1. NAAM VAN HET GENEESMIDDEL

Aderolio 0,25 mg, tabletten
Aderolio 0,5 mg, tabletten
Aderolio 0,75 mg, tabletten
Aderolio 1 mg, tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[Nationally completed name] 0.25 mg tablets
Each tablet contains 0.25 mg of everolimus.

[Nationally completed name] 0.5 mg tablets
Each tablet contains 0.5 mg of everolimus.

[Nationally completed name] 0.75 mg tablets
Each tablet contains 0.75 mg of everolimus.

[Nationally completed name] 1.0 mg tablets
Each tablet contains 1.0 mg of everolimus.

Excipient(s) with known effect

[Nationally completed name] 0.25 mg tablets
Each tablet contains 53 mg of lactose.

[Nationally completed name] 0.5 mg tablets
Each tablet contains 79 mg of lactose.

[Nationally completed name] 0.75 mg tablets
Each tablet contains 118 mg of lactose.

[Nationally completed name] 1.0 mg tablets
Each tablet contains 157 mg of lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
The tablets are white to yellowish, marbled, round, flat with a bevelled edge.

0.25 mg (diameter of 6 mm): engraved with “C” on one side and “NVR” on the other.
0.5 mg (diameter of 7 mm): engraved with “CH” on one side and “NVR” on the other.
0.75 mg (diameter of 8.5 mm): engraved with “CL” on one side and “NVR” on the other.
1.0 mg (diameter of 9 mm): engraved with “CU” on one side and “NVR” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Kidney and heart transplantation
[Nationally completed name] is indicated for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving an allogeneic renal or cardiac transplant. In kidney and heart transplantation, [Nationally completed name] should be used in combination with ciclosporin for microemulsion and corticosteroids.

Liver transplantation
[Nationally completed name] is indicated for the prophylaxis of organ rejection in adult patients receiving a hepatic transplant. In liver transplantation, [Nationally completed name] should be used in combination with tacrolimus and corticosteroids.

4.2 Posology and method of administration

Treatment with [Nationally completed name] should only be initiated and maintained by physicians who are experienced in immunosuppressive therapy following organ transplantation and who have access to everolimus whole blood concentration monitoring.

Posology
Adults
An initial dose regimen of 0.75 mg twice daily in co-administration with ciclosporin is recommended for the general kidney and heart transplant population, administered as soon as possible after transplantation.

The dose of 1.0 mg twice daily in co-administration with tacrolimus is recommended for the hepatic transplant population with the initial dose approximately 4 weeks after transplantation.

Patients receiving [Nationally completed name] may require dose adjustments based on blood concentrations achieved, tolerability, individual response, change in co-medications and the clinical situation. Dose adjustments can be made at 4-5 day intervals (see *Therapeutic drug monitoring*).

Special population
Black patients
The incidence of biopsy-proven acute rejection episodes was significantly higher in black renal transplant patients compared with non-black patients. There is limited information indicating that black patients may require a higher [Nationally completed name] dose to achieve similar efficacy to non-black patients (see section 5.2). Currently, the efficacy and safety data are too limited to allow specific recommendations for use of everolimus in black patients.

Paediatric population
In paediatric renal and hepatic transplant patients, [Nationally completed name] should not be used. The safety and efficacy of everolimus in paediatric cardiac transplant patients has not been established (see section 5.1).

Elderly patients (≥65 years)
Clinical experience in patients >65 years of age is limited. Although data are limited, there are no apparent differences in the pharmacokinetics of everolimus in patients ≥65-70 years of age (see section 5.2).

Patients with renal impairment
No dosage adjustment is required (see section 5.2).

Patients with impaired hepatic function
Everolimus whole blood trough concentrations should be closely monitored in patients with impaired hepatic function. The dose should be reduced to approximately two thirds of the normal dose for patients with mild hepatic impairment (Child-Pugh Class A), to approximately one half of the normal dose for patients with moderate hepatic impairment (Child Pugh Class B), and to approximately one third of the normal dose for patients with severe hepatic impairment (Child Pugh Class C). Further dose titration should be based on therapeutic drug monitoring (see section 5.2). Reduced doses rounded to the nearest tablet strength are tabulated below:

Table 1 [Nationally completed name] dose reduction in patients with hepatic impairment

	Normal hepatic function	**Mild hepatic impairment (Child-Pugh A)**	**Moderate hepatic impairment (Child-Pugh B)**	**Severe hepatic impairment (Child-Pugh C)**
Renal and cardiac transplantation	0.75 mg *b.i.d.*	0.5 mg *b.i.d.*	0.5 mg *b.i.d.*	0.25 mg *b.i.d.*
Hepatic transplantation	1 mg *b.i.d.*	0.75 mg *b.i.d.*	0.5 mg *b.i.d.*	0.5 mg *b.i.d.*

Therapeutic drug monitoring
The use of drug assays with adequate performance characteristics when targeting low concentrations of ciclosporin or tacrolimus is recommended.
[Nationally completed name] has a narrow therapeutic index which may require adjustments in dosing to maintain therapeutic response. Routine everolimus whole blood therapeutic drug concentration monitoring is recommended. Based on exposure-efficacy and exposure-safety analysis, patients achieving everolimus whole blood trough concentrations ≥3.0 ng/ml have been found to have a lower incidence of biopsy-proven acute rejection in renal, cardiac and hepatic transplantation compared with patients whose trough concentrations are below 3.0 ng/ml. The recommended upper limit of the therapeutic range is 8 ng/ml. Exposure above 12 ng/ml has not been studied. These recommended ranges for everolimus are based on chromatographic methods.

It is especially important to monitor everolimus blood concentrations in patients with hepatic impairment during concomitant administration of strong CYP3A4 inducers and inhibitors, when switching formulation, and/or if ciclosporin dosing is markedly reduced (see section 4.5). Everolimus concentrations might be slightly lower following dispersible tablet administration.

Ideally, dose adjustments of [Nationally completed name] should be based on trough concentrations obtained >4-5 days after the previous dosing change. There is an interaction between ciclosporin and everolimus, and everolimus concentrations may therefore decrease if ciclosporin exposure is markedly reduced (i.e. trough concentration <50 ng/ml).

Patients with hepatic impairment should preferably have trough concentrations in the upper part of the 3-8 ng/ml exposure range.

After starting treatment or after a dose adjustment, monitoring should be performed every 4 to 5 days until 2 consecutive trough concentrations show stable everolimus concentrations, as the prolonged half-lives in hepatically impaired patients delay the time to reach steady state (see sections 4.4 and 5.2). Dose adjustments should be based on stable everolimus trough concentrations.

Ciclosporin dose recommendation in renal transplantation
[Nationally completed name] should not be used long-term together with full doses of ciclosporin.

Reduced exposure to ciclosporin in [Nationally completed name]-treated renal transplant patients improves renal function. Based on experience gained from study A2309, ciclosporin exposure reduction should be started immediately after transplantation with the following recommended whole blood trough concentration windows:

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

Target ciclosporin C_0 (ng/ml)	**Month 1**	**Months 2-3**	**Months 4-5**	**Months 6-12**
[Nationally completed name] groups	100-200	75-150	50-100	25-50

(Measured C_0 and C2 concentrations are shown in section 5.1).

Prior to dose reduction of ciclosporin it should be ascertained that steady-state everolimus whole blood trough concentrations are equal to or above 3 ng/ml.

There are limited data regarding dosing [Nationally completed name] with ciclosporin trough concentrations below 50 ng/ml, or C2 concentrations below 350 ng/ml, in the maintenance phase. If the patient cannot tolerate reduction of ciclosporin exposure, the continued use of [Nationally completed name] should be reconsidered.

Ciclosporin dose recommendation in cardiac transplantation
Cardiac transplant patients in the maintenance phase should have their ciclosporin dose reduced as tolerated in order to improve kidney function. If impairment of renal function is progressive or if the calculated creatinine clearance is <60 ml/min, the treatment regimen should be adjusted. In cardiac transplant patients, the ciclosporin dose may be based on ciclosporin blood trough concentrations. See section 5.1 for experience with reduced ciclosporin blood concentrations.

In cardiac transplantation, there are limited data regarding dosing [Nationally completed name] with ciclosporin trough concentrations of 50-100 ng/ml after 12 months.

Prior to dose reduction of ciclosporin it should be ascertained that steady-state everolimus whole blood trough concentrations are equal to or above 3 ng/ml.

