NOVARTIS

Drug Regulatory Affairs

CERTICAN® (everolimus)

0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg tablets

Basic Prescribing Information

Notice

The Basic Prescribing Information is the Novartis Core Data Sheet. It displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

National Prescribing Information is based on this BPI. However, because regulatory requirements and medical practices vary between countries, National Prescribing Information (incl. US Prescribing Information or European SPCs) may differ in several respects, including but not limited to characterisation of risk and benefits.

Author(s): Dr. Mireille Collombat, Dr. Nicola Barbara Mertens, Sheila Richards, Dr. Dania Al-Midani, Stéphanie Cébe

GLC approval: 25 March 2004, amended 11 October 2005, 22 May 2007, 27 November 2007 and 16-Mar-2010

Release date: 22-Mar-2010

Tracking number: 2010-PSB/GLC-0257-s

Document status: Final

Number of pages:

1 Name of the medicinal product

0.25 mg tablets

CERTICAN® 0.25 mg tablets

0.5 mg tablets

CERTICAN® 0.5 mg tablets

0.75 mg tablets

CERTICAN® 0.75 mg tablets

1.0 mg tablets

CERTICAN® 1.0 mg tablets

2 Qualitative and quantitative composition

The active substance is everolimus.

0.25 mg tablets

Each tablet contains 0.25 mg everolimus.

0.5 mg tablets

Each tablet contains 0.5 mg everolimus.

0.75 mg tablets

Each tablet contains 0.75 mg everolimus.

1.0 mg tablets

Each tablet contains 1.0 mg everolimus.

For a full list of excipients, see section 6.1 List of excipients.

3 Pharmaceutical form

The tablets are white to yellowish, marbled, round, flat with a bevelled edge.

0.25 mg: engraved with “C” on one side and “NVR” on the other.

0.5 mg: engraved with “CH” on one side and “NVR” on the other.

0.75 mg: engraved with “CL” on one side and “NVR” on the other.

1.0 mg: engraved with “CU” on one side and “NVR” on the other.

4 Clinical particulars

4.1 Therapeutic indications

Certican® is indicated for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving an allogeneic renal or cardiac transplant. Certican should be used in combination with ciclosporin for microemulsion and corticosteroids.

4.2 Posology and method of administration

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.

Adults

An initial dose regimen of 0.75 mg b.i.d., which is recommended for the general kidney and heart transplant population, should be administered as soon as possible after transplantation. The daily dose of Certican should always be given orally in two divided doses (b.i.d.). Certican should be consistently given either with or without food (see section 5.2 Pharmacokinetic properties) and at the same time as ciclosporin for microemulsion (see Therapeutic drug monitoring).

Certican is for oral use only.

Certican tablets should be swallowed whole with a glass of water and not crushed before use. For patients unable to swallow whole tablets, Certican dispersible tablets are also available (see Certican dispersible tablets Basic Prescribing Information).

Patients receiving Certican may require dose adjustments based on blood levels achieved, tolerability, individual response, change in co-medications and the clinical situation. Dose adjustments can be made at 4-5 days intervals (see Therapeutic drug monitoring) [48].

Black patients

The incidence of biopsy-proven acute rejection episodes was significantly higher in black patients than in non-black patients [6]. Limited information indicates that black patients, may require a higher Certican dose to achieve efficacy similar to that achieved in non-black patients at the recommended adult dose (see section 5.2 Pharmacokinetic properties) [6,7]. Currently the efficacy and safety data are too limited to allow specific recommendations for use of everolimus in Black patients.

Use in children and adolescents

There are no adequate data of the use of Certican in children and adolescents to support its use in patients in these age groups. Limited information is, however, available in renal transplant paediatric patients [8,9] (see section 5.2 Pharmacokinetic properties).

Elderly patients (≥ 65 years)

Clinical experience is limited in patients ≥ 65 years of age. Nevertheless, there are no apparent differences in the pharmacokinetics of everolimus in patients ≥ 65-70 years of age as compared with younger adults (see section 5.2 Pharmacokinetic properties) [6,7].

Patients with renal impairment

No dosage adjustment is required (see section 5.2 Pharmacokinetic properties) [10,11].

Patients with impaired hepatic function

Whole blood trough levels (C0) of everolimus should be closely monitored in patients with impaired hepatic function. For patients with mild or moderate hepatic impairment (Child-Pugh Class A or B), the dose should be reduced to approximately one-half of the normal dose if two of the following conditions apply: bilirubin > 34 micro mol/L (> 2 mg/dL), albumin < 35 g/L (< 3.5 g/dL), INR > 1.3 (prothrombin time> 4 sec prolongation). Further dose titration should be based on therapeutic drug monitoring (see section 5.2 Pharmacokinetic properties). Everolimus has not been evaluated in patients with severe hepatic impairment (Child-Pugh Class C, see section 4.4 Special warnings and precautions for use) [12].

