HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

26 June 2013

CERTICAN 0.1 mg, dispersible tablets

B/60 dispersible tablets (CIP: 34009 364 115 9 3)

CERTICAN 0.25 mg, dispersible tablets

B/60 dispersible tablets (CIP: 34009 364 118 8 3)

CERTICAN 0.25 mg, tablets

B/60 tablets (CIP: 34009 364 111 3 5)

CERTICAN 0.50 mg, tablets

B/60 tablets (CIP: 34009 364 108 2 4)

CERTICAN 0.75 mg, tablets

B/60 tablets (CIP: 34009 364 103 0 5)

Applicant: NOVARTIS

INN	**Everolimus**
ATC code (year)	**L04AA18 (selective immunosuppressants)**
Reason for the review	**Extension of the indication**
List(s) concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2)
Indication(s) concerned	**"Prophylaxis of transplant rejection in liver allograft recipients. In liver transplantation, CERTICAN must be used in combination with tacrolimus and corticosteroids."**

Actual Benefit	**The actual benefit is substantial.**
Improvement in Actual Benefit	**No comparison is available with the triple therapy recommended for the prophylaxis of liver transplant rejection, combining mycophenolate mofetil/low-dose tacrolimus/corticosteroids. However, in view of the lesser reduction in glomerular filtration rate demonstrated with CERTICAN/low-dose tacrolimus/corticosteroids compared to standard-dose tacrolimus/corticosteroids at 12 months and 24 months, CERTICAN in combination with low-dose tacrolimus and corticosteroids provides a minor (IAB IV) improvement in actual benefit in the prophylaxis of transplant rejection in liver allograft recipients, in comparison with standard-dose tacrolimus combined with corticosteroids.**
Therapeutic use	**CERTICAN combined with low-dose tacrolimus and corticosteroids is a first-line therapy for the prophylaxis of liver transplant rejection that enables the tacrolimus dose to be reduced.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Start date (mutual recognition): 15 April 2004 **Extension of the indication:** 19 February 2013 Risk Management Plan including monitoring of "important" risks (see 08.2 Adverse Effects).
Prescribing and dispensing conditions / special status	**List I** Initial 6-month hospital prescription

ATC Classification	2012	
	L	Antineoplastic and immunomodulating agents
	L04	Immunosuppressants
	L04A	Immunosuppressants
	L04AA	Selective immunosuppressants
	L04AA18	Everolimus

02 BACKGROUND

On 8 December 2004, the Transparency Committee recommended inclusion of CERTICAN 0.10 mg, 0.25 mg, 0.50 mg and 0.75 mg in the indications "prophylaxis of transplant rejection in adult kidney or heart allograft recipients with a low to moderate immunological risk. CERTICAN must be used in combination with ciclosporin microemulsion and corticosteroids," with:

- *substantial actual benefit*
- *IAB V compared to CELLCEPT in kidney allograft recipients*
- *IAB IV in terms of potential efficacy in the prophylaxis of chronic rejection compared to azathioprine (IMUREL) in heart allograft recipients.*

On 21 July 2010, the Transparency Committee recommended continued inclusion (substantial actual benefit).

The current application concerns an extension of the indication to "prophylaxis of transplant rejection in liver allograft recipients. In liver transplantation, CERTICAN must be used in combination with tacrolimus and corticosteroids."

03 THERAPEUTIC INDICATIONS

"Kidney and heart transplantation
CERTICAN is indicated for the prophylaxis of transplant rejection *in adult kidney or heart allograft recipients with a low to moderate immunological risk*. In kidney and heart transplantation, CERTICAN must be used in combination with ciclosporin microemulsion and corticosteroids.

Liver transplantation
CERTICAN is indicated for the prophylaxis of transplant rejection in liver allograft recipients. In liver transplantation, CERTICAN must be used in combination with tacrolimus and corticosteroids."

04 DOSAGE

"The dosage of 1 mg twice daily is recommended for liver allograft recipients, and the initial dose should be administered approximately 4 weeks after transplantation.

The daily dosage of CERTICAN should always be administered orally, in two divided doses, at the same time as tacrolimus, either always during or always between meals.

CERTICAN is for oral use only.

The CERTICAN tablets should be swallowed whole with a glass of water and should not be crushed before use.

For patients who cannot swallow whole tablets, CERTICAN dispersible tablets are also available.

Patients taking CERTICAN may require dose adjustments depending on blood concentrations obtained, tolerability, individual response, changes to concomitant medicines and the clinical picture.

Dosage adjustments may be made at 4-5 day intervals.

Black patients: The incidence of biopsy-proven acute rejection has been higher in black kidney transplant patients than in other patients. The available data indicate that black patients may require a higher dose of CERTICAN in order to obtain an efficacy comparable to other patients. The efficacy and safety data are currently too limited for specific recommendations to be made regarding the use of everolimus in black patients.

Paediatric population: There is insufficient clinical experience to recommend the use of CERTICAN in children and adolescents. The available data concerning paediatric kidney allograft recipients are limited.

Elderly patients (≥ 65 years): Clinical experience in elderly patients over 65 years of age is limited. Although the data are limited, there is no apparent difference in everolimus pharmacokinetics in patients aged over 65-70 years.

Renal impairment: No dosage adjustment required.

Hepatic impairment: Everolimus whole blood trough levels should be carefully monitored in patients with hepatic impairment. The dose should be reduced to about two thirds of the standard dose in patients with mild hepatic impairment (Child-Pugh class A), to about half of the standard

dose in patients with moderate hepatic impairment (Child-Pugh class B) and to about one third of the standard dose in patients with severe hepatic impairment (Child-Pugh class C). Any further dosage adjustments should be based on the results of monitoring concentrations of the medicine. Once reduced, the dose of CERTICAN must be rounded to the nearest available tablet size (see SPC).

