic rejection as defined by allograft nephropathy and cardiac allograft vasculopathy. Preclinical experiments with everolimus show inhibition of neointima formation in a rat aorta allotransplantation model.

Pharmacokinetics

Everolimus pharmacokinetics have been characterized after oral administration of single and multiple doses to adult kidney transplant patients, hepatically-impaired patients, and healthy subjects.

Pharmacokinetics in Kidney Transplant Patients

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.

Table 3: Pharmacokinetic Parameters (mean +/- SD) following administration of 0.75mg Twice Daily

C_{max}	T_{max}	AUC	CL/F[1]	Vc/F[1]	Half-life ($T_{1/2}$)
11.1 ± 4.6 ng/mL	1-2 h	75 + 31 ng.h/mL	8.8 L/h	110 L	30 ± 11h

1 Pharmacokinetic population analysis of everolimus from pooled studies RADB251 and RADB201

The half-life estimates from 12 maintenance renal transplant patients who received single doses of everolimus capsules at 0.75 mg or 2.5 mg with their maintenance cyclosporine regimen indicate that the pharmacokinetics of everolimus are linear over the clinically-relevant dose range. Results indicate the half-life of everolimus in maintenance renal transplant patients receiving single doses of 0.75 mg or 2.5 mg everolimus during steady-state cyclosporine treatment was 30 ± 11 hours (range 19-53 hours).

Absorption:

After oral administration, peak everolimus concentrations occur 1 to 2 h post dose. Over the dose range of 0.5 mg to 2 mg bid, everolimus C_{max} and AUC are dose proportional in transplant patients at steady-state.

Food Effect

In 24 healthy subjects, a high-fat breakfast (44.5 g fat) reduced everolimus C_{max} by 60%, delayed t_{max} by a median 1.3 hours, and reduced AUC by 16% compared with a fasting administration. To minimize variability, everolimus 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 ng/mL to 5000 ng/mL. Plasma protein binding is approximately 74% in healthy subjects and in patients with moderate hepatic impairment. The apparent distribution volume associated with the terminal phase (Vz/F) from a single-dose pharmacokinetic study in maintenance kidney transplant patients is 342 + 107 L (range 128 to 589 L).

Metabolism:

Everolimus is a substrate of CYP3A4 and P-glycoprotein. Following oral administration, it is the main circulating component in human blood. Six main metabolites of everolimus have been detected in human blood, including three monohydroxylated metabolites, two hydrolytic ring-opened products, and a phosphatidylcholine conjugate of everolimus. These metabolites were also identified in animal species used in toxicity studies, and showed approximately 100-times less activity than everolimus itself. Hence, the parent substance is considered to contribute the majority of the overall pharmacological activity of everolimus.

Excretion:

After a single dose of radiolabeled everolimus was given to transplant patients receiving cyclosporine, the majority (80%) of radioactivity was recovered from the feces and only a minor amount (5%) was excreted in urine. Parent drug was not detected in urine and feces.

Special Populations and Conditions

Pediatrics:

The safety and effective use of Certican in pediatric kidney transplant patients has not been established.

Geriatrics:

A limited reduction in everolimus oral CL of 0.33% per year was estimated in adults (age range studied was 16 to70 years. There is no evidence to suggest that elderly patients will require a different dosage recommendation from younger adult patients.

Race:

Based on analysis of population pharmacokinetics, oral clearance (CL/F) is, on average, 20% higher in Black transplant patients.

Hepatic Impairment / Insufficiency:

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 studies 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; and in 6 patients with severe hepatic impairment (Child-Pugh Class C) the average AUC was 3.6- fold higher. Mean half-lives were 52, 59, and 78 hours in mild, moderate, and severe hepatic impairment. The prolonged half-lives delay the time to reach steady-state everolimus blood levels

Everolimus whole blood trough levels (C0) should be closely monitored and everolimus dose should be adjusted based on blood concentration in patients with moderate impaired hepatic function.

Renal Impairment /Insufficiency:

Post-transplant renal function (creatinine clearance range 11-107 mL/min) did not affect the pharmacokinetics of everolimus.

STORAGE AND STABILITY

Storage

Store between 15-30°C in the original package. Protect from light and moisture.

Keep out of the reach and sight of children.

SPECIAL HANDLING INSTRUCTIONS

None

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage form:

Description of Certican Tablets			
Dosage Strength	**0.25 mg**	**0.5 mg**	**0.75 mg**
Appearance	White to yellowish, marbled, round, flat tablets with bevelled edge		
Imprint	"C" on one side and "NVR" on the other	"CH" on one side and "NVR" on the other	"CL" on one side and "NVR" on the other

Composition:

Medicinal Ingredients
everolimus

Non-medicinal Ingredients
butylated hydroxytoluene
crospovidone
hypromellose
lactose anhydrous
lactose monohydrate
magnesium stearate

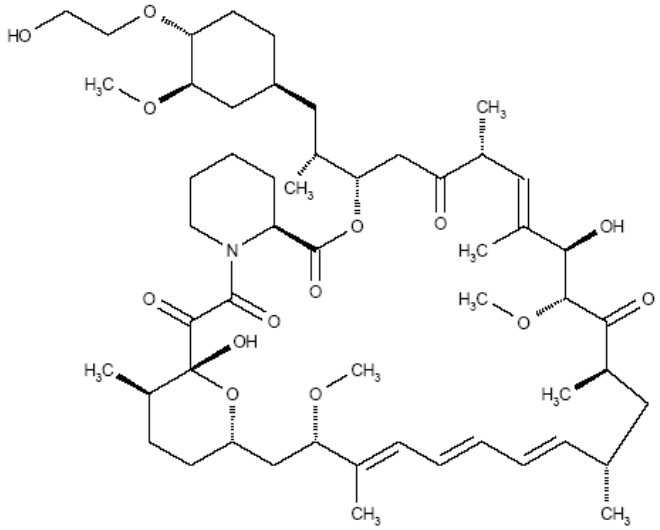
Packaging:

Each strength is available in boxes of 60 (6 blister strips of 10 tablets each).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common name:	Everolimus
Chemical name:	(1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-Dihydroxy-12-{(1R)-2-[(1S, 3R, 4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-azatricyclo [30.3.1.04,9]-hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone
Molecular formula:	$C_{53}H_{83}NO_{14}$
Molecular mass:	958.2
Structural formula:	
Physicochemical properties	
Physical description:	White to faintly white powder
Solubility:	The drug substance is practically insoluble in water, but it is soluble in organic solvents.
pH:	Because the solubility in water is very low (<0.01 %) the pH of an aqueous solution was not determined. The pH value of 0.1 % suspension of several batches in 1 % aqueous solution of KNO_3 were measured and the values lie in the range 4-6.
pKa:	No pKa value can be determined (neutral compound).
Partition Coefficient:	Because of the low solubility of everolimus stabilized with BHT in

	water and in aqueous buffers, the partition coefficient could not be determined.
Melting Point:	Not applicable since the drug substance is amorphous.

