NOVARTIS

Drug Safety & Epidemiology

Everolimus

RAD001

EU Safety Risk Management Plan Elements for a Public Summary

Active substance(s) (INN or common name):	Everolimus
Pharmacotherapeutic group (ATC Code):	LO4A18
Name of Marketing Authorization Holder / Applicant:	Novartis Europharm Limited
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	Certican®
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1 Part VI.2 Elements for a Public Summary

1.1 Part VI.2.1 Overview of disease epidemiology

Certican® belongs to a group of medicines called immunosuppressants. It is used to prevent the body's immune system from rejecting a transplanted kidney, heart or liver. Certican is used together with other medicines, such as ciclosporin for kidney and heart transplantation, tacrolimus for liver transplantation, and corticosteroids.

Kidney transplantation: In 2010, approximately 70,000 kidney transplant cases were performed worldwide. Approximately 85% of adults and 82% of children receiving a kidney from a living donor are expected to be alive with a functioning kidney at 5 years after the transplantation. In patients receiving a kidney transplant from a deceased donor, 70% of adults and 70% of children are expected to be alive with a functioning kidney at 5 years.

Heart transplantation: In 2010, approximately 5,600 heart transplant cases were performed worldwide. About 75% of adults and 72% of children receiving a heart transplant are alive at 5 years from transplantation.

Liver transplantation: In 2010, about 21,000 cases of liver transplant were performed in the World. Approximately 72% of adults and 82% of children receiving a liver transplant from a living donor are expected to be alive with a functioning liver at 5 years after the transplantation. In patients receiving a liver from a deceased donor, 68% of adults and 75% of children are expected to be alive with a functioning liver at 5 years.

1.2 Part VI.2.2 Summary of treatment benefits

The active substance of the medicinal product named Certican is everolimus. Everolimus belongs to a group of medicines called immunosuppressants. It is used to prevent the body's immune system from rejecting a transplanted kidney, heart or liver. Certican is used together with other medicines, such as ciclosporin and corticosteroids for kidney and heart transplantation. The usual starting dose is 1.5 mg/day in kidney and heart transplantation. For this regimen, the incidence of rejection, graft loss or death was similar to the control group. A regimen with higher everolimus dose (3 mg) was efficacious but, overall safety was worse. Therefore the recommended regimen is everolimus 1.5 mg (with dose adjusted to maintain adequate blood drug concentrations), combined with reduced-dose ciclosporin and corticosteroids.

In liver transplantation, Certican at a starting dose of 2.0 mg/day was tested with reduced-dose tacrolimus and corticosteroids. For this combination efficacy (prevention of rejection, graft loss or death) was similar and renal function was better compared to the control group treated with tacrolimus.

1.3 Part VI.2.3 Unknowns relating to treatment benefits

In the main and supporting studies nearly all patients were Caucasians, aged between 18 and 70. With respect to race, the percentage of Black patients was limited in all Certican studies and results suggest that the rate of rejection is higher in this population. However, similar results have been demonstrated for other immunosuppressive treatments.

In adult Certican studies there is no difference in results between age groups. Up to date there is insufficient data in children and adolescents to recommend the use of Certican in kidney transplantation. In liver transplant paediatric patients, Certican should not be used.

1.4 Part VI.2.4 Summary of safety concerns

Table 1-1 Important identified risks

Risk	What is known	Preventability
Abnormal renal function caused by Certican and other transplant drugs of the class of calcineurin inhibitors (e.g.ciclosporin, tacrolimus) (Certican and calcineurin inhibitor induced renal dysfunction)	• In renal and heart transplantation, reduced doses of ciclosporin are required in combination with Certican to avoid renal dysfunction. • A liver transplant study showed, Certican with reduced tacrolimus dosage did not worsen renal function in comparison to standard exposure tacrolimus.	• Regular monitoring of renal function is recommended. • The physician should adjust Certican dose if the patient has abnormal renal function test result. • Caution is needed if co-administered drugs are known to cause renal impairment.
High level of protein in urine (Proteinuria)	The use of Certican with other transplant drugs of the class of calcineurin inhibitors • Causes high level of protein in urine (proteinuria) in 1 to 10 patients out of 100 patients. • The risk increases with higher Certican blood levels. This is a common side effect in heart and liver transplant. • Protein level in urine is back to normal once Certican is replaced by a transplant drug of the class of the calcineurin inhibitors.	Regular monitoring of renal function (Protein/creatinine level) is recommended.
Wound healing complications	The use of Certican • Increases the risk of impaired healing and occurrence of complications after the transplantation such as wound ruptures along surgical suture, fluid accumulation and wound infection. • Renal transplant patients	• Patient and physician should take special care if the patient had a recent major surgery, or if he/she still has an unhealed wound following surgery, as Certican may increase the risk of wound-healing problems.