Therapeutic Drug Monitoring

Routine whole blood, therapeutic drug level monitoring of everolimus is recommended. 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 both renal and heart transplantation than patients whose trough levels (C0) are below 3.0 ng/mL [6,7,13]. The recommended upper limit of the therapeutic range is 8 ng/mL. Exposure above 12 ng/mL has not been studied. These recommended ranges for everolimus are based on chromatographic methods [2-5,49,58].

It is especially important to monitor everolimus blood concentrations, in patients with hepatic impairment, during concomitant administration of strong CYP3A4 inducers and inhibitors, when switching formulation and/or if ciclosporin dosing is markedly reduced (see section 4.5 Interactions with other medicinal products and other forms of interactions). Everolimus concentrations might be slightly lower following the dispersible tablet administration [1].

Ideally, dose adjustments of Certican should be based on trough levels (C0) obtained > 4-5 days after the previous dose change. Since ciclosporin interacts with everolimus, everolimus levels may decrease if ciclosporin exposure is markedly reduced (i.e. trough concentration (C0) < 50 ng/mL) [51].

Ciclosporin dose recommendation in renal transplantation [49,50,64]

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

Renal transplantation: recommended target ciclosporin blood trough-level windows

Target ciclosporin C_0 (ng/mL)	Month 1	Months 2-3	Months 4-5	Months 6-12
Certican groups	100-200	75-150	50-100	25-50

(Measured levels are shown in section 5.1 Pharmacodynamic properties.).

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

There are limited data regarding dosing Certican with ciclosporin trough concentrations (C0) below 50 ng/mL, or C2 levels below 350 ng/mL, in the maintenance phase. If the patient cannot tolerate reduction of ciclosporin exposure, the continued use of Certican should be reconsidered [51].

Ciclosporin dose recommendation in cardiac transplantation [13,52,63]

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

Cardiac transplantation: recommended target ciclosporin blood trough-level windows

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

(Measured levels are shown in section 5.1 Pharmacodynamic properties).

Prior to dose reduction of ciclosporin it should be ascertained that steady state everolimus whole blood trough concentrations (C0) are equal to or above 3 ng/mL [2-5].

In cardiac transplantation, there are limited data regarding dosing Certican with reduced ciclosporin trough concentrations (C0) of 50-100 ng/mL after 12 months. If the patient cannot tolerate reduction of ciclosporin exposure, the continued use of Certican should be reconsidered.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Management of immunosuppression

In clinical trials [6,7,13], Certican has been administered concurrently with ciclosporin for microemulsion, basiliximab and corticosteroids. Certican in combination with immunosuppressive agents other than these has not been adequately investigated.

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

Severe liver function impairment

Everolimus 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 [12].

Interaction with strong inhibitors, inducers of CYP3A4

Co-administration with strong CYP3A4-inhibitors (e.g. ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir) and inducers (e.g. rifampicin, rifabutin) is not recommended unless the benefit outweighs the risk.

Monitoring of whole blood trough levels (C0) of everolimus is recommended whenever inducers or inhibitors of CYP3A4 are co-administered or discontinued (see section 4.5 Interactions with other medicinal products and other forms of interactions).

Lymphomas and other malignancies

Patients on a regimen of immunosuppressive medicinal products, including Certican, are at increased risk of developing lymphomas or other malignancies, particularly of the skin (see section 4.8 Undesirable effects). The absolute risk seems related to the duration and intensity of immunosuppression rather than to the use of a specific medicinal product. Patients should be monitored regularly for skin neoplasms and advised to minimise exposure to UV light sunlight, and to use an appropriate sunscreen.

Serious and opportunistic infections

Patients on a regimen of immunosuppressive medicinal products, including Certican, are at increased risk of developing infections especially infections with opportunistic pathogens pathogens (bacterial, fungal, viral, protozoal). Fatal infections and sepsis have been reported in patients treated with Certican (see section 4.8 Undesirable effects). Among opportunistic conditions to which immunosuppressed patients may be vulnerable are polyomavirus infections which include BK virus-associated nephropathy which can lead to kidney graft loss and the potentially fatal JC virus-associated progressive multiple leukoencephalopathy (PML). These infections, often related to total immunosuppressive burden, should be considered in the differential diagnosis of immunosuppressed patients with deteriorating kidney graft function or neurological symptoms [64].