Monitoring of drug concentrations: Everolimus whole blood concentrations should be regularly monitored. In kidney, heart and liver transplantation, analysis of the efficacy-exposure and safety-exposure ratio has shown a lower incidence of biopsy-proven acute rejection in patients with whole blood trough levels of everolimus ≥ 3 ng/ml in comparison with patients whose trough levels are below 3 ng/ml. The upper limit of the recommended therapeutic range is 8 ng/ml. Exposure greater than 12 ng/ml has not been studied. The recommended ranges for everolimus have been determined using chromatography.
It is particularly important to monitor blood concentrations of everolimus in patients with hepatic impairment, during the concomitant administration of potent inhibitors or inducers of CYP3A4, when the pharmaceutical form of ciclosporin is changed and/or when ciclosporin doses are greatly reduced. Everolimus concentrations may be slightly lower following administration of the dispersible tablet.
Dose adjustments should optimally be based on trough levels obtained more than 4-5 days after a previous dose adjustment.
Ciclosporin interacts with everolimus and everolimus concentrations may consequently decrease in the case of greatly reduced exposure to ciclosporin (trough level < 50 ng/ml).

It is preferable for everolimus trough levels in patients with hepatic impairment to be at the upper limit of the therapeutic range of 3-8 ng/ml. After initiation of treatment or dose adjustment, patients should be monitored every 4-5 days until 2 consecutive trough blood levels of everolimus show stabilisation. The long half-life of everolimus in patients with hepatic impairment prolongs the time required to obtain stabilisation. Dose adjustments should be based on stable trough blood levels of everolimus.

Dosage recommendations for tacrolimus in liver transplantation:
In liver allograft recipients, exposure to tacrolimus should be reduced in order to minimise the nephrotoxicity associated with calcineurin inhibitors. The reduction in tacrolimus dose should begin about 3 weeks after the CERTICAN combination is started and the dose should target trough blood levels of tacrolimus (C0) in the range of 3-5 ng/ml. In a controlled clinical trial, stopping tacrolimus completely was associated with an increased risk of acute rejection.

In controlled clinical trials, CERTICAN has not been evaluated with standard (non-reduced) doses of tacrolimus."

05 THERAPEUTIC NEED

Following liver transplantation, in order to prevent graft rejection, it is essential that patients receive immunosuppressant treatment which will be continued for life.

Treatment protocols are constantly evolving, and treatment combinations largely depend on centres' usual practice as well as the profiles of the recipient (age, pre-sensitisation) and the donor (borderline transplanted organ, compatibility with the recipient, etc.).
The optimal immunosuppressive treatment combines several types of immunosuppressant so that, by reducing their respective doses, the adverse effects of each medicine can be limited without losing efficacy at the same time.

The initial prophylactic immunosuppressive therapy is usually triple therapy (sometimes dual therapy) combining:
- a calcineurin inhibitor: tacrolimus or ciclosporin
- an antiproliferative agent: mycophenolate mofetil or azathioprine
- a glucocorticoid.

These drugs all have different but synergistic mechanisms of action and their own toxicity issues. Anti-rejection protocols take the patient's risk of rejection and comorbidities into account to find the best possible compromise between preventing rejection and the adverse effects of immunosuppressants. Patients should therefore be monitored regularly and have their dose adjusted according to trough levels.

In terms of preventing acute rejection, protocols which use an induction therapy followed by a combination of calcineurin inhibitor and mycophenolate mofetil have helped to reduce the incidence of acute rejection, steroid-resistant rejection and refractory rejection.

Although the dosage may be reduced over time, immunosuppressant treatment must be continued for life, and most often continues to include a calcineurin inhibitor.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

NAME (INN) *Company*	Indications	Date of opinion	AB	IAB (Wording)
Selective immunosuppressants (L04AA)				
CELLCEPT 250 mg, capsules 500 mg, tablets (Mycophenolate mofetil) *Roche Pharma*	In combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or **hepatic transplants**.	18/12/2002	Substantial	Kidney transplants in adults and children, heart and liver transplants in adults: IAB II compared to azathioprine (IMUREL) in terms of efficacy.
CELLCEPT 1 g/5 ml, powder for oral suspension (Mycophenolate mofetil) *Roche Pharma*	In combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or **hepatic transplants**.	08/06/2005	Substantial	Despite the constraints associated with reconstituting the powder for oral suspension, which have been imposed for safety reasons, the Committee emphasises that CELLCEPT in this dosage form retains all of its benefit in kidney allograft recipients. Its benefit should be emphasised particularly in children, notably 2 to 6 years of age, because of the lack of an alternative and of an appropriate dosage form.
Calcineurin inhibitors (L04AD)				
SANDIMMUN 25 mg, 50 mg, 100 mg, soft gelatin capsules 100 mg/ml, oral solution (Ciclosporin) *Novartis Pharma SAS*	Organ and tissue transplantation: - **Prevention of graft rejection** - Treatment of transplant rejection in patients previously receiving other immunosuppressive agents (to avoid the risks associated with excessive immunosuppression).	12/06/1991	Substantial	IAB I in the prevention of graft rejection.
NEORAL 10 mg, 25 mg, 50 mg, 100 mg, soft gelatin capsules 100 mg/ml, oral solution (Ciclosporin) *Novartis Pharma SAS*	Organ and tissue transplantation: - **Prevention of graft rejection, including in the initial phase of liver transplantation** - Treatment of transplant rejection in patients previously receiving other immunosuppressive agents (to avoid the risks associated with excessive immunosuppression).	09/04/1998	Substantial	IAB III (liver) and IV (other organs) compared to SANDIMMUN because of advantages related to its pharmacokinetics.

