Reviewer’s report

Title: Analysis of lipid-lowering drug expenditure growths in South Korea

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Reviewer: Brian Godman

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A) General Comments

I found this paper overall well written (although some typographical errors) and very interesting. Consequently, should be published. I endorse the focus on statins as there is controversy surrounding the use of fibrates – some fibrates have shown a reduction in CV events whilst others have not and there is still ongoing controversy surrounding ezetimibe and whether it lowers CV events in practice after the ENHANCE study. I also endorse the use of DDDs to compare utilisation over time as this is the recognised WHO standard for such comparisons rather than units, etc.

However, I believe there is more information that could come out of the paper that will be of interest to others. There is also certain information that was lacking that will translate this paper into an important Health Policy paper not only to provide future direction to HIRA in the future but also to health authorities in other countries. This especially as my understanding is that patient co-payment has recently been abolished in South Korea – which is likely to further enhance statin utilisation.

For instance, multiple policies in the Netherlands and the UK (e.g. Scotland) appreciably enhanced prescribing efficiency for the statins with all statins seen as essentially similar in all/ nearly all patients at appropriate doses in meta analyses as well as by health authorities across Europe, e.g. (i) Weng et al - A systematic review and meta-analysis on the therapeutic equivalence of statins. J. Clin. Pharm. Ther. 2010; 35,139-151 (ii) the IDEAL study, which failed to show a significant reduction in coronary vascular events for patients prescribed high dose atorvastatin (80mg/ day) versus low dose simvastatin (20mg/ day) Pedersen et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA 2005; 294:2437-45; (iii) van Woerkom M et al. Ongoing measures to enhance the efficiency of prescribing of PPIs and statins in the Netherlands; influence and future implications. Journal of Comparative Effectiveness Research 2012; 1: 527-38; (iv) Godman B et al. Essential to increase the use of generics in Europe to maintain comprehensive healthcare? Farmeconomia: Health Economics and Therapeutic Pathways 2012; 13 (Suppl 3): 5-20; (v) Bennie M et al. Multiple initiatives continue to enhance the prescribing efficiency for the proton pump inhibitors and statins in Scotland. Expert Review Pharmacoeconomics and Outcomes Research 2012; 12: 125-130; (vi) Sakshaug S et al. Switching statins
in Norway after new reimbursement policy – a nationwide prescription study. Br J Clin Pharmacol 2007; 64, 476-81 and (vii) Godman B et al. Update of recent reforms in Germany to enhance the quality and efficiency of prescribing of proton pump inhibitors and lipid lowering drugs. Pharmacoeconomics 2009; 27: 435-438. In the Netherlands (van Woerkom et al), reimbursed expenditure for the statins fell by 14% in 2010 vs. 2000 despite a 3.8 fold increase in utilisation and in Scotland – statin utilisation increased 6.2 fold between 2001 and 2010 but expenditure by only by 7% (Bennie et al). Both situations are very different from South Korea where utilisation of all statins increased over 3.4 fold between 2005 and 2009 and expenditure by approx. 2 fold.

In addition, studies undertaken in Stockholm Region have shown no difference in outcomes (lipid levels) in patients prescribed generic simvastatin vs. patented statins such as atorvastatin (Norman et al. Potential savings without compromising the quality of care. Int J Clin Pract 2009: 63:1320–6) and patients in the UK have been successfully switched from atorvastatin to simvastatin without affecting care - Usher-Smith at al. Evaluation of the clinical outcomes of switching patients from atorvastatin to simvastatin and losartan to candesartan in a primary care setting: 2 years on. Int J Clin Pract 2008; 62:480-4. Consequently, care does not appear to be compromised by the use of e.g. generic simvastatin vs. patented atorvastatin.

This appreciable increase in the utilisation of statins in the UK (Scotland and England) vs. other Northern European countries (outlined in Godman B et al. Policies to enhance prescribing efficiency in Europe: findings and future implications. Frontiers Pharmacol. 2011; 1 (141): 1-16 doi: 10.3389/fphar.2010.00141) appeared to be influenced by incentives to GPs to identify and treat patients with CHD, hypertension and diabetes to target lipid levels. As a result, increase prescribing of higher strength statins than e.g. Ireland or Sweden (Bennie et al – above).