In clinical trials with Certican, antimicrobial prophylaxis for Pneumocystis jiroveci (carinii) pneumonia was administered for the first 12 months following transplantation. Cytomegalovirus (CMV) prophylaxis was recommended for 3 months after transplantation, particularly for patients at increased risk for CMV disease [6,7,13].

Hyperlipidemia

In transplant patients, concomitant use of Certican and ciclosporin for microemulsion has been associated with an increase in serum cholesterol and triglycerides that may require treatment [6,7,13]. Patients receiving Certican should be monitored for hyperlipidaemia and, if necessary, treated with lipid-lowering medicinal products and appropriate dietary

adjustments made (see section 4.5 Interactions with other medicinal products and other forms of interactions). The risk/benefit should be considered in patients with established hyperlipidaemia before initiating an immunosuppressive regimen including Certican. Similarly the risk/benefit of continued Certican therapy should be re-evaluated in patients with severe refractory hyperlipidaemia.

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 Prescribing Information of these medicinal products (see section 4.5 Interaction with other medicinal products and other forms of interaction) [64].

Angioedema

Certican has been associated with the development of angioedema. In the majority of cases reported patients were receiving ACE inhibitors as co-medication [64].

Nephrotoxicity

Certican with full-dose ciclosporin increases the risk of renal dysfunction. Reduced doses of ciclosporin are required for use in combination with Certican in order to avoid renal dysfunction. Regular monitoring of renal function is recommended in all patients. Appropriate adjustment of the immunosuppressive regimen, in particular reduction of the ciclosporin 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.

Proteinuria

The use of Certican with ciclosporin in *de-novo* renal transplant recipients has been associated with increased proteinuria. The risk increases with higher everolimus blood levels.

In renal transplant patients with mild proteinuria while on maintenance immunosuppressive therapy including a calcineurin inhibitor (CNI) there have been reports of worsening proteinuria when the CNI is replaced by Certican. Reversibility has been observed with interruption of Certican and reintroduction of the CNI. The safety and efficacy of conversion from CNI to Certican in such patients have not been established.

Patients receiving Certican should be monitored for proteinuria [64].

Renal graft thrombosis

An increased risk of kidney arterial and venous thrombosis, resulting in graft loss, has been reported, mostly within the first 30 days post-transplantation [64].

Wound-healing complications

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

mass index. The frequency of pericardial and pleural effusion is increased in cardiac transplant recipients [64].

Thrombotic microangiopathy/Thrombotic thrombocytopenic purpura/ Haemolytic uraemic syndrome

The concomitant administration of Certican with a calcineurin inhibitor (CNI) may increase the risk of CNI-induced haemolytic uraemic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy [64].

Interstitial lung disease/non-infectious pneumonitis

A diagnosis of interstitial lung disease (ILD) should be considered in patients presenting with symptoms consistent with infectious pneumonia but not responding to antibiotic therapy and in whom infectious, neoplastic and other non-drug causes have been discounted through appropriate investigations. Cases of ILD have been reported with Certican which resolve on drug interruption with or without glucocorticoid therapy (see section 4.8 Undesirable effects) [61].

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 [64].

Male infertility

There are literature reports of reversible azoospermia and oligospermia in patients treated with mTOR inhibitors. Preclinical toxicology studies having shown that everolimus can reduce spermatogenesis, male infertility must be considered a potential risk of prolonged Certican therapy [64].

Risk of intolerance to excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

Everolimus is mainly metabolised in the liver and, to some extent, in the intestinal wall by CYP3A4. It is also a substrate for the multidrug efflux pump, P-glycoprotein (PgP). Therefore, absorption and subsequent elimination of systemically absorbed everolimus may be influenced by medicinal products that affect CYP3A4 and/or PgP. Concurrent treatment with strong CYP3A4-inhibitors and/or inducers is not recommended. Inhibitors of PgP may decrease the efflux of everolimus from intestinal cells and increase everolimus blood concentration. *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 having a narrow therapeutic index. All *in vivo* interaction studies were conducted without concomitant use of ciclosporin [15].

Ciclosporin (CYP3A4/PgP inhibitor)

The bioavailability of everolimus was significantly increased by co-administration of ciclosporin. In a single-dose study in healthy subjects, ciclosporin for microemulsion (Neoral) increased the AUC of everolimus by 168% (range, 46% to 365%), and Cmax by 82% (range, 25% to 158%), as compared with everolimus alone [16]. Dose adjustment of everolimus may be needed if the ciclosporin dose is altered (see section 4.2 Posology and method of administration). Certican had only a minor clinical influence on ciclosporin pharmacokinetics in renal and heart transplant patients receiving ciclosporin for microemulsion [6,7,13].