CLINICAL TRIALS

Study demographics and trial design

Table 4 Summary of patient demographics for clinical trials in specific indication

Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Multicenter, randomized, open-label, non-inferiority study of efficacy and safety comparing concentration-controlled Certican with reduced Neoral* versus 1.44 g Myfortic* with standard dose Neoral* in *de novo* renal transplant recipients	Dosage: 0.75mg BID Route of administration: oral Duration: 24 month	N= 554	Mean age: 46.5 Range: 18-70	Females: 33.9% Males: 65.9%

Caucasians (69.1%), Blacks (13.2%), Asians (12.3%) and a limited proportion of Native Americans (0.2%). The most frequent diseases leading to end stage renal disease were hypertension/nephrosclerosis (17.1%), diabetes mellitus (15.2%), and glomerulonephritis/glomerular disease (15.0%). The majority of patients were receiving hemodialysis at the time of transplantation, and approximately one-half had not had a previous blood transfusion. Over one-half of patients had at least one HLA mismatch at the A, B and DR loci and over 70% of patients had more than 3 mismatches. The mean percentage of panel reactive antibodies was 1.5% (most recent evaluation) and 3.7% (peak evaluation). Donor mean age was 41.6 years. Donors were predominantly Caucasian (70.4%), Black (8.1%) and Asian (11.4%). The majority of organs came from living donors (53.2%).

Prevention of Organ Rejection after Renal Transplantation

A Phase III, multi-national, open-label, randomized (1:1:1) trial was conducted comparing two concentration-controlled everolimus regimens of 1.5 mg per day starting dose (targeting 3-8 ng/mL) and 3.0 mg per day starting dose (targeting 6-12 ng/mL) with reduced doses of cyclosporine and corticosteroids, to 1.44 gm per day of mycophenolic acid with standard doses of cyclosporine and corticosteroids. The mean cyclosporine starting dose was 5.2, 5.0 and 5.7 mg/kg body weight/day in the everolimus 1.5mg, 3.0mg and in mycophenolic acid groups respectively. The cyclosporine dose in everolimus group was then adjusted to the blood trough concentration ranges indicated in Table 6, whereas in the myfortic group the target ranges were 200 to300 starting Day 5: 200 to300 ng/mL, and 100to250 ng/mL from Month 2 to Month 12.

All patients received basiliximab induction therapy. The study population consisted of 18-70 year old male and female low to moderate risk renal transplant recipients undergoing their first transplant. Low to moderate immunologic risk was defined in the study as an ABO blood type compatible first organ or tissue transplant recipient with anti-HLA Class I PRA <20% by a complement dependant cytotoxicity-based assay, or <50% by a flow cytometry or ELISA-based assay, and with a negative T-cell cross match. Eight hundred thirty-three (833) patients were randomized after transplantation; 277 randomized to the everolimus 1.5 mg per day group, 279 to the everolimus 3.0 mg per day group and 277 to the Myfortic* 1.44 gm per day group. The study was conducted at 79 renal transplant centers across Europe, South Africa, North and South America, and Asia-Pacific. At 12 months, there were no major baseline differences between treatment groups with regard to recipient or donor disease characteristics. The majority of transplant recipients in all groups (70-76%) had three or more HLA mismatches; mean percentage of panel reactive antibodies ranged from 0.9% to 2.0%. The rate of premature treatment discontinuation at 12-months was 30% v. 22% in the everolimus 1.5mg and Myfortic* groups, respectively (p=0.03, Fisher's exact test) and was driven by significant differences between groups among female patients. Results at 12-months indicated that everolimus 1.5 mg per day is comparable to Myfortic* with respect to efficacy failure, defined as treated biopsy-proven acute rejection, graft loss, death or loss to follow-up. The percentage of patients experiencing this endpoint and each individual variable in the everolimus and Myfortic* groups is shown in Table 5. The incidence of efficacy failure was 25.3% and 24.2% in the everolimus and Myfortic* groups respectively.

Table 5 Composite and individual efficacy endpoints at 6 and 12 months (incidence in ITT population)

	Certican 1.5 mg N=277 % (n)		MPA 1.44 g N=277 % (n)	
	6 month	12 month	6 month	12 month
Composite endpoint (1º criterion)	**19.1** (53)	**25.3** (70)	**18.8** (52)	**24.2** (67)
Difference % *(Certican- MPA)*	0.4%	1.1%	-	-
95% CI	(-6.2, 6.9)	(-6.1, 8.3)	-	-
Individual endpoints (2º criteria)				
Treated BPAR	**10.8** (30)	**16.2** (45)	**13.7** (38)	**17.0** (47)
Graft loss	**4.0** (11)	**4.3** (12)	**2.9** (8)	**3.2** (9)
Death	**2.2** (6)	**2.5** (7)	**1.1** (3)	**2.2** (6)
Loss to follow-up	**3.6** (10)	**4.3** (12)	**1.8** (5)	**3.2** (9)
Combined endpoints (2º criteria)				
Graft loss / Death	**5.8** (16)	**6.5** (18)	**4.0** (11)	**5.4** (15)
Graft loss / Death / Loss to FU	**9.4** (26)	**10.8** (30)	**5.8** (16)	**8.7** (24)

The calculated mean glomerular filtration rate (using the MDRD equation) for everolimus 1.5 mg (target trough concentrations 3 to 8 ng/mL) and mycophenolic acid were comparable at Day 7 (48.69 vs 45.85), Month 1 (59.67 vs 55.89), Month 6 (57.20 vs 52.11) respectively, and at Month 12 in the ITT population (Table 6). However, urine protein results (Table 7) indicate that everolimus combined with cyclosporine is potentially associated with an increased incidence of sub-nephropathy.

