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Response from PHARMAC: difficult choices

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We appreciate being given the opportunity to respond to the viewpoint offered by Professor Begg and colleagues.[1] Our perspectives differ, but we do agree on the desirability of open and vigorous debate.

PHARMAC is a Crown entity reporting to the Minister of Health and Parliament, and is responsible for subsidising most prescription medicines sold in New Zealand. It would be hard to imagine a different structure. The model is similar to that used by many other developed countries, including Australia, the United Kingdom, France and Sweden. Other countries that use reference pricing in various forms include Australia, Canada, Germany, Spain, Norway, and Belgium.

PHARMAC's focus must be on health gain and costs versus savings to the health sector as a whole, as we have pointed out elsewhere in this issue of the Journal.[2] We have to be concerned with "opportunity cost", which we define as the health gains that are lost if scarce health funds are spent (squandered?) on less worthwhile services. It is for that reason PHARMAC relies so heavily on its decision criteria and assesses cost effectiveness.

At the time of the decision in 1997 to reference price HMG-CoA inhibitors (statins), PHARMAC was faced with the dilemma that there were fewer than 50 000 patients* eligible in New Zealand for statins (with an uptake of about 12 000), although the National Heart Foundation (NHF) guidelines recommended access to about 186 000. If PHARMAC had widened access to statins at the then price of simvastatin, total spending on statins could have reached nearly $200 million each year. This would have represented 40% of all community pharmaceutical spending and would have meant not funding all the significant new investments PHARMAC has made in other (non-statin) areas and more.[3]

In 1997, the opportunity arose for PHARMAC to widen access by subsidising fluvastatin and reference pricing all available statins to it. For the 12 000 existing patients this meant either a change in medicine or an additional surcharge, but it also offered access for some 112 500 new patients.† When considering this, PHARMAC had to ask how fluvastatin compared to simvastatin, and what the possible risks of reference pricing were. It was recognised that fluvastatin was a drug that had some outcome data[4,5] although no significant mortality data. Although it was acknowledged that the lipid-lowering effect of fluvastatin might not have been equivalent to simvastatin[6] (35% low-density lipoprotein (LDL) reduction with fluvastatin 80 mg/day versus 41% for simvastatin 40 mg/day),[7] the potential to give benefit to many more patients was compelling.

There has been no good evidence of any harm that resulted from the switch from simvastatin to fluvastatin, and certainly no evidence of increased mortality as a result of the application of reference pricing. Although Begg et al quote the observational analysis by Thomas and Mann, who reviewed data in Dunedin,[8] that paper was well

criticised internationally.[9–11] 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. 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. Additionally, 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. In addition, that analysis tabulated but failed to comment on a key possible reason behind the reported increase in cholesterol concentrations: the possible subtherapeutic dosing of patients with the substituted drug (fluvastatin).[11,12]

At the time of the 1997 decision to reference price, the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) had commented that there was then little evidence for or against a statin class effect.[7] However, CCOHTA considered that since cholesterol reduction had been associated with a reduction in coronary events, it could legitimately be assumed, until proven otherwise, that because all statins decreased LDL levels and increased high-density lipoprotein (HDL), all would produce a decrease in coronary events. This statement came with the caution that lipid level was a surrogate outcome, and that surrogate outcomes should be regarded in light of their limitations. CCOHTA concluded that there was no clear evidence that one approach was better than the other.

For class effects, it has been commented that there exists in evidence-based medicine a continuum between those who are prepared to assert a class effect after a single clinical trial and others who believe that drug use must be restricted to only those drugs proven in mortality-based studies and at doses used in clinical trials and for similar populations. Where one stands on this continuum is probably a matter of individual clinical judgment. However, it seems sensible that if three or more compounds are beneficial in clinical studies, have very similar pharmacological characteristics, and have similar multiple surrogate endpoint data, a class effect may well exist for other drugs that show similar properties across the range of surrogate endpoints. A balance has to be struck between the requirement for absolute proof for each compound in mortality studies ("at substantial ethical cost")[13] and the inhibition of innovation by a different form of monopolistic marketing lock-in. Multiple drug options stimulate price competition, can reduce healthcare costs and increase access for patients to possibly superior compounds before absolute proof of their efficacy becomes available. "Evidence-based medicine is a difficult concept to practise and each physician needs to think carefully about how they stand on the issue with each drug."[13]

