NOVARTIS

Departament of pharmaceutical product

CERTICAN ®
(everolimus)

0,25 mg, 0,5 mg y 0,75 mg tablets

Prospect (NPI)

Reference number:	NPI based on the prospect of the Spanish Medicines Agency and Health Products (AEMPS, by its acronym in spanish) of July 17th, 2024, corresponding to the Core Labelling Package N/A update v3.0 of May 25th, 2022.
Document version:	July 2024

PRODUCT LABEL / SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Certican 0.25 mg Tablets
Certican 0.5 mg Tablets
Certican 0.75 mg Tablets
Certican 1.0 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.25 / 0.5 / 0.75 / 1.0 mg everolimus.

Excipient(s) with known effect:
Each tablet contains 2 / 4 / 7 / 9 mg lactose monohydrate and 51 / 74 / 112 / 149 mg anhydrous lactose.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet
White to yellowish, marbled, round, flat tablets with bevelled edges.
0.25 mg (6 mm diameter): imprinted with 'C' on one side and 'NVR' on the other side.
0.5 mg (7 mm diameter): imprinted with 'CH' on one side and 'NVR' on the other side.
0.75 mg (8.5 mm diameter): imprinted with 'CL' on one side and 'NVR' on the other side.
1.0 mg (9 mm diameter): imprinted with 'CU' on one side and 'NVR' on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic 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 kidney or heart transplant. For these indications, 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 liver transplant. For this indication, Certican should be used in combination with tacrolimus and corticosteroids.

4.2. Posology and method of administration

Treatment with Certican should be initiated and maintained by doctors who are experienced in the use of immunosuppressive therapy following organ transplantation and who also have access to everolimus whole-blood concentration monitoring.

Dosage

Adults

An initial dose of 0.75 mg twice daily in co-administration with ciclosporin is recommended for the general kidney and heart transplant population, administered as soon as possible after transplantation.

The dose of 1.0 mg twice daily in co-administration with tacrolimus is recommended for the liver transplant population, with the initial dose administered approximately 4 weeks after transplantation.

Patients receiving Certican may require dose adjustments based on blood concentrations achieved, tolerability, individual response, change in concomitant medication and the clinical condition. Dose adjustments can be made at 4-5-day intervals (see *Therapeutic Drug Monitoring*).

Special population

Black patients

The incidence of biopsy-proven acute rejection episodes was significantly higher in Black kidney transplant patients compared with non-Black patients. There is limited information indicating that Black patients may require a higher Certican dose to achieve similar efficacy to non-Black patients (see section 5.2). Currently, efficacy and safety data are insufficient to allow specific recommendations for the use of everolimus in Black patients.

Paediatric population

Certican should not be used in paediatric kidney and liver transplant patients. The safety and efficacy of Certican in paediatric heart transplant patients have not been established (see section 5.1).

Elderly patients (≥65 years)

Clinical experience in patients over 65 years of age is limited. Although data are limited, there are no apparent differences in the pharmacokinetics of everolimus in patients ≥65-70 years of age (see section 5.2).

Patients with renal impairment

No dose adjustments are required (see section 5.2).

Patients with hepatic impairment

Everolimus whole-blood trough concentrations should be closely monitored in patients with hepatic impairment. The dose should be reduced to approximately two-thirds of the normal dose in patients with mild hepatic impairment (Child-Pugh Class A), to approximately one half of the normal dose in patients with moderate hepatic impairment (Child-Pugh Class B) and to approximately one-third of the normal dose in patients with severe hepatic impairment (Child-Pugh Class C). Further dose titration should be based on therapeutic drug monitoring (see section 5.2). Reduced doses rounded to the nearest tablet strength are tabulated below:

Table 1 Certican dose reduction in patients with hepatic impairment

	Normal liver function	**Mild hepatic impairment (Child-Pugh A)**	**Moderate hepatic impairment (Child-Pugh B)**	**Severe hepatic impairment (Child-Pugh C)**
Kidney and heart transplantation	0.75 mg b.i.d.	0.5 mg b.i.d.	0.5 mg b.i.d.	0.25 mg b.i.d.
Liver transplantation	1 mg b.i.d.	0.75 mg b.i.d.	0.5 mg b.i.d.	0.5 mg b.i.d.

Therapeutic Drug Monitoring

The use of drug assays with adequate performance characteristics is recommended when targeting low concentrations of ciclosporin or tacrolimus.

Certican has a narrow therapeutic index which may require adjustments in dosing to maintain therapeutic response. Routine everolimus whole-blood therapeutic drug concentration monitoring is recommended. Based on exposure-efficacy and exposure-safety data, patients achieving everolimus whole-blood trough concentrations ≥3.0 ng/mL have been observed to have a lower incidence of biopsy-proven acute rejection in kidney, heart and liver transplantation compared with patients whose trough concentrations are below 3.0 ng/mL. 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.

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). Everolimus concentrations might be slightly lower following administration of dispersible tablets.

Ideally, Certican dose adjustments should be based on trough concentrations obtained more than 4-5 days after the previous dosing change. There is an interaction between ciclosporin and everolimus, and everolimus concentrations may therefore decrease if ciclosporin exposure is markedly reduced (i.e. trough concentration <50 ng/mL).

Patients with hepatic impairment should preferably have trough concentrations in the upper part of the 3-8 ng/mL exposure range.

After starting treatment or after a dose adjustment, monitoring should be performed every 4 to 5 days until 2 consecutive trough concentrations show stable everolimus concentrations as the prolonged half-life in patients with hepatic impairment delays the time to reach steady state (see sections 4.4 and 5.2). Dose adjustments should be based on stable everolimus trough concentrations.

Ciclosporin dose recommendation in kidney transplantation

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

Table 2 Kidney transplantation: recommended target ciclosporin blood trough concentration ranges

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

(Measured C_0 and C2 concentrations are shown in section 5.1).

Prior to ciclosporin dose reduction, it should be ascertained that steady-state everolimus whole-blood trough concentrations are ≥3 ng/mL.

There are limited data regarding Certican dosing with ciclosporin trough concentrations below 50 ng/mL or C2 concentrations below 350 ng/mL, in the maintenance phase. If patients do not tolerate ciclosporin exposure reduction, the continued use of Certican should be reconsidered.

Ciclosporin dose recommendation in heart transplantation

Heart transplant patients in the maintenance phase should have their ciclosporin dose reduced as tolerated in order to improve kidney function. If impairment of kidney function is progressive or if the calculated creatinine clearance is <60 mL/min, the treatment regimen should be readjusted. In heart

transplant patients, the ciclosporin dose may be based on ciclosporin blood trough concentrations. See section 5.1 for experience with reduced ciclosporin blood concentrations.

In heart transplantation, there are limited data regarding Certican dosing with ciclosporin trough concentrations of 50-100 ng/mL after 12 months.

