



PHARMAC and statins—correction is needed

Last year Dr. Chris Ellis and Professor Harvey White discussed past aspects of PHARMAC's operations relating to the provision of statins to improve cardiovascular risk.¹ We made a brief response at the time (<http://www.nzma.org.nz/journal/119-1238/2092/>),² and we are now providing additional information.

While welcoming different perspectives, a number of comments were made that PHARMAC considers to be factually incorrect. Our main focus is to correct these misperceptions, which we do in Table 1 (below). It is important that PHARMAC does this—not just in terms of responding to criticism, but because of the important role of statins in the management of cardiovascular disease in New Zealand.

Evidence underpinning our views is on public record in the Journal—both for statins²⁻⁴ and wider.⁵⁻²⁴ Previous access restrictions for statins related to their prohibitive prices; simvastatin is now 1/20th the price of what it was 13 years ago. There is a continual need to balance priorities in order to maximise health gain across the population.

PHARMAC welcomes close scrutiny of its decisions and constructive suggestions for improvement. Ongoing improvement in processes and system—as for all organisations—is critical to best practice and keeping well-prepared for future challenges. PHARMAC's recent consultations on its cost-utility analysis framework²⁵ and how best to fund high cost medicines (<http://www.pharmac.govt.nz/highcostmeds.asp>) are examples of valuable opportunities to contribute. The Government's medicines strategy work ([http://www.moh.govt.nz/moh.nsf/pagesmh/5633/\\$File/towards-newzealand-medicines-strategy-consult.pdf](http://www.moh.govt.nz/moh.nsf/pagesmh/5633/$File/towards-newzealand-medicines-strategy-consult.pdf)) is also an opportunity to look at potential improvements across the whole medicines system—from research and registration, through to whether medicines are optimally used, and important parts in-between like PHARMAC's role and prescribing decisions.

We believe that PHARMAC's approach for the funding of statins has, over time, successfully targeted access to give long-term health gains. While readers will draw their own conclusions,¹⁻⁵ PHARMAC is satisfied that its work has been careful and, in our view, robust, mindful of responsibilities to all patient groups across the population—as with all medicines.

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Table 1. Specific claims with PHARMAC responses

Topic/claim	PHARMAC response	Comment
Population coverage of statins	NZ's statin usage is comparable internationally and now equals Australia's, at 1/3rd the cost	<p>Material on the British Medical Journal website (http://bmj.bmjournals.com/cgi/eletters/328/7436/385#52963) shows the use of statins has been comparable to other countries.</p> <p>New Zealand's per-capita use of statins is now the same as that of Australia²—despite the per-capita nominal costs in New Zealand being 1/3rd that of Australia (Australia spent AUS\$886 million on statins in 2005).²⁶</p>
Patient access to atorvastatin is less than for simvastatin	<p>The known differences in potency between simvastatin and atorvastatin are probably overstated</p> <p>Access to simvastatin is now unrestricted, and atorvastatin remains available as a second-line agent</p> <p>A recent British Medical Journal editorial²⁷ advocates reference pricing atorvastatin to generic simvastatin in the United Kingdom, as happens in Germany</p>	<p>The authors cite an incomplete published meta-analysis (Law et al BMJ 2003²⁸) that did not include head-to-head trials. Up to April 2004, we had identified 20 additional published head-to-head randomised parallel group or cross-over studies directly comparing simvastatin and atorvastatin for LDL-C lowering, with 8,855 patients. Overall it seems that simvastatin is around 80% as potent at reducing LDL-C as atorvastatin at lower nominal daily doses (10–40mg) and 90% as potent at 80mg/day.</p> <p>These differences are less than those indicated by Law meta-analysis,²⁸ which was of largely less-comparable non-head-to-head studies. The Law meta-analysis also did not include studies published after 2001—e.g. STELLAR,²⁹ Karalis et al 2002³⁰—and only two of the 164 studies it used directly compared atorvastatin and simvastatin in the same group of patients (with 290 patients studied).^{31,32}</p> <p>The Pharmacology and Therapeutics Committee (PTAC) has previously noted that measures such as LDL-cholesterol reduction (the commonest way to compare between statins) are ultimately surrogate markers, not clinically relevant outcomes. There is no head-to-head dose-equivalent outcomes evidence comparing atorvastatin with simvastatin, and hence no firm basis for stating that either is better than the other. In terms of surrogate markers, simvastatin appears to be more effective than atorvastatin for other important surrogate measures such as raising HDL-C.^{33,34}</p> <p>PTAC in February 2006 reviewed the evidence for the current dose equivalence between atorvastatin and simvastatin, and considered that 1:2 dose equivalence provides a rough guide, and that in clinical practice the dose of any statin should be adjusted according to the individual patient's response [in light of absolute cardiovascular risk].</p>
Cholesterol target levels	The New Zealand recommendations seem reasonable	<p>PTAC in February 2006 noted the focus on greater reductions in LDL cholesterol. It noted that LDL targets have been progressively lowered, and also that by increasing doses to lower LDL levels the risk of side-effects also increased, and that this can occur with limited additional clinical gains. PTAC recommended that the target LDL levels remain unchanged, but noted that it may reassess them if the New Zealand Guidelines Group (NZGG) recommended changes to target LDL levels.</p> <p>A recent paper in the BMJ³⁵ (http://bmj.bmjournals.com/cgi/content/full/332/7555/1419) suggests that adopting the approach recommended by the</p>