Risk	What is known	Preventability
	with higher body mass index are at increased risk of collection of lymphatic fluid within the body (Lymphocele). • Heart transplant patients are at increased risk of fluid accumulation in the sac around the heart and in the lungs and chest cavity (pericardial and pleural effusion), which if severe, can make the patient breathless • Liver transplant patients are at increased risk of hernia caused by an incompletely-healed surgical wound (incisional hernias). This may affect more than 1 in 10 patients.	
High level of fats in the blood (Hyperlipidemia)	• The use of Certican with other transplant drugs of the class of calcineurin inhibitors associated with increased serum cholesterol and triglycerides. • The use of Certican with a drug of the class of HMG-CoA reductase inhibitor (e.g., statins) and/or fibrate (bezafibrate, ciprofibrate etc.) can cause a breakdown of muscle fibers (rhabdomyolysis) or other side effects. • Certican cause high level of fats (lipids, cholesterol and triglycerides) in the blood in 1 out of 10 patients.	• If the patient has a history of high lipid level, he / she should inform the physician before starting Certican. • Regular monitoring of blood lipid level is recommended. • If required, the physician may treat the patient with lipid-lowering medicinal products and the patient may need to make dietary adjustments.
Blood clot in transplanted kidney (Renal graft thrombosis)	• With Certican use, within the first 30 days of transplantation, patients may develop blood clot in transplanted kidney (kidney arterial and venous thrombosis). In most severe case this can result in graft loss.	• Regular monitoring of kidney function is recommended in all patients. • Patients should take special care if the co-administering medicinal products are known to have a negative effect

Risk	What is known	Preventability
	• Certican can cause clotting in the blood vessels of the kidney in 1 to 10 out of 100 patients.	on kidney function.
High blood sugar (New onset diabetes mellitus)	• Certican increases the risk of high blood sugar (New onset diabetes mellitus) after transplantation.	• Blood glucose concentrations should be monitored closely in patients treated with Certican.
Blood clot in capillaries and arterioles (Thrombotic microangiopathies)	• The use of Certican with other transplant drugs of the class of calcineurin inhibitors is associated with increased risk of kidney damage with low blood platelets and low red blood cell counts, with or without a rash) in 1 to 10 patients out of 100 patients. (thrombocytopenic purpura/ hemolytic uremic syndrome)	• Regular monitoring of kidney function and blood test are recommended in all patients.
Lung disease of unknown origin (Interstitial lung disease)	• Certican causes interstitial lung disease in 1 to 10 patients out of 1000 patients. • Interstitial lung disease generally resolved if Certican is stopped. Sometimes patient needs glucocorticoid therapy. • In most severe cases interstitial lung disease causes death.	• If the patient experiences respiratory symptoms (e.g. coughing, difficulty in breathing and wheezing), the patient should inform the physician. • The physician may decide whether and how the patient needs to continue Certican, and/or whether he/she needs to receive other medicines to resolve this condition.
Infections	• Medicines that suppress the immune system like Certican reduce body's ability to fight against infections. One out of 10 patients develops infections (bacterial, fungal, viral and protozoal). • In most severe cases this may lead to inflammation of whole body (sepsis) or	• The physician should be consulted if the patient has a fever or generally feels unwell, or has local symptoms such as coughing or a burning sensation when urinating that are severe or persistent over several days. • The physician must be contacted immediately