Prior to ciclosporin dose reduction, it should be ascertained that steady-state everolimus whole-blood trough concentrations are ≥3 ng/mL.

Tacrolimus dose recommendation in liver transplantation
Liver transplant patients should have their tacrolimus exposure reduced to minimise calcineurin-related renal toxicity. The tacrolimus dose should be reduced starting approximately 3 weeks after initiating concomitant administration with Certican, based on targeted tacrolimus blood trough concentrations (C_0) of 3-5 ng/mL. In a controlled clinical trial, complete withdrawal of tacrolimus has been associated with an increased risk of acute rejections.

Certican has not been evaluated with full-dose tacrolimus in controlled clinical trials.

Method of administration
Certican is for oral use only.

The daily dose of Certican should always be administered orally, divided into two doses, either with or without food, but always in the same way (see section 5.2) and at the same time as ciclosporin for microemulsion or tacrolimus (see *Therapeutic Drug Monitoring*).

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 Product Label/Summary of Product Characteristics).

4.3. Contraindications

Certican is contraindicated in patients with a known hypersensitivity to everolimus, sirolimus or to any of the excipients listed in section 6.1.

4.4. Special warnings and precautions for use

Management of immunosuppression
In clinical trials, Certican has been administered concurrently with ciclosporin for microemulsion, basiliximab, or with tacrolimus and corticosteroids. Administration of 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
Strict caution is advised with the use of thymoglobulin (rabbit anti-thymocyte globulin) as induction and the Certican/ciclosporin/steroid therapeutic regimen. In a clinical trial in heart transplant recipients (Study A2310, see section 5.1), an increased incidence of serious infections, including fatal infections, was observed within the first three months after transplantation in the subgroup of patients who had received induction with rabbit anti-thymocyte globulin.

Serious and opportunistic infections
Patients treated with immunosuppressants, including Certican, are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal). Among these conditions are BK virus-associated nephropathy and JC virus-associated progressive multifocal leukoencephalopathy (PML). These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that doctors should consider in the differential diagnosis in immunosuppressed patients with

deteriorating kidney function or neurological symptoms. Fatal infections and sepsis have been reported in patients treated with Certican (see section 4.8).

In clinical trials with Certican, antimicrobial prophylaxis for *Pneumocystis jirovecii (carinii)* pneumonia and cytomegalovirus (CMV) was recommended following transplantation, particularly for patients at increased risk for opportunistic infections.

Impaired liver function
Close monitoring of everolimus whole-blood trough concentrations (C0) and everolimus dose adjustment are recommended in patients with impaired liver function (see section 4.2).

Due to the long half-life of everolimus in patients with hepatic impairment (see section 5.2), therapeutic drug monitoring of everolimus should be performed after starting treatment or after a dose adjustment until stable concentrations are reached.

Interaction with oral CYP3A4 substrates
Caution should be exercised when Certican is given in combination with orally administered CYP3A4 substrates with a narrow therapeutic index due to the potential for drug interactions. If Certican is given with orally administered CYP3A4 substrates with a narrow therapeutic index (e.g. pimozide, terfenadine, astemizole, cisapride, quinidine or ergot alkaloid derivatives), the patient should be monitored for the adverse reactions described in the Product Label/Summary of Product Characteristics for the orally administered CYP3A4 substrates (see section 4.5).

Interaction with strong CYP3A4 and/or P-glycoprotein (Pgp) inhibitors or inducers
Co-administration with strong CYP3A4 and/or multidrug efflux pump P-glycoprotein (Pgp) inhibitors (e.g. ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir) may increase everolimus blood levels and is not recommended unless the benefit outweighs the risk.
Concomitant administration with strong CYP3A4 and/or Pgp inducers (e.g. rifampicin, rifabutin, carbamazepine, phenytoin) is not recommended unless the benefit outweighs the risk.
If concomitant administration of CYP3A4 and/or Pgp inducers or inhibitors cannot be avoided, it is recommended that everolimus trough concentrations in whole blood and the patient's clinical condition be monitored when co-administered with everolimus and after discontinuation. Everolimus dose adjustment may be necessary (see section 4.5).

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

Hyperlipidaemia
The use of Certican with ciclosporin for microemulsion or tacrolimus in transplant patients has been associated with increased serum cholesterol and triglycerides that may require treatment. Patients receiving Certican should be monitored for high serum lipid levels and, if necessary, treated with lipid-lowering medicinal products and have appropriate dietary adjustments made (see section 4.5). The risk/benefit ratio should be considered in patients with established hyperlipidaemia before initiating an immunosuppressive regimen including Certican. Similarly, the risk/benefit ratio of continued Certican therapy should be re-evaluated in patients with severe refractory hyperlipidaemia. Patients being treated with 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 Product Label/Summary of Product Characteristics for the medicinal product(s) concerned (see section 4.5).

Angioedema
Certican has been associated with the development of angioedema. In the majority of cases reported, patients were receiving angiotensin-converting enzyme inhibitors (ACE inhibitors) as concomitant medication.

Everolimus- and calcineurin inhibitor-induced kidney dysfunction
In kidney and heart transplantation, Certican with full-dose ciclosporin increases the risk of kidney dysfunction. Reduced doses of ciclosporin are required for use in combination with Certican in order to avoid kidney dysfunction. In patients with elevated serum creatinine levels, appropriate adjustment of the immunosuppressive regimen, in particular reduction of the ciclosporin dose, should be considered.

In a liver transplant study, Certican with reduced tacrolimus exposure has not been observed to worsen kidney function in comparison to standard tacrolimus exposure without Certican. Regular monitoring of kidney function is recommended in all patients. Caution should be exercised when co-administering other medicinal products known to have a negative effect on kidney 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 concentrations. In kidney 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 on discontinuing treatment with Certican and reintroducing the CNI. The safety and efficacy of switching from a CNI to Certican in such patients have not been established. Patients receiving Certican should be monitored for proteinuria.

Renal graft thrombosis
An increased risk of renal artery and vein thrombosis, resulting in graft loss, has been reported, mostly within the first 30 days post-transplantation.

Wound-healing complications
Certican, like other mTOR inhibitors, can impair healing, increasing the occurrence of post-transplant complications such as wound dehiscence, fluid build-up and wound infection, which may require further surgery. Lymphocele is the most commonly reported event in kidney transplant recipients and tends to be more common in patients with a higher body mass index. The frequency of pericardial and pleural effusion is increased in heart transplant recipients and the frequency of incisional hernias is increased in liver transplant recipients.

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

Vaccinations
Immunosuppressants may affect the response to vaccination and vaccination may be less effective during treatment with immunosuppressants, including everolimus. The use of live vaccines should be avoided.