		<p>NZGG's cardiovascular guidelines³⁶ may be highly efficient. Modelling the theoretical impacts of various international guidelines on the Canadian population, the researchers estimated that the New Zealand guideline was the most efficient of all the guidelines, potentially avoiding nearly as many deaths as predicted by applying the Australian and British guidelines while recommending treatment to the fewest number of people (12.9% of people v 17.3% with the Australian and British guidelines)—important when treating some patients unnecessarily means not funding other health priorities.</p> <p>If their 'optional' recommendations are included, the use of the US guidelines' recommendations would mean treating about twice as many people as the New Zealand guidelines (24.5% of the population, an additional 1.4 million people) with almost no increase in the number of deaths avoided.</p>
<p>PHARMAC responsiveness to new evidence, as exemplified by issues around statin switching in 1997.</p>	<p>Access was extended to more patients, using a satisfactory if not the best statin. PHARMAC has already acknowledged that in hindsight the implementation process was imperfect.³⁷</p> <p>PHARMAC subsequently fully funded simvastatin for patients who met defined criteria by January 1998, and atorvastatin later that year.</p> <p>There is a continuum of belief for class effects between evidence from a single clinical trial and mortality-based studies at doses used in clinical trials in similar populations.³⁸</p> <p>There has been no good evidence of any harm that resulted from the switch from simvastatin to fluvastatin, and nor of increased mortality as a result of the application of reference pricing.</p>	<p>In 1997, PHARMAC widened access to statins by subsidising fluvastatin and reference pricing all available statins to it. This meant for the 12,000 existing patients either a change in medicine or an additional surcharge, but it also offered access for some 112,500 new patients. PHARMAC had to consider how fluvastatin compared to simvastatin and the possible risks of reference pricing.</p> <p>Fluvastatin did have limited outcome data^{39,40} although no significant mortality data. The lipid-lowering effect of fluvastatin was expected to be 85% that of simvastatin's at equipotent doses,⁴¹ which needed to be weighed against the potential to give benefit to many more patients within available resources.⁴²</p> <p>There has been no good evidence of any harm that resulted from the switch from simvastatin to fluvastatin, and nor of increased mortality as a result of the application of reference pricing. The Dunedin paper was criticised internationally⁴⁴⁻⁴⁶ for the following limitations:</p> <ol style="list-style-type: none"> 1. Comparable mortality data were not collected—patients treated on simvastatin before the switch would have had to survive to remain in the cohort, and since no such restriction occurred after switching to fluvastatin, deaths after the switch logically should have been excluded. 2. Because it was an uncontrolled before-and-after study, potential bias was introduced by the unmasking of clinicians who admitted and then assessed patients, and of the evaluators who extracted and assessed the data. 3. The data before the switch were obtained from the hospital computer system (not fully reliable), whereas the data after the switch appeared to have been collected systematically and with care. 4. The analysis tabulated but failed to comment on a key possible reason behind the reported increase in cholesterol concentrations—being the possible subtherapeutic dosing of patients with the substituted drug (fluvastatin).^{46,47}

		Both the New Zealand and Canadian experience has suggested that switching of other cardiovascular medicines such as DHP CCBs and ACE inhibitors—associated with reference pricing policies—has not been associated with clear evidence of worsening population health outcomes. ⁴⁸⁻⁵⁰ We are not aware of any similar population-based observational analyses for statins. We do acknowledge here the known biases with such analyses, which need to be interpreted in light of their methodological limitations versus the costs and availability of more robust evidence.
Atorvastatin 2004—PHARMAC response to consultation concerns over proposed switch to simvastatin for patients using 40mg atorvastatin	PHARMAC takes consultation seriously. The supplier would have withdrawn for other reasons.	It is not clear to PHARMAC that there is any causative link between pharmaceutical sales in a country and the commercial evaluation of where to locate research programmes.
Safety of the 80mg simvastatin dose	PTAC considers that statin adverse effects are a class effect	PTAC's February 2006 meeting examined claims by the supplier that the safety of high-dose atorvastatin was superior to that of high dose simvastatin. PTAC noted that the risk of adverse effects were dose-related, and considered that risk factors (dose and potency) were the important issue and that the increase in adverse effects with increased doses was a class effect and could occur with an increase in dose of any statin. PTAC also considered the use of atorvastatin 80 mg, and noted that in comparison to moderate doses or 80mg simvastatin, treatment with atorvastatin 80 mg results in a small additional decrease in LDL cholesterol but may be associated with the potential for an increase in the risk of adverse effects. Members considered that if atorvastatin 80 mg was listed in the Pharmaceutical Schedule there would be a risk that patients would begin atorvastatin at the 80 mg daily dose.
Need to protect patients	This argument goes both ways	The authors cite Begg et al ⁵¹ on the need to advocate for patients. PHARMAC's response at the time (http://www.nzma.org.nz/journal/116-1170/361/) ³ was that patients' needs extend beyond individuals presenting in limited clinical settings, and the need for a population approach. Historically, patients at highest overall cardiovascular risk have tended not to receive statin treatment, particularly Māori and Pacific men. That is why PHARMAC is working with DHBs and communities with its One Heart Many Lives programme attempting to redress this. It is PHARMAC's role to represent the public interest. PHARMAC's staff are very mindful of their responsibilities to all patients across all disease and disability groups—to achieve the best health gains for the New Zealand population within the funding available.

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