Tacrolimus dose recommendation in hepatic transplantation
Hepatic transplant patients should have their tacrolimus exposure reduced to minimise calcineurin-related renal toxicity. The tacrolimus dose should be reduced starting approximately 3 weeks after initiating co-administration with [Nationally completed name], based on targeted tacrolimus blood trough concentrations (C_0) of 3-5 ng/ml. In a controlled clinical trial, complete withdrawal of tacrolimus has been associated with an increased risk of acute rejections.

[Nationally completed name] has not been evaluated with full-dose tacrolimus in controlled clinical trials.

Method of administration
[Nationally completed name] is for oral use only.

The daily dose of [Nationally completed name] should always be given orally in two divided doses consistently either with or without food (see section 5.2) and at the same time as ciclosporin for microemulsion or tacrolimus (see *Therapeutic drug monitoring*).

[Nationally completed name] tablets should be swallowed whole with a glass of water and not crushed before use. For patients unable to swallow whole tablets, [Nationally completed name] dispersible tablets are also available (see [Nationally completed name] dispersible tablets Summary of Product

Characteristics).

4.3 Contraindications

[Nationally completed name] is contraindicated in patients with a known hypersensitivity to everolimus, sirolimus, or to any of the excipients.

4.4 Special warnings and precautions for use

Management of immunosuppression
In clinical trials, [Nationally completed name] has been administered concurrently with ciclosporin for microemulsion, basiliximab, or with tacrolimus, and corticosteroids. [Nationally completed name] in combination with immunosuppressive agents other than these has not been adequately investigated.

[Nationally completed name] has not been adequately studied in patients at high immunological risk.

Combination with thymoglobulin induction
Strict caution is advised with the use of thymoglobulin (rabbit anti-thymocyte globulin) induction and the [Nationally completed name]/ciclosporin/steroid regimen. In a clinical study in heart transplant recipients (Study A2310, see section 5.1), an increased incidence of serious infections including fatal infections was observed within the first three months after transplantation in the subgroup of patients who had received induction with rabbit anti-thymocyte globulin**.**

Serious and opportunistic infections
Patients treated with immunosuppressants, including [Nationally completed name], are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal). Among these conditions are BK virus-associated nephropathy and JC virus-associated progressive multiple leukoencephalopathy (PML). These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms. Fatal infections and sepsis have been reported in patients treated with [Nationally completed name] (see section 4.8).

In clinical trials with [Nationally completed name], antimicrobial prophylaxis for *Pneumocystis jiroveci (carinii)* pneumonia and Cytomegalovirus (CMV) was recommended following transplantation, particularly for patients at increased risk for opportunistic infections.

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

Because of longer everolimus half-lives in patients with hepatic impairment (see section 5.2), everolimus therapeutic monitoring after starting treatment or after a dose adjustment should be performed until stable concentrations are reached.

Interaction with oral CYP3A4 substrates
Caution should be exercised when [Nationally completed name] is taken in combination with orally administered CYP3A4 substrates with a narrow therapeutic index due to the potential for drug interactions. If [Nationally completed name] is taken with orally administered CYP3A4 substrates with a narrow therapeutic index (e.g. pimozide, terfenadine, astemizole, cisapride, quinidine or ergot alkaloid derivatives), the patient should be monitored for undesirable effects described in the product information of the orally administered CYP3A4 substrate (see section 4.5).

Interaction with strong inhibitors or inducers of CYP3A4 and/or P-glycoprotein (PgP)
Co-administration with strong inhibitors of CYP3A4 and/or the multidrug efflux pump P- glycoprotein

(PgP) (e.g. ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir) may increase everolimus blood levels and is not recommended unless the benefit outweighs the risk.
Co-administration with strong inducers of CYP3A4 and/or PgP (e.g. rifampicin, rifabutin, carbamazepine, phenytoin) is not recommended unless the benefit outweighs the risk.
If co-administration of inducers or inhibitors of CYP3A4 and/or PgP cannot be avoided, it is recommended that everolimus whole blood trough concentrations and the clinical condition of the patient be monitored while they are concurrently administered with everolimus and after their discontinuation. Dose adjustments of everolimus may be required (see section 4.5).

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

Hyperlipidaemia
The use of [Nationally completed name] with ciclosporin for microemulsion or tacrolimus in transplant patients has been associated with increased serum cholesterol and triglycerides that may require treatment. Patients receiving [Nationally completed name] should be monitored for hyperlipidaemia and, if necessary, treated with lipid-lowering medicinal products and have appropriate dietary adjustments made (see section 4.5). The risk/benefit should be considered in patients with established hyperlipidaemia before initiating an immunosuppressive regimen including [Nationally completed name]. Similarly, the risk/benefit of continued [Nationally completed name] therapy should be re-evaluated in patients with severe refractory hyperlipidaemia. Patients administered a HMG-CoA reductase inhibitor and/or fibrate should be monitored for the possible development of rhabdomyolysis and other adverse effects as described in the Summary of Product Characteristics for the medicinal product(s) concerned (see section 4.5).

Angioedema
[Nationally completed name] has been associated with the development of angioedema. In the majority of cases reported, patients were receiving ACE inhibitors as co-medication.

Everolimus and calcineurin inhibitor-induced renal dysfunction
In renal and cardiac transplantation, [Nationally completed name] with full-dose ciclosporin increases the risk of renal dysfunction. Reduced doses of ciclosporin are required for use in combination with [Nationally completed name] in order to avoid renal dysfunction. Appropriate adjustment of the immunosuppressive regimen, in particular reduction of the ciclosporin dose, should be considered in patients with elevated serum creatinine levels.

In a liver transplant study, [Nationally completed name] with reduced tacrolimus exposure has not been found to worsen renal function in comparison to standard exposure tacrolimus without [Nationally completed name]. Regular monitoring of renal function is recommended in all patients. Caution should be exercised when co-administering other medicinal products that are known to have a negative effect on renal function.

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

[Nationally completed name] should be monitored for proteinuria.

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

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

Thrombotic microangiopathy/Thrombotic thrombocytopenic purpura/Haemolytic uraemic syndrome
The concomitant administration of [Nationally completed name] with a calcineurin inhibitor (CNI) may increase the risk of CNI-induced haemolytic uraemic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy.

Vaccinations
Immunosuppressants may affect the response to vaccination. During treatment with immunosuppressants, including everolimus, vaccination may be less effective. The use of live vaccines should be avoided.

Interstitial lung disease/non-infectious pneumonitis
A diagnosis of interstitial lung disease (ILD) should be considered in patients presenting with symptoms consistent with infectious pneumonia but not responding to antibiotic therapy and in whom infectious, neoplastic and other non-drug causes have been ruled out through appropriate investigations. Cases of ILD have been reported with [Nationally completed name], which generally resolve on drug interruption with or without glucocorticoid therapy. However, fatal cases have also occurred (see section 4.8).

New onset diabetes mellitus
[Nationally completed name] has been shown to increase the risk of new onset diabetes mellitus after transplantation. Blood glucose concentrations should be monitored closely in patients treated with [Nationally completed name].

Male infertility
There are literature reports of reversible azoospermia and oligospermia in patients treated with mTOR inhibitors. As preclinical toxicology studies have shown that everolimus can reduce spermatogenesis, male infertility must be considered a potential risk of prolonged [Nationally completed name] therapy.

Risk of intolerance of excipients
[Nationally completed name] tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Everolimus is mainly metabolised by CYP3A4 in the liver and to some extent in the intestinal wall and is a substrate for the multidrug efflux pump, P-glycoprotein (PgP). Therefore, absorption and subsequent elimination of systemically absorbed everolimus may be influenced by medicinal products that affect CYP3A4 and/or P-glycoprotein. Concurrent treatment with strong 3A4 inhibitors and inducers is not recommended. Inhibitors of P-glycoprotein may decrease the efflux of everolimus from intestinal cells and increase everolimus blood concentrations. *In vitro*, everolimus was a competitive

inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6. All *in vivo* interaction studies were conducted without concomitant ciclosporin.

