Expiry of patent protection on statins: effects on pharmaceutical expenditure in Australia

Steven R A Simoens

To the Editor: Clarke and Fitzgerald showed that substantial savings could arise from the implementation of alternative pricing arrangements for off-patent statins that provide incentives to reduce prices and increase generic substitution.[1] This is exemplified by comparing statin prices between Australia and England. Europe offers some more lessons with respect to savings based

on generic medicine usage and how they can be attained.

The size of savings reported by Clarke and Fitzgerald needs to be interpreted with caution. A scenario of 100% generic substitution is proposed. Such a scenario has not been observed in any European country and, for therapeutic reasons, is probably not desirable.[2] Furthermore, the comparator country matters: for instance, generic medicine prices in England are lower than in France, the Netherlands and Germany, but are higher than those in Scandinavian countries.[3] Finally, the implementation of a tendering system for statins may create unintended effects, such as a switch in prescribing behaviour. For example, the Belgian tendering system for simvastatin reduced expenditure on off-patent medicines containing simvastatin by 30%, but increased expenditure for patented medicines containing atorvastatin or rosuvastatin by 16% and 40%, respectively.[4]

Clarke and Fitzgerald's article does not go into detail on how savings can be attained through use of generic medicines. The majority of European countries regulate generic medicine prices by pricing rules or reference pricing. For instance, the implementation of a minimum price difference between originator and generic medicines is the driver of savings arising from generic substitution in some countries, including France, Portugal and Spain. The reference pricing system in Norway stimulated generic competition to a greater extent and led to lower prices than regulation that imposed maximum prices.[4] However, price regulation may constitute a barrier for further price competition: no additional price reductions may occur beyond those imposed by regulation.[4]

The European experience also indicates that the ability of the generic medicine industry to deliver competitive prices can be achieved if it is assured a high volume of the pharmaceutical market. High volume is dependent on demand-side measures that create incentives for physicians, pharmacists and patients to use generic medicines. For example, a European study showed that savings as a result of price competition are higher in countries that have a higher market share of generic medicines.[5] Therefore, demand-side measures are critical to increase the generic substitution rate and to maximise the effect of competition based on generic medicine prices.

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1 Clarke PM, Fitzgerald EM. Expiry of patent protection on statins: effects on pharmaceutical expenditure in Australia. *Med J Aust* 2010; 192: 633-636.
2 Simoens S, De Coster S. Potential savings from increased substitution of generic for originator medicines in Europe. *J Generic Med* 2006; 4: 43-45.
3 Simoens S. International comparison of generic medicine prices. *Curr Med Res Opin* 2007; 23: 2647-2654.
4 Dylst P, Simoens S. Generic medicine pricing policies in Europe: current status and impact. *Pharmaceuticals* 2010; 3: 471-481.
5 Dylst P, Simoens S. Does the market share of generic medicines influence the price level? A European analysis. *Pharmacoeconomics* 2010. In press. ❑

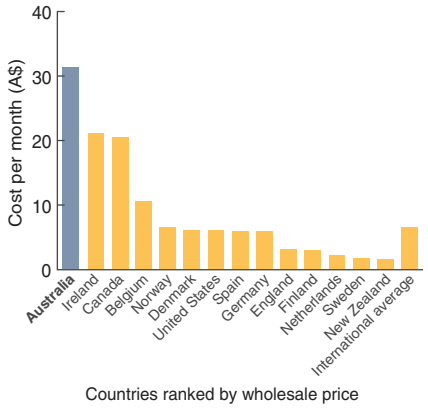
Philip M Clarke and Edmund M Fitzgerald

In reply: The main purpose of our recent article[1] was to quantify estimates of pharmaceutical expenditure over the next decade using various assumptions regarding the price and use of generic statins. We report estimates of billions of dollars in potential savings associated with various scenarios that increase the current off-patent statin use in Australia from around 25% of prescriptions to between 50% and 100%. Simoens misinterprets our conclusions as recommending only using generic statins in Australia. We do not advocate any particular level of generic substitution, but argue that the optimal mix of patented and generic statins should be determined by using cost-effectiveness analysis.