Risk	What is known	Preventability
	death.	if the patient is confused, has problems speaking, memory loss, a headache, impaired vision or seizures, as these may be symptoms of a rare but very serious condition affecting the brain called progressive multiple leukoencephalopathy. • In clinical trials, patients with Certican were also treated with drugs which prevent germs from growing). This gave protection against pneumonia (*Pneumocystis jiroveci/carinii)* and Cytomegalovirus infections.
Cancers and benign tumors (Malignancies)	• Medicines that suppress the immune system like Certican increase the risk of developing cancers, particularly of the skin and the lymphoid system (lymphoma/post-transplant lymphoproliferative disorder). • Certican causes Cancers, benign tumors and skin cancers in 1 to 10 patients out of 100 patients.	• Patient should limit contact to sunlight and UV light by wearing appropriate protective clothing and frequently applying a sunscreen with a high protection factor.
Swelling mainly in the face and throat due to allergic reaction (Angioedema)	• The use of Certican with a class of medicine known as ACE inhibitor results in swelling in the face and throat due to allergic reaction (Angioedema) in 1 to 10 out of 100 patients.	• If the patient develops swelling of face, lips, tongue or throat, he/she should stop taking Certican and tell his/her physician straight away.
Swelling (Edema, including peripheral edema)	• Certican causes swelling in 1 to 10 patients out of 100 patients.	• If the side effect gets serious, the patient should inform his /her physician or pharmacist.
Certican level Drug interaction with other drugs	• Certican should not be used with a class of medicine known as	• Regular monitoring of Certican level in blood is recommended if the

Risk	What is known	Preventability
increasing/decreasing the speed of the wash out of Certican that use the same enzymes as Certican called cytochrome P450 3A4 (CYP3A4) and/or P-glycoprotein (P-gP) (Interaction with inhibitors/ inducers of CYP3A4 and P-glycoprotein[e.g. . ketokonazol, itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir, rifampicin, rifabutin, carbamazepine, phenytoin, pimozide, astemizole, cisapride, quinidine and ergot alkaloid derivative])	CYP3A4-inhibitors (e.g. ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir) and inducers (e.g. rifampicin, rifabutin) and/or P-glycoprotein unless the benefit is more than the side effects.	patient is taking inhibitors/ inducers of CYP3A4 and P-gP.
Venous thrombosis (blockage of a major vein by a blood clot)	• One out of 10 patients develops venous thrombosis (blockage of a major vein by a blood clot).	• The pathophysiology of everolimus induced venous thrombosis is unknown. Based on the limited data available from clinical trials suggesting that everolimus could potentiate the risk of venous thrombosis no guidance for the preventability could be established.

Table 1-2 Important potential risks

Risk	What is known
Impaired male fertility	Certican may have an impact on male fertility.
Abnormalities of physiological development in newborns (Teratogenicity)	• There are no adequate data from the use of Certican in pregnant women. Studies in animals have shown toxic effect on embryo/fetus (fetotoxicity). • The potential risk for humans is not known. Certican should not be given to pregnant women unless the possible benefit is more than possible side effects. • Women of childbearing potential should be advised to use effective measures to prevent pregnancy (contraception methods) while they are receiving Certican and up to 8 weeks after treatment has been stopped.

Table 1-3 Missing information

Risk	What is known
Treatment with Certican	• There are no adequate data from the use of Certican in

Risk	What is known
during pregnancy or while breast-feeding (Exposure in pregnancy/breast-feeding women)	pregnant women. Certican should not be given to pregnant women unless the possible benefit is more than possible side effects in fetus. • It is not known whether Certican is excreted in human milk. In animal studies, Certican and/or its metabolites were readily transferred into the milk of lactating rats. Therefore, women who are taking Certican should not breast feed.
Use in children and adolescents (pediatric population)	Results from the subset analyses of studies CRAD001A2314 and CRAD001H2305 are currently available and briefly described as follows: Study CRAD001A2314 (30 patients, 15 treated with everolimus): Appropriate antirejection efficacy and improvement of renal function with a safety profile according to what was expected for the indication and the targeted population Study CRAD001H2305 (25 patients treated with everolimus): Appropriate antirejection efficacy and improvement of renal function. Higher frequency than expected of the following safety findings, especially in the age group of ≤ 7 years: discontinuation of study medication; PTLD and serious infections leading to hospitalization. The mentioned findings were the based of the changes in the study conduct following the recommendations from the DMC (closure of recruitment, discontinuation of study medication in children ≤ 7 years of age). • Both studies are currently ongoing: A2314 to complete recruitment of the full sample size (106 patients); H2305 to complete follow up of patients recruited in the study (56) until Dec 2014, when enrolment in the study was terminated.
Severe liver function impairment (Severe liver function impairment)	• Close monitoring of Certican level in whole blood levels (trough level) and Certican dose adjustment is recommended in patients with liver disorder. The dose should be reduced to approximately two thirds of the normal dose for patients with mild liver disease (Child-Pugh Class A), approximately one half of the normal dose for patients with moderate liver disease (Child-Pugh Class B), and approximately one third of the normal dose for patients with severe liver disease (Child Pugh Class C). • Close monitoring of Certican whole blood trough levels (C_0) and Certican dose adjustment is recommended in patients with impaired liver function.
Patients at high immunological risk	• There are no adequate data from the use of Certican in patients at high immunological risk.
Use of everolimus with immunosuppressive agents other than ciclosporin for microemulsion, basiliximab, tacrolimus and corticosteroids	• There are no adequate data from the use of Certican with immunosuppressive agents other than conventional immunosuppressive therapy.