Table 3 Effects of other active substances on everolimus

Active substance by interaction	**Interaction – Change in Everolimus AUC/C_{max} Geometric mean ratio (observed range)**	**Recommendations concerning co-administration**
***Strong* CYP3A4/PgP inhibitors**		
Ketoconazole	AUC ↑15.3-fold (range 11.2-22.5) C_{max} ↑4.1-fold (range 2.6-7.0)	Co-administration with strong CYP3A4/PgP-inhibitors is not recommended unless the benefit outweighs the risk.
Itraconazole, posaconazole, voriconazole	Not studied. Large increase in everolimus concentration is expected.	
Telithromycin, clarithromycin		
Nefazodone		
Ritonavir, atazanavir, saquinavir, darunavir, indinavir, nelfinavir		
***Moderate* CYP3A4/PgP inhibitors**		
Erythromycin	AUC ↑4.4-fold (range 2.0-12.6) C_{max} ↑2.0-fold (range 0.9-3.5)	Everolimus whole blood trough concentrations should be monitored whenever inhibitors of CYP3A4/PgP are concurrently administered and after their discontinuation. Use caution when co-administration of moderate CYP3A4 inhibitors or PgP inhibitors cannot be avoided. Closely monitor for side effects and adjust the everolimus dose as needed (see sections 4.2 and 4.4).
Imatinib	AUC ↑3.7-fold C_{max} ↑2.2-fold	
Verapamil	AUC ↑3.5-fold (range 2.2-6.3) C_{max} ↑2.3-fold (range1.3-3.8)	
Ciclosporin oral	AUC ↑2.7-fold (range 1.5-4.7) C_{max} ↑1.8-fold (range 1.3-2.6)	
Cannabidiol (P-gp inhibitor)	AUC ↑ 2.5-fold Cmax ↑ 2.5-fold	
Fluconazole	Not studied. Increased exposure expected.	
Diltiazem, nicardipine		
Dronedarone	Not studied. Increased exposure expected.	

Amprenavir, fosamprenavir	Not studied. Increased exposure expected.	
Grapefruit juice or other food affecting CYP3A4/PgP	Not studied. Increased exposure expected (the effect varies widely).	Combination should be avoided.
Strong and moderate CYP3A4 inducers		
Rifampicin	AUC ↓63% (range 0-80%) C_{max} ↓58% (range 10-70%)	Co-administration with strong CYP3A4-inducers is not recommended unless the benefit outweighs the risk.
Rifabutin	Not studied. Decreased exposure expected.	
Carbamazepine	Not studied. Decreased exposure expected.	
Phenytoin	Not studied. Decreased exposure expected.	
Phenobarbital	Not studied. Decreased exposure expected.	Everolimus whole blood trough concentrations should be monitored whenever inducers of CYP3A4 are concurrently administered and after their discontinuation.
Efavirenz, nevirapine	Not studied. Decreased exposure expected.	
St John's Wort (*Hypericum perforatum*)	Not studied. Large decrease in exposure expected.	Preparations containing St John's Wort should not be used during treatment with everolimus

Agents whose plasma concentrations may be altered by everolimus:

Octreotide
Co-administration of everolimus (10 mg daily) with depot octreotide increased octreotide C_{min} with a geometric mean ratio (everolimus/placebo) of 1.47-fold.

Ciclosporin
[Nationally completed name] had a minor clinical influence on ciclosporin pharmacokinetics in renal and heart transplant patients receiving ciclosporin for microemulsion.

Atorvastatin (CYP3A4substrate) and pravastatin (PgPsubstrate)
Single-dose administration of [Nationally completed name] with either atorvastatin or pravastatin to healthy subjects did not influence the pharmacokinetics of atorvastatin, pravastatin and everolimus, as well as total HMG-CoA reductase bioreactivity in plasma to a clinically relevant extent. However, these results cannot be extrapolated to other HMG-CoA reductase inhibitors. Patients should be monitored for the development of rhabdomyolysis and other adverse events as described in the Summary of Product Characteristics of HMG-CoA reductase inhibitors.

Oral CYP3A4A substrates
Based on in vitro results, the systemic concentrations obtained after oral daily doses of 10 mg make inhibition of PgP, CYP3A4 and CYP2D6 unlikely. However, inhibition of CYP3A4 and PgP in the

gut cannot be excluded. An interaction study in healthy subjects demonstrated that co-administration of an oral dose of midazolam, a sensitive CYP3A4 substrate probe, with everolimus resulted in a 25% increase in midazolam C_{max} and a 30% increase in midazolam AUC. The effect is likely to be due to inhibition of intestinal CYP3A4 by everolimus. Hence, everolimus may affect the bioavailability of orally co-administered CYP3A4 substrates. However, a clinically relevant effect on the exposure of systemically administered CYP3A4 substrates is not expected. If everolimus is taken with orally administered CYP3A4 substrates with a narrow therapeutic index (e.g. pimozide, terfenadine, astemizole, cisapride, quinidine or ergot alkaloid derivatives), the patient should be monitored for undesirable effects described in the product information of the orally administered CYP3A4 substrate.

Vaccinations
Immunosuppressants may affect the response to vaccination and vaccination during treatment with [Nationally completed name] may be less effective. The use of live vaccines should be avoided.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of [Nationally completed name] in pregnant women. Studies in animals have shown reproductive toxicity effects including embryo/foetotoxicity (see section 5.3). The potential risk for humans is unknown. [Nationally completed name] should not be given to pregnant women unless the potential benefit outweighs the potential risk for the foetus. Women of childbearing potential should be advised to use effective contraception methods while they are receiving [Nationally completed name] and up to 8 weeks after treatment has been stopped.

Breast-feeding
It is not known whether everolimus is excreted in human milk. In animal studies, everolimus and/or its metabolites were readily transferred into the milk of lactating rats. Therefore, women who are taking [Nationally completed name] should not breast feed.

Fertility
There are literature reports of reversible azoospermia and oligospermia in patients treated with mTOR inhibitors (see section 4.4, 4.8, and 5.3). The potential for everolimus to cause infertility in male and female patients is unknown, however, male infertility and secondary amenorrhoea have been observed.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a) Summary of the safety profile
The frequencies of adverse reactions listed below are derived from analysis of the 12-month incidences of events reported in multicentre, randomised, controlled trials investigating [Nationally completed name] in combination with calcineurin inhibitors (CNI) and corticosteroids in adult transplant recipients. All but two of the trials (in renal transplantation) included non-[Nationally completed name], CNI-based standard-therapy arms. [Nationally completed name] combined with ciclosporin was studied in five trials in renal transplant recipients totalling 2,497 patients (including two studies without a non-[Nationally completed name] control group), and three trials in heart transplant recipients totalling 1,531 patients (ITT populations, see section 5.1).

[Nationally completed name] combined with tacrolimus was studied in one trial, which included 719

liver transplant recipients (ITT population, see section 5.1).

The most common events are: infections, anaemia, hyperlipidaemia, new onset of diabetes mellitus, insomnia, headache, hypertension, cough, constipation, nausea, peripheral oedema, impaired healing (including pleural and pericardial effusion).

The occurrence of the adverse events may depend on the immunosuppressive regimen (i.e. degree and duration). In the studies combining [Nationally completed name] with ciclosporin, elevated serum creatinine was observed more frequently in patients administered [Nationally completed name] in combination with full-dose ciclosporin for microemulsion than in control patients. The overall incidence of adverse events was lower with reduced-dose ciclosporin for microemulsion (see section 5.1).

The safety profile of [Nationally completed name] administered with reduced-dose ciclosporin was similar to that described in the 3 pivotal studies in which full-dose ciclosporin was administered, except that elevation of serum creatinine was less frequent, and mean and median serum creatinine values were lower, than in the Phase III studies.

b) Tabulated summary of adverse reactions
Table 4 contains adverse drug reactions possibly or probably related to [Nationally completed name] seen in Phase III clinical trials. Unless noted otherwise, these disorders have been identified by an increased incidence in the Phase III studies comparing [Nationally completed name]-treated patients with patients on a non-[Nationally completed name], standard-therapy regimen, or the same incidence in case the event is a known ADR of the comparator MPA in renal and heart transplant studies (see section 5.1). Except where noted otherwise, the adverse reaction profile is relatively consistent across all transplant indications. It is compiled according to MedDRA standard organ classes.