Consequently, the aim of health authorities when there is an opportunity to enhance the use of generics in a class such as the statins should be to:

a) engineer low prices for generics, e.g. increased transparency the pricing of generics such as Netherlands, Sweden and the UK, prices for generic simvastatin can be as low as 2% to 4% of pre-patent loss prices (e.g. Godman B, Wettermark B et al. Multifaceted national and regional drug reforms and initiatives in ambulatory care in Sweden; global relevance. Expert Rev Pharmacoeconomics Outcomes Research 2009; 9:65-83; van Woerkom M et al above; Godman B et al. Farmeconomia above and Bennie M et al - above).

b) Enhance their prescribing vs. originators. This can be achieved through a variety of means including for instance (I) encouraging high voluntary INN prescribing as seen in the UK, e.g. Godman B, Bishop I et al. Reforms and initiatives in Scotland in recent years to encourage the prescribing of generic drugs, their influence and implications for other countries. Expert Rev. Pharmacoecon. Outcomes Res. 2013; 13(4): 469–82; (ii) compulsory INN prescribing, e.g. Lithuania (in Garuoliene K et al. European countries with small populations can obtain low prices for drugs: Lithuania as a case history. Expert
Rev. Pharmacoeconomics Outcomes Res 2011; 11: 343-9); (iii) compulsory
generic substitution as seen in Sweden (Godman, Wettermark et al above); (iv)
health insurance groups working with physicians e.g. Austria (Vogler S et al. How
do regional sickness funds encourage more rational use of medicines, including
the increase of generic uptake? A case study from Austria. 2013; 2 (2): 65-75);
(v) Alternatively a mixture of education, benchmarking, financial incentives, etc., to
all key stakeholder groups as seen in France (Godman B et al, Farmacoeconomic 2012 above and Pichetti S et al. Multilevel analysis of the
influence of patients' and general practitioners' characteristics on patented
versus multiple-sourced statin prescribing in France. Appl Health Econ Health
Policy 2013; 11:205-18)
c) Enhancing their use vs. patented statins. This through multiple measures as
outlined in Godman B, Shrank W, Andersen M et al. Comparing policies to
enhance prescribing efficiency in Europe through increasing generic utilisation:
changes seen and global implications. Expert Rev. Pharmacoeconomics
Outcomes Res 2010; 10: 707–722. In this study, prescribing costs for statins in
Sweden in 2007 with its multiple measures (when adjusted for population sizes)
was approx. 1/10th of that in Ireland with its limited demand side measures at the
time which led to increased and not decreased use of patented statins. Similarly
in the Netherlands (van Woerkom et al – above). Other measures include
prescribing restrictions for patented statins limiting their prescribing to second
line, e.g. Norway (Sakshaug S et al – above for Norway or Martikainen JE et al -
Impact of restricted reimbursement on the use of statins in Finland: a
register-based study. Med Care. 2010 Sep;48:761-6) or reference pricing for the
class based on the cheapest molecule, e.g. Poland and Germany
d) Enhancing the quality of care through enhancing compliance as well as
enhancing appropriate dosing. The quality and Outcome Framework in the UK is
an attempt to try and ensure patients with hyperlipidaemia associated with CHD, hypertension or diabetes achieve target lipid levels are identified and adequately
treated through identification and monitoring of patients. This is because
compliance in patients with chronic diseases can be poor (consolidated in e.g.
crater et al. The significance of compliance and persistence in the treatment of
diabetes, hypertension and dyslipidaemia: a review. Int J Clin Pract 2008; 62:
76-87). The Heart Protection study in particular highlighted the benefits of 40mg
simvastatin (Collins R et al. MRC/BHF Heart Protection Study of
cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised
(guideline group well recognised Internationally) recently just advocating 40mg
simvastatin in these patients (highlighted in Bennie M et al – above). These 2
measures in Scotland appear to enhance the prescribing of higher strength
statins – certainly when compared with for instance Ireland and Stockholm
County in Sweden (Refs in Bennie M et al). It seems that though compliance was
reasonable with the statins in Korea as seen by the continued use of core
medicines (e.g. Table 1) - great to comment on this (if this is the case)