NAME (INN) *Company*	Indications	Date of opinion	AB	IAB (Wording)
PROGRAF 0.5 mg, 1 mg, 5 mg, capsules 5 mg/ml, concentrate for solution for infusion (Tacrolimus) *Astellas Pharma SAS*	**Prophylaxis of transplant rejection in liver**, kidney or heart **allograft recipients.** Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products.	04/09/2002 09/05/2007	Substantial Substantial	Kidney and liver transplantation: IAB III, in terms of efficacy and safety, compared to ciclosporin (SANDIMMUN) and ciclosporin microemulsion (NEORAL). Heart transplantation ETI: IAB III, in terms of efficacy and safety, compared to ciclosporin.
ADVAGRAF 0.5 mg, 1 mg, 5 mg, prolonged-release capsules (Tacrolimus) *Astellas Pharma SAS*	**Prophylaxis of transplant rejection in adult** kidney or **liver allograft recipients.** Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients.	06/02/2008	Substantial	ADVAGRAF prolonged-release capsules administered once daily do not provide an IAB compared to PROGRAF capsules administered twice daily. However, the Committee emphasises the simplified nature of this dosing regimen.
ADVAGRAF 3 mg, prolonged-release capsules (Tacrolimus) *Astellas Pharma SAS*	**Prophylaxis of transplant rejection in adult** kidney or **liver allograft recipients.** Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients.	07/10/2009	Substantial	ADVAGRAF 3 mg prolonged-release capsules administered once daily are a justified addition to the range which do not provide an IAB compared to ADVAGRAF 0.5 mg, 1 mg and 5 mg prolonged-release capsules. However, the Committee emphasises the simplified nature of this dosing regimen.
MODIGRAF 0.2 mg, 1 mg, granules for oral suspension (Tacrolimus) *Astellas Pharma SAS*	**Prophylaxis of transplant rejection in adult and paediatric** kidney, **liver** or heart **allograft recipients.** Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult and paediatric patients.	21/10/2009	Substantial	Due to a better method of administration likely to enable more accurate dosing and the clinical consequences of this, this granule form of tacrolimus provides a minor (level IV) IAB in the prophylaxis of transplant rejection and the treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in paediatric patients. In its MA indications in adults, this granule form of tacrolimus does not provide an IAB.
Other immunosuppressants (L04AX)				
IMUREL 25 mg, 50 mg, film-coated tablets (Azathioprine) *H.A.C Pharma*	Organ transplantation: **Prophylaxis of transplant rejection in combination with corticosteroids or other immunosuppressive agents**	01/02/2006 (renewal of inclusion)	Substantial	

06.2 Other health technologies

Not applicable.

◗ Conclusion

The comparators listed are all clinically relevant.
However, as everolimus is used in combination with tacrolimus (a calcineurin inhibitor) at a reduced dose in order to minimise renal toxicity, the most relevant comparators are the antiproliferative agents (mycophenolate mofetil or azathioprine) which have the same treatment objective.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	Refunded
United Kingdom	No
Germany	Yes
Spain	Not requested
Italy	Assessment in progress
USA	No
Japan	No

08 ANALYSIS OF AVAILABLE DATA

This assessment of the efficacy and safety of CERTICAN (everolimus) in the prophylaxis of liver transplant rejection is based on a phase III, randomised, controlled, open-label study (H2304) evaluating everolimus in combination with low-dose tacrolimus versus standard-dose tacrolimus in *de novo* liver transplant recipients. This study was conducted over 24 months with evaluation of the primary endpoint at 12 months.

The company also submitted two phase III studies:

- PROTECT (HDE10), a randomised, controlled, open-label study evaluating the effects on renal function at 12 months of everolimus together with gradual discontinuation of calcineurin inhibitor (CNI) versus standard CNI treatment, in *de novo* liver transplant recipients
- RESCUE (H2401), a randomised, controlled, open-label study evaluating the effects on renal function at 6 months of everolimus together with reduction or discontinuation of CNI ± corticosteroids versus standard CNI treatment ± mycophenolate or azathioprine ± corticosteroids, in patients with CNI-related impaired renal function (GFR ≤ 60 ml/min) some time after liver transplantation.

The results of these studies will not be taken into account in this assessment for the following reasons:

- In the PROTECT study, CERTICAN was administered at a different dosage and with a different regimen to those recommended in the Marketing Authorisation, namely at a dosage of 1.5 mg twice daily and in combination with either tacrolimus or ciclosporin. Eight weeks after randomisation, the CNI treatment was stopped as long as no rejection had occurred in the previous 4 weeks. In addition, the patients received basiliximab (SIMULECT) on D0 and on D4. Basiliximab is not indicated for the prophylaxis of liver transplant rejection, but only for the prophylaxis of acute rejection following *de novo* allogeneic renal transplantation.
- In the RESCUE study, everolimus was administered at a later stage, namely 12 to 60 months after transplantation; at a different dosage from that recommended in the Marketing Authorisation, namely 1.5 mg twice daily; and in combination with either tacrolimus or ciclosporin. After a gradual reduction in dosage, the tacrolimus or ciclosporin treatment was stopped.

Therefore, because the way CERTICAN was administered in these two studies does not comply with its Marketing Authorisation, they cannot be used to analyse the therapeutic role of everolimus in the prophylaxis of liver transplant rejection.

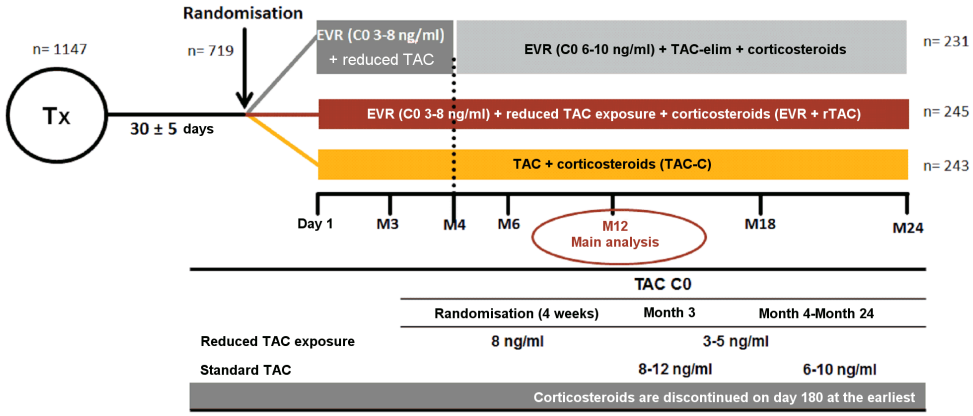
In addition, the company cited data from studies that have not been taken into account because of their methodology:

- Two pharmacokinetics studies (B202 and A2303) with administration of a single dose of everolimus (7.5 mg or 2 mg).

