



PHARMAC responds to Stewart Mann on dihydropyridine calcium channel antagonists

Associate Professor Stewart Mann recently described changes in PHARMAC's funding of dihydropyridine calcium channel antagonists (DHP CCBs) and resultant changes for patients over the past 5–10 years (<http://www.nzma.org.nz/journal/118-1218/1569/>). We found the article to be a good summary of a complex issue.

We make the following observations:

PHARMAC's processes

PHARMAC's legislative objective is "to secure for eligible people in need of pharmaceuticals, the best health outcomes that are reasonably achievable from pharmaceutical treatment and from within the amount of funding provided."¹ Two of the ways in which PHARMAC achieves this is by reference pricing and by negotiating sole supply contracts with pharmaceutical suppliers. When managed appropriately,² these strategies free up funding to invest in other unsubsidised medicines, gaining additional clinical benefit elsewhere.

Reference pricing and sole supply occurs only where it is clear that a loss of choice between one equivalent brand of drug and another is not considered critical. PHARMAC bases such decisions on available clinical evidence; it is not part of PHARMAC's Operating Policies and Procedures² to conduct compliance and/or bio-equivalency testing. Before a medicine can be marketed in New Zealand it must first meet the necessary standards set by the Ministry of Health. As part of the registration process, the New Zealand Medicines and Medical Devices Safety Authority (Medsafe) requires safety and compliance testing of all medicines.

With every reference pricing initiative, PHARMAC seeks independent expert clinical advice from PTAC,³ and consults (and is required to consult) with relevant clinical and patient groups⁴⁻⁶ to ensure it has all the information before making a decision. PHARMAC is always looking to improve its processes, and although for practical reasons we may not have replied individually to each consultation response we received, every response is (and was) provided to and considered by PHARMAC's Board before a decision is made. This is an obligation that the PHARMAC Board takes extremely seriously.

Reference pricing

Reference pricing is a commonly used strategy to control the cost of multiple drugs within a drug class, and in New Zealand is based upon the principle that reimbursement is set at the price of the least expensive member(s) of a drug class. Reference pricing happens in a number of countries including Germany, Canada, The Netherlands, France, Japan, Sweden, and Australia,^{7,8} and has been used in New Zealand since PHARMAC's inception in 1993.

There is limited evidence on the impact of reference pricing of DHP CCBs on health outcomes:

- PHARMAC did commission an independent follow up evaluation of the DHP CCB reference pricing in 1999,⁹ analysing data from the 1–2 consultations per patient funded by PHARMAC for GPs to monitor changes in blood pressure. This analysis provided some evidence that there were no clinically significant changes in blood pressure following the switch, although there were limitations with the data.*
- We are aware of one other example where outcomes data are available following the reference pricing of DHP CCBs. In British Columbia (Canada) there was no associated increase in rates of physician visits, hospitalisations, and long-term care admissions¹⁰—as also occurred with ACE inhibitor reference pricing.¹¹

The putative lack of any significant observable impact on blood pressure control in New Zealand may of course have been more short-term due to increased awareness and medical monitoring (Hawthorne effect) than the change to the newly subsidised DHPs themselves, and there was no evidence that such improvements would be maintained long-term with just routine management of blood pressure. Nevertheless, there was no evidence that changing to the newly subsidised DHPs caused deterioration across users, at least short term in the context of more intensive dedicated monitoring.

Although the British Columbian data are less than ideal, they are possibly the best available under the circumstances.†

As noted by Associate Professor Mann, PHARMAC put in place Special Authority provisions to allow fully funded access to alternative DHP CCBs based on advice from PTAC's Cardiovascular Subcommittee and the Cardiac Society.

While we acknowledge arguments around patient inconvenience and resistance to change, these must be considered against the alternative—that when funds are constrained, tradeoffs must be made, so that patients elsewhere in the health sector are less likely to have to pay for their own treatment, or simply miss out.

Bioequivalence

It is important to note that Adalat CC (coat core) was assessed and approved by Medsafe, the Medicines Regulator, as a new medicine on the basis of clinical trial and other data supplied by the sponsor of the product in New Zealand. Medsafe has advised PHARMAC that it did not consider Adalat CC to be either bioequivalent to, or interchangeable with, Adalat Oros (Medsafe, personal communication).