Table 6 Renal function (MDRD calculated GFR) at 12 months (ITT population)

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

Table 7 **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)
	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)

Two earlier studies compared fixed doses of everolimus 1.5 mg per day and 3 mg per day, without therapeutic drug monitoring, combined with standard doses of cyclosporine and corticosteroids to mycophenolate mofetil 2.0 gm per day and corticosteroids. Antilymphocyte antibody induction was prohibited in both studies. Both were multicenter, double-blind (for first 12 months), randomized trials (1:1:1) of 588 and 583 *de novo* renal transplant patients, respectively. The 12 month analysis of GFR showed increased rates of renal impairment in both the everolimus groups compared to the mycophenolate mofetil group in both studies. Therefore, reduced doses of cyclosporine should be used in combination with everolimus in order to avoid renal dysfunction and everolimus trough concentrations should be adjusted using therapeutic drug monitoring to maintain trough concentrations between 3 to 8 ng/mL. (See **Boxed Warning, Dosage and Administration and Warnings and Precautions**).

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. In the B201 study, the incidence of biopsy-proven acute rejection at 6 months in the Certican 1.5 mg/day, Certican 3 mg/day and MMF groups was 21.6%, 18.2%, and 23.5%, respectively. In the B251 study the incidences for the Certican 1.5 mg/day, Certican 3 mg/day and MMF groups was 17.1%, 20.1%, and 23.5%, respectively. Drug concentration-pharmacodynamic analysis showed that renal function could be improved with reduced exposure to cyclosporine 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 b studies (A2306 and A2307, including 237 and 256 patients respectively) which evaluated the efficacy and safety of Certican 1.5 and 3 mg Certican per day (initial dosing; subsequent dosing based on target trough concentration (C0) $\geq$ 3 ng/mL) in combination with reduced exposure to cyclosporine. In both studies, renal function was improved without compromising efficacy. In these studies however there was no non-Certican comparative arm.

A dose of 3.0 mg everolimus per day in combination with reduced cyclosporine was studied. This high dose provided no additional efficacy and had higher frequencies of adverse drug reactions in comparison with the 1.5mg everolimus per day group. This 3.0 mg dose is not recommended to use.

DETAILED PHARMACOLOGY

Certican (everolimus) is an orally active proliferation inhibitor and a macrolide immunosuppressant [40-O-(2-hydroxyethyl)-rapamycin] which is derived by chemical modification of the natural product rapamycin, which is a secondary macrolide metabolite produced by certain strains of *Streptomyces hygroscopicus.*

Certican, the everolimus tablet, shows: rapid absorption, dose proportionality, and a good correlation between trough and exposure (area under the curve [AUC]). Everolimus has a short half-life, and an intracellular distribution pattern with potential impact on neuro- and nephrotoxicity.

At steady-state for the recommended starting dose of 0.75 mg bid, the predose trough blood concentration (C_{min}) averages 4.1 ± 2.1 ng/mL, C_{max} averages 11.1 ± 4.6 ng/mL, and AUC averages 75 ± 31 ng.h/mL. 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 concentration is 31 %. The half-life estimate from 12 maintenance renal transplant patients was 30 ± 11 hours (range 19-53 hours).

Everolimus shows potent immunosuppressive activity *in vitro*. In animal models, including non-human primate models, everolimus effectively prevents allograft rejection resulting in prolonged graft survival (orthotopic kidney, heterotopic heart, and unilateral lung allotransplantation in the rat; orthotopic kidney and unilateral lung allotransplantation in cynomolgus monkeys). It is also able to reverse ongoing allograft rejection as shown in rat unilateral lung allotransplantation. *In vitro* experiments and rat transplantation studies indicate synergistic immunosuppressive activity of everolimus and Neoral*. In line with these results, the combination of everolimus and Neoral has also been demonstrated to be considerably more effective in cynomolgus monkey models of unilateral lung allotransplantation than either compound alone.

Everolimus does not have significant effect on nerve system and on the cardiovascular system.
Growth factor-stimulated vascular smooth muscle cell proliferation, triggered by injury to endothelial cells, plays a key role in the pathogenesis of chronic rejection as defined by allograft nephropathy and cardiac allograft vasculopathy. Preclinical experiments with everolimus show inhibition of neointima formation in rat aorta allotransplantation. Everolimus is also found to inhibit the key events involved in restenotic lesion formation following vascular injury in multiple species including rats, rabbits, and pigs.

In addition, everolimus prevents the growth of Epstein-Barr virus-transformed lymphoma lines both *in vitro* and in mouse models. It has antifungal activity against clinically relevant yeasts (e.g., a number of *Candida* spp., including *Candida albicans*, *Cryptococcus neoformans*), but is inactive against the filamentous pathogens (*Aspergillus fumigatus*).

MICROBIOLOGY

(Not applicable)

TOXICOLOGY

Acute Toxicology

Acute oral toxicity studies were conducted in mice and rats. Everolimus showed relatively low acute toxicity when administered orally (LD-50 was less than 2000 mg/kg). Intravenous administration, however, produced lethality at about 63 and 96 mg/kg in rats and mice, respectively.

Chronic Toxicology

The preclinical safety profile of everolimus has been evaluated in a number of animal studies. Repeated-dose toxicity studies were performed with durations up to 4 weeks in minipigs, 13 weeks in mice, 26 weeks in rats and up to 52 weeks in monkeys. The monkey was selected as a non-rodent species, since gastrointestinal intolerability of everolimus in the dog was seen after rising-doses between 2 and 18 mg/kg during only 9 days, precluding this species from treatment for longer periods. Tables 8-10 summarize the long term toxicity studies conducted with everolimus (oral administration). Effects attributable to immunosuppression were evident in all species.

