



All Wales Therapeutics
and Toxicology Centre

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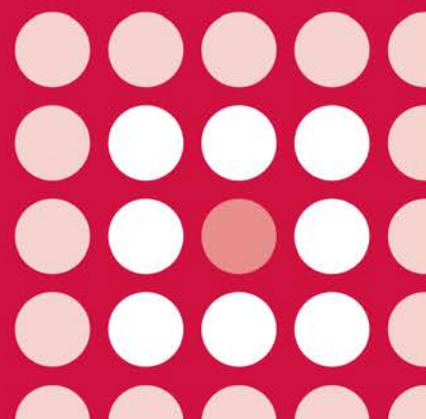
AWMSG SECRETARIAT ASSESSMENT REPORT

Tacrolimus (Envarsus®)

0.75 mg, 1 mg, 4 mg prolonged-release tablets

Reference number: 2586

LIMITED SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics & Medicines Evaluation, Bangor University.

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AWMSG Secretariat Assessment Report Tacrolimus (Envarsus®) 0.75 mg, 1 mg, 4 mg prolonged-release tablets

This assessment report is based on evidence from a limited submission by Chiesi Ltd on 20 February 2015¹.

1.0 PRODUCT AND APPRAISAL DETAILS

Licensed indication under consideration	Tacrolimus (Envarsus®) for the 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 ² .
Dosing	For the prophylaxis of kidney transplant rejection, tacrolimus therapy should commence at 0.17 mg/kg/day administered once-daily in the morning. For the prophylaxis of liver transplant rejection, tacrolimus therapy should commence at a dose of 0.11–0.13 mg/kg/day administered once-daily in the morning. For both of these indications, administration should commence within 24 hours of the completion of surgery. These doses are intended to act solely as a guideline, refer to the Summary of Product Characteristics (SPC) for further information on treatment of allograft rejection, therapeutic drug monitoring and special populations ² .
Marketing authorisation date	18 July 2014 ³
Comparators	The comparator included in the company submission was tacrolimus (Prograf®) ¹ .
Limited submission details	Tacrolimus (Envarsus®) for the above indication met the following criteria for eligibility for a limited submission: <ul style="list-style-type: none"> • Significant new formulation with a pro-rata or lower cost per treatment. • Anticipated usage in NHS Wales is considered to be of minimal budgetary impact. • Estimated small difference in cost compared to comparator.

2.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

2.1 Phase II pharmacokinetic studies

The company submission included details of two phase II studies comparing the pharmacokinetics and safety of once-daily extended-release tacrolimus (Envarsus®) versus twice-daily tacrolimus capsules (Prograf®). Study 2011 and study 2012 were both open-label conversion studies in 47 stable renal transplant patients and 59 stable liver transplant patients respectively^{4,5}. Results were consistent for both studies and demonstrated similar systemic exposure and trough levels for both preparations. Envarsus® resulted in more consistent exposure over the course of 24 hours with increased time of maximum concentration (T_{max}) and reduced peak to trough fluctuations compared to Prograf®. The greater bioavailability of Envarsus® allowed for an approximately 30% reduction in total daily dose compared to Prograf® to achieve similar exposure^{4,5}. In both studies, most adverse events (AEs) were mild or moderate, did not significantly differ between treatment groups and the incidence, type and severity of AEs were within the range expected for this patient population¹.

2.2 Phase III efficacy studies

The phase III studies, 3001 and 3002, compared the efficacy and safety of Envarsus[®] (once-daily) and Prograf[®] (twice-daily) in 326 stable renal transplant patients and 543 *de novo* renal transplant patients respectively^{6,7}. Study 3001 was an open-label, randomised, conversion study in which stable renal transplant patients were randomised from Prograf[®] to either continue on Prograf[®] or receive Envarsus[®]. After 12 months, Envarsus[®] demonstrated non-inferiority to Prograf[®] in efficacy failure rates⁶. The mean required total daily Envarsus[®] dose was approximately 20% lower than the mean pre-conversion Prograf[®] dose^{1,6}.

In study 3002, *de novo* kidney transplant patients were randomised to receive either Envarsus[®] (once-daily) or Prograf[®] (twice-daily)⁷. Non-inferiority of Envarsus[®] to Prograf[®] was demonstrated based on efficacy failure rates; follow-up data at 24 months supported these 12 month findings¹.

In both phase III studies, the incidence of AEs was similar for both treatment groups¹.

Post hoc analyses of pooled data for the two phase III studies showed that in two key subgroups, namely black patients and older patients (> 65 years), significantly less efficacy failure was associated with Envarsus[®] compared with Prograf[®]¹.

A phase IIIb study (STRATO), conducted in a small number of patients (n = 38) who experienced tremor as an AE of twice-daily tacrolimus, showed a statistically significant reduction in tremor at seven days post-switch to Envarsus[®], with a corresponding improvement in quality-of-life scores as assessed by both clinicians and patients⁸.