Simoens questions whether our results would change if we had compared statin prices with a country other than England. To address this issue we have compiled a comparison of current or recent wholesale price of 40 mg simvastatin across 13 countries in the Organisation for Economic Co-operation and Development (Box). Although there is some variation between countries, the main difference is with Australia, which has the highest wholesale price — about five times greater than the average price across all comparator countries. This price ratio is similar to the one used in our original study.

Also, Simoens highlights several issues relating to alternative pricing arrangements for statins and other generic drugs in European countries. We agree that Australia may be able to learn from overseas experience when reforming its system of pricing generic pharmaceuticals.

Wholesale price of simvastatin 40 mg in 13 countries in the OECD*



OECD = Organisation for Economic Co-operation and Development.
* Comparator prices were converted to Australian dollars using the average exchange rate over the past 3 years, and 1 month supply was assumed to be equivalent to 30 tablets. ◆

The impact on expenditure of the tendering system for supply of generic pharmaceuticals may have been counteracted by changes in prescribing behaviour in Belgium, but it has been successfully used in the Netherlands to cut the price of simvastatin and other major generics by over 80%. This has been estimated to save around 310 million euros annually.[2]

However, tenders are not the only way to reduce the price of generic pharmaceuticals. In Canada, the Ontario Ministry of Health and Long-Term Care has recently introduced a policy which sets the subsidy for generics at 25% of the original price under patent. Generic 40 mg atorvastatin, whose patent in Canada recently expired, now costs just A$17 per month.[3] In contrast, under the recent Memorandum of Understanding[4] between the Australian Government and Medicines Australia, the current wholesale price of A$61 for 40 mg atorvastatin will decline by only 16% after the patent expires in Australia in 2012, and there will be no further downward adjustment until at least 2014.

Competing interests: Philip Clarke has received funding from Servier Laboratories Australia for travel to attend the International Society for Pharmacoeconomics and Outcomes Research 2010 Conference to present work related to the ADVANCE study.

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1 Clarke PM, Fitzgerald EM. Expiry of patent protection on statins: effects on pharmaceutical expenditure in Australia. *Med J Aust* 2010; 192: 633-636.
2 Kanavos P, Seeley L, Vandoros S. Tender systems for outpatient pharmaceuticals in the European Union: evidence from the Netherlands, Germany and Belgium. London: LSE Health, 2009.
3 Ontario Ministry of Health and Long-Term Care. Update R1 Ontario Drug Benefit Formulary/Comparative Drug Index No. 41. Effective June 18, 2010. Summary of changes. http://www.health. gov.on.ca/english/providers/program/drugs/formulary/41_update_r1_20100608.pdf (accessed Sep 2010).
4 Memorandum of Understanding between the Australian Government and Medicines Australia. http://www.health.gov.au/internet/main/publishing.nsf/Content/C6EC4D1258BBFFB6CA257721000520A2/$File/MOU%20MA.pdf (accessed Sep 2010). ❑

Managing residual risk in patients receiving statin therapy

Marilyn K Mann

To the Editor: I am writing about important errors contained in a letter of reply by Hamilton-Craig.[1] In his response to a letter by Montgomery,[2] he states:

> The Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial (in which patients with aortic stenosis were treated for 52.2 months with statin plus ezetimibe or statin plus placebo) showed a 4.7% reduction in ischaemic [cardiovascular disease] events in the ezetimibe group ($P = 0.02$; number needed to treat, 23), driven by a reduced need for coronary artery bypass grafting.

However, in the SEAS trial, patients were treated with statin plus ezetimibe *or* with placebo, not with *statin plus placebo*. Therefore, the reduction in ischaemic events in the statin/ezetimibe group cannot be attributed to ezetimibe, as it could have been caused by the effect of simvastatin alone (or by the combined effect of the two drugs). I note also that the absolute reduction in ischaemic events over the course of the trial was 4.4% (15.7% v 20.1%), not 4.7%.[3]

With respect to the ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) trial, Hamilton-Craig states:

> As no placebo group was included, neither lack of benefit nor harm from ezetimibe therapy can be inferred.[1]

In the ENHANCE trial, patients with familial hypercholesterolaemia were treated with simvastatin plus ezetimibe or simvastatin plus placebo. There was no significant difference in progression of mean carotid intima media thickness (CIMT) between the two groups (0.0058 mm in the simvastatin/placebo group v 0.0111 mm in the simvastatin/ezetimibe group [$P = 0.29$]).[4] Therefore, contrary to Hamilton-Craig's statement, there *was* a placebo group, and a lack of benefit from ezetimibe *was* shown in the trial.

