**SCHEDULING STATUS**

S4

## 1 NAME OF THE MEDICINE

CERTICAN® 0, 25 MG (tablets)

CERTICAN® 0, 75 MG (tablets)

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0, 25/0, 75 mg everolimus.

Contains sugar:

CERTICAN® 0, 25 mg (tablets) contains 53 mg lactose

CERTICAN® 0, 75 mg (tablets) contains 119 mg lactose

For full list of excipients, see **section 6.1**.

## 3 PHARMACEUTICAL FORM

Tablets are white to yellowish, marbled, round, flat with bevelled edge.

0, 25 mg: engraved with “C” on one side and “NVR” on the other

0, 75 mg: engraved with “CL” on one side and “NVR” on the other

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

- **Kidney and heart transplant:**

  To reduce the risk 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 acute organ rejection in patients receiving a hepatic transplant. In liver transplantation, CERTICAN should be used in combination with tacrolimus and corticosteroids.

### 4.2 Posology and method of administration

**Posology**

Treatment with CERTICAN should only be initiated and maintained by medical practitioners who are experienced in immunosuppressive therapy following organ transplantation and who have access to CERTICAN whole blood level monitoring.

**Adults**

- *Kidney and heart transplantation*

  - An initial dose regimen of 0, 75 mg twice daily, is recommended for the general kidney and heart transplant population, administered as soon as possible after transplantation.

- *Liver transplantation*

    - The dose of 1, 0 mg twice daily is recommended for the hepatic transplant population with the initial dose approximately 4 weeks after transplantation.

- The daily dose of CERTICAN should always be given orally in two divided doses twice daily. CERTICAN should be consistently given either with or without food (see **section 5.2**) and at the same time as ciclosporin for microemulsion or tacrolimus (see **Therapeutic drug monitoring below**).
- CERTICAN is for oral use only.
- CERTICAN tablets should be swallowed whole with a glass of water and not crushed before use.
- **Patients receiving CERTICAN require dose adjustments based on blood levels achieved, tolerability, individual response, change in co-medications and the clinical situation. Dose adjustments can be made at 4 - 5 days intervals** (see **Therapeutic drug monitoring**).

**Black patients:**

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

**Special populations**

**Paediatric population**

**Use in children and adolescents (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 pharmacokinetic data, however, are available in kidney transplant paediatric patients (see **section 5.2**)

**Elderly population**

**Elderly patients (≥ 65 years):**

Clinical experience is limited in patients ≥ 65 years of age. Nevertheless, there are no apparent differences in the pharmacokinetics of CERTICAN in patients ≥ 65-70 years of age as compared with younger adults (see **section 5.2**)

**Patients with renal impairment:**

No dosage adjustment is required (see **section 5.2**).

**Patients with hepatic impairment:**

Whole blood trough levels ($C_0$) of CERTICAN 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 Class B) the dose should be reduced to approximately one half of the normal dose. For patients with severe hepatic impairment (Child-Pugh Class C), the dose should be reduced to approximately one third of the normal dose. Further dose titration should be based on therapeutic drug monitoring (see **section 5.2**).

**Table 1 CERTICAN dose reduction in patients with hepatic impairment**

| | **Normal hepatic function** | **Mild hepatic impairment (Child Pugh A)** | **Moderate hepatic impairment (Child Pugh B)** | **Severe hepatic impairment (Child Pugh C)** |
|---|---|---|---|---|
| **Renal and cardiac 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.* |
| **Hepatic 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:**

CERTICAN has a narrow therapeutic index, which may require adjustments in dosing to maintain therapeutic response.

Routine whole blood therapeutic drug level monitoring of CERTICAN is recommended. Based on exposure-efficacy and exposure-safety analysis, patients achieving CERTICAN whole blood trough levels ($C_0$) ≥ 3,0 ng/mL have been found to have a lower incidence of biopsy-proven acute rejection in renal, hepatic and heart transplantation than patients whose trough levels ($C_0$) 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 CERTICAN are based on chromatographic methods.

It is especially important to monitor CERTICAN 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**)

Ideally, dose adjustments of CERTICAN should be based on trough levels ($C_0$) obtained > 4-5 days after the previous dosing change. Since ciclosporin interacts with CERTICAN, CERTICAN levels may decrease if ciclosporin exposure is markedly reduced (i.e. trough concentration ($C_0$) < 50 ng/mL).

**Ciclosporin dose recommendation in renal transplantation:**

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.