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 treatment and in whom infectious, neoplastic and other non-drug causes have been ruled out through appropriate diagnostic tests. Cases of ILD have been reported with Certican, which generally resolve after withdrawing the drug, with or without glucocorticoid therapy. However, fatal cases have also been reported (see section 4.8).

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

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

Risk of intolerance of excipients
Certican tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5. Interaction with other medicinal products and other forms of interaction

Everolimus is mainly metabolised by CYP3A4 in the liver and to some extent in the intestinal wall and is a substrate of 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 P-glycoprotein. Concurrent treatment with strong CYP3A4 inhibitors and inducers is not recommended. P-glycoprotein inhibitors may decrease the efflux of everolimus from intestinal cells and increase everolimus blood concentrations. *In vitro*, everolimus was a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6. All *in vivo* interaction studies were conducted without concomitant ciclosporin.

Table 3. Effects of other active substances on everolimus

Active substance by interaction	**Interaction – Change in everolimus AUC/C_{max} geometric mean ratio (observed range)**	**Recommendations concerning co-administration**
***Strong* CYP3A4/Pgp inhibitors**		
Ketoconazole	AUC ↑15.3-fold (range 11.2-22.5) C_{max} ↑4.1-fold (range 2.6-7.0)	Co-administration with strong CYP3A4/Pgp inhibitors is not recommended unless the benefit outweighs the risk.
Itraconazole, posaconazole, voriconazole	Not studied. Large increase in everolimus concentrations expected.	
Telithromycin, clarithromycin		
Nefazodone		
Ritonavir, atazanavir, saquinavir, darunavir, indinavir, nelfinavir		
***Moderate* CYP3A4/Pgp inhibitors**		
Erythromycin	AUC ↑4.4-fold (range 2.0-12.6) C_{max} ↑2.0-fold (range 0.9-3.5)	Everolimus whole-blood trough concentrations should be monitored whenever CYP3A4/Pgp inhibitors are administered concurrently and after their discontinuation.

Imatinib	AUC ↑3.7-fold C_{max} ↑2.2-fold	Caution should be exercised when moderate CYP3A4 or Pgp inhibitors are administered concomitantly. Adverse effects should be closely monitored and the dose of everolimus adjusted as necessary (see sections 4.2 and 4.4).
Verapamil	AUC ↑3.5-fold (range 2.2-6.3) C_{max} ↑2,3-fold (range 1.3-3.8)	
Oral ciclosporin	AUC ↑2.7-fold (range 1.5-4.7) C_{max} ↑1.8-fold (range 1.3-2.6)	
Cannabidiol (Pgp inhibitor)	AUC ↑2.5-fold C_{max} ↑2.5-fold	
Fluconazole **Diltiazem, nicardipine**	Not studied. Increased exposure expected.	
Dronedarone	Not studied. Increased exposure expected.	
Amprenavir, fosamprenavir	Not studied. Increased exposure expected.	
Grapefruit juice or other food affecting CYP3A4/Pgp	Not studied. Increased exposure expected (the effect varies widely).	Combination should be avoided.
***Strong* and *moderate* CYP3A4 inducers**		
Rifampicin	AUC ↓63% (range 0-80%) C_{max} ↓58% (range 10-70%)	Co-administration with strong CYP3A4 inducers is not recommended unless the benefit outweighs the risk.
Rifabutin	Not studied. Decreased exposure expected.	
Carbamazepine	Not studied. Decreased exposure expected.	
Phenytoin	Not studied. Decreased exposure expected.	
Phenobarbital	Not studied. Decreased exposure expected.	Everolimus whole-blood trough concentrations should be monitored whenever CYP3A4 inducers are administered concurrently and after their discontinuation.
Efavirenz, nevirapine	Not studied. Decreased exposure expected.	
St John's Wort (*Hypericum perforatum*)	Not studied. Large decrease in exposure expected.	Preparations containing St John's Wort should not be used during treatment with everolimus.

Compounds whose plasma concentrations may be altered by everolimus:

Octreotide

Concomitant administration of everolimus (10 mg daily) with long-acting octreotide increased octreotide C_{min} with a geometric mean ratio (everolimus/placebo) of 1.47 fold.

Ciclosporin

Certican has little clinical influence on the pharmacokinetics of ciclosporin in kidney and heart transplant patients receiving ciclosporin for microemulsion.

Atorvastatin (CYP3A4 substrate) and pravastatin (Pgp substrate)
Administration of a single dose of Certican with either atorvastatin or pravastatin to healthy volunteers did not affect the pharmacokinetics of atorvastatin, pravastatin and everolimus or total HMG-CoA reductase bioreactivity in plasma to a clinically significant extent. However, these results cannot be extrapolated to other HMG-CoA reductase inhibitors. Patients should be monitored for the development of rhabdomyolysis and other adverse reactions as described in the Product Label/Summary of Product Characteristics for HMG-CoA reductase inhibitors.

Oral CYP3A4A substrates
Based on *in vitro* results, the systemic concentrations obtained after oral daily doses of 10 mg make inhibition of Pgp, CYP3A4 and CYP2D6 unlikely. However, inhibition of CYP3A4 and Pgp in the gut should not be ruled out. An interaction study in healthy volunteers demonstrated that co-administration of an oral dose of midazolam, a sensitive probe substrate for CYP3A4, with everolimus resulted in a 25% increase in midazolam C_{max} and a 30% increase in midazolam AUC. The effect is likely to be due to inhibition of intestinal CYP3A4 by everolimus. Therefore, everolimus may affect the bioavailability of orally co-administered CYP3A4 substrates. However, no clinically significant effect on the exposure of systemically administered CYP3A4 substrates is expected. If everolimus is given with orally administered CYP3A4 substrates with a narrow therapeutic index (e.g. pimozide, terfenadine, astemizole, cisapride, quinidine or ergot alkaloid derivatives), the patient should be monitored for the adverse reactions described in the Product Label/Summary of Product Characteristics for the orally administered CYP3A4 substrates.

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

Paediatric population
Interaction studies have only been conducted in adults.

4.6. Fertility, pregnancy, and lactation

Pregnancy
There are no adequate data on the use of Certican in pregnant women. Animal studies have shown reproductive toxicity effects including embryo/foetotoxicity (see section 5.3). The potential risk for humans is unknown. Certican should not be administered to pregnant women unless the potential benefit outweighs the possible risk for the foetus. Women of childbearing potential should be advised to use an effective method of birth control during treatment and for 8 weeks after treatment has stopped.

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

Fertility
There are literature reports of reversible oligospermia and azoospermia in patients treated with mTOR inhibitors (see sections 4.4, 4.8, and 5.3). The potential for everolimus to cause infertility in male and female patients is unknown but male infertility and secondary amenorrhoea have been observed.

4.7. Effects on ability to drive and use machines

Certican has no or negligible influence on the ability to drive and use machines.