Rifampicin (CYP3A4 inducer)

Pre-treatment of healthy subjects with multiple-doses of rifampicin followed by a single dose of Certican increased everolimus clearance nearly 3-fold, decreasing Cmax by 58% and AUC by 63% [17]. Combination with rifampicin is not recommended (see section 4.4 Special warnings and precautions for use).

Atorvastatin (CYP3A4-substrate) and pravastatin (PgP-substrate)

Single-dose administration of Certican with either atorvastatin or pravastatin to healthy subjects did not influence the pharmacokinetics of atorvastatin, pravastatin and everolimus, as well as total HMG-CoA reductase bioreactivity in plasma to a clinically relevant extent [18]. 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 Prescribing Information of HMG-CoA reductase inhibitors.

Other possible interactions

Moderate inhibitors of CYP3A4 and PgP may increase everolimus blood levels (e.g. **antifungal substances:** fluconazole, **macrolide antibiotics:** erythromycin, **calcium channel blockers:** verapamil, nicardipin, diltiazem; **protease inhibitors**: nelfinavir, indinavir, amprenavir [55]. Inducers of CYP3A4 may increase the metabolism of everolimus and decrease everolimus blood levels (e.g. St. John's wort (*Hypericum perforatum*, **anticonvulsants:** carbamazepine, phenobarbital, phenytoin, **anti HIV drugs:** efavirenz, nevirapine) [53].

Grapefruit and grapefruit juice affect cytochrome P450 and PgP activity and should therefore be avoided.

Vaccination

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

4.6 Use during pregnancy and lactation

Pregnancy

There are no adequate data from the use of Certican in pregnant women. Studies in animals have shown reproductive toxicity effects including embryotoxicity and fetotoxicity (see section 5.3 Preclinical safety data). The potential risk to humans is unknown. Certican should not be given to pregnant women unless the potential benefit outweighs the potential risk to the fetus. Women of childbearing potential should be advised to use effective contraception methods while they are receiving Certican, and for up to 8 weeks after ending treatment.

Lactation

It is not known whether everolimus is excreted in breast milk, but in animal studies, everolimus and/or its metabolites readily passed into the milk of lactating rats. Women taking Certican should therefore not breast feed.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The frequencies of adverse reactions listed below represent those observed in patients being treated with a regimen of Certican combined with ciclosporin and corticosteroids in multi-centre, randomised, controlled studies. These include five studies in *de-novo* renal transplant recipients totalising 2497 patients, and two studies in *de-novo* heart transplant recipients totalising 810 patients (see section 5.1 Pharmacodynamic properties) [6,7,13,49,50,59,63,64].

Table 1 contains adverse drug reactions possibly or probably related to Certican seen in phase III clinical trials (renal and heart transplantation). Unless noted as otherwise, these disorders have been identified by an increased incidence in the phase III studies comparing patients on a Certican + ciclosporin regimen with patients on a non-Certican, ciclosporin-based regimen (see section 5.1 Pharmacodynamic properties). It is compiled according to MedDRA standard organ classes:

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

Table 1 Adverse drug reactions possibly or probably related to Certican

Infections and infestations	
Common:	Viral, bacterial and fungal infections, pneumonia, sepsis, urinary tract infection.
Uncommon:	Wound infection.

Blood and lymphatic system disorders	
Very common:	Leucopenia[1].
Common:	Thrombocytopenia[1], anaemia[1], coagulopathy, thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome.
Uncommon:	Haemolysis, pancytopenia[6] [64].
Cardiac disorder	
Very common:	Pericardial effusion[2] [63]
Endocrine disorders	
Uncommon:	Male hypogonadism (decreased testosterone, increased FSH and LH).
Metabolism and nutrition disorders	
Very common:	Hypercholesterolaemia, hyperlipidaemia.
Common:	Hypertriglyceridaemia, new onset diabetes mellitus [64].
Vascular disorders	
Common:	Hypertension, lymphocele[3], venous thromboembolism, raft thrombosis[3] [64].
Rare:	Leukocytoclastic vasculitis[6] [64]
Respiratory, thoracic and mediastinal disorders	
Very common:	Pleural effusion[2] [63]
Uncommon:	Interstitial lung disease [61].
Rare:	Pulmonary alveolar proteinosis [61].
Gastrointestinal disorders	
Common:	Abdominal pain, diarrhoea, nausea, pancreatitis [61], vomiting, stomatitis/mouth ulceration [64].
Hepato-biliary disorders	
Uncommon:	Hepatitis, hepatic disorders, jaundice, liver function test abnormal[4].
Skin and subcutaneous tissue disorders	
Common:	Angioneurotic oedema[5] [60], acne, surgical wound complication.
Uncommon:	Rash.
Musculoskeletal and connective tissue disorders	
Uncommon:	Myalgia.
Renal and urinary disorders	
Common:	Proteinuria[3] [64].
Uncommon:	Renal tubular necrosis[3] , pyelonephritis.
Reproductive system and breast disorders	
Common	Erectile dysfunction [64]
General disorders and administration site conditions	
Common:	Oedema, pain, impaired healing [64].

