CONSULTATION

PHARMAC
Pharmaceutical Management Agency

5 December 2012

Proposal for sole supply of tacrolimus

PHARMAC is seeking feedback on a proposal to:

- List Sandoz's brand of tacrolimus 0.5 mg, 1 mg and 5 mg capsules (Tacrolimus Sandoz) in Section B, and Part II of Section H, of the Pharmaceutical Schedule from 1 March 2013; and
- Award Sole Subsidised Supply Status (the only funded brand in the community) and Hospital Supply Status (the only available brand in DHB hospitals, subject to a 1% discretionary variance limit) to Tacrolimus Sandoz from 1 September 2013 to 31 August 2017;

through a provisional agreement with Sandoz Pty Ltd.

Further details of this proposal, including how to provide feedback and background information including proposed transition timelines and how brand switching would be managed, can be found below and on the following pages.

Feedback sought

PHARMAC welcomes feedback on this proposal. To provide feedback, please submit it in writing by **5 pm, Wednesday 19 December 2012** to:

Jackie Evans
Therapeutic Group Manager
PHARMAC
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Email: Jackie.evans@pharmac.govt.nz
Fax: 04 460 4995

All feedback received before the closing date will be considered by PHARMAC's Board (or Chief Executive acting under delegated authority) prior to making a decision on this proposal.

We are not able to treat any part of your feedback as confidential unless you specifically request that we do. If you would like us to withhold any commercially sensitive, confidential proprietary, or personal information included in your submission, please clearly state this in your submission and identify the relevant sections of your submission that you would like withheld.

Feedback we receive is subject to the Official Information Act 1982 (OIA) and we will consider any request to have information withheld in accordance with our obligations under the OIA.

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Details of the proposal

- From 1 March 2013, Sandoz's brand of tacrolimus capsules 0.5 mg, 1 mg and 5 mg (Tacrolimus Sandoz) would be listed in Section B, and Part II of Section H, of the Pharmaceutical Schedule at the following subsidies and prices (ex-manufacturer and excluding GST):

Chemical	Presentation	Brand	Pack size	Price and subsidy
Tacrolimus	Cap 0.5 mg	Tacrolimus Sandoz	100	$85.60
Tacrolimus	Cap 1 mg	Tacrolimus Sandoz	100	$171.20
Tacrolimus	Cap 5 mg	Tacrolimus Sandoz	50	$428.00

- From 1 September 2013, the incumbent brand of tacrolimus capsules 0.5 mg, 1 mg and 5 mg (Prograf, Janssen-Cilag (New Zealand) Ltd) would be delisted from Section B, and Part II of Section H, of the Pharmaceutical Schedule.

- Tacrolimus Sandoz would be the Sole Subsidised brand of tacrolimus capsules in the community and DHB hospitals from 1 September 2013 to 31 August 2017.

- Tacrolimus Sandoz capsules would be funded subject to the current Special Authority criteria, which limits its funding to patients who are organ transplant recipients.

Transition timelines

- For the avoidance of doubt the proposed implementation process and timelines would be as follows:

    - **1 March 2013** – listing of Sandoz's brand of tacrolimus capsules at the prices and subsidies specified above. There would be no change to the prices and subsidies of the currently funded Prograf brand of tacrolimus capsules.

    - **1 March 2013 to 31 August 2013** – two brands of tacrolimus capsules (Tacrolimus Sandoz and Prograf) would be listed fully funded. It is anticipated that this 6-month period would provide sufficient time for patients who had been receiving funded Prograf to be transitioned to the Tacrolimus Sandoz brand.

      We note that whilst Tacrolimus Sandoz is bioequivalent to Prograf, switching patients would require careful therapeutic monitoring by a transplant specialist (see 'Background' and "Managing the proposed brand switch' sections below for more information).

      During this time we would recommend that **doctors prescribe by brand**, and that **pharmacists check with prescribers where a prescription is not by brand**, to avoid inadvertent, unmonitored, brand switches occurring at the pharmacy level.

- **1 September 2013** – The Prograf brand of tacrolimus capsules 0.5 mg, 1 mg and 5 mg would be delisted from Section B, and Part II of Section H, of the Pharmaceutical Schedule.