4.8. Adverse reactions

a) Summary of the safety profile

The frequencies of the adverse reactions listed below are derived from the analysis of 12-month incidences of events reported in multicentre, randomised, controlled trials investigating Certican in combination with calcineurin inhibitors (CNI) and corticosteroids in adult transplant recipients. Two of the trials (in kidney transplantation) included non-Certican, CNI-based standard therapy arms. Certican combined with ciclosporin was studied in five trials in kidney transplant recipients with a total of 2,497 patients (including two studies without a non-Certican control group) and three trials in heart transplant recipients with a total of 1,531 patients (intention-to-treat population, see section 5.1).

Certican combined with tacrolimus was studied in one trial, which included 719 liver transplant recipients (intention-to-treat population, see section 5.1).

The most common adverse reactions are infections, anaemia, hyperlipidaemia, new-onset diabetes mellitus, insomnia, headache, hypertension, cough, constipation, nausea, peripheral oedema, impaired healing (including pleural and pericardial effusion).

The occurrence of adverse reactions may depend on the immunosuppressive regimen (i.e. intensity and duration). In those studies combining Certican with ciclosporin, elevated serum creatinine was observed more frequently in patients treated with Certican in combination with full-dose ciclosporin for microemulsion than in control patients. The overall incidence of adverse reactions was lower with reduced-dose ciclosporin for microemulsion (see section 5.1).

The safety profile of Certican administered with reduced-dose ciclosporin was similar to that described in the three pivotal trials in which full-dose ciclosporin was administered, except that elevated serum creatinine was less common, and mean and median serum creatinine values were lower than in the Phase 3 trials.

b) Tabulated summary of adverse reactions

Table 4 contains adverse reactions possibly related to Certican observed in Phase 3 clinical trials. Unless indicated otherwise, these disorders have been identified by an increased incidence in the Phase 3 studies comparing Certican-treated patients with patients on a non-Certican, standard therapy regimen, or the same incidence if the event is a known adverse drug reaction of the comparator MPA in kidney and heart transplant studies (see section 5.1). Except where indicated otherwise, the adverse reaction profile is relatively consistent across all transplant indications. It has been compiled according to MedDRA system organ classes.

Adverse reactions are listed according to their frequencies, which are defined as: 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 4: Adverse reactions possibly related to Certican

SOC	Frequency	Adverse reaction
Infections and infestations	Very common	Infections (viral, bacterial and fungal), upper and lower respiratory tract and lung infections (including pneumonia)[1], urinary tract infections[2]
	Common	Sepsis, wound infection

SOC	Frequency	Adverse reaction
Neoplasms benign, malignant and unspecified	Common	Malignant or unspecified tumours, malignant and unspecified skin neoplasms
	Uncommon	Lymphomas/post-transplant lymphoproliferative disorders (PTLD)
Blood and lymphatic system disorders	Very common	Leukopenia, anaemia/erythrocytopenia, thrombocytopenia[1]
	Common	Pancytopenia, thrombotic microangiopathy (including thrombotic thrombocytopenic purpura/haemolytic-uraemic syndrome)
Endocrine disorders	Uncommon	Male hypogonadism (testosterone decreased, FSH and LH increased)
Metabolism and nutrition disorders	Very common	Hyperlipidaemia (cholesterol and triglycerides), new-onset diabetes mellitus, hypokalaemia
Psychiatric disorders	Very common	Insomnia, anxiety
Nervous system disorders	Very common	Headache
Heart disorders	Very common	Pericardial effusion[3]
	Common	Tachycardia
Vascular disorders	Very common	Hypertension, venous thromboembolic events
	Common	Lymphocele[4], epistaxis, renal graft thrombosis
Respiratory, thoracic and mediastinal disorders	Very common	Pleural effusion[1], cough[1], dyspnoea[1]
	Uncommon	Interstitial lung disease[5]
Gastrointestinal disorders	Very common	Abdominal pain[9], diarrhoea, nausea, vomiting
	Common	Pancreatitis, stomatitis/mouth ulcer, oropharyngeal pain
Hepatobiliary disorders	Uncommon	Non-infectious hepatitis, jaundice
Skin and subcutaneous tissue disorders	Common	Angioedema[6], acne, rash
Musculoskeletal and connective tissue disorders	Common	Myalgia, arthralgia
Kidney and urinary disorders	Common	Proteinuria[2], renal tubular necrosis[7]
Reproductive system and breast disorders	Common	Erectile dysfunction, menstrual disorder (including amenorrhoea and menorrhagia)
	Uncommon	Ovarian cyst

SOC	Frequency	Adverse reaction
General disorders and administration site conditions	Very common	Peripheral oedema, pain, healing impaired, pyrexia
	Common	Incisional hernia
Investigations	Common	Liver enzyme abnormal[8]

[1] common in kidney and liver transplantation
[2] common in heart and liver transplantation
[3] in heart transplantation
[4] in kidney and heart transplantation
[5] the SMQ-based search for ILD showed the frequency of ILD in the clinical trials. This broad search also included cases caused by related adverse reactions, e.g. by infections. The frequency category given here is derived from the medical review of the known cases
[6] predominantly in patients receiving concomitant ACE inhibitors
[7] in kidney transplantation
[8] elevated γ-GT, AST, ALT

c) Description of selected adverse reactions

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

In controlled clinical trials, a total of 3,256 patients receiving Certican in combination with other immunosuppressants were monitored for at least 1 year and a total of 3.1% developed malignancies, with 1.0% developing skin malignancies and 0.60% developing lymphomas or lymphoproliferative disorders.

Cases of interstitial lung disease, with intraparenchymal pulmonary inflammation (pneumonitis) and/or fibrosis of non-infectious aetiology, some with fatal outcome, have been observed in patients receiving rapamycin and derivatives, including Certican. In most cases, this condition resolves after discontinuation of Certican therapy and/or addition of glucocorticoids. However, fatal cases have also occurred.

d) Adverse reactions from post-marketing spontaneous reports

The following adverse reactions have been derived from post-marketing experience with Certican via spontaneous case reports and literature data. Since these effects are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency, which is therefore classified as not known. Adverse reactions are listed according to MedDRA system organ classes. Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

Table 5 Adverse reactions from spontaneous case reports and literature data (frequency not known)

SOC	Frequency	Adverse reaction
Metabolism and nutrition disorders	Not known	Iron deficiency
Vascular disorders	Not known	Leukocytoclastic vasculitis, lymphoedema
Respiratory, thoracic and mediastinal disorders	Not known	Pulmonary alveolar proteinosis
Skin and subcutaneous tissue disorders	Not known	Erythroderma

Paediatric population
Safety information in children and adolescents is based on data covering 36 months in paediatric kidney transplant patients and 24 months in paediatric liver transplant patients (see section 5.1).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk ratio of the medicinal product. Healthcare professionals are invited to report suspected adverse reactions through the Pharmacovigilance System in the country.

