NOVARTIS

Regulatory Affairs

# **CERTICAN®** (everolimus)
0.25 mg Tablet

## Summary of Product Characteristics (SmPC)

## Version 3.0

## Table of contents



## List of tables

# 1 Trade name(s)

## Tablets

CERTICAN® 0.25 mg tablets

# 2 Description and composition

## Pharmaceutical form(s)

### Tablets

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

Information might differ in some countries.

## Active substance

### Tablet

Certican® tablets contain 0.25 mg everolimus.

## Excipients

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

# 3 Indications

## Kidney and heart transplantation

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. In kidney and heart transplantation, Certican should be used in combination with ciclosporin for microemulsion and corticosteroids.

## Liver transplantation

Certican is indicated for the prophylaxis of organ rejection in adult patients receiving a hepatic transplant. In liver transplantation, Certican should be used in combination with tacrolimus and corticosteroids.

# 4 Dosage regimen and 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 level monitoring.

## Dosage regimen

## General target population

## Adults

***Kidney and heart transplantation***

An initial dosage 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.

***Liver transplantation***

A dosage of 1.0 mg b.i.d. is recommended for the hepatic transplant population with the initial dose approximately 4 weeks after transplantation [66].

## Special populations

## Black patients

The incidence of biopsy-proven acute rejection episodes was significantly higher in black renal transplant 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 11 Clinical pharmacology, Pharmacokinetics) [6,7]. Currently the efficacy and safety data are too limited to allow specific recommendations for use of everolimus in black patients.

## Pediatric patients (below 18 years)

- 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 and hepatic transplant pediatric patients [8,9,72] but no dosage recommendation can be made (see sections 11 Clinical pharmacology, Pharmacokinetics and 12 Clinical Studies).

## Geriatric patients (65 years of age or above)

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

## Renal impairment

No dosage adjustment is required (see section 11 Clinical pharmacology, Pharmacokinetics) [10,11].

## Hepatic impairment

Whole blood trough levels (C0) of everolimus should be closely monitored in patients with impaired hepatic function. For patients with mild hepatic impairment (Child-Pugh Class A), the dose should be reduced to approximately two-thirds of the normal dose. For patients with moderate hepatic impairment (Child-Pugh 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 [67]. Further dose titration should be based on therapeutic drug monitoring (see section 11 Clinical pharmacology, Pharmacokinetics) [12,66].

## Method of administration

Certican is for oral use only.

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 11 Clinical pharmacology, Pharmacokinetics) and at the same time as ciclosporin for microemulsion or tacrolimus (see Therapeutic drug monitoring).

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 to 5 days intervals (see Therapeutic drug monitoring) [48].

***Certican tablets 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.

***Certican dispersible tablets only***: For further instructions for use and handling of dispersible tablets see section 14 Pharmaceutical information.

## Therapeutic drug monitoring

Certican has a narrow therapeutic index which may require adjustments in dosing to maintain therapeutic response [68]. 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 renal, cardiac and hepatic 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 8 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 to 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:

**Table 4-1 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 to 200 | 75 to 150 | 50 to 100 | 25 to 50 |

(Measured levels are shown in section Pharmacodynamics).

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 and confirmed in study 2310 in which Certican was administered with ciclosporin with recommended reduced target trough concentrations (C0) as follows:

**Table 4-2 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 to 350 | 150 to 250 | 100 to 200 | 75 to 150 | 50 to 100 |

(Measured levels are shown in section Pharmacodynamics).

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 to 100 ng/mL after 12 months. If the patient cannot tolerate reduction of ciclosporin exposure, the continued use of Certican should be reconsidered.

**Tacrolimus dose recommendation in hepatic transplantation [66]**

Hepatic transplant patients should have the tacrolimus exposure reduced to minimize calcineurin related renal toxicity. The tacrolimus dose should be reduced starting approximately 3 weeks after initiation of dosing in combination with Certican based on tacrolimus blood trough levels (C0) targeting 3 to 5 ng/mL. Certican has not been evaluated with full dose tacrolimus in controlled clinical trials.

# 5 Contraindications

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

# 6 Warnings and precautions

## Management of immunosuppression

There are limited data regarding the use of Certican without calcineurin inhibitor (CNI) (ciclosporin or tacrolimus). An increased risk of acute rejection was observed in patients who discontinued the administration of CNI compared with those who continued the administration of CNI [67].

In clinical trials [6,7,13,66], Certican has been administered concurrently with ciclosporin for microemulsion, or with tacrolimus, basiliximab and corticosteroids. Certican in combination with immunosuppressive agents other than these has not been adequately investigated.

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

## Combination with thymoglobulin induction

Caution is advised with the use of thymoglobulin (rabbit anti-thymocyte globulin) induction and the Certican/ciclosporin/steroid regimen. In a clinical study in heart transplant recipients (Study A2310, see section Pharmacodynamics), an increased incidence of serious infections was observed within the first three months after transplantation in the subgroup of patients who had received induction with rabbit anti-thymocyte globulin combined with Certican, steroid and ciclosporin at the blood concentration recommended for heart transplantation (higher than in kidney transplantation). This was associated with greater mortality among patients who were both hospitalized and required ventricular assistance device prior to transplantation suggesting that they may have been particularly vulnerable to increased immunosuppression [65].

## Serious and opportunistic infections

Patients on a regimen of immunosuppressive medicinal products, including Certican, are at increased risk of developing infections, especially infections with opportunistic pathogens

(bacterial, fungal, viral, protozoal) Fatal infections and sepsis have been reported in patients treated with Certican (see section 7 Adverse drug reactions). 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 and Cytomegalovirus (CMV) was recommended following transplantation, particularly for patients at increased risk for opportunistic infections [6,7,13,66].

### Liver function impairment

Close monitoring of everolimus whole blood trough levels (C0) and everolimus dose adjustment is recommended in patients with impaired hepatic function (see section 4 Dosage regimen and administration) [12,66].

### 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 8 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 7 Adverse drug reactions). 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 minimize exposure to UV light sunlight, and to use an appropriate sunscreen.

### Hyperlipidemia

In transplant patients, concomitant use of Certican and ciclosporin for microemulsion or tacrolimus 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 hyperlipidemia and, if necessary, treated with lipid-lowering medicinal products and appropriate dietary adjustments made (see section 8 Interactions). The risk/benefit should be considered in patients with established hyperlipidemia before initiating an immunosuppressive regimen including Certican. Similarly the risk/benefit of continued Certican therapy should be re-evaluated in patients with severe refractory hyperlipidemia.

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 8 Interactions) [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].

### Everolimus and calcineurin inhibitor-induced renal dysfunction

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

In a liver transplant study Certican with reduced tacrolimus exposure has not been found to worsen renal function in comparison to standard exposure tacrolimus [66].

Regular monitoring of renal function is recommended in all patients. Caution should be exercized when co-administering other medicinal products that are known to have a deleterious effect on renal function.

### Proteinuria

The use of Certican with calcineurin inhibitors in transplant recipients has been associated with increased proteinuria. The risk increases with higher everolimus blood levels.

In renal transplant patients with mild proteinuria while on maintenance immunosuppressive therapy including a 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 and the frequency of incisional hernias is increased in liver transplant recipients [64,66].

