



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Everolimus

Proprietary Product Name: Certican

Sponsor: Novartis Pharmaceuticals Australia
Pty Ltd

May 2013

TGA Health Safety
Regulation

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I. Introduction to product submission

Submission details

<i>Type of Submission:</i>	Extension of indications; new dosage recommendations; other changes to the Product Information
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	23 January 2013
<i>Active ingredient:</i>	Everolimus
<i>Product Name:</i>	Certican
<i>Sponsor's Name and Address:</i>	Novartis Pharmaceuticals Australia Pty Ltd 54 Waterloo Road North Ryde NSW 2113
<i>Dose forms:</i>	Tablet and dispersible tablet
<i>Strengths:</i>	Tablet: 0.25 mg, 0.5 mg, 0.75 mg and 1 mg Dispersible tablet: 0.1 mg and 0.5 mg
<i>Container:</i>	Blister pack
<i>Pack sizes:</i>	50, 60, 100 and 120
<i>Approved Therapeutic use:</i>	Certican is indicated for the prophylaxis of organ rejection in adult patients receiving an allogeneic hepatic transplant (see Precautions)
<i>Route of administration:</i>	Oral
<i>Dosage (abbreviated):</i>	<p>Treatment with Certican should only be initiated and maintained by physicians who are experienced in immunosuppressive therapy following organ transplantation. Everolimus should be used in combination with cyclosporin microemulsion and corticosteroids with cyclosporin exposure reduced over time post-transplantation (see Therapeutic Drug Monitoring).</p> <p>An initial dose regimen of 0.75 mg twice a day is recommended for the general kidney and heart transplant population, administered as soon as possible after transplantation. The dose of 1.0 mg twice a day is recommended for the hepatic transplant population with the initial dose approximately 4 weeks after transplantation. A higher Certican dosage regimen (1.5 mg twice daily) was shown to be as effective as the recommended dosage regimen but the overall safety was worse. Therefore this higher-dosage regimen is not recommended. The daily dose of Certican should always be given orally in two divided doses, consistently either with or without food and at the same time as cyclosporin microemulsion or tacrolimus.</p>
<i>ARTG Numbers:</i>	97500, 97506, 97509, 97516, 97520, 97527

Product background

The immunosuppressant agent everolimus is an inhibitor of mammalian target of rapamycin (mTOR), which is an intracellular protein with a key role in cellular protein synthesis and energy balance that influences many aspects of cell growth and proliferation. Everolimus exerts its immunosuppressive effect by inhibiting cell cycle progression as well as by inhibiting the activation of lymphocytes (T and B cells) and interleukin clonal expansion.

Everolimus was first registered in Australia in 2005 with the trade name Certican. The approved indication is:

Certican is indicated for the prophylaxis of organ rejection in adult patients at mild to moderate immunological risk receiving an allogeneic renal or cardiac transplant.

This AusPAR describes the application by Novartis Pharmaceuticals Australia Pty Ltd (the sponsor) to extend the indications for Certican to include hepatic transplant. The proposed indication (addition shown in bold font) is:

*Certican is indicated for the prophylaxis of organ rejection in adult patients at mild to moderate immunological risk receiving an allogeneic renal or cardiac **or hepatic** transplant.*

The sponsor also proposes several changes to the *Dosage and Administration* section of the Certican Product Information (PI). These include:

- New dosing for the hepatic transplant indication.
- Changes to the dosage for patients with impaired hepatic function. These include a greater reduction in everolimus dose (from one half to two-thirds of the dose) in patients with mild hepatic impairment.
- Amendments to the section on cyclosporin dose recommendations in renal transplantation based on data from Study A2309. There is also a new recommendation that everolimus “should not be used long-term together with full doses of cyclosporin”.
- Amendments to the section on cyclosporin dose recommendations in cardiac transplantation based on data from Studies A2411 and A2310.
- A new section on tacrolimus dose recommendation in hepatic transplantation.

Other proposed changes to the PI

The proposed PI has a large number of other changes including:

- Data on pharmacokinetics (PK) in hepatic impairment.
- Updates in the Clinical trials section on renal transplantation from Study A2309, on cardiac transplantation from Studies A2411 and A2310, and on hepatic transplantation from Study H2304.
- Rewording of the precaution in hepatic impairment.
- Additional information relating to cyclosporin dose in renal dysfunction.
- Rewording of the precaution relating to wound healing complications.
- Additional data on drug interactions with midazolam.
- Updating of the adverse effects section with the additional clinical data.

The focus of this AusPAR is on the proposal to include hepatic transplant in the indications. Details of revisions to the PI outside of the indications, including those to the

Dosage and Administration section, are beyond the scope of this AusPAR except where they relate to discussions of general safety issues.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) in March 2005. At the time this application was considered, a similar application was under review in the USA and Switzerland, and had been approved in the European Union (EU).

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Everolimus (also referred to as RAD001) exerts its immunosuppressant effect by inhibiting the proliferation of antigen-activated T-cells and clonal expansion driven by interleukins released from activated T-cells, which is the main mechanism underlying acute transplant rejection. Everolimus is currently approved in Australia for use in the prophylaxis of organ rejection following cardiac or renal transplantation. This application is to extend its use to the prevention of acute allograft rejection in adult patients who have received a liver transplant.

Renal function has been cited as an important prognostic factor post liver transplant. One of the major contributors to renal impairment in liver transplant recipients is the use of calcineurin inhibitors (CNIs) such as cyclosporin and tacrolimus. Consequently, it is believed that reducing exposure to CNIs post transplant may improve renal function. Tacrolimus is generally the first line therapy in liver transplant due to improved results over cyclosporin on acute rejection and graft loss and survival. The sponsor proposes that treatment with everolimus may allow a reduction or elimination of tacrolimus early post transplant and may also improve progression of fibrosis in liver allografts in hepatitis C virus (HCV) positive patients.

Scope of the clinical dossier

The submission's clinical information was divided in three sections by therapeutic area outlined below.

- Cardiac
 - One efficacy/safety study (Study A2310) and literature references.
- Hepatic
 - Two PK studies (Studies X2102 and X2103).
 - One pivotal efficacy/safety study in hepatic transplant (H2304) and a report on exploratory modelling of exposure-infection.
 - One dose-finding study (B158) with its extensions (B158E1 and B158E2) and associated PK report.
 - Two other efficacy/safety studies (HDE10, H2401 with 6 and 12 month reports)
 - A preliminary safety report for study H2301.
 - Appendices for the sponsor's *Summary of Clinical Efficacy* and *Summary of Clinical Safety*, and literature references.
 - Post-marketing data including a bridging Periodic Safety Update Report (PSUR) and a PSUR addendum report.
- Renal
 - One efficacy/safety study (A2309).
 - A comparative safety update for Studies B251, B201 and A2309 in renal transplantation, data listings for appendix 3 of the sponsor's *Summary of Clinical Safety* and literature references.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

The sponsor provided a statement in the *Clinical Overview* that all studies were conducted in compliance with Good Clinical Practice.

Pharmacokinetics**Studies providing pharmacokinetic data**

Table 1 shows the studies relating to each PK topic. None of the PK studies had deficiencies that excluded their results from consideration.

Table 1. Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID
PK in healthy adults	-	-
PK in special populations	TARGET POPULATION§ Hepatic transplantation	B158 H2304
PK in special populations	Hepatic Impairment	X2102

PK topic	Subtopic	Study ID
Gender/Genetic-related PK	-	-
PK interactions	Midazolam	X2103
	Cyclosporin	B158
	Tacrolimus	H2304
Population PK	-	-

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

Evaluator's overall conclusions on pharmacokinetics

The dossier included PK studies in hepatic impairment and a drug interaction study with midazolam. There were also some PK data from two studies in the target population of hepatic transplantation. The sponsor only proposes alterations to the PK sections of the PI in relation to PK in hepatic impairment and the drug interaction with midazolam.

In the dose finding Study B158, the PK of everolimus was assessed when administered with cyclosporin and prednisolone in *de novo* hepatic transplant patients. This found that trough everolimus concentrations were correlated with area under the concentration-time curve (AUC) over the dose interval (tau) at steady state (SS) ($AUC_{\tau,ss}$) and so supports use of trough levels for therapeutic drug monitoring. A doubling of the dose resulted in a 1.8 fold increase in AUC, indicating some under proportionality. There was also a notable level of intra and inter subject variability for AUC (approximately 30% for both).

In the pivotal Phase III hepatic transplantation study (Study H2304), a commencing everolimus dose of 1 mg twice daily (bid) (2 mg/day) was given with tacrolimus and resulted in a mean everolimus trough level of 3.4 ng/mL after one week, with 45% of samples in the target range (3-8 ng/mL). Consequently, the dose needed to be up titrated by 62% (average 1.73 mg bid) in the first month to reach target levels.

A starting dose of everolimus 1 mg bid with concomitant tacrolimus compares to the 0.75 mg bid commencing dose with concomitant cyclosporin due to the ability of cyclosporin to increase everolimus exposure 2 to 3 fold.

The administration of everolimus in subjects with hepatic impairment (Study X2102) resulted in a significant increase in exposure. In subjects with mild hepatic impairment the mean AUC extrapolated to infinity (AUC_{0-inf}) of everolimus was increased by 1.6 fold, and in subjects with moderate and severe hepatic impairment the mean AUC_{0-inf} increased by 3.2 fold and 3.6 fold, respectively. There was a positive correlation between everolimus exposure and bilirubin and International Normalisation Ratio (INR, a measure of blood coagulation time) and a negative correlation with albumin, although the relationships were not strong.

When midazolam (a cytochrome P450 (CYP) 3A4 substrate) was co-administered with everolimus, there was a 25% increase in the maximum concentration (C_{max}) and a 30% increase in AUC for midazolam, with similar results for the major metabolite, 1-hydroxymidazolam. There was little effect on the terminal half life of midazolam. This demonstrates that everolimus is a weak inhibitor of CYP3A4. There was no reported effect of midazolam on the PK of everolimus.

The everolimus starting dose is dictated by the concomitant CNI used in hepatic transplantation and, as in other transplant patients, doses must continue to be tailored to patients by close therapeutic drug monitoring.

Pharmacodynamics

Studies providing pharmacodynamic data

There were no specific pharmacodynamic (PD) studies in the dossier. Pharmacodynamic data were available from two studies in hepatic transplantation (Studies B158 and H2304) in which the relationships between exposure and safety and efficacy were explored.

Evaluator's overall conclusions on pharmacodynamics

In hepatic transplantation patients, exposure-safety analyses (Study B158) found a positive relationship between increasing trough everolimus levels and increased cholesterol and reduced platelets. However, no relationship was evident in Study H2304 when everolimus was used in combination with tacrolimus. In fact, contrary to expectations, there was a higher rate of the selected adverse events (AEs), including infection, with lower trough levels. The reason for this is unclear.

In hepatic transplantation patients, exposure-efficacy analyses suggested increased efficacy with increased exposure in Study B158, although the numbers in this analysis were small. In Study H2304, the highest rate of efficacy failure was noted with levels < 3 ng/mL, although a trend was not evident.

Efficacy

Dosage selection for the pivotal study

Study B158 was a randomised, double-blind, parallel group, dose-finding study in 119 *de novo* liver transplant recipients who received placebo or everolimus 0.5 mg bid, 1 mg bid or 2 mg bid together with cyclosporin and corticosteroids. Data from this study found a greater risk of acute rejection in patients with trough levels < 3 ng/mL compared to those with levels \geq 3 ng/mL.

The target trough level of everolimus for the pivotal Study H2304 was based on data from studies of other transplant indications and Study B158. The target level was 3-8 ng/mL, which aligns with recommendations in the current PI for renal and cardiac transplantation.

The starting dose of 1.0 mg bid was higher than the 0.75 mg bid dose recommended for renal and cardiac transplantation. This is due to the concomitant use of cyclosporin in renal and cardiac transplantation (which is known to increase everolimus concentrations), while in the hepatic transplantation Study H2304, the concomitant CNI was tacrolimus, which was expected to have less of an effect on everolimus levels.

Hepatic transplant pivotal efficacy study

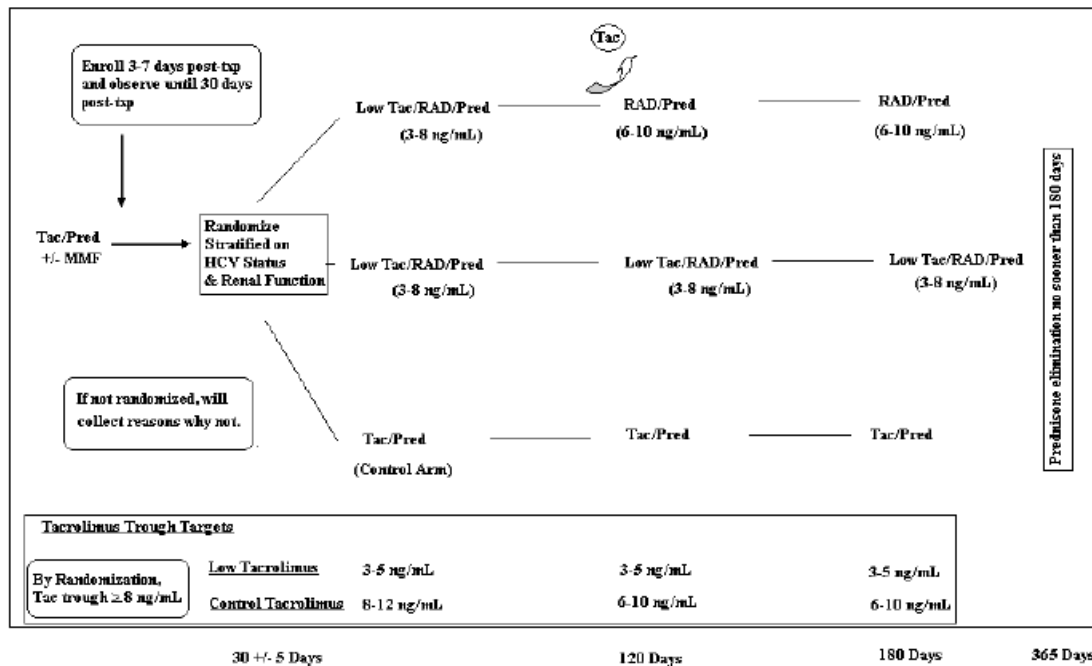
Study H2304

Study H2304 was a 24 month, Phase III, multicentre, open label, randomised, controlled trial in 719 *de novo* liver transplant recipients, which evaluated the efficacy and safety of concentration controlled everolimus with eliminated or reduced dose tacrolimus, compared to a standard dose tacrolimus regimen. It was conducted between January 2008

and April 2011 (12 month data) at 89 centres in 19 countries (including Australia, South America, North America, Western and Eastern Europe and Israel). There was a central laboratory, a central pathologist for liver biopsy review and an independent Data Monitoring Committee (DMC). The clinical study report (CSR) in the dossier was for the first 12 months of treatment.