Adverse reactions are listed according to their frequencies, which are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 4 Adverse drug reactions possibly or probably related to [Nationally completed name]

Body system	Incidence	Adverse reaction
Infections and infestations	Very common	Infections (viral, bacterial, fungal), upper respiratory tract infection, lower respiratory tract and lung infections (including pneumonia)[1], urinary tract infections[2]
	Common	Sepsis, wound infection
Neoplasms benign, malignant and unspecified	Common	Malignant or unspecified tumours, malignant and unspecified skin neoplasms
	Uncommon	Lymphomas/post-transplant lymphoproliferative disorders (PTLD)
Blood and lymphatic system disorders	Very common	Leukopaenia, anaemia/erythropenia, thrombocytopenia[1]

	Common	Pancytopenia, thrombotic microangiopathies (including thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome)
Endocrine disorders	Uncommon	Hypogonadism male (testosterone decreased, FSH and LH increased)
Metabolism and nutrition disorders	Very common	Hyperlipidaemia (cholesterol and triglycerides), new onset diabetes mellitus, hypokalaemia
Psychiatric disorders	Very common	Insomnia, anxiety
Nervous system disorders	Very common	Headache
Cardiac disorders	Very common	Pericardial effusion[3]
	Common	Tachycardia
Vascular disorders	Very common	Hypertension, venous thromboembolic events
	Common	Lymphocoele[4], epistaxis, renal graft thrombosis
Respiratory, thoracic and mediastinal disorders	Very common	Pleural effusion[1], cough[1], dyspnoea[1]
	Uncommon	Interstitial lung disease[5]
Gastrointestinal disorders	Very common	Abdominal pain, diarrhoea ,nausea, vomiting
	Common	Pancreatitis, stomatitis/mouth ulceration, oropharyngeal pain
Hepatobiliary disorders	Uncommon	Non infectious hepatitis, jaundice
Skin and subcutaneous tissue disorders	Common	Angiooedema[6], acne, rash
Musculoskeletal and connective tissue disorders	Common	Myalgia, arthralgia
Renal and urinary disorders	Common	Proteinuria[2], renal tubular necrosis[7]
Reproductive system and breast disorders	Common	Erectile dysfunction, menstrual disorder (including amenorrhoea and menorrhagia)
	Uncommon	Ovarian cyst

General disorders and administration site conditions	Very common	Peripheral oedema, pain, healing impaired, pyrexia
	Common	Incisional hernia
Investigations	Common	Hepatic enzyme abnormal[8]

[1]common in renal and liver transplantation

[2]common in cardiac and liver transplantation

[3]in cardiac transplantation

[4]in renal and cardiac transplantation[5]the SMQ-based search for ILD showed the frequency of ILD in the clinical trials. This broad search also included cases caused by related events, e.g. by infections. The frequency category given here is derived from the medical review of the known cases.

[6]predominantly in patients receiving concomitant ACE inhibitors

[7]in renal transplantation

[8]γ-GT, AST, ALT elevated

c) Description of selected adverse reactions
As preclinical toxicology studies have shown that everolimus can reduce spermatogenesis, male infertility must be considered a potential risk of prolonged [Nationally completed name] therapy. There are literature reports of reversible azoospermia and oligospermia in patients treated with mTOR inhibitors.

In controlled clinical trials in which a total of 3,256 patients receiving [Nationally completed name] in combination with other immunosuppressants were monitored for at least 1 year, a total of 3.1% developed malignancies, with 1.0% developing skin malignancies and 0.60% developing lymphomas or lymphoproliferative disorders.

Cases of interstitial lung disease, implying lung intraparenchymal inflammation (pneumonitis) and/or fibrosis of non-infectious aetiology, some fatal, have occurred in patients receiving rapamycin and derivatives, including [Nationally completed name]. Mostly, the condition resolves after discontinuation of [Nationally completed name] and/or addition of glucocorticoids. However, fatal cases have also occurred.

d) Adverse drug reactions from post-marketing spontaneous reports
The following adverse drug reactions have been derived from post-marketing experience with [Nationally completed name] via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency, which is therefore categorised as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 5 Adverse drug reactions from spontaneous reports and literature (frequency not known)

Body system	**Incidence**	**Adverse reaction**

Metabolism and nutrition disorders	Not known	Iron deficiency
Vascular disorders	Not known	Leukocytoclastic vasculitis, lymphoedema
Respiratory, thoracic and mediastinal disorders	Not known	Pulmonary alveolar proteinosis
Skin and subcutaneous tissue disorders	Not known	Erythroderma

Paediatric population
The safety information in children and adolescents is based on the data of 36-months in renal and 24-months in hepatic paediatric transplant patients (see section 5.1).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In animal studies, everolimus showed low acute toxic potential. No lethality or severe toxicity was observed after single oral doses of 2000 mg/kg (limit test) in either mice or rats.

Reported experience with overdose in humans is very limited; there is a single case of accidental ingestion of 1.5 mg everolimus in a 2-year-old child where no adverse events were observed. Single doses up to 25 mg have been administered to transplant patients with acceptable acute tolerability.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: selective immunosuppressive agents. ATC code: L04AA18.

Mechanism of action
Everolimus, a proliferation signal inhibitor, prevents allograft rejection in rodent and non-human primate models of allotransplantation. It exerts its immunosuppressive effect by inhibiting the proliferation, and thus clonal expansion, of antigen-activated T cells, which is driven by T cell-specific interleukins, e.g. interleukin-2 and interleukin-15. Everolimus inhibits an intracellular signalling pathway, which is triggered upon binding of these T cell growth factors to their respective receptors, and which normally leads to cell proliferation. The blockage of this signal by everolimus leads to an arrest of the cells at the G_1 stage of the cell cycle.

At the molecular level, everolimus forms a complex with the cytoplasmic protein FKBP-12. In the presence of everolimus, the growth factor-stimulated phosphorylation of the p70 S6 kinase is inhibited. Since p70 S6 kinase phosphorylation is under the control of FRAP (also called mTOR), this finding suggests that the everolimus-FKBP-12 complex binds to and thus interferes with the function

of FRAP. FRAP is a key regulatory protein that governs cell metabolism, growth and proliferation; disabling FRAP function thus explains the cell cycle arrest caused by everolimus.

Everolimus thus has a different mode of action to ciclosporin. In preclinical models of allotransplantation, the combination of everolimus and ciclosporin was more effective than either compound alone.

The effect of everolimus is not restricted to T cells. It inhibits growth factor-stimulated proliferation of hematopoietic as well as non-hematopoietic cells in general, such as vascular smooth muscle cells. Growth factor-stimulated vascular smooth muscle cell proliferation, triggered by injury to endothelial cells and leading to neointima formation, plays a key role in the pathogenesis of chronic rejection. Preclinical studies with everolimus have shown inhibition of neointima formation in a rat aorta allotransplantation model.

Clinical efficacy and safety

Renal transplantation

[Nationally completed name] in fixed doses of 1.5 mg/day and 3 mg/day, in combination with standard doses of ciclosporin for microemulsion and corticosteroids, was investigated in two Phase III *de novo* adult renal transplant trials (B201 and B251). Mycophenolate mofetil (MMF) 1 g *b.i.d* was used as comparator. The co-primary composite endpoints were efficacy failure (biopsy-proven acute rejection, graft loss, death or loss to follow-up) at 6 months, and graft loss, death or loss to follow-up at 12 months. [Nationally completed name] was, overall, non-inferior to MMF in these trials. The incidence of biopsy-proven acute rejection at 6 months in the B201 study was 21.6%, 18.2%, and 23.5% for the [Nationally completed name] 1.5 mg/day, [Nationally completed name] 3 mg/day and MMF groups, respectively. In study B251, the incidences were 17.1%, 20.1%, and 23.5% for the [Nationally completed name] 1.5 mg/day, [Nationally completed name] 3 mg/day and MMF groups, respectively.

Reduced allograft function with elevated serum creatinine was observed more frequently among subjects using [Nationally completed name] in combination with full-dose ciclosporin for microemulsion than in MMF patients. This effect suggests that [Nationally completed name] increases ciclosporin nephrotoxicity. Drug concentration-pharmacodynamic analysis showed that renal function was not impaired with reduced exposure to ciclosporin, while conserving efficacy for as long as the blood trough everolimus concentration was maintained above 3 ng/ml. This concept was subsequently confirmed in two further Phase III studies (A2306 and A2307, including 237 and 256 patients, respectively), which evaluated the efficacy and safety of [Nationally completed name] 1.5 mg and 3 mg per day (initial dosing; subsequent dosing based on target trough concentration ≥3 ng/ml) in combination with reduced exposure to ciclosporin. In both studies, renal function was preserved without compromising efficacy. In these studies, however, there was no non-[Nationally completed name] comparative arm. A Phase III, multicentre, randomised, open-label, controlled trial (A2309) has been completed in which 833 *de novo* renal transplant recipients were randomised to one of two [Nationally completed name] regimens, differing by dosage, and combined with reduced-dose ciclosporin or a standard regimen of sodium mycophenolate (MPA) + ciclosporin, and treated for 12 months. All patients received induction therapy with basiliximab pre-transplant, and on Day 4 post-transplant. Steroids were given as required post-transplant.

Starting dosages in the two [Nationally completed name] groups were 1.5 mg/d and 3 mg/d, given in two divided doses, subsequently modified from Day 5 onwards to maintain target blood trough everolimus concentrations of 3-8 ng/ml and 6-12 ng/ml, respectively. Sodium mycophenolate dosage was 1.44 g/d. Ciclosporin dosages were adapted to maintain target blood trough concentration windows as shown in Table6. The actual measured values for blood concentrations of everolimus and ciclosporin (C_0 and C2) are shown in Table7.