### Thrombotic microangiopathic disorders

The concomitant administration of Certican with a calcineurin inhibitor (CNI) may increase the risk of CNI-induced hemolytic uremic syndrome, thrombotic thrombocytopenic purpura and thrombotic microangiopathy [64].

### Interstitial lung disease (ILD)/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. However, fatal cases have also occurred [61,66].

### 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.

## 7 Adverse drug reactions

### Summary of the safety profile

Certican combined with ciclosporin, was studied in five trials in renal transplant recipients totaling 2,497 patients (including two studies without a non-Certican control group), and three trials in heart transplant recipients totaling 1,531 patients (intent to treat (ITT) populations, see section Pharmacodynamics) [6,7,13,49,50,59,63,64,65].

Certican, combined with tacrolimus, was studied in one trial which included 719 liver transplant recipients (ITT population, see section Pharmacodynamics) [66]. The overall safety profile was not distinct from previous experiences with Certican and expectations in a liver transplant population up to 36 months [70].

The occurrence of the adverse events may depend on the degree and duration of the immunosuppressive regimen. In the studies combining Certican with full dose ciclosporin for

microemulsion elevated serum creatinine was observed more frequently than in control patients. The elevation of serum creatinine was less frequent and mean and median serum creatinine values were lower in the trials in which Certican was administered with reduced-dose ciclosporin.

With the exception of elevation of serum creatinine, the safety profile of Certican in the trials in which it was administered with reduced-dose ciclosporin was similar to that described in the three pivotal studies in which full dose of ciclosporin was administered, although he overall incidence of adverse events was lower with reduced dose ciclosporin (see section 12 Clinical studies) [14,49,50]. In controlled clinical trials in which a total of 3,256 patients receiving Certican in combination with other immunosuppressants were monitored for at least 1 year, a total of 3.1% developed malignancies, with 1.0% developing skin malignancies and 0.6% developing lymphoma or lymphoproliferative disorder [66].

## Tabulated summary of adverse drug reactions (ADRs) from clinical trials

The frequencies of adverse reactions listed below are derived from analysis of the 12-month incidences of events reported in multicenter, randomized, controlled trials investigating Certican in combination with calcineurin inhibitors (CNI) and corticosteroids in transplant recipients. All of the trials included non-Certican, CNI-based standard-therapy arms.

Table 7-1 contains adverse drug reactions possibly or probably related to Certican seen in phase III clinical trials. Unless noted as otherwise, these disorders have been identified by an increased incidence in the phase III studies comparing Certican-treated patients with patients on a non-Certican, standard-therapy regimens, or the same incidence in case the event is known as an ADR of the comparator (MPA in renal and heart transplant studies) (see section 11 Clinical pharmacology, Pharmacodynamics). Except where noted otherwise, the adverse reaction profile is relatively consistent across all transplant indications.

Adverse drug reactions from clinical trials are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

**Table 7-1 Percentage of patients with adverse drug reactions in clinical trials [67]**

| | | Phase III trial experiences by indication. | | | | | |
|---|---|---|---|---|---|---|---|
| | | Kidney transplant (Study A2309) | | Heart transplant (Study A2310) | | Liver transplant (Study H2304) | |
| **Adverse drug reactions** | **Frequency category** | EVR[9] 1.5mg N=274 (100%) | MPA[9] regimen N=273 (100%) | EVR 1.5mg N=279 (100%) | MPA regimen N=268 (100%) | EVR + red TAC[9] N=245 (100%) | TAC[9] control N=241 (100%) |
| **Infections and infestations** | | | | | | | |
| Infection (bacterial, fungal, viral) | Very common | 173 (63.1) | 190 (69.6) | 174 (62.4) | 161 (60.1) | 124 (50.6) | 104 (43.2) |
| Lower respiratory tract and lung infections (including pneumonia) | Very common[1] | 20 (7.3) | 15 (5.5) | 36 (12.9) | 32 (11.9) | 14 (5.7) | 14 (5.8) |
| Upper respiratory tract infections | Very common | 68 (24.8) | 76 (27.8) | 51 (18.3) | 63 (23.5) | 38 (15.5) | 32 (13.3) |
| Urinary tract infections | Very common[2] | 68 (24.8) | 66 (24.2) | 22 (7.9) | 22 (8.2) | 21 (8.6) | 11 (4.6) |
| Sepsis | Common | 10 (3.6) | 9 (3.3) | 17 (6.1) | 7 (2.6) | 11 (4.5) | 8 (3.3) |
| Wound infection | Common | 6 (2.2) | 4 (1.5) | 1 (0.4) | 0 | 8 (3.3) | 0 |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | | | | | | | |
| Malignant or unspecified tumours | Common | 4 (1.5) | 7 (2.6) | 12 (4.3) | 8 (3.0) | 5 (2.0) | 11 (4.6) |
| Malignant and unspecified skin neoplasms | Common | 3 (1.1) | 6 (2.2) | 5 (1.8) | 2 (0.7) | 0 | 3 (1.2) |
| Lymphomas / Post-transplant lymphoproliferative disorders (PTLD) | Uncommon | 0 | 0 | 0 | 1 (0.4) | 2 (0.8) | 0 |
| **Blood and lymphatic system disorders** | | | | | | | |
| Anaemia/erythropenia | Very common | 72 (26.3) | 71 (26.0) | 117 (41.9) | 88 (32.8) | 23 (9.4) | 22 (9.1) |
| Leukopenia | Very common | 15 (5.5) | 44 (16.1) | 44 (15.8) | 94 (35.1) | 35 (14.3) | 17 (7.1) |
| Thrombocytopenia | Very common | 8 (2.9) | 6 (2.2) | 31 (11.1) | 29 (10.8) | 14 (5.7) | 5 (2.1) |
| Pancytopenia [64] | Common | 2 (0.7) | 4 (1.5) | 0 | 0 | 9 (3.7) | 2 (0.8) |

