

Background on PHARMAC's decision to fund dabigatran

What was the rationale for PHARMAC's decision to fund dabigatran?

- Doctors have long sought an effective alternative to warfarin to treat patients needing anticoagulant therapy. Warfarin is a drug that is difficult to manage, requiring constant monitoring by health professionals and frequent painful blood tests for patients. Warfarin levels can be affected by what patients eat, or by other medicines. This can lead to under or overdosing of warfarin, which can lead to elevated risk of strokes or of bleeding.
- A significant proportion of patients needing anticoagulant treatment are currently being treated inadequately with aspirin because they are unable to tolerate or manage treatment with warfarin. This puts them at increased risk of strokes.

What process did PHARMAC follow in considering funding dabigatran?

- PHARMAC followed its usual process in considering dabigatran, which included cost-utility analyses, consideration by the clinical advisory committee PTAC and its Cardiovascular Subcommittee, negotiation with the supplier and public consultation prior to a decision being made.
- **June 2008** – Medsafe registers dabigatran for prevention of venous thromboembolism (VTE) in patients undergoing major orthopaedic surgery making it available for private sale and marketing in NZ.
- **September 2008** - PHARMAC receives first funding application for dabigatran, for prevention of VTE in patients undergoing major orthopaedic surgery.
- **November 2008** – PTAC [considers VTE funding application](#).
- **December 2009** – PHARMAC receives application to fund dabigatran for atrial fibrillation. PHARMAC defers referring to advisory committee until reviewed by Medsafe for this indication.
- **May 2010** – Boehringer Ingelheim re-applies for dabigatran funding in atrial fibrillation.
- **October 2010** – Dabigatran [considered by the Cardiovascular Subcommittee of PTAC](#).
- **November 2010** – [PTAC reviews dabigatran](#). Recommends funding with a low priority.
- **February 2011** – Medsafe approves dabigatran for use in New Zealand to treat atrial fibrillation making it available for private sale and marketing in NZ for this indication.
- **April 2011** – PHARMAC begins consultation on a proposal to fund dabigatran, following a commercial proposal from the supplier.
- **May 2011** – PHARMAC Board approves funding.
- **1 July 2011** – Dabigatran listed on the Pharmaceutical Schedule.

**Did PHARMAC's funding decision include a review of international trial data?
What did this show?**

- Yes. PHARMAC and its clinical advisory committees reviewed clinical trials involving dabigatran in VTE prophylaxis following orthopaedic surgery and atrial fibrillation (AF), involving a total of approx 26,000 patients worldwide.
- The trial data show dabigatran to be at least as effective as warfarin in reducing strokes in patients with AF. Dabigatran resulted in more gastrointestinal disturbances and gastrointestinal bleeding, but significantly lower rate of bleeding into the brain which is a feared side effect of warfarin.
- Dabigatran is not suitable for patients with severe kidney impairment.

Why has PHARMAC chosen not to restrict prescriber access to dabigatran?

- PHARMAC determines funding restrictions on medicines. Safety restrictions are decided by Medsafe. Medsafe has determined that the benefits of dabigatran outweigh the risks, and therefore it can be prescribed in New Zealand for certain indications. This means that, even without PHARMAC funding, dabigatran could have been prescribed by any doctor.
- PHARMAC's targeting mechanisms for medicines are used to ensure medicines are prescribed for the people most likely to benefit, to ensure medicines are used cost-effectively. With the commercial arrangements for dabigatran PHARMAC negotiated, there was no justification for restricting access to dabigatran.
- PHARMAC thinks carefully about when to apply funding restrictions to medicines. 70% of funded medicines, including warfarin do not have funding restrictions.
- Advice PHARMAC received was that a large proportion of the approximately 30,000 patients receiving warfarin therapy for atrial fibrillation are managed by general practitioners. Limiting dabigatran use to specialists would be unnecessarily prohibitive.

Was patient safety taken into consideration in PHARMAC's decision?

