CONSULTATION

PHARMAC
Pharmaceutical Management Agency

30 January 2014

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 May 2014; 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 November 2014 to 31 October 2018.

In summary, this proposal, if approved, would result in:

- The Prograf brand of tacrolimus capsules no longer being listed in the Pharmaceutical Schedule; instead the Tacrolimus Sandoz brand would be the only brand of tacrolimus capsules listed until at least 31 October 2018;
- PHARMAC continuing to fully fund the Prograf brand of tacrolimus capsules for the small number of existing intestinal transplant patients via the Named Patient Pharmaceutical Assessment (NPPA) policy; and
- Existing patients (other than intestinal transplant patients), switching from the Prograf brand to the Tacrolimus Sandoz brand in order to continue to receive fully funded tacrolimus capsules.

Feedback sought

PHARMAC welcomes feedback on this proposal. To provide feedback, please submit it in writing by 5 pm on **Friday, 14 February 2014** to:

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All feedback received before the closing date will be considered by PHARMAC's Board (or its delegate) prior to making a decision on this proposal.

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. Anyone providing feedback, whether on their own account or on behalf of an organisation, and whether in a personal or professional capacity, should be aware that the content of their feedback and their identity may need to be disclosed in response to an OIA request.

We are not able to treat any part of your feedback as confidential unless you specifically request that we do, and then only to the extent permissible under the OIA and other relevant laws and requirements. If you would like us to withhold any commercially sensitive, confidential proprietary, or personal information included in your submission, please clearly

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state this in your submission and identify the relevant sections of your submission that you would like it withheld. PHARMAC will give due consideration to any such request

Details of the proposal

- From 1 May 2014, 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 prices and subsidies (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 November 2014, the incumbent brand of tacrolimus capsules 0.5 mg, 1 mg and 5 mg (Prograf, Janssen-Cilag Pty 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 November 2014 to 31 October 2018.

- Tacrolimus Sandoz capsules would be listed subject to the current Special Authority criteria and HML restriction for tacrolimus capsules, which limit funding to patients who are organ transplant recipients.

- The Prograf brand of tacrolimus capsules would continue to be funded for the small number of exisiting intestinal transplant patients via the NPPA policy.

Transition timelines

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

    - **1 May 2014** – 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 listed Prograf brand of tacrolimus capsules.

    - **1 May 2014 – 31 October 2014** – two brands of tacrolimus capsules (Tacrolimus Sandoz and Prograf) would be listed, fully funded. During this time period existing intestinal transplant patients would automatically be issued with an EXCP number for funded Prograf via the NPPA Policy. It is anticipated that a 6-month period would provide sufficient time for all other patients who have 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 monitoring (see 'Background' and "Managing the proposed brand switch' sections below for more information).

      Should this proposal proceed, during the transition period 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 November 2014** – 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 November 2014 – 31 October 2018** – 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, heart, intestinal and bone marrow 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. There are also a small number of patients with other immune related conditions currently receiving Exceptional Circumstances/NPPA funded tacrolimus. 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 as bioequivalent to the current brand Prograf. 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. In addition, there is published data in transplant recipients demonstrating that Tacrolimus Sandoz is bioequivalent to Prograf.

Tacrolimus Sandoz is approved and sold in large markets overseas including the United States, Europe and Australia. We are not aware of any problems in these markets when patients have been intentionally switched from Prograf to Tacrolimus Sandoz and monitored appropriately.

PHARMAC previously consulted on this proposal in December 2012 (a copy of the consultation letter is available on PHARMAC's website via the following link: http://www.pharmac.govt.nz/2012/12/05/tacrolimus%20consultation.pdf). Some issues were raised in response to this consultation that required PHARMAC undertake further work on the proposal.

We are now re-consulting on the proposal and are keen to receive feedback on whether you consider the issues raised in the initial round of consultation have been addressed; see section 'Initial Consultation Feedback' below for details regarding changes made to the original proposal, or if there are any other issues we need to consider when making a decision on this proposal.

Managing the proposed brand switch

Tacrolimus is a drug with variable absorption and a narrow therapeutic index. PHARMAC is very aware 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 be managed by each patients' own transplant service. Patients would be contacted by their own transplant co-ordinator for further advice. A patient registry would be developed and managed by transplant clinicians to collect specific data on the brand switch.

Patients who currently have access to tacrolimus approved via the EC/NPPA policy for non-transplant indications would also need to have their brand switched to continue to receive fully funded tacrolimus. PHARMAC would directly communicate with the relevant clinicians and pharmacists involved in the care of these patients regarding the process for switching these patients.

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. 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 available in the initial consultation letter (see above link).

If this proposal is approved by the PHARMAC Board (or its delegate acting under delegated authority), PHARMAC would work with clinicians and transplant co-ordinators managing the brand switch; including by producing general brand switch guidelines and information for clinicians, pharmacists and patients which could be utilised and modified by each transplant service 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. Resources would also be developed to support primary and secondary care and reminders in prescribing and dispensing software utilised to address this risk.

Initial Consultation Feedback

Following our previous consultation on this proposal (5 December 2012) we received a number of responses. We appreciate all the feedback that we received and acknowledge the time people took to respond. All consultation responses have been considered in their entirety when reframing the proposal.