- One dose-ranging study (B158) in which everolimus was combined with ciclosporin and corticosteroids. Everolimus was administered at a fixed dose with no adjustments according to trough levels.
- One study (H2301) including 43 patients who had received a transplant at least 6 months previously and comparing everolimus monotherapy (which does not comply with the conditions of the Marketing Authorisation) to standard CNI treatment with or without mycophenolate and/or corticosteroids.

08.1 Efficacy: Study H2304

	Protocol of Study H2304
Primary objective of the study:	To demonstrate the non-inferiority (delta threshold = 12%) at 12 months of introducing everolimus 4 weeks after liver transplantation in combination with a reduction in tacrolimus versus standard tacrolimus treatment on a composite "efficacy failure" endpoint (treated biopsy-proven acute rejection, graft loss or death).
Method:	Phase III, randomised, controlled, open-label, parallel-group study.
Study duration:	24 months.
Inclusion criteria:	**Main inclusion criteria at transplantation (selection)** - Male or female recipients, aged 18-70 years, of a primary liver transplant from a deceased donor - Initiation of an immunosuppressive regimen that includes tacrolimus and corticosteroids, 3-7 days post-transplantation. **Main inclusion criteria on randomisation (D30 post-transplantation)** - Liver allograft functioning - Renal function: eGFR ≥ 30 ml/min/1.73m² - Tacrolimus trough level of ≥ 8 ng/ml in the week prior to randomisation - Oral administration possible at the time of randomisation.
Non-inclusion criteria included:	**Main non-inclusion criteria at transplantation (selection)** - Recipients of multiple solid organ or islet cell tissue transplants, or patients who have previously received an organ or tissue transplant - Recipients of a liver from a living donor, or of a split liver - History of malignancy within the past 5 years, other than non-metastatic basal or squamous cell carcinoma or hepatocellular carcinoma (see next criterion) - Hepatocellular carcinoma that does not fulfil Milan criteria (1 nodule ≤ 5 cm, 2-3 nodules ≤ 3 cm) at the time of transplantation as per explant histology of the recipient liver - Any use of antibody induction therapy. **Main non-inclusion criteria on randomisation (D30 post-transplantation)** - Acute rejection requiring antibody therapy, or more than one corticosteroid treatment during the selection period. Patients treated for acute rejection with corticosteroids in the 7 days prior to randomisation. - Doppler ultrasound revealing thrombosis of the hepatic arteries, hepatic veins, portal vein or inferior vena cava - Severe hypercholesterolaemia (> 9 mmol/l) or hypertriglyceridaemia (> 8.5 mmol/l) in the 6 months prior to transplantation; patients with controlled hyperlipidaemia may be included. - HIV positive patients (results obtained in the 6 months prior to randomisation) - Clinically significant systemic infection requiring the use of IV antibiotics at the time of randomisation.
Treatment groups:	- **Everolimus (EVR) + low-dose tacrolimus (reduced TAC) group:** Everolimus started 4 weeks after transplantation with concomitant reduction of the tacrolimus dose. Patients received an initial everolimus dose of 1 mg twice daily. The dose of everolimus was then adjusted to maintain trough levels between 3 and 8 ng/ml. Once the target everolimus trough levels were reached, the tacrolimus dosage was reduced until a trough blood level between 3 and 5 ng/ml was obtained (by 3 weeks after randomisation). - **Standard-dose tacrolimus (standard TAC) group:** Tacrolimus trough levels had to be maintained between 8 and 12 ng/ml until the end of month 3, then between 6 and 10 ng/ml from month 4 until the end of the study. - **Everolimus (EVR) + complete elimination of tacrolimus (TAC elimination) group:** Everolimus started 4 weeks after transplantation with initial concomitant reduction in tacrolimus exposure, then complete elimination of tacrolimus 4 months after transplantation (i.e. 3 months after randomisation). From M3 post-

	randomisation (i.e. M4 post-transplantation), everolimus trough levels should increase to between 6 and 10 ng/ml. Corticosteroids were administered in all three groups. Corticosteroids could not be stopped before D180 post-transplantation.
Course of the study:	Patients included at transplantation and 4 weeks later were randomised (1:1:1 ratio) into one of the groups, after stratification by hepatitis C serology and renal function. During the selection phase, all patients received treatment with standard-dose tacrolimus and corticosteroids, with or without mycophenolate mofetil according to the centre's usual practice (stopped in all cases upon randomisation). 
Primary efficacy endpoint:	Composite efficacy failure at 12 months, combining: - treated biopsy-proven acute rejection - graft loss - death.
Secondary endpoints included:	Change in renal function (glomerular filtration rate or GFR) from randomisation to month 12 and month 24 post-transplantation Efficacy failure at 24 months At 12 and 24 months: - treated biopsy-proven acute rejection - biopsy-proven acute rejection - graft loss - death.
Calculation of number of participants required	A figure of 242 patients per group enabled the non-inferiority (delta threshold = 12%) of EVR + reduced TAC to standard TAC to be demonstrated with a power of between 80% and 85% and a unilateral α risk of 0.0125, on the basis of an estimated transplantation failure rate between 20% and 24%.
Statistical analysis:	**Primary efficacy endpoint:** The non-inferiority limit was defined as 12% for composite efficacy failure. Non-inferiority was demonstrated if the upper limit of the 97.5% confidence interval for the difference between the two groups was below 12%. **Secondary endpoints:** GFR: The EVR + reduced TAC group was compared to the standard TAC group at 12 months with a non-inferiority limit defined as -6 ml/min/1.73m² (unilateral α risk: 0.0125). Non-inferiority between the everolimus + reduced TAC group and the standard TAC group was demonstrated if the lower limit of the confidence interval was greater than -6. In the event of the demonstration of non-inferiority, a superiority analysis was planned using an analysis of covariance (ANCOVA). The intention-to-treat (ITT) population consisted of all randomised patients. The per-protocol (PP) population consisted of all randomised patients who completed the study without any major deviations from the protocol. Analyses were performed in the per-protocol (PP) and intention-to-treat (ITT) populations.

