

**9.1 EZETIMIBE + SIMVASTATIN
tablets, 10 mg – 10 mg, 10 mg – 20 mg,
10 mg – 40 mg and 10 mg – 80 mg;
Vytorin[®]; Merck Sharp & Dohme (Australia) Pty Ltd.**

1 Purpose of Application

- 1.1 The major submission requested the PBAC advise the Minister that the November 2008 compliance advice for Vytorin under subsection 101(4AC) of the Act for Vytorin be maintained.

Note: These minutes refer to the ezetimibe with simvastatin fixed dose combination items as Vytorin.

2 Requested listing

- 2.1 The submission did not request any changes to the current PBS restriction.

3 Background

- 3.1 Vytorin was first TGA registered on 7 January 2005. Vytorin is currently indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia where use of a combination product is appropriate; and for homozygous familial hypercholesterolaemia.
- 3.2 Vytorin was initially recommended on a cost-minimisation basis compared to the sum of the corresponding strengths of the individual components during the March 2005 PBAC meeting.
- 3.3 Since 2007, subsection 101(4AC) of the Act has required the PBAC to advise the Minister for Health when it is satisfied that therapy involving a combination item provides, for some patients, either (a) a significant improvement in patient compliance with the therapy, or (b) a significant improvement in efficacy or a reduction in toxicity, over alternative therapies.
- 3.4 The PBAC has previously considered two compliance submissions for Vytorin. At its April 2008 special meeting, the PBAC advised that the appropriate alternative therapies at that time, for combination items containing ezetimibe with simvastatin were ezetimibe taken concomitantly with any statin with a potency equivalent to, or higher than 40 mg of simvastatin. At that meeting, the PBAC decided it was not satisfied of the matters in subsection 101(4AC) and decided not to provide advice on these matters to the Minister in relation to Vytorin.
- 3.5 Subsequently, at its November 2008 meeting, the PBAC advised that the sponsor's resubmission provided a sufficient basis to conclude that there is a significant improvement in compliance for the combination item over its alternative therapies for

some patients. The PBAC noted that the clinical importance for treated patients of this compliance improvement remained uncertain.

- 3.6 In 2008, the PBAC requested that the Compliance to Medicines Working Group (CMWG) be established to gather information from experts and published literature on methods for evaluating and interpreting evidence used to support claims that combination products improve compliance and health outcomes. The CMWG had 14 members including representatives of the pharmaceutical industry, researchers, clinicians, consumers, DUSC and PBAC. The CMWG report was endorsed by the PBAC in April 2010.
- 3.7 In July 2013, in the context of a submission to list a co-pack containing atorvastatin tablets and ezetimibe tablets, the PBAC recalled its November 2008 advice to the Minister under subsection 101(4AC) of the Act that Vytorin had a significant improvement in compliance over its alternative therapies for some patients. The PBAC recalled also that this advice was given before the finalisation of the CMWG report, and that the criteria of that report had therefore not been used to assess the compliance claims for Vytorin.
- 3.8 The PBAC considered that the impending PBS listing of ezetimibe and atorvastatin co-pack would allow that co-pack to be considered as an alternative therapy to Vytorin for the purposes of subsection 101(4AC) of the Act. The PBAC therefore considered that the basis of its previous advice to the Minister under subsection 101(4AC) for Vytorin should be reviewed, given that the new alternative therapy will be available.
- 3.9 The PBAC invited the sponsor of Vytorin to submit data in support of its continued claim of compliance benefit and noted that any future submission seeking PBAC advice to the Minister of a compliance benefit would need to address the approach for measuring compliance set out in the CMWG Report to the PBAC.

4 Clinical place for the proposed therapy

- 4.1 Hypercholesterolaemia is characterised by high levels of cholesterol in the blood, and is associated with a higher risk of cardiovascular diseases (e.g. heart attack or stroke).
- 4.2 The submission did not propose any changes to the current place in therapy for Vytorin.

5 Alternative therapies

- 5.1 The submission specified that prescribers could consider three possible alternative therapies to Vytorin: statin monotherapy, combination therapy with a statin and ezetimibe given concomitantly; or the atorvastatin + ezetimibe (Atozet[®]) composite pack.
- 5.2 The submission argued that the alternative therapy likely to be used in most patients who are currently controlled on Vytorin is dual combination therapy with simvastatin

and ezetimibe. The main argument provided in support of this nomination is that patients are most likely to be switched to the individual components should Vytorin be de-listed.

- 5.3 The CMWG report suggests that for applications seeking consideration under subsection 101(4AC) the comparison should be against the alternative therapy that prescribers would most replace in practice if the combination item were removed from the PBS. The CMWG report also considers that, in keeping with the principles already established for submissions to the PBAC, there may also be circumstances where a comparison should be presented against more than one alternative therapy.
- 5.4 The evaluation of the submission considered that the individual components (ezetimibe and simvastatin) are not the only appropriate alternate therapies. Atorvastatin-ezetimibe co-pack (currently listed) and atorvastatin and rosuvastatin with ezetimibe FDC/co-packs which have been recommended by PBAC, are also appropriate alternative therapies. Both the 10% Medicare sample analyses and the commissioned market survey suggest that patients switch to Vytorin from statins other than simvastatin (the most frequently reported being atorvastatin). This suggested that prescribers are willing to consider switching between statins. It appears likely that patients, especially those with previous experience on atorvastatin, would be switched to atorvastatin and ezetimibe co-pack should Vytorin be delisted (particularly given the saving of one co-payment).
- 5.5 DUSC agreed with the evaluation that the atorvastatin-ezetimibe combination and the rosuvastatin-ezetimibe combination items (if listed) are likely to be alternate therapies. DUSC noted that the PBAC (July 2013) had previously considered that the PBS listing of ezetimibe and atorvastatin co-pack would allow the co-pack to be considered as an alternative therapy to Vytorin. During the November 2013 PBAC meeting, the PBAC considered that ezetimibe and rosuvastatin co-pack should be treated as interchangeable on an individual patient basis with Vytorin. During the July 2014 PBAC meeting, the PBAC considered that ezetimibe and rosuvastatin FDC should be treated as interchangeable on an individual patient basis with Vytorin.
- 5.6 DUSC acknowledged the Sponsor's comments in the pre-subcommittee response (PSCR) that it is not possible to conduct adherence and persistence studies in the PBS data available for the recently listed atorvastatin combination products. However the availability of these combination products on the PBS does mean that in the future Vytorin users could switch to these products, particularly patients who are concerned about the cost of an additional co-payment and/or have prior experience with other statins.
- 5.7 DUSC agreed with the submission that statin monotherapy is not an alternate therapy. Statin monotherapy would only be an alternate therapy if patients were initiated on Vytorin without first up titrating to the maximum tolerated dose of a statin, which is outside of the PBS restriction.
- 5.8 In the pre-PBAC response, the sponsor noted that rosuvastatin and ezetimibe combination is not PBS listed and therefore cannot be an alternative therapy. Atorvastatin with ezetimibe co-pack has only been PBS listed for 10 months. The Sponsor considered that uptake has been low and that it is unlikely that Vytorin patients would move to the co-pack in the absence of Vytorin.

For more detail on PBAC's view, see section 7 "PBAC outcome"

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Evidence presented

6.3 The submission was based on:

- One retrospective observational study using the 10% Medicare sample, referred to as the Vytorin Compliance Study IV, comparing Vytorin to concomitant use of ezetimibe and statins. Cohort 1 is a before and after study measuring adherence (n=between 304 and 1,205). Cohort 2 is used for the persistence analysis (n=16,594).
- One commissioned cross-sectional online market study of general practitioners (n=192) and patients (n=189) to gather 'quantitative' information about compliance with medicines.
- Four systematic reviews: one investigating the factors affecting compliance to statins and three investigating the impact of compliance to statins on patient outcomes.
- Two narrative reviews: one discussing the factors affecting compliance to statins and one discussing the impact of compliance to lipid-lowering therapy on patient outcomes.
- 40 observational studies: one study describing the usage pattern, effectiveness and tolerability of Vytorin, one study investigating compliance to single-pill combination versus multiple-pill combination lipid-modifying therapy, 15 studies reporting on factors affecting compliance to statins, and 23 studies reporting on patient outcomes associated with statin compliance.