| Adverse drug reactions | Frequency category | Phase III trial experiences by indication. | | | | | |
|---|---|---|---|---|---|---|---|
| | | Kidney transplant (Study A2309) | | Heart transplant (Study A2310) | | Liver transplant (Study H2304) | |
| | | EVR[9] 1.5mg N=274 (100%) | MPA[9] regimen N=273 (100%) | EVR 1.5mg N=279 (100%) | MPA regimen N=268 (100%) | EVR + red TAC[9] N=245 (100%) | TAC[9] control N=241 (100%) |
| Thrombotic microangiopathies (incl. thrombotic thrombocytopenic purpura, hemolytic uremia syndrome) | Common | 4 (1.5) | 0 | 3 (1.1) | 0 | 0 | 0 |
| **Endocrine disorders** | | | | | | | |
| Male hypogonadism (decreased testosterone, increased FSH and LH) | Uncommon | 0 | 2 (1.1) | 0 | 0 | 1 (0.6) | 0 |
| **Metabolism and nutrition disorders** | | | | | | | |
| Hyperlipidaemia (cholesterol and triglycerides) | Very common | 143 (52.2) | 105 (38.5) | 83 (29.7) | 60 (22.4) | 58 (23.7) | 23 (9.5) |
| New Onset Diabetes Mellitus [64] | Very common | 58 (21.2) | 68 (24.9) | 53 (19.0) | 52 (19.4) | 28 (11.4) | 29 (12.0) |
| Hypokalaemia | Very common | 33 (12.0) | 32 (11.7) | 36 (12.9) | 32 (11.9) | 7 (2.9) | 5 (2.1) |
| **Psychiatric disorders** | | | | | | | |
| Insomnia | Very common | 47 (17.2) | 43 (15.8) | 75 (26.9) | 54 (20.1) | 14 (5.7) | 19 (7.9) |
| Anxiety | Very common | 26 (9.5) | 19 (7.0) | 42 (15.1) | 32 (11.9) | 11 (4.5) | 4 (1.7) |
| **Nervous system disorders** | | | | | | | |
| Headache | Very common | 49 (17.9) | 40 (14.7) | 78 (28.0) | 63 (23.5) | 47 (19.2) | 46 (19.1) |
| **Cardiac disorders** | | | | | | | |
| Pericardial effusion [63] | Very common[3] | 1 (0.4) | 1 (0.4) | 111 (39.8) | 74 (27.6) | 1 (0.4) | 2 (0.8) |
| Tachycardia | Common | 14 (5.1) | 8 (2.9) | 18 (6.5) | 19 (7.1) | 5 (2.0) | 8 (3.3) |
| **Vascular disorders** | | | | | | | |
| Hypertension | Very common | 89 (32.5) | 89 (32.6) | 129 (46.2) | 127 (47.4) | 44 (18.0) | 38 (15.8) |
| Venous thromboembolic events | Very common | 15 (5.5) | 8 (2.9) | 34 (12.2) | 22 (8.2) | 9 (3.7) | 3 (1.2) |
| Epistaxis | Common | 6 (2.2) | 3 (1.1) | 15 (5.4) | 7 (2.6) | 5 (2.0) | 1 (0.4) |

| Adverse drug reactions | Frequency category | Phase III trial experiences by indication. | | | | | |
|---|---|---|---|---|---|---|---|
| | | Kidney transplant (Study A2309) | | Heart transplant (Study A2310) | | Liver transplant (Study H2304) | |
| | | EVR[9] 1.5mg N=274 (100%) | MPA[9] regimen N=273 (100%) | EVR 1.5mg N=279 (100%) | MPA regimen N=268 (100%) | EVR + red TAC[9] N=245 (100%) | TAC[9] control N=241 (100%) |
| Lymphocele | Common[4] | 21 (7.7) | 16 (5.9) | 12 (4.3) | 6 (2.2) | 0 | 1 (0.4) |
| Renal graft thrombosis [64] | Common | 6 (2.2) | 3 (1.1) | - | - | - | - |
| **Respiratory, thoracic and mediastinal disorders** | | | | | | | |
| Pleural effusion [63] | Very common[1] | 8 (2.9) | 5 (1.8) | 71 (25.4) | 58 (21.6) | 11 (4.5) | 11 (4.6) |
| Cough | Very common[1] | 20 (7.3) | 30 (11.0) | 57 (20.4) | 42 (15.7) | 15 (6.1) | 15 (6.2) |
| Dyspnoea | Very common[1] | 20 (7.3) | 24 (8.8) | 47 (16.8) | 43 (16.0) | 15 (6.1) | 12 (5.0) |
| Interstitial lung disease [61] | Uncommon[5] | 2 (0.7) | 2 (0.7) | 7 (2.5) | 2 (0.7) | 1 (0.4) | 1 (0.4) |
| **Gastrointestinal disorders** | | | | | | | |
| Diarrhoea | Very common | 51 (18.6) | 54 (19.8) | 51 (18.3) | 63 (23.5) | 47 (19.2) | 50 (20.7) |
| Nausea | Very common | 81 (29.6) | 86 (31.5) | 58 (20.8) | 71 (26.5) | 33 (13.5) | 28 (11.6) |
| Vomiting | Very common | 40 (14.6) | 60 (22.0) | 29 (10.4) | 42 (15.7) | 14 (5.7) | 18 (7.5) |
| Abdominal pain | Very common | 50 (18.2) | 67 (24.5) | 32 (11.5) | 38 (14.2) | 45 (18.4) | 35 (14.5) |
| Oropharyngeal pain [66] | Common | 14 (5.1) | 10 (3.7) | 17 (6.1) | 10 (3.7) | 13 (5.3) | 5 (2.1) |
| Pancreatitis [61] | Common | 1 (0.4) | 1 (0.4) | 4 (1.4) | 0 | 2 (0.8) | 2 (0.8) |
| Stomatitis/mouth ulceration [64] | Common | 24 (8.8) | 7 (2.6) | 23 (8.2) | 13 (4.9) | 23 (9.4) | 3 (1.2) |
| **Hepatobiliary disorders** | | | | | | | |
| Non-infectious hepatitis | Uncommon | 1 (0.4) | 1 (0.4) | 1 (0.4) | 1 (0.4) | 5 (2.0) | 5 (2.1) |
| Jaundice | Uncommon | 0 | 0 | 1 (0.4) | 2 (0.7) | 2 (0.8) | 5 (2.1) |
| **Skin and subcutaneous tissue disorders** | | | | | | | |
| Acne | Common | 26 (9.5) | 23(8.4) | 21 (7.5) | 28 (10.4) | 4 (1.6) | 0 |
| Angioedema [60] | Common[6] | 11 (4.0) | 10 (3.7) | 14 (5.0) | 7 (2.6) | 3 (1.2) | 3 (1.2) |

| Adverse drug reactions | Frequency category | Phase III trial experiences by indication. Kidney transplant (Study A2309) EVR[9] 1.5mg N=274 (100%) | Kidney transplant (Study A2309) MPA[9] regimen N=273 (100%) | Heart transplant (Study A2310) EVR 1.5mg N=279 (100%) | Heart transplant (Study A2310) MPA regimen N=268 (100%) | Liver transplant (Study H2304) EVR + red TAC[9] N=245 (100%) | Liver transplant (Study H2304) TAC[9] control N=241 (100%) |
|---|---|---|---|---|---|---|---|
| Rash | Common | 13 (4.7) | 17 (6.2) | 15 (5.4) | 17 (6.3) | 9 (3.7) | 9 (3.7) |
| **Musculoskeletal and connective tissue disorders** | | | | | | | |
| Myalgia | Common | 15 (5.5) | 10 (3.7) | 20 (7.2) | 18 (6.7) | 7 (2.9) | 4 (1.7) |
| Arthralgia | Common | 25 (9.1) | 26 (9.5) | 17 (6.1) | 23 (8.6) | 17 (6.9) | 18 (7.5) |
| **Renal and urinary disorders** | | | | | | | |
| Proteinuria [64] | Common[2] | 25 (9.1) | 20 (7.3) | 9 (3.2) | 4 (1.5) | 7 (2.9) | 2 (0.8) |
| Renal tubular necrosis | Common[7] | 15 (5.5) | 13 (4.8) | 2 (0.7) | 1 (0.4) | 0 | 0 |
| **Reproductive system and breast disorders** | | | | | | | |
| Erectile dysfunction [64] | Common | 10 (5.7) | 5 (2.7) | 15 (6.7) | 7 (3.2) | 3 (1.7) | 5 (2.8) |
| **General disorders and administration site conditions** | | | | | | | |
| Pain | Very common | 27 (9.9) | 27 (9.9) | 43 (15.4) | 33 (12.3) | 8 (3.3) | 10 (4.1) |
| Pyrexia | Very common | 51 (18.6) | 41 (15.0) | 46 (16.9) | 40 (14.9) | 32 (13.1) | 25 (10.4) |
| Peripheral oedema | Very common | 123 (44.9) | 108 (39.6) | 124 (44.4) | 103 (38.4) | 43 (17.6) | 26 (10.8) |
| Healing impairment [64] | Very common | 89 (32.5) | 77 (28.2) | 55 (19.7) | 52 (19.4) | 27 (11.0) | 19 (7.9) |
| Incisional hernia [66] | Common | 5 (1.8) | 3 (1.1) | 9 (3.2) | 4 (1.5) | 17 (6.9) | 13 (5.4) |
| **Investigations** | | | | | | | |
| Abnormal hepatic enzyme | Common[8] | 6 (2.2) | 12 (4.4) | 6 (2.2) | 5 (1.9) | 16 (6.5) | 24 (10.0) |