There were 3 treatment groups: 1. everolimus + tacrolimus elimination (the EVR + TAC elimination group, also called the 'TAC elimination' group); 2. everolimus + reduced tacrolimus (the EVR + reduced TAC group); and 3. tacrolimus alone (the TAC control group). The study design is summarised in Figure 1.

Figure 1. Summary of Study H2304 design



Abbreviations: RAD: everolimus; TAC: tacrolimus; txp: transplant; Pred: prednisone; MMF: mycophenolate mofetil; HCV: hepatitis C virus.

The primary objective was to assess, at 12 months, the efficacy outcomes of failure rate of treated biopsy proven acute rejection (tBPAR), graft loss (GL) or death (D) with early tacrolimus minimisation (facilitated by everolimus introduction 4 weeks after liver transplantation), compared to standard exposure tacrolimus.

Other efficacy studies

Study HDE10 was a 12 month, Phase III, multicentre, randomised, open label, parallel group study of the safety, tolerability and efficacy of an everolimus based regimen compared to a CNI based regimen in 203 adult patients with *de novo* liver transplantation. The primary objective was to demonstrate, at 11 months post randomisation, superiority of renal function for the everolimus based regimen with discontinuation of CNI therapy compared to a CNI based regimen.

Study H2401 was a Phase III, six month, multicentre, randomised, open-label study of the safety and efficacy of an everolimus based regimen compared to a CNI based regimen in 145 maintenance liver transplant recipients with CNI related renal impairment. The primary objective was to determine whether everolimus together with a reduction or discontinuation of CNI in maintenance liver transplant patients with CNI related renal impairment would improve renal function, as measured by the change in calculated glomerular filtration rate (cGFR) from baseline to Month 6.

An interim CSR for Study H2301 (dated August 2011) was included in the dossier. Study H2301 was described as an exploratory study which aimed to assess the efficacy of everolimus in inhibiting fibrosis progression in 43 liver transplant recipients with recurrent hepatitis C. It is also known as REVERT.¹ It was a 24 month, randomised, multicentre, open label, parallel group trial conducted at 6 centres in Argentina between November 2006 and January 2010. The study was terminated prematurely after the 12 Month biopsy due to a high drop-out rate. The primary objective was to demonstrate a slower progression of liver fibrosis, as assessed by the Ishak-Knodell (IK) staging score,² at 24 Months post randomisation in HCV positive patients after orthotopic liver transplantation who were receiving everolimus versus standard treatment.

Evaluator's conclusions on clinical efficacy for hepatic transplantation

The hepatic transplantation dossier included 4 Phase III studies. Study H2304 was the pivotal study and provided the most appropriate data for assessing efficacy. There were two studies, HDE10 and H2401, which were primarily safety studies assessing change in renal function, with efficacy being a secondary objective. These studies provided minimal supportive evidence. Efficacy endpoints in these 3 studies are summarised in Table 2.

Table 2. Efficacy endpoints across studies

	Study H2304			Study HDE10		Study H2401	
	EVR+Reduced TAC N=245 n (%)	TAC Elimination N=231 n (%)	TAC Control N=243 n (%)	EVR N=96 n (%)	CNI N=98 n (%)	EVR N=72 n (%)	CNI N=73 n (%)
Graft loss [#]	6 (2.4)	5 (2.2)	3 (1.2)	2 (2.1)	2 (2.0)	0	0
Death [#]	9 (3.7)	8 (3.5)	6 (2.5)	4 (4.2)	4 (4.1)	1 (1.4)**	0
BPAR	10 (4.1)*	46 (19.9)	26 (10.7)	17 (17.7)	15 (15.3)	1 (1.4)	1 (1.4)
tBPAR	7 (2.9)*	38 (16.5)	17 (7.0)	13 (13.5)	10 (10.2)	1 (1.4)	1 (1.4)
tBPAR/graft loss/death	16 (6.7) [^]	45 (24.2) [^]	23 (9.7) [^]	17 (17.7)	14 (14.3)	-	-
tBPAR/graft loss/death/Loss to Follow-up	26 (10.6)	63 (27.3)	38 (15.6)	-	-	-	-
BPAR/graft loss/death/Loss to Follow-up	-	-	-	20 (20.8)	20 (20.4)	-	-

* Comparison of EVR+Reduced TAC vs. TAC Control statistically significant (p<0.05) in favor of EVR+Reduced TAC.

**for 6 month study H2401: The endpoint is graft loss/death

[^] In H2304, Kaplan-Meier estimate of the event rates were calculated for tBPAR/graft loss/death

In Study H2304: # = exact confidence interval and two-sided Fisher exact test used for that variable. For others, asymptotic confidence interval and Pearson Chi-square test are used.

In Study HDE10: treatment comparisons used Fisher exact test.

Study H2304 is an ongoing, 24 month, Phase III, multicentre, open label, randomised, controlled trial in 719 *de novo* liver transplant recipients. It was a non-inferiority study assessing the efficacy and safety of concentration controlled everolimus with reduced or eliminated tacrolimus compared to tacrolimus alone. Treatment with everolimus commenced one month post transplantation and whole blood monitoring targeted a trough everolimus level of 3-8 ng/mL. This level was lower than the target in Studies HDE10 and H2401 where the upper limit was 12 ng/mL. For subjects in the EVR + reduced TAC group, the tacrolimus target level was 3-5 ng/mL after 3 weeks, while the TAC control group's target was 6-10 ng/mL from Month 4. Corticosteroids were allowed in all groups.

The study's group of everolimus in combination with TAC elimination was discontinued prematurely due to a higher rate of acute rejection and AEs. Discontinuation of study medication by Month 12 was 26.9% in the EVR + reduced TAC group, compared to 22.2% in the TAC control group and 55.8% in the EVR + TAC elimination group.

¹ Efficacy of Everolimus as Inhibitor of Fibrosis Progression in Liver Transplant Patients With Recurrence of Hepatitis C Viral Infection (REVERT).

² The Knodell score is composed of the summation of 4 individual scores representing periportal and/or bridging necrosis, intralobular degeneration and focal necrosis, portal inflammation, and fibrosis; the score ranges from 0 to 2. The Ishak-Knodell score is a modification with 6 stages of fibrosis, permitting more detailed evaluation of changes in fibrosis compared with the standard Knodell fibrosis score, which has only 3 stages.

The study met its primary objective, as treatment commencing one month post transplantation with a regimen of everolimus and reduced tacrolimus dose was found to be statistically non-inferior (NI; margin 12%) to treatment with tacrolimus alone at 12 Months, when measured by the composite efficacy endpoint of tBPAR/GL/D (6.7% versus 9.7%), with a difference of -3.0% (97.5% confidence interval (CI): -8.7%, 2.6%, $p < 0.001$). Non-inferiority was also achieved on other efficacy endpoints of GL/D/loss to follow up and GL/D, and was supported by the per protocol (PP) analysis. There was statistically superior renal function, as measured by mean change in estimated GFR (eGFR), with a difference of 8.50 mL/min/1.73 m² (97.5% CI: 3.74, 13.27, $p < 0.001$) in favour of EVR + reduced TAC compared to the TAC control group. Results of both primary and key secondary efficacy outcomes were consistent across subgroups of age, gender, race, region, eGFR, HCV status, model for end stage liver disease (MELD) score³ and cause of end stage liver disease (ESLD).

Overall, the effect appeared more related to a reduced rate of acute rejection episodes (3.7% versus 10.7%) rather than reduced GL or D. The study found that a reduction of tacrolimus was possible with the addition of everolimus post hepatitis transplantation without an increase in efficacy failure at 12 Months post transplantation. It was also found that efficacy was unacceptable when everolimus was used without continuing tacrolimus concomitantly.

HDE10 was a study in 203 *de novo* liver transplant patients. It did not reach its primary endpoint of superiority of renal function with an everolimus based immunosuppressive regimen compared to a CNI based regimen. Regarding efficacy, there were no significant differences between the treatment groups in single events or in the composite endpoint of efficacy failure (BPAR, GL, D, loss to follow up; 17.7% versus 14.3%, $p = 0.56$).

Study H2401 examined renal function in 145 patients with CNI related renal impairment (GFR 20-60 mL/min) who were, on average, 3 years post hepatic transplantation. Efficacy was a secondary objective and the study did not find any significant difference in efficacy failure between groups after 6 Months of treatment. The number of events was very limited.

The dossier also included an interim report for an exploratory study in 43 liver transplant patients with recurrent HCV (Study H2301). This study was terminated early due to a high drop-out rate. Biopsy data were available at 12 Months rather than the 24 Month endpoint and there were baseline imbalances between groups. There was an indication of a lower mean fibrosis (IK) score at Month 12 with everolimus compared to CNI treatment. However, due to the factors listed above the results of this study cannot be viewed as conclusive.

The pivotal trial was amended to comply with the current European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) *Guidelines on the clinical investigation of immunosuppressants for solid organ transplant* (CHMP/EWP/263148/06; July 2008; effective from 1 February 2009). The PI adequately summarises the clinical efficacy data in hepatic transplantation, with the exception of a failure to state the risks of tacrolimus elimination. Details of the evaluator's comments on this and other aspects of PI are beyond the scope of this AusPAR.

³ MELD score uses the patient's values for serum bilirubin, serum creatinine, and the international normalised ratio for prothrombin time (INR) to predict survival.

Safety

Studies providing evaluable safety data

For the hepatic transplantation indication, the safety data comes primarily from the pivotal Study H2304. There was no pooling of safety data for this indication. A comparison of data from this study and the renal transplant Study A2309 was also provided. H2304 extension Study H2304E1 provided data on serious AEs (SAEs) and deaths to the cut-off of 31 May 2011.

Studies that assessed safety as a primary outcome

Studies HDE10 and H2401 assessed safety, in terms of renal function, as a primary outcome. These studies also provided supportive safety data in liver transplant recipients.

Dose-response and non-pivotal efficacy studies

The dose-response and non-pivotal efficacy studies provided safety data as follows:

- Study B158 with extensions B158E1 and B158E2 (fixed dose everolimus with standard dose cyclosporin) provided long term data.
- Study H2301 was in recurrent hepatitis C patients and was prematurely discontinued. Deaths and SAEs were reported.

Other studies evaluable for safety only

Clinical pharmacology Studies X2102 and X2103 provided little safety data. Studies not included in the dossier were B202 (single dose PK in liver transplant), A2303 (single dose PK in moderate hepatic impairment) and B258 (single dose PK in paediatric liver transplant patients).

Cardiac transplant study A2310 and renal transplant study A2309

The primary safety variable was renal function measured by cGFR using the Modification of Diet in Renal Disease (MDRD) formula⁴ in both studies (another formula, known as the Nankivell formula, was also used in A2309). Mid-stream spot urine was analysed for protein/creatinine ratio to assess proteinuria. Collection of AEs and SAEs together with monitoring of haematology, blood chemistry, urine, vital signs and physical examination were all undertaken. Electrocardiograms (ECGs) were conducted in A2310. Infections, severe rejection episodes, major cardiac events, wound healing events and other events of special interest were also assessed in both studies.

Patient exposure

In the controlled hepatic transplantation studies 759 patients were exposed to everolimus (see Table 3 below).

Table 3. Exposure to everolimus and comparators in clinical studies

Study type/ Indication	Controlled studies				Uncontrolled studies	Total Everolimus
	Everolimus	CNI (TAC/CsA)	Mycoph- enolate	Placebo		
Clinical					59	59

⁴ The abbreviated MDRD or MDRD-4 estimates GFR using four variables: serum creatinine, age, race, and gender. The original MDRD used six variables with the additional variables being the blood urea nitrogen and albumin levels. The equations have been validated in patients with chronic kidney disease.

Study type/ Indication	Controlled studies			Uncontrolled studies	Total Everolimus
pharmacology					
Hepatic transplant					
H2304	475	241 (TAC)			475
HDE10	101	102 (either)			101
H2401	72	73 (either)			72
H2301	22	21 (either)			22
B158	89			30	89
Subtotal Hepatic Tx	759				818
Cardiac transplant					
A2310	444	*CsA	271		444
Renal transplant					
A2309	552	*CsA	273		552
TOTAL	1755				1814

*Treatment was everolimus + reduced dose cyclosporin (CsA) or myophenolate +standard dose CsA.

Evaluator's overall conclusions on clinical safety

Hepatic transplantation

For the hepatic transplantation indication, the safety data comes primarily from the pivotal study (H2304) in 719 patients, of who 475 received everolimus. In addition, there were two hepatic transplant studies which examined renal safety as the primary outcome. In total, the hepatic transplant studies in the dossier included 759 patients exposed to everolimus. There was no pooling of safety data for this indication. The safety data from two other major studies, one in renal (A2309) and the other in cardiac (A2310) transplant patients was also reviewed. While the 3 main studies (H2304, A2309, A2310) were 24 month studies, all data presented was from the 12 Month analyses. The mean exposure in H2304 was 284, 223 and 290 days, respectively, in the EVR + reduced TAC, EVR + TAC elimination group and TAC control groups. A comparison of notable events in H2304, HDE10 and A2309 is shown in Table 4.