6.4 Details of the studies presented in the submission are provided in the table below.

Studies and associated reports presented in the submission

| Study ID/ First Author | Protocol title/ Publication title | Publication citation |
|--|---|----------------------------------|
| Commissioned studies | | |
| Vytorin [®] Compliance Study IV | Vytorin [®] Compliance Study IV: A longitudinal, retrospective descriptive study using a 10% sample of the Medicare Australia claims database (historical cohort). | Unpublished |
| Commissioned market survey | Lipid lowering medications research: findings from quantitative research with general practitioners and patients. | Unpublished. Prepared July 2014. |
| Systematic reviews | | |
| Lemstra | Proportion and Risk Indicators of Non-adherence to statin therapy: A Meta-analysis. | Can J Cardiol 2012; 28: 574-580. |

Public Summary Document – November 2014 PBAC Meeting

| | | |
|------------------------------|---|--|
| Simpson | The effects of adherence and persistence on clinical outcomes in patients treated with statins: A systematic review. | J Clin Lipidology 2010; 4(6):462-471. |
| Chowdhury | Adherence to cardiovascular therapy: A meta-analysis of prevalence and clinical consequences. | Eur Heart J 2013; 4(38):2940-2948. |
| Gomez | Statin discontinuation in high-risk patients: A systematic review of the evidence. | Curr Pharm Des 2011; 17(33):3669-3689. |
| De Vera | Impact of Statin Adherence on Cardiovascular Disease and Mortality Outcomes: A Systematic Review. | Br J Clin Pharmacol 2014; DOI: 10.1111/bcp.12339 |
| Mann | Predictors of nonadherence to statins: a systematic review and meta-analysis. | Ann Pharmacother 2010; 44(9):1410-21. |
| Narrative reviews | | |
| Bates | Non-adherence to statin therapy: a major challenge for preventive cardiology. | Expert Opin Pharmacother 2009; 10(18): 2973-2985. |
| Liberopoulos | Compliance with lipid-lowering therapy and its impact on cardiovascular morbidity and mortality. | Expert Opin Drug Saf 2008; 7(6):717-725. |
| Observational studies | | |
| Hildemann | Sustained effects in hypercholesterolaemic patients on combined simvastatin/ ezetimibe treatment: observational cohort study in clinical practice. | Curr Med Res Opin 2008; 24 (10): 2777 – 2784 |
| Kamat | Adherence to single-pill combination versus multiple-pill combination lipid modifying therapy among patients with mixed dyslipidaemia in a managed care population. | Curr Med Res Opin 2011; 27(5): 961-968 |
| Avorn | Persistence of use of lipid-lowering Medications: A Cross-National Study. | JAMA 1998; 279:1458-1462. |
| Benner | Association between short-term effectiveness of statins and long-term adherence to lipid-lowering therapy. | Am J Health-Syst Pharm 2005; 62:1468-75. |
| Catalan | Predictors of long-term persistence on statins in a subsidized clinical population. | Value Health 2000; 3(6):417-426 |
| Chan | Patient, physician, and payment predictors of statin adherence. | Med Care 2010; 48(3):196-202. |
| Di Martino | Underuse of lipid-lowering drugs and factors associated with poor adherence: A real practice analysis in Italy. | Eur J Clin Pharmacol 2005; 61(3):225-230. |
| Helin-Salmivaara | Long-term persistence with statin therapy: A nationwide register study in Finland. | Clin Ther 2008; 30(PART 2): 2228-2240 |
| Kardas | Prevalence and reasons for non-adherence to hyperlipidaemia treatment. | Cent Eur J Med 2013; 8(5):539-547. |
| Kim | Determinants of non-compliance with lipid-lowering therapy in hyperlipidemic patients. | Pharmacoepidemiol Drug Saf 2002; 11: 593-600. |
| Kiortsis | Factors associated with low compliance with lipid-lowering drugs in hyperlipidemic patients. | J Clin Pharm Ther 2000; 25(6): 445-451. |
| Wiegand | Factors of Hyperlipidemia Medication Adherence in a Nationwide Health Plan. | Am J Manag Care 2012; 18(4):193-199. |
| Wong | Adherence to lipid-lowering agents among 11,042 patients in clinical practice. | Int J Clin Pract 2011; 65(7):741-748. |
| Mann | Predictors of adherence to statins for primary prevention. | Cardiovasc Drugs Ther 2007; 21(4): 311-316. |
| Warren | Factors influencing adherence in long-term use of statins. | Pharmacoepidemiol Drug Saf 2013; 22(12):1298-1307. |

Public Summary Document – November 2014 PBAC Meeting

| | | |
|------------|--|---|
| Wei | Predictors of statin adherence, switching and discontinuation in the USAGE survey: Understanding the use of statins in America and gaps in patient education. | J Clin Lipidology 2013; 7(5): 471-483. |
| Xie | Factors associated with compliance to lipid-lowering treatment in China. | Eur J Prev Cardiol 2013; 20(2):229-37. |
| Gislason | Persistent use of evidence-based pharmacotherapy in heart failure is associated with improved outcomes. | Circulation 2007; 116(7):737-744. |
| Haukka | Statin usage and all-cause and disease-specific mortality in a nationwide study. | Pharmacoepidemiol Drug Saf 2012; 21(1):61-69. |
| Corrao | Results of a retrospective database analysis of adherence to statin therapy and risk of nonfatal ischemic heart disease in daily clinical practice in Italy. | Clin Ther 2010; 32(2):300-310. |
| Bouchard | Impact of adherence to statins on coronary artery disease in primary prevention. | Br J Clin Pharmacol 2007; 63(6):698-708. |
| Perreault | Effect of Statin Adherence on Cerebrovascular Disease in Primary Prevention. | Am J Med 2009; 122(7):647-655. |
| Perreault | Impact of better adherence to statin agents in the primary prevention of coronary artery disease. | Eur J Clin Pharmacol 2009; 65(10):1013-1024. |
| Wei | Adherence to statin treatment and readmission of patients after myocardial infarction: A six year follow up study. | Heart 2002; 88(3):229-233. |
| Rasmussen | Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. | J Am Med Assoc 2007; 297(2):177-186. |
| Wei | Adherence to statin or aspirin or both in patients with established cardiovascular disease: Exploring healthy behaviour vs. drug effects and 10-year follow-up of outcome. | Br J Clin Pharmacol 2008; 66(1):110-116. |
| Colivicchi | Discontinuation of statin therapy and clinical outcome after ischemic stroke. | Stroke 2007; 38(10):2652-2657. |
| Pittman | Adherence to statins, subsequent healthcare costs, and cardiovascular hospitalizations. | Am J Cardiol 2011; 107(11):1662-1666. |
| Kumbhani | Adherence to secondary prevention medications and four-year outcomes in outpatients with atherosclerosis. | Am J Med 2013; 126(8):693-700. |
| Ho | Medication nonadherence is associated with a broad range of adverse outcomes in patients with coronary artery disease. | Am Heart J 2008; 155(4):772-779. |
| Allonen | Mortality rate increases steeply with nonadherence to statin therapy in patients with acute coronary syndrome. | Clin Cardiol 2012; 35(11):E22-E27. |
| Ho | Adherence to cardio protective medications and mortality among patients with diabetes and ischemic heart disease. | BMC Cardiovasc Disord 2006; 6:48. |
| McGinnis | Statin adherence and mortality in patients enrolled in a secondary prevention program. | Am J Managed Care 2009; 15(10):689-695. |
| Kazerooni | Association between statin adherence and cholesterol level reduction from baseline in a veteran population. | Pharmacotherapy 2013; 33(10):1044-1052. |
| Ho | Effect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. | Arch Intern Med 2006; 166(17):1836-1841. |
| Ho | Impact of medication therapy discontinuation on mortality after myocardial infarction. | Arch Intern Med 2006; 166(17): 1842-1847 |
| Parris | Adherence to statin therapy and LDL Cholesterol Goal attainment by patients with diabetes and dyslipidaemia. | Diabetes Care 2005; 28(3):595-9 |
| Shalev | Continuation of statin treatment and all-cause mortality. | Arch Intern Med 2009; 169(3): 260 -268. |
| Shalev | Continuation of statin therapy and primary prevention of nonfatal cardiovascular events. | Am J Cardiol 2012; 110: 1779-1786. |
| Shalev | Association between persistence with statin therapy and reduction in | Pharmacotherapy |

| | | |
|--------|--|--|
| | Low Density Lipoprotein cholesterol level: Analysis of Real-Life data from Community Settings. | 2014; 34(1):1-8. |
| Simons | Long term persistence with statin therapy – Experience in Australia 2006-2010. | Aust Fam Physician 2011; 40(5):319-22. |

Source: Tables B.1.1-2 (p14), B.2-3 (p33), B.2-5 (p35), B.2-6 (p35), B.5-2 (pp86-7), and B.5-4 (p89) of the submission.