Although the higher-dosage [Nationally completed name] regimen was as effective as the lower-dosage regimen, the overall safety was poorer, and so the higher-dosage regimen is not recommended.

The lower-dosage regimen for [Nationally completed name] is recommended (see section 4.2).

Table 6 Study A2309: Target ciclosporin blood trough concentration windows

Target ciclosporin C_0 (ng/ml)	**Mo 1**	**Mo 2-3**	**Mo 4-5**	**Mo 6-12**
[Nationally completed name] groups	100-200	75-150	50-100	25-50
MPA group	200-300	100-250	100-250	100-250

Table 7 Study A2309: Measured trough blood concentrations of ciclosporin and everolimus

Trough concentrations (ng/ml)	**[Nationally completed name] groups** (low-dose ciclosporin)				**MPA** (standard ciclosporin)	
	[Nationally completed name] 1.5 mg		**[Nationally completed name] 3.0 mg**		**Myfortic 1.44 g**	
Ciclosporin	*C_o*	*C2*	*C_o*	*C2*	*C_o*	*C2*
Day 7	195 ± 106	847 ± 412	192 ± 104	718 ± 319	239 ± 130	934 ± 438
Month 1	173 ± 84	770 ± 364	177 ± 99	762 ± 378	250 ± 119	992 ± 482
Month 3	122 ± 53	580 ± 322	123 ± 75	548 ± 272	182 ± 65	821 ± 273
Month 6	88 ± 55	408 ± 226	80 ± 40	426 ± 225	163 ± 103	751 ± 269
Month 9	55± 24	319 ± 172	51 ± 30	296 ± 183	149 ± 69	648 ± 265
Month 12	55 ± 38	291 ± 155	49 ± 27	281 ± 198	137 ± 55	587± 241
Everolimus	(Target C_o 3-8)		(Target C_o 6-12)		-	
Day 7	4.5 ± 2.3		8.3 ± 4.8		-	
Month 1	5.3 ± 2.2		8.6 ± 3.9		-	
Month 3	6.0 ± 2.7		8.8 ± 3.6		-	
Month 6	5.3 ± 1.9		8.0 ± 3.1		-	
Month 9	5.3 ± 1.9		7.7 ± 2.6		-	
Month 12	5.3 ± 2.3		7.9 ± 3.5		-	

Numbers are mean ± SD of measured values with C_0 = trough concentration, C2 = value 2 hours post-dose.

The primary efficacy endpoint was a composite failure variable (biopsy-proven acute rejection, graft loss, death or loss to follow-up). The outcome is shown in Table8.

Table 8 Study A2309: Composite and individual efficacy endpoints at 6 and 12 months (incidence in ITT population)

	[Nationally completed name] 1.5 mg N=277 % (n)		**[Nationally completed name] 3.0 mg N=279 % (n)**		**MPA 1.44 g N=277 % (n)**	
	6 mo	**12 mo**	**6 mo**	**12 mo**	**6 mo**	**12 mo**
Composite endpoint (1^0 criterion)	**19.1** (53)	**25.3** (70)	**16.8** (47)	**21.5** (60)	**18.8** (52)	**24.2** (67)
Difference % *([Nationally completed name] - MPA)*	0.4%	1.1%	-1.9%	-2.7%	-	-
95% CI	(-6.2, 6.9)	(-6.1, 8.3)	(-8.3, 4.4)	(-9.7, 4.3)	-	-
Individual endpoints (2^0 criteria)						
Treated BPAR	**10.8** (30)	**16.2** (45)	**10.0** (28)	**13.3** (37)	**13.7** (38)	**17.0** (47)
Graft loss	**4.0** (11)	**4.3** (12)	**3.9** (11)	**4.7** (13)	**2.9** (8)	**3.2** (9)
Death	**2.2** (6)	**2.5** (7)	**1.8** (5)	**3.2** (9)	**1.1** (3)	**2.2** (6)
Loss to follow-up	**3.6** (10)	**4.3** (12)	**2.5** (7)	**2.5** (7)	**1.8** (5)	**3.2** (9)
Combined endpoints (2^0 criteria)						
Graft loss / Death	**5.8** (16)	**6.5** (18)	**5.7** (16)	**7.5** (21)	**4.0** (11)	**5.4** (15)
Graft loss / Death / Loss to FU	**9.4** (26)	**10.8** (30)	**8.2** (23)	**10.0** (28)	**5.8** (16)	**8.7** (24)

mo = months, 1^0 = primary, 2^0 = secondary, CI = confidence interval, non-inferiority margin was 10%
Composite endpoint: treated biopsy-proven acute rejection (BPAR), graft loss, death, or loss to follow-up (FU)

Changes in renal function, as shown by calculated glomerular filtration rate (GFR) using the MDRD formula, are shown in Table9.

Proteinuria was assessed at scheduled visits by spot analysis of urinary protein/creatinine (see Table10). A concentration effect was shown relating proteinuria levels to everolimus trough concentrations, particularly at C_{min} values above 8 ng/ml.

Adverse events reported more frequently in the recommended (lower-dosage) [Nationally completed name] regimen than in the MPA control group have been included in Table4. A lower frequency of viral infections was reported for [Nationally completed name]-treated patients, resulting principally from lower reporting rates for CMV infection (0.7% vs. 5.95%) and BK virus infection (1.5% vs. 4.8%).

Table 9 Study A2309: Renal function (MDRD-calculated GFR) at 12 months (ITT population)

	[Nationally completed name] 1.5 mg N=277	**[Nationally completed name] 3.0 mg N=279**	**MPA 1.44 g N=277**
12-month mean GFR (ml/min/1.73 m^2)	54.6	51.3	52.2
Difference in mean (everolimus - MPA) 95% CI	2.37 (-1.7, 6.4)	-0.89 (-5.0, 3.2)	- -

12-month GFR missing value imputation: graft loss = 0; death or loss to follow-up for renal function = LOCF1 (last-observation-carried-forward approach 1: End of Treatment (up to Month 12)).
MDRD: modification of diet in renal disease

Table 10 Study A2309: Urinary protein to creatinine ratio

		Category of proteinuria (mg/mmol)			
	Treatment	**normal%**(n) (<3.39)	**mild%**(n) (3.39-<33.9)	**sub-nephrotic%**(n) (33.9-<339)	**nephrotic%**(n) (>339)
Month 12 (TED)	[Nationally completed name] 1.5 mg	**0.4** (1)	**64.2** (174)	**32.5** (88)	**3.0** (8)
	[Nationally completed name] 3 mg	**0.7** (2)	**59.2** (164)	**33.9** (94)	**5.8** (16)
	MPA 1.44 g	**1.8** (5)	**73.1** (198)	**20.7** (56)	**4.1** (11)

1 mg/mmol = 8.84 mg/g
TED: Treatment endpoint (Mo 12 value or last observation carried forward)

Cardiac transplantation
In the Phase III cardiac study (B253), both [Nationally completed name] 1.5 mg/day and 3 mg/day, in combination with standard doses of ciclosporin for microemulsion and corticosteroids, was investigated vs. azathioprine (AZA) 1-3 mg/kg/day. The primary endpoint was a composite of the incidence of acute rejection ≥ISHLT grade 3A, acute rejection associated with haemodynamic compromise, graft loss, patient death or loss to follow-up at 6, 12 and 24 months. Both doses of [Nationally completed name] were superior to AZA at 6, 12 and 24 months. The incidence of biopsy-proven acute rejection ≥ISHLT grade 3A at month 6 was 27.8% for the 1.5 mg/day group, 19% for the 3 mg/day group and 41.6% for the AZA group, respectively (p = 0.003 for 1.5 mg vs. control, <0.001 for 3 mg vs. control).

Based on coronary artery intravascular ultrasound data obtained from a subset of the study population, both [Nationally completed name] doses were statistically significantly more effective than AZA in preventing allograft vasculopathy (defined as an increase in maximum intimal thickness from baseline ≥0.5 mm in at least one matched slice of an automated pullback sequence), an important risk factor for long-term graft loss.

Elevated serum creatinine was observed more frequently among subjects using [Nationally completed name] in combination with full-dose ciclosporin for microemulsion than in AZA patients. These results indicated that [Nationally completed name] increases ciclosporin-induced nephrotoxicity.