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

[2]In cardiac transplantation

[3] In renal transplantation

[4] γ-GT, AST, ALT elevated

[5]Predominantly in patients receiving concomitant ACE inhibitors

[6] Post-marketing finding

In controlled clinical trials in which a total of 2335 patients receiving Certican (1.5 mg or 3.0 mg/day) in combination with other immunosuppressants were monitored for at least

1 year, a total of 2.6% developed malignancies, with 1.0% developing skin malignancies and 0.43% developing lymphoma or lymphoproliferative disease.

The occurrence of the adverse events may depend on the degree and duration of the immunosuppressive regimen. In the pivotal studies, elevated serum creatinine was observed more frequently in patients given Certican in combination with full dose ciclosporin for microemulsion than in control patients. The overall incidence of adverse events was lower with reduced dose ciclosporin for microemulsion (see section 5.1 Pharmacodynamic properties – clinical studies) [14,49,50].

The safety profile of Certican in the trials in which it was administered with reduced-dose ciclosporin was similar to that described in the 3 pivotal studies in which full dose of ciclosporin was administered, except that elevation of serum creatinine was less frequent, and mean and median serum creatinine values were lower, than in the other phase III studies. A lower rate of viral infections, primarily due to CMV and BK virus, has been shown with the currently-recommended Certican-based immunosupressive regimen in renal transplant recipients (see section 5.1 Pharmacodynamic properties-clinical studies) [64].

Cases of interstitial lung disease, implying lung intraparenchymal inflammation (pneumonitis) and/or fibrosis of non-infectious etiology, some fatal, have occurred in patients receiving rapamycins and their derivatives, including Certican. Mostly, the condition resolves after discontinuation of Certican and/or addition of glucocorticoids [61].

4.9 Overdose

In animal studies, everolimus showed a low acute toxic potential. No lethality or severe toxicity were observed in either mice or rats given single oral doses of 2000 mg/kg (limit test) [19,20].

Reported experience with overdose in humans is very limited. There was a single case of accidental ingestion of 1.5 mg everolimus by a 2-year old child, but no adverse events were observed. Single doses of up to 25 mg have been administered to transplant patients with acceptable acute tolerability.

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

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: selective immunosuppressive agents. ATC code: L04A A18

Everolimus, a proliferation signal inhibitor, prevents allograft rejection in rodent and non-human primate models of allotransplantation [21,22,30-33]. It exerts its immunosuppressive effect by inhibiting the antigen-activated T-cell proliferation, and thus clonal expansion, driven by T-cell-specific interleukins, e.g. interleukin-2 and interleukin-15 [23]. Everolimus inhibits an intracellular signalling pathway that normally leads to cell proliferation when triggered by the binding of these T-cell growth factors to their receptors. The blockage of this signal by everolimus causes cells to be arrested at the G_1 stage of the cell cycle.

At the molecular level, everolimus forms a complex with the cytoplasmic protein FKBP-12 [27]. In the presence of everolimus the growth factor-stimulated phosphorylation of the p70 S6 kinase is inhibited [28]. Since p70 S6 kinase phosphorylation is under the control of FRAP (also called m-TOR) [34], this finding suggests that the everolimus-FKBP-12 complex binds to and thus interferes with the function of FRAP. FRAP is a key regulatory protein which governs cell metabolism, growth and proliferation [35]; disabling FRAP function thus explains the cell cycle arrest caused by everolimus.

Everolimus thus has a different mode of action than ciclosporin. In preclinical models of allotransplantation, the combination of everolimus and ciclosporin was more effective than either compound alone [21,24].

The effect of everolimus is not restricted to T cells. Everolimus generally inhibits growth-factor-stimulated proliferation of haematopoietic cells and non-haematopoietic cells such as vascular smooth muscle cells [25]. Growth-factor-stimulated proliferation of vascular smooth muscle cells, triggered by injury to endothelial cells and leading to neointima formation, plays a key role in the pathogenesis of chronic rejection [26]. Preclinical studies with everolimus have shown inhibition of neointima formation in a rat aorta allotransplantation model.