- 6.5 The Vytorin Compliance Study IV used the 10% Medicare sample (claims database) and was designed to:
- Measure the adherence characteristics of Vytorin using medication possession ratio (MPR) and continuous measure of medication gaps (CMG) versus concomitant therapy in the same patient (Cohort 1).
 - Measure persistence to Vytorin compared to concomitant therapies, accounting for switching (Cohort 2).
- 6.6 The submission used data from a subgroup of approximately 1,200 patients who met the criteria for inclusion into Cohort 1 was used to characterise the current levels of adherence to Vytorin. The study used a before and after study design, with two measures of adherence (CMG and MPR). Patients were included in Cohort 1 if they were on concomitant ezetimibe with a statin ‘immediately prior’ to receiving Vytorin. Thus, the comparison was concomitant ezetimibe and statin prior to switching (referred to as the pre-period) versus Vytorin after the switch (referred to as the post-period).
- 6.7 The submission stated that the advice under subsection 101(4AC) of the Act refers to a significant improvement in compliance in some patients. Therefore, the sponsor further selected a sub-population of Cohort 1 with <85% in MPR to a statin (n=304) or CMG (n=500) as the population at need of improved compliance. The submission also then analysed MPR and CMG by patient age in each of these subgroups.
- 6.8 The persistence analysis was conducted in a different cohort to the adherence analysis (Cohort 2, n=16,594). The analysis was aimed at measuring how long patients remain on therapy and the differences in persistence based on the last form of ezetimibe dispensed (i.e. Vytorin or ezetimibe as Ezetrol).
- 6.9 The key features of the Vytorin Compliance Study IV and the market survey are summarised in the table below.

Key features of the included evidence

| Study | N | Design/ duration | Risk of bias | Population | Outcome |
|-------------------------------------|--------------------|---|-----------------|---|---|
| Vytorin® Compliance Study IV | | | | | |
| Cohort 1 - Current MPR | 1,230 ^b | Retrospective historical cohort (10% Medicare sample); reported as between 2006 and 2013 ^a | High | Switched from concomitant therapy to Vytorin® – other characteristics unknown | Medication possession ratio for Vytorin® (MPR) |
| Cohort 1 - Current CMG | 1,205 | | | Switched from concomitant ezetimibe + atorvastatin/ simvastatin/ rosuvastatin to Vytorin® and at least 3 scripts of each item | Continuous measure of medication gap for Vytorin® (CMG) |
| Cohort 1 - Comparative MPR | 304 | | | Switched from concomitant ezetimibe + atorvastatin/ simvastatin/ rosuvastatin to Vytorin®, at least 3 scripts of each item, sub-optimally compliant to statin (MPR) | Medication possession ratio (MPR) |

| | | | | | |
|-----------------------------------|--------|---|------|--|---|
| | | | | between 27.5% and 82.5%) and Vytorin® MPR <102.5% | |
| Cohort 1 - Comparative CMG | 500 | | | Switched from concomitant ezetimibe + atorvastatin/ simvastatin/ rosuvastatin to Vytorin®, at least 3 scripts of each item, sub-optimally compliant to statin (CMG <82.5%) | Continuous measure of medication gap (CMG) |
| Cohort 2 | 16,594 | | | Dispensed ezetimibe or Vytorin® | Persistence to ending ezetimibe formulation |
| Commissioned market survey | | | | | |
| General practitioners | 192 | Cross-sectional online survey July 2014 | High | GPs working ≥ 4 days and who actively prescribe Vytorin® (regularly or occasionally) | - |
| Patients | 189 | | | Patients on Vytorin® or any statin + ezetimibe for at least 6 months | - |

Source: compiled during the evaluation

Abbreviations: CMG, continuous measure of medication gap; GPs, general practitioners; MPR, medication possession ratio

^a There appear to be data available beyond the reported study period

^b Also reported as 1,203 patients in the submission

- 6.10 Three additional published studies were identified as being relevant: two systematic reviews (De Vera et al. epub 2014 and Mann et al. 2010) and one retrospective observational study (Simons et al. 2011).
- 6.11 The evaluation concluded that the Vytorin Compliance Study IV was at high risk of bias (for both Cohort 1 and Cohort 2). The systematic reviews which were largely based on observational data were also considered at high risk of bias.
- 6.12 The submission did not present data or make any claim under subsection 101(4AC) on the comparative efficacy or toxicity of Vytorin over its alternative therapies.

Comparative compliance to therapy

- 6.13 The April 2010 CMWG report to the PBAC provides a framework based on important questions from a funder perspective in evaluating evidence to support claims of increased compliance to combination items. The submission and these Minutes are structured around these six questions.

What is currently known about the level of compliance with Vytorin? (Question 1 in the CMWG report)

- 6.14 The submission reviewed the literature and undertook analyses of PBS data to measure the current level of compliance with Vytorin.
- 6.15 Two studies from the literature review reporting on the current level of compliance to Vytorin: Hildemann (2008) and Kamat (2011) were presented by the submission.
- 6.16 The study by Hildemann (2008) concluded that, compared to patients with therapy discontinuations or switches, those remaining on the combination had better outcomes regarding lipid status. DUSC noted that the sponsor had acknowledged some limitations of the study and agreed with the evaluation that the study had a high risk of bias and lacked clarity on other included therapies. DUSC added that:

- The populations in the study were not comparable. The cohort of patients remaining on the combination was subject to survivor bias; and the cohort of patients switching or discontinuing was subject to non-responder bias.
 - The paper did not report the baseline characteristics of the study populations separately, nor did it report lipid profile results at 8 weeks separately.
 - The study has low applicability to the Australian population, particularly noting that the majority of patients were on ezetimibe/simvastatin 10 mg/10 mg and 10 mg/20 mg, where as in Australia 10 mg/40 mg and 10 mg/80 mg are the most commonly prescribed strengths.
- 6.17 For the above reasons, DUSC considered that Hildemann (2008) did not provide any evidence on the overall compliance to Vytorin or the concomitant or alternative therapies available on the PBS. DUSC concluded that the evidence was insufficient for ascertaining that any reported differences in lipid levels or compliance are due to differences arising from using a combination item.
- 6.18 The second study by Kamat (2011) concluded that adherence to single pill statin combinations including Vytorin is statistically significantly higher than adherence to multiple pill statin regimens, based on the proportion of days covered (PDC) of 56% versus 47% respectively. This study used the PDC method to compare adherence between the two study groups. DUSC considered that:
- The method biases in favour of the single pill combination. It did not allow flexible allocation of days around the dispensing of separate prescriptions on different days and favours single pill combinations, which by default are dispensed on the same day.
 - There were differences between the study groups – patients on the separate components were sicker as indicated by more hospitalisations and more co-morbidity at baseline. Furthermore, the odds ratios presented in Table 4 of the publication show that patients with pre-existing cardiovascular disease will be more compliant, independent of whether they are on the single or multi-pill regimen.
 - The study may not be applicable to the Australian population noting that adherence in both groups of this study was very low compared to that measured in the PBS population taking statins and ezetimibe.
- 6.19 For measuring compliance, the submission provided a retrospective cohort study (Cohort 1) based on PBS data and two adherence measures: MPR and CMG in the Vytorin population.
- 6.20 Patients were included in Cohort 1 if they had been dispensed at least three prescriptions of Vytorin within the study period (2006-2013) and were on concomitant therapy with any statin and ezetimibe 'immediately prior' to Vytorin. The number of patients in Cohort 1 was not clearly and consistently presented in the submission. Cohort 1 is presented as 1,203 and 1,230 records in the submission MPR analysis, and 1,205 records for the submission CMG analysis. The evaluation was unable to replicate all of the values presented in the submission.
- 6.21 For the initial analysis for the complete Cohort 1 (approximately 1,200 patients), the submission reported a mean MPR of 92% and mean CMG of 84% for Vytorin.