Study results

A total of 719 patients were randomised, comprising:
- 245 in the **everolimus + reduced TAC group**
- 243 in the **standard TAC group**
- 231 in the **everolimus + TAC elimination group**

In April 2010, the study's independent data monitoring committee decided to stop recruitment for the **everolimus + TAC elimination** group due to an increased incidence of acute rejection and treatment discontinuation following the elimination of tacrolimus between D120 and D180 post-randomisation. On this date, 690 patients had been randomised. The patients that remained to be included were randomised equally between the two remaining groups (EVR + reduced TAC or standard TAC). The results of the **everolimus + TAC elimination** group are not presented.

Patient characteristics were comparable between the groups.
The mean patient age was 54 years, with men predominating (> 70%). One third of patients were seropositive for the hepatitis C virus (HCV) and the mean estimated GFR on selection was approximately 80 ml/min/1.73m². The most common indications for transplantation were hepatitis C, alcoholic cirrhosis and hepatocellular carcinoma. The mean MELD (model for end-stage liver disease) score was 19.2 and the median duration of cold ischaemia was 7.3 hours. The mean time from transplantation to the first dose of tacrolimus was 1.9 days.

The numbers in the different study populations are shown in Table 1.

Table 1: Populations in study H2304

	Everolimus + reduced TAC	Standard TAC
ITT population at 12 months and 24 months	245 (100%)	243 (100%)
Safety population at 12 months	245 (100%)	241 (99.2%)
Safety population at 24 months	245 (100%)	242 (99.6%)
Per-protocol population at 12 months	157 (64.1%)	161 (66.3%)
Per-protocol population at 24 months	156 (63.7%)	160 (65.8%)

The treatment discontinuation rate at 12 months was 26.9% in the everolimus + reduced TAC group versus 22.2% in the standard TAC group; at 24 months this was 42.4% versus 32.5% (Table 2). The main reason for stopping treatment was the occurrence of an adverse event: 19.2% in the everolimus + reduced TAC group versus 11.1% in the standard TAC group at 12 months, and 28.6% versus 18.1% at 24 months.

Table 2: Treatment discontinuation and withdrawal from the study at 12 and 24 months (ITT)

N (%)	At 12 months		At 24 months	
	EVR + reduced TAC (N=245)	Standard TAC (N=243)	EVR + reduced TAC (N=245)	Standard TAC (N=243)
Patients who completed the study	**220 (89.8%)**	**218 (89.7%)**	**202 (82.4%)**	**204 (84.0%)**
Patients who completed treatment	**179 (73.1%)**	**189 (77.8%)**	**141 (57.6%)**	**164 (67.5%)**
Patients who stopped treatment	**66 (26.9%)**	**54 (22.2%)**	**104 (42.4%)**	**79 (32.5%)**
Due to:				
Adverse event	*47 (19.2%)*	*27 (11.1%)*	*70 (28.6%)*	*44 (18.1%)*
Death	*4 (1.6%)*	*5 (2.1%)*	*5 (2.0%)*	*7 (2.9%)*
Graft loss	*2 (0.8%)*	*0 (0%)*	*3 (1.2%)*	*2 (0.8%)*

Results for the primary efficacy endpoint (see Table 3):

In the PP analysis, the percentage of treatment failures was 1.9% in the EVR + reduced TAC group versus 5.0% in the standard TAC group, i.e. a difference of -3.1%, 97.5% CI [-7.6; 1.5]. As the upper limit of the 97.5% confidence interval for the difference between treatments was below the non-inferiority threshold of 12%, the non-inferiority of EVR + reduced TAC to standard TAC was demonstrated in terms of composite efficacy failure (consisting of treated biopsy-proven acute rejection, graft loss and death). The results of the ITT analysis confirmed the results of the PP analysis.

Table 3: Results for the primary endpoint: composite efficacy failure (comprising treated biopsy-proven acute rejection, graft loss and death) at 12 months

	PP population		ITT population	
	EVR + reduced TAC n=157	**Standard TAC n=161**	**EVR + reduced TAC n=245**	**Standard TAC n=243**
Number of treatment failures	3	8	16	23
Percentage of treatment failures	1.9%	5.0%	6.7%	9.7%
Difference (vs. standard TAC)	-3.1%		-3.0%	
97.5% CI	(-7.6%, 1.5%)		(-8.7%, 2.6%)	
p-value for non-difference	0.133		0.230	
p-value for non-inferiority	<0.001		<0.001	

Results for secondary endpoints (see Table 4):

- **Efficacy failure at 24 months**

The non-inferiority of EVR + reduced TAC to standard TAC in terms of composite efficacy failure (consisting of treated biopsy-proven acute rejection, graft loss and death) at 24 months was demonstrated with a 97.5% CI for the difference of [-8.8%, 4.4%].

- **Graft loss, death, treated biopsy-proven acute rejection (= sub-criteria of the composite endpoint) and biopsy-proven acute rejection at 12 months and 24 months**

For the three sub-criteria of the composite efficacy failure endpoint, a statistically significant difference favouring the EVR + reduced TAC group was demonstrated only for treated biopsy-proven acute rejection at 12 months (2.9% in the EVR + reduced TAC group versus 7.0% in the standard TAC group, p=0.0345).
Conversely, no difference between the two groups was demonstrated for the endpoints “graft loss” or “death” at 12 months or 24 months.