Major target organs in all animal species were organs of immune system such as atrophic changes in thymus, spleen, and lymph nodes. Male and female reproductive organs were affected in all animal species (see **Reproduction and Teratology**). Renal tubular degeneration was observed in mice at > 5 mg/kg/day dose. In studies with combination treatments (with cyclosporine or tacrolimus), the renal degenerative effects were enhanced, indicating that the adverse effects of cyclosporine or tacrolimus on the kidney may be exaggerated also in combination therapy in humans. Chronic myocarditis was observed in rat and monkey studies. High titers of coxsackie virus in the plasma and heart was found in monkey especially after everolimus treatment. Gastrointestinal inflammation in monkeys treated at 0.9 mg/kg/day dose for 52-weeks and intestinal effects in minipigs due to coccidial infestation caused premature termination of study. A slight depletion of cortical bone mass in the rat at higher doses might be related to hormonal imbalance. Lungs were identified as rodent-specific, and eyes as rat-specific target organ. The pancreas was affected in the minipig (4-weeks) and monkey (26-weeks) studies. Skin lesions in rodents including abrasion, ulceration, inflammation and scabs were associated with secondary effects of immunosuppression. Monkeys showed hemorrhage and arteritis in several organs.

Mutagenicity

Everolimus was devoid of clastogenic or mutagenic effects in *in vitro* tests (bacterial reverse mutation, mouse lymphoma thymidine kinase assay, and V79 Chinese hamster cells chromosome aberration tests) and in vivo following two daily doses of 500 mg/kg in the mouse micronucleus assay. (mouse micronucleus test).

Carcinogenicity

Carcinogenicity studies were performed over 2 years in mice and rats. Administration of everolimus for up to 2 years did not indicate any oncogenic potential in mice and rats up to the highest dose tested (0.9 mg/kg). In these studies, AUCs in mice corresponded to at least 20 times compared to those in humans receiving 0.75 mg b.i.d., and AUCs in rats were in the same range as those in humans receiving 0.75 mg b.i.d.

These studies are summarized in Table 11.

Reproduction and Teratology

The reproductive organs were the primary targets in the general toxicity studies in all species. In a 13-week male fertility oral gavage study in rats, testicular morphology was affected at 0.5 mg/kg and above, and sperm motility, sperm head count and plasma testosterone concentrations were diminished at 5 mg/kg which caused a decrease in male fertility. There was evidence of reversibility of these findings in animals examined after 13 weeks post-dosing. The 0.5 mg/kg dose in male rats resulted in AUCs in the range of clinical exposures, and the 5 mg/kg dose resulted in AUCs approximately 5 times the AUCs in humans receiving 0.75 mg b.i.d.

Everolimus did not affect female fertility in nonclinical studies but everolimus crossed the placenta and was toxic to the conceptus. In rats, everolimus caused embryo/fetotoxicity, at systemic exposure below the therapeutic dose in human that was manifested as mortality and reduced fetal weight. The incidence of skeletal variations and malformations at 0.3 mg/kg and 0.9 mg/kg (e.g., sternal cleft) was increased. In rabbits, embryotoxicity was evident by an increase in late resorptions at a maternal toxic dose.

Effects on pre- and post-natal development of rats were limited to slightly affected body weight and survival in the F1-generation. There were no effects noted on the morphological development, motor activity, learning ability or fertility assessment of the F1 generation at dose level up to 0.3 mg/kg.

Table 8 Long-Term Toxicity Studies - Oral Administration in Mice and Rats

Species (Strain)	N (sex/group)	Dose everolimus (mg/kg/bwt/day) Route Duration	Observations
CD-1 mice	240 (10 males and 10 females per group)	0, 0.15, 0.5, 1.5, 5, 15 p.o. 13 weeks	NTEL = 0.15 mg/kg/day (males); C_{max}: 55 ng/mL; A.UC $_{(0\text{-}24H)}$: 803 ng.h/mL NTEL = 0.5 mg/kg/day (females); C_{max}: 272 ng/mL; A.UC $_{(0\text{-}24H)}$: 1258 ng.h/mL ≥0.5 mg/kg: thymic medullary atrophy; depletion of germ cells and vacuolat. of germinal epithelium of the testes; reduced sperm content in epididymides; increased microvesiculation of adrenals (m). ≥1.5 mg/kg: increased cholesterol (m); skin lesions; few foamy alveolar macrophages (f); reduced ovarian follicular development and uterine atrophy. ≥5.0 mg/kg: increased cholesterol (m); increased cholesterol (m/f); renal tubular degeneration/karyomegaly and increased interstitial inflammation (m); few foamy alveolar macrophages (m/f) ≥15 mg/kg: increased plasma creatinine (m); decreased albumin and Alb/Glob ratio (m); renal tubular degeneration/daryomegaly and increased interstitial inflammation (m/f). Doses lower than 1.5 mg/kg were proposed for the oncogenicity study due to skin changes.
rat, Hanlbm: WIST (SPF)	40 (4 males and 4 females per group)	0, 2.5, 10, 40 p.o. 17 days	NTEL < 2.5 mg/kg ≥2.5 mg/kg: reduced body weight gain, food intake (m); decrease in lymphocytes, platelets and albumin; thymic atrophy; lymphoid depletion of spleen and lymph nodes; atrophy/decreased secretion of prostate and seminal vesicles; increased focal myocardial degeneration; decreased extramedullary splenic hemopoiesis; increase in alveolar macrophages in lungs. ≥10 mg/kg: reduced body weight gain, food intake (m/f); increased cholesterol (m); skin lesions; bone marrow depletion (m). 40 mg/kg: increased WBC/neutrophils; degenerative changes in testes; increased incidence of diestrus stage. No major differences in toxicity profile compared with rapamycin.
rat Hanlbm: WIST (SPF)	120 (10 males and 10 females per group)	0, 1.5, 15 p.o 2 weeks	The results of this study showed no relevant differences in the toxicological profile or in exposure to everolimus between the micro-emulsion and the solid dispersion.