- 6.22 The evaluation noted that the submission did not present the current level of adherence for the vast majority of patients on PBS Vytorin or the concomitant therapies, only those who meet the criteria for inclusion in Cohort 1 (i.e. those on 'concomitant' therapy with statin and ezetimibe 'immediately prior' to switching to Vytorin receiving at least 3 scripts of each item).
- 6.23 In addition, the evaluation noted that no comparison of adherence measures for the same group (complete Cohort 1) pre-Vytorin were presented in the submission. This comparison was performed by the evaluator and it was found that adherence was similar in this group (i.e. MPR to a statin, 88.9%, or ezetimibe, 88.3%, prior to switching to Vytorin).
- 6.24 The adherence presented in the submission for Vytorin and the adherence calculated by the evaluation for statin and ezetimibe in the pre-Vytorin period, are provided in the table below.

Adherence results for complete Cohort 1

| | Vytorin® | Statin | Ezetimibe |
|---|--|-----------------------------|----------------------------|
| Number of records | 1,205 ^a | 1,205 | |
| Mean duration of medication supplied in yrs | 2.78 ^b | NE | |
| Mean length of pre/post-period in yrs ± SD | 3.40 ^a ± 2.45 | 1.80 ± 1.45 | |
| Median length of pre/post-period in yrs (quartiles) | 2.84 (1.15, 5.64) | 1.36 (0.80, 2.26) | |
| MPR | | | |
| Mean ± SD | 92.21% ± 14.20% | 88.89% ± 17.46% | 88.25% ± 16.81% |
| Median (quartiles) | 95.45% (87.48%, 99.12%) | 92.51% (81.36%, 98.90%) | 92.49% (80.07%, 98.90%) |
| 10 th percentile | 74.06% | 65.69% | 65.50% |
| 90 th percentile | 102.77% | 103.45% | 103.45% |
| CMG | | | |
| Mean ± SD | 84.20% ^b ± 11.58% | 80.87% ± 14.44% | 82.69% ± 13.22% |
| Median (quartiles) | 87.47% (79.98% ^b , 91.98%) | 84.89% (75.384%, 90.60%) | 86.46% (77.43%, 91.80%) |
| 10 th percentile | 69.41% ^c | 61.48% | 64.53% |
| 90 th percentile | 95.62% | 94.20% | 94.91% |

Source: Adapted from Tables B.1.2-4 to B.1.2-5 (p27) of the submission and calculated during the evaluation.

Abbreviations: CMG, continuous measure of medication gap; MPR, medication possession ratio; NE, not estimated; SD, standard deviation; yrs, years

^a Attempts during the evaluation at duplicating the submissions results for existing MPR level failed (unable to replicate N=1,203 or 1,230 or the results). Due to premature rounding, the value in the evaluation (1,205) does not match the values reported in the submission.

^b The average medication supplied and length of period were not defined. The length of period was calculated using the column for length of pre-period and post-period+30 days during the evaluation.

^c There were slight discrepancies compared to values calculated during the evaluation - may be due to rounding differences

- 6.25 DUSC noted that compliance to the components given concomitantly was high prior to switching to Vytorin (i.e. MPR to a statin, 88.9%, or ezetimibe, 88.3%, prior to switching to Vytorin), and continued to be high after switching to Vytorin (MPR 92.2%). Although the MPR for Vytorin was numerically higher, there was no evidence that this is a clinically significant difference.
- 6.26 The evaluation identified a number of limitations of the adherence analysis including a lack of transparency in the reporting of the study, with limited information provided

on the definitions used. The evaluation also observed that there were concerns regarding the validity of the data, and that it was difficult to verify the results. No measures of uncertainty around the differences were presented. Limited statistical testing and sensitivity analyses were provided.

- 6.27 In the PSCR, the sponsor provided some additional information on the Vytorin Compliance Study IV design. The PSCR (p.2) stated that 'Previous compliance submissions were criticised for utilising different patient cohorts [8.2.ESC ADV Nov 2008] and thus the sponsor has tried to use the same patients i.e. those that have dual therapy for a period of time and then also used Vytorin for a period of time to enable a compliance comparison. This limits the selection bias which is a common concern raised in the CMWG paper and associated with most studies measuring compliance benefits.' DUSC considered that inherent biases remain in the study design when comparing adherence measures in the same population pre and post a switch to Vytorin: Comparisons before and after a switch to Vytorin may introduce time-dependent confounding. The submission did not provide a comparison with a similar population who see the doctor for a new prescription and continue on a statin + ezetimibe separate pill combination.
- 6.28 DUSC raised the following additional methodological concerns:
- The pre-Vytorin and post-Vytorin time periods were non-equivalent: the look back period was shorter than the look forward period on average. The scatter plots presented in Figure B.1.3 of the evaluation indicated that there is likely a different application of the method in the pre- and post-Vytorin period.
 - The definitions of MPR and CMG in the submission logically imply that MPR must always be greater than CMG. Figure B.1.3 shows that this is the case for Vytorin for all 1,205 patients in the post-period. However in the pre-period there are many instances where MPR is less than CMG. This most likely introduces a bias, with MPR being less in the pre-period compared to the post-period.
 - The reason for MPR being less than CMG in the pre-period is not clear. One possibility is that although inclusion criteria included the concomitant use of both ezetimibe and a statin supplied as separate products, the start date of the pre-period is defined by the date of the first prescription of the second drug initiated (in most cases this would be the first ezetimibe prescription, as ezetimibe is usually added to a statin and not vice versa). For example, if a statin was supplied on 1/1/2010 and the patient's first ezetimibe was supplied on 15/1/2010 then the period start date would be 15/1/2010. However if the next statin script was supplied on 1/2/2010 and this was counted as the first statin script in the period then, in the calculation of the statin MPR, the first 14 days of the pre-period will be included in the denominator, but not in the numerator. This would artificially lower the value of MPR. This scenario is not possible in the post-period as the start date is only determined by one product (i.e. Vytorin). As a consequence, DUSC agreed with the evaluation that it is not possible to ascertain if the small difference in compliance in the pre- and post-Vytorin period is a real difference or an artefact of the method.
 - The submission defined discontinuation as a gap of at least 183 days (6 months). The evaluation considered that there did not appear to be a clinical basis for the gap duration selection. Table 1 of the PSCR states that '...any less and you get a lot of poorly compliant patients that interferes with the data...'. DUSC noted that a

gap of 6 months allows for some inclusion of restart and overall considered the gap to be reasonable.

- Table 1 in the PSCR stated that patients do have to have an overlap in therapy to define co-administration. However, DUSC considered that there may still be patients included who do not have overlapping supply of any duration. For example three statin supplies followed by three ezetimibe supplies. The effect of this on the MPRs for the individual component pre-Vytorin is unknown.
- The PSCR (p1) claimed that “the DUSC PVA Utilisation Analysis for Vytorin 10/10 and 10/20mg being considered at this same meeting (Item 7.5 October 2014) has shown that the number of prevalent patients on ezetimibe, including Vytorin is increasing over time, thereby further supporting MSD’s claim of a compliance benefit associated with Vytorin.” DUSC considered that the utilisation report shows that there are a lot of patients on ezetimibe and Vytorin. DUSC did not agree with the Sponsor’s claim that this supports a compliance benefit under subsection 101(4AC) of the Act as it does not establish the compliance of Vytorin compared with alternate therapies.