- Medsafe is the New Zealand agency with responsibility for ensuring medicines are safe, effective and of good quality. Medsafe's judgement is that the benefits of dabigatran outweigh the risks, so it is approved for use in New Zealand.
- All medicines have risks and that is why, in NZ, we have a strong regulatory framework around them. Health professionals who prescribe medicines take into account the known side-effects of a medicine before determining whether it is appropriate for a particular patient. Health professionals also review patients' medicine regimes to ensure the medicines work for the patient.
- PHARMAC has a legislative responsibility to promote the responsible use of medicines, and this includes taking steps to ensure medicines are used

appropriately in the community. For dabigatran, to improve patient safety we developed guidelines for the management of dabigatran around surgery and in the event of bleeding which were distributed widely before funding began on 1 July 2011. Also before funding began, an article highlighting relevant prescribing information was also distributed to general practitioners through the Best Practice Advocacy Centre (BPACnz).

Did PHARMAC take into account the benefits and risks of warfarin in thinking about funding dabigatran?

- Yes, dabigatran was compared to warfarin for AF in clinical trials and was considered the comparator in our analysis of cost-effectiveness of dabigatran.
- Warfarin has been the standard anticoagulant treatment for many years and its benefits and risks are well understood. Warfarin is a drug that is difficult to manage, requiring constant monitoring by health professionals and frequent painful blood tests for patients. Warfarin levels can be affected by what patients eat, or by other medicines. This can lead to under or overdosing of warfarin, which can lead to elevated risk of strokes. Where bleeding occurs, Vitamin K can be applied as an antidote but it can take several days for this to work, about as long as withdrawal of dabigatran can take. However, the risk of brain bleeds with warfarin remains, a risk that appears to be lower with dabigatran.

What advice did PHARMAC receive from its clinical advisors?

- PTAC considered that dabigatran was at least as effective as warfarin in AF. Patients who would benefit most are those not being adequately managed on warfarin and have been treated with aspirin instead.
- PTAC considered the difficulties with dabigatran therapy would be that it had no known direct reversal agent and its effects were not easily monitored.
- PTAC recommended that it be funded with low priority relative to its other funding recommendations. A factor in its priority recommendation was dabigatran's high cost.
- PTAC also considered it was appropriate for PHARMAC to list dabigatran without restriction by indication or prescriber as it enabled it to be funded at a much more cost-effective price. PTAC considered that educational support should be provided to prescribers when it is listed. PTAC recommended that PHARMAC consider delaying funding to allow educational programmes to be implemented for prescribers.

Did PHARMAC take the advice it received from clinical advisors?

- Yes. In terms of prescriber education, in consultation with haematologists and a surgeon, we prepared bleeding guidelines and guidelines for management of dabigatran around surgery which were distributed before listing. PHARMAC with input from a team of clinicians (cardiologists, stroke physicians, general physicians and GPs) prepared an article containing important prescriber information, and this was distributed to general practitioners before funding began through the Best Practice Journal.
- Consideration was given to delaying the funding of dabigatran by a few months, but in view of the positive feedback received from clinicians in consultation responses, the successful development of educational material for clinicians and the possibility of confusion in the sector if funding was delayed, a decision was made to progress with funding on 1 July 2011. By then, dabigatran had also been registered for AF in other countries, including the US, Australia and Japan.

What supporting information on dabigatran prescribing was provided for doctors?

- An expert group of haematologists, convened by PHARMAC, developed [bleeding and management of bleeding following surgery guidelines](#) for dabigatran which were distributed on 12 June. These guidelines were a first for New Zealand and have been used as the basis of similar guidance by Australian medical authorities.
- An article on dabigatran prescribing was prepared by PHARMAC and a group of clinicians including cardiologists, stroke physicians, general physicians and GPs. The article was distributed to GPs through BPAC's regular magazine ([Best Practice Journal June 2011](#)) and was also highlighted on the PHARMAC website.
- Alerts were sent to doctors through Royal New Zealand College of General Practitioners and the New Zealand Medical Association newsletters on necessary precautions (age, renal function and INR) in July 2011.
- After funding began, two further articles on dabigatran were published in the [September](#) and [October](#) 2011 editions of Best Practice Journal. These were written with the help of cardiologists, stroke physicians, general physicians, GPs, and haematologists.

Is PHARMAC planning further reviews of dabigatran?

- As with all medicines listed on the Pharmaceutical Schedule, we remain alert to emerging evidence and will refer any new information in relation to dabigatran to our clinical committees for advice.
- We are working closely with Medsafe and CARM on monitoring dabigatran's usage and adverse effects reporting. As is our usual practice, we are forwarding

any reports of adverse events to CARM as this is the appropriate mechanism for tracking medicine events in New Zealand.