4.9. Overdosage

In animal studies, everolimus showed low acute toxic potential. No fatality or severe toxicity was observed after single oral doses of 2,000 mg/kg (limit test) in either rats or mice.

Reported experience with overdose in humans is very limited; there is only one case of accidental ingestion of 1.5 mg everolimus in a 2-year-old child where no adverse reactions 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 overdosage.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: mammalian target of rapamycin (mTOR) kinase inhibitors.
ATC code: L04AH02.

Mechanism of action
Everolimus, a proliferation signal inhibitor, prevents allograft rejection in rodent and non-human primate models of allotransplantation. It exerts its immunosuppressive effect by inhibiting the proliferation, and therefore clonal expansion, of antigen-activated T cells, which is mediated by T-cell-specific interleukins, e.g. interleukin-2 and interleukin-15. Everolimus inhibits an intracellular signalling pathway, which is triggered upon binding of these T-cell growth factors to their respective receptors, and which normally leads to cell proliferation. The blockage of this signal by everolimus leads to an arrest of the cells at the G_1 stage of the cell cycle.

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

Everolimus therefore has a different mechanism of action compared to ciclosporin. In non-clinical models of allotransplantation, the combination of everolimus and ciclosporin was more effective than either compound alone.

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

Clinical efficacy and safety
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 3 *de novo* adult kidney transplant trials (B201 and B251). Mycophenolate mofetil (MMF) at a dose of 1 g twice daily was used as comparator. The co-primary composite endpoint was efficacy failure (biopsy-proven acute rejection, graft loss, death, or loss to follow-up) at 6 months, and graft loss, death, or loss to follow-up at 12 months. Certican was, overall, non-inferior to MMF in these trials. The incidence of biopsy-proven acute rejection at 6 months in trial B201 was 21.6%, 18.2% and 23.5% for the Certican 1.5 mg/day, Certican 3 mg/day and MMF groups, respectively. In trial B251, the incidences were 17.1%, 20.1%, and 23.5% for the Certican 1.5 mg/day, Certican 3 mg/day and MMF groups, respectively.

Reduced allograft function with elevated serum creatinine was observed more frequently among patients treated with Certican in combination with full-dose ciclosporin for microemulsion than in patients treated with MMF. This effect suggests that Certican increases ciclosporin nephrotoxicity. Drug concentration-pharmacodynamic analysis showed that kidney function was not impaired with reduced exposure to ciclosporin while conserving efficacy for as long as the blood trough everolimus concentration was maintained above 3 ng/mL. This finding was subsequently confirmed in two further Phase 3 trials (A2306 and A2307, which included 237 and 256 patients, respectively), which evaluated the efficacy and safety of Certican 1.5 mg and 3 mg per day (initial dosing and subsequent dosing based on target trough concentration ≥3 ng/mL) in combination with reduced exposure to ciclosporin. In both trials, kidney function was preserved without compromising efficacy. However, in these trials, there was no non-Certican comparative arm. A Phase 3, multicentre, randomised, open-label, controlled trial (A2309) has been completed in which 833 *de novo* kidney transplant recipients were randomised to one of two Certican regimens, differing by dosage, and combined with reduced-dose ciclosporin or a standard regimen of mycophenolate sodium (MPA) + ciclosporin and treated for 12 months. All patients received induction therapy with basiliximab pre-transplant and on Day 4 post-transplant. Steroids were administered 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 everolimus blood trough concentrations of 3-8 ng/mL and 6-12 ng/mL, respectively. The mycophenolate sodium dose was 1.44 g/day. Ciclosporin dosages were adapted to maintain target blood trough concentration windows as shown in Table 6. Table 7 shows the actual measured values for blood concentrations of everolimus and ciclosporin (C_0 and C2).

Although the higher-dosage Certican regimen was as effective as the lower-dosage regimen, the overall safety was poorer and therefore the higher-dosage regimen is not recommended.

The lower-dosage Certican regimen is recommended (see section 4.2).

Table 6 Trial A2309: Target ciclosporin blood trough concentration 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
MPA group	200-300	100-250	100-250	100-250

Table 7 Trial A2309: Measured ciclosporin and everolimus blood trough concentrations

Trough concentrations (ng/mL)	**Certican groups** (low-dose ciclosporin)				**MPA** (standard ciclosporin)	
	Certican 1.5 mg		**Certican 3.0 mg**		**Myfortic 1.44 g**	
Ciclosporin	*C_0*	*C2*	*C_0*	*C2*	*C_0*	*C2*
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 C_0 3-8)		(Target C_0 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		-	
Values are the mean ± SD of measured values with C_0 = trough concentration, C2 = value 2 hours post-dose.						

The primary efficacy endpoint was a composite failure variable (biopsy-proven acute rejection, graft loss, death, or loss to follow-up). The results are shown in Table 8.

Table 8 Trial A2309: Composite and individual efficacy endpoints at 6 and 12 months (incidence in intention-to-treat population)

	Certican 1.5 mg N=277 % (n)		**Certican 3.0 mg N=279 % (n)**		**MPA 1.44 g N=277 % (n)**	
	6 months	**12 months**	**6 months**	**12 months**	**6 months**	**12 months**
Composite endpoint (primary endpoint)	**19.1** (53)	**25.3** (70)	**16.8** (47)	**21.5** (60)	**18.8** (52)	**24.2** (67)
% Difference *(Certican - MPA)* 95% CI	0.4% (-6.2, 6.9)	1.1% (-6.1, 8.3)	-1.9% (-8.3, 4.4)	-2.7% (-9.7, 4.3)	- -	- -
Individual endpoint (secondary criterion)						
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)
Composite endpoint (secondary endpoint)						
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 follow-up	**9.4** (26)	**10.8** (30)	**8.2** (23)	**10.0** (28)	**5.8** (16)	**8.7** (24)

CI = confidence interval, non-inferiority margin was 10%
Composite endpoint: treated biopsy-proven acute rejection (BPAR), graft loss, death, or loss to follow-up

Table 9 shows changes in kidney function, as shown by the glomerular filtration rate (GFR) calculated using the MDRD (Modification of Diet in Renal Disease) formula.

Proteinuria was assessed at scheduled visits by spot analysis of urinary protein/creatinine ratio (see Table 10). A concentration effect was shown relating proteinuria levels to everolimus trough concentrations, particularly at C_{min} values above 8 ng/mL.

Table 4 above includes adverse reactions reported more commonly in the recommended (lower dosage) Certican regimen group than in the MPA control group. A lower frequency of viral infections was reported for Certican-treated patients, resulting primarily from lower reporting rates for CMV infection (0.7% vs. 5.95%) and BK virus infection (1.5% vs. 4.8%).