- 6.29 The PBAC noted that pre-PBAC response restated the definitions used for the pre- and post-Vytorin analyses, but did not explain the reason the MPR is less than CMG in the pre-period. Therefore, it was not possible to ascertain if the small difference in compliance in the pre- and post-Vytorin period is a real difference or an artefact of the method.
- 6.30 The submission also undertook a persistence analysis (Cohort 2). DUSC considered that the submission’s approach of assigning a patient to either the ezetimibe or Vytorin curve was likely to be subject to survivor bias, favouring Vytorin. This issue was further dealt with under Question 4 below.
- 6.31 Overall, DUSC considered there were biases and applicability issues in the studies and analyses presented.
- 6.32 DUSC also noted that compliance is high with both Vytorin and the component agents given concomitantly.

What is known about the factors that affect compliance to lipid lowering therapies? (Question 2 in the CMWG report)

- 6.33 From a literature review the submission identified age, co-morbid conditions requiring increased pill burden, costs and adverse events as the main factors associated with non-compliance.
- 6.34 The evaluation considered that these factors appear inconsistent with the presented observational evidence. Pill burden does not appear to be consistently associated with non-compliance. The presence of hypertension and diabetes, and previous cardiovascular disease is associated with better compliance. Increased lipid testing is a factor predicting compliance not identified by the submission.

- 6.35 DUSC considered that the Warren (2013) paper¹ is the most applicable for identifying factors that influence compliance in the Australian environment. The study reports high rates of compliance that are comparable to those in the current submission and in the 2012 statin review.²
- 6.36 The Warren (2013) paper was identified, but not discussed in detail in the submission. This paper reported that:
- Poor adherence to statins is associated with smoking, employment, higher levels of education, those who speak a language other than English at home and psychological distress.
 - Increased adherence to statins is associated with older age, poor self-rated health, pre-existing heart conditions, obesity and private health insurance.
- 6.37 Overall, DUSC considered that factors affecting compliance to medicines need to be established in the Australian setting. Warren (2013) is applicable for identifying these factors.

How and to what extent can Vytorin affect the factors contributing to non-compliance? (Question 3 in the CMWG report)

- 6.38 The submission addressed this question with literature searches, plausible explanations and market research.
- 6.39 The market research was a commissioned market survey of patients and general practitioners. The evaluation considered that the survey design and questions may have influenced the results. Some responses rely on recall of practice, thus may be subject to recall bias. The representativeness of the patient population was unknown. The results for general practitioners were not representative as general practitioners who do not prescribe Vytorin were excluded.
- 6.40 The key findings of the commissioned market survey included:
- The average number of days per month (30 days) that patients report taking Vytorin was 29 days, whereas patients on concomitant therapy report taking **both** tablets for an average of 25 days. The submission therefore claimed that the use of two tablets results in a 14% reduction in adherence. It was unclear whether patients on Vytorin and patients on concomitant therapy were comparable and whether anchoring the question to both tablets for patients on concomitant therapy may underestimate compliance.
 - Patients are price sensitive and rely on medical advice. The presentation (i.e. one or two tablets; two tablets in one or two boxes) appears to have limited impact on anticipated acceptance, compliance or persistence (anchored to lifetime) for the majority of patients.
 - General practitioners who prescribe Vytorin believe that Vytorin improves compliance (compared to two tablets) and reduces the out-of-pocket costs to patients.

¹ Warren JR, Falster MO, Fox D, Jorm L. Factors influencing adherence in long-term use of statins. *Pharmacoepidemiol Drug Saf* 2013; 22(12):1298-1307.

² www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2012-07/review-of-statin-therapies

- The presence of adverse events was identified by both general practitioners and patients as a factor with the most potential impact on persistence, with patients identifying cost of medication as another factor.
- 6.41 The submission considered that age may affect compliance. In the patient survey, 72% of the patients taking Vytorin were ≥55 years. DUSC noted that the Warren (2013) study found that older age was associated with increased adherence. The submission also considered that co-morbidity may affect compliance. The Warren (2013) study showed prior disease is associated with improved compliance. There was conflicting evidence in the literature on the relationship between pill burden and compliance with studies suggesting increased pill burden is associated with increased or decreased compliance.^{3,4}
- 6.42 The submission considered that adverse events may affect compliance. DUSC considered that adverse events are a pharmacological issue, not a compliance issue and the two issues should not be conflated. The same pharmacological ingredients are contained in both Vytorin and the separate pill regimen of ezetimibe and simvastatin. The PBS restrictions require patients to be on the maximally tolerated dose of a statin before adding ezetimibe.
- 6.43 The submission considered that cost to patients may affect compliance. DUSC agreed that the market research infers that Vytorin may improve compliance in some patients because of reduced patient cost (i.e. one co-payment instead of two). In the unprompted GP answers in the market research, cost was the main driver of medication cessation followed by side effects, then too many tablets and news stories. For 40% of patients, the costs of medication were found to have a very big impact on medication cessation; whereas the number of tablets had much less impact.
- 6.44 Overall, DUSC concluded that patient cost is a driver for switching from component products to a FDC. However, while Vytorin can help to address costs, DUSC considered that this creates a question about the appropriateness of addressing an overall policy issue on co-payments with a case by case fix through a FDC.

Is there evidence available to show that there are measured differences in compliance and, if so, that these are associated with use of Vytorin versus its alternative therapies? (Question 4 in the CMWG report)

- 6.45 The submission measured differences in compliance of Vytorin against concomitant statin and ezetimibe, in the same patient, using subpopulations of the retrospective cohort study (Cohort 1) based on PBS data and the two adherence measures: MPR and CMG. Persistence to therapy was also measured in a different cohort (Cohort 2).
- 6.46 Methodological concerns regarding the MPR and CMG analyses raised by the evaluator and by DUSC were presented under Question 1 (What is currently known

³ Zuckerman IH, Sato M, Rattinger GB, et al. Does an increase in non-antihypertensive pill burden reduce adherence with antihypertensive drug therapy? *Journal of Pharmaceutical Health Services Research*. 2012;3(3):135-9.

⁴ Shalansky S, Levy A. Effect of number of medications on cardiovascular therapy adherence. *The Annals of pharmacotherapy*. 2002;36(10):1532.

about the level of compliance with Vytorin?). The same issues were relevant for the analysis presented in Question 4 of the submission.

- 6.47 The adherence analysis presented focused on patients that the submission considered to be ‘most in need of improved compliance’. The submission identified patients from Cohort 1 who recorded MPR or CMG scores <85% to a statin prior to switching to Vytorin leaving n=304 for the MPR analysis and n=500 for the CMG analysis. The evaluation could not replicate the results but noted that the submission appeared to apply a threshold of 82.5%, likely due to premature rounding.
- 6.48 The submission claimed that several studies have demonstrated that MPR >80% is associated with significantly greater reduction in LDL and reduced cardiovascular events. This is discussed under Question 5.
- 6.49 In the group of 304 patients on concomitant therapy with an MPR score <85% prior to switching to Vytorin, the submission found a 14% improvement in MPR versus the statin component and a 6% improvement versus the ezetimibe component, based on the differences in mean MPRs. The mean MPR prior to initiation of Vytorin for statin was 67% and for ezetimibe was 75%. After initiation to Vytorin, the MPR for Vytorin was 81%.
- 6.50 The adherence results, pre- and post-initiation with Vytorin, for the subpopulation with an MPR score <85% to a statin prior to switching to Vytorin, are shown in the table below.