Table 4. Frequency of notable events across studies

	Study H2304 (LTx 12 month)			Study HDE10 (LTx 12 month)		Study A2309 (RTx 12 month)		
	EVR+ Reduced TAC N=245 n (%)	TAC Elimin N=230 n (%)	TAC Control N=241 n (%)	EVR N=101 n (%)	CNI N=102 n (%)	EVR 1.5 mg N=274 n (%)	EVR 3.0 mg N=278 n (%)	Myfortic N=273 n (%)
Deaths	9 (3.7)	8 (3.5)	6 (2.5)	4 (4.0)	4 (3.9)	7 (2.6)	9 (3.2)	6 (2.2)
Graft loss#	6 (2.4)	5 (2.2)	3 (1.2)	2 (2.1)	2 (2.0)	-	-	-
SAEs	122 (49.8)	130 (56.5)	104 (43.2)	67 (66.3)	58 (56.9)	153 (55.8)	167 (60.1)	146 (53.5)
DAE	63 (25.7)	60 (26.1)	34 (14.1)	30 (29.7)	14 (13.7)	64 (23.4)	79 (28.4)	43 (15.8)
Dropouts due to:								
Adverse Events	47 (19.2)	46 (20.0)	27 (11.2)	28 (27.7)	16 (15.7)	50 (18.2)	56 (20.1)	26 (9.5)
Abnormal lab values	4 (1.6)	1 (0.4)	2 (0.8)	7 (6.9)	3 (2.9)	1 (0.4)	4 (1.4)	1 (0.4)
Abnormal test procedure results	0	1 (0.4)	0	1 (1.0)	0	0	1 (0.4)	0

As Study A2309 is a renal transplant study comparisons to H2304 and HDE10 would not be applicable.

Dropout due to notable events (recorded on Treatment and Study Completion CRF, with reason for premature discontinuation of study medication = Adverse events, Abnormal laboratory values or Abnormal test procedure results).

Adverse events were virtually universal in the transplant studies. In H2304 over 12 months, the most commonly reported AEs were diarrhoea, headache, pyrexia, hypertension, peripheral oedema, nausea, abdominal pain, hepatitis C, leukopenia, anaemia, fatigue and tremor.

In H2304, AEs tended to be moderate (49%) or severe (31%) and the rate of severe events was greater than in the TAC control group (20.3%). The higher rate of severe AEs was also found in the supportive Study HDE10 (52% versus 35%).

Compared to the renal transplant study, there was a lower rate of anaemia, angioedema, cardiovascular events, hyperlipidaemia, peripheral oedema, proteinuria, renal failure, thrombotic/thromboembolic events, and wound healing complications. Hepatic transplant patients had more incisional hernia, ascites, thrombocytopenia and new onset diabetes.

In H2304, the mortality rate was slightly higher in the everolimus groups (3.7% and 3.5%, versus 2.5% in the TAC control group), although adjudication considered only 2 deaths in everolimus treated patients were treatment-related (due to biliary

complications/cholangiosepsis/cerebral infarction and interstitial lung disease). Most deaths were related to liver complications or infection.

Serious AE rates were higher in the everolimus groups in the liver transplant studies, particularly the EVR + TAC elimination group in H2304 (56.5% versus 43.2% in the control group). There were higher rates of pyrexia, cholangitis, cholestasis, hepatitis C, incisional hernia, renal failure and serious bacterial infection. Graft loss rates were low, but were higher with everolimus (2.4% and 2.2%, versus 1.2% in the TAC control group).

Premature discontinuation due to AEs occurred in one quarter of patients treated with everolimus and reduced dose tacrolimus and this was higher than the control regimen (25.7% versus 14.1%). Higher AE discontinuation rates with everolimus were also seen in HDE10 (29.7% versus 13.7%). These rates were similar to the discontinuation rates seen in the renal and cardiac transplant studies. The main reasons for discontinuation that occurred at a higher rate than in the control group were: proteinuria, hepatitis C, graft loss and pancytopenia.

In H2304, renal function was a main secondary objective and the EVR + reduced TAC regimen resulted in a statistically superior renal function (cGFR of 8.5 mL/min/1.73 m² (97.5% CI: 3.74, 13.27)) at Month 12 when compared to the standard tacrolimus regimen. An improvement in renal function was seen from Month 2 onwards. The result was robust across other renal function assessment methods and patient subgroups.

HDE10 assessed the effect on renal function of an everolimus based regimen compared to a CNI based regimen in 203 patients with *de novo* liver transplantation. The study did not meet its primary endpoint since after 11 Months of treatment the cGFR measured by the Cockcroft-Gault method was not significantly different between the everolimus and CNI group (least squares (LS) mean difference of -2.92 mL/min, 95% CI: -10.66, 4.81). Secondary analyses of the PP population and using different methods for calculating the GFR also found no significant differences.

H2401 examined renal function in 145 patients with CNI related renal impairment (cGFR 20-60 mL/min) who were, on average, 3 years post hepatic transplantation. The study did not meet its primary endpoint as there was no significant difference in renal function (as estimated by Cockcroft-Gault formula) after 6 Months' treatment in the everolimus group (with CNI withdrawal) compared to continuing on the CNI based regimen. Twelve Month follow up still found no difference in renal function.

In hepatic transplantation patients, renal failure/impairment AEs occurred at a slightly lower rate in the everolimus based regimens than in the control groups. Proteinuria levels and AE rates were higher with everolimus treatment.

For other events of clinical significance (comparing EVR + reduced TAC versus TAC control group in H2304) it was found that there was no higher rate of malignancy (2.4% versus 4.6%), major cardiovascular events (2.0% versus 3.7%) or gastrointestinal haemorrhage or perforation. Patients received prophylaxis for pneumocystitis and cytomegalovirus (CMV) (if required) in H2304. The everolimus treated patients did have higher rates of infections in all three hepatic transplant studies (50.2% versus 43.6%) and discontinuation due to infections was also higher (5.3% versus 2.1%).

Recurrent hepatitis C was higher in the everolimus group (11.4% versus 7.9%), while the hepatitis C activity index was not higher and the mean change from baseline to Month 12 in HCV viral load was similar. Data on the impact of everolimus on liver fibrosis was non-conclusive.

There was a higher rate of thromboembolic events in the everolimus group versus the control group (5.3% versus 3.7%), although the risk of hepatic artery thrombosis appears to be reduced by delayed treatment commencement, with only one case post randomisation in the EVR + TAC elimination group.

The rate of peripheral oedema was higher (19.6% versus 12.4%), although ascites and pleural effusion rates were similar. Wound healing complications were also more frequent (11.0% versus 7.9%), as were hernias (11.0% versus 7.5%); however, the rates were lower than in the renal transplant study where treatment was initiated earlier.

The increased risk of new onset diabetes was generally high (about one third of patients) with a slightly higher rate in the everolimus group (32.0% versus 28.6%).

Stomatitis and mouth ulcers were more frequent, as is known to occur with mTOR inhibitors. The known risks of angioedema and interstitial lung disease were rare in the liver transplant studies.

Anaemia rates and notably low haemoglobin rates were similar in H2304. Thrombocytopenia rates were higher, although notably low platelets were infrequent. Neutropenia and pancytopenia rates were higher (2.4% versus 0.8% and 3.7% versus 0.8%, respectively), as was notably low white blood cells (13.5% versus 6.6%). There were higher rates of increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT), though Hy's Law⁵ cases were no greater in the everolimus groups. Hyperlipidaemia (cholesterol and triglycerides) was notable with everolimus treatment.

While females had higher rates of some AEs, the overall rate was similar between genders, as it was between those aged < 60 years and ≥ 60 years. There were too few non-Caucasians to draw safety conclusions in other racial groups.

List of questions

None.

Clinical summary and conclusions

Benefit-risk assessment

Assessment of benefits

The benefits of everolimus in the proposed usage (hepatic transplantation) are:

- Treatment with everolimus allowed a reduction in tacrolimus exposure without affecting efficacy in terms of prevention of the composite endpoint of tBPAR, GL and D at 12 months post-transplantation.
- The everolimus and reduced dose tacrolimus regimen resulted in significantly fewer episodes of acute rejection than the standard dose tacrolimus regimen (3.7% versus 10.7%).
- Efficacy results were consistent across subgroups of age, gender, region, eGFR, HCV status, MELD score and cause of ESLD.
- Over the 12 months post transplantation, the decline in renal function (eGFR by MDRD-4 (with 4 variables)) with everolimus and reduced dose tacrolimus treatment was significantly less than with standard dose tacrolimus (-2.2 mL/min/1.73 m² versus -10.7 mL/min/1.73 m²). The finding was consistent across other methods of renal function assessment and patient subgroups. The rate of renal failure/impairment AEs was slightly lower with everolimus.

⁵ Hy's Law provides prognostic indicators for pure drug-induced liver injury.

- There were lower rates of malignancy in the everolimus and reduced dose tacrolimus group compared to the standard dose tacrolimus regimen (2.4% versus 4.6%).

Assessment of risks

The risks of everolimus in the proposed usage (hepatic transplantation) are:

- Treatment with everolimus does not allow elimination of concomitant tacrolimus. Elimination of tacrolimus resulted in an unacceptable increased risk of acute rejection and treatment discontinuation.
- There was an increased risk of efficacy failure with everolimus trough levels < 3 ng/mL and higher doses than recommended have an unacceptable safety profile. Everolimus treatment needs to be concentration-controlled through active therapeutic drug monitoring.
- Adverse events are virtually universal in this patient population. Over the 12 months, the most commonly reported AEs were diarrhoea, headache, pyrexia, hypertension, peripheral oedema, nausea, abdominal pain, hepatitis C, leukopenia, anaemia, fatigue and tremor.
- Compared to the renal transplantation study, there were higher rates of incisional hernia, ascites, thrombocytopenia and new onset diabetes. There were, however, lower risks of hyperlipidaemia, peripheral oedema, proteinuria, angioedema, cardiovascular events, renal failure excluding proteinuria, anaemia and thromboembolic events.
- There was a higher rate of severe AEs (31% versus 20%) and SAEs (50% versus 43%) with everolimus and reduced tacrolimus compared to the tacrolimus control regimen. There was also a higher rate of premature discontinuation due to AEs (26% versus 14%).
- There was an increase risk of thromboembolic events (5.3% versus 3.7%), however major cardiovascular events were not more prevalent (2.0% versus 3.7%) and the delayed treatment commencement (at one month post transplantation) appears to have reduced the potential risk of hepatic artery thrombosis.
- About one third of patients developed new onset diabetes mellitus, with a slightly higher rate than in the tacrolimus control group.
- Other known risks with everolimus were present, including stomatitis and mouth ulcers, wound healing events, interstitial lung disease, angioedema, pleural effusion and infections.
- There are no long term efficacy data.
- There are only limited data on non-Caucasians.

Assessment of benefit-risk balance

Use in hepatic transplantation

In Australia and New Zealand in 2010 there were 192 liver transplants in adults, with chronic viral hepatitis (HCV and hepatitis B virus) being the most common primary indication. The one year survival in the 2005-2009 patient cohort was 92% for adults with an overall survival at 5 years of 75%.⁶ The treatment of liver transplantation is a balancing act between the risk of rejection and the risk of toxicity from treatment. This occurs in a patient population that may tolerate a high risk of AEs due to the very serious nature of their condition. Nevertheless, with improvement in management of acute rejection, there

⁶ Australia and New Zealand Liver Transplant Registry report 2010. Editors: Lynch SV and Balderson GA. Brisbane. Reports are available at <http://www.anzltr.org/>

is now a need to reduce the long term complications of immunosuppression including renal disease, hyperlipidaemia, diabetes and malignancy.

The clinical development program of everolimus in liver transplantation consisted of one main pivotal Study H2304 and two supportive studies. There was a small study in hepatitis C patients which was terminated prematurely and did not provide conclusive results. The pivotal Study H2304 was in 719 patients with *de novo* liver transplantation, of whom 475 were exposed to everolimus. The design, including primary efficacy endpoint, was in line with current EMA guidelines⁷ as it was amended following the implementation of the guidelines on immunosuppressants for solid organ transplantation.

For decisions based on only one pivotal efficacy study, Guidelines⁸ state the study should be large, multicentred, well-controlled, internally consistent, and have robust results which are consistent across study subsets as well as being statistically persuasive. The results also need to be clinically relevant and able to be extrapolated to the target population. Study H2304 was found to meet these methodological considerations and so the evaluator believes its results are valid for use in assessment of the proposed usage.

Given the non-inferiority design of the pivotal study, it was important to see that the results from the intention to treat (ITT) population were supported by the PP population as this allows a more robust interpretation of the data.⁹ The open label design was necessary for therapeutic drug monitor, however it could have introduced bias particularly in safety event ascertainment. As the primary safety endpoint was renal function based on spot urine analysis, this should not have been greatly affected by such bias.

Study H2304 found that everolimus treatment allowed a reduction in the dose of tacrolimus without an increase in rejection and with a beneficial effect on renal function. The efficacy impact was most notable on a reduced rate of acute rejection rather than a reduction in mortality or GL. It was shown that everolimus cannot replace tacrolimus due to an unacceptably high efficacy failure rate (24.2%) in the treatment arm where concomitant tacrolimus was eliminated. This risk needs to be brought to the attention of prescribers. In addition, as the efficacy data was derived from a set treatment regimen with tacrolimus, the evaluator believes this should be reflected in the indication.

In the hepatic transplantation population, the safety risks of adding everolimus to reduced dose tacrolimus treatment were notable, with increased rates of severe AEs, SAEs and premature discontinuation due to AEs compared to rates in those treated with the tacrolimus control regimen. There were also the significant AEs which were, however, not unexpected as the safety profile of everolimus has been delineated in the renal and cardiac transplantation patient populations. In comparisons of data from H2304 and A2309, the safety profile was no worse than in renal transplantation, with the exception of increased risks of incisional hernia, ascites, thrombocytopenia and new onset diabetes. The delay in treatment commencement (to one month post transplantation) appears to have assisted in reducing events of hepatic artery thrombosis and wound healing complications where the rate was lower than in the renal transplant study. There are other risks of peripheral oedema, mouth ulcers and erectile dysfunction which, while appearing less severe, may have a major impact on a patient's quality of life.

⁷ CHMP. *Guidelines on the clinical investigation of immunosuppressants for solid organ transplant* (CHMP/EWP/263148/06; July 2008; effective from 1 February 2009)

⁸ CHMP. *Points to Consider on Application with 1. Meta-analysis; 2. One Pivotal study*; (CPMP/EWP/2330/99, May 2001)

⁹ CHMP. *Points to consider on switching between superiority and non-inferiority* (CPMP/EWP/482/99, July 2000).

The drug interaction study with midazolam found that everolimus is a weak inhibitor of CYP3A4 and as such the possibility of an interaction between everolimus and contraceptive hormones is unlikely.