Study A2411 was a randomised, 12-month, open-label study comparing [Nationally completed name]

in combination with reduced doses of ciclosporin microemulsion and corticosteroids to mycophenolic mofetil (MMF) and standard doses of ciclosporin microemulsion and corticosteroids in *de novo* cardiac transplant patients. [Nationally completed name] was initiated at 1.5 mg/day and the dose was adjusted to maintain target blood everolimus trough concentrations of 3-8 ng/ml. MMF dosage was initiated at 1500 mg *b.i.d.* Ciclosporin microemulsion doses were adjusted to the following target trough concentrations (ng/ml):

Table 11 Target ciclosporin trough concentrations by month

Target ciclosporin C_0	Mo 1	Mo 2	Mo 3-4	Mo 5-6	Mo 7-12
[Nationally completed name] group	**200-350**	**150-250**	**100-200**	**75-150**	**50-100**
MMF group	200-350	200-350	200-300	150-250	100-250

Actual blood concentrations measured are shown in Table12.

Table 12 Study A2411: Summary statistics for CsA blood concentrations* (mean ± SD)

	[Nationally completed name] group (N=91)	**MMF group (N=83)**
Visit	**C_0**	**C_0**
Day 4	154 ± 71 n=79	155 ± 96 n=74
Mo 1	245 ± 99 n=76	308 ± 96 n=71
Mo 3	199 ± 96 n=70	256 ± 73 n=70
Mo 6	157 ± 61 n=73	219 ± 83 n=67
Mo 9	133 ± 67 n=72	187 ± 58 n=64
Mo 12	110 ± 50 n=68	180 ± 55 n=64

*:whole blood trough concentrations (C_0)

Changes in renal function are shown in Table 13. Efficacy outcome is shown in Table 14.

Table13 Study A2411: Changes in creatinine clearance during study (patients with paired values)

		Estimated creatinine clearance (Cockcroft-Gault)* ml/mn		
		Baseline Mean (± SD)	**Value at timepoint Mean (± SD)**	**Difference between groups Mean (95% CI)**
Month 1	[Nationally completed name] (n=87)	73.8 (± 27.8)	68.5 (± 31.5)	-7.3 (-18.1, 3.4)
	MMF (n=78)	77.4 (± 32.6)	79.4 (± 36.0)	
Month 6	[Nationally completed name] (n=83)	74.4 (± 28.2)	65.4 (± 24.7)	-5.0 (-13.6, 2.9)
	MMF (n=72)	76.0 (± 31.8)	72.4 (± 26.4)	
Month 12	[Nationally completed name] (n=71)	74.8 (± 28.3)	68.7 (± 27.7)	-1.8 (-11.2, 7.5)
	MMF (n=71)	76.2 (± 32.1)	71.9 (± 30.0)	

* includes patients with value at both baseline and visit

Table 14 Study A2411: Efficacy event rates (incidence in ITT population)

Efficacy endpoint	**[Nationally completed name] n=92**	**MMF n=84**	**Difference in event rates Mean (95% CI)**
At 6 months			
Biopsy-proven acute rejection ≥ ISHLT grade 3A	18 (19.6%)	23 (27.4%)	-7.8 (-20.3, 4.7)
Composite efficacy failure *	26 (28.3%)	31 (36.9%)	-8.6 (-22.5, 5.2)
At 12 months			
Biopsy-proven acute rejection ≥ ISHLT grade 3A	21 (22.8%)	25 (29.8%)	-6.9 (-19.9, 6.1)
Composite efficacy failure*	30 (32.6%)	35 (41.7%)	-9.1 (-23.3, 5.2)
Death or graft loss/re-transplant	10 (10.9%)	10 (11.9%)	-

* Composite efficacy failure: any of the following – acute rejection ≥ grade 3A, acute rejection with haemodynamic compromise, graft loss, death or loss to follow-up.

Study A2310 is a Phase III, multicentre, randomised, open-label study comparing two [Nationally completed name]/reduced-dose ciclosporin regimens against a standard mycophenolate mofetil (MMF)/ciclosporin regimen over 24 months. The use of induction therapy was centre-specific (no-induction or basiliximab or thymoglobulin). All patients received corticosteroids.

Starting doses in the [Nationally completed name] groups were 1.5 mg/d and 3 mg/d, and were adjusted to target blood trough everolimus concentrations of 3-8 ng/ml and 6-12 ng/ml, respectively. The MMF dose was 3 g/d. Ciclosporin dosages targeted the same blood trough concentration as in study A2411. Blood concentrations of everolimus and ciclosporin are shown in Table 15.

Recruitment to the experimental, higher-dosage [Nationally completed name] treatment arm was prematurely discontinued because of an increased rate of fatalities, due to infection and cardiovascular disorders, occurring within the first 90 days post-randomisation.

Table 15 Study A2310: Measured trough blood concentrations of ciclosporin (CsA) and everolimus

Visit window	**[Nationally completed name] 1.5 mg/reduced-dose CsA N=279**		**MMF 3 g/std-dose CsA N=268**
	everolimus ($C_{0\ ng}$/ml)	ciclosporin ($C_{0\ ng}$/ml)	
Day 4	5.7 (4.6)	153 (103)	151 (101)
Month 1	5.2 (2.4)	247 (91)	269 (99)
Month 3	5.4 (2.6)	209 (86)	245 (90)
Month 6	5.7 (2.3)	151 (76)	202 (72)
Month 9	5.5 (2.2)	117 (77)	176 (64)
Month 12	5.4 (2.0)	102 (48)	167 (66)

Numbers are the mean (standard deviation) of measured values of C_0=trough concentration

Efficacy outcome at 12 months is shown in Table16.

Table 16 Study A2310: Incidence rates of efficacy endpoints by treatment group (ITT population – 12-month analysis)

	[Nationally completed name] 1.5 mg N=279	**MMF N=271**
Efficacy endpoints	n (%)	n (%)
Primary: Composite efficacy failure	99 (35.1)	91 (33.6)
- AR associated with HDC	11 (3.9)	7 (2.6)
- BPAR of ISHLT grade ≥ 3A	63 (22.3)	67 (24.7)
- Death	22 (7.8)	13 (4.8)
- Graft loss/re-transplant	4 (1.4)	5 (1.8)
- Loss to follow-up	9 (3.2)	10 (3.7)

Composite efficacy failure: biopsy-proven acute rejection (BPAR) episodes of ISHLT grade ≥ 3A, acute rejection (AR) associated with haemodynamic compromise (HDC), graft loss/re-transplant, death, or loss to follow-up.

The higher fatality rate in the [Nationally completed name] arm relative to the MMF arm was mainly the result of an increased rate of fatalities from infection in the first three months among [Nationally completed name] patients receiving thymoglobulin induction therapy. The imbalance in fatalities within the thymoglobulin subgroup was particularly evident among patients hospitalised prior to transplantation and with L-ventricular assistance devices (see section 4.4).

Renal function over the course of study A2310, assessed by calculated glomerular filtration rate (GFR) using the MDRD formula, was 5.5 ml/min/1.73 m^2 (97.5% CI -10.9, -0.2) lower for the everolimus 1.5 mg group at Month 12.

This difference was mainly observed in centres where the mean ciclosporin concentrations were similar throughout the study period in patients receiving [Nationally completed name] and in patients randomised to the control arm. This finding underlines the importance of reducing the ciclosporin concentrations when combined with everolimus as indicated in Table 17 (see also section 4.2):

Table 17 Target ciclosporin trough concentrations per month

Target ciclosporin C_0	Mo 1	Mo 2	Mo 3-4	Mo 5-6	Mo7-12
[Nationally completed name] group	**200-350**	**150-250**	**100-200**	**75-150**	**50-100**
MMF group	200-350	200-350	200-300	150-250	100-250

Additionally, the difference was mainly driven by a difference developed during the first month post-transplantation when patients are still in an unstable haemodynamic situation, possibly confounding the analysis of renal function. Thereafter, the decrease in mean GFR from Month 1 to Month 12 was significantly smaller in the everolimus group than in the control group (-6.4 vs. -13.7 ml/min, p=0.002).

Proteinuria, expressed as urinary protein: creatinine levels measured in spot urine samples, tended to be higher in the [Nationally completed name]-treated patients. Sub-nephrotic values were observed in 22% of the patients receiving [Nationally completed name] compared to MMF patients (8.6%). Nephrotic levels were also reported (0.8%), representing 2 patients in each treatment group (see section 4.4).

The adverse reactions for the everolimus 1.5 mg group in Study A2310 are consistent with the adverse drug reactions presented in Table4. A lower rate of viral infections was reported for [Nationally completed name]-treated patients, resulting principally from a lower reporting rate for CMV infection compared to MMF (7.2% vs. 19.4%).