Ciclosporin exposure reduction should be started immediately post-transplantation. (see **section 5.2).**

**Table 2 Renal transplantation: recommended target ciclosporin blood trough concentration windows**

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

(Measured $C_0$ and $C_2$ concentrations are shown in section 5.1).

It is important to ensure that both CERTICAN and ciclosporin levels do not fall below the therapeutic range early after transplantation to minimize the risk of efficacy failure.

Prior to dose reduction of ciclosporin it should be ascertained that steady state CERTICAN whole blood trough concentrations ($C_0$) are equal to or above 3 ng/mL.

There are limited data regarding dosing CERTICAN with ciclosporin trough concentrations ($C_0$) below 50 ng/mL, or $C_2$ 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.

**Ciclosporin dose recommendation in cardiac transplantation with CERTICAN:**

Cardiac transplant patients in the maintenance phase should have dose reduced 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.

In cardiac transplant patients, the ciclosporin dose should be based on ciclosporin blood trough levels.

**Table 3 Cardiac transplantation: recommended target ciclosporin blood trough concentration windows**

| **Target ciclosporin $C_0$ (ng/mL)** | **Month 1** | **Month 2** | **Month 3 – 4** | **Month 5 - 6** | **Month 7 - 12** |
|---|---|---|---|---|---|
| Certican groups | 200 - 350 | 150 - 250 | 100 – 200 | 75 - 150 | 50 - 100 |

In cardiac transplantation, there are limited data regarding dosing CERTICAN with ciclosporin trough ($C_0$) concentrations of 50-100 ng/mL after 12 months If the patient cannot tolerate reduction of ciclosporin exposure, the continued use of CERTICAN should be reconsidered.

Prior to dose reduction of ciclosporin it should be ascertained that steady state CERTICAN whole blood trough concentrations ($C_0$) are equal to or above 3 ng/mL.

**Use with basiliximab:**

There is limited experience of the use of CERTICAN together with basiliximab.

**Tacrolimus dose recommendation in hepatic transplantation:** (for more information refer to the Tacrolimus professional information leaflet)

Hepatic transplant patients should have the tacrolimus exposure reduced to minimise 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 ($C_0$) targeting 3-5 ng/mL. In a controlled clinical trial, complete withdrawal to tacrolimus has been associated with increased risk of acute rejection. CERTICAN has not been evaluated with full dose tacrolimus in controlled clinical trials.

**Method of administration**

For oral use.

## 4.3 Contraindications

- CERTICAN is contraindicated in patients with a known hypersensitivity to everolimus, sirolimus, or to any of the excipients.
- Pregnancy and lactation.
- Use with live vaccines.

## 4.4 Special warnings and precautions for use

**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.

In clinical trials, 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:**

The use of thymoglobulin (rabbit anti-thymocyte globulin) induction and the CERTICAN/ciclosporin/steroid regimen is not recommended. In a clinical study in heart transplant recipients 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 thymoglobulin combined with CERTICAN, steroid and ciclosporin at the blood concentration recommended for heart transplantation (higher than in kidney transplantation). This was associated with greater infection-related mortality among patients.

The death rate was 10 % when CERTICAN was used with thymoglobulin induction.

**Serious and opportunistic infections:**

Patients on a regimen of CERTICAN, are at increased risk of developing infections especially infections with opportunistic pathogens (bacterial, fungal, viral and protozoal). Fatal infections and sepsis have been reported in patients treated with CERTICAN (see **section 4.8)**. 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 multifocal leukoencephalopathy (PML).

These infections, often related to total immunosuppressive burden, should be considered in the differential diagnosis of immunosuppressed patients with deteriorating kidney graft function or neurological symptoms.

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

**Interaction with strong inhibitors or inducers of CYP3A4 and/or P-glycoprotein (PgP):**

Co-administration with strong inhibitors of CYP3A4 and/or the multidrug efflux pump P-glycoprotein (PgP) (e.g. ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir) may increase everolimus blood levels and is not recommended unless the benefit outweighs the risk.

Coadministration with strong inducers of CYP3A4 and /or PgP (e.g. rifampicin, rifabutin) is not recommended unless the benefit outweighs the risk.

If co-administration if inducers or inhibitors of CYP3A4 and/or PgP cannot be avoided, it is recommended that everolimus whole blood trough concentration and the clinical condition of the patient be monitored while they are concurrently administered with everolimus and after their discontinuation. Dose adjustments of everolimus may be required (see **section 4.5**).