Additional safety considerations

In hepatic impairment, the use of Child-Pugh scores¹⁰ was believed to offer a more conservative scale for reduction of dose compared to the use of bilirubin or INR level. Given the results from study X2102, the sponsor proposed dosage based on the Child-Pugh classification of hepatic impairment as follows: two thirds the normal dose for mild impairment and half the normal dose for moderate or severe impairment. The rationale for the dose to be only reduced by half in severe hepatic impairment was that if the exposure is too low there may be a risk of acute organ rejection. Although this appears to be too high a dose, the evaluator acknowledges the potential counter risk of acute rejection and assessed that the risk may in part be mitigated by the therapeutic drug monitoring. In general, for subjects with Child-Pugh C (severe) hepatic impaired status, the administration of everolimus should be with extreme caution and only when it is in the best interest of the subject. Vigilant therapeutic drug monitoring will be critical in these patients and these factors need to be adequately outlined in the PI.

The cardiac and renal transplantation studies demonstrated significant and unacceptable risks when the everolimus 3.0 mg per day dose was used with target trough levels of 6-12 ng/mL. This risk must be thoroughly specified in the PI and communication plans. In addition, in cardiac transplant patients receiving induction with thymoglobulin there was an increased risk of death with the lower and recommended 1.5 mg dose. This risk needs to be included in the PI under a specific precaution.

Pericardial effusions were notable in cardiac transplant patients and there was an increased risk of haemodynamic compromise and requirement for surgical intervention as well as of resultant study drug discontinuation. Such risks need to be added to the precautions in the PI.

In the cardiac transplant study, efficacy was comparable to the mycophenolate control regimen and there were positive effects on cardiac graft vasculopathy. There was however, deterioration in renal function with everolimus which was not evident in the hepatic or renal studies. It was considered by the sponsor that this risk was due to non-compliance by investigators to sufficiently lower the cyclosporin dose to the recommended levels. This reticence on the part of treating physicians may perhaps be due to a fear of graft rejection. Unless this poorer effect on renal function is appropriately addressed, the evaluator contends that there appears no overwhelming reason why the everolimus regimen should be adopted. In order to ensure a potentially positive benefit-risk balance for everolimus in cardiac transplant, adherence to the reduced dose target levels of cyclosporin will need to be achieved and renal function monitored.

The cyclosporin trough levels used in A2309 and A2310 have been included in the proposed PI for both cardiac and renal transplant patients. The risk of everolimus and CNI induced renal dysfunction is also addressed. This, however, may not be sufficient and the evaluator recommends further communication and education on these risks and dosing recommendations.

Therapeutic drug monitoring will be crucial, not just for everolimus but also for cyclosporin. The factors contributing to this are: the risk of CNI induced renal dysfunction; the drug interaction with cyclosporin which results in increased everolimus levels so the

¹⁰ The Child-Pugh score is used to assess the prognosis of chronic liver disease. The score employs 5 clinical measures of liver disease, each measure scored 1-3, with 3 indicating most severe derangement. Chronic liver disease is classified as: mild impairment (Child-Pugh A, score 5-6); moderate impairment (Child-Pugh B, score 7-9); and severe impairment (Child-Pugh C, score 10-15).

dose changes in cyclosporin must lead to a careful monitoring of everolimus; the relatively long half life of everolimus which means that physicians must wait 5 days to measure trough levels after dose changes; and the increased risk of acute rejection if trough levels fall below 3 ng/mL. Again, prescribers need to be made aware of these factors.

Cardiovascular events are a major cause of mortality in renal transplant patients and treatment with everolimus resulted in significantly increased rates of the risk factors of diabetes, hyperlipidaemia and thrombogenicity. It is therefore feasible that this treatment may not have such an evident benefit in the longer term. Such potential effects need to be assessed and so it will be very important to evaluate the 24 Month data from the three studies as well as any further long term extensions. Collection of prospective long term data should be considered.

In renal transplantation, the everolimus regimen resulted in comparable efficacy and renal function, with reduced rates of cyclosporin-related events and CMV infections. On the other hand, there were greater risks of discontinuation due to AEs as well as of events such as graft thrombosis, proteinuria, new onset diabetes, interstitial lung disease, thrombocytopenia and hyperlipidaemia. In the context of significant toxicities with immunosuppressant drugs, the evaluator finds that the data from A2309 continue to support the current indication in renal transplantation. Treatment with everolimus 1.5 mg using therapeutic drug monitoring targeting trough levels of 3-8 ng/mL in combination with reduced doses of cyclosporin represents an alternative to a combination of mycophenolate and standard dose cyclosporin.

In cardiac transplantation the results from study A2310 are not as compelling. While the everolimus regimen allowed reduction in cyclosporin, maintained efficacy, reduced cardiac allograft vasculopathy and reduced CMV associated disease, it was at a cost of significant safety concerns as outlined above. These risks will need to be managed by more stringent labelling, communication and education, and ongoing close pharmacovigilance (PV) monitoring.

Conclusion regarding use in hepatic transplant

In conclusion, the evaluator finds the benefit-risk balance of everolimus, given the proposed usage in hepatic transplantation, is favourable subject to adoption of changes to the proposed PI¹¹ and a risk management plan (RMP) that takes into account the issues discussed.

There is a manifest need to communicate the serious risks with everolimus to all those involved in organ transplantation. This needs to be fully captured within the RMP.

There is also an evident lack of long term data. The 24 months data from the three main transplants studies, together with any extensions, will be important to better delineate longer term risks of immunosuppression, such as chronic rejection, malignancy, renal function and cardiovascular disease.

Recommendation regarding authorisation

The evaluator recommends extension of the indication for everolimus (Certican) to include hepatic transplant patients. This is subject to the proposed changes to the draft PI being satisfactorily addressed. In addition, a condition of this indication extension should be the submission of the further data from Study H2304 as it becomes available. This includes the data to Month 24 and then the extension Study data. These need to be evaluated to ensure no alterations to the risk-benefit balance.

¹¹ Details of PI revisions outside of the proposed extension of indications are beyond the scope of this AusPAR.

The proposed changes to the PI in relation to data from studies A2309 and A2310 are acceptable, apart from recommended alterations not described in this AusPAR. The 24 Month data from these two studies must be submitted for evaluation as soon as available.

Concerning the wording of the proposed indication, the evaluator noted that the sponsor proposed the following:

Certican is indicated for the prophylaxis of organ rejection in adult patients at mild to moderate immunological risk receiving an allogeneic renal cardiac or hepatic transplant.

The efficacy data in the three main transplant studies (A2310, A2309 and H2304) was obtained with a specific concomitant medication regimen in each study. The evaluator believes that this should be included in the indication as data with other regimens is either not available or not supportive of the indication. It is therefore recommended that the indication include wording to the effect of:

In hepatic transplantation Certican should be used in combination with tacrolimus and corticosteroids.

In renal and cardiac transplantation Certican should be used in combination with cyclosporine microemulsion and corticosteroids.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a RMP (Version 2.0 (release date 14 Oct 2011), with the RMP Australian Implementation Version 2.1 (release date 16 August 2012)), which was reviewed by the TGA's Office of Product Review (OPR). A summary of the RMP is shown at Table 5.

Table 5. Summary of Risk Management Plan

Safety Concern	Proposed Pharmacovigilance (PV) activities	Proposed risk minimisation activities (modified by incorporating information from Australian-specific Annex)
Important identified risks		
Everolimus and CNI induced renal function	Routine PV including cumulative analysis in PSUR. Additional PV: Study CRAD001A2310	Routine: Precautions <i>Everolimus and calcineurin inhibitor-induced renal dysfunction</i> section of PI.
Increased proteinuria in <i>de novo</i> renal transplant recipients	Routine PV including cumulative analysis in PSUR.	Routine: Precautions <i>Proteinuria</i> section, and Adverse Effects section of PI.

Safety Concern	Proposed Pharmacovigilance (PV) activities	Proposed risk minimisation activities (modified by incorporating information from Australian-specific Annex)
Wound-healing complications	Routine PV including cumulative analysis in PSUR.	Routine: Precautions <i>Wound-healing complications</i> section, and Adverse Effects section of PI.
Hyperlipidemia	Routine PV including cumulative analysis in PSUR.	Routine: Precautions <i>Hyperlipidemia</i> section, and Adverse Effects section of PI.
Renal graft thrombosis	Routine PV including cumulative analysis in PSUR.	Routine: Precautions <i>Renal graft thrombosis</i> section, and Adverse Effects section of PI.
New onset diabetes mellitus	Routine PV including cumulative analysis in PSUR.	Routine: Precautions <i>New onset diabetes mellitus</i> section, and Adverse Effects section of PI.
Thrombotic microangiopathy	Routine PV including cumulative analysis in PSUR.	Routine: Precautions <i>Thrombotic microangiopathy/Thrombotic thrombocytopenic purpura/Haemolytic uraemic syndrome</i> section, and Adverse Effects section of PI.
Interstitial lung disease	Routine PV including cumulative analysis in PSUR.	Routine: Precautions <i>Interstitial lung disease/non-infectious pneumonitis</i> section, and Adverse Effects section of PI.
Infections	Routine PV including cumulative analysis in PSUR.	Routine: Precautions <i>Serious and opportunistic infections</i> section, and Adverse Effects section of PI.
Malignancies	Routine PV including cumulative analysis in PSUR.	Routine: Precautions <i>Lymphomas and other malignancies</i> section, and Adverse Effects section of PI.

Safety Concern	Proposed Pharmacovigilance (PV) activities	Proposed risk minimisation activities (modified by incorporating information from Australian-specific Annex)
Angioedema	Routine PV including cumulative analysis in PSUR.	Routine: Precautions <i>Angioedema</i> section, and Adverse Effects section of PI.
Oedema/oedema peripheral	Routine PV including cumulative analysis in PSUR.	Routine: Adverse Effects section of PI.
Important identified interactions		
Interaction cytochrome CYP3A4 modifiers	Routine PV	Co-administration with strong CYP3A4-inhibitors (such as ketoconazol, itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir) and inducers (such as rifampicin, rifabutin) is not recommended.
Important potential risks		
Teratogenicity	Routine PV including cumulative analysis in PSUR.	Routine: Precautions <i>Use in Pregnancy (Category C)</i> section of PI.
Important missing information		
Exposure in pregnancy, during breast-feeding	Routine PV.	Routine: Precautions <i>Use in Pregnancy (Category C)</i> section of PI.
Use in a paediatric population	Routine PV. Paediatric Investigational Plan	Routine: Dosage and Administration – <i>Administration via nasogastric tube</i> section of PI.
Severe liver function impairment	Routine PV.	Routine: Precautions <i>Liver function impairment</i> section, and Dosage and Administration – <i>Patients with impaired hepatic function</i> section of PI.

Safety specification

Subject to the evaluation of the clinical aspects of the Safety Specifications by the Office of Medicines Safety (OMA), the summary of ongoing safety concerns is as specified in Table 5, above. Pursuant to the evaluation of the clinical aspects of the safety specifications, it is recommended that the summary of the ongoing safety concerns be revised as recommended by the clinical evaluator. The recommended revisions include the addition of the following safety concerns: pericardial infusion, haemodynamic compromise, leukopenia, thrombocytopenia, pancytopenia, and to broaden the important identified risk 'Increased proteinuria in *de novo* renal transplant recipients' to 'proteinuria'. In addition, it is recommended that 'long-term safety' is added as an area of missing information of the safety specifications for ongoing monitoring.

Pharmacovigilance plan

Routine PV activities are proposed for all ongoing safety concerns. In addition, three studies, including two as part of the EMA Paediatric Investigational Plan (PIP) are proposed as additional PV activities for the important identified risk 'Everolimus and CNI induced renal dysfunction' and the area of missing information 'Use in paediatric population'.

Risk minimisation activities

The sponsor proposed that routine risk minimisation activities in the form of safety information/precautionary statements provided in the PI and Consumer Medicine Information (CMI) are sufficient. This may not be acceptable because additional safety concerns have been identified for inclusion as safety specifications of the RMP (see *Safety specification*, above).

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application:

- the implementation of the Safety RMP Version 2.0 (release date 14 Oct 2011), with the Safety RMP Australian Implementation Version 2.1 (release date 16 August 2012), and any subsequent updates is imposed as a condition of registration with the provisions as stated below.

If this submission is approved, it is recommended that the Delegate considers requesting the sponsor address the following deficiencies, unless an acceptable justification has been provided for why any of these changes are not required:

Safety concerns:

- To revise the safety specifications as recommended by the clinical evaluator, to ensure that these safety concerns are formalised in the RMP for ongoing monitoring commitment. This includes the addition of the following safety concerns: pericardial infusion, haemodynamic compromise, leukopenia, thrombocytopenia, pancytopenia, and to broaden the important identified risk 'increased proteinuria in *de novo* renal transplant recipients' to 'proteinuria'. In addition, it is recommended that 'long-term safety' is added as an area of missing information of the safety specifications for ongoing monitoring.

Pharmacovigilance activities:

- To propose adequate and appropriate PV activities for each of the relevant additional safety concerns: pericardial infusion, haemodynamic compromise, leukopenia, thrombocytopenia, pancytopenia, proteinuria and long-term safety.
- To incorporate the information relevant to the PIP changes approved by the EMA and the results from Study CRAD001A2310 in a future update to the RMP.

Risk minimisation activities:

- To propose adequate and appropriate risk minimisation activities for each of the relevant additional safety concerns: pericardial infusion, haemodynamic compromise, leukopenia, thrombocytopenia, pancytopenia, 'proteinuria' and 'long-term safety'.
- To propose adequate and appropriate additional risk minimisation activities (for example, in the form of educational materials or "Dear Healthcare Professional (HCP)" communications as recommended by the clinical evaluator, particularly to inform of and manage the serious risks associated with the use of Certican and to highlight the importance of careful therapeutic drug monitoring for not only everolimus but also for cyclosporin and tacrolimus. An appropriate strategy to assess the effectiveness of the proposed risk minimisation strategy should also be provided.

The OPR reviewer also recommended several revisions to the PI and CMI; details of these are beyond the scope of this AusPAR.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Everolimus was first registered in Australia in 2005 with the trade name Certican. The approved indication is:

For the prophylaxis of organ rejection in adult patients at mild to moderate immunological risk receiving an allogeneic renal or cardiac transplant.