Adherence results for the MPR base population

| | Vytorin® | Statin | Ezetimibe |
|---|----------------------------|----------------------------|----------------------------|
| Number of records | 304 | 304 | |
| Mean duration of medication supplied in yrs | 2.67 ^a | 1.03 ^a | |
| Mean length of pre/post-period in yrs ± SD | 3.20 ^a ± 2.35 | 1.51 ± 1.13 | |
| Median length of pre/post-period in yrs (quartiles) | 2.49 (0.97, 5.14) | 1.19 (0.71, 1.96) | |
| MPR | | | |
| Mean ± SD | 81% ± 15.91% | 67% ± 12.84% | 75% ± 18.22% |
| Median (quartiles) | 84.30% (69.74%, 94.04%) | 71.66% (58.95%, 77.41%) | 75.91% (63.29%, 89.40%) |
| CMG | | | |
| Mean ± SD | 75.82% ± 14.12% | 64.60% ± 14.34% | 71.57% ± 15.88% |
| Median (quartiles) | 78.90% (67.32%, 86.48%) | 68.44% (56.56%, 74.21%) | 74.05% (62.59%, 84.00%) |

Source: Adapted from Table B.4-1 (p64) of the submission. *Additional data calculated during the evaluation.*

Abbreviations: CMG, continuous measure of medication gap; MPR, medication possession ratio; SD, standard deviation; yrs, years

^a The duration of medication supplied and length of period were not defined. The length of period was calculated using the column for length of pre-period and post-period+30 days during the evaluation

- 6.51 The evaluation considered that selection of patients who were sub-optimally compliant to the statin component was a likely driver of the apparent larger improvement in the MPR results to the statin component. The results of the CMG were numerically lower than the MPR results. No measures of uncertainty around the differences were presented.
- 6.52 Similarly, the evaluation considered that the selected cohort represented only a small

proportion of patients who qualify for PBS-subsidised Vytorin, and also considered that it may not be applicable to the broader population of patients on Vytorin (e.g. those who initiate Vytorin following statin monotherapy). The evaluation further noted the results indicate that not all Vytorin patients in the selected cohort achieve the nominate threshold of 80%.

- 6.53 The submission claimed that 156 of the 304 patients (51%) demonstrated an improvement in MPR >10% when switched to Vytorin, regardless of their previous statin.
- 6.54 DUSC considered that the clinical significance of an improvement in MPR >10% had not been established for Vytorin.
- 6.55 DUSC noted that the number of people in the MPR analysis (N=304) is a small subset of Cohort 1 (N ≈ 1,200) and a very small subset of all Vytorin patients identified in the persistence analysis data (N=14,806). DUSC also noted that the 156 patients with a claimed improvement in MPR >10% represented approximately 1% of the total population who started Vytorin in Cohort 2 (n=14,806), and that standard deviations were large and statistical significance was not reported.
- 6.56 The PBAC noted that the pre-PBAC response considered the 1% ratio cited by DUSC to be incorrect due to an arithmetic error. The sponsor contended that the 1% is a ratio between two unrelated numbers stating that 'The denominator is the total number of patients in Cohort 2 – i.e. all patients who ever started ezetimibe (in whatever form) in combination with a statin, to measure their persistence to therapy'. The PBAC noted that DUSC was highlighting the very small size of the cohort relied upon for the key submission claims in the context of the number of patients dispensed Vytorin over the study period (2006 to 2013 for both cohorts). That is, the 14% mean improvement in MPR for Vytorin compared to concomitant statin + ezetimibe was based on 304 patients, of whom 156 had an increase of >10% in MPR. The PBAC also noted that the number of patients dispensed Vytorin between 2006 and 2013 provided in the submission for Cohort 2 varies depending on whether the count is based on the number of patients receiving Vytorin at the beginning of the study period (n=14,806), at the end of the study period (n=14,342), at start or finish (n =15,830), or receiving ezetimibe in whatever form (n=16,594). Regardless, DUSC's observation that the subpopulation relied upon in the submission to demonstrate an improvement in MPR by >10% represented approximately 1% of patients dispensed a prescription for Vytorin during the 2006 to 2013 study period remains the same.
- 6.57 The submission undertook further analysis to identify those patients who receive a significant compliance benefit with Vytorin. The submission presented results stratified by age of switch versus the statin component. The submission considered that older patients (≥65 years) represent an important segment of those treated with lipid lowering therapy. Of the subpopulation of 304 patients on concomitant therapy with an MPR score <85% prior to switching to Vytorin, 115 patients were aged 65 years and older. Of these 115 patients, 80% demonstrated any improvement in statin MPR, with 63% (73 patients) experiencing an improvement of >10% after switching to Vytorin. The evaluation found that the classification of patients by level of change in MPR appeared to be subject to premature rounding, and could not be verified by the evaluation.

- 6.58 Of the 73 patients aged 65 years and older with a statin MPR improvement of >10%, the mean statin MPR improvement was 27% [median not reported]. The submission used the evidence from this subgroup to claim that Vytorin provides improvement in patient compliance for some patients as required under subsection 101 (4AC) of the Act. No measures of uncertainty around the difference in the MPRs were presented. The submission did not present descriptive statistics of the adherence measures for this subgroup.
- 6.59 The CMG analysis subgroup reported by the submission included more patients (n=500) compared with the MPR analysis subgroup (n=304). The results for the CMG analysis subgroup are presented in the table below.

Adherence results for the CMG base population

| | Vytorin® | Statin | Ezetimibe |
|---|----------------------------|----------------------------|----------------------------|
| Number of records | 500 | 500 | |
| Mean duration of medication supplied in yrs | 2.45 ^a | 1.19 ^a | 1.26 ^a |
| Mean length of pre/post-period in yrs ± SD | 3.20 ^a ± 2.40 | 1.69 ± 1.31 | |
| Median length of pre/post-period in yrs (quartiles) | 2.50 (0.99, 5.18) | 1.33 (0.76, 2.15) | |
| MPR | | | |
| Mean ± SD | 86.93% ± 17.85% | 76.80% ± 18.01% | 80.13% ± 18.18% |
| Median (quartiles) | 90.95% (77.22%, 97.57%) | 78.66% (66.39%, 87.98%) | 82.99% (68.11%, 93.56%) |
| CMG | | | |
| Mean ± SD | 79% ± 13.68% | 68% ± 14.05% | 75% ± 14.84% |
| Median (quartiles) | 81.98% (72.33%, 88.39%) | 72.61% (61.73%, 78.55%) | 77.92% (67.51%, 85.27%) |

Source: Adapted from Table B.4-2 (p65) of the submission. *Additional data calculated during the evaluation.*

Abbreviations: CMG, continuous measure of medication gap; MPR, medication possession ratio; SD, standard deviation; yrs, years

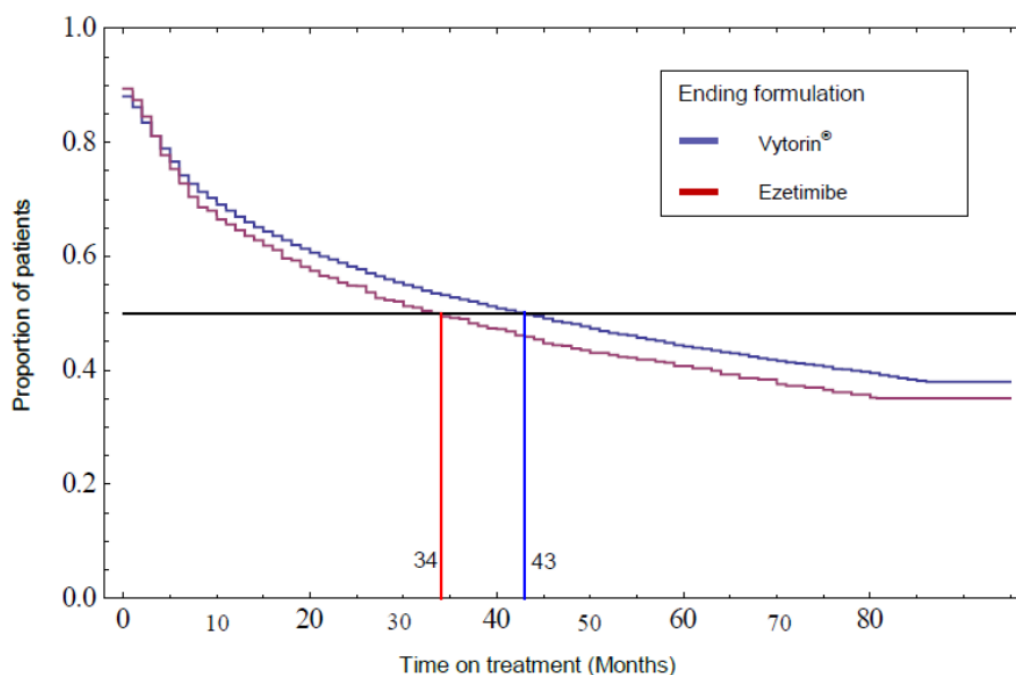
^a The duration of medication supplied and length of period were not defined. The length of period was calculated using the column for length of pre-period and post-period+30 days during the evaluation.