PHARMAC has accepted that the implementation of reference pricing of statins did not go perfectly.[14] PHARMAC subsequently fully funded simvastatin for patients who met defined criteria by January 1998, and atorvastatin later that year. However, fluvastatin is still widely used around the world, and randomised evidence has shown that it too can produce health outcomes equivalent to other statins in terms of one-year cardiac events in hyperlipidaemic patients with symptomatic coronary heart disease (CHD).[4] Subsequent publication of FLARE concluded fluvastatin treatment in patients with average cholesterol levels undergoing their first successful percutaneous

coronary interventions significantly reduces the risk of major adverse cardiac events.[15]

Begg et al have not criticised the seemingly inappropriate very high ongoing uptake of atorvastatin, despite what they say is lack of clinical evidence of superiority (along with fluvastatin) over simvastatin. If atorvastatin does not have the hard clinical outcomes evidence then, to be consistent, simvastatin and pravastatin should have been used ahead of atorvastatin too.

What price should we all pay for atorvastatin, when simvastatin is largely as effective at reducing LDL/HDL ratios for the few patients needing very high doses?[16,17] Recent HealthPAC data (for October 2002) indicate there are some 46 417 patients using atorvastatin at a nominal cost of $23.1 million each year (excluding rebates). Simvastatin at equivalent doses would cost some $17.8 million. Special authority data have shown that less than 1% of patients with pre-existing CHD had total cholesterol levels of 10 mmol/l and over – maybe 1600 patients.[‡] In fact, 20% of atorvastatin patients are currently using very high doses at greater than 40 mg/day – some 9202 patients. (Further details can be found at http://www.pharmac.govt.nz/pdf/AppendixToDifficultChoices.pdf)

Simplistically, even at high doses of atorvastatin for patients at highest risk (here, patients with total cholesterol >7.5 mmol/l with pre-existing CHD), we would need to treat perhaps 49 patients with atorvastatin for five years to prevent one more CHD event than if we were to use simvastatin, for what is a much more expensive agent. At $52 100 per quality-adjusted year of life (QALY) gained[§] this compares poorly with other options. Arguably, resources have been ostensibly squandered through patients using atorvastatin when simvastatin was both as effective and was cheaper at equivalent doses.

PHARMAC was able to remove special authority requirements (hence widen access) in April 2002 because of a favourable price agreed with Merck Sharp and Dohme (making simvastatin much more cost effective)[18] – not in response to "considerable external pressure". Access increased to potentially around 300 000 people, up from 180 000. This compares with the fewer than 50 000 people eligible for statin treatment before the 1997 changes, potentially "saving" in just three months to June 2002 an estimated 37 extra "statistical lives" and freeing up a nominal $531 000[¦] to the health sector.[2] Statins have not always been favourably priced, which was the main contributor to the "delays" in widening access criteria.[3]

It is tempting to advocate solely for the patient sitting in front of you and not for others. We think this approach is unacceptable when resources are limited and we have to make choices. If prescribing overly expensive treatments leads to other patients missing out altogether, then we have to reconsider the ethical issues. Under these circumstances, we stand firmly by the comments made by the Chairman of PTAC (Dr John Hedley), and note that the Medical Council of New Zealand's position includes principle 6 that "Doctors must not waste money allocated to health care or misuse resources that are at their command."[19]

For PHARMAC, the patient is not just the individual person with disease or disability. It is the whole New Zealand population that may benefit from pharmaceutical treatment. Different "patients", but the same duty of care met in different ways. What happens for those patients who do not have the advantages of well-organised effective

clinical advocates? Or who are comparatively less well organised? Who advocates for the silent or less media-genic patients, those unseen, and people with health needs not even yet identified as patients? We note that, despite being particularly affected by cardiovascular disease, Maori and Pacific peoples have had much lower rates of statin use than NZ Europeans (see Table 1).