**Lymphomas and other malignancies:**

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

**Porphyria:**

Safety has not been established.

**Liver function impairment:**

Close monitoring of everolimus whole blood trough levels ($C_0$) and everolimus dose adjustment is recommended in patients with impaired hepatic function (see **section 4.2**).

**Hyperlipidaemia:**

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. Patients receiving CERTICAN should be monitored for hyperlipidaemia and if necessary treated with lipid-lowering medicinal products and appropriate dietary adjustments made (see **section 4.5**)

The risk/benefit should be considered in patients with established hyperlipidaemia before initiating an immunosuppressive regimen including CERTICAN. Similarly, the risk/benefit of continued CERTICAN therapy should be re-evaluated in patients with severe refractory hyperlipidaemia.

Patients administered an HMG-CoA reductase inhibitor and/or fibrate should be monitored for the possible development of adverse effects as described in the respective professional information leaflets of these medicinal products (see **section 4.5**).

**Angioedema**

CERTICAN has been associated with the development of angioedema.

**CERTICAN and calcineurin inhibitor-induced renal dysfunction:**

In renal and cardiac transplantation 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 (see **section 4.2)**.

In a liver transplant study CERTICAN with reduced tacrolimus exposure has not been found to worsen renal function in comparison to standard exposure tacrolimus without CERTICAN.

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

**Proteinuria:**

The use of CERTICAN with calcineurin inhibitors in transplant recipients has been associated with increased proteinuria. The risk increases with higher everolimus blood levels. In renal transplant patients with mild proteinuria while on maintenance immunosuppressive therapy including a calcineurin inhibitor (CNI) there have been reports of worsening proteinuria when the CNI is replaced by CERTICAN. Reversibility has been observed with interruption of CERTICAN and reintroduction of the CNI. The safety and efficacy of conversion from CNI to CERTICAN in such patients have not been established.

Patients receiving CERTICAN should be monitored for proteinuria.

**Renal graft thrombosis:**

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

**Wound-healing complications:**

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

**Thrombotic microangiopathic disorders**

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

**Interstitial lung disease/non-infectious pneumonitis:**

Cases of interstitial lung disease, implying lung intraparenchymal inflammation (pneumonitis) and/or fibrosis of non-infectious etiology, some fatal, have occurred in patients receiving rapamycin 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. Cases of ILD have been reported with CERTICAN, which resolve on drug interruption with or without glucocorticoid therapy (see section 4.8 Undesirable effects). However, fatal cases have been reported.

**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 reports of reversible azoospermia and oligospermia in patients treated with CERTICAN. As preclinical toxicology studies have shown that everolimus can reduce spermatogenesis, male infertility must be considered a potential risk of prolonged CERTICAN therapy.

**Lactose warning:**

CERTICAN contains lactose, which may have an effect on the glycaemic control of patients with diabetes mellitus.

Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take CERTICAN.

## 4.5 Interaction with other medicines and other forms of Interaction

CERTICAN is mainly metabolised in the liver and, to some extent, in the intestinal wall by CYP3A4. It is also a substrate for the multidrug efflux pump, P-glycoprotein (PgP).

Therefore, absorption and subsequent elimination of systemically absorbed CERTICAN may be influenced by medicinal products that affect CYP3A4 and/or PgP.

Concurrent treatment with strong CYP3A4-inhibitors and/or inducers is not recommended. Inhibitors of PgP may decrease the efflux of CERTICAN from intestinal cells and increase CERTICAN blood concentrations. In vitro, CERTICAN was a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6, potentially increasing the concentrations of medicinal products eliminated by these enzymes.

Thus, caution should be exercised when co-administering CERTICAN with CYP3A4- and CYP2D6 substrates having a narrow therapeutic index. All *in vivo* interaction studies were conducted without concomitant use of ciclosporin.

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

The bioavailability of CERTICAN was significantly increased by co-administration of ciclosporin. In a single-dose study in healthy subjects, ciclosporin for microemulsion (Neoral) increased the AUC of CERTICAN by 168 % (range, 46 % to 365 %), and $C_{max}$ by 82 % (range, 25 % to 158 %), as compared with administration of CERTICAN alone. Dose adjustment of CERTICAN might be needed if the ciclosporin dose is altered (see **section 4.2**).

CERTICAN had only a minor clinical influence on ciclosporin pharmacokinetics in renal and heart transplant patients receiving ciclosporin for micro emulsion.