*[1] common in renal and liver transplantation*
*[2] common in cardiac and liver transplantation*
*[3] in cardiac transplantation*
*[4] in renal and cardiac transplantation*
*[5] the SMQ based search for interstitial lung disease (ILD) showed a frequency of ILD in the clinical trials as presented in table 7-1. This broad search also included cases which are caused by related events e.g. by infections. The frequency category given here is derived after medical review of the known cases*
*[6] predominantly in patients receiving concomitant ACE inhibitors*
*[7] in renal transplantation*
*[8] AST, ALT, GGT elevated, frequencies given here are derived from PT liver function test abnormal, reviewed were enzyme levels across the studies*
*[9] EVR: Everolimus, MPA: sodium mycophenolate, TAC: tacrolimus*

### Adverse drug reactions from post-marketing spontaneous reports

The following adverse drug reactions have been derived from post-marketing experience with Certican via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. 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.

**Table 7-2 Adverse drug reactions from spontaneous reports and literature (frequency not known)**

| |
|---|
| **Vascular disorders** |
| Leukocytoclastic vasculitis [64] |
| **Respiratory, thoracic and mediastinal disorders** |
| Pulmonary alveolar proteinosis [61] |
| **Skin and subcutaneous disorders** |
| Erythroderma |
| **Reproductive system and breast disorders** |
| Ovarian cyst [71] |

## 8 Interactions

Everolimus is mainly metabolized 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.

### Observed interactions resulting in concomitant use not being recommended

#### *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 $C_{max}$ by 58% and AUC by 63% [17]. Combination with rifampicin is not recommended (see section 6 Warnings and precautions).

#### *Ketoconazole (CYP3A4 inhibitor)*

Pre-treatment of healthy subjects with multiple-dose ketoconazole followed by a single dose of Certican increased everolimus $C_{max}$ by 3.9-fold and AUC by 15.0-fold (see section 6 Warnings and precautions) [67].

## Anticipated interactions resulting in concomitant use not being recommended

*Strong inhibitors, inducers of CYP3A4*

Concurrent treatment with strong CYP3A4-inhibitors and/or inducers is not recommended (e.g itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir, and/or rifampicin, rifabutin), (see section 6 Warnings and precautions) [67].

## Observed interactions to be considered

### Interactions affecting use of Certican

***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 increased the AUC of everolimus by 168% (range, 46% to 365%), and $C_{max}$ 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 Dosage regimen and administration).

***Erythromycin (CYP3A4 inhibitor)***

Pre-treatment of healthy subjects with multiple-dose erythromycin followed by a single dose of Certican increased everolimus $C_{max}$ by 2.0-fold and AUC by 4.4-fold [67].

***Verapamil (CYP3A4 inhibitor)***

Pre-treatment of healthy subjects with multiple-dose verapamil followed by a single dose of Certican increased everolimus $C_{max}$ by 2.3-fold and AUC by 3.5-fold [67].

### Interactions resulting in effects on other drugs

***Ciclosporin (CYP3A4/PgP inhibitor)***

Certican had only a minor clinical influence on ciclosporin pharmacokinetics in renal and heart transplant patients receiving ciclosporin for microemulsion [6,7,13].

***Octreotide***

Coadministration of everolimus with depot octreotide increased octreotide $C_{min}$ with a geometric mean ratio (everolimus/placebo) of 1.47-fold [67].

***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.

***Midazolam (CYP3A4A substrate)***

In a two-period, fixed-sequence, crossover drug interaction study, 25 healthy subjects received a single oral 4 mg dose of midazolam in period 1. In period 2, they received everolimus 10 mg once-daily for 5 days and a single 4 mg dose of midazolam with the last dose of everolimus. The $C_{max}$ of midazolam increased 1.25-fold (90% CI, 1.14 to 1.37) and the $AUC_{inf}$ increased 1.30-fold (1.22 to 1.39). The half-life of midazolam was unaltered. This study indicated that everolimus is a weak inhibitor of CYP3A4 [66].

## Anticipated interactions to be considered

### Interactions affecting the use of Certican

***Moderate inducers of CYP3A4***

Inducers of CYP3A4 may increase the metabolism of everolimus and decrease everolimus blood levels (e.g. St. John's wort (*Hypericum perforatum)*, anticonvulsants (e.g. carbamazepine), phenobarbital, phenytoin, anti HIV drugs (e.g. efavirenz, nevirapine)) [53].

***Moderate inhibitors of CYP3A4***

Moderate inhibitors of CYP3A4 and PgP may increase everolimus blood levels (e.g. **antifungal substances:** fluconazole, **calcium channel blockers:** nicardipine, diltiazem; **protease inhibitors**: nelfinavir, indinavir, amprenavir [55].

***Inhibitors of PgP***

Inhibitors of PgP may decrease the efflux of everolimus from intestinal cells and increase everolimus blood concentration.

***CYP3A4 and CYP2D6 substrates***

*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 exercized 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].

## 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.

### Drug-food/drink interactions

#### Grapefruit

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

# 9 Pregnancy, lactation, females and males of reproductive potential

## 9.1 Pregnancy

### Risk Summary

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. 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.

### Animal Data

In rats, everolimus crossed the placenta and was toxic to the conceptus [44]. Everolimus caused embryo/fetotoxicity that was manifested as mortality, reduced fetal weight, and an increased incidence of skeletal variations and malformations at systemic exposures below the target therapeutic exposure in humans. In rabbits, embryotoxicity was evident by an increase in late resorptions at systemic exposures similar to those in humans [46,69].

## 9.2 Lactation

It is not known whether everolimus is transferred into 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.

## 9.3 Females and males of reproductive potential

### Contraception

Females of reproductive potential should be advised to use effective contraception (methods that result in less than 1 % pregnancy rates) while they are receiving Certican and for up to 8 weeks after ending treatment.

### Infertility

There are literature reports of reversible azoospermia and oligospermia in patients treated with mTOR inhibitors (see sections 6 Warnings and precautions and 13 Non-clinical safety data).

# 10 Overdosage

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 2,000 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.

# 11 Clinical pharmacology

## Pharmacotherapeutic group, ATC

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

## Mechanism of action (MOA)

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 hematopoietic cells and non-hematopoietic 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.