Clinical studies

Kidney transplantation

Certican in fixed doses of 1.5 mg/day and 3 mg/day, in combination with standard doses of ciclosporin for microemulsion and corticosteroids was investigated in two phase III *de novo* renal transplant trials (B201 [6,54] and B251 [7,55]). Mycofenolate mofetil (MMF) 1 g b.i.d. was used as comparator. The co-primary composite endpoints were efficacy failure (biopsy-proven acute rejection, graft loss, death or loss to follow-up) at 6 months and graft loss, death or loss to follow-up at 12 months. Certican was, overall, non-inferior to MMF in these trials. 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 incidence for the Certican 1.5 mg/day, Certican 3 mg/day and MMF groups was 17.1%, 20.1%, and 23.5%, respectively.

Reduced allograft function with elevated serum creatinine was observed more frequently among subjects using Certican in combination with full dose ciclosporin for microemulsion than in MMF patients. This effect suggests that Certican increases ciclosporin nephrotoxicity. Drug concentration-pharmacodynamic analysis showed that renal function could be improved with reduced exposure to ciclosporin while conserving efficacy for as long as blood trough everolimus concentration was maintained above 3ng/mL. This concept was subsequently confirmed in

two further Phase III studies (A2306 and A2307, including 237 and 256 patients respectively) [49,50] 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 ciclosporin. In both studies, renal function was improved without compromising efficacy. In these studies however there was no non-Certican comparative arm.

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

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

Although the higher dosage Certican regimen was as effective as the lower-dosage regimen, the overall safety was worse and so the upper-dosage regimen is not recommended

The lower dosage regimen for Certican is that recommended (see section 4.2 Posology and method of administration).

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

Target ciclosporin C_0 (ng/mL)	**Mo 1**	**Mo 2-3**	**Mo 4-5**	**Mo 6-12**
Certican groups	100-200	75-150	50-100	25-50
MPA group	200-300	100-250	100-250	100-250

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

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

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

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

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

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

mo = months, 1^0 = primary, 2^0 = secondary, CI = confidence interval, non-inferiority margin was 10%
Composite endpoint: treated biopsy proven acute rejection (BPAR), graft loss, death, or loss to follow-up (FU)

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

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

Adverse events reported more frequently in the recommended (lower-dosage) Certican regimen than in the MPA control group have been included above (Table 1). A lower frequency for viral infection was reported for Certican-treated patients resulting principally from lower reporting rates for CMV infection (0.7% versus 5.95%) and BK virus infection (1.5% versus 4.8%).

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

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

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

MDRD: modification of diet in renal disease

Table 6 Study A2309: Urinary protein to creatinine ratio

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

1 mg/mmol = 8.84 mg/g

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

Heart transplantation [56,63]

In the phase III heart study (B253) [13], Certican 1.5 mg/day and 3 mg/day, in combination with standard doses of ciclosporin for microemulsion and corticosteroids, were both compared with azathioprine (AZA) 1-3 mg/kg/day. The primary endpoint was a composite of the incidence of the following acute rejection ≥ ISHLT grade 3A, acute rejection associated with haemodynamic compromise, graft loss, patient death or loss to follow-up at 6, 12 and 24 months. The incidence of biopsy proven acute rejection ≥ ISHLT grade 3A at month 6 was 27.8% for the 1.5 mg/day group, 19% for the 3 mg/day group and 41.6% for the AZA group respectively ($p = 0.003$ for 1.5 mg vs control, < 0.001 for 3 mg vs control).

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

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

Study A2411 was a randomized, 12 month, open-label study comparing Certican in combination with reduced doses of ciclosporin microemulsion and corticosteroids to mycophenolic mofetil (MMF) and standard doses of ciclosporin microemulsion and corticosteroids in de-novo cardiac transplant patients. Certican was initiated at 1.5 mg/day and the dose was adjusted to maintain target blood everolimus trough levels between 3-8 ng/mL. MMF dosage was initiated at 1,500 mg bid. Ciclosporin microemulsion doses were adjusted to target the following trough levels (ng/mL):

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

Actual blood levels measured are shown in table 7.

Table 7

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

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

*:whole blood trough levels (C0)

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

Table 8

A2411: Changes in creatinine clearance during study (patients with paired values)				
		Estimated Creatinine Clearance (Cockroft-Gault)* mL/mn		
		Baseline Mean (± SD)	**Value at timepoint Mean (± SD)**	**Difference between groups Mean (95% CI)**
Month 1	Certican (n=87) MMF (n=78)	73.8 (± 27.8) 77.4 (± 32.6)	68.5 (± 31.5) 79.4 (± 36.0)	-7.3 (-18.1, 3.4)
Month 6	Certican (n=83) MMF (n=72)	74.4 (± 28.2) 76.0 (± 31.8)	65.4 (± 24.7) 72.4 (± 26.4)	-5.0 (-13.6, 2.9)
Month 12	Certican (n=71) MMF (n=71)	74.8 (± 28.3) 76.2 (± 32.1)	68.7 (± 27.7) 71.9 (± 30.0)	-1.8 (-11.2, 7.5)