Hepatic transplantation
In the Phase III adult hepatic transplant study (H2304), reduced exposure tacrolimus and [Nationally completed name] 1.0 mg twice daily was administered to patients, with the initial [Nationally completed name] dose 4 weeks after transplantation, and was investigated versus standard exposure tacrolimus. [Nationally completed name] was dose adjusted to maintain target blood everolimus trough concentrations between 3-8 ng/ml for the [Nationally completed name] + reduced tacrolimus arm. Tacrolimus doses were subsequently adjusted to achieve target trough concentrations between 3-5 ng/ml during 12 months in the [Nationally completed name] + reduced tacrolimus arm.

Only 2.6% of study participants in H2304 were black so this study provides only limited efficacy and safety data on this population (see section 4.2)

Overall, in the 12-month analysis, the incidence of the composite endpoint (tBPAR, graft loss or death) was lower in the [Nationally completed name] + reduced tacrolimus arm (6.7%) compared to the tacrolimus control arm (9.7%) and consistent results were observed at 24 months (see Table 18).

The results of individual components of the composite endpoint are shown in Table 19.

Table 18 Study H2304: Comparison between treatment groups for Kaplan-Meier incidence rates of primary efficacy endpoints (ITT population – 12 and 24-month analysis)

Statistic	**EVR+Reduced TAC N=245**		**TAC control N=243**	
	12-month	**24-month**	**12-month**	**24-month**
Number of composite efficacy failures (tBPAR, graft loss or death) from randomisation till Month 24/12	16	24	23	29
KM estimate of incidence rate of composite efficacy failure (tBPAR*, graft loss or death) at Month 24/12	6.7%	10.3%	9.7%	12.5%
Difference in KM estimates (vs. control)	-3.0%	2.2%		
97.5% CI for difference	(-8.7%, 2.6%)	(-8.8%, 4.4%)		
P-value Z-test (EVR+Reduced TAC - Control = 0) (No difference test)	0.230	0.452		
P-value* Z-test (EVR+Reduced TAC - Control ≥0.12) (Non-inferiority test)	<0.001	<0.001		

*tBPAR = treated biopsy-proven acute rejection

Table 19 Study H2304: Comparison between treatment groups for incidence rates of secondary efficacy endpoints (ITT population – 12 and 24-month analysis)

Efficacy endpoints	**EVR/Reduced TAC N=245 n (%)**	**TAC control N=243 n (%)**	**Risk diff. (95% CI)**	**P-value***
Graft loss				
12-month	6 (2.4)	3 (1.2)	1.2 (-7.8, 10.2)	0.5038
24-month	9 (3.9)	7 (3.2)	0.8% (-3.2, 4.7)	0.661
Death				
12-month	9 (3.7)	6 (2.5)	1.2 (-7.8, 10.1)	0.6015
24-month	12 (5.2)	10 (4.4)	0.8% (-3.7, 5.2)	0.701
BPAR[1]				
12-month	10 (4.1)	26 (10.7)	-6.6 (-11.2, -2.0)	0.0052
24-month	14 (6.1)	30 (13.3)	-7.2% (-13.5, -0.9)	0.010
tBPAR[2]				
12-month	7 (2.9)	17 (7.0)	-4.1 (-8.0, -0.3)	0.0345
24-month	11 (4.8)	18 (7.7)	-2.9% (-7.9, 2.2)	0.203

1. BPAR = biopsy-proven acute rejection; 2. tBPAR = treated biopsy-proven acute rejection
*All p-values are for two-sided test and were compared to 0.05 significance level.

Comparison between treatment groups for change in eGFR (MDRD4) [ml/min/1.73 m^2] from time of randomisation (day 30) to Month 12 and 24 demonstrated superior renal function for the [Nationally completed name] + reduced tacrolimus arm (see Table 20).

Table 20 Study H2304: Comparison between treatment groups for eGFR (MDRD 4) at Month 12 (ITT population – 12 and 24-month analysis)

Difference vs. control						
Treatment	N	LS mean (SE)	LSM mean (SE)	97.5% CI	P-value(1)	P-value(2)
EVR+Reduced TAC						
12-month	244	-2.23 (1.54)	8.50 (2.12)	(3.74, 13.27)	<0.001	<0.001
24-month	245	-7.94 (1.53)	6.66 (2.12)	(1.9, 11.42)	<0.0001	0.0018
TAC control						
12-month	243	-10.73 (1.54)				
24-month	243	-14.60 (1.54)				

Least squares means, 97.5% confidence intervals and p-values are from an ANCOVA model containing treatment and HCV status as factors, and baseline eGFR as a covariate.
P-value (1): Non-inferiority test with NI margin = -6 ml/min/1.73m^2, at one-sided 0.0125 level.
P-value (2): Superiority test at two-sided 0.025 levels.

Paediatric population
. In paediatric renal and hepatic transplant patients, [Nationally completed name] should not be used. The European Medicines Agency has waived the obligation to submit the results of studies with paediatric cardiac transplant patients (see section 4.2).

In paediatric renal allograft recipients (1-18 years of age; n=106), [Nationally completed name] was assessed in a 12-month trial with 24 months additional follow-up. This multi-center, randomized, open-label trial with two parallel groups (1:1) evaluated the use of [Nationally completed name] in combination with reduced tacrolimus and corticosteroid withdrawal at 6 months post transplantation in comparison to mycophenolate mofetil with standard tacrolimus. At 12 months, the efficacy for [Nationally completed name] with reduced tacrolimus and steroid withdrawal was comparable to mycophenolate mofetil with standard tacrolimus [9.6% (5/52) vs 5.6% (3/54)] for the primary composite efficacy failure (CEF) endpoint of BPAR, graft loss and death. All of the events were BPAR; graft loss and death did not occur.
At 36 months follow-up, the CEF endpoint was similar in both treatment groups, while treated BPAR occurred in five patients in each group. Graft loss was reported in one patient (2.1%) in the group receiving everolimus with reduced tacrolimus versus two patients (3.8%) in the group receiving mycophenolate mofetil with standard tacrolimus. No deaths were reported during the study.
Extrapolation from [Nationally completed name] adult kidney transplant data to [Nationally completed name] paediatric study data and literature showed that the efficacy composite endpoint was lower than that observed in adults. Renal function calculated by estimated glomerular filtration rate (eGFR) was comparable between both study groups.

Altogether 35% (18/52) patients in the [Nationally completed name] group vs. 17% (9/54) in the control group were withdrawn from study therapy due to AEs/Infections. Most of the AEs/infections leading to premature discontinuation of study medication were singular events and were not reported in more than one patient. In the everolimus with reduced tacrolimus group two patients were reported with post-transplant lymphoproliferative disease and one patient with hepatocellular carcinoma.

In paediatric hepatic transplant recipients (month 1-18 years of age; n=56) receiving either a full-size liver allograft or a technically modified liver allograft from a deceased or living donor, [Nationally completed name] with reduced tacrolimus or ciclosporin was evaluated in a 24-month, multi-center, single arm study. Efficacy failure was defined as a composite endpoint (tBPAR, graft loss or death at 12 months). Out of 56 patients, two patients met the primary composite efficacy failure endpoint or

any of its components. There were no deaths or graft losses over 24 months of treatment. An improvement in renal function, as measured by the gain in mean estimated glomerular filtration rate (eGFR) from randomization to 12-months was 6.3 mL/min/1.73m^2. An improvement in renal function was also observed at 24-months, with an increase in mean eGFR from baseline of 4.5 mL/min/1.73m^2.

In paediatric hepatic transplant recipients, there was no negative impact in growth or sexual maturation observed. However, three main safety concerns were identified from the analysis of the safety in paediatric hepatic transplant recipients compared to adults and published literature: high rates of premature discontinuation of study medication, serious infections leading to hospitalization and PTLD. Incidence rates for PTLD in the 2 - <18 years age group, and notably in EBV negative children under 2 years of age, were higher compared to adults and published literature. Based on the safety data the benefit/risk profile does not support recommendations for use.

5.2 Pharmacokinetic properties

Absorption
After oral administration, peak everolimus concentrations occur 1 to 2 hours post-dose. Everolimus blood concentrations are dose proportional over the dose range of 0.25 to 15 mg in transplant patients. The relative bioavailability of the dispersible tablet compared with the tablet is 0.90 (90% CI 0.76-1.07) based on the AUC ratio.

Food effect
Everolimus C_{max} and AUC are reduced by 60% and 16% when the tablet formulation is given with a high-fat meal. To minimise variability, [Nationally completed name] should be taken consistently with or without food.