**Rifampicin (CYP3A4 inducer):**

Pre-treatment of healthy subjects with multiple-dose of rifampicin followed by a single dose of CERTICAN increased CERTICAN clearance nearly 3-fold, decreasing $C_{max}$ by 58 % and AUC by 63 %. Combination with rifampicin is not recommended (see **section 4.4**).

**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 CERTICAN, as well as total HMG-CoA reductase bioreactivity in plasma to a clinically relevant extent. However, these results cannot be extrapolated to other HMG-CoA reductase inhibitors.

Patients should be monitored for the development of rhabdomyolysis and other adverse events as described in the package inserts of HMG-CoA reductase inhibitors.

**Midazolam (CYP3A4A substrate):**

In a single dose midazolam 4 mg study, CERTICAN had no clinically significant effect on pharmacokinetic of midazolam. The $C_{max}$ of midazolam increased 1,25-fold (90 % CI, 1,14 – 1,37) and the $AUC_{inf}$ increased 1,30-fold (1,22 – 1,39). The half-life of midazolam was unaltered. This study indicated that everolimus is a weak inhibitor of CYP3A4.

**Other possible interactions:**

Use caution when co-administration of moderate CYP3A4 inhibitors or PgP inhibitors cannot be avoided.

Moderate inhibitors of CYP3A4 and PgP may increase CERTICAN blood levels (e.g. **antifungal medicines**: fluconazole, itraconazole; **macrolide antibiotics**: clarithromycin, toleandomycin, telithromycin; **calcium channel blockers**: nicardipin, diltiazem: **other substances:** cisapride, metoclopramide, bromocriptine, cimetidine, danazol; **HIV protease inhibitors:** nelfinavir, indinavir, amprenavir.

Following concomitant administration of everolimus and cannabidiol (Pgp inhibitor), the Cmax and AUC of everolimus were increased by approximately 2.5-fold.

Closely monitor for side effects and adjust the everolimus dose as needed (see s**ections 4.2** and **4.4**).

Inducers of CYP3A4 may increase the metabolism of CERTICAN and decrease CERTICAN blood levels (e.g. St. John's wort (Hypericum perforatum), **anticonvulsants**: carbamazepine, phenobarbital, phenytoin; **anti-HIV medicines:** efavirenz, nevirapine.

**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 (90 % CI 3.4-4.6) and AUC by 15.0-fold (90 % CI 13.6-16.6) (see **section 4.4**).

**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 (90 %CI 1.8-2.3) and AUC by 4.4-fold (90 % CI 3.5-5.4).

**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 (90 % CI: 1.9-2.7) and AUC by 3.5-fold (90 % CI: 3.1-3.9).

**Antibiotics:**

**Rifabutin**

Not studied. Decreased exposure expected.

**Grapefruit:**

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

**Vaccination:**

Immunosuppressants may affect the response to vaccination and vaccination during treatment with CERTICAN may therefore be less effective. The use of live vaccines should be avoided. (see **section 4.3).**

**Octreotide:**

Coadministration of everolimus with depot octreotide increased octreotide $C_{min}$ with a geometric mean ratio (everolimus/placebo) of 1.47-fold (90 % CI: 1.32 to 1.64).

## 4.6 Fertility, pregnancy and lactation

**Women of childbearing potential/ Contraception in males and females**

Women of childbearing potential should be advised to use effective contraception methods while they are receiving CERTICAN and for up to 8 weeks after treatment has been stopped (see **section 4.3).**

**Pregnancy**

CERTICAN should not be given to pregnant women.

Studies in animals have shown reproductive toxicity effects including embryotoxicity and fetotoxicity.

**Breastfeeding**

Women taking CERTICAN should not breastfeed their infants. CERTICAN and/or its metabolites were readily transferred into the milk of lactating rats.

**Fertility**

The potential for CERTICAN to cause infertility in male and female patients is unknown. Male infertility and secondary ammenorrhoea have been observed with reports in the literature of reversible azoospermia and oligospermia in patients treated with mTOR inhibitors.

## 4.7 Effects on ability to drive and use machines

CERTICAN may affect mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision.

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

## 4.8 Undesirable effects

### a. Summary of the safety profile

The frequencies of the adverse drug reactions listed below are derived from analysis of the 12-month incidences of events reported in multicentre, randomised, controlled trials investigating CERTICAN in combination with calcineurin inhibitors (CNI) and corticosteroids in transplant recipients. CERTICAN combined with ciclosporin~~,~~ was studied in five trials in renal transplant recipients totalising 2 497 patients, and three trials in heart transplant recipients totalising 1 531 patients.