This application seeks approval for several different changes:

- a. Extension of indications for everolimus (Certican) to include recipients of allogeneic hepatic transplants in addition to the current recipients of allogeneic renal and cardiac transplants. The proposed revised indication is:

Certican is indicated for the prophylaxis of organ rejection in adult patients at mild to moderate immunological risk receiving an allogeneic renal, cardiac or hepatic transplant.

- b. Changes to the PI in relation to cardiac transplant recipients.

- c. Change of the *Dosage and Administration* section of the PI based on a study in renal transplant recipients.
- d. Other changes to the PI.

This AusPAR includes only the discussions in the overview relevant to the proposed extension of indications to include use of Certican in recipients of allogenic hepatic transplants.

Extension of indications to include use in recipients of allogenic hepatic transplants

The submitted data relating to use in hepatic transplantation include PK, PD, interactions, efficacy, and safety. In addition, the reporting of the pivotal clinical study was complex, with introduction of everolimus late after hepatic transplantation and modification of the design part way through the study.

Pharmacokinetics.

Pharmacokinetics in patients with liver transplants.

No new bioavailability, bioequivalence, or food effect data were submitted. A previously submitted single dose PK Study (B202) assessed factors which might alter the absorption of everolimus in liver transplantation. These included external bile diversion, administration *via* a nasogastric or nasoduodenal tube and time post-transplant. The sponsor reported that these factors did not significantly alter the PK of everolimus.

A secondary objective of Study B158 related to PK and included characterisation of the SS PK of everolimus in *de novo* liver allograft recipients, exploration of the exposure-response relationships with reference to acute rejection episodes and changes in pertinent laboratory parameters, and assessment of the influence of SS everolimus on SS cyclosporin PK. The average whole blood concentration before the morning dose at SS ($C_{0,ss}$) over 6 months of treatment was 3.0 ± 1.7 ng/ml at 1 mg, 5.8 ± 5.0 ng/ml at 2 mg, and 8.9 ± 5.0 ng/ml at 4 mg. At Month 3, T_{max} at SS was 1.6 h, 1.9 h and 1.2 h, respectively in the three groups. Trough everolimus concentrations were correlated with $AUC_{\tau,ss}$ (correlation coefficient = 0.91). The regression slope for dose versus $AUC_{\tau,ss}$ was 0.75 (90% CI: 0.57, 0.92) at Week 1, 0.80 (90% CI: 0.58, 1.02) at Month 2 and 0.82 (90% CI: 0.65, 0.98) at Month 3. This relationship found that doubling the dose resulted in a 1.8 fold increase in AUC, which indicated some under proportionality. There was a notable level of intra-subject (31.5% for $AUC_{\tau,ss}$) and inter-subject (26.7% for $AUC_{\tau,ss}$) variability.

Some PK data also came from the pivotal efficacy Study H2304. Everolimus was given together with tacrolimus and whole blood trough levels monitored for dose adjustment. In the EVR + reduced TAC group, everolimus dose commenced at 1 mg bid with target levels of 3-8 ng/mL. When the everolimus target was met, the tacrolimus dose was tapered from full exposure (≥ 8 ng/mL) to trough levels of 3-5 ng/mL. After one week, the mean everolimus $C_{0,ss}$ was 3.4 ng/mL with 48.4% of patients in the target window and over the first month there was a 62% increase in dose (1.73 mg bid) to reach a mean $C_{0,ss}$ of 4.8 ng/mL and 79% of trough levels within the target range. Between 6 and 12 months, the mean $C_{0,ss}$ was 5.6 ng/mL with 80% within the target range.

Pharmacokinetic interaction studies

Midazolam: The interaction between everolimus and midazolam was investigated in healthy male volunteers after 5 days of everolimus 10 mg daily to ensure therapeutic everolimus concentrations. Co-administration increased the midazolam C_{max} by 25% (90% CI: 1.14, 1.37) and the overall exposure (AUC_{0-inf}) by 30% (90% CI: 1.22, 1.39). There was a decrease in midazolam clearance by 23% with co-administration (63.45 ± 25.91 L/h compared to 82.24 ± 32.37 L/h when given alone), while the terminal half life was similar (5.33 ± 1.79 h alone compared to 5.40 ± 1.63 h with everolimus). The major metabolite of

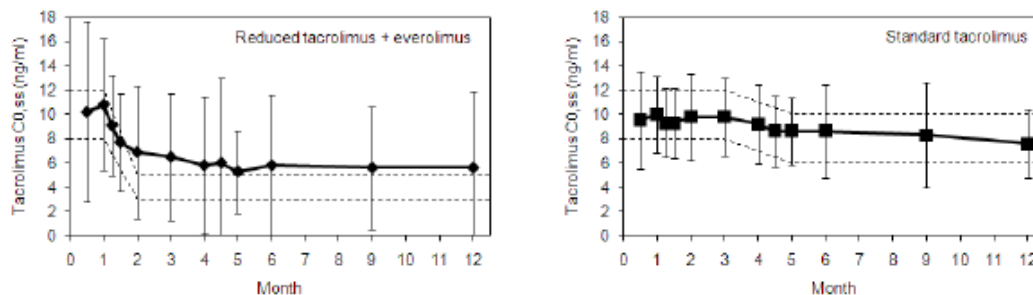
midazolam, 1-hydroxymidazolam, also increased with co-administration, with a 20% increase in C_{max} and 25% increase in AUC_{0-inf}.

The PK parameters of everolimus when administered with midazolam included a median T_{max} of 2.0 h (range 1.0-4.0 h), C_{max} of 53.80 ± 11.56 ng/mL, minimum concentration (C_{min}) of 9.06 ± 2.28 ng/mL and mean exposure (AUC over time 0 to the last measurement point) of 418.0 ± 186.64 ng.h/mL. The sponsor claimed that these everolimus results are compatible with monotherapy.

Cyclosporin: Study B158 examined 454 evaluable trough cyclosporin levels in 94 patients with *de novo* hepatic transplant. There was some down titration of cyclosporin dose over time. The average dose at Week 1 was 347 ± 161 mg bid, in Month 3 it was 172 ± 72 mg bid and in Month 6 it was 152 ± 67 mg bid; corresponding trough levels were, respectively, 258 ± 121 ng/mL, 211 ± 95 ng/mL and 188 ± 87 ng/mL (all everolimus doses combined). The cyclosporin trough levels in the placebo group were 277 ± 121 ng/mL at Week 1, 213 ± 88 ng/mL at Month 3 and 207 ± 84 ng/mL at Month 6. These cyclosporin levels in the placebo group were similar to those found in the everolimus group.

Tacrolimus: There was no specific interaction study. In the pivotal efficacy study there was a tacrolimus control arm with target concentrations of 8-12 ng/mL as well as the EVR + reduced TAC group with a target level of 3-5 ng/mL. Mean levels from the 12 month study are in Figure 2. Down titration of tacrolimus took about 3 months to reach stable mean level of 5.7 ng/mL. There were 45 subjects with targets above the upper level of the range.

Figure 2. Mean tacrolimus concentrations. Study H2304



Mean tacrolimus predose concentration (C_{0,ss}) trajectory in the reduced-tacrolimus with everolimus arm. Bars represent one standard deviation of the mean. Dashed lines demarcate the target concentration ranges.

As in left panel for the standard-tacrolimus control arm.

Pharmacodynamics.

Exposure-efficacy analyses were conducted in the pivotal hepatic transplantation Study H2304. This was a 24 month, multicentre, open label, randomised, controlled study in 719 *de novo* hepatic transplant patient who were randomised to one of 3 groups:

EVR + reduced TAC, EVR + TAC elimination group and TAC control. Trough everolimus and tacrolimus levels were collected for making dose adjustment decisions. For the primary efficacy composite outcome of tBPAR/GL/D, the rates in the EVR + reduced TAC group were 17.6%, 5.3%, 15.4% in those with an average trough (C₀) everolimus level of < 3, 3-8 and > 8 ng/mL, respectively. In patients with high everolimus levels (> 8 ng/mL) there was one tBPAR, one GL and no D.

Exposure-efficacy relationship was also assessed in Study B158. Efficacy was assessed on tBPAR between Day 1 and 225 post transplantation. Exposure was assessed on the geometric mean everolimus trough levels at SS divided into groups of < 3 ng/mL, 3-6 ng/mL and > 6 ng/mL. Freedom from tBPAR was 63%, 50%, 86% and 88% in the

0 ng/mL (placebo), < 3 ng/mL, 3-6 ng/mL and > 6 ng/mL exposure groups, respectively. Logistic regression suggested increased efficacy with increased exposure ($p = 0.0137$). The clinical evaluator noted that the numbers in each group were small and so the data needs to be interpreted with caution.

In hepatic transplantation patients, exposure-efficacy analyses suggested increased efficacy with increased exposure (Study B158), although the numbers in this analysis were small. In Study H2304, the highest rate of efficacy failure was noted with levels < 3 ng/mL, although a trend was not evident.

Efficacy in hepatic transplant

Pivotal efficacy study

Study H2304 was a 24 month, Phase III, multicentre, open label, randomised, controlled trial in 719 *de novo* liver transplant recipients, which evaluated the efficacy and safety of concentration controlled everolimus with eliminated or reduced dose tacrolimus, compared to a standard dose tacrolimus regimen. Subjects had a screening period prior to transplantation, a baseline period of 3 to 7 days post transplantation and a run-in period to 30 days (± 5 days) post transplantation. In the baseline period, patients received a tacrolimus based regimen with corticosteroids and with or without mycophenolate mofetil (MMF) according to the local practice. Mycophenolate mofetil was discontinued at randomisation. Patients were stratified on HCV status and renal function which was assessed by the abbreviated MDRD formula. There were 3 treatment groups: 1. EVR + TAC elimination; 2. EVR + reduced TAC; and 3. TAC control. The study design is summarised in Figure 1 of this AusPAR, above.

After completion of 24 months on study, patients could continue in a 12 month extension Study (H2304E1). In April 2010, the DMC recommended ceasing enrolment in the group from which tacrolimus had been eliminated due to an increased rate of acute rejection and discontinuation in this group. At this point, 690 patients had been randomised. There was no further randomisation into this group and enrolled patients who had not reached Day 180 post-randomisation were discontinued and switched to local standard treatment. Those who were > 180 days post-randomisation could continue on treatment or swap to local standard treatment. The remaining eligible patients ($n = 51$) were randomised equally to groups 2 and 3.

In addition, changes were made to align with recent CHMP guidelines.¹² To assess the early impact of TAC minimisation, the primary endpoint was changed from GL/D/loss to follow up to tBPAR/GL/D. This resulted in a change in the NI margin from 10% to 12%.

Everolimus was taken each 12 h together with tacrolimus. Drug level monitoring was mandated in the study. Central everolimus levels were used to adjust everolimus dosing and local tacrolimus levels were used to adjust tacrolimus dosing.

In group 1, the EVR + TAC elimination group, patients received low dose tacrolimus (until Month 4, then tacrolimus was eliminated) + everolimus + corticosteroids. Everolimus commenced within 24 h of randomisation at 1.0 mg bid (2 mg daily) and everolimus whole blood trough levels (taken 5 days \pm 2 days post dose change) were targeted to be maintained between 3-8 ng/mL. When everolimus trough levels were confirmed to be in the target range (3-8 ng/mL), tacrolimus tapering started, with a tacrolimus whole blood trough level target of 3-5 ng/mL by three weeks after randomisation. At Day 120 (Month 4) everolimus whole blood trough levels were targeted to 6-10 ng/mL and when in this range, tacrolimus elimination started and was completed by the end of Month 4 post-

¹² CHMP. *Guidelines on the clinical investigation of immunosuppressants for solid organ transplant* (CHMP/EWP/263148/06; July 2008; effective from 1 February 2009)

transplantation. Tacrolimus elimination did not commence until there was evidence of a functioning allograft (AST, ALT and total bilirubin $\leq 3 \times$ the upper limit of normal (ULN) and alkaline phosphatase (ALP) and gamma glutamate transferase (GGT) $\leq 5 \times$ ULN).

In group 2, EVR + reduced TAC, patients received low dose tacrolimus + everolimus + corticosteroids. Everolimus was commenced (as per group 1) at 1.0 mg bid and the target trough level of 3-8 ng/mL was to be maintained for the duration of the study. The dose could be altered to maintain this level. As in group 1, tacrolimus dose tapering began when everolimus was at this level to target a level of 3-5 ng/mL. It was maintained at this level for the study duration.

In group 3, the TAC control group, patients received tacrolimus + corticosteroids. Tacrolimus trough levels were targeted at 8-12 ng/mL to Month 4 then decreased to 6-10 ng/mL for the rest of the study. Corticosteroids were commenced at or prior to transplantation according to local practice. Treatment was required to continue until 180 Days post transplantation.

Dose reduction of everolimus was permitted if there were decreases in white blood cells or platelets, increases in cholesterol or triglycerides, or AEs. Reduction was by 0.25 mg intervals. Everolimus was discontinued if trough levels ≥ 3 ng/mL could not be maintained due to toxicity. Everolimus was interrupted during antibody treatment of rejection episodes and switched to tacrolimus during surgical treatment.

Rescue medication was based on local practice. All patients received pneumocystis prophylaxis. Cytomegalovirus and hepatitis B prophylaxis was as per local practice. Oral candida treatment was topical and HCV treatment was only given for histological evidence of recurrent disease.

There were 1378 patients screened, 1147 received a liver transplant and entered the run-in period and 719 were randomised to study treatment. The screen failure and randomisation failure rates were 16.8% and 37.3%, respectively. The main reasons for randomisation failure were inadequate allograft function (5.9%), tacrolimus levels < 8 ng/mL (5.7%), medical/surgical condition (5.5%), requiring critical care (3.6%), inadequate renal function (3.5%), antibody induction therapy (3.0%) and other (15.1%).

There were 231, 245 and 243 patients in the EVR + TAC elimination, EVR + reduced TAC and TAC control groups, respectively, and the study medication completion rates were 44.2%, 73.1% and 77.8%, respectively.

The submitted data were for the first 12 months of treatment.