A summary of the key issues/questions raised in response to prior consultation and PHARMAC comments on these issues and actions taken when reconsidering this proposal are discussed in the table on the following pages:

Theme	PHARMAC Comment
Lack of data to support absorption of Tacrolimus Sandoz being equivalent to Prograf in patients who have received an intestinal transplant (2 to 3 patients in NZ).	Under the revised proposal existing intestinal transplant patients would continue to receive the Prograf brand of tacrolimus capsules via the NPPA Policy. We consider it reasonable for this specific, small, existing patient group to continue to have access to funded Prograf due to intestinal transplant-related absorption issues which may be different from the general transplant population. There would be direct communication with the clinicians and pharmacists involved in the care of this group regarding the process for ongoing funding for these patients.
Limited data for the use of Tacrolimus Sandoz in children.	PHARMAC is aware of international paediatric transplant services that have switched patients from Prograf capsules to generic tacrolimus capsules. PHARMAC staff would work closely with paediatric transplant services to assess the resources required to safely manage the proposed brand switch. Careful monitoring of all patients would be undertaken to ensure tacrolimus doses are adjusted appropriately. For children, this may involve more frequent blood tests for a period of time to check tacrolimus levels.
Ability to prepare Tacrolimus Sandoz into an oral suspension for patients unable to swallow capsules who are not able to be managed with opening capsules (primarily paediatrics). Compounding of tacrolimus requires protective equipment and is not possible in every pharmacy.	PHARMAC acknowledges that whilst there is information available regarding compounding of Prograf capsules, at the time we originally consulted there was no such information for Tacrolimus Sandoz. Stability information is now available for the preparation of tacrolimus 1mg/ml oral suspension with Tacrolimus Sandoz. As with Prograf, results from this testing indicate that a 30 day shelf life would be appropraite. The New Zealand standardised formulation batch sheet for tacrolimus would be updated by the Compounding Pharmacists Working Group to include Tacrolimus Sandoz. PHARMAC acknowledges the concerns expressed about needing protective equipment for compounding which are not available in every pharmacy; but notes that this is not a matter that relates to the brand which is funded, these concerns currently exist for Prograf. PHARMAC would however work with paediatric transplant services and pharmacists to determine what resources could alleviate this issue. PHARMAC notes that is an off-label use for both Prograf and Tacrolimus Sandoz.

Theme	PHARMAC Comment
Is it possible to open the capsules and mix with water for administration to patients unable to swallow capsules?	It is possible to open Tacrolimus Sandoz capsules and mix with water for whole doses (0.5mg increments) as is the current practice for some patients who are unable to swallow whole Prograf capsules. As tacrolimus is an immunosuppressant, precautionary measures are required to prevent unnecessary exposure to the person administering the medicine. PHARMAC notes that this is an off-label use for both Prograf and Tacrolimus Sandoz.
Continued access to the injectable formulation of tacrolimus	PHARMAC is not proposing any change to the listing of Prograf injection (5mg per mL, 1 ml ampoule. This would continue to be listed in Section H of the Pharmaceutical Schedule meaning hospitals would continue to be able to use it. PHARMAC notes it does not currently have a supply agreement for this formulation and this would not change under this proposal.
Has Tacrolimus Sandoz been tested for bioequivalence in transplant patients?	There is published data supporting the bioequivalence of Tacrolimus Sandoz and Prograf in 68 renal transplant recipients (Alloway et al. A randomized pharmacokinetic study of generic tacrolimus versus reference tacrolimus in kidney transplant recipients. American J of Transplantation 2012;12:2826-2831). Data from this study indicates that Tacrolimus Sandoz is bioequivalent to Prograf in transplant patients.
Will it be possible to obtain funded Prograf for patients that have genuine clinical difficultly with Tacrolimus Sandoz?	As with all medicines, PHARMAC is able to consider funding in exceptional circumstances and does so in accordance with its NPPA Policy. PHARMAC would be willing to assess NPPA applications for the funding of the Prograf brand of tacrolimus.
There will be additional costs to the DHBs in terms of clinic time, blood tests	Although this proposal would incur costs to DHB hospitals, even after setting these off against the drug cost, overall the proposal would result in large savings to DHBs . PHARMAC would work with transplant services to determine what additional resources would be needed to safely manage the proposed brand switch.
Request for further detail regarding proposed switch guidelines and close monitoring process. Request to review such guidelines prior to implementation.	PHARMAC staff would work closely with transplant services to develop and produce the resources required to safely manage the proposed brand switch. Guidelines and resources developed would be made available on the PHARMAC website and widely communicated with the transplant and primary care sector. PHARMAC would also support transplant services to develop their own detailed guidelines.

Theme	PHARMAC Comment
Access to contact details of transplant services for community pharmacies and GPs	Contact details for transplant services would be included with the switch guidelines and resources developed.
Community pharmacies having sufficient information regarding switching schedules for individual patients	PHARMAC would work with transplant services to develop switch guidelines and resources for primary care, including community pharmacies. These resources would include how to confirm details for a specific patient if necessary.
Risk of inadvertent switching between Prograf and Tacrolimus Sandoz during the 6-month transition period. Specific mention of concerns raised in other countries.	Switch guidelines and processes would be developed to help minimize this risk. PHARMAC notes that there has been international experience and concerns with switching tacrolimus products. However, these concerns were principally due inadvertent/unmonitored switching between multiple *formulations* (capsules to granules or extended release tablets) rather than switching between *brands* of the same formulation as is being proposed here.
Patients should be advised to return unused Prograf supplies to ensure they don't advertently switch between brands at home.	Noted. PHARMAC would incorporate this advice into switch guidelines and resources.
Prescribing systems, GP patient management systems, pharmacy dispensing systems etc require a temporary reminder/alert for the 6 month transition period when tacrolimus is selected either by brand or generic.	Noted. PHARMAC would take steps towards implementing reminders/alerts in the relevant software.