## Pharmacokinetics (PK)

### 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 to 1.07) based on the AUC-ratio [1]. **Food effect:** the $C_{max}$ 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].

### Biotransformation/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 [67].

### Pediatric patients (below 18 years)

Everolimus CL/F increased in a linear manner with patient age (1 to 16 years), body surface area (0.49 to 1.92 $m^2$), and weight (11 to 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 pediatric *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].

### Geriatric patients (65 years of age or above)

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

### Race/Ethnicity

Based on analysis of population pharmacokinetics, oral clearance (CL/F) is, on average, 20% higher in black transplant patients (see section 4 Dosage regimen and administration) [6,7].

### Excretion

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

### 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.

### Renal impairment

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

### Hepatic impairment

Relative to the AUC of everolimus in subjects with normal hepatic function, the average AUC in 6 patients with mild hepatic impairment (Child-Pugh Class A) was 1.6-fold higher; in two independently studied groups of 8 and 9 patients with moderate hepatic impairment (Child-Pugh Class B) the average AUC was 2.1-fold and 3.3-fold higher; 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 (see section 4 Dosage regimen and administration) [12,66,67].

### Exposure-response relationships

The average everolimus trough concentration (C0) over the first 6 months post-transplant was related to the incidence of biopsy-confirmed acute rejection and of thrombocytopenia in renal and cardiac transplant patients (Table 11-1) [6]. In hepatic transplant patients the relationship of everolimus trough concentrations and clinical events is less well defined, however, higher exposures do not correlate with an increase in adverse events.

**Table 11-1 Exposure-response relationships for everolimus in transplant patients**

| | | | | | |
|---|---|---|---|---|---|
| **Renal 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% |
| **Cardiac 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% |
| **Hepatic transplantation** | | | | | |
| Trough level (C0) (ng/ml) | ≤3 | 3-8 | | | ≥8 |
| Freedom from treated BPAR | 88% | 98% | | | 92% |
| Thrombocytopenia (≤75×$10^9$/L) | 35% | 13% | | | 18% |
| Neutropenia (<1.75 x $10^9$/L) | 70% | 31% | | | 44% |

# 12 Clinical studies

## Renal 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 3 ng/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) ≥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, multicenter, randomized, open-label, controlled trial (A2309) has been completed in which 833 *de-novo* renal transplant recipients were randomized 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/day and 3 mg/day, given in two divided doses, subsequently modified from Day 5 onwards to maintain target blood trough everolimus levels of 3 to 8 ng/mL and 6 to 12 ng/mL respectively. Sodium mycophenolate dosage was 1.44 g/day. Ciclosporin dosages were adapted to maintain target blood trough-level windows as shown in Table 12-1. The actual measured values for blood concentrations of everolimus and ciclosporin (Co and C2) are shown in Table 12-2.

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 Dosage regimen and administration).

**Table 12-1 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 12-2 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 12-3.

**Table 12-3 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° 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° 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° 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 12-4.

Proteinuria was assessed at scheduled visits by spot analysis of urinary protein/creatinine and categorized by levels of clinical relevance as represented in Table 12-5. 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 $C_{min}$ above 8 ng/mL.

Adverse drug reactions reported with Certican regimen have been included above (Table 7-1). 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 12-4 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 12-5 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)*

In a 24-month, randomized, multicenter, open-label, 2-arm study (A2433), 2,037 adult recipients were randomized within 24 hours of renal transplantation to receive either EVR+rCNI or MPA+sCNI. In the EVR+rCNI group, the starting dose of everolimus was 3 mg/day as 1.5 mg b.i.d (when given with tacrolimus) or 1.5 mg/day as 0.75 mg b.i.d (when given with ciclosporin). Incidence rates of all efficacy endpoints at month 12 and month 24 are summarized in Table 12-6. Both treatment groups have shown good and comparable immunosuppressive efficacy with a low rate of tBPAR and well preserved graft function during the first and second post-transplant year. The safety findings are consistent with the known safety profiles of everolimus, MPA, ciclosporin and tacrolimus. In the EVR+rCNI group, viral infections, in particular CMV and BKV infections, were less frequently reported compared to those treated with MPA [72].

**Table 12-6 Study A2433: Comparison between treatments for incidence rates of the composite endpoints (full analysis set)**

| **Efficacy endpoints** | **EVR+rCNI N = 1022** | **MPA+sCNI N = 1015** | **Difference (95% CI)** | ***P value*** | **EVR+rCNI N = 1022** | **MPA+sCNI N = 1015** | **Difference (95% CI)** | ***P value*** |
|---|---|---|---|---|---|---|---|---|
| | **Month 12** | | | | **Month 24** | | | |
| tBPAR, graft loss, or death | 146 (14.4) | 131 (13.0) | 1.4 (−1.6, 4.4) | 0.353 | 169 (18.0) | 147 (17.3) | 0.8 (−4.6, 6.1) | 0.782 |
| tBPAR | 107 (10.8) | 91 (9.2) | 1.6 (−1.1, 4.2) | 0.243 | 118 (12.8) | 98 (12.1) | 0.7 (−4.4, 5.8) | 0.794 |
| Graft loss | 33 (3.3) | 28 (2.8) | 0.5 (−1.0, 2.0) | 0.542 | 37 (3.7) | 32 (3.2) | 0.5 (−1.1, 2.1) | 0.572 |
| Death | 20 (2.0) | 28 (2.8) | -0.8 (−2.2, 0.5) | 0.234 | 32 (3.7) | 36 (4.2) | −0.5 (−2.7, 1.6) | 0.634 |
| Graft loss or death | 51(5) | 54(5.4) | -0.3 (-2.3,1.6) | 0.732 | 67(7.1) | 65(7.1) | 0.0(-2.5, 2.6) | 0.970 |
| eGFR < 50mL/min/1.73m$^2$# | 456 ( 44.6) | 424 ( 41.8) | 2.9 [ -1.5, 7.2] | 0.201 | 474 ( 46.4) | 423 ( 41.6) | 4.7 [ 0.2, 9.2] | 0.040 |

*95% CI and p-value to test for no difference ([EVR+rCNI] – [MPA+sCNI] = 0); endpoint highlighted with # is compared using raw incidence rates, other endpoints are compared using Kaplan-Meier incidence rates; BPAR, biopsy-proven acute rejection; CI, confidence interval; eGFR, estimated glomerular filtration rate; EVR, everolimus; MPA, mycophenolic acid; rCNI, reduced-exposure calcineurin inhibitor; sCNI, standard-exposure calcineurin inhibitor; tBPAR, treated BPAR*

In a 12-month, multicenter, open label, randomized, controlled study A2314 with a 24-month additional safety follow-up, 106 pediatric renal transplant patients were randomized to evaluate the efficacy, tolerability and safety of early introduction of everolimus, reduced tacrolimus, and steroid withdrawal at 6 months post transplantation (52 patients in the EVR+rTAC group) compared to a standard tacrolimus, MMF, and steroid regimen (54 patients in the MMF+sTAC group). At 12 months, the incidence rate of CEF (BPAR, graft loss or death) were 9.6 % and

5.6% in EVR+rTAC group and MMF+sTAC group respectively. At 36 months follow-up, the CEF endpoint was similar in both treatment groups (9.8% vs 9.6%), while treated BPAR occurred in five patients in each group. Graft loss was reported in one patient (2.1%) in the group receiving EVR+rTAC versus two patients (3.8%) in the group receiving MMF+sTAC. Renal function calculated by estimated glomerular filtration rate (eGFR) was comparable between both study groups. In total, 35% patients in the EVR+rTAC group versus 17% in the sTAC group were withdrawn from study therapy due to AEs or infections. Most of the AEs/infections leading to premature discontinuation of study medication were singular events and were not reported in more than one patient. In the EVR+rTAC group, two patients were reported with post-transplant lymphoproliferative disease and one patient with hepatocellular carcinoma [72] (See section 4 Dosage regimen and administration).