* includes patients with value at both baseline and visit

Table 9

A2411: Efficacy event rates (incidence in ITT population)			
Efficacy endpoint	**Certican n=92**	**MMF n=84**	**Difference in event rates Mean (95% CI)**
At 6 months			
Biopsy-proven acute rejection ≥ ISHLT grade 3A	18 (19.6%)	23 (27.4%)	-7.8 (-20.3, 4.7)
Composite efficacy failure *	26 (28.3%)	31 (36.9%)	-8.6 (-22.5, 5.2)
At 12 months			
Biopsy-proven acute rejection ≥ ISHLT grade 3A	21 (22.8%)	25 (29.8%)	-6.9 (-19.9, 6.1)
Composite efficacy failure*	30 (32.6%)	35 (41.7%)	-9.1 (-23.3, 5.2)
Death or graft loss/retransplant	10 (10.9%)	10 (11.9%)	-

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

5.2 Pharmacokinetic properties

Absorption

Peak everolimus concentrations are reached 1 to 2 hours after administration of an oral dose. Everolimus blood concentrations in transplant patients are dose-proportional-over the dose range of 0.25 to 15 mg [37]. The relative bioavailability of the dispersible tablet compared with the conventional tablet is 0.90 (90% CI 0.76-1.07) based on the AUC-ratio [1]. **Food effect:** the Cmax and AUC of everolimus are reduced by 60% and 16%, respectively, when the tablet formulation is given with a high-fat meal [38]. To minimize variability, Certican should either be consistently taken with food, or consistently taken without it.

Distribution

The blood-to-plasma ratio of everolimus, which is concentration-dependent over the range of 5 to 5000 ng/mL, is 17% to 73%. Plasma protein binding is approximately 74% in healthy subjects and patients with moderate hepatic impairment [12]. The distribution volume associated with the terminal phase (Vz/F) in maintenance renal transplant patients is 342 ± 107 L [37].

Metabolism

Everolimus is a substrate of CYP3A4 and P-glycoprotein. The main metabolic pathways identified in man were mono-hydroxylations and O-dealkylations. Two main metabolites were formed by hydrolysis of the cyclic lactone. Everolimus was the main circulating component in the blood. None of the main metabolites are likely to contribute significantly to the immunosuppressive activity of everolimus [10].

Excretion

After a single dose of radiolabelled everolimus in transplant patients receiving ciclosporin, most of the radioactivity (80%) was recovered from the faeces, and only a minor amount (5%) was excreted in urine [10]. Parent drug was not detected in the urine or faeces.

Steady-state pharmacokinetics

The pharmacokinetics were comparable in kidney and heart transplant patients receiving everolimus twice daily with ciclosporin for microemulsion. Steady state is reached by day 4, with a 2 to 3-fold accumulation in blood levels as compared with exposure after the first dose. T_{max} occurs at 1 to 2 h postdose. At 0.75 and 1.5 mg b.i.d., C_{max} averages 11.1 ± 4.6 and 20.3 ± 8.0 ng/mL, respectively, and AUC averages 75 ± 31 and 131 ± 59 ng•h/mL, respectively. At 0.75 and 1.5 mg b.i.d., predose trough blood levels (C_{min}) average 4.1 ± 2.1 and 7.1 ± 4.6 ng/mL, respectively. Everolimus exposure remains stable over time in the first post-transplant year. C_{min} is significantly correlated with AUC, yielding a correlation coefficient between 0.86 and 0.94. Based on analysis of population pharmacokinetics 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) [6-8]. Residual variability in blood concentrations is 31%. The elimination half-life is 28 ± 7 h.

Hepatic impairment

The average AUC of everolimus in 8 patients with moderate hepatic impairment (Child-Pugh Class B) was twice as high as that found in 8 healthy subjects. AUC was positively correlated with serum bilirubin concentration and with prolongation of prothrombin time and negatively correlated with serum albumin concentration. The AUC of everolimus tended to be greater than that in healthy subjects if bilirubin was > 34 micro mol/L, INR was > 1.3 (prothrombin time > 4 sec prolongation) and/or albumin concentration was < 35 g/L. The impact of severe hepatic impairment (Child-Pugh Class C) has not been assessed but the effect on the AUC of everolimus is likely to be as large as, or larger than, the effect of moderate impairment (see section 4.2 Posology and method of administration) [12].