Table 8 Long-Term Toxicity Studies - Oral administration in Rats

Species (Strain)	N (sex/group)	Dose everolimus (mg/kg/bwt/day) Route Duration	Observations
rat Hanlbm, WIST (SPF)	62 males 62 females	0, 0.5, 1.5, 5, 15 p.o. 4 weeks + 2 weeks recovery	NTEL approx. 0.5 mg/kg; C_{max}: 8.5 ng/mL (m + f combined) ≥0.5 mg/kg: reduced body weight gain, food intake (m); hemoconcentration; low platelets; increased cholesterol (m); chronic myocarditis (m). ≥1.5 mg/kg: reduced body weight gain, food intake (m/f); increased triglycerides (f); chronic myocarditis (m/f); medullary atrophy of thymus; foamy alveolar macrophages; loss of germ cells in testes; atrophy/reduced secretion of seminal vesicles; interstitial cell hypertrophy of ovaries; depletion of secretory granules in salivary glands. ≥5 mg/g: increased neutrophils; increased cholesterol (m/f); low albumin; anterior suture line opacities in lens; swelling/disruption of anterior cortical lens fibers; atrophy/reduced secretion of prostate; uterus atrophy; thinning of cortical bone. 15 mg/kg: reduced sperm counts in testes; reduced contents in epididymides. Recovery of changes except for lungs, heart, eyes and testes.
rat (Hanlbm Wistar)	62 males 62 females	0, 0.1, 0.25, 0.5, 1.5 p.o. 4 weeks + 2 weeks recovery	NTEL = 0.5 mg/kg; m: C_{max}: 10 ng/mL; AUC $_{(0\text{-}24H)}$: 102 ng.h/mL; f: C_{max}: 6 ng/mL; AUC $_{(0\text{-}24H)}$: 56 ng.h.mL ≥0.5 mg/kg: medullary atrophy of the thymus. 1.5 mg/kg: reduced body weight gain, food intake; anterior suture line opacities in lens; hemoconcentration; decreased platelets; increased cholesterol (m); chronic myocarditis; increased alveolar macrophages with vacuoles and multilamellar bodies; interstitial cell hyperplasia of ovaries; uterus atrophy; depletion of secretory granules in salivary glands. Recovery of changes except for heart.

Table 8 Long-Term Toxicity Studies - Oral administration in Rats (continued)

Species (Strain)	N (sex/group)	Dose everolimus (mg/kg/bwt/day) Route Duration	Observations
rat (Hanlbm Wistar)	150 males 150 females	0, 0.05, 0.1, 0.15, 0.5, 1.5 p.o. 26 weeks + 4 weeks recovery	NTEL = 0.15 mg/kg ; m: C_{max}: 1.5 ng/mL: AUC $_{(0\text{-}24H)}$: 7.1 ng.h/mL; f: C_{max}: 1.1 ng/mL; AUC: 8.1 ng.h/mL ≥0.15 mg/kg: reduced body weight gain (f); medullary atrophy of thymus (f). ≥0.5 mg/kg: hemoconcentration (m); low platelets (m); increased amylase (m); medullary atrophy of thymus (m); lymphoid atrophy of LN; pigment (lipofuscin) in renal tubular epithelial cells; increased hydronephrosis (m); increased alveolar macrophages and perivascular lymphoid infiltration; mucus cell hypertrophy/-plasia of stomach; follicular cell hypertrophy/vacuolation of thyroids (m). 1.5 mg/kg: reduced body weight gain (m/f), food intake; hemoconcentraton (m/f), decreased albumin (m) and iron; interstitial pneumonitis (m); splenic hemosiderosis, deplation of germ cells, tubular vacuolation and spermatid giant cells in testes. Recovery of changes except for lungs or testes. Special investigations on the liver drug metabolizing enzyme levels and on the overall metabolism: minor increase in total metabolite formation and reduction of P450 2B1/2.

m=male, f=female, NTEL=no-toxic-effect level

Table 9: Long-Term Toxicity Studies - Oral administration in Dogs and Minipigs

Species (Strain)	**N (Sex/ group)**	**Dose everolimus (mg/kg/bwt/day) Route Duration**	**Observations**
dog (Beagle)	1 male 1 female	2/6/18 p.o. 3/3/3 days	No MTD. ≥2 mg/kg: Body weight loss. ≥6 mg/kg: Reduced food intake. 18 mg/kg: Sedation; diarrhea; decreased platelets and lymphocytes; prolonged part. thromboplastin time and sedimentation rate; increased cholesterol, triglycerides, total bilirubin, alkaline phosphatase; decreased glucose; multifocal ulceration in gastrointestinal tract; hemorrhagic bronchopneumonia.
minipig (Göttingen SPF)	4 males 4 females	0, 0.5, 1.5, 5 p.o. 2 weeks	≥0.5 mg/kg: Decreased platelets and lymphocytes; increased creatinine (f); increased seminiferous tubular atrophy in testes; thymic cortical lymphocytolysis; decreased germinal centre activity in LN. ≥1.5 mg/kg: Decreased albumin, (-globulins and Alb/Glob ratio; increase in ß1 globulins. 5 mg/kg: Early sacrifice (f) due to pneumonitis; increased creatinine (m).
minipig (Göttingen SPF)	12 males 16 females	0, 1.5, 5, 15 p.o. 4 weeks + 4 weeks recovery	NTEL < 1.5 mg/kg. m: C_{max}: 145 ng/mL; AUC $_{(1\text{-}24H)}$: 2937 ng·h/mL f: C_{max}: 153 ng/mL; AUC $_{(1\text{-}24H)}$: 2403 ng·h/mL ≥1.5 mg/kg: Diarrhea related to increased coccidial infestation of intestine (m); reduced body weight gain and food intake (m); increased fibrinogen and neutrophils (m); decreased albumin and Alb/Glob ratio (m); decreased phosphorus, alkaline phosphatase and γ-globulins; increased α2 and β1 globulins; increased percentage. of β -lipoproteins and decreased percentage of chylomicrons (m); thymic atrophy; atrophy/decreased lymphoid activity in LN; myelitis and focal encephalitis (m); increased dermatitis; increased testicular tubular atrophy and oligospermia in epididymides. ≥5 mg/kg: Lymphoid depletion of spleen (1f); necrotic follicles in uterus; microvacuolation of adrenals. 15 mg/kg: Diarrhea related to intestinal erosion with coccidial infestation (m/f) leading to one death (m) and early sacrifices (3m/1f); reduced body weight gain and food intake (m/f); decreased platelets (m); increased urea and creatinine (2f); decreased cholinesterase; increased LDL (LDL-3 to LDL-6) and decreased HDL-2a; lymphoid depletion of spleen (m); vacuolation of exocrine pancreatic cells with necrosis (m); atrophy of vagina and uterus. Recovery of all changes except for the testes.