## Cardiac transplantation [56,63,65]

In the phase III cardiac 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 hemodynamic 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. Studies A2411 and A2310 have subsequently been carried out to investigate this.

Study A2411 was a randomized, 12 months, 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. The study included a total of 174 patients. Certican (N=92) was initiated at 1.5 mg/day and the dose was adjusted to maintain target blood everolimus trough levels between 3 to 8 ng/mL. MMF (N=84) was initiated at a dosage of 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 |

Renal function was improved with the reduced ciclosporin dosage regimen with mean creatinine clearance (Cockcroft-Gault formula) at 6 months: Certican: 65.4 v. MMF: 72.2 mL/mn, and at 12 months: Certican: 68.7 v. MMF: 71.8 mL/mn. Efficacy, expressed as the rate of biopsy-proven acute rejection episodes (ISHLT grade ≥3A), was maintained as comparable in the two groups at 12 months (Certican: 22.8% v. MMF: 29.8%).

Study A2310 was a phase III [13], multicenter, randomized, open-label study comparing the efficacy and safety of two Certican/reduced-dose ciclosporin regimens against a standard mycophenolate mofetil (MMF)/ciclosporin regimen over 24 months. The use of induction therapy was center-specific, the options being no-induction or induction with either basiliximab or thymoglobulin. All patients received corticosteroids.

Starting doses in the two Certican groups were 1.5 mg/day and 3 mg/day, subsequently modified from Day 4 onwards to maintain target blood trough everolimus levels of 3 to 8 ng/ml and 6 to 12 ng/ml respectively. The MMF dose was 3 g/day. Ciclosporin dosages were adapted to maintain the same target blood trough level windows as in study A2411. Blood concentrations of everolimus and ciclosporin are shown in Table 12-7.

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

Statistical comparisons are limited to comparisons between the completed treatment arms. The drug blood concentration levels actually achieved are described in Table 12-6.

**Table 12-7 Study A2310: Measured trough blood levels of ciclosporin (CsA) and everolimus**

| Visit window | Certican 1.5 mg/reduced-dose CsA N=279 | | MMF 3 g/std-dose CsA N=268 |
|---|---|---|---|
| | Everolimus ($C_0$ ng/mL) | Ciclosporin ($C_0$ ng/mL) | Ciclosporin ($C_0$ ng/mL) |
| Day 4 | 5.7 (4.6) | 153 (103) | 151 (101) |
| Month 1 | 5.2 (2.4) | 247 (91) | 269 (99) |
| Month 3 | 5.7 (2.3) | 209 (86) | 245 (90) |
| Month 6 | 5.5 (2.2) | 151 (76) | 202 (72) |
| Month 9 | 5.4 (2.0) | 117 (77) | 176 (64) |
| Month 12 | 5.6 (2.5) | 102 (48) | 167 (66) |

*Numbers are mean ± SD of measured values with $C_0$=trough level*
*Source: PT-Table 14.3-1.5, PT-Table 14.3-1.7a*

The primary efficacy endpoint was a composite failure variable, implying occurrence of any of the following: Biopsy Proven Acute Rejection (BPAR) episode of ISHLT grade >=3A, acute rejection (AR) episode associated with hemodynamic compromise (HDC), graft loss/re-transplant, death, or loss to follow-up. Efficacy outcome at 12 months is shown in Table 12-8.

**Table 12-8 Study A2310: Incidence rates of efficacy endpoints by treatment group (ITT population - 12 month Analysis)**

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

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

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

*Source: PT-Table 14.2-1.1a*

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

Intravascular ultrasound (IVUS) studies were performed on a subset of patients to investigate changes post-transplantation (Month 12 value relative to a baseline value effected during the first three months post-transplant) in intimal thickness within a segment of the left anterior descending (LAD) coronary artery. The results of the measured change in maximum intimal thickness along with frequency of patients with cardiac allograft vasculopathy (defined as an increase in the maximal intimal thickness of 0.5 mm or more) are described in Table 12-9.

**Table 12-9 Change in average maximum intimal thickness (mm) from baseline to month 12 and incidence of cardiac allograft vasculopathy (CAV) by donor disease and treatment (IVUS population – 12 month analysis)**

| | Certican 1.5mg N=88 | MMF N=101 | p-value of t-test (Certican vs MMF) |
|---|---|---|---|
| **Change in average maximum intimal thickness (mm) from baseline to month 12** | | | |
| Mean (SD) | 0.03 (0.05) | 0.07 (0.11) | <0.001 |

| | Certican 1.5mg N=88 | MMF N=101 | p-value of t-test (Certican vs MMF) |
|---|---|---|---|
| Median (range) | 0.02 (-0.12, 0.19) | 0.03 (-0.15, 0.56) | |
| **Cardiac allogr aft vasculopathy (CAV) by donor disease and treatment** | | | |
| Donor disease | n/M (%) | n/M (%) | n/M (%) |
| -Total | 11/88 (12.5) | 27/101 (26.7) | 0.018 |
| Donor disease | 10/42 (23.8) | 24/54 (44.4) | 0.052 |
| No donor disease | 1/46 (2.2) | 3/47 (6.4) | 0.617 |

*Baseline IVUS assessment was performed up to Day 105.*
*The p-value for change from baseline should be compared to the two-sided 0.025 significance level.*

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

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

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

Renal function over the course of study A2310, assessed by calculated glomerular filtration rate (GFR) using the MDRD formula, indicates a statistically significant difference of 5.5 mL/min/1.73m$^2$ (97.5% CI -10.9, -0.2) lower for the everolimus 1.5 mg group at Month 12.

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

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

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

The adverse reactions for everolimus 1.5 mg group in Study A2310 are consistent with adverse drug reactions presented in Table 7-1. A lower rate of viral infections was reported for Certican-treated patients resulting principally from a lower reporting rate for CMV infection compared to MMF (7.2% vs 19.4%).

## Hepatic transplantation

In the phase III adult hepatic transplant study (H2304), reduced exposure tacrolimus and Certican 1.0 mg b.i.d. was administered to HCV+ and HCV- patients with the initial Certican dose starting approximately 4 weeks after transplantation and was investigated versus standard exposure tacrolimus up to 24 months (core study) and for an additional 12 month extension

period up to 36 months post-transplant. Certican was dose adjusted to maintain target blood everolimus trough levels between 3 to 8 ng/mL for the Certican + Reduced tacrolimus arm. Mean everolimus trough levels were within the target ranges at all time points ranging from 3.4 to 6.3 ng/mL in the Certican + Reduced tacrolimus arm. Tacrolimus doses were subsequently adjusted to achieve target trough levels between 3 to 5 ng/mL through 12 months in the Certican + Reduced tacrolimus arm.