CERTICAN, combined with tacrolimus, was studied in one trial which included 719 liver transplant recipients. The overall safety profile was not distinct from previous experiences with CERTICAN and expectations in a liver transplant population followed for up to 36 months.

Table 1 below contains adverse drug reactions possibly or probably related to CERTICAN seen in phase III clinical trials.

Except where noted otherwise, the adverse reaction profile is relatively consistent across all transplant indications. It is compiled according to MedDRA standard organ classes. 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 4 Adverse drug reactions possibly or probably related to Certican**

| Body system | Incidence | Adverse reaction |
|---|---|---|
| Infections and infestations | Very common | Infections (viral, bacterial, fungal), upper respiratory tract infection, lower respiratory |

| Body system | Incidence | Adverse reaction |
|---|---|---|
| | | tract and lung infections (including pneumonia)[1], urinary tract infections [2] |
| | Common | Sepsis, wound infection |
| Neoplasms benign, malignant and unspecified | Common | Malignant or unspecified tumours, malignant and unspecified skin neoplasm |
| | Uncommon | Lymphomas/post-transplant lymphoproliferative disorders (PTLD) |
| Blood and lymphatic system disorders | Very common | Leukopaenia, anaemia/erythropenia, thrombocytopenia[1] |
| | Common | Pancytopenia, thrombotic microangiopathies (including thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome) |
| Endocrine disorders | Uncommon | Hypogonadism male (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 |
| Cardiac disorders | Very common | Pericardial effusion[3] |
| | Common | Tachycardia |
| Vascular disorders | Very common | Hypertension, venous thromboembolic events |
| | Common | Lymphocoele[4], epistaxis, renal graft thrombosis |
| | Very common | Pleural effusion[1], cough[1], dyspnoea[1] |

| Body system | Incidence | Adverse reaction |
|---|---|---|
| Respiratory, thoracic and mediastinal disorders | Uncommon | Interstitial lung disease[5] |
| Gastrointestinal disorders | Very common | Abdominal pain, diarrhoea, nausea, vomiting |
| | Common | Pancreatitis, stomatitis/mouth ulceration, 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 |
| Renal 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 |
| General disorders and administration site conditions | Very common | Peripheral oedema, pain, healing impaired, pyrexia |
| | Common | Incisional hernia |
| Investigations | Common | Hepatic enzyme abnormal[8] |

*[1]common in renal and liver transplantation*

*[2]common in cardiac and liver transplantation*

*[3]in cardiac transplantation*

*[4]in renal and cardiac transplantation5the SMQ-based search for ILD showed the frequency of ILD in the clinical trials.*

*[5]This broad search also included cases caused by related events, 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 renal transplantation*

*[8]γ-GT, AST, ALT elevated*

In controlled clinical trials in which patients were monitored for at least 1 year, a total of 3,1 % developed lymphoma or lymphoproliferative disease malignancies, with 1,0 % developing skin malignancies and 0,6 % developing lymphoma or lymphoproliferative disorder.

The occurrence of the adverse events may depend on the degree and duration of the immunosuppressive regimen. In the studies, combining CERTICAN with ciclosporin elevated serum creatinine was observed more frequently in patients given CERTICAN in combination with full dose ciclosporin for microemulsion than in control patients. The overall incidence of adverse events was lower with reduced dose ciclosporin for microemulsion (see **section 5.1).** The safety profile of CERTICAN in the trials in which it was administered with reduced-dose ciclosporin was similar to that described in the in which full dose of ciclosporin was administered, except that elevation of serum creatinine was less frequent, and mean and median serum creatinine values were lower, than in the other phase III studies.

Cases of interstitial lung disease, implying lung intraparenchymal inflammation (pneumonitis) and/or fibrosis of non-infectious etiology, some fatal, have occurred in patients receiving rapamycin and their derivatives, including CERTICAN.

**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.

**Adverse drug reactions from spontaneous reports and literature (frequency not known)**

| Body system | Incidence | 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 |

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "Report Drug Reaction Process", found online under SAHPRA's safety publications: https://www.sahpra.org.za/

## 4.9 Overdose

- In overdose, side effects can be precipitated and/or be of increased severity (see **section 4.8).**
- In animal studies, CERTICAN showed a low acute toxic potential.
- No lethality or severe toxicity was observed in either mice or rats given single oral doses of 2 000 mg/kg (limit test).
- Reported experience with overdose in humans is very limited.
- There was a single case of accidental ingestion of 1, 5 mg CERTICAN by a 2-year old child, but no adverse events were observed.
- Single doses of up to 25 mg have been administered to transplant patients with acceptable acute tolerability.