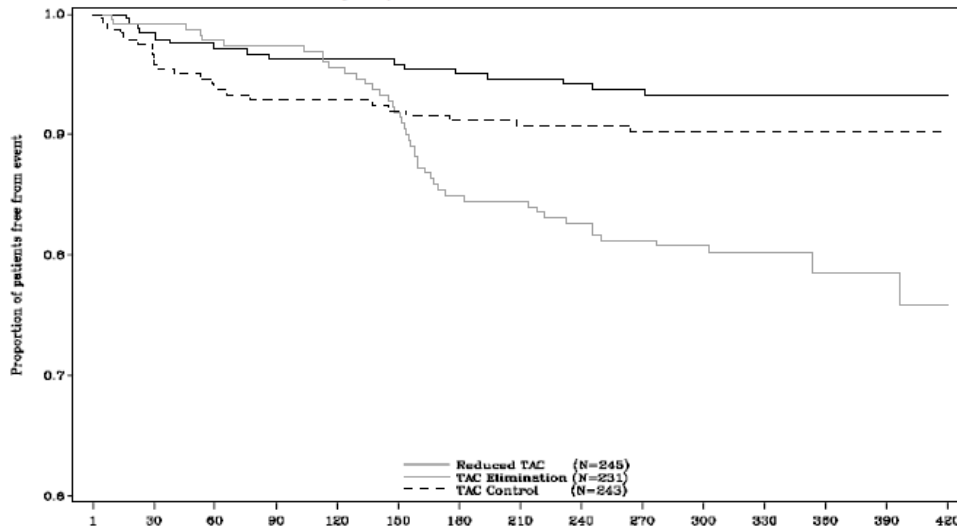
In the EVR + reduced TAC group to Month 2, 48.4% of patients were within the target everolimus trough level of 3-8 ng/mL. From Month 2 to 12 the proportion within target was between 78% and 82%. Between Week 5 and Month 12 in this group the mean everolimus trough level ranged from 3.4 to 6.3 ng/mL.

In the EVR + reduced TAC group prior to Month 2, only 9-19% of patients had tacrolimus levels after tapering within the trough target level of 3-5 ng/mL. Between Months 2 and 12, the proportion within the target range was between 32% (at Month 2) and 48% (at Month 12). At Month 12, 16% were below, 48% were within and 36% were above TAC target. In the TAC control group, 54% were within the target range at Month 12 with 19% above target and 27% below target. The CER notes that *'This finding may indicate some reticence by the investigators to reduce tacrolimus to protocol defined levels in this open label study'*.

The result for the primary efficacy outcome (rate of the composite primary endpoint (tBPAR/GL/D) at Month 12) was slightly lower in the EVR + reduced TAC group compared to the TAC control group (6.7% versus 9.7%), with a difference of -3.0% (97.5% CI: -8.7%, 2.6%). As the upper bound of the CI was less than the NI margin of 12%, the EVR + reduced TAC treatment was found to be non-inferior to TAC control ($p < 0.001$).

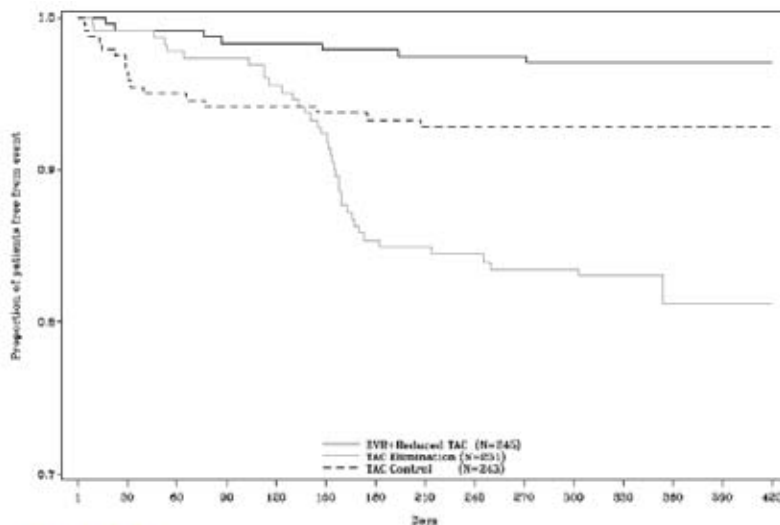
In the PP population analysis, the rate of tBPAR/GL/D was 1.9% and 5.0% in the EVR + reduced TAC and TAC control groups, respectively, with a difference of -3.1% (97.5% CI: -7.6%, 1.5%). Again, this result was non-inferior and statistically significant ($p < 0.001$). The Kaplan-Meier plot for the primary endpoint is shown in Figure 3.

Figure 3. Kaplan-Meier plot for the proportion of patients free from primary composite efficacy failure tBPAR, graft loss or death (ITT population – 12 month analysis)



At 12 Months, the rate of GL (2.4% versus 1.2%) and D (3.7% versus 2.5%) was higher in the EVR + reduced TAC group compared to the TAC control group, however the risk difference was not statistically significant ($p = 0.504$ and $p = 0.602$, respectively). The rate of acute rejection was lower in the EVR + reduced TAC group compared to the TAC control group (3.7% versus 10.7%) with a significant risk difference of -7.0% (95% CI: -11.6%, -2.5%, $p = 0.003$). This finding was consistent across the other definitions of acute rejection (treated, biopsy proven, and treated biopsy proven). The Kaplan-Meier plot of patients free from tBPAR at the 12 Month analysis by treatment (Figure 4) shows the poorer outcome in the EVR + TAC elimination group.

Figure 4. Kaplan-Meier plot for the proportion of patients free from tBPAR (ITT population – 12 month analysis)



Concerning renal function in this study, the adjusted LS mean change in eGFR (MDRD-4) from randomisation to Month 12 in the ITT population was -2.23 mL/min/1.73 m² in the

EVR + reduced TAC group, compared to $-1.51 \text{ mL/min/1.73 m}^2$ in the EVR + TAC elimination group and $-10.73 \text{ mL/min/1.73 m}^2$ in the TAC control group. The difference between the EVR + reduced TAC and TAC control group was $8.50 \text{ mL/min/1.73 m}^2$ (97.5% CI: 3.74, 13.27), which was non-inferior (-6 NI margin) and also statistically superior ($p < 0.001$). Results from the PP population were similar with a LS mean difference of $10.40 \text{ mL/min/1.73 m}^2$ (97.5% CI: 4.76, 16.05, $p < 0.0001$). This effect on eGFR was statistically superior from Month 2 through to Month 12 in the ITT population. Similar results were also found when renal function was assessed by serum creatinine or when eGFR was estimated by several other methods.

Results of both primary and key secondary efficacy outcomes were consistent across subgroups of age, gender, race, region, eGFR, HCV status, MELD score and cause of ESLD. Elimination of tacrolimus when patients were treated with everolimus was associated with a significant risk of efficacy failure and treatment with the regimen was required to be prematurely terminated.

Other efficacy studies

Study HDE10 was a 12 month, Phase III, multicentre, randomised, open label, parallel group study of the safety, tolerability and efficacy of an everolimus-based regimen compared to a CNI-based regimen in 203 adult patients with *de novo* liver transplantation.

The primary objective was to demonstrate, at 11 months post randomisation, superiority of renal function for the everolimus based regimen with discontinuation of CNI therapy compared to a CNI based regimen. Efficacy was a secondary objective. Patients received basiliximab induction treatment and then at Week 4, if eligible, were randomised to either continued CNI therapy or everolimus (1.5 mg bid) treatment with tapering CNI dose (reduced by 70% of dose then discontinued). The everolimus target level was 5-12 ng/mL.

The study did not reach its primary endpoint of superiority of renal function with an everolimus based immunosuppressive regimen. For the secondary objectives relating to efficacy, there were no significant differences between the treatment groups in single events or in the composite event of efficacy failure (BPAR, GL, D, loss to follow up) (17.7% versus 14.3% $p = 0.56$). There were also no significant differences in these endpoints on Kaplan-Meier estimates.

Study H2401 was a Phase III, 6 month, multicentre, randomised, open-label study of the safety and efficacy of everolimus-based regimen compared to a CNI-based regimen in 145 maintenance liver transplant recipients with CNI-related renal impairment. The primary objective was to determine whether everolimus together with reduction or discontinuation of CNI in maintenance liver transplant patients with CNI-related renal impairment would improve renal function as measured by the change in cGFR from baseline to Month 6. Measures of efficacy (BPAR, GL and D) and safety were secondary objectives. Patients were followed up again at 12 months.

At 6 months, the composite efficacy failure (BPAR/GL/D) rate was 2.8% ($n = 2$) in the everolimus group and 1.4% ($n = 1$) in the CNI control group. The difference of 1.5% (95% CI: -3.2, 6.0%) was not significant ($p = 0.552$). In the follow up from 7 to 12 months, there were a further 2 deaths and 2 cases of acute rejection in the EVR group and 2 deaths in the CNI control group. It was noted that after Month 6, other immunosuppressant therapies were allowed.

Study H2301: An interim CSR for H2301 (dated August 2011) was included in the dossier. H2301 was described as an exploratory study which aimed to assess the efficacy of everolimus in inhibiting fibrosis progression in 43 liver transplant recipients with recurrent hepatitis C. It was a 24 month, randomised, multicentre, open label, parallel group trial conducted at 6 centres in Argentina between November 2006 and January

2010. The study was terminated prematurely after the 12 month biopsy due to a high drop-out rate.

This exploratory study in 43 liver transplant patients with recurrent HCV was terminated early due to a high drop-out rate, particularly due to AEs, and only an interim CSR was provided. Data were primarily based on 32 biopsies at 12 months, rather than at 24 months. In addition, the groups were not well balanced at baseline. The data showed a lower mean fibrosis (IK) score at Month 12 with everolimus compared to CNI treatment. However, due to the factors listed, the results of this study cannot be viewed as conclusive.

There were no efficacy analyses across trials.

Efficacy conclusions

The pivotal study met its primary objective as treatment commencing one month post transplantation with a regimen of everolimus and reduced tacrolimus dose was found to be statistically non-inferior (NI margin 12%) to treatment with tacrolimus alone at 12 months when measured by the composite endpoint of tBPAR/GL/D (6.7% versus 9.7%) with a difference of -3.0% (97.5% CI: -8.7%, 2.6%, $p < 0.001$). Non-inferiority was also achieved on other efficacy endpoints of GL/D/loss to follow up and GL/D, and was supported by the PP analysis. There was statistically superior renal function as measured by mean change in eGFR with a difference of 8.50 mL/min/1.73 m² (97.5% CI: 3.74, 13.27, $p < 0.001$) in favour of the EVR + reduced TAC group compared to the TAC control.

Overall, the effect appeared more related to a reduced rate of acute rejection episodes (3.7% versus 10.7%) rather than reduced GL or D. The study found that a reduction of tacrolimus was possible with the addition of everolimus post hepatitis transplantation without an increase in efficacy failure at 12 months post transplantation. It was also found that efficacy was unacceptable when everolimus was used without continuing tacrolimus concomitantly.

The PI adequately summarises the clinical efficacy data in hepatic transplantation with the exception of a failure to state the risks of tacrolimus elimination.

One supportive study (HDE10) did not reach its primary endpoint of superiority of renal function with an everolimus based immunosuppressive regimen compared to a CNI based regimen. Regarding efficacy, there were no significant differences between the treatment groups in single events or in the composite of efficacy failure (BPAR, GL, D, loss to follow up) (17.7% versus 14.3% $p = 0.56$).

The two other studies do not add to the pivotal findings.

Safety in recipients of hepatic transplants

In the controlled hepatic transplantation studies in the dossier there were 759 patients exposed to everolimus (see Table 3 of this AusPAR, above)

In Study H2304, AEs were reported in 94.7%, 93.9% and 95.0% of the EVR + reduced TAC, EVR + TAC elimination and TAC control groups, respectively. The most commonly reported primary System Organ Classes (SOCs) were gastrointestinal disorders, infections/infestations, metabolism/nutrition disorders and general/administrative site conditions. Infections/infestations (50.2% versus 43.6%) and blood/lymphatic disorders (26.9% versus 19.5%) were notably more frequent in the everolimus 1.5 mg than the control group.

In H2304 over 12 months, the commonly reported AEs (rates for the everolimus 1.5 mg versus TAC control group) were diarrhoea (19.2% versus 20.7%), headache (19.2% versus 19.1%), pyrexia (13.1% versus 10.4%), hypertension (17.1% versus 15.8%), peripheral oedema (17.6% versus 10.8%), nausea (13.5% versus 11.6%) and abdominal pain (13.1% versus 9.1%).

The rate of mild, moderate and severe AEs was, respectively, 14.3%, 49.0% and 31.4% in the everolimus 1.5 mg group. These proportions were similar in the everolimus 3.0 mg group, while in the TAC control group there were more mild and less severe AEs (27.8%, 46.5% and 20.3%, respectively).

Compared to Study A2309 in renal transplant (everolimus + reduced cyclosporin group), the most frequent AEs did not occur at a higher rate in Study H2304 (EVR + reduced TAC group) (Table 6).

Table 6. Number (%) of patients with most frequent ($\geq 10\%$ in any treatment group) AEs including infections by primary SOC, preferred term and treatment in Study H2304 compared to Study A2309 (Study H2304, Safety population – 12 month analysis; Study A2309, Safety population – 12 month analysis)

Primary System Organ Class Preferred term	Study	EVR+Reduced CNI n/N (%)
Blood and lymphatic system disorders		
Leukopenia	A2309	8/274 (2.9)
	H2304	29/245 (11.8)
Gastrointestinal disorders		
Abdominal pain	A2309	36/274 (13.1)
	H2304	32/245 (13.1)
Diarrhoea	A2309	51/274 (18.6)
	H2304	47/245 (19.2)
Nausea	A2309	79/274 (28.8)
	H2304	33/245 (13.5)
General disorders and administration site conditions		
Fatigue	A2309	25/274 (9.1)
	H2304	22/245 (9.0)
Oedema peripheral	A2309	123/274 (44.9)
	H2304	43/245 (17.6)
Pyrexia	A2309	51/274 (18.6)
	H2304	32/245 (13.1)
Infections and infestations		
Hepatitis C	A2309	1/274 (0.4)
	H2304	28/245 (11.4)
Nervous system disorders		
Headache	A2309	49/274 (17.9)
	H2304	47/245 (19.2)
Tremor	A2309	23/274 (8.4)
	H2304	23/245 (9.4)
Vascular disorders		
Hypertension	A2309	81/274 (29.6)
	H2304	42/245 (17.1)

The CER notes that in Study H2304 there was a delay of one month post transplantation prior to commencing everolimus. The sponsor states this has assisted in reducing wound healing complications.