Table 10 Long-Term Toxicity Studies - Oral administration in Monkeys

Species (Strain)	N (Sex/group)	Dose everolimus (mg/kg/bwt/day) Route Duration	Observations
monkey (Cynomolgus)	1 male 1 female	1 /2/4/10/20/40/60 p.o. 4/3/4/3/4/3/3 days	≥ 2 mg/kg: Quietness (f). ≥20 mg/kg: Increased WBC. ≥40 mg/kg: Quietness (m), piloerection and huddled posture (f). 60 mg/kg: Piloerection and huddled posture (m/f); reduced lymphoid activity in thymus, spleen, LN. Histopathological examinations after exposure to escalating dosages from 1 to 60 mg/kg/day revealed changes consistent with the expected pharmacological action of an immunosuppressant.
monkey (Cynomolgus)	4 males 4 females	0, 5, 15, 45 p.o. 2 weeks	NTEL < 5 mg/kg. ≥5 mg/kg: Piloerection, rash on chest; increased fibrinogen (m), activated partial thromboplastin time; decreased lymphoid activity in thymus, spleen and LN; subendocardial/interstitial hemorrhage in heart; reduced cellularity of bone marrow (f). ≥15 mg/kg: Quietness; increased fibrinogen (m/f); subendocardial/interstitial hemorrhage in heart (m). 45 mg/kg: Rough coat, huddled posture (f); body weight loss and reduced food intake; increased glucose and cholesterol (m); decreased phosphorus (m); increased globulins; subendocardial/ interstitial hemorrhage in heart (f); reduced cellularity of bone marrow (f).
monkey (Cynomolgus)	16 males 16 females	0, 1.5, 5, 15 p.o. 4 weeks + 2 weeks recovery	NTEL = 1.5 mg/kg. m: C_{max}: 95 ng/mL; $AUC_{(0\text{-}24H)}$: 975 ng·h/mL; f: C_{max}: 131 ng/mL; $AUC_{(0\text{-}24H)}$: 1196 ng·h/mL ≥1.5 mg/kg: Reduced food intake (f); increased fibrinogen; decreased phosphorus; splenic lymphoid atrophy. ≥5 mg/kg: Increase in skin lesions; reduced food intake (m/f); reduced RBC parameters; increased α2/β globulins, decreased albumin and Alb/Glob ratio (m); thymic medullary atrophy; increased histiocytosis in small intestine (f). 15 mg/kg: Piloerection, reddening of abdomen (m); increased WBC, neutrophils, monocytes; increased alanine and aspartate aminotransferases; increased α2/β globulins and decreased albumin and Alb/Glob ratio (m/f); reduced urine sodium; increased histiocytosis in small intestine (m/f).

Table 10 Long-Term Toxicity Studies - Oral administration in Monkeys (continued)

Species (Strain)	N (Sex/group)	Dose everolimus (mg/kg/bwt/day) Route Duration	Observations
monkey (Cynomolgus)	16 males 16 females	0, 0.1, 0.25, 0.5 p.o. 4 weeks + 2 weeks recovery	NTEL = 0.5 mg/kg. No findings indicating toxicity up to 0.5 mg/kg.
monkey (Cynomolgus)	26 males 26 females	0, 0.1, 0.5, 1.5, 5 p.o. 26 weeks	NTEL = 0.5 mg/kg. m: C_{max}: 68 ng/mL; AUC $_{(0\text{-}24H)}$: 358 ng·h/mL; f: C_{max}: 59 ng/mL; AUC $_{(0\text{-}24H)}$: 466 ng·h/mL ≥0.5 mg/kg: Increased skin lesions (m); reduced body weight gain; splenic lymphoid atrophy; lymphoid depletion in LN; macrophage aggregation in small intestine. ≥1.5 mg/kg: Early sacrifice (2m) in weeks 14/25 due to poor health condition; increased skin lesions (m/f); reduced food intake; reduced RBC parameters; increased neutrophils/monocytes, fibrinogen; decreased phosphorus; increased cholesterol; thymic cortical and medullary atrophy; myocardial degeneration/necrosis (1m); degranulation of pancreatic exocrine cells (m); reduced follicular development and atresia of ovaries. 5 mg/kg: Early termination in weeks 9/10 due to skin lesions, poor health condition, body weight loss; increased α2/β globulins and decreased albumin and Alb/Glob ratio; increased triglycerides, increased mucosal inflammation of large intestine; myocardial degeneration/necrosis (m); degranulation of pancreatic exocrine cells and increased islet cell degeneration; vacuolation of adrenals. Virology: Coxsackievirus in plasma (including pretest) and heart tissue.
monkey (Cynomolgus)	16 males and 16 females	0.1, 0.3, 0.9 p.o. 39/52 weeks	NOAEL = 0.1 mg/kg; m: C_{max}: 8.5 ng/mL; AUC $_{(0\text{-}24H)}$: 98.0 ng·h/mL; f: C_{max}: 10.1 ng/mL; AUC $_{(0\text{-}24H)}$: 59.6 ng·h/mL ≥0.3 mg/kg: Diarrhea/soft feces (m); reduced body weight/food intake (2m); increased neutrophils (f); inflammatory changes in gastointestinal tract; atrophy of testes. 0.9 mg/kg: Termination after 39 weeks; 1m and 2f sacrificed early due to poor health condition consequent to diarrhea/soft feces and inflammation/ ulceration of large intestine; body weight loss and reduced food intake; increased fibrinogen (f).