- **1 September 2013 to 31 August 2017** – Tacrolimus Sandoz would be the sole subsidised brand of tacrolimus capsules in the community (Sole Subsidised Supply Status) and the only available brand in DHB hospitals, subject to a 1% discretionary variance limit (Hospital Supply Status).

Background

Tacrolimus is a treatment used following organ transplantation (including liver, kidney, pancreas, lung and heart transplants) to prevent and treat transplant rejection. Tacrolimus is a treatment with variable absorption when taken orally and it has a narrow therapeutic range, which means that patients on treatment require routine monitoring of their tacrolimus blood concentrations with associated dose adjustments if necessary.

Currently in New Zealand the Prograf (Janssen-Cilag) brand of tacrolimus capsules 0.5 mg, 1 mg and 5 mg are fully funded for use following organ transplantation. In November 2010, PHARMAC ran a competitive process (Request for Proposals (RFP) for the sole supply of tacrolimus capsules in hospitals and in the community.

Sandoz's proposal for its brand of tacrolimus capsules (Tacrolimus Sandoz) is the preferred bid received in the RFP. Tacrolimus Sandoz capsules 0.5 mg, 1 mg and 5 mg are marketed overseas and have been approved by Medsafe. Because tacrolimus is a drug with variable absorption and a narrow therapeutic index, in order to be approved by Medsafe Tacrolimus Sandoz had to demonstrate tighter bioequivalence margins than normally required for generic medicines. Tacrolimus Sandoz is considered therapeutically equivalent to Prograf in that it contains the same medicine, in the same amount and acts in the same way when compared to Prograf.

Managing the proposed brand switch

Because tacrolimus is a drug with variable absorption and a narrow therapeutic index, careful therapeutic drug level monitoring would be required for patients to switch brands. The exact tests, procedures and visits to be undertaken in order to switch brands safely may be different for different transplant populations and individual patients; therefore, brand switching would need to be managed by each patients' own transplant centre. Patients would be contacted by their own transplant co-ordinator for further advice.

Tacrolimus Sandoz is approved and sold in large markets overseas including the United States, Europe and Australia, and we understand that in these markets patients have been switched from Prograf to Tacrolimus Sandoz without problems.

The proposal to award sole supply and a potential brand switch for tacrolimus has been reviewed by PTAC, the Tender Medical Evaluation Committee and the Transplant Immunosuppressant Subcommittee of PTAC on a number of occasions. Most recently it was discussed at PTAC's Transplant Immunosuppressant Subcommittee's September 2012 meeting. In summary, the Subcommittee considered there was no clinical reason not to award a sole supply tender for tacrolimus, was supportive of the proposal to award sole supply to Tacrolimus Sandoz, and discussed measures to manage a brand switch from Prograf to Tacrolimus Sandoz. The relevant minutes from this meeting are attached below.

If this proposal is approved by the PHARMAC Board (or Chief Executive acting under delegated authority), PHARMAC will work with clinicians to manage the brand switch

including producing general brand switch guidelines and information for clinicians, pharmacists and patients which can be utilized and modified by each transplant centre as appropriate. During the proposed transition period, when both Prograf and Tacrolimus Sandoz would be fully funded, we would recommend that doctors prescribe by brand, and pharmacists check with prescribers where prescriptions are not by brand, to avoid inadvertent, unmonitored, brand switches occurring at the pharmacy level.

Transplant Immunosuppressant Subcommittee of PTAC minute September 2012

(please note that some portions of the Subcommittee's discussion relating to another unapproved brand of tacrolimus (for which a bid received in the RFP) have not been included below as they are not relevant to the proposal.)

Tacrolimus Brand Switch Guidelines

The Subcommittee noted a paper from PHARMAC staff regarding the outstanding 2010 Request for Proposals (RFP) for the sole supply of tacrolimus. Members noted that in May 2012 PHARMAC had written to all bidders amending the RFP parameters and that the RFP remained unresolved.