Concerning infections, the rate of infections was highest in the EVR + TAC elimination group (49.4%, 53.0% and 45.6%, respectively, in the EVR + reduced TAC, EVR + TAC elimination and TAC control groups). The most frequent infections were *Escherichia coli*, HCV and unknown organism. In H2304, randomisation was stratified by HCV status.

Rates of specific interest AEs in H2304 and A2309 were compared. The hepatic transplantation patients showed a lower rate of anaemia, angioedema, cardiovascular events, hyperlipidaemia, peripheral oedema, proteinuria, renal failure, thrombotic/thromboembolic events and wound healing complications. Hepatic transplant patients versus renal implant patients had higher rates of incisional hernia (6.9% versus 1.8%), ascites (4.1% versus 0.4%), thrombocytopenia (5.7% versus 2.9%) and new onset diabetes (19.6% versus 9.1%).

In Study HDE10, the AE rate was 97% and 94% in the everolimus and CNI groups, respectively. The most frequent SOCs were similar to H2304, with rates generally higher in the EVR than CNI groups. AEs with a $\geq 10\%$ difference between groups were diarrhoea (27.7% versus 13.7%), hepatic enzyme increased (22.8% versus 11.8%), hypercholesterolemia (22.8% versus 10.8%), leukopenia (20.8% versus 9.8%) and headache (19.8% versus 9.8%). Other higher AEs were: oral herpes, sinusitis, wound infection, stomatitis, hypertension and anaemia. Infections were more frequent with everolimus (72.3% versus 54.9%).

In the 6 months of H2401, the AE rate was again higher in the everolimus than CNI group (96% versus 70%).

In the combined hepatic transplant studies, malignancy rate was not higher in the everolimus than in the TAC control group in H2304 (2.4%, 3.0% versus 4.6%). There was one recurrence of hepatocellular carcinoma (HCC) in the EVR + TAC elimination group and one in the TAC control group. In HDE10, neoplasm SOC AEs were lower in the everolimus than in the CNI group (4.0% versus 8.8%).

Hepatitis C: The mean hepatitis activity index (HAI) score at Month 12 in H2304 was 3.4, 4.6. and 4.5 in the EVR + reduced TAC, EVR + TAC elimination and TAC control groups, respectively. Viral load increased over 12 months, although the mean change was similar between groups. (0.54, 0.51 and 0.51). In H2301, the HCV viral load at Month 12 and mean change from baseline were similar between groups.

Hepatic artery thrombosis was reported in one EVR + TAC elimination group patient. During the post transplantation phase (prior to study medication) there were 14 cases recorded.

The clinical evaluator assessed the risks of everolimus for use in hepatic transplantation as:

- Treatment with everolimus does not allow elimination of concomitant tacrolimus. Elimination of tacrolimus resulted in an unacceptable increased risk of acute rejection and treatment discontinuation.
- There was an increased risk of efficacy failure with everolimus trough levels < 3 ng/mL and higher doses than recommended have an unacceptable safety profile. Everolimus treatment needs to be concentration-controlled through active therapeutic drug monitoring.
- Adverse events are virtually universal in this patient population and, over the 12 months, the most commonly reported AEs were diarrhoea, headache, pyrexia, hypertension, peripheral oedema, nausea, abdominal pain, hepatitis C, leukopenia, anaemia, fatigue and tremor.
- Compared to the renal transplantation study, there were higher rates of incisional hernia, ascites, thrombocytopenia and new onset diabetes. There were, however, lower risks of hyperlipidaemia, peripheral oedema, proteinuria, angioedema, cardiovascular events, renal failure excluding proteinuria, anaemia and thromboembolic events.
- There was a higher rate of severe AEs (31% versus 20%) and SAEs (50% versus 43%) with everolimus and reduced dose tacrolimus, compared to the tacrolimus control regimen. There was also a higher rate of premature discontinuation due to AEs (26% versus 14%).
- There was an increase risk of thromboembolic events (5.3% versus 3.7%), however major cardiovascular events were not more prevalent (2.0% versus 3.7%) and the delayed treatment commencement (at one month post transplantation) appears to have reduced the potential risk of hepatic artery thrombosis.

- About one third of patients developed new onset diabetes mellitus with a slightly higher rate than in the tacrolimus control group.
- Other known risks with everolimus were present, including stomatitis and mouth ulcers, wound healing events, interstitial lung disease, angioedema, pleural effusion and infections.
- There are no long term efficacy data.
- There are only limited data on non-Caucasians.

The clinical evaluator assessed the benefits in hepatic transplantation as:

- Treatment with everolimus allowed a reduction in tacrolimus exposure without affecting efficacy in terms of prevention of the composite endpoint of tBPAR, GL and D at 12 months post-transplantation.
- The everolimus and reduced dose tacrolimus regimen resulted in significantly fewer episodes of acute rejection than the standard dose tacrolimus regimen (3.7% versus 10.7%).
- Efficacy results were consistent across subgroups of age, gender, region, eGFR, HCV status, MELD score and cause of ESLD.
- Over the 12 months post transplantation, the decline in renal function (eGFR by MDRD-4) with everolimus and reduced dose tacrolimus treatment was significantly less than with standard dose tacrolimus (-2.2 versus -10.7 mL/min/1.73 m²). The finding was consistent across other methods of renal function assessment and patient subgroups. The rate of renal failure/impairment AEs was slightly lower with everolimus.
- There were lower rates of malignancy in the EVR + reduced TAC group compared to the standard dose tacrolimus regimen (2.4% versus 4.6%).

Clinical evaluator's recommendation

The clinical evaluator recommended approval of the extension of the indication for everolimus (Certican) to include hepatic transplant patients. This is subject to the proposed changes to the draft PI being satisfactorily addressed.

In addition, a condition of this indication extension should be the submission of the further data from Study H2304 as it becomes available. This includes the data to Month 24 and then the extension Study data. These need to be evaluated to ensure no alterations to the risk-benefit balance.

The evaluator has highlighted that the rationale for the dose to be only reduced by half in severe hepatic impairment was that if the exposure is too low there may be a risk of acute organ rejection. This appears to be too high a dose, however the evaluator acknowledges the potential counter risk of acute rejection and assessed that the risk may in part be mitigated by the therapeutic drug monitoring. In general, for subjects with Child-Pugh C (severe) hepatic impaired status, the administration of everolimus should be with extreme caution and only when it is in the best interest of the subject. Vigilant therapeutic drug monitoring will be critical in these patients and these factors need to be adequately outlined in the PI.

The Delegate discussed additional amendments to the PI regarding hepatic transplantation and other changes; details of these are beyond the scope of this AusPAR.

Risk management plan

The RMP evaluation noted the clinical evaluator's comment that: *"There is a manifest need to communicate the serious risks with everolimus to all those involved in organ transplantation. This needs to be fully captured within the RMP."*

There is also an evident lack of long term data. The 24 months data from the three main transplants studies, together with any extensions, will be important to better delineate longer term risks of immunosuppression, such as chronic rejection, malignancy, renal function and cardiovascular disease."

The RMP evaluation report has made recommendations as follows:

If this submission is approved, it is recommended that the Delegate considers requesting the sponsor address the following deficiencies, unless an acceptable justification has been provided for why any of these changes are not required:

Safety concerns:

- To revise the safety specifications as recommended by the clinical evaluator, to ensure that these safety concerns are formalised in the RMP for ongoing monitoring commitment. This includes the addition of the following safety concerns: pericardial infusion, haemodynamic compromise, leukopenia, thrombocytopenia, pancytopenia, and to broaden the important identified risk 'increased proteinuria in *de novo* renal transplant recipients' to 'proteinuria'. In addition, it is recommended that 'long-term safety' is added as an area of missing information of the safety specifications for ongoing monitoring.

Pharmacovigilance activities:

- To propose adequate and appropriate PV activities for each of the relevant additional safety concerns: pericardial infusion, haemodynamic compromise, leukopenia, thrombocytopenia, pancytopenia, 'proteinuria' and 'long-term safety'.
- To incorporate the information relevant to the PIP changes approved by the EMA and the results from Study CRAD001A2310 in a future update to the RMP.

Risk minimisation activities:

- To propose adequate and appropriate risk minimisation activities for each of the relevant additional safety concerns: pericardial infusion, haemodynamic compromise, leukopenia, thrombocytopenia, pancytopenia, 'proteinuria' and 'long-term safety'.
- To propose adequate and appropriate additional risk minimisation activities (for example, in the form of educational materials or "Dear HCP" communications), particularly to inform of and manage the serious risks associated with the use of Certican and to highlight the importance of careful therapeutic drug monitoring for not only everolimus but also for cyclosporin and tacrolimus. An appropriate strategy to assess the effectiveness of the proposed risk minimisation strategy should also be provided.

Risk-benefit analysis

Delegate considerations

The Delegate noted that the care of patients after liver transplant in Australia will be supervised by a small number of physicians and surgeons with specialist expertise in this area. This provides an assurance that the matters relating to safe use should be well understood. There are needs for reported AEs to be closely monitored, for information

about safe use to be communicated effectively, and for information about longer-term use to be assessed as it becomes available.

Proposed action

The Delegate proposed to approve the extension of indications to include hepatic transplantation, subject to the following conditions:

- that the sponsor will address to the satisfaction of the TGA the requested amendments (or justifications) for the further amendment of the RMP Version 2.0 (release date 14 Oct 2011), with the Safety RMP Australian Implementation Version 2.1 (release date 16 August 2012);
- that the sponsor will amend the PI to the satisfaction of the TGA;
- that the sponsor will commit to submit to TGA the reports of Study H2304 to Month 24 and then the extension Study data within three months of the reports being signed by the Principal Investigator;
- that the sponsor will commit to submit to TGA the report of the foreshadowed “*open label, single arm, multicentre, prospective, observational study to evaluate safety/tolerability and efficacy of everolimus in combination with reduced CNI in de novo paediatric full-size liver allograft recipients, and sequentially in paediatric split liver recipients, from 1 months to 18 years old*” within three months of the reports being signed by the Principal Investigator.

Indication wording

The extended indications statement proposed by the sponsor is:

Certican is indicated for the prophylaxis of organ rejection in adult patients at mild to moderate immunological risk receiving an allogeneic renal, cardiac or hepatic transplant.

The CER expresses concern that the efficacy data in the 3 main transplant studies (A2310, A2309 and H2304) were obtained with a specific concomitant medication regimen in each study. The clinical evaluator believes that this should be included in the indication as data with other regimens is either not available or not supportive of the indication. The evaluator therefore recommended that the indication include wording to the effect of:

In hepatic transplantation Certican should be used in combination with tacrolimus and corticosteroids.

In renal and cardiac transplantation Certican should be used in combination with cyclosporin microemulsion and corticosteroids.

In the Delegate’s opinion, this direct type of instruction is unusual. An alternative wording for the indications is proposed for consideration:

Certican is indicated for the prophylaxis of organ rejection in adult patients at mild to moderate immunological risk receiving an allogeneic renal; cardiac or hepatic transplant (See Precautions).

The *Precautions* section of the PI would then have the following, or similar, words.

The clinical development of Certican has involved use of specific combinations of medicines. In hepatic transplantation Certican should be used in combination with tacrolimus and corticosteroids. In renal and cardiac transplantation Certican should be used in combination with cyclosporin microemulsion and corticosteroids. Information about other combinations is lacking.

The Delegate proposed to seek the advice of the Advisory Committee on Prescription Medicines (ACPM) concerning the preferred form for expressing the restricted nature of the sources of clinical data. The Delegate also sought general advice on this application from the ACPM.

Response from Sponsor

The Delegate proposes to seek the ACPM's advice on the preferred form for expressing the restricted nature of clinical data in the PI. Novartis accepts the form for the indications and changes to the *Precautions* section that were recommended by the Delegate, rather the changes recommended by the clinical evaluator. Presented below are the reasons the Delegate's proposal is considered to be the more appropriate.

Proposed indication

The Delegate, in the overview, proposes to approve a slightly modified indication for Certican to that which was proposed by Novartis. Novartis accepts the Delegate's recommendations. The sponsor propose a slight modification to the wording of the indication for consideration by the ACPM (underlined text below):

Certican is indicated for the prophylaxis of organ rejection in adult patients at mild to moderate immunological risk receiving an allogeneic renal or cardiac transplant and in adult patients receiving an allogeneic hepatic transplant.

Novartis also accepts the Delegate's proposal to include the text regarding the specific concomitant medications in the *Precautions* section of the PI. Novartis shares the Delegate's view that it would be unusual to include such direct instructions in the indication section as proposed by the clinical evaluator. Detailed information on concomitant medication is comprehensively reported in the appropriate sections of the PI. In relation to current use in renal and cardiac transplant, details of the use of specific combinations already appear in the *Clinical Trials* and *Dosage and Administration* sections. Pending the approval of the current application to extend use to hepatic transplantation, similar instructions on the use of concomitant medications would be included in *Precautions* sections of the PI. As the information will appear in all the appropriate sections of the PI, it would also seem unnecessary to include a cross-reference in the indications. It is worth noting that the wording proposed by the Delegate for the current application to extend the indication to hepatic transplantation is entirely consistent with the TGA advice for the original application to register Certican in that the Delegate's overview for that application stated '*... it would be appropriate to limit the indication to be consistent with that for sirolimus.*' It is also consistent with the TGA approved indication for the similar compounds tacrolimus (Prograf) and sirolimus (Rapamune).