- 6.60 The submission claimed that based on the differences in mean CMG in the 500 patient CMG cohort, patients switching from concomitant therapy to Vytorin experienced an 11% improvement in CMG versus the statin component and a 4% improvement versus the ezetimibe component. Similarly, the evaluation considered that the larger improvement in CMG versus the statin component was likely to be driven by the selection of sub-optimally compliant patients to the statin component.
- 6.61 When analysing CMG the submission claimed ‘that the patient cohort experienced a mean gain in both statin and ezetimibe. Half of patients aged 65 and over, showed an improved statin CMG of >10%’. DUSC reiterated its concern that the cohorts for measuring CMG and MPR were different and therefore the benefit of using multiple measures of compliance was diminished.
- 6.62 DUSC also noted that, whilst there were greater improvements in MPR and CMG for the older age-groups, 19-22% of people less than 55 years had a worse MPR (of the n=304 cohort) and 23-28% of those less than 55 years that had worse CMG (of the n=500 cohort). From the literature, younger patients are also the group where

compliance is poorer.

- 6.63 The submission also estimated persistence in patients receiving Vytorin or the two pill regimen of simvastatin and ezetimibe in Cohort 2 using a Kaplan Meier analysis. Patients were included in Cohort 2 if they were dispensed a prescription for Vytorin or ezetimibe as a single agent (Ezetrol).

The results of this analysis are reproduced below:



| Number at risk | | | | | | | | | Ending formulation |
|----------------|-------|-------|-------|-------|-------|-------|-------|-----|--------------------|
| 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | |
| 15,366 | 9,333 | 7,181 | 5,720 | 4,603 | 3,567 | 2,629 | 1,768 | 858 | Vytorin® |
| 1,228 | 763 | 579 | 442 | 355 | 273 | 219 | 144 | 69 | Ezetimibe |

- 6.64 The submission claimed that the ‘bottom 50% of patients, in relation to persistence, gain an additional ten months when treated with Vytorin versus concomitant ezetimibe and a statin’.
- 6.65 The evaluation identified limitations of the persistence analysis including that limited information was provided regarding the rules and definitions used, classification based on the last script did not allow accurate classification exposure, it was unclear whether the comparison groups were similar due to a lack of baseline characteristics, and there were no statistical tests, measures of uncertainty or sensitivity analyses presented in the submission, and there were no adjustments for confounding. Further, the submission did not report the patient numbers informing the analyses. There appeared to be a large difference in the number of patients whose last dispensed formulation was Vytorin versus ezetimibe (15,366 versus 1,228). There was a large amount of censoring in the dataset and the reasons for censoring patients were not provided, and there were apparent differences in the pattern of switching based on the starting and ending therapy.

- 6.66 DUSC considered this analysis was flawed because the patients were allocated to the ezetimibe or Vytorin arms based only on their last prescription dispensed. This was likely to favour Vytorin because of “survivor” bias. That is, a patient that persists is more likely to be switched from ezetimibe + any statin to Vytorin, than vice versa.
- 6.67 DUSC advised the PBAC that the data analyses presented in the submission provided insufficient evidence to determine if a compliance advantage exists for Vytorin. There were methodological issues with the compliance analyses presented including time-dependent bias, possible differences in application of methods pre- and post-Vytorin, and that the compliance measures were assessed in different groups. DUSC considered that the persistence analysis did not support a claim of improved compliance because the impact of last script ascertainment on grouping was not able to be assessed.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

Identification and review of data that supports the claim that the compliance benefit associated with Vytorin is sufficient to affect health outcomes (e.g. MI, mortality) in the appropriate Australian patients (Question 5 in the CMWG report)

- 6.68 The submission stated that the literature search for the current compliance benefit for Vytorin located only two studies that assessed compliance to Vytorin. Of these, only one study reported lipid profiles (Hildemann et al. 2008). Therefore, the search strategy was widened to include compliance to statins. The submission claimed that any improvement in adherence to Vytorin implies an improvement to the statin component.
- 6.69 In the context of Question 5 of the CMWG report, the submission included three systematic reviews (Chowdhury et al. 2013), Gomez et al. (2013) and Simpson et al. (2010)), one narrative review and 24 observational studies. A targeted independent search by the evaluation located other potentially relevant studies (De Vera et al, epub 2014 was included in the evaluation as it is a systematic review).
- 6.70 The submission further nominated Haukka et al (2012) to translate the claimed adherence benefit to clinical outcomes. The submission also used another unidentified study (which may have been Rasmussen et al (2007)) to translate the claimed adherence benefit.
- 6.71 The submission did not investigate the compliance benefits of Vytorin versus statin monotherapy, or the compliance benefit of ezetimibe, on patient-relevant outcomes.
- 6.72 The submission claimed that switching patients from concomitant ezetimibe and statin to Vytorin results in a mean improvement in MPR from 67% to 81% based on the analyses from the Vytorin Compliance Study IV, indicating that the average patient on Vytorin would have good compliance. The submission claimed that this translates to a reduction in mortality risk of 12% in Vytorin treated patients compared with patients treated with concomitant ezetimibe and statin (appeared to be based on Rasmussen et al. 2007). The submission argued that there would also be reductions in non-fatal cardiac events and hospitalisations. The submission claimed that similar results would be seen if CMG was used as the measure of compliance.

- 6.73 The submission further claimed that patients aged over 65 years derive the most substantial compliance benefit from being switched to Vytorin, estimating that the mean improvement in MPR of 27% [median not reported] seen in among the 73 patients aged 65 years and over with an MPR improvement of >10% translates into approximately a 15% reduction in coronary artery disease mortality (Haukka et al. 2012). The submission stated that although the mean CMG improvement was lower (17%), this would still translate into a reduction in coronary artery disease mortality of almost 10%.
- 6.74 The evaluation identified the following reasons why the submission's claims with respect to a compliance benefit being sufficient to affect health outcomes may have been inadequately supported:
- The authors of the systematic review by De Vera et al. (2014), identified confounders and biases (including 'healthy adherer' bias) as limitations of the review.
 - Limitations of the Chowdhury et al. (2013) systematic review included the 'healthy adherer effect', the inclusion of studies based on medication databases using a wide range of definitions of adherence with arbitrary thresholds to define good adherence, and heterogeneity among studies which were only partially explained by differences in location, study design and sample size. Testing for publication bias indicated a lack of smaller studies that may have identified a null or negative association between statin adherence and cardiovascular events. The high I^2 values indicated statistically significant heterogeneity across the meta-analysed studies in Chowdhury et al. (2013).
 - Limitations of the Gomez et al. (2011) systematic review included methodological differences across studies precluding meta-analyses and the evidence base was mostly studies using claims databases.
 - The observational study by Hildemann et al. (2008) was considered by the evaluation to be at high risk of bias and the results to be largely uninformative.
 - The submission argued that LDL-C is a valid surrogate outcome, as the correlation between LDL-C level and cardiovascular events has been noted, particularly in secondary prevention. The submission referenced the systematic review by Delahoy et al. (2009) aimed at quantifying the relationship between the reduction in LDL-C achieved by statin treatment and reduction in cardiovascular risk. The review found a significant positive relationship between the reduction in LDL-C and reduction in the risk of major cardiovascular events. However, the evaluation noted that the ENHANCE trial found no significant differences in the changes in intima-media thickness of the walls of the carotid and femoral arteries between concomitant ezetimibe and simvastatin versus simvastatin alone in patients with familial hypercholesterolaemia despite decreases LDL-C levels (Kastelein et al. 2008).
 - No direct evidence had been provided by the submission suggesting that improved compliance to Vytorin is associated with improvements in cardiovascular and mortality outcomes.
 - The magnitude of benefit associated with increased adherence to statins appeared to differ between observational studies (which are prone to bias and unknown confounding), thus the evaluation considered that any translation of the claimed compliance benefits was highly uncertain.