Table 1. Cumulative statin approvals until March 2000

Ethnic group	Number of patients	% of all patients	% of patients of known ethnicity	Crude rate per 1000 population aged 35+	RR vs European
European	40 605	57	77	38.4	1.00
NZ Maori	2118	3	4	14.8	0.39
Pacific Island	669	1	1	13.7	0.36
Other	9521	13	18	26.0	0.68
Not stated or (blank)	17 976	25	n/a		
Total	**70 889**	**100**			
Total, where ethnicity identifiable	**52 913**		**100**	**32.8**	**0.85**

Source: analysis of HBL data supplied to PHARMAC 5 June 2000

If PHARMAC uses commercial processes to achieve fair prices for medicines, it is because it is dealing with commercial multi-national companies. Switching between medicines is not ideal. But nor is it ideal for large numbers of people to miss out on beneficial medicines because they cost too much, when cost-effective alternatives are available.

These events occurred in 1997, since when many other medicines have been funded and PHARMAC has made changes. We appreciate Begg et al raising this issue openly and hope this debate will inform and enhance the work of prescribers and policy-makers alike.

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Conflicts of interest: Scott Metcalfe is externally contracted to work with PHARMAC for public health advice.

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Endnotes:

[*] 1991 SA criteria (NHF groups A1:1-2,A2 with total cholesterol (TC) >7.0 mmol/l, other A and B-E TC >9.0 mmol/l) applied to [age/sex/Framingham CHD risk/total cholesterol and total:HDL cholesterol ratio] prevalence rates derived from 1993/94 Fletcher Challenge-University of Auckland Heart and Health Study (FCUAHHS) (unpublished prevalence data supplied by Rod Jackson and Roy Lay Yee, University of Auckland), applied to age/sex-specific intercensal estimates for NZ population.

† 124 500 patients estimated eligible under proposed 1997 SA criteria, minus 11 960 patient-month equivalent usage of all statins. Number eligible calculated from 1997 SA criteria (NHF groups A1:1,A1:3-4,A2,A3 with total cholesterol (TC) >6.0 mmol/l, A1:2 TC >5.5, B-E TC>9.0 mmol/l) applied to FCUAHHS [age/sex/Framingham CHD risk/total cholesterol and total:HDL cholesterol ratio] prevalence rates and age/sex-specific intercensal estimates for NZ population.

‡ Based on 190 200 patients estimated from FCUAHHS [age/sex/CHD status] prevalence, applied to age/sex-specific intercensal estimates for NZ population; and HealthPAC special authority data for statins, where of 26 045 approvals patients were identified as being in group A1:1 and where total cholesterol (TC) was stated, and 216 had TC of 10 mmol/l or more (0.83%).

§ $52 069 based on nominal atorvastatin price of $1.30/day versus simvastatin $0.45/day, using the same model as for simvastatin (http://www.pharmac.govt.nz/pdf/statin02CUA.pdf) with 54% improvement in LDL/HDL with atorvastatin versus 49% with simvastatin[16] (RR 1.09). After taking into account the effects of prevented CHD and stroke events on life expectancy and quality of life, the model suggests patients using atorvastatin might save 0.0200 extra QALYs for every five years' treatment beyond what they might have saved using simvastatin. This equals treating 50 patients for five years to gain one extra QALY. Includes 4% offsets from potential savings to DHBs through fewer cardiovascular events because of the small surrogate advantages of atorvastatin over simvastatin. QALYs and costs discounted at 10%.

¦ 357.9 QALYs for 70 073 extra person-months treated, based on discounted cost/QALYs of $2111/QALY for simvastatin (http://www.pharmac.govt.nz/pdf/statin02CUA.pdf, >10% five-year cardiovascular risk excluding pre-existing CHD) and $7690 for atorvastatin (as for simvastatin, but atorvastatin price), hence volume-weighted discounted offsets at 37% of pharmaceutical spending. Net extra costs and patient-year equivalents are above that predicted from simvastatin and atorvastatin individual trends for the pervious 12 months, hence total gain in QALYS, discounting both costs and QALYS at 10%. The $531 152 nominal potential "savings: to the health sector are hospitalisation and other DHB costs averted by preventing cardiovascular events, permitting those funds to be used to treat other health needs.
Total QALYs can translate to "statistical lives saved", where each saved life is equivalent to living a full quality of life for 36.4 remaining years expected for the average New Zealand citizen, which with discounting has a present value of 9.7 years (10% discount rate); no. 'statistical lives saved' = no. total discounted QALYs/9.7. Hence, the above 358 QALYs translate to 36.9 'statistical lives saved'.