Table 11 Carcinogenicity Studies

Species (Strain)	N (sex/group)	Doses everolimus (mg/kg/bwt/day) Route Duration Batch No.	Number of Tumors in all animals evaluated (without consideration of causes and relevance)	Observations
mice (CD-1)	792 (60 X 2 controls, 60/dose group)	0, 0.1, 0.3, 0.9 oral gavage (solid dispersion 9.09%) 101 / 104 weeks	adrenal cortex (25), adrenal medulla (3), brain (2), cecum (1), femur (3), harderian gland (66), jejunum (2), kidneys (8), liver (102), lungs (133), mammary area (8), ovaries (13), pancreas (1), pituitary (5), seminal vesicles (2), spleen (1), stomach (2), submandibular Sl. Gland (1), testes (7), thymus (1), thyroids (4), uterine cervix (10), uterus (33), abdomen (1), buccal cavity (2), h'poietic tumor (112), musculoskeletal (7) peritoneum (1), skin (2), thorax (1)	No oncogenic potential up to 0.9 mg/kg. C_{max}: 178 ng/mL; AUC $_{(0\text{-}24H)}$: 2231 ng·h/mL Reduced body weight gain and higher survival at 0.9 mg/kg. Toxicity and pharmacological effects similar to previous toxicity studies.
Rats (Hanlbm Wistar)	712 (60 X 2 controls, 60/dose group)	0.1, 0.3, 0.9 oral gavage 104 weeks Batch No: X081 0596, X011 0397, X176 1297 (solid dispersion 9.1%)	Adrenal cortex (3), adrenal medulla (10), brain (22), colon (1), duodenum (1), eyes (1), jejunum 1), kidneys (2), lymph node - mesenteric (39), liver (10), lungs (4), mammary area (50), ovaries (10), pancreas (11), parathyroids (4), pituitary (224), prostate (1), rectum (1), spleen (3), submand. sl.gland (2), testes (3), thymus (46), thyroids (67), urinary bladder (1), uterine cervix (5), uterus (42), vagina (1), abdomen (2), fallopian tubes (1), h'poietic tumor (4), lymph node - inguinal (1), lymph node - renal (1), musculoskeletal (2), skin (27), ureter (4)	No oncogenic potential up to 0.9 mg/kg. C_{max}: 10.5 ng/mL; AUC $_{(0\text{-}24H)}$: 91 ng·h/mL Reduced body weight gain and higher survival at 0.3 and 0.9 mg/kg. Toxicity and pharmacoogical. effects similar to previous toxicity studies.

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PART III: CONSUMER INFORMATION

PrCERTICAN®
(everolimus)

This leaflet is part III of a three-part "Product Monograph" published when PrCERTICAN® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PrCERTICAN.Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Certican (everolimus) is used to prevent your body from rejecting your transplanted organ. Certican is used together with medicines called cyclosporine (Neoral*****) and corticosteroids to prevent rejection of transplanted kidneys.

What it does:

Certican (everolimus) belongs to a group of medicines known as immunosuppressants. In order to prevent organ rejection, Certican suppresses the activity of white blood cells which act to get rid of the transplanted organ.

When it should not be used:

Do not take Certican if you are hypersensitive (allergic) to everolimus, sirolimus or to any of the other components that make up Certican. (The ingredients contained in each tablet are listed in this leaflet.)

Tell your doctor if you suspect you may have had an allergic reaction to any of these ingredients in the past.

What the medicinal ingredient is:

everolimus

What the important nonmedicinal ingredients are:

butylated hydroxytoluene
crospovidone
hypromellose
lactose anhydrous
lactose monohydrate
magnesium stearate

What dosage forms it comes in:

Certican is available as 0.25 mg, 0.5 mg, 0.75 mg, tablets.

Certican 0.25mg tablets are white to yellowish, marbled, round, flat with bevelled edge, engraved “C” on one side and “NVR” on the other.

Certican 0.5 tablets are white to yellowish, marbled, round, flat with bevelled edge, engraved “CH” on one side and “NVR” on the other.

Certican 0.75 tablets are white to yellowish, marbled, round, flat with bevelled edge, engraved “CL” on one side and “NVR” on the other.

Certican tablets are supplied in packs containing 60 tablets.

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

- **Increased risk of infections and the possible development of cancers such as skin and lymphoid may result from immunosuppression**
- **Only doctors experienced in immunosuppressive therapy and management of organ transplant patients should use Certican. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite fo**r the follow-up of the patient. (see Warnings and Precautions)
- **Increased kidney damage can occur with standard doses of cyclosporine in combination with everolimus. Therefore reduced doses of cyclosporine should be used in combination with everolimus. It is important to monitor the cyclosporine and everolimus drug levels with a blood test to ensure the optimal dose for you is being used.** (see Dosage and Administration, Warnings and Precautions and Clinical Pharmacology)
- **A risk of kidney clots known as thrombosis resulting in graft loss, have been reported mostly within the first 30 days post-transplantation** (see Warnings and Precautions)

Tell your doctor before using Certican if:

- You have problems of galactose intolerance, Lapp lactase deficiency or glucose/galactose malabsorption, as this product contains lactose.
- You are taking any other medicines, including vaccines, as Certican may reduce the effectiveness of vaccines (See Interactions With This Medication).
- You have, or have had any liver problems, as the doctor may modify the Certican dose.

- You are pregnant or **think you are pregnant**. Certican should not be used in pregnancy unless your doctor feels this is necessary. You should use an effective contraceptive before, during and for 8 weeks after Certican treatment.
- You are breastfeeding or **thinking of breastfeeding**. It is not known if Certican passes into human breastmilk. Breastfeeding should be discontinued while taking Certican.
- You are male and want to father children. Certican may reduce sperm production in men which may reduce the ability to have children. Discuss with your doctor.

Tell your doctor immediately if the following develop while taking Certican:

- Swelling of the face, throat or tongue.
- Skin bruising without obvious cause
- Pain, hernia, swelling, oozing or unusual warmth at the site of surgery
- Difficulty in breathing, wheezing, coughing. Your doctor may decide on other of further treatments.
- Fever, malaise, fatigue, burning sensation when urinating, cough as Certican may suppress your immune system and reduce your body's ability to fight infections.

Immunosuppressants such as Certican may increase the risk of developing cancers, particularly of the skin and lymphoid system. Therefore, you should limit your exposure to sunlight and UV light by wearing appropriate protective clothing and frequently applying sunscreen with a high protection factor.

INTERACTIONS WITH THIS MEDICATION

Taking other medicines

Please inform your doctor if you are taking or have recently taken any other medicines, even those you have obtained without a prescription.

Some medicines may interfere with the action of Certican or Certican may interfere with other drugs. In particular, you should inform your doctor if you are taking one of the following medicines:

- Live vaccines
- Immunosuppressive medicines other than cyclosporine microemulsion or corticosteroids.
- Antibiotics or antifungal medicines used to treat infections, e.g. amphotericin B, clarithromycin, telithromycin, ketoconazole, itraconazole, erythromycin, voriconazole, fluconazole
- Medicines used to treat tuberculosis like rifampicin or rifabutin
- *Hypericum perforatum* (St. John's Wort) – a herbal product used to treat depression and other conditions.
- Anti convulsants such as phenytoin, carbamazepine, phenobarbital,
- Calcium channel blockers, such as verapamil, nicardipine, diltiazem, used to treat heart conditions or high blood pressure.
- Protease inhibitors such as nelfinavir, indinavir amprenavir, anti-HIV drugs such as ritonavir, efavirenz, nevirapine used to treat AIDS.
- HMG-CoA reductase inhibitors such as simvastatin, lovastatin as these interfere with cyclosporine used in this combination treatment.
- Midazolam, a medicine used to treat acute seizures, or used as a sedative before or during surgery or other medicinal procedure.
- Octreotide, a medicine used to treat acromegaly, a rare hormonal disorder that usually occurs in middle-aged adults.