Renal impairment

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

Paediatrics

Everolimus CL/F increased in a linear manner with patient age (1 to 16 years), body surface area (0.49-1.92 m^2), and weight (11-77 kg). Steady-state CL/F was 10.2 ± 3.0 L/h/m^2 and elimination half-life was 30 ± 11 h [8]. Nineteen paediatric *de novo* renal transplant patients (1 to 16 years) received Certican dispersible tablets at a dose of 0.8 mg/m^2 (maximum 1.5 mg) twice daily with ciclosporin for microemulsion. They achieved an everolimus AUC of 87 ± 27 ng•h/mL which is similar to adults receiving 0.75 mg twice daily. Steady-state trough levels (C0) were 4.4 ± 1.7 ng/mL [9].

Elderly

A limited reduction in everolimus oral CL of 0.33% per year was estimated in adults (age range studied was 16-70 years [6,7]. No dose adjustment is considered necessary.

Ethnicity

Based on analysis of population pharmacokinetics, oral clearance (CL/F) is, on average, 20% higher in Black transplant patients (see section 4.2 Posology and method of administration) [6,7].

Exposure-response relationships

The average everolimus trough concentration (C0) over the first 6 months posttransplant was related to the incidence of biopsy-confirmed acute rejection and of thrombocytopenia in kidney and heart transplant patients (see Table 10) [6].

Table 10

Kidney transplantation					
Trough level (C0) (ng/mL)	≤ 3.4	3.5-4.5	4.6-5.7	5.8-7.7	7.8-15.0
Freedom from rejection	68%	81%	86%	81%	91%
Thrombocytopenia (< 100 x 10^9/L)	10%	9%	7%	14%	17%
Heart transplantation					
Trough level (C0) (ng/mL	≤ 3.5	3.6-5.3	5.4-7.3	7.4-10.2	10.3-21.8
Freedom from rejection	65%	69%	80%	85%	85%
Thrombocytopenia (< 75 x 10^9/L)	5%	5%	6%	8%	9%

5.3 Preclinical safety data

The preclinical safety profile of everolimus was assessed in mice, rats, minipigs, monkeys and rabbits. The major target organs were male and female reproductive systems (testicular tubular degeneration, reduced sperm content in epididymides and uterine atrophy) in several species, and, only in rats, lungs (increased alveolar macrophages) and eyes (lenticular anterior suture line opacities). Minor kidney changes were seen in the rat (exacerbation of age-related lipofuscin in tubular epithelium) and the mouse exacerbation of background lesions). There was no indication of kidney toxicity in monkeys or minipigs [57].

Everolimus appeared to exacerbate spontaneously background diseases (chronic myocarditis in rats, coxsackie virus infection of plasma and heart in monkeys, coccidian infestation of GI tract in minipigs, skin lesions in mice and monkeys). These findings were generally observed at systemic exposure levels within the range of therapeutic exposure or above, with the exception of findings in rats, which occurred below therapeutic exposure due to a high tissue distribution [57].

Ciclosporin in combination with everolimus caused higher systemic exposure to everolimus and increased toxicity [39-42]. There were no new target organs in the rat. Monkeys showed haemorrhage and arteritis in several organs.

In a male fertility study in rats [43], testicular morphology was affected at 0.5 mg/kg and above, and sperm motility, sperm head count and plasma testosterone levels were diminished at 5 mg/kg which is within the range of therapeutic exposure and caused a decrease in male fertility. There was evidence of reversibility. Female fertility was not affected, but everolimus crossed the placenta and was toxic to the conceptus [44,45]. In rats, everolimus caused embryo/fetotoxicity, at systemic exposure below the therapeutic one, that was manifested as mortality and reduced fetal weight. The incidence of skeletal variations and malformations at 0.3 and 0.9 mg/kg (e.g. sternal cleft) was increased. In rabbits, embryotoxicity was evident by an increase in late resorptions [46].

Genotoxicity studies covering relevant genotoxicity end-points showed no evidence of clastogenic or mutagenic activity [47]. Administration of everolimus for up to 2 years did not indicate any oncogenic potential in mice and rats up to the highest doses corresponding respectively to 8.6 and 0.3 times the estimated clinical exposure.

6 Pharmaceutical particulars

6.1 List of excipients

Certican Tablets

Butylated hydroxytoluene (E321), magnesium stearate, lactose monohydrate, hypromellose, crospovidone, lactose anhydrous.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months [62].

6.4 Special precautions for storage

Store in the original package in order to protect from light and moisture.

Keep out of the reach and sight of children.

6.5 Nature and contents of container

Aluminium / Aluminium/polyamide/aluminium/PVC blister.

Packs containing 50/60/100/250 tablets.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling (and disposal)

Tablets

No special requirements.