B) Discretionary suggestions (General)
I believe we should get a sense of relevant ongoing supply- and demand-side initiatives in South Korea in this paper especially as the principal authors are part of the National Health Insurance Agency (HIRA) in South Korea. In addition, the authors state at the end of the Conclusion in the abstract that ‘various recommendations for promoting cost-effective drug use should be developed based on the data from this and future investigations’. I believe this is impossible without knowledge of the supply- and demand-side measures for statins in South Korea during this period and subsequently.

As a result, I would like to see the following if possible embedded in the paper:

• Annual time line of all general supply-side measures during the study period such as (i) any compulsory price reductions of pharmaceuticals – there was a brief mention of such policies in the discussion but no mention in either the Introduction or Results; (ii) pricing policy for generics. Both will help explain the reduction in Exp/ DDD over time of 42% (Table 2)

• Availability of each of the statin as multiple sourced (generic) products or as originators (single source) between 2005 and 2009, e.g. we know from the discussion that generic atorvastatin became available in 2008 – presumably simvastatin was available as multiple sourced products throughout the study but good to know this. Similarly for any new statin entrant during the study period

• Annual time line summarising policies in South Korea during this period to enhance the prescribing of generics vs. originators (general as well as for the statins if different) as well as generics vs. patented products in a class (for the statins). The latter in particular will help enhance the interpretation of Figure 3 – especially the appreciable change for both simvastatin and atorvastatin from 2006/2007 onwards. In addition, good to know what was the influence (if known) of any inducements to physicians/pharmacists during this period to encourage e.g. the prescribing of certain statins, i.e. prior to the recent anti-rebate legislation highlighted in Yu SY, Yang BM, Kim JH. New anti-rebate legislation in South Korea. Appl Health Econ Health Policy. 2013 Aug;11(4):311-8

C) More specific recommendations/ suggestions (discretionary unless indicated):

• Background
o Line 9 – I believe this should be ‘recommendations’ and not ‘recommendation’

• Methodology Data – which year for the DDDs as I believed these changed during the study period. The WHO and others recommend that the latest DDDs

• Methodology – method
  o Line 5 and in the various tables, etc., I believe ‘Exiting’ should be ‘Existing’
  o No apparent reference in the methodology for converting Korean currency to US$ during the study period – this should be addressed (compulsory minor revision)
  o Initially, it may be better to just concentrate on Korean currency for the various Tables and then convert the figures later to US$ if wished – especially if there has been reasonably fluctuation in currency conversion rates during the course of the study
  o Lastly, are we discussing ‘expenditure’ reimbursed or total expenditure including patient co-payments? This is not clear in the methodology (compulsory minor revision)

• Results
  o In Table 2 good to have a last column computing total changes in DDDs, Expenditure and exp/ DDD between 2005 and 2009.
  o Second paragraph in results – I presume line 6 should be ‘lovastatin declined to’ rather than ‘lovastatin continued to’
  o Figure 3 – I presume the horizontal access should be 2005 to 2009 (and not 2005 throughout). In addition, the vertical axis is % of single statins vs. total statins (DDD basis). This is not entirely clear from the heading, etc. (compulsory minor revision)
  o Table 3 – and building on my earlier comments - I would like to see a supplementary table that documents % use of generic vs. originator simvastatin as well as for atorvastatin once generics are available to give a better understanding of existing policies to enhance the prescribing of a generic vs. originator and their impact/ influence ready to make suggestions for future policies (if needed) in the Discussion. I can see from Figure 3 that there was a considerable increase in the utilisation of patented statins during the study period – 2005 to 2008. The dynamics changed slightly in 2009 with the continued increase in the utilisation of atorvastatin (with stable rosuvastatin and pitavastatin) despite atorvastatin now available as a generic
• Discussion - I would like to see much more discussion regarding suggested ways forward – building on current/planned policies in South Korea to meet the requirements of the last sentence in discussion. This can build in experiences in other countries.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

Nothing to declare