NOVARTIS

CERTICAN® (everolimus)
0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg Tablets
0.1 mg or 0.25 mg Dispersible Tablets

Basic Succinct Statement (BSS)

Version 2.1

Code: BSS RD 05 Oct 18; APPR 29 Nov 19

This material is only meant for Healthcare Professionals

CERTICAN® Tablets
CERTICAN® Dispersible Tablets

Important note: Before prescribing, consult full prescribing information.

Presentation: Everolimus. Tablet containing 0.25, 0.5, 0.75, or 1.0 mg of everolimus, and dispersible tablets containing 0.1 or 0.25 mg of everolimus.

Indications: ♦Prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving an allogeneic renal or cardiac transplant in combination with ciclosporin for microemulsion and corticosteroids. ♦Prophylaxis of organ rejection in adult patients receiving a hepatic transplant in combination with tacrolimus and corticosteroids.

Dosage and administration: ♦Recommended general daily dose is 0.75 mg b.i.d. for kidney and heart transplant population. For the hepatic transplant population, recommended general daily dose is 1.0 mg b.i.d with the initial dose starting approximately 4 weeks after transplantation. ♦Whole blood trough levels of everolimus should be closely monitored in patients with impaired hepatic function. Dose should be reduced to approximately two-thirds in patients with mild hepatic impairment and to approximately one half in patients with moderate or severe hepatic impairment. ♦Very limited experience in children.

Contraindications: Hypersensitivity to everolimus, sirolimus or to any of the excipients.

Warnings and precautions: ♦An increased risk of acute rejection and an improved renal function were observed in patients who discontinued the administration of ciclosporin from month 4.5 after renal transplantation compared with those who continued the administration of ciclosporin. ♦Caution is advised with the use of thymoglobulin (rabbit anti-thymocyte globulin) induction and the Certican/ciclosporin/steroid regimen. ♦Increased risk of developing lymphomas and other malignancies, particularly of the skin. ♦Oversuppression of the immune system with increased susceptibility to infections, especially infections with opportunistic pathogens (bacterial, fungal, viral, protozoal) which can include BK virus-associated nephropathy which can lead to kidney graft loss and the potentially fatal JC virus-associated progressive multiple leukoencephalopathy (PML). ♦Patients should be monitored for hyperlipidemia. ♦Angioedema has been observed with Certican, in the majority of cases reported, patients were receiving ACE inhibitors as co-medication. ♦Proteinuria is increased in transplant recipients and may increase in severity when Certican is substituted for a calcineurin inhibitor in a maintenance therapy renal transplant patient with pre-existing mild proteinuria. ♦Reduced doses of ciclosporin are required for use in combination with Certican in order to avoid renal dysfunction. In liver transplant study Certican with reduced exposure tacrolimus has not been found to worsen renal function in comparison to standard exposure tacrolimus. Regular monitoring of blood drug levels (everolimus and ciclosporin), proteinuria and renal function is recommended. ♦Co-administration of everolimus with known strong CYP3A4 inhibitors and inducers is not recommended unless the benefit outweighs the risk. ♦Increased risk of kidney arterial and venous thrombosis, resulting in graft loss, mostly within the first 30 days post-transplantation. ♦Certican, like other mTOR inhibitors, can impair healing increasing the occurrence of post-transplant complications. 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 in liver transplant recipients. ♦The concomitant administration of Certican with a calcineurin inhibitor (CNI) may increase the risk of CNI-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy. ♦Cases of interstitial lung disease (ILD), some fatal, have been reported with Certican. Mostly, the condition resolves after discontinuation of Certican and/or addition of glucocorticoids. However, fatal cases have also occurred. ♦Certican may increase the risk of new-onset diabetes mellitus. Blood glucose concentrations should be monitored closely in patients treated with Certican.

Pregnancy, lactation, females and males of reproductive potential

Pregnancy: Should not be used during pregnancy unless clearly necessary.

Lactation: Should not be used by breast-feeding women.

Females and males of reproductive potential: Highly effective contraception methods must be used while receiving Certican and for up to 8 weeks after ending treatment.

Infertility: There are literature reports of reversible azoospermia and oligospermia in patients treated with mTOR inhibitors. Potential risk for male infertility with prolonged Certican therapy.

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

Adverse drug reactions:

♦**Very common (>10%):** Infections (viral, bacterial, fungal), lower respiratory tract infection, upper respiratory tract infection, urinary tract infections, anaemia/erythropenia, leukopenia, thrombocytopenia, hyperlipidaemia (cholesterol and triglycerides), new onset diabetes mellitus, hypokalaemia, insomnia, anxiety, headache, venous thromboembolic events, hypertension, cough, dyspnoea, diarrhoea, nausea, vomiting, abdominal pain, pericardial and pleural effusion, peripheral oedema, healing impairment, pain and pyrexia.

♦**Common (1 to 10%):** Malignant and unspecified tumours, skin neoplasms, wound infection, sepsis, pancytopenia, thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome, tachycardia, epistaxis, lymphocele, renal graft thrombosis, stomatitis/mouth ulceration, oropharyngeal pain, myalgia angioedema, acne arthralgia, pancreatitis, proteinuria, erectile dysfunction, renal tubular necrosis, incisional hernia and hepatic enzyme abnormal.

♦**Uncommon (0.1 to 1%):** Lymphomas, male hypogonadism, interstitial lung disease, hepatitis (non-infectious) and jaundice.

♦**Unknown:** Pulmonary alveolar proteinosis, erythroderma, leukocytoclastic vasculitis, and ovarian cyst.

Interactions: ♦Caution should be exercized when co-administering everolimus with CYP3A4- and CYP2D6-substrates having a narrow therapeutic index. ♦Caution with concomitant use of rifampicin, rifabutin or ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin or ritonavir, as it may be necessary to modify the dose of Certican. ♦Caution with inducers of CYP3A4 (e.g St. John's Wort, anticonvulsants, (e.g carbamazepine), phenobarbital, phenytoin, anti-HIV drugs (e.g efavirenz, nevirapine),

erythromycin, verapamil, inhibitors of PgP, and moderate inhibitors of CYP3A4 (e.g. antifungal substances: fluconazole, calcium channel blockers: nicardipine, diltiazem, protease inhibitors: nelfinavir, indinavir, amprenavir, octreotide and midazolam. ♦Avoid grapefruit juice, grapefruit. ♦Avoid use of live vaccines.