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

Overall, in the 12 month analysis, the incidence of the composite endpoint (tBPAR, graft loss or death) was lower in Certican + Reduced tacrolimus arm (6.7%) compared to the tacrolimus control arm (9.7%) (Table 12-9). The difference in estimates between Certican+Reduced tacrolimus and tacrolimus control was - 3.0% with 97.5% CI: (-8.7% to 2.6%). Regarding the rates of graft loss and fatal cases the Certican + Reduced tacrolimus arm was non-inferior compare to the tacrolimus control arm indicating no increased mortality risk in this population. A statistically significantly lower rate of acute rejection was seen in the Certican + Reduced tacrolimus arm (3.7%) compared to tacrolimus control arm (10.7%) (Table 12-10). Results are similar between HCV+ and HCV- patients.

**Table 12-10 Study H2304: Comparison between treatment groups for Kaplan-Meier (KM) incidence rates of primary efficacy endpoints (ITT population – 12 and 24 month analysis)**

| Statistic | EVR + Reduced TAC n=245 | | TAC Control n=243 | |
|---|---|---|---|---|
| | 12-months | 24-months | 12-months | 24-months |
| Number of composite efficacy failures (tBPAR, graft loss or death) from randomization until month 12 and 24 | 16 | 24 | 23 | 29 |
| KM estimate of incidence rate of composite efficacy failure (tBPAR, graft loss or death) at month 12 and 24 | 6.7% | 10.3% | 9.7% | 12.5% |
| Difference in KM estimates (vs. control) | -3.0% | -2.2% | | |
| 97.5% CI for difference | (-8.7%, 2.6%) | (-8.8%, 4.4%) | | |
| P-value of Z-test for (Reduced TAC - Control = 0) (No Difference Test) | 0.230 | 0.452 | | |
| P-value* of Z-test for (Reduced TAC - Control ≥ 0.12) (Non-inferiority Test) | <0.001 | <0.001 | | |

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

**Table 12-11 Study H2304: Comparison between treatment groups for incidence rates of secondary efficacy endpoints (ITT population – 12 and 24 month analysis)**

| Efficacy endpoints | EVR/Reduced TAC N=245 n (%) | TAC Control N=243 n (%) | Risk Diff. (CI*) | P-value |
|---|---|---|---|---|
| **Graft loss**** | | | | |
| 12-months | 6 (2.4) | 3 (1.2) | 1.2 (-7.8, 10.2) | 0.5038 |
| 24-months | 9 (3.9) | 7 (3.2) | 0.8% (-3.2, 4.7) | 0.6605 |
| **Death**** | | | | |
| 12-months | 9 (3.7) | 6 (2.5) | 1.2 (-7.8, 10.1) | 0.6015 |
| 24-months | 12 (5.2) | 10 (4.4) | 0.8% (-3.7, 5.2) | 0.7012 |
| **AR** | | | | |
| 12-months | 9 (3.7) | 26 (10.7) | -7.0 (-11.6, -2.5) | 0.0026 |
| 24-months | 11 (4.8) | 28 (12.4) | -7.6 (-13.5, -1.7) | 0.0039 |
| **tAR** | | | | |
| 12-months | 6 (2.4) | 17 (7.0) | -4.5 (-8.3, -0.8) | 0.0178 |
| 24-months | 8 (3.5) | 17 (7.2) | -3.7 (-8.3, 1.0) | 0.0765 |
| **BPAR** | | | | |
| 12-months | 10 (4.1) | 26 (10.7) | -6.6 (-11.2, -2.0) | 0.0052 |
| 24-months | 14 (6.1) | 30 (13.3) | -7.2% (-13.5, -0.9) | 0.0100 |
| **tBPAR** | | | | |
| 12-months | 7 (2.9) | 17 (7.0) | -4.1 (-8.0, -0.3) | 0.0345 |
| 24-months | 11 (4.8) | 18 (7.7) | -2.9 (-7.9, 2.2) | 0.2031 |
| **Subclinical AR**** | | | | |
| 12-months | 1 (0.4) | 5 (2.1) | -1.6 (-10.6, 7.3) | 0.1216 |
| 24-months | 3 (1.4) | 7 (3.5) | -2.1 (-5.6, 1.3) | 0.1640 |

*1. AR = Acute rejection; BPAR = biopsy proven acute rejection; tBPAR = treated biopsy proven acute rejection; tAR = treated acute rejection. Local laboratory biopsy results are used to define BPAR and tBPAR.*
*2. Loss to follow-up for 'graft loss, death or loss to follow-up' is defined as a patient who does not die, does not have graft loss, and whose last day of contact is prior to the lower limit of the Month 12/24 visit window.*
*3. * Risk difference 95% for 12-month data and 97.5% for 24-month data*
*4. ** = exact confidence interval and two-sided Fisher exact test used for that variable. For others, asymptotic confidence interval and Pearson Chi-square test are used.*
*5. All p-values are for two-sided test and were compared to 0.05 significance level.*

**Extension - primary efficacy results at 36 months:** Of the total 231 patients who entered the extension for Certican +Reduced tacrolimus (n=106) and tacrolimus control (n=125), 84% and 86% of patients completed study medication, 91% and 94% of patients completed the study phase with 16% and 14% of patients discontinuing study medication, respectively.

The incidence of patients with composite efficacy failure events (tBPAR, graft loss or death) at Month 36 since extension baseline (Month 24) was low and similar across the treatment arms at 1.9% (n=2), and 2.4% (n=3) in the Certican +Reduced tacrolimus and tacrolimus control arms respectively.

For the ITT population (all patients randomized in the core study), the Kaplan-Meier estimates of the primary composite efficacy endpoint (tBPAR, graft loss or death) to 36 months were lower in the Certican +Reduced tacrolimus arm (11.5%) than in the tacrolimus control arm

(14.6%). The difference between Certican +Reduced tacrolimus and tacrolimus control was −3.2% (97.5% CI: −10.5%, 4.2%; p-value 0.3337).

**Renal function:** Comparison between treatment groups for change in eGFR (MDRD4) [mL/min/1.73 $m^2$] from time of randomization (day 30) to Months 12, 24 and 36 for the ITT population is presented in Table 12-12. The eGFR at 12 months was higher for Certican + Reduced tacrolimus (80.6 mL/min/1.73 $m^2$) in comparison to the tacrolimus control (70.3 mL/min/1.73$m^2$) and a higher eGFR was also observed throughout the entire study.