2.2 Points to note

- Clinical trial data provided in the company submission demonstrated non-inferiority of Envarsus[®] (once-daily) compared with Prograf[®] (twice-daily) for both efficacy and safety^{6,7}.
- As a result of pharmacokinetic studies, the equivalent dose of tacrolimus in the Envarsus[®] once-daily preparation is approximately 30% less than the Prograf[®] twice-daily preparation². Envarsus[®] is not interchangeable with other existing tacrolimus containing medicines (immediate or prolonged release) on an equal dose by dose basis².
- Studies provided in the company submission showed no difference in the safety profile of Envarsus[®] compared with Prograf[®]¹. The Committee for Medicinal Products for Human Use (CHMP) concluded that no new safety issues were associated with Envarsus[®]⁹.
- The company suggest that a once-daily dosing regimen may offer superior compliance over twice-daily dosing and reduce pill burden¹; however, the pill burden will depend on the combination of strengths required to achieve the optimum daily dose for individual patients and may not necessarily be reduced by a once-daily regimen.
- Clinical expert opinion sought by All Wales Therapeutic and Toxicology Centre (AWTTC) suggest that the once-daily modified preparation Advagraf[®] would be the most appropriate comparator for Envarsus[®]. The company have only provided clinical data for comparison with Prograf[®], the twice-daily standard release preparation. Prograf[®] has the highest market share in Wales based on prescription cost analysis^{1,10}.
- Subgroup post hoc analyses suggest that Envarsus[®] may have higher efficacy in black patients and in the elderly (> 65 years)¹. These analyses should be interpreted with caution as the studies were not powered to investigate efficacy in these subgroups. A randomised controlled study is ongoing to further investigate the pharmacokinetics of Envarsus[®] in stable black renal transplant patients¹¹.

- The improvement of tremor on switching from twice-daily tacrolimus to once-daily Envarsus[®] is postulated to be a result of less variability and lower peak serum concentrations of tacrolimus; it is possible that this benefit may extend to other AEs related to high peak serum levels⁸.
- Envarsus[®] does not contain gelatine and is therefore suitable for vegetarians and patients who avoid gelatine for religious reasons¹.

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence

The company have provided an annual cost per patient, comparison of Envarsus[®] with Prograf[®] based on an average daily dose of immediate-release tacrolimus 3 mg (twice-daily)¹².

Prograf[®] is available in different strengths and the cost varies depending on the strength used. The company have applied a weighting to each strength of Prograf[®] (based on prescribing data for 2013¹³) to calculate an average cost of £1.72 per milligram¹.

Envarsus[®] 4.25 mg (once-daily) was used in the cost comparison based on the recommended conversion from Prograf[®] to Envarsus[®] of 1:0.7 (mg:mg)². Envarsus[®] has a cost of £1.97 per milligram across all strengths^{1,14}.

Using the above figures, the company have calculated the average daily cost per patient to be £10.32 for Prograf[®] (3 mg twice-daily) and £8.37 for Envarsus[®] (4.25 mg once-daily)¹. This equates to an average annual cost per patient of £3,767 for Prograf[®] and £3,055 for Envarsus[®].

The company anticipate that the majority of patients started on Envarsus[®] to be *de novo* patients¹. In addition a proportion of patients currently taking twice-daily tacrolimus may be converted to Envarsus[®] if tolerability or treatment failure was an issue. It is assumed that patients currently treated with once-daily tacrolimus (Advagraf[®]) would only be converted to Envarsus[®] if they could not tolerate Advagraf[®]. In Wales in 2013-2014 there were 148 kidney transplants¹⁵, 90% of patients would be expected to be prescribed a tacrolimus product equating to approximately 133 *de novo* tacrolimus patients in Wales annually¹. The company estimate the total number of patients to be on Envarsus[®] (*de novo* and conversion patients) to be eight in year one increasing to 52 patients in year three. Using data from prescription cost analysis for Wales to estimate market share between the branded tacrolimus products the budget impact has been calculated as a cost saving of £4,750 in year one rising to a saving of £20,784 in year three¹.

3.1.1 AWTTTC critique

- To facilitate comparison of the cost of Envarsus[®] with Prograf[®], the price per mg of Prograf[®] was calculated using a weighting for each strength based on prescription cost analysis for Wales^{1,16}. This is subject to uncertainty because it doesn't include the prescriptions dispensed in hospital and includes prescriptions for heart transplants.
- The market share of branded tacrolimus products was estimated using data from prescription cost analysis for Wales, the predominant product being Prograf[®] with an 86.8% share. Clinical expert advice sought by AWTTTC suggests that current practice in Wales is to use Adoport[®] for all new patients, and to switch as many Prograf[®] patients to Adoport[®] as possible. Comparison against Adoport[®] was not included in budget impact.

3.2 Comparative unit costs

Table 1. Examples of costs for tacrolimus in kidney and liver transplant patients

Medicine	Example dose*	Example posology	Cost per mg tacrolimus [†]	Approximate annual cost
Tacrolimus immediate-release (Prograf [®])	3 mg twice-daily.	3 x 1 mg capsule twice-daily.	£1.72 [§]	£3,766.80
Tacrolimus immediate-release (Adoport [®])	3 mg twice-daily	3 x 1 mg capsule twice-daily.	£1.21	£2,649.90
Tacrolimus modified-release (Envarsus [®])	4.25 mg once-daily, (closest to 4.2 mg) [¶]	3 x 0.75 mg and 2 x 1 mg tablets once-daily	£1.97	£3,055.96
Tacrolimus modified-release (Advagraf [®])	6 mg once-daily	2 x 3 mg capsules once-daily	£1.34 [§]	£2,934.60

*Based on the average daily dose of immediate-release tacrolimus in kidney transplantation¹².
[†]Costs are based on Monthly Index of Medical Specialities (MIMS) prices as of March 2015¹⁴.
[§]Averaged cost per mg tacrolimus across all capsule strengths.
[¶]Dose converted as per Summary of Product Characteristics (SPC) 1:0.7 (mg:mg)². This table does not imply therapeutic equivalence of medicines or the stated doses. See relevant SPCs for full dosing details^{2,17-19}.

4.0 ADDITIONAL INFORMATION

4.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, tacrolimus (Envarsus[®]) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company do not anticipate that tacrolimus (Envarsus[®]) will be supplied by a home healthcare provider.

4.2 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

4.3 Evidence search

Date of evidence search: 06 March 2015.

Date range of evidence search: No date limits were applied to database searches.

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