Table 9 Trial A2309: Kidney function (MDRD-calculated GFR) at 12 months (intention-to-treat 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) 95% CI	2.37 (-1.7, 6.4)	-0.89 (-5.0, 3.2)	- -

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

MDRD: Modification of Diet in Renal Disease

Table 10 Trial 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 (Month 12 value or last observation carried forward)

In a 24-month, randomised, multicentre, open-label, 2-arm study (A2433), 2,037 adult recipients at low immunological risk were randomised within 24 hours of renal transplantation to receive either everolimus and reduced-dose CNI (EVR+rCNI) or MPA and standard-dose CNI (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 summarised in Table 11. The safety findings are consistent with the known safety profiles of everolimus, MPA, ciclosporin and tacrolimus. The incidence of viral infections such as CMV and BKV infections was 28 (2.8%) and 59 (5.8%), respectively, in the EVR+rCNI group, and 137 (13.5%) and 104 (10.3%), respectively, in the MPA+sCNI group.

Table 11 Trial 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	(95% CI)	*P-value*
	Month 12				Month 24			
eGFR < 50mL/min/ 1.73m^2 or tBPAR#	489 (47.9)	456 (44.9)	3.0 (−1.4, 7.3)	0.187	489 (47.9)	443 (43.7)	4.2 (−0.3, 8.7)	0.067
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; tBPAR, treated 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.

Heart transplantation

In the Phase 3 heart transplant trial (B253), both Certican 1.5 mg/day and 3 mg/day, in combination with standard doses of ciclosporin for microemulsion and corticosteroids, were investigated vs azathioprine (AZA) 1-3 mg/kg/day. The primary endpoint was a composite of the incidence of acute rejection ≥ISHLT grade 3A, acute rejection associated with haemodynamic compromise, graft loss, patient death or loss to follow-up at 6, 12 and 24 months. Both doses of Certican were superior to AZA at 6, 12 and 24 months. The incidence of biopsy-proven acute rejection ≥ISHLT grade 3A at month 6 was 27.8% for the 1.5 mg/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, p<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 automatic pullback sequence), an important risk factor for long-term graft loss.

Elevated serum creatinine was observed more frequently among patients treated with Certican in combination with full-dose ciclosporin for microemulsion than in patients treated with AZA. These results indicated that Certican increases ciclosporin-induced nephrotoxicity.

Trial A2411 was a randomised, 12-month, open-label study comparing Certican in combination with reduced doses of ciclosporin for microemulsion and corticosteroids to mycophenolate mofetil (MMF) and standard doses of ciclosporin for microemulsion and corticosteroids in *de novo* heart transplant patients. Certican was initiated at a dose of 1.5 mg/day and adjusted to maintain target everolimus blood

trough concentrations of 3-8 ng/mL. The initial MMF dose was 1500 mg twice daily. Ciclosporin microemulsion doses were adjusted to the following target trough concentrations (ng/mL):

Table 12 Target ciclosporin trough concentrations by month

Target ciclosporin C_0	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
MMF group	200-350	200-350	200-300	150-250	100-250

Table 13 shows the actual blood concentrations measured.

Table 13 Trial A2411: Summary statistics for ciclosporin (CsA) blood concentrations* (mean ± SD)

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

*: whole blood trough concentrations (C_0)

Table 14 shows changes in kidney function. Table 15 shows efficacy outcomes.

Table 14 Trial A2411: Changes in creatinine clearance during the study (patients with paired values)

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

* includes patients with values at both baseline and visit

Table 15 Trial A2411: Efficacy event rates (incidence in intention-to-treat 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/ re-transplant	10 (10.9%)	10 (11.9%)	-

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

Trial A2310 is a Phase 3, multicentre, randomised, open-label study comparing a Certican/reduced-dose ciclosporin treatment regimen to a standard mycophenolate mofetil (MMF)/ciclosporin regimen over 24 months. The use of induction therapy was centre specific (no induction or basiliximab or thymoglobulin). All patients received corticosteroids.

Starting dosages in the Certican groups were 1.5 mg/day and 3 mg/day and were adjusted to target everolimus blood trough concentrations of 3-8 ng/mL and 6-12 ng/mL, respectively. The MMF dose was 3 g/day. Ciclosporin doses were adjusted to achieve the same target blood trough concentrations as in trial A2411. Blood concentrations of everolimus and ciclosporin are shown in Table 16.

Recruitment to the experimental, higher-dosage Certican treatment arm was discontinued prematurely due to an increased rate of fatalities caused by infections and cardiovascular disorders, occurring within the first 90 days post-randomisation.

Table 16 Trial A2310: Measured blood trough concentrations of ciclosporin (CsA) and everolimus

Visit window	Certican 1.5 mg/reduced-dose CsA N=279		MMF 3 g/standard-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	5.4 (2.6)	209 (86)	245 (90)
Month 6	5.7 (2.3)	151 (76)	202 (72)
Month 9	5.5 (2.2)	117 (77)	176 (64)
Month 12	5.4 (2.0)	102 (48)	167 (66)

Values are the mean (standard deviation) of measured values of C_0=trough concentration

Table 17 shows efficacy outcomes at 12 months.

Table 17 Trial A2310: Incidence rates of efficacy endpoints by treatment group (intention-to-treat 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)
- Biopsy-proven acute rejection >= 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)

Composite efficacy failure: biopsy-proven acute rejection >= ISHLT grade 3A, acute rejection (AR) associated with haemodynamic compromise (HDC), graft loss/re-transplant, death, or loss to follow-up.

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 receiving thymoglobulin induction therapy. The imbalance in fatalities within the thymoglobulin subgroup was particularly evident among patients hospitalised prior to transplantation and with left ventricular assistance devices (see section 4.4).

Kidney function over the course of trial A2310 was assessed by calculated glomerular filtration rate (GFR) using the MDRD formula and was 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.

This difference was mainly observed at centres where the mean ciclosporin concentrations were similar throughout the study period in patients receiving Certican and in patients randomised to the control arm. These findings underline the importance of reducing ciclosporin concentrations when combined with everolimus, as shown in Table 18 (see also section 4.2):

Table 18 Target ciclosporin trough concentrations per month

Target ciclosporin C_0	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
MMF group	200-350	200-350	200-300	150-250	100-250

In addition, the difference was mainly due to a difference developed during the first month post-transplantation when patients were still in an unstable haemodynamic situation, possibly confounding the kidney function analysis. 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:creatinine levels measured in spot urine samples, tended to be higher 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 (see section 4.4).

The adverse reactions for the everolimus 1.5 mg group in trial A2310 are consistent with the adverse reactions shown in Table 4. A lower rate of viral infections was reported for patients treated with Certican, resulting primarily from a lower reporting rate for CMV infection compared to MMF (7.2% vs. 19.4%).