However, a statistically significant difference favouring the everolimus + reduced TAC group was demonstrated for the secondary endpoint “biopsy-proven acute rejection” at 12 months (4.1% in the EVR + reduced TAC group versus 10.7% in the standard TAC group, p=0.0052) and at 24 months (6.1% in the EVR + reduced TAC group versus 13.3% in the standard TAC group, p=0.010).

Table 4: Comparison of treatment groups in terms of secondary efficacy endpoint incidence at 12 and 24 months (ITT population)

	12 months		24 months	
	EVR + reduced TAC N=245 n (%)	**Standard TAC N=243 n (%)**	**EVR + reduced TAC N=245 n (%)**	**Standard TAC N=243 n (%)**
Graft loss	6 (2.4%)	3 (1.2%)	9 (3.9%)	7 (3.2%)
Difference (95% CI) p	1.2% (-7.8, 10.2) 0.50		0.8% (-3.2, 4.7) 0.66	
Death	9 (3.7%)	6 (2.5%)	12 (5.2%)	10 (4.4%)
Difference (95% CI) p	1.2 (-7.8, 10.1) 0.60		0.8% (-3.7, 5.2) 0.70	
tBPAR[1]	7 (2.9%)	17 (7.0%)	11 (4.8%)	18 (7.7%)
Difference (95% CI) p	-4.1% (-8.0, -0.3) 0.0345		- 2.9% (-7.9, 2.2) 0.20	
BPAR[2]	10 (4.1%)	26 (10.7%)	14 (6.1%)	30 (13.3%)
Difference (95% CI) p	-6.6 (-11.2, -2.0) 0.0052		- 7.2% (-13.5, -0.9) 0.010	

1. tBPAR = treated biopsy-proven acute rejection

2. BPAR = biopsy-proven acute rejection

- **Change in estimated glomerular filtration rate (GFR)**

The renal function results demonstrated a lesser reduction in GFR in the EVR + reduced TAC group than in the standard TAC group at 12 months and 24 months (Tables 5 and 6).

Table 5: Change in estimated GFR (MDRD4) at 12 months (PP population)

	EVR + reduced TAC (n=156)	**Standard TAC (n=161)**
GFR on randomisation (mean ± standard error)	ND	ND
Change at 12 months: Least squares mean (standard error)	-0.5 (1.9)	-10.9 (1.8)
Difference of means (standard error) 97.5% CI p-value for non-inferiority* p-value for superiority**	10.4 (2.5) [4.8; 16.1] <0.0001 <0.0001	

* Non-inferiority test with NI margin = -6 ml/min/1.73m² and a unilateral significance threshold of 0.0125

** Superiority test with a bilateral significance threshold of 0.025

Table 6: Change in estimated GFR (MDRD4) at 12 and 24 months (ITT population)

	EVR + reduced TAC (n=245)	**Standard TAC (n=243)**
GFR on randomisation (mean ± standard error) p	81.1 ± 32.6	78.1 ± 27.5 0.58
Change at 12 months: Least squares mean (standard error)	-2.2 (1.5)	-10.7 (1.5)
Difference of means (standard error) 97.5% CI p-value for non-inferiority* p-value for superiority**	8.5 (2.1) [3.7; 13.3] <0.001 <0.001	
Change at 24 months: Mean ± standard error	-7.9 (1.5)	-14.6 (1.5)
Difference of means (standard error) 97.5% CI p-value for non-inferiority* p-value for superiority**	6.7 (2.1) [1.9; 11.4] <0.0001 <0.0018	

ANCOVA model adjusted for treatments, HCV status and estimated GFR on randomisation.

* Non-inferiority test with NI margin = -6 ml/min/1.73m² and a unilateral significance threshold of 0.0125

** Superiority test with a bilateral significance threshold of 0.025

08.2 Adverse effects

8.2.1 Safety data from study H2304

The incidence of adverse events was:

- 94.7% (n=232/245) in the EVR + reduced TAC group versus 95.0% (n=229/241) in the standard TAC group at 12 months
- 96.3% (n=236/245) in the EVR + reduced TAC group versus 97.9% (n=237/242) in the standard TAC group at 24 months.

The percentage of treatment discontinuations due to adverse events was:

- 19.2% in the EVR + reduced TAC group versus 11.1% in the standard TAC group at 12 months
- 28.6% in the EVR + reduced TAC group versus 18.1% in the standard TAC group at 24 months.

The noteworthy adverse events were (see Table 7):

Table 7: Incidence of noteworthy AEs (incidence > 5%) at 12 and 24 months (safety population)

	Everolimus + reduced TAC (N = 245)	**Everolimus + reduced TAC (N = 245)**	**Standard TAC (N = 241)**	**Standard TAC (N = 242)**
	12 months	**24 months**	**12 months**	**24 months**
Anaemia	19 (7.8)	24 (9.8)	21 (8.7)	25 (10.3)
New-onset diabetes mellitus	48 (19.6)	51 (20.8)	40 (16.6)	40 (16.5)
Ascites	10 (4.1)	11 (4.5)	8 (3.3)	11(4.5)
Healing complications	27 (11.0)	27 (11.0)	19 (7.9)	20 (8.3)
Pleural effusion	11 (4.5)	15 (6.1)	11 (4.6)	13 (5.4)
Cardiovascular events	5 (2.0)	10 (4.1)	9 (3.7)	15 (6.2)
Thromboembolic events	13 (5.3)	18 (7.3)	9 (3.7)	14 (5.8)
Incisional hernia	17 (6.9)	24 (9.8)	13 (5.4)	19 (7.9)
Hyperlipidaemia	58 (23.7)	66 (26.9)	23 (9.5)	28 (11.6)
CMV infection	11 (4.5)	12 (4.9)	12 (5.0)	13 (5.4)
Renal impairment – excluding proteinuria	35 (14.3)	52 (21.2)	48 (19.9)	74 (30.6)
Neutropenia	34 (14.3)	38 (15.5)	17 (7.1)	19 (7.9)
Peripheral oedema	48 (19.6)	55 (22.4)	30 (12.4)	36 (14.9)
Malignancies	6 (2.4)	19 (7.8)	11 (4.6)	17 (7.0)
Stomatitis, mouth ulcer	23 (9.4)	26 (10.6)	3 (1.2)	3 (1.2)
Thrombocytopenia	14 (5.7)	20 (8.2)	5 (2.1)	7 (2.9)