Taking Certican with food and drink

Take Certican consistently, either with or without food. Do not take Certican with grapefruit or grapefruit juice since this can interfere with certain enzymes in the body that influence Certican's effects

PROPER USE OF THIS MEDICATION

Your doctor will decide exactly what dose of Certican is best for you. Follow your doctor's instructions and never alter the dose of Certican on your own. Certican is for oral use only.

Usual adult dose:

The daily dose of Certican (everolimus) should be taken orally twice a day consistently either with or without food. The general recommended daily dose is 1.5 mg taken as two separate doses as 0.75 mg in the morning and in the evening, together with cyclosporine (Neoral*****).

You should be advised that any change of cyclosporine (Neoral*****) should be made cautiously and only under physician supervision as it may result in the need for a change in your Certican dosage.

Monitoring during your treatment with Certican

Your doctor will perform blood tests to monitor the everolimus and cyclosporine to ensure the optimal dose for you is being used. Your doctor will also carefully monitor your kidney function, blood lipids, blood sugar as well as the amount of proteins in your urine

The first dose will be given as soon as possible after transplantation.

When and how to take Certican

Swallow the tablets whole with a glass of water. Do not crush Certican tablets before use.

How long to take Certican

Treatment will continue for as long as you need immunosuppression to prevent you from rejecting your transplanted organ.

Overdose:

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional poison control centre, even if there are no symptoms.

Missed Dose:

If you forget to take Certican, take it as soon as you remember, then continue to take it at the usual times. Ask your doctor for advice.

Do not stop taking your medicine unless your doctor tells you to. Stopping your treatment with Certican may increase the chance of rejection of your transplanted organ.

Do not double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, Certican can have side effects. However, since it is taken in combination with other medicines, the side effects cannot always be directly attributed with certainty to Certican itself.

The most common (incidence greater than 30%) adverse events observed in Certican clinical studies are: constipation, nausea, anemia, peripheral edema (e.g. swelling of extremities such as hands or feet), infections and high blood pressure.

Very common side effects:

These side effects may affect between 10 or more in every 100 patients

Infections

upper respiratory tract infection,

diarrhea, nausea, vomiting, abdominal pain,

fever, headache,

insomnia,

high blood pressure,

accumulation of fluid in the tissues (peripheral edema),

anemia,

high cholesterol, lipids and triglycerides,

anxiety,

low levels of white blood cells,

fluid collection in the sac around the heart, which if severe, can decrease the heart's ability to pump blood,

fluid collection on the lungs/chest cavity, which if severe, could make you breathless,

onset of diabetes (high level sugar in the blood),

hernia at the site of surgery,

abnormal healing of the surgical wound

Common side effects:

These side effects may affect between 1 and 10 in every 100 patients

- urinary tract infections
- wound infection
- lower respiratory tract infection
- general pain
- pain in the ear, nose or throat
- fatigue
- tremor
- cough
- acne
- impaired healing of general wounds
- blockage of a blood vessel by a blood clot formed somewhere in the body, defect in blood clotting, low blood platelet count, bleeding and/or bruising underneath the skin, low red blood cell count, reduced numbers of blood cells (symptoms may include weakness, bruising and frequent infections),
- allergic reaction with patchy swelling of the face, lips, mouth, tongue or throat often associated with rash and itching,
- inflammation of the pancreas (symptoms may include severe upper stomach pain, vomiting and loss of appetite),
- mouth sores
- protein in the urine
- impotence.
- ovarian cyst

Uncommon side effects:

These side effects may affect between 1 and 10 in every 1,000 patients

- rash,
- muscle pain,
- destruction of red blood cells,
- inflammation of the lungs (symptoms may include coughing, difficulty breathing and wheezing),
- kidney disorders,
- liver disease with feeling generally unwell, yellowing of the skin, eyes and dark coloured urine,
- decreased functioning of the male gonads.

Rare side effects:

These side effects may affect between 1 and 10 in every 10,000 patients

- abnormal accumulation of protein in the lungs (symptoms may include persistent dry cough, fatigue and difficulty in breathing)
- inflammation of blood vessels.
- There may be side effects that you are not aware of, such as abnormal results of laboratory tests, including tests of kidney function. Your doctor will therefore perform blood tests to monitor any changes. If you notice any side effects not mentioned in this leaflet or are concerned about those listed, please inform your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN **THEY HAPPEN AND WHAT TO DO ABOUT THEM**				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
Very common	High blood levels of lipids / cholesterol		√	
	Low white blood cell count		√	
	Accumulation of fluid in some organs		√	
	high blood pressure		√	
	Anemia		√	
Common	diarrhea, nausea, vomiting		√	
	abdominal/general pain (can be a sign of ovarian cyst)		√	
	accumulation of fluid in tissues, cysts, acne, mouth sores, allergic reactions		√	
	Increased risk of infection, abnormal healing of surgical wounds		√	
	blood clots, clotting defects, low blood platelet /red blood cell count, bleeding and/or bruising underneath the skin		√	
	inflammation of the pancreas (symptoms may include severe upper stomach pain, vomiting and loss of appetite)		√	
	onset of diabetes (high level sugar in the blood)		√	
	protein in the urine		√	
	impotence		√	

This is not a complete list of side effects. For any unexpected effects while taking Certican, contact your doctor or pharmacist.

HOW TO STORE IT

- Store Certican between 15-30°C (59-86°F) in the original package in order to protect from light and moisture.
- Do not use Certican after the expiry date stated on the box.
- Do not use any Certican pack that is damaged or shows signs of tampering.
- Keep Certican out of the reach and sight of children.
- Any unused product or waste material should be disposed of in accordance with local requirements.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 1908C
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.novartis.ca or by contacting the sponsor, Novartis Pharmaceuticals Canada Inc. at: 1-800-363-8883

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