Liver transplantation
In the Phase 3 adult liver transplant trial (H2304), reduced-dose tacrolimus and Certican 1.0 mg twice daily were administered to patients, with the initial dose of Certican given 4 weeks after transplantation, and was investigated in comparison with standard-dose tacrolimus. Certican was dose-adjusted to maintain target everolimus blood trough concentrations at 3-8 ng/mL for the Certican + reduced-dose tacrolimus arm. Tacrolimus doses were subsequently adjusted to achieve target trough concentrations of 3-5 ng/mL for 12 months in the Certican + reduced-dose tacrolimus arm.

Only 2.6% of participants in trial H2304 were Black so this trial provides only limited efficacy and safety data for this population (see section 4.2).

Overall, in the 12-month analysis, the incidence of the composite primary endpoint (treated biopsy-proven acute rejection (tBPAR), graft loss or death) was lower in the Certican + reduced-dose tacrolimus arm (6.7%) than in the tacrolimus control arm (9.7%) and consistent results were observed at 24 months (see Table 19).

Table 20 shows the results of individual components of the composite primary endpoint.

Table 19 Trial H2304: Comparison between treatment groups for Kaplan-Meier (KM) incidence rates of primary efficacy endpoints (intention-to-treat population – 12-month and 24-month analyses)

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 randomisation to Month 24/12	16	24	23	29
KM estimate of incidence rate of composite efficacy failure (tBPAR*, graft loss or death) at Month 24/12	6.7%	10.3%	9.7%	12.5%
Difference in KM estimates (vs. control)	-3.0%	2.2%		
97.5% CI for differences	(-8.7%, 2.6%)	(-8.8%, 4.4%)		
Z-test P-value (EVR+Reduced TAC - Control = 0) (No difference test)	0.230	0.452		
Z-test P-value* (EVR+Reduced TAC - Control ≥0.12) (Non-inferiority test)	<0.001	<0.001		

* tBPAR = treated biopsy-proven acute rejection

Table 20 Trial H2304: Comparison between treatment groups for incidence rates of secondary efficacy endpoints (intention-to-treat population – 12-month and 24-month analyses)

Efficacy endpoints	EVR/Reduced TAC N=245 n (%)	TAC Control N=243 n (%)	Risk diff. (95% 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)	0.661
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)	0.701
BPAR[1]				
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)	0.010
tBPAR[2]				
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)	0.203

1. BPAR = biopsy-proven acute rejection; 2. tBPAR = treated biopsy-proven acute rejection

*All p-values are from a two-sided test and were compared at 0.05 significance level.

Comparison between treatment groups for change in eGFR (MDRD4) [mL/min/1.73 m^2] from time of randomisation (day 30) to Month 12 and 24 demonstrated superior kidney function for the Certican + reduced-dose tacrolimus arm (see Table 21).

Table 21 Trial H2304: Comparison between treatment groups for eGFR (MDRD4) at Month 12 (intention-to-treat population – 12-month and 24-month analyses)

Difference vs. control						
Treatment	**N**	**LS mean (SD)**	**LSM mean (SD)**	**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)	<0.001	<0.001
24 months	245	-7.94 (1.53)	6.66 (2.12)	(1.9, 11.42)	<0.0001	0.0018
TAC Control						
12 months	243	-10.73 (1.54)				
24 months	243	-14.60 (1.54)				

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

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

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

A 24-month, multicentre, open-label, randomised, 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 composite efficacy failure (CEF) endpoint (tBPAR, graft loss or death) and at least one comparable 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 randomised 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. Adverse events in the EVR+rTAC group in the H2307 trial are consistent with the safety results of the pivotal studies presented in the 'Adverse Drug Reactions' section.

Paediatric population
Certican should not be used in paediatric kidney and liver transplant patients. The European Medicines Agency has waived the obligation to submit the results of studies with paediatric heart transplant patients (see section 4.2).

Certican was assessed in paediatric kidney allograft recipients (1-18 years of age; n=106) in a 12-month trial with 24 months additional follow-up. This multicentre, randomised, open-label trial with two parallel groups (1:1) evaluated the use of Certican in combination with reduced-dose tacrolimus and corticosteroids, which were withdrawn at 6 months post-transplantation, in comparison with mycophenolate mofetil and standard-dose tacrolimus. At 12 months, the efficacy of Certican with reduced-dose tacrolimus and steroid withdrawal was comparable to that of mycophenolate mofetil with standard-dose tacrolimus [9.6% (5/52) vs. 5.6% (3/54)] for the primary composite efficacy failure (CEF) endpoint of BPAR, graft loss and death. All of the events were BPAR; graft loss and death did not occur. At 36 months follow-up, the CEF endpoint was similar in both treatment groups, while treated BPAR occurred in five patients in each group. Graft loss was reported in one patient (2.1%) in the group receiving Certican with reduced-dose tacrolimus versus two patients (3.8%) in the group receiving mycophenolate mofetil with standard-dose tacrolimus. No deaths were reported during the trial. Extrapolation from Certican adult kidney transplant data to Certican paediatric study data and literature showed that the composite efficacy endpoint was lower than that observed in adults. Kidney function calculated by estimated glomerular filtration rate (eGFR) was comparable between both study groups.

In total, 35% (18/52) patients in the Certican group vs. 17% (9/54) in the control group were withdrawn from the study treatment due to adverse reactions/infections. Most of the adverse reactions/infections leading to premature discontinuation of the study drug were singular reactions and were not reported in more than one patient. In the Certican with reduced-dose tacrolimus group, two patients with post-transplant lymphoproliferative disease and one patient with hepatocellular carcinoma were reported.

In a 24-month, multicentre, single arm study, Certican with reduced-dose tacrolimus or ciclosporin was evaluated in paediatric liver transplant recipients (1 month-18 years of age, n=56) receiving either a full-size liver allograft or a technically modified liver allograft from a deceased or living donor. Efficacy failure was defined as a composite endpoint (tBPAR, graft loss or death at 12 months). Out of 56 patients, two met the primary composite efficacy failure endpoint or any of its components. There were no deaths or graft losses during the 24 months of treatment. An improvement in kidney function, as determined by the gain in mean estimated glomerular filtration rate (eGFR) from randomisation to Month 12, was 6.3 mL/min/1.73m^2. An improvement in kidney function was also observed at 24 months, with an increase in mean eGFR from baseline of 4.5 mL/min/1.73m^2.

No negative impact on growth or sexual maturation was observed in paediatric liver transplant recipients. However, three main safety concerns were identified from the safety analysis in paediatric liver transplant recipients compared to adults and published literature: high rates of premature discontinuation of study drug, serious infections leading to hospitalisation and PTLD. Incidence rates for PTLD in the 2-<18 years age group, and notably in Epstein-Barr virus negative children under 2 years of age, were higher compared to adults and published literature. Based on the safety data, the benefit/risk balance does not support recommendations for use.