The most common events considered as possibly related to the study treatments were, at 12 months (see Table 8):

Table 8: Incidence (> 5%) of possibly treatment-related AEs (safety population)

	Everolimus + reduced TAC (N = 245) N (%)	**Standard TAC (N = 241) N (%)**
All adverse events	160 (65.3)	132 (54.8)
Blood and lymphatic system disorders	37 (15.1)	7 (2.9)
Leukopenia	***20 (8.2)***	***3 (1.2)***
Gastrointestinal disorders	38 (15.5)	17 (7.1)
Diarrhoea	***15 (6.1)***	*13 (5.4)*
Metabolism and nutrition disorders	53 (21.6)	24 (10.0)
Hypercholesterolaemia	*13 (5.3)*	*0*
Hyperlipidaemia	*16 (6.5)*	*4 (1.7)*
Nervous system disorders	32 (13.1)	37 (15.4)
Migraine	*13 (5.3)*	*15 (6.2)*

	Everolimus + reduced TAC (N = 245) N (%)	Standard TAC (N = 241) N (%)
Tremor	*17 (6.9)*	*22 (9.1)*
Renal and urinary disorders	27 (11.0)	29 (12.0)
Renal impairment	*13 (5.3)*	*17 (7.1)*
Vascular disorders	20 (8.2)	20 (8.3)
Hypertension	*16 (6.5)*	*17 (7.1)*

The incidence of serious adverse events was 49.8% in the EVR + reduced TAC group versus 43.2% in the standard TAC group at 12 months, and 56.3% versus 54.1% at 24 months. Between randomisation and month 12, 15 deaths were reported (9 in the EVR + reduced TAC group versus 6 in the standard TAC group), with the causes of death mostly related to hepatic complications or to infections and sepsis. The majority of these deaths (14/15) were considered as not related to treatment.

The overall graft survival rate was 98.1% (9/486). Graft loss was reported in 6 patients (2.4%) in the EVR + reduced TAC group and 3 patients (1.2%) in the standard TAC group. No cases of graft loss were considered to be treatment-related. Of the 9 patients affected, 7 died and 2 were given a successful re-transplant.

8.2.2 Safety data from PSURs

Most adverse events of special interest – important identified and potential risks – that are subject to specific pharmacovigilance monitoring and collected when everolimus is used in liver transplantation (CNI-induced impairment of renal function, proteinuria, hyperlipidaemia, thrombotic microangiopathy, angioedema, cancer) make up less than 5% of all pharmacovigilance cases involving everolimus used in transplantation. Some, particularly graft thrombosis, relate specifically to kidney transplantation. In liver transplantation, the adverse effects with a notification rate between 5% and 10% of all pharmacovigilance cases involving everolimus in transplantation are: interstitial lung disease (5.3%), diabetes (7%), impaired wound healing (8.5%), malignant neoplasm (10%) and infections (10.6%).

8.2.3 Risk management plan

This proprietary medicinal product has a risk management plan that includes specific monitoring of the following “important” risks:

- Identified risks: impaired renal function induced by calcineurin inhibitors, proteinuria, renal graft thrombosis, impaired healing, hyperlipidaemia, new-onset diabetes, thrombotic microangiopathy, interstitial lung disease, infections, malignant neoplasm, angioedema, oedema.

- Potential risks: teratogenicity

8.2.4 Safety data from the SPC

The adverse events observed during phase III clinical trials which have a possible or probable causal link with CERTICAN and are listed as “very common” in the SPC are:

- *infections (viral, bacterial, fungal), upper respiratory tract infections*
- *leukopenia*
- *hyperlipidaemia (cholesterol and triglycerides), new-onset diabetes mellitus*
- *hypertension*
- *pericardial effusion (in heart transplantation)*
- *pleural effusion (in heart transplantation)*
- *abdominal pain (in liver transplantation)*
- *peripheral oedema, incisional hernia (in liver transplantation).*

08.3 Summary & discussion

In the extension of its indication to the prophylaxis of transplant rejection in liver allograft recipients, everolimus (CERTICAN) has been evaluated in a randomised, open-label, non-inferiority study. Everolimus in combination with tacrolimus at a reduced dose to obtain a trough blood level between 3 and 5 ng/ml (in the 3 weeks following randomisation) was compared to standard-dose tacrolimus (tacrolimus trough levels maintained between 8 and 12 ng/ml until the end of month 3, then between 6 and 10 ng/ml from month 4 until the end of the study). All patients received corticosteroids.

The primary efficacy endpoint was a composite “efficacy failure” endpoint comprising treated biopsy-proven acute rejection, graft loss and death. The non-inferiority limit was defined as 12% for composite efficacy failure. Non-inferiority was demonstrated if the upper limit of the 97.5% confidence interval for the difference between the two groups was below 12%.

Efficacy: everolimus + low-dose tacrolimus versus standard-dose tacrolimus

In the PP analysis, after 12 months of treatment the efficacy failure rate was 1.9% with everolimus + low-dose tacrolimus versus 5.0% with standard-dose tacrolimus, i.e. a difference of -3.1% (97.5% CI [-7.6; 1.5]), demonstrating the non-inferiority of everolimus + low-dose tacrolimus to standard-dose tacrolimus. This result was confirmed in the ITT analysis (6.7% versus 9.7%; difference -3.0%; 97.5% CI [-7.6; 1.5]).

- Treated biopsy-proven acute rejection was reduced at 12 months (2.9% versus 7.0%, p=0.0345) but no longer at 24 months (4.8% versus 7.7%).
- There was no difference in graft loss or death at 12 months or 24 months.
- Biopsy-proven acute rejection was reduced at 12 months (4.1% versus 10.7%, p=0.0052) and at 24 months (6.1% versus 13.3%, p=0.010).
- The reduction in glomerular filtration rate was less substantial at 12 months (difference of means 8.50, $p < 0.001$) and at 24 months (difference of means 6.66, $p < 0.0018$).

