Summary of the risk management plan for Certican® (Everolimus)

I. The medicine and what it is used for

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 (Kasiske et al 2013). 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 (Matas et al 2013).

Heart transplantation: In 2010, approximately 5,600 heart transplant cases were performed worldwide (Kasiske et al 2013). About 75% of adults and 72% of children receiving a heart transplant are alive at 5 years from transplantation (Colvin-Adams et al 2013).

Liver transplantation: In 2010, about 21,000 cases of liver transplant were performed in the World (Kasiske et al 2013). 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 (Kim et al 2013).

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Certican, together with measures to minimize such risks and the proposed studies for learning more about Certican's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment - so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Certican is not yet available, it is listed under 'missing information' below.

II.A: List of important risks and missing information

Important risks of Certican are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of *Certican*. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Table 1 List of important risks and missing information

Important identified risks	New onset diabetes mellitus (NODM)
	Thrombotic microangiopathies (TMA)
	Malignancies
Important potential risks	Impaired male fertility
	Unfavourable outcome of everolimus exposure during pregnancy and breast-feeding
Missing information	Use in pediatric population
	Severe liver function impairment
	Patients at high immunological risk

II.B: Summary of important risks

Table 2 Important identified risk: New onset diabetes mellitus (NODM)

Evidence for linking the risk to the medicine	Current evidence is based on the review of clinical trial data, published literature and post marketing evidence (Montori et al 2002, Fabrizi et al 2005, Cosio et al 2001, Kasiske et al 2003, Woodward et al 2003, Davidson et al 2003, Gourishankar et al 2004, Abbott et al 2005, Matas et al 2002, Rodrigo et al 2006, Johnston et al 2008, Hariharan 2006).
Risk factors and risk groups	Risk factors have not been identified in Certican studies specifically. Otherwise, unmodifiable factors predisposing to development of NODM have been described as: older age, black and hispanic ethnicity, and family history of diabetes mellitus. Modifiable risk factors include overweight/obesity, viral infection, drugs (steroids, CNIs), and dosage. Also, the use of mTOR inhibitors has been described as a factor (Rodrigo et al 2006; Johnston et al 2008).
Risk minimization measures	**Routine risk minimization measures** • SmPC Section 4.4 and Section 4.8. **Additional risk minimization measures** None

Table 3 Important identified risk: Thrombotic microangiopathies (TMA)

Evidence for linking the risk to the medicine	Current evidence is based on the review of clinical trial data, published literature and post marketing evidence (Candinas et al 1994, Hochstetler et al 1994, Randhawa et al 1996, Zent et al 1997, Bren et al 1998, Zarifian et al 1999, Reynolds et al 2003, Ponticelli and Banfi 2006, Ponticelli 2007).
Risk factors and risk groups	Familial or idiopathic TMA can exist in individuals in the absence of transplantation and use of drugs, the familial form being linked to genetic disorders. Such individuals can have a considerably increased risk of recurrent TMA, making it important for such a predisposition to be looked for in the routine screening of renal failure patients who are candidates for transplantation. In transplant recipients, ischemia-reperfusion injury, acute rejection, and viral infection have been described as predisposing to TMA, as well as therapy with CNI and mTOR inhibitors.
Risk minimization measures	**Routine risk minimization measures** • SmPC Section 4.4 and Section 4.8. **Additional risk minimization measures** None

Table 4 Important identified risk: Malignancies

Evidence for linking the risk to the medicine	Current evidence is based on the review of clinical trial data, published literature and post marketing evidence (Andreone et al 2003, Paya et al 1999, U.S. OPTN/SRTR 2003, Smith et al 2006, Adam and Hoti 2009, Faull et al 2005, Chapman and Webster 2004, Kasiske et al 2004, Jensen et al 1999, Gjersvik et al 2000, London et al 1995, Buell et al 2005, Campistol et al 2007, ANZDATA Registry report 2008, Smith et al 2013, Debray et al 2009).
Risk factors and risk groups	No analysis has been carried out for specific risk factors for malignancy associated with everolimus. Epidemiology studies have identified the following as risk factors: intensity of immunosuppression, Epstein-Barr virus infection (PTLD), chronic viral hepatitis (hepatoma), and duration of end-stage renal disease (renal cell carcinoma) (Buell et al 2005).
Risk minimization measures	**Routine risk minimization measures** • SmPC Section 4.4 and Section 4.8. **Additional risk minimization measures** None

Table 5 Important potential risk: Impaired male fertility

Evidence for linking the risk to the medicine	Not available. There are literature reports of reversible azoospermia and oligospermia in patients treated with mTOR inhibitors. Preclinical toxicology studies have shown that mTOR inhibitors can reduce spermatogenesis
Risk factors and risk groups	Risk factors are unknown
Risk minimization measures	**Routine risk minimization measures** • SmPC Section 4.4. **Additional risk minimization measures** None

Table 6 Important potential risk: Unfavourable outcome of everolimus exposure during pregnancy and breast-feeding

Evidence for linking the risk to the medicine	Limited data is available for association of use of Certican and adverse outcome of pregnancy. Experimentation has suggested that in mammals the PI-3/AKT/mTOR pathway plays an important role in the control and growth of embryonic cells, with the possibility for this to be interrupted, at least partially, by mTOR inhibition (Murakami et al 2004).
Risk factors and risk groups	Not relevant
Risk minimization measures	**Routine risk minimization measures** • SmPC Section 4.6 **Additional risk minimization measures** None

Table 7 Missing information: Use in pediatric population

Evidence for linking the risk to the medicine	The clinical experience in pediatric population remains limited and provide insufficient experience to recommend the use of everolimus in pediatric population. Evidence generation by regular monitoring of data from pediatric use to identify new safety information with use of everolimus or any trends/patterns in AEs reported in pediatric cases that are different from general population AEs.
Risk factors and risk groups	Not relevant
Risk minimization measures	**Routine risk minimization measures** • SmPC Section 4.2 **Additional risk minimization measures** None

Table 8 Missing information: Severe liver function impairment

Evidence for linking the risk to the medicine	The clinical experience in patients with liver impairment remains limited. CDS describes recommendations for the use of everolimus in people with underlying liver impairment, however data is limited. Evidence generation by regular monitoring of data from this population to identify new safety information or any trends/patterns in AEs that are different from general population AEs.
Risk factors and risk groups	Not relevant
Risk minimization measures	**Routine risk minimization measures** • SmPC Section 4.4 **Additional risk minimization measures** None

Table 9 Missing information: Patients at high immunological risk

Evidence for linking the risk to the medicine	Certican has not been adequately studied in patients at high immunological risk (e.g. black, anti-HLA Class I panel reactive antibodies > 20% by a complement dependent cytotoxicity based assay or > 50% by a flow cytometry or enzyme linked immunosorbent assay based assay). Evidence generation by regular monitoring of data from this population to identify new safety information or any trends/patterns in AEs that are different from general population AEs.
Risk factors and risk groups	Not relevant
Risk minimization measures	**Routine risk minimization measures** • SmPC Section 4.4 **Additional risk minimization measures** None

II.C: Post-authorization development plan

II.C.1. Studies which are conditions of the marketing authorization

This section is not applicable as there are no studies which are under conditions for marketing authorization.

II.C.2. Other studies in post-authorization development plan

There are no studies in the post-authorization development plan.