Distribution
The blood-to-plasma ratio of everolimus is concentration-dependent, ranging from 17% to 73% over the range of 5 to 5,000 ng/ml. Plasma protein binding is approximately 74% in healthy subjects and patients with moderate hepatic impairment. The distribution volume associated with the terminal phase (Vz/F) in maintenance renal transplant patients is 342 ± 107 litres.

Biotransformation
Everolimus is a substrate of CYP3A4 and P-glycoprotein. Following oral administration, it is the main circulating component in human blood. Six main metabolites of everolimus have been detected in human blood, including three monohydroxylated metabolites, two hydrolytic ring-opened products, and a phosphatidylcholine conjugate of everolimus. These metabolites were also identified in animal species used in toxicity studies, and showed approximately 100 times less activity than everolimus itself. Hence, the parent substance is considered to contribute the majority of the overall pharmacological activity of everolimus.

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

Steady-state pharmacokinetics
Pharmacokinetics were comparable for kidney and heart transplant patients receiving everolimus twice daily simultaneously with ciclosporin for microemulsion. Steady-state is reached by day 4 with an accumulation in blood concentrations of 2 to 3-fold compared with exposure after the first dose. T_{max} occurs at 1 to 2 hours post-dose. C_{max} averages 11.1 ± 4.6 and 20.3 ± 8.0 ng/ml and AUC averages 75 ± 31 and 131 ± 59 ng.h/ml at 0.75 and 1.5 mg *b.i.d.*, respectively. Pre-dose trough blood concentrations (C_{min}) average 4.1 ± 2.1 and 7.1 ± 4.6 ng/ml at 0.75 and 1.5 mg *b.i.d.*, respectively. Everolimus exposure remains stable over time in the first post-transplant year. C_{min} is significantly correlated with AUC, yielding a correlation coefficient between 0.86 and 0.94. Based on a population

pharmacokinetic analysis, oral clearance (CL/F) is 8.8 litres/hour (27% interpatient variation) and the central distribution volume (Vc/F) is 110 litres (36% interpatient variation). Residual variability in blood concentrations is 31%. The elimination half-life is 28 ± 7 hours.

Special populations

Hepatic impairment

Relative to the AUC of everolimus in subjects with normal hepatic function, the average AUC in 6 patients with mild hepatic impairment (Child-Pugh Class A) was 1.6-fold higher; in two independently studied groups of 8 and 9 patients with moderate hepatic impairment (Child-Pugh Class B), the average AUC was 2.1-fold and 3.3-fold higher, respectively; and in 6 patients with severe hepatic impairment (Child-Pugh Class C), the average AUC was 3.6-fold higher. Mean half-lives were 52, 59 and 78 hours in mild, moderate and severe hepatic impairment. The prolonged half-lives delay the time to reach steady-state everolimus blood concentrations.

Renal impairment

Post-transplant renal impairment (C_{Cr} range 11-107 ml/min) did not affect the pharmacokinetics of everolimus.

Paediatric population

Fourteen paediatric *de novo* renal transplant patients (2 to 16 years) received [Nationally completed name] dispersible tablets at a starting dose of 0.8 mg/m^2 (maximum 1.5 mg) twice daily with ciclosporin for microemulsion. Their doses were subsequently individualised based on therapeutic drug monitoring to maintain everolimus pre-dose trough concentrations ≥3 ng/ml. At steady state, the everolimus trough level was 6.2 ± 2.4 ng/ml, C_{max} was 18.2 ± 5.5 ng/ml, and AUC was 118 ± 28 ng.h/ml, which are comparable to adults receiving [Nationally completed name] targeted to similar pre-dose trough concentrations. The steady-state CL/F was 7.1 ± 1.7 l/h/m^2 and the elimination half-life was 30 ± 11 h in paediatric patients.

Elderly patients

A limited reduction in everolimus oral clearance by 0.33% per year was estimated in adults (age range studied was 16-70 years). No dose adjustment is considered necessary.

Ethnicity

Based on a population pharmacokinetic analysis, oral clearance (CL/F) is, on average, 20% higher in black transplant patients. See section 4.2.

Exposure-response relationships

The average everolimus trough concentration over the first 6 months post-transplant was related to the incidence of biopsy-confirmed acute rejection and of thrombocytopenia in renal and cardiac transplant patients (see Table 21). In hepatic transplant patients, the relationship between average everolimus trough concentrations and the incidence of biopsy-proven acute rejection is less well defined. No correlation between higher everolimus exposure and adverse events such as thrombocytopenia has been observed (see Table21).

Table 21 Exposure-response relationships for everolimus in transplant patients

Renal transplantation:					
Trough concentration (ng/ml)	≤3.4	3.5 - 4.5	4.6 - 5.7	5.8 - 7.7	7.8 - 15.0
Freedom from rejection	68%	81%	86%	81%	91%
Thrombocytopenia (<100 x 10^9/l)	10%	9%	7%	14%	17%
Cardiac transplantation:					
Trough concentration (ng/ml)	≤3.5	3.6 - 5.3	5.4 - 7.3	7.4 - 10.2	10.3 - 21.8
Freedom from rejection	65%	69%	80%	85%	85%
Thrombocytopenia (<75 x 10^9/l)	5%	5%	6%	8%	9%
Hepatic transplantation:					
Trough concentration (ng/ml)	≤3	3-8			≥8
Freedom from treated BPAR	88%	98%			92%
Thrombocytopenia (≤75 x 10^9/l)	35%	13%			18%

5.3 Preclinical safety data

The preclinical safety profile of everolimus was assessed in mice, rats, minipigs, monkeys and rabbits. The major target organs were male and female reproductive systems (testicular tubular degeneration, reduced sperm content in epididymides and uterine atrophy) in several species, and, in rats only, lungs (increased alveolar macrophages) and eyes (lenticular anterior suture line opacities). Minor kidney changes were seen in the rat (exacerbation of age-related lipofuscin in tubular epithelium) and the mouse (exacerbation of background lesions). There was no indication of kidney toxicity in monkeys or minipigs.

Spontaneously occurring background diseases (chronic myocarditis in the rat, Coxsackie virus infection in plasma and heart in monkeys, coccidial infestation of GI tract in minipigs, skin lesions in mice and monkeys) appeared to be exacerbated by treatment with everolimus. These findings were generally observed at systemic exposure concentrations within the range of therapeutic exposure or above, with the exception of findings in rats, which occurred below therapeutic exposure due to high tissue distribution.

Ciclosporin in combination with everolimus caused higher systemic exposure to everolimus and increased toxicity. There were no new target organs in the rat. Monkeys showed haemorrhage and arteritis in several organs.

In a male fertility study in rats, testicular morphology was affected at 0.5 mg/kg and above, and sperm motility, sperm count and plasma testosterone levels were diminished at 5 mg/kg, which is within the range of therapeutic exposure and caused a decrease in male fertility. There was evidence of reversibility. Female fertility was not affected, but everolimus crossed the placenta and was toxic to the conceptus. In rats, everolimus caused embryo/foetotoxicity at systemic exposure below the therapeutic exposure, which was manifested as mortality and reduced foetal weight. The incidence of skeletal variations and malformations at 0.3 and 0.9 mg/kg (e.g. sternal cleft) was increased. In rabbits, embryotoxicity was evident by an increase in late resorptions.

Genotoxicity studies covering relevant genotoxicity endpoints showed no evidence of clastogenic or mutagenic activity. Administration of everolimus for up to 2 years did not indicate any oncogenic potential in mice and rats up to the highest doses, corresponding respectively to 8.6 and 0.3 times the estimated clinical exposure.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Butylhydroxytoluene (E 321)
Magnesium stearate (E 470 B)
Lactose monohydrate
Hypromellose Type 2910
Crospovidone Type A
Lactose anhydrous

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Polyamide/aluminium/PVC-Aluminium blister.
Packs containing 50/60/100/250 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

Sandoz B.V.
Veluwezoom 22
1327 AH Almere
Nederland

8. NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

RVG 121989 - Aderolio 0,25 mg, tabletten
RVG 121991 - Aderolio 0,5 mg, tabletten
RVG 121992 - Aderolio 0,75 mg, tabletten
RVG 121993 - Aderolio 1 mg, tabletten

9. DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/VERLENING VAN DE VERGUNNING

Datum van eerste verlening van de vergunning: 19 februari 2019
Datum van laatste verlenging: 18 september 2023

10. DATUM VAN HERZIENING VAN DE TEKST

Laatste gedeeltelijke wijziging betreft rubriek 9: 10 juli 2023