Adverse effects: everolimus + low-dose tacrolimus versus standard-dose tacrolimus
- The percentage of patients who reported at least one adverse effect was comparable: 94.7% vs. 95.0% at 12 months and 96.3% vs. 97.9% at 24 months.
- Treatment discontinuation due to an adverse event was more common at 12 months (19.2% versus 11.1%) and at 24 months (28.6% versus 18.1%).
- The incidence of serious adverse events was 49.8% versus 43.2%.
- The incidence of the following possibly treatment-related adverse events was higher: leukopenia (8.2% versus 1.2%), diarrhoea (6.1% versus 5.4%), hypercholesterolaemia (5.3% versus 0%) and hyperlipidaemia (6.5% versus 1.7%).
- The incidence of the following possibly treatment-related adverse events was lower: migraine (5.3% versus 6.2%), tremor (6.9% versus 9.1%), renal impairment (5.3% versus 7.1%) and hypertension (6.5% versus 7.1%).

Pharmacovigilance data show that in liver transplantation, the adverse effects accounting for between 5% and 10% of all adverse events for everolimus in transplantation are: interstitial lung disease (5.3%), diabetes (7%), impaired wound healing (8.5%), malignant neoplasm (10%) and infections (10.6%).

CERTICAN has a risk management plan.

There are no studies comparing CERTICAN/low-dose tacrolimus/corticosteroids to the immunosuppressive triple therapy recommended for the prophylaxis of liver transplant rejection, consisting of an antiproliferative (mycophenolate mofetil or azathioprine) in combination with a CNI and corticosteroids.

08.4 Planned studies

Not applicable.

09 THERAPEUTIC USE

The initial prophylactic immunosuppressive therapy is usually triple therapy (sometimes dual therapy) combining:
- a calcineurin inhibitor: tacrolimus or ciclosporin
- an antiproliferative agent: mycophenolate mofetil or azathioprine
- a glucocorticoid.

Among the calcineurin inhibitors, tacrolimus reduces the incidence of acute rejection in comparison with ciclosporin and can be used to manage early chronic rejection. It is the calcineurin inhibitor of choice in liver transplantation and is used in combination with an antiproliferative agent and corticosteroids.

Among the antiproliferative agents, mycophenolate mofetil is superior to azathioprine in the prevention of acute rejection at 6 months, which is why it is used in liver transplantation in preference to azathioprine.

The standard immunosuppressive therapy for liver transplantation is a combination of low-dose tacrolimus, mycophenolate mofetil and corticosteroids.

CERTICAN combined with low-dose tacrolimus and corticosteroids is a first-line therapy for the prophylaxis of liver transplant rejection that enables the tacrolimus dose to be reduced.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual benefit

◗ Immunosuppressive treatments for organ transplantation are administered in the context of serious clinical situations that can be life-threatening.
◗ These medicinal products are intended as preventative therapy for organ rejection in liver *transplant recipients.*
◗ The efficacy/adverse effects ratio for these medicinal products is high.
◗ There are treatment alternatives.
◗ These medicinal products are a first-line therapy.

◗ Public health benefit:
The public health burden of liver transplant rejection can be considered as low because of the small number of patients concerned.
Improvement in the prevention and treatment of transplant rejection is a public health need which is an established priority (GTNDO[1] priorities).
In view of the available data (a non-inferiority trial), CERTICAN is not expected to have any additional impact on the morbidity and mortality of patients treated in comparison with therapy combining tacrolimus and corticosteroids. In view of the available data, an impact on preservation of renal function is expected but this is at best low. Due to the current lack of data, the impact of CERTICAN on patients' quality of life cannot be quantified. No impact on the provision of healthcare is expected. The transferability of the data to current clinical practice is acceptable.
Therefore, the proprietary medicinal product CERTICAN should not be expected to provide any additional response to an identified public health need.
Consequently, in view of the current therapeutic management of transplant rejection, it is not expected that the proprietary medicinal product CERTICAN will benefit public health in this indication.

Taking account of these points, the Committee considers that the actual benefit of CERTICAN is substantial, in combination with low-dose tacrolimus and corticosteroids, in the prophylaxis of transplant rejection in liver allograft recipients.

010.2 Improvement in actual benefit (IAB)

No comparison is available with the triple therapy recommended for the prophylaxis of liver transplant rejection, combining mycophenolate mofetil/low-dose tacrolimus/corticosteroids. However, in view of the lesser reduction in glomerular filtration rate demonstrated with CERTICAN/low-dose tacrolimus/corticosteroids compared to standard-dose tacrolimus/corticosteroids at 12 months and 24 months, CERTICAN in combination with low-dose tacrolimus and corticosteroids provides a minor (level IV) improvement in actual benefit in the prophylaxis of transplant rejection in liver allograft recipients, in comparison with standard-dose tacrolimus combined with corticosteroids.

[1] Groupe Technique National de Définition des Objectifs [National Technical Group for the Definition of Public Health Objectives] (DGS-2003)

010.3 Target population

The target population for CERTICAN in this extension of the indication is represented by the adult population who have received a liver transplant and consequently require treatment to prevent graft rejection.
According to data from the Biomedicine Agency, a total of 1,164 patients received a liver transplant in 2011, including 1,079 adults.
For information, on 1 January 2012, 941 patients were on the liver transplant waiting list.

Estimate/conclusion
The target population for CERTICAN in the indication “prophylaxis of transplant rejection in adult liver allograft recipients” is about 1,100 patients per year.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and/or on the list of medicines approved for hospital use in this extension of the indication and at the dosages in the Marketing Authorisation.

- **Proposed reimbursement rate:** 100%

- **Packaging**

Appropriate for the prescription conditions.