Thus, the SEAS trial was unable to confirm a benefit of ezetimibe, as the active treatment arm included both a statin and ezetimibe, while the ENHANCE trial showed no additional benefit of ezetimibe on the surrogate endpoint of CIMT progression in patients taking a statin.

Author's note: The United States Securities and Exchange Commission disclaims responsibility for any private publication or statement of any Commission employee or Commissioner. This letter expresses my views and does not necessarily reflect those of the Commission, the Commissioners, or other members of the Commission staff.

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1 Hamilton-Craig IR. Managing residual risk in patients receiving statin therapy [letter]. *Med J Aust* 2010; 193: 375-376.
2 Montgomery BD. Managing residual risk in patients receiving statin therapy [letter]. *Med J Aust* 2010; 193: 375.
3 Rossebø AB, Pedersen TR, Boman K, et al; SEAS Investigators. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med* 2008; 359: 1343-1356.
4 Kastelein JJ, Akdim F, Stroes ES, et al; ENHANCE Investigators. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med* 2008; 358: 1431-1443. ❑

Brett H Forge

To the Editor: I would like to endorse the letter by Montgomery[1] questioning the efficacy of ezetimibe. As yet there are no data to support its use in clinical trials using carotid intima media thickness (CIMT) as a measure of treatment effectiveness, and there is also some evidence to suggest it could be harmful.

A randomised trial conducted by Berneis et al[2] suggested that ezetimibe may induce an unfavourable pro-atherogenic low-density lipoprotein (LDL) subfraction profile by increasing small, dense LDLs.

The Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial[3] compared simvastatin/ezetimibe 40/10 mg daily with placebo, so any benefit from that treatment may have been from either the ezetimibe or the simvastatin. It tells us nothing about the effectiveness of ezetimibe alone.

Until the results of clinical trials are available, I believe ezetimibe should be used with much reluctance and only considered as a last resort. I agree with Hamilton-Craig[4] that it is a matter of concern that slow-release niacin, which is effective and safe, is not available under the Pharmaceutical Benefits Scheme in Australia. Searching for supplies of this drug in Australia or overseas seems the best option for treating patients whose levels of LDL cholesterol are inadequately controlled with statin therapy.

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1 Montgomery BD. Managing residual risk in patients receiving statin therapy [letter]. *Med J Aust* 2010; 193: 375.
2 Berneis K, Rizzo M, Berthold HK, et al. Ezetimibe alone or in combination with simvastatin increases small dense low-density lipoproteins in healthy men: a randomized trial. *Eur Heart J* 2010; 31: 1633-1639.
3 Rossebø AB, Pedersen TR, Allen C, et al. Design and baseline characteristics of the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study. *Am J Cardiol* 2007; 99: 970-973.
4 Hamilton-Craig IR. Managing residual risk in patients receiving statin therapy [letter]. *Med J Aust* 2010; 193: 375-376. ❑

Ian R Hamilton-Craig

In reply: In the interests of scientific exactitude, I am indebted to Marilyn Mann for corrections regarding the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial. However, as the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial did not include the control group ezetimibe versus placebo, the effects of ezetimibe on carotid intima media thickness remain somewhat speculative.[1]

Competing interests: I have served on lipid advisory boards for Merck Sharp and Dohme, Solvay/Abbott and AstraZeneca, and have received speaker fees and reimbursement for travel/accommodation expenses to attend scientific meetings from these companies. I have also received honoraria from these companies and from Novartis, Pfizer, Schering Plough and Servier for presentations at postgraduate scientific meetings.

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1 Stein E. After ENHANCE: is more LDL cholesterol lowering even better? *Clin Chem* 2008; 54: 940-942. ❑