**Table 12-12 Study H2304: Comparison between treatment groups for eGFR (MDRD 4) (ITT population – 12, 24 and 36 month analysis)**

| | | | Difference vs control | | | |
|---|---|---|---|---|---|---|
| **Treatment** | **N** | **LS mean (SE)** | **LSM mean (SE)** | **97.5% CI** | **P-value(1)** | **P-value(2)** |
| **EVR+Reduced TAC** | | | | | | |
| 12 months | 244 | -2.23 (1.54) | 8.50 (2.12) | (3.74, 13.27) | <0.0001 | <0.0001 |
| 24 months | 245 | -7.94 (1.53) | 6.66 (2.12) | (1.9, 11.42) | <0.0001 | 0.0018 |
| 36 months | 106 | -4.98 (2.06) | 12.37 (2.66) | (6.38, 18.37) | <0.0001 | <0.0001 |
| **TAC Control** | | | | | | |
| 12 months | 243 | -10.73 (1.54) | | | | |
| 24 months | 243 | -14.60 (1.54) | | | | |
| 36 months | 125 | -17.36 (1.88) | | | | |

*1. Least squares means, 97.5% confidence intervals, and p-values are from an ANCOVA model containing treatment and HCV status as factors, and baseline eGFR as a covariate.*

*2. Imputation rules of missing Month 12, 24 and 36 eGFR (MDRD4) values: 1) use the last available value before/at randomization for patients with no post-randomization eGFR; 2) use the minimal value between randomization and Month 6 if the last value is observed between randomization and Month 6; 3) use the minimal value between Month 6 and Month 12 if the last value is observed at or after Month 6; 4) use the minimal value between Month 12 and Month 24 if the last value is observed at or after Month 12; 5) use the minimal value between Month 24 and Month 36 if the last value is observed at or after Month 24; 6) use 15 mL/min/1.73$m^2$ if the patient was on dialysis after randomization.*

*3. P-value (1): Non-inferiority test with NI margin = -6 mL/min/1.73$m^2$, at one-sided 0.0125 level.*

*4. P-value (2): Superiority test at two-sided 0.025 levels.*

Statistically significant between-treatment group difference (Certican+Reduced tacrolimus vs. tacrolimus control arm) was observed in favor of Certican+Reduced tacrolimus arm for the mean eGFR from Week 6 up to Month 36 (including at study endpoint and treatment endpoint). At randomization, mean eGFR was 85.0 and 78.0 mL/min/1.73$m^2$ for the Certican+Reduced tacrolimus and tacrolimus control arms respectively. At the Month 36 time point, the difference in mean eGFR between Certican+Reduced tacrolimus and tacrolimus control was 15.2 mL/min/1.73$m^2$. The mean eGFR at Month 36 was 78.7 and 63.5 mL/min/1.73$m^2$ for the Certican+Reduced tacrolimus and tacrolimus control arms respectively [70].

A 24-month, multicenter, open-label, randomized, controlled study (H2307), was conducted in adult living donor liver transplant (LDLT) recipients with everolimus in combination with reduced tacrolimus (EVR+rTAC) compared to standard exposure tacrolimus (sTAC) to demonstrate comparable efficacy as measured by the CEF (tBPAR, GL or death) and at least comparable renal function as measured by eGFR. The recommended whole blood concentration before morning dose (C-0h) trough exposure (3 to 8 ng/mL) for the EVR+rTAC arm was maintained during the study. The target tacrolimus range of 3 to 5 ng/mL in combination with

everolimus was chosen for the sTAC arm. This approach was supported by the 12 month data from Study H2304. In this study, the majority (N=223, 78.5%) of patients were of Asian origin. 284 patients were randomized to the EVR+rTAC group (N = 142) or sTAC group (N = 142). KM estimates for incidence of the primary CEF events (tBPAR, graft loss or death) at month 12 and month 24 were comparable for EVR+rTAC and sTAC control arms. The eGFR was improved at month 12 and consistently maintained up to month 24. The study results suggest that LDLT recipients demonstrated comparable efficacy between EVR+rTAC and sTAC control arm while EVR+rTAC showed improved renal function and less HCC recurrence. The efficacy and safety results of the H2307 study in *de novo* LDLT were aligned with those observed in study H2304 conducted in *de novo* deceased donor liver transplant (DDLT) [72].

In the extension phase of H2307 (H2307E1), 18 patients (Japanese only) participated in the respective arms of EVR+rTAC: n=13; sTAC Control: n=5. At month 36, the lower CEF rate was maintained in the EVR+rTAC arm versus the sTAC control arm along with comparable renal function and no additional HCC recurrence in both treatment arms.

A 24-month, multicenter, single arm, prospective study (H2305) was conducted in pediatric liver transplant recipients (n=56; month 1-18 years of age) to evaluate renal function, efficacy, safety and tolerability of everolimus in combination with reduced exposure ciclosporin or tacrolimus. The KM estimates of composite efficacy failure (tBPAR, graft loss or death) were 1.9% and 5.9% at 12 and 24 months post transplantation, respectively. There were no deaths or graft losses over 24 months of treatment. An improvement in renal function was observed as measured in mean eGFR, by 6.2 mL/min/1.73m$^2$ and 4.5 mL/min/1.73m$^2$ at month 12 and 24 respectively, as compared to baseline. No negative impact on growth or sexual maturation was observed. However, high rates of premature discontinuation of study medication, serious infections leading to hospitalization and post-transplant lymphoproliferative disorder (PTLD) were observed. PTLD was reported in 3 patients in the less than 2 years age group and in 2 patients in the 2 to less than 18 years age group during the study period. The overall balance of benefit to risk for the evaluated regimen of everolimus combined with tacrolimus at the tested concentrations in the study has not been established in pediatric liver transplant recipients [72] (See section 4 Dosage regimen and administration).

# 13 Non-clinical safety data

The non-clinical 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 rats. Monkeys showed hemorrhage and arteritis in several organs.

For information on reproductive toxicity (see section 9 Pregnancy, lactation, females and males of reproductive potential).

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.

In rat studies, female fertility was not affected [45].

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.

# 14 Pharmaceutical information

## Incompatibilities

***Tablets***

Not applicable

***Dispersible tablets***

When ciclosporin for microemulsion is administered via nasogastric tube it should be administered before Certican. The two medicinal products should not be mixed.

## Special precautions for storage

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

Information might differ in some countries.

Certican must be kept out of the reach and sight of children.

## Instructions for use and handling

***Tablets***

No special requirements.

***Dispersible tablets***

**Administration in a 10 mL oral syringe**

Place the Certican dispersible tablets into a syringe. The maximum amount of Certican that can be dispersed in a 10 mL syringe is 1.25 mg. Add water to the 5 mL mark. Wait 90 sec while shaking gently. After dispersion deliver directly into the mouth. Rinse the syringe with 5 mL water and administer into the mouth. Further drink 10 to 100 mL of water or diluted syrup.

**Administration with a plastic cup**

Place the Certican dispersible tablets in approximately 25 mL of water in a plastic cup. The maximal amount of Certican that can be dispersed in 25 mL of water is 1.5 mg. The cup is left for approx. 2 minutes to allow the tablets to dissolve and gently agitated before drinking. Immediately rinse the cup with an additional 25 mL of water and drink completely.

**Administration via nasogastric tube**

Place the Certican dispersible tablets in a small plastic medicine beaker, which contain 10 mL water, wait 90 sec while swirling gently. Put the dispersion into a syringe and inject slowly (within 40 sec) into the nasogastric tube. Rinse the beaker (and the syringe) 3 times with 5 mL water and inject into the tube. Finally flush the tube with 10 mL water. The nasogastric tube should be clamped for a minimum of 30 minutes after Certican administration.

## 15 Marketing Authorization Number

Certican 0.25 mg Tablet – NAFDAC Reg. No.: A4-4292

## 16 Marketing Authorization Holder

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