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

# 5 PHARMACOLOGICAL ACTION PROPERTIES

## 5.1 Pharmacodynamic properties

A 34 Other: selective immunosuppressive agents

Pharmacotherapeutic group: selective immunosuppressive agents. ATC code: L04AA18

***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 antigen-activated T-cell proliferation, and thus clonal expansion, driven by T-cell-specific interleukins, e.g. interleukin-2 and interleukin-15. 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 G1 stage of the cell cycle.

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

Everolimus thus has a different mode of action from ciclosporin. In preclinical 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. Everolimus generally inhibits growth-factor-stimulated proliferation of haematopoietic cells and non-haematopoietic cells such as vascular smooth muscle cells. Growth-factor-stimulated proliferation of vascular smooth muscle cell, triggered by injury to endothelial cells and leading to neointima formation, plays a key role in the pathogenesis of chronic rejection. Preclinical studies with everolimus have shown inhibition of neointima formation in rat aorta allotransplantation model.

## 5.2 Pharmacokinetic properties

**Absorption:**

Peak everolimus concentrations are reached 1 to 2 hours after administration of an oral dose. Everolimus blood concentrations in transplant patients are dose-proportional-over the dose range of 0,25 to 15 mg.

**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. To minimise 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 5 000 ng/mL, is 17 % to 73 %. Plasma protein binding is approximately 74 % in healthy subjects and patients with moderate hepatic impairment. The distribution volume associated with the terminal phase (Vz/F) in maintenance renal transplant patients is 342 ± 107 litres.

**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.

**Excretion:**

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

**Steady-state pharmacokinetics:**

The pharmacokinetics was 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 hours post dose. 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., pre-dose 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 pharmacokinetic oral clearance (CL/F) is 8,8 L/h (27 % interpatient variation) and the central distribution volume (Vc/F) is 110 litres (36 % interpatient variation).

Residual variability in blood concentrations is 31 %. The elimination half-life is 28 ± 7 h.

**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 4.2**).

**Renal impairment:**

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

**Paediatrics:**

Everolimus CL/F increased in a linear manner with patient age (1 to 16 years), body surface area (0,49-1,92 m2), and weight (11-77 kg). Steady-state CL/F was 10,2 ± 3,0 L/h/m2 and elimination half-life was 30 ± 11 h.

**Elderly:**

A limited reduction in everolimus oral CL of 0,33 % per year was estimated in adults (age range studied was 16-70 years). No dose adjustment is considered necessary.

**Ethnicity:**

Based on population pharmacokinetics 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 ($C_0$) over the first 6 months post-transplant was related to the incidence of biopsy-confirmed acute rejection and of thrombocytopenia in kidney and heart transplant patients (see Table 1 below )

**Table 1**

| | | | | | |
|---|---|---|---|---|---|
| **Renal 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 % |
| **Cardiac 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 % |
| **Hepatic transplantation:** | | | | | |
| Trough concentration (ng/mL) | ≤3 | 3 – 8 | | | ≥ 8 |

| | | | |
|---|---|---|---|
| Freedom from rejection | 88 % | 98 % | 92 % |
| Thrombocytopenia (<75 x $10^9$/L) | 35 % | 13 % | 18 % |

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Butylated hydroxytoluene (E321), magnesium stearate, lactose monohydrate (see **section 4.4**), hypromellose, crospovidone, lactose anhydrous

Contains sugar: Lactose

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

36 months.

### 6.4 Special precautions for storage

Store at or below 30 °C.

Protect from light and moisture.

Store in original package.

### 6.5 Nature and contents of container

Clear transparent thermoformed Aluminium /Aluminium blister packs containing 50/60/100/250 tablets.

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

Any unused product or waste material should be disposed of in accordance with local requirements.

## 7 THE HOLDER OF THE CERTIFICATE OF REGISTRATION

NOVARTIS SOUTH AFRICA (PTY) LTD

Magwa Crescent West

Waterfall City, Jukskei View

2090

## 8 REGISTRATION NUMBER(S)

CERTICAN® 0.25 mg tablets: 38/34/0686

CERTICAN® 0.75 mg tablets: 38/34/0687

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 July 2005

## 10 DATE OF REVISION OF TEXT

27 February 2023