The Subcommittee noted that several suppliers had submitted dossiers for generic tacrolimus to Medsafe, however, during its review process Medsafe notified the suppliers that it would apply new EU guidelines for bioequivalence data for generic tacrolimus. Members noted that the new EU guidelines required narrower bioequivalence margins for tacrolimus, and other narrow therapeutic range drugs, of AUC(0-t) and Cmax 90% confidence intervals of 90.00 -111.11% (compared with standard bioequivalence margins of 80.00-125.00%).

The Subcommittee noted that to date only one generic tacrolimus had been approved, Tacrolimus Sandoz.

The Subcommittee noted that at its March 2010 meeting it had considered that there was no clinical reason not to award a sole supply tender for tacrolimus. However, because of pharmacokinetic variability, members considered that a brand switch for tacrolimus may require that patients undertake a clinic visit for therapeutic drug monitoring and potential dose adjustment and the Subcommittee had recommended that PTAC review bioequivalence data for relevant generic brand(s) of tacrolimus.

The Subcommittee noted that PTAC had reviewed the bioequivalence data for Tacrolimus Sandoz at its May 2010 meeting and PTAC concluded that it could be considered bioequivalent to Prograf. The Subcommittee noted, and agreed with PTACs view that inter-individual variability of blood concentrations occurs with tacrolimus, and that monitoring of patients would be important following a switch from Prograf to a generic product.

Overall, members considered that the bioequivalence data for Tacrolimus Sandoz was more robust. Members noted that Tacrolimus Sandoz was available overseas and several hospitals overseas had already switched their transplant patients from Prograf to Tacrolimus Sandoz with no known problems.

The Subcommittee noted that they were comfortable with the Tacrolimus Sandoz product and could see no clinical reason not to award a sole supply tender to Tacrolimus Sandoz. However, the Subcommittee considered that since such a move would be a cost containment exercise only, any decision regarding implementation of a brand switch for tacrolimus needed to balance the savings to be made with the costs of the additional resources required to switch patients safely.

The Subcommittee discussed the potential resource impacts of a brand switch for tacrolimus and appropriate transition timelines and guideline requirements.

The Subcommittee considered that there were pros and cons to both long and short transition periods. On balance, the Subcommittee **recommended** a transition period of 6 months. Members considered that this would result in the additional costs associated with resources, such as patient visits or testing needed in order to manage a switch safely, being absorbed into routine clinical practice. However, members acknowledged that a long transition period increased the risks of

inadvertent, unmonitored, switches occurring at the pharmacy level. Therefore, members **recommended** that patients, pharmacists and prescribers should be provided with information regarding the switch and during the transition period prescribers should prescribe by Brand.

The Subcommittee reviewed 'switching guidelines' from various overseas sources where a switch from Prograf to a generic tacrolimus had been implemented. Members noted that the level of detail differed between the various guidelines.

The Subcommittee noted that prior to any decisions being made on a brand switch PHARMAC would consult with transplant clinicians which would give sufficient notice of the timelines for any brand switch prior to it being implemented.

The Subcommittee **recommended** that PHARMAC develop high level 'brand switch' guidelines targeted at patients, clinicians prescribing tacrolimus and pharmacies dispensing tacrolimus. Members **recommended** that these guidelines include details of the brand switch, including timelines and photographs of the relevant products and that they clearly state that the switch must be managed by a transplant centre and that the patient should contact his/her transplant co-ordinator for more information.

The Subcommittee considered that in order to safely switch brands every transplant patient would need to have at least one visit to the transplant centre and would require a routine organ function assessment and three blood samples taken for tacrolimus trough concentration analysis. Members considered that this should be sufficient for most renal, liver and cardiac transplant recipients, however, paediatric patients and lung transplant recipients may require additional visits, tests to be performed and/or blood samples taken at the discretion of the transplant centre.

The Subcommittee considered that it was not appropriate for PHARMAC to provide detailed national switch guidelines/protocols. Members considered different transplant populations may need different tests, procedures and visits to be undertaken in order to switch brands safely. Therefore, members considered that it was appropriate that each transplant centre should develop its own switching protocols based on the patient populations it serviced and its assessment of the risks and resources required to switch patients safely. The Subcommittee considered that PHARMAC high level 'brand switch' guidelines would help these centres to develop more specific guidelines for appropriate for each patient population and centre.