When it was considering a submission by the supplier (separate to the application for Medsafe registration), the Cardiovascular Subcommittee of PTAC noted that several pharmacokinetic parameters of the CC product differed from those seen for Adalat Oros. The subcommittee also raised questions about whether these differences would impact on patient well being if patients were changed from other formulations of Adalat to the CC formulation. The subcommittee took advice on this issue from both the Cardiac Society and Associate Professor Richard Robson (who is the current Chair of Medsafe's Medicines Assessment Advisory Committee (MAAC)) before making a recommendation on funding within this therapeutic group.

The Cardiovascular Subcommittee also took into account several other factors including dropout rates and adverse effects in the CC groups versus the Oros groups, the overall blood pressure control in the Glasser et al study,^{13,14} and also the fact that the CC preparation was unlikely to gain registration in New Zealand for the angina indication.

Medsafe advises that Adalat CC and Adalat Oros utilise distinct dose release systems and are designed to have different release characteristics. This is not the case for Felo and Plendil, where both were designed to be taken once daily and were amenable to standard bioequivalence testing. While MAAC's Generic Subcommittee (GSC) did note and discuss differences in the bioequivalence studies conducted to demonstrate that Felo and Plendil were bioequivalent, these issues were resolved as more data were provided. Medsafe is of the opinion that it is inappropriate to link the issues of the differences in pharmacokinetics between Adalat CC and Adalat Oros with those noted and discussed by the GSC with respect to Felo and Plendil (Medsafe, personal communication¹²).

Generic changes

Generic substitution of brands of the same active ingredient (such as Felo ER for Plendil ER) is a very regular occurrence internationally, with it being common place in countries such as Hungary, Canada, Italy, Germany, the United Kingdom and Australia. Furthermore, in many of these countries the patient is potentially switched (again and again) every time they go back to the pharmacy. Some countries, for example Denmark, have mandatory substitution at pharmacy level. This is accepted in those countries because of the regulatory requirement that bioequivalence is to be shown before a generic can be marketed.

The regulatory requirements in New Zealand are no different—bioequivalence must be demonstrated. As well, the guidelines for showing equivalence used in New Zealand are based on the guidelines used internationally.¹⁵ Generic medicines are also required to meet the same quality and manufacturing standards as all manufacturers of branded medicines; this makes it difficult to compare them to used cars.

Comment

It is not uncommon for a greater than usual number of people to report adverse events when reference pricing, or a brand change through the tender, occurs. We understand from Medsafe that usually there is a “spike” in reports to Medsafe's Medicines Adverse Reactions Committee (MARC), which then quickly returns to a normal level. It is difficult to ascertain the exact reason for this phenomenon, or indeed how many additional patients are able to take the ‘new’ medicine when they were unable to tolerate the previously subsidised one. The same “spike” can occur when there is no change to a drug other than the name—for example as occurred with simvastatin's brand name changing from ‘Zocor®’ to ‘Lipex®’ (Medsafe, personal communication¹⁶).

Reference pricing and generic substitution are methods that are accepted in many countries as a clinically acceptable way of managing pharmaceutical expenditure. PHARMAC is careful to consult with interested parties and take clinical advice before undertaking reference pricing, and hopes to maintain a constructive line of communication with the medical community. To deem these processes “experiments”

is comparable to calling every prescription a doctor writes an experiment, as none of us know with absolute certainty how a particular patient is going to react to a particular drug. Provided we are all aware of the risks and benefits generally associated with a particular treatment as they are highlighted in clinical studies, we can manage changes in medication both from a funding and clinical perspective.

Remember too that all on-patent medicines are sole supply. PHARMAC considers that tendering for off-patent medicines is an effective way to secure the supply of pharmaceutical agents and to achieve lower prices for generic medicines. Reference pricing frees up funding from the pharmaceutical budget that can then be reinvested into other priority areas. In this sense, reference pricing has a positive effect on health outcomes, as it allows PHARMAC to invest in new medicines that either extend or improve the quality of life that otherwise would not happen.