5.2. Pharmacokinetic properties

Absorption

After oral administration, peak everolimus concentrations are reached 1 to 2 hours post-dose. Everolimus blood concentrations are dose proportional over the dose range of 0.25 to 15 mg in transplant patients. The relative bioavailability of the dispersible tablets compared with the tablets is 0.90 (90% CI 0.76-1.07) based on the AUC ratio.

Effect of food

Everolimus C_{max} and AUC are reduced by 60% and 16% when the tablet formulation is administered with a high-fat meal. To minimise variability, Certican should be taken consistently with or without food.

Distribution

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

Biotransformation

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 compounds 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. The parent substance is therefore considered to contribute most of the overall pharmacological activity of everolimus.

Elimination

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

Steady-state pharmacokinetics

Pharmacokinetics were comparable for kidney and heart transplant patients receiving everolimus twice daily concomitantly with ciclosporin for microemulsion. Steady state was reached by day 4 with a 2- to 3-fold accumulation in blood levels as compared with exposure after the first dose. T_{max} was reached 1 to 2 hours post-dose. C_{max} averaged 11.1 ± 4.6 and 20.3 ± 8.0 ng/mL and AUC averaged 75 ± 31 and 131 ± 59 ng.h/mL at doses of 0.75 and 1.5 mg twice daily, respectively. Pre-dose blood trough concentrations (C_{min}) averaged 4.1 ± 2.1 and 7.1 ± 4.6 ng/mL at doses of 0.75 and 1.5 mg twice daily, respectively. Everolimus exposure remains stable over time in the first post-transplant year. C_{min} is significantly correlated with AUC, yielding a correlation coefficient between 0.86 and 0.94. Based on a population pharmacokinetic analysis, oral clearance (CL/F) is 8.8 L/h (27% interpatient variation), and the central distribution volume (Vc/F) is 110 L (36% interpatient variation). Residual variability in blood concentrations is 31%. The elimination half-life is 28 ± 7 h.

Special populations

Hepatic impairment

Relative to the AUC of everolimus in subjects with normal liver function, the average AUC in 6 patients with mild hepatic impairment (Child-Pugh Class A) was 1.6-fold higher; in two independently studied groups of 8 and 9 patients with moderate hepatic impairment (Child-Pugh Class B), the average AUC was 2.1-fold and 3.3-fold higher, respectively; and in 6 patients with severe hepatic impairment (Child-Pugh Class C), the average AUC was 3.6-fold higher. Mean half-lives were 52, 59 and 78 hours in mild, moderate and severe hepatic impairment. The prolonged half-life delayed the time to reach steady-state everolimus blood concentrations.

Renal impairment
Post-transplant renal impairment (creatinine clearance (C_{Cr}) range 11-107 mL/min) did not affect the pharmacokinetics of everolimus.

Paediatric population
Fourteen paediatric *de novo* kidney transplant patients (2 to 16 years) received Certican dispersible tablets at a starting dose of 0.8 mg/m^2 (maximum 1.5 mg) twice daily with ciclosporin for microemulsion. Their doses were subsequently individualised based on therapeutic drug monitoring to maintain everolimus pre-dose trough concentrations ≥3 ng/mL. At steady state, the everolimus trough concentration was 6.2 ± 2.4 ng/mL, C_{max} was 18.2 ± 5.5 ng/mL and AUC was 118 ± 28 ng.h/mL, which are comparable to values measured in adults receiving Certican targeted to similar pre-dose trough concentrations. The steady-state CL/F was 7.1 ± 1.7 L/h/m^2, and the elimination half-life was 30 ± 11 h in paediatric patients.

Elderly patients
In adults (age range studied was 16-70 years), a limited reduction in everolimus oral clearance by 0.33% per year was estimated. No dosage adjustment is considered necessary.

Ethnicity
Based on a population pharmacokinetic analysis, oral clearance (CL/F) is, on average, 20% higher in Black transplant patients. See section 4.2.

Exposure-response relationships
The average everolimus trough concentration over the first 6 months post-transplant was related to the incidence of biopsy-proven acute rejection and thrombocytopenia in kidney and heart transplant patients (see Table 22). In liver transplant patients, the relationship between average everolimus trough concentrations and the incidence of biopsy-proven acute rejection is not well defined. No correlation between higher everolimus exposure and adverse reactions such as thrombocytopenia has been observed (see Table 22).

Table 22 Exposure-response relationships for everolimus in transplant patients

Kidney transplantation:					
Trough concentration (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 concentration (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%
Liver transplantation:					
Trough concentration (ng/mL)	≤3	3-8		≥ 8	
Freedom from tBPAR	88%	98%		92%	
Thrombocytopenia (≤75×10^9/L)	35%	13%		18%	

5.3. Non-clinical safety data

The non-clinical safety profile of everolimus was assessed in mice, rats, mini-pigs, 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, in rats only, 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 were no signs of renal toxicity in monkeys or mini-pigs.

Spontaneously occurring background diseases (chronic myocarditis in rats, Coxsackie virus infection in plasma and heart in monkeys, coccidial infestation of the gastrointestinal tract in mini-pigs, skin lesions in mice and monkeys) appeared to be exacerbated by treatment with everolimus. These findings were generally observed at systemic exposure concentrations within the therapeutic exposure range or above, with the exception of findings in rats, which occurred below therapeutic exposure due to high tissue distribution.

Ciclosporin in combination with everolimus caused higher systemic exposure to everolimus and increased toxicity. There were no new target organs in rats. Monkeys showed haemorrhage and arteritis in several organs.

In a male fertility study in rats, testicular morphology was affected at doses of 0.5 mg/kg and above, and sperm motility, sperm count, and plasma testosterone levels were decreased at 5 mg/kg, which is within the therapeutic exposure range 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 foetus. In rats, everolimus caused embryo-foetal toxicity at systemic exposure below the therapeutic exposure, which was manifested as mortality and reduced foetal weight. The incidence of skeletal variations and malformations at doses of 0.3 and 0.9 mg/kg (e.g. sternal cleft) was increased. In rabbits, embryotoxicity was evident by an increase in late resorptions.

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Butylated hydroxytoluene (E321)
Magnesium stearate (E470 B)
Lactose monohydrate
Hypromellose Type 2910
Crospovidone Type A
Lactose anhydrous

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

Store below 30°C, in the original package in order to protect from light and moisture.

6.5. Nature and contents of container

Aluminium/polyamide/aluminium/PVC blister.

Containers with 50/60/100/250 tablets.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and handling

No special precaution.

7. MARKETING AUTHORISATION HOLDER

Novartis Pharma AG

Switzerland

8. DATE OF TEXT REVISION

JUL-2024

NPI based on the prospect of the Spanish Medicines Agency and Health Products (AEMPS, by its acronym in spanish) of July 17th, 2024, corresponding to the Core Labelling Package N/A update v3.0 of May 25th, 2022.