1.5 Part VI.2.5 Summary of additional risk minimization measures by safety concern

Not applicable. No additional risk minimization measures proposed.

1.6 Part VI.2.6 Planned post authorization development plan

1.6.1 List of studies in post authorization development plan

None.

1.6.2 Studies which are a condition of the marketing authorization

None.

1.7 Part VI.2.7 Summary of changes to the Risk Management Plan over time

Table 1-4 Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
RMP v 1.1	04 Oct 2011	**Identified risks**: Increased ciclosporin nephrotoxicity Increased proteinuria in *de novo* renal transplant recipients Wound-healing complications Hyperlipidemia Renal graft thrombosis New onset diabetes mellitus (NODM) Thrombotic microangiopathy (TMA) Interstitial lung disease (ILD) Infections Malignancies Angioedema Peripheral edema **Potential risks**: Teratogenicity **Missing information**: Pregnancy/breast-feeding women Use in a pediatric population Severe liver failure	**Pharmacovigilance activities**: **Study CRAD001A2310**: A phase 3 study comparing recommended Certican/CsA regimen against non-Certican, CsA-based regimen in *de novo* heart transplant recipients. **Study CRAD001X2102**: An open-label, single-dose study to assess the pharmacokinetics of oral Certican in subjects with impaired hepatic function. **Risk minimization activity**: Not applicable
RMP v 2.0	14 Oct 2011	**Identified risks**: Renaming:'Increased ciclosporin nephrotoxicity' changed to 'Certican and calcineurin inhibitor (CNI) induced renal dysfunction' 'Increased proteinuria in *de novo* renal transplant' changed to 'proteinuria'. Peripheral edema changed to edema/peripheral edema **Addition**:	**Pharmacovigilance activities**: Addition: Study **CRAD001H2304E1** (Extension study of liver transplant study CRAD001H2304) **CRAD001H2305** (Information about the pediatric liver transplant

Version	Date	Safety Concerns	Comment
		Interaction with inhibitors/ inducers of CYP3A4 and P-gP (e.g. ketokonazol, itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir,rifampicin, rifabutin) **Potential risks**: No change **Missing information**: **Renaming**: "Severe liver failure' to 'severe liver function impairment'	study was added in accordance with EMA final decision P/0006/2012) **CRAD001A2314** (PIP renal study) **CRAD001A2313** (PIP heart study code) Deletion: **CRAD001A2310** (due to study completion, result was included) and **CRAD001X2102** (due to study completion, result was included) **Risk minimization activity**: No change
EU RMP v 2 updated with respons e to day 85 question s	03. Jul 2012	**Identified risks**: No change **Potential risks**: No change **Missing information**: No change	**Pharmacovigilance activities**: Deletion **CRAD001A2313** (because Novartis received a waiver). **Risk minimization activity**: No change
EU RMP v 2.2	22 Oct 2012	**Identified risks**: No change **Potential risks**: No change **Missing information**: No change	**Pharmacovigilance activities**: No change **Risk minimization activity**: No change
EU RMP v 3.0	20 Mar 2013	**Identified risks**: No change **Potential risks**: No change **Missing information**: No change	**Pharmacovigilance activities**: No change **Risk minimization activity**: No change
EU RMP v 4.0	20-May-2015	**Identified risks**: - Venous thrombosis **Potential risks**: Impaired male fertility **Missing information**: - Patientat high immunological risk - Use of everolimus with immunosuppressive agents other than ciclosporin for microemulsion, basiliximab, tacrolimus and corticosteroids	**Pharmacovigilance activities**: Post authorization efficacy study CRAD001H2304E1 completed **Risk minimization activity**: No change
EU	21-Oct-2015	**Identified risks**: No change	**Pharmacovigilance**

Version	Date	Safety Concerns	Comment
RMP v 4.1		**Potential risks**: No change **Missing information**: No change	**activities**: No change **Risk minimization activity**: No change