Footnotes:

*The analysis was careful to caveat that evaluators had no control over experimental design or data collection, and that the reliability and the validity of the raw data (which had not been collected in a controlled research environment) could not be assessed – particularly the accuracy of the blood pressure recordings. It was stated that deficiencies in claim form design, lack of standardised protocols for blood pressure measurement, and some inconsistencies in interpretation of claim form items meant that these results must be reported cautiously.

†To clearly determine whether there were excessive risks from switching associated with reference pricing would require a very large randomised controlled trial (to control for confounding and other bias), for what is likely to be small difference between the drugs. Such studies would be unlikely to be feasible/affordable, particularly in New Zealand. Otherwise there are ongoing issues of comparability (differences in measurement, different patient populations, selection bias, measurement bias etc.). The only alternative would be to allow the original supplier's patented monopoly to remain in perpetuity.

Conflict of interest: Scott Metcalfe is externally contracted to work with PHARMAC for public health advice. Andrew Davies, Wayne McNee and Peter Moodie declare no conflicts.

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References:

1. New Zealand Public Health and Disability Act 2000, Section 47 Objectives of Pharmac.
2. PHARMAC. Operating policies and procedures of the Pharmaceutical Management Agency ("PHARMAC"), 2nd edition. January 2001. Available online. URL: <http://www.pharmac.govt.nz/pdf/opps.pdf> Accessed August 2005.
3. <http://www.pharmac.govt.nz/ptac.asp> Accessed August 2005.
4. New Zealand Public Health and Disability Act 2000, Section 49 Pharmac to consult in implementing objectives and carrying out functions. Available online. URL: http://www.legislation.govt.nz/browse_vw.asp?content-set=pal_statutes Accessed August 2005.
5. PHARMAC. Operating policies and procedures of the Pharmaceutical Management Agency ("PHARMAC"), 2nd edition. January 2001. Available online. URL: <http://www.pharmac.govt.nz/pdf/opps.pdf> Section 4.2 Consultation. Accessed August 2005.
6. PHARMAC. Operating policies and procedures of the Pharmaceutical Management Agency ("PHARMAC"), 2nd edition. January 2001. <http://www.pharmac.govt.nz/pdf/opps.pdf> Section 3.3.3 "PHARMAC will carry out appropriate consultation on the classification of pharmaceuticals into therapeutic sub-groups and its application of reference pricing in respect of a particular sub-group." Accessed August 2005.
7. Ioannides-Demos LL, Ibrahim JE, McNeil JJ. Reference-based pricing schemes: effect on pharmaceutical expenditure, resource utilisation and health outcomes. *Pharmacoeconomics*. 2002;20:577-91.
8. Curt Furberg, personal communication, 2005.
9. Gribben B. Analysis of DHP CCB Claim Forms. RNZCGP Research Unit, University of Auckland; 1999.
10. Schneeweiss S, Soumerai SB, Maclure M, et al. Clinical and economic consequences of reference pricing for dihydropyridine calcium channel blockers. *Clin Pharmacol Ther*. 2003;74:388-400.
11. Schneeweiss S, Walker AM, Glynn RJ, et al. Outcomes of reference pricing for angiotensin-converting-enzyme inhibitors. *N Engl J Med*. 2002;346:822-9. Available online. URL: <http://content.nejm.org/cgi/reprint/346/11/822.pdf> Accessed August 2005.
12. Medsafe email to PHARMAC, 1 August 2005.
13. Glasser SP, Jain A, Allenby KS, et al. The efficacy and safety of once-daily nifedipine: the coat-core formulation compared with the gastrointestinal therapeutic system formulation in patients with mild-to-moderate diastolic hypertension. Nifedipine Study Group. *Clin Ther*. 1995;17:12-29.
14. Glasser SP, Ripa SR, Allenby KS, et al. The efficacy and safety of once-daily nifedipine administered without food: the coat-core formulation compared with the gastrointestinal therapeutic system formulation in patients with mild-to-moderate hypertension. Nifedipine Study Group. *Clin Ther*. 1995;17:296-312.
15. MedSafe. Guidance notes for applicants for consent to distribute new and changed medicines and related products, October 2001. Section 6.9 Technical Guidelines to be followed. Available online. URL: <http://www.medsafe.govt.nz/reg.htm> Accessed August 2005.
16. Stewart Jessamine (Medsafe), 5 August 2005