Novartis proposes a slight modification to the wording in relation to the proposed extension, which is believed to more accurately reflect the supporting data. In the EU, the indication was approved without "*mild to moderate immunological risk*" for hepatic transplant to more accurately reflect the submitted data and clinical practice. EU discussions highlighted that it was not the intent of Novartis to specify immunological considerations in the indication statement as strictly this is not medically accurate. Histocompatibility testing is commonly used to minimise allograft rejection and to reduce donor-specific immune responses in kidney transplantation, however, this is not typically performed in liver transplantation. The study population in the pivotal Study H2304 was not selected based on immunological considerations. In Study H2304 the non-inferiority of the primary efficacy endpoint for EVR + reduced TAC compared to TAC Control was demonstrated, even for the (non-immunologic) high risk subgroups such as donor age ≥ 60 years, recipient age ≥ 60 years, cold ischemic time (CIT) > 6 h, and MELD score 20-24. Therefore, no specifications in terms of immunological risk categories should be proposed

for liver transplant recipients. For these reasons, Novartis would like to include “**and in adult patients receiving an allogenic hepatic transplant**” to the indication statement for ACPM consideration.

In summary, consistent with the Delegate’s proposal, the original Delegate’s approval for Certican and the concomitant medication information in the *Clinical Trials, Precautions* and *Dosage and Administration* sections of the PI, Novartis believes that the proposed indication statement for hepatic transplant is appropriate and warranted.

PI statements

The sponsor commented on revisions under *Pharmacology, Clinical Trials, Precautions, Adverse Effects*, and *Dosage and Administration* sections of the PI. Details of these are beyond the scope of this AusPAR.

Other issues raised in the Delegate’s overview

Delegates overview:

Safety Concerns: To revise the safety specifications as recommended by the clinical evaluator, to ensure that these safety concerns are formalised in the RMP for ongoing monitoring commitment. This includes the addition of the following safety concerns: pericardial infusion, haemodynamic compromise, leukopenia, thrombocytopenia, pancytopenia, broaden the important identified risk ‘increased proteinuria in de novo renal transplant recipients’ to ‘proteinuria’.

Sponsor’s response:

Pericardial effusion is a common procedural related complication after cardiac transplantation and occurs in approximately 10-20% of patients, essentially within 30-60 days post-transplant. This has been confirmed by the results of the heart transplant study A2310. Kaplan-Meier estimates demonstrate that the majority of the effusion events occurred within the first month after heart transplantation (Study A2310). Pericardial effusion did require more interventional therapy (approximately 3 fold increase in surgery and thoracentesis) in A2310. Subsequently, pericardial and, in addition, pleural effusions are included as adverse drug reactions in the proposed Australian Certican PI, reflecting the finding that both events may occur in the postoperative period after heart transplantation.

The results from the liver transplant Study H2304 (EVR + reduced tacrolimus (n = 245) versus EVR + TAC elimination (n = 230) versus TAC control (n = 241)) did not show any evidence for a risk of pericardial effusions in liver transplantation (0.4% versus 0.4% versus 0.8%). Consequently, pericardial effusion is considered in the Australian PI as an Adverse Drug Reaction (ADR) specific for the heart transplant population and is considered to be related to an impaired wound healing in the postoperative period. Similar, pericardial effusion is addressed in the RMP (for example, in the safety specifications) under the identified risk ‘wound healing complications’ also specifically for heart transplant patients. Details on pericardial effusion events (including Medical Dictionary for Regulatory Activities (MedDRA) terms: preferred terms (PTs) of cardiac tamponade, pericardial effusion, and pericardial haemorrhage) are given in the RMP.

Hemodynamic compromise in the heart transplant Study A2310 was either a symptom of rejection and was included as such in the composite efficacy endpoint, or a symptom of pericardial effusion, which is addressed in the Australian PI and in the RMP under the topic ‘wound healing complications’.

Haematological events: Leukopenia, thrombocytopenia and pancytopenia are frequently observed laboratory abnormalities in transplant patients, mostly as AEs of the immunosuppressive drugs (for example, due to an antiproliferative effect of mTOR inhibition). Most of these events obtained from Certican clinical trials were not serious and were of mild to moderate severity only. The haematological events are sufficiently addressed in the Certican Australian PI.

As a separate entity the concomitant administration of Certican with a CNI may increase the risk of CNI-induced thrombotic microangiopathy with a secondary thrombocytopenia, and mechanical injury to erythrocytes. With few exceptions, the condition presents in the early post-transplant period. This important identified risk of thrombotic microangiopathies (TMA) is included in the RMP and also addressed in the Australian PI.

Assessment of haematological parameters belongs to the standard procedures in transplant patients. The Certican label (PI) correctly informs about haematological events. Thus it is not deemed necessary to include leukopenia, thrombocytopenia, and pancytopenia in the RMP.

Delegates overview:

Safety concerns: In addition, it is recommended that 'long-term safety' is added as an area of missing information of the safety specifications for ongoing monitoring.

Sponsor's response:

Certican is approved in over 85 countries for use in cardiac and renal transplantation. On 17th October 2012 the approval to extend use to liver transplantation recipients was granted in Europe for all countries participating in the Mutual Recognition Procedure (MRP). The safety profile is well established. Information on effects of long term treatment has regularly been evaluated in all PSURs, including the most recent PSUR 9 (1 August 2012 to 31 July 2012) without any additional safety findings. The overall safety profile of everolimus in the liver transplant indication is comparable to the safety profile in the other transplant indications.

Long term safety is not considered as an area of missing information and the addition of this topic to the RMP is not warranted given the broad experience with the drug. As part of the routine on-going monitoring and to address specific questions on the risk of wound healing complications, the extension Study H2304E1 is included in the RMP as PV activity.

Delegates overview:

Pharmacovigilance activities: To propose adequate and appropriate PV activities for each of the relevant additional safety concerns: pericardial effusion, haemodynamic compromise, leukopenia, thrombocytopenia, pancytopenia, proteinuria and long term safety.

Sponsor's response:

For the reasons mentioned above, Novartis believes that these risks are adequately addressed in the Australian PI and the RMP for Certican. Close monitoring, including review in PSURs, will be performed for the identified risks of wound healing complications (including pericardial effusion) and proteinuria. For all other safety topics, routine monitoring is considered appropriate and will be re-evaluated upon receipt of relevant new information.

Delegates overview:

Pharmacovigilance activities: To incorporate the information relevant to the PIP changes approved by the EMA and the results from study CRAD001A2310 in a future update of the RMP.

Sponsor's response:

Information relevant to the PIP has been included in the most recent version of the RMP. This updated RMP v2.0 for implementation will be submitted to TGA. A copy of the most recent EMA/Paediatric Committee (PDCO) opinion will also be submitted to TGA.

The 24 month CSR for Study A2310 is also available and will be submitted to TGA.

Delegates overview:

Risk minimisation activities: To propose adequate and appropriate risk minimisation activities for each of the relevant additional safety concerns: pericardial effusion, haemodynamic compromise, leukopenia, thrombocytopenia, pancytopenia, proteinuria and long term safety.

Sponsor's response:

The RMP includes proteinuria as an important identified risk in the use of Certican. Details on this risk are communicated *via* the *Precaution* section Australian PI as well as in the 'undesirable event' section. Pericardial effusion is relevant for cardiac transplant patients only and is addressed in the RMP as part of the wound healing complications. As far as the hemodynamic compromise in the cardiac transplant Study A2310 is concerned, it was either associated with rejection reactions or a symptom of pericardial effusion. For leukopenia, thrombocytopenia, and pancytopenia, the PI is considered as an adequate tool to communicate relevant information to the physicians. The long term safety of Certican is well described and covered in the PSURs. No additional activities are warranted at present.

Delegates overview:

Risk minimisation activities: To propose adequate and appropriate additional risk minimisation activities (for example, in the form of educational material or "Dear HCP" communications) as recommended by the clinical evaluator, particularly to inform of and manage the serious risks associated with the use of Certican and to highlight the importance of careful therapeutic drug monitoring for not only everolimus but also for cyclosporin and tacrolimus. An appropriate strategy to assess the effectiveness of the proposed risk minimisation strategy should also be provided.

Sponsor's response:

Novartis accepts to address serious risks associated with the use of Certican in a "Dear HCP" communication, highlighting the importance of careful therapeutic drug monitoring for everolimus, cyclosporin and tacrolimus. This HCP letter will be provided to the Delegate for discussion. All safety topics will routinely be monitored and will be re-evaluated upon receipt of relevant new information. In addition, the RMP identified risks will be closely monitored including review in PSURs.

Delegates overview:

Sponsor will address to the satisfaction of the TGA the requested amendments (or justifications) for the further amendment of the RMP Version 2.0 (release date 14 Oct 2011), with Safety RMP Australian Implementation Version 2.1 (release date 16 August 2012)

Sponsor's response:

Addressed above under *Pharmacovigilance activities*.

Delegates overview:

Sponsor will commit to submit to TGA the reports of the Study H2304 to month 24 and then the extension study data within three months of the reports being signed by the Principal Investigator.

Sponsor will commit to submit to TGA the report of the foreshadowed “open label, single arm, multicentre, prospective, observational study to evaluate safety/tolerability and efficacy of everolimus in combination with reduced CNI in de novo paediatric full-size liver allograft recipients, and sequentially in paediatric split liver recipients, from 1 months to 18 years old” within three months of the reports being signed by the Principal Investigator.

Sponsor’s response:

The 24 month CSR for Study H2304 is also available and will be submitted to TGA. Novartis commits to submit the final CSR for Study H2304E and the final CSR for Study H2305 within 3 months of the report being signed by the Principal Investigator.

Sponsor’s conclusion

Novartis welcomes the Delegate’s recommendation and accepts the Delegate’s indication recommendation, and most of the recommendations proposed by the Delegate and clinical evaluator to the Certican PI.¹³ Novartis’ proposed indication statement is believed to be warranted on the basis that it is:

- consistent with the Delegate’s proposal without the “*See Precautions*”, as the concomitant medication text is adequately covered in the *Clinical Trials, Precautions* and the *Dosage and Administration* sections of the PI. As noted in this pre-ACPM response, Novartis has included the Delegate’s proposed text regarding concomitant medication in the *Precautions* section of the PI, as recommended by the Delegate.
- consistent with the Delegate’s original approval to register Certican.
- corrected to remove “*mild to moderate immunological risk*” for an allogeneic hepatic transplant to more accurately reflect the submitted data and clinical practice.

In conclusion, Certican provides another treatment option with a different benefit-risk profile in a therapeutic area with high medical need where options are clearly needed. All the data that have emerged from Novartis’s PV activities support the position that the benefit-risk profile of everolimus continues to be favourable, including on comparison with other mTOR inhibitors and for this proposed new patient population. There is, therefore, sufficient evidence to support the favourable benefit-risk profile of Certican for the extension of indications to include use in hepatic transplant recipients; a view supported by the TGA Delegate and clinical evaluator.

Advisory Committee Considerations

The ACPM, having considered the evaluations and the Delegate’s overview, as well as the sponsor’s response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered these products to have an overall positive benefit-risk profile for the indication;

¹³ Details of PI revisions other than those to the *Indications* section are beyond the scope of this AusPAR.

For the prophylaxis of organ rejection

- *in adult patients at mild to moderate immunological risk receiving an allogeneic renal or cardiac transplant: or*
- *in adult patients receiving an allogeneic hepatic transplant.*

In making this recommendation, the ACPM agreed with the Delegate on the amendments to the PI and CMI in relation to cardiac transplant recipients and in renal transplant recipients, subject to the sponsor addressing the conditions of registration and to the provision of the foreshadowed studies.

The ACPM advised that the sponsor should be required to develop a more appropriate education strategy, other than a letter writing programme, in consideration of the highly experienced specialist prescribers for these products.

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- A correction in the *Dosage and Administration / Precautions / Clinical Trials* sections of the PI in cardiac transplantation to ensure the accurate report of renal function and estimated glomerular filtration rate (Cockcroft-Gault formulae) at 6 and 12 months, as highlighted by the Delegate. The renal transplant section should also be reviewed to ensure minor corrections have been made.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Certican tablets, containing everolimus 0.25 mg, 0.5 mg, 0.75 mg and 1 mg, and Certican dispersible tablets, containing everolimus 0.1 mg and 0.5 mg, for the following new indication:

Certican is indicated for the prophylaxis of organ rejection in adult patients receiving an allogeneic hepatic transplant (see Precautions)

The full indications are now:

Certican is indicated for the prophylaxis of organ rejection

- *in adult patients at mild to moderate immunological risk receiving an allogeneic renal; or cardiac transplant; and*
- *in adult patients receiving an allogeneic hepatic transplant (See Precautions).*

The TGA approval letter to the sponsor states the following specific conditions of registration for these goods:

Specific Conditions Applying to these Therapeutic Goods

The Certican RMP, version 2, dated 25 October 2012, and any subsequent revisions as agreed with the TGA and its OPR will be implemented in Australia. All safety topics will routinely be monitored and will be re-evaluated upon receipt of relevant new information. In addition, the RMP identified risks will be closely monitored including review in PSURs. An obligatory component of RMPs is Routine PV. Routine PV includes the submission of PSURs. Such reports are to be provided annually until the period covered by such reports is not less than three years from the date of this approval letter. No fewer than three annual reports are required. The reports are to meet the requirements for PSURs as described in the EMA's *Guideline on Good Pharmacovigilance practices (GVP) Module VII-*

Periodic Safety Update Report. Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available. Submission of the report must be within the seventy calendar days of the data lock point for the report (or, where applicable, the second of the two six monthly reports), as required by the Guideline for PSURs covering intervals up to 12 months, (including intervals of exactly 12 months).

In addition, your company will address the serious risks associated with the use of Certican in a “Dear HCP” communication, highlighting the importance of careful therapeutic drug monitoring for everolimus, cyclosporin and tacrolimus. This HCP letter will be provided to the Delegate for discussion prior to distribution.

In addition also, your company will meet its commitments to submit the 24 month CSR for Study A2310 and the 24 month CSR for Study H2304, both of which are now available, and will submit the final CSR for Study H2304E and the final CSR for Study H2305 within 3 months of the respective reports being signed by the Principal Investigator.

You are reminded that sections 29A and 29AA of the *Therapeutic Goods Act 1989* provide for penalties where there has been failure to inform the Secretary in writing, as soon as a person has become aware, of:

- a. information that contradicts information already given by the person under this Act;
- b. information that indicates that the use of the goods in accordance with the recommendations for their use may have an unintended harmful effect;
- c. information that indicates that the goods, when used in accordance with the recommendations for their use, may not be as effective as the application for registration or listing of the goods or information already given by the person under this Act suggests;
- d. information that indicates that the quality, safety or efficacy of the goods is unacceptable.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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