- Given the known heterogeneity across the compliance studies that is only partially explained by location, study design and sample size, the selection of the two studies (Haukka et al. 2012 and Rasmussen et al. 2007) to translate the claimed adherence benefit to clinical outcomes was considered by the evaluation to be inadequately justified. The studies used different measures of adherence. Rasmussen et al. (2007) included elderly Canadians post-acute myocardial infarction. Haukka et al. (2012) was in Finnish patients. These studies may not be applicable to the Vytorin Compliance Study IV and the broader Australian population.
- Any quantification of the claimed compliance benefits was highly uncertain, due to the use of observational studies. The submission did not indicate the use of relative measures in quantifying the claimed reduction in mortality from Rasmussen et al. (2007). The baseline mortality risk, and therefore the claimed absolute risk reduction, was unknown. The submission inappropriately applied population aggregate data to categories assigned to individual patients in Rasmussen et al. (2007). There were patients who did not achieve 'high' adherence on switching to Vytorin. It was unclear whether Haukka et al. (2012) reported relative measures for the results used to translate the claimed compliance benefit.

- 6.75 DUSC added that the majority of observational studies assessing compliance and outcomes suffer from immortal time bias, due to the fact that participants are assessed as compliant or not compliant and then subsequently the same time period in which compliance is assessed is used to ascertain the outcome. That is those who remain compliant on therapy in the study have done so because they have not suffered from more severe disease causing them to die or be hospitalised etc. DUSC considered that this is often not well recognised in published studies.
- 6.76 DUSC considered a key issue to be that there was no randomised controlled trial evidence to show that the addition of ezetimibe to a statin improves health outcomes.
- 6.77 Overall, DUSC considered that the literature review in the submission provided insufficient evidence to determine if an improvement in compliance in Vytorin users of 10% or more is associated with improved health outcomes.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Cost to the government of providing compliance advice over the next five years (Question 6 in the CMWG report)

- 6.78 Vytorin currently costs the PBS more than the individual components given concurrently, and atorvastatin with ezetimibe.

| Current Ex-Man Prices | | | | | |
|---|--------------|---|--------------|---|--------------|
| Sum of components (Ezetimibe with Simvastatin) | | Vytorin (Ezetimibe with Simvastatin) | | Atozet Composite Pack (Ezetimibe and Atorvastatin) | |
| Strength | Ex-Man Price | Strength | Ex-Man Price | Strength | Ex-Man Price |
| 10 / 10 mg | \$56.69 | 10 / 10 mg | \$69.64 | 10 / 10 mg | \$59.61 |
| 10 / 20 mg | \$57.62 | 10 / 20 mg | \$76.24 | 10 / 20 mg | \$62.00 |
| 10 / 40 mg | \$58.95 | 10 / 40 mg | \$85.76 | 10 / 40 mg | \$65.03 |
| 10 / 80 mg | \$60.86 | 10 / 80 mg | \$99.39 | 10 / 80 mg | \$69.52 |

Prices current at 1 October 2014. Ex-man price for ezetimibe is \$54.57.

- 6.79 The submission investigated the financial impact of maintaining the current prices of Vytorin (with the price premium due to the November 2008 compliance advice) versus the potential price based on the expected prices of the individual components as of 1 October 2014. The estimates were informed by Vytorin PBS items statistics data available online, excluding RPBS prescriptions. DUSC noted that the net cost to PBS of maintaining the Vytorin price premium was estimated by the submission to be \$30 million per year and \$150 million over 5 years. These estimates are summarised in the table below:

Estimated utilisation and cost to the PBS in the first five years of listing

| | 2014 | 2015 | 2016 | 2017 | 2018 |
|---|---------------------|---------------------|---------------------|---------------------|---------------------|
| Number of items of Vytorin® (Assumption 0% growth from 2013) | | | | | |
| 10mg – 10mg | 45,438 | 45,438 | 45,438 | 45,438 | 45,438 |
| 10mg – 20mg | 61,963 | 61,963 | 61,963 | 61,963 | 61,963 |
| 10mg – 40mg | 368,726 | 368,726 | 368,726 | 368,726 | 368,726 |
| 10mg – 80mg | 330,244 | 330,244 | 330,244 | 330,244 | 330,244 |
| Total | 806,371 | 806,371 | 806,371 | 806,371 | 806,371 |
| Cost to PBS of Vytorin® if compliance advice is maintained | | | | | |
| 10mg – 10mg (\$15.85/item ^a) | \$720,192 | \$720,192 | \$720,192 | \$720,192 | \$720,192 |
| 10mg – 20mg (\$22.72/item ^a) | \$1,407,799 | \$1,407,799 | \$1,407,799 | \$1,407,799 | \$1,407,799 |
| 10mg – 40mg (\$32.66/item ^a) | \$12,042,591 | \$12,042,591 | \$12,042,591 | \$12,042,591 | \$12,042,591 |
| 10mg – 80mg (\$46.88/item ^a) | \$15,481,839 | \$15,481,839 | \$15,481,839 | \$15,481,839 | \$15,481,839 |
| Overall net cost to PBS | \$29,652,422 | \$29,652,422 | \$29,652,422 | \$29,652,422 | \$29,652,422 |

Source: Evaluation Table E.2.2 (p64) based on Submission Tables B.6-1 (p104), B.6-4 (p106) and B.6-5 (p106)

^a calculated using current DPMQ of the FDC for each strength less co-payment (\$14.07) minus potential DPMQ of the FDC for each strength should the compliance advice be reversed less co-payment (\$14.07).

- 6.80 The issues identified in the evaluation with the financial estimates included:
- The lack of justification in removing RPBS prescriptions from the estimates;
 - Deficiencies in the date-of-processing PBS items statistics data in late 2013 which may have resulted in an underestimate of the baseline prescriptions and subsequent market growth, and
 - The lack of consideration of the market dynamics given the recent and future PBS-listings of other ezetimibe with statin combination products.
- 6.81 The evaluation considered the presented estimates were potentially an underestimate of the cost to government if the compliance advice is maintained and the cost of alternative therapies continue to fall due to PBS price disclosure policies. DUSC agreed with the evaluation that the cost difference between Vytorin and the concomitant therapies or other statin plus ezetimibe combinations may be an underestimate due to the effects of price reductions that may apply to the alternate therapies over the forward estimates. However, DUSC also considered the market

share for Vytorin is a likely overestimate if ezetimibe + atorvastatin or ezetimibe + rosuvastatin combinations become preferred treatments to Vytorin.

- 6.82 DUSC considered that the overall size of the market for ezetimibe in combination with a statin will ultimately be dependent on the results of the IMPROVE-IT trial which is investigating clinical outcomes of patients taking Vytorin versus the equivalent dose of simvastatin post-acute coronary syndrome. If the study findings support the addition of ezetimibe to simvastatin, use of Vytorin and other ezetimibe/statin combinations could grow faster than the current trend, thus underestimating the financial impact of Vytorin maintaining a price premium. Conversely, if the results are negative, then, costs will be overestimated.
- 6.83 The pre-PBAC response, whilst maintaining that “Vytorin, when used for the treatment of hypercholesterolaemia, provides “... a significant improvement in compliance for the combination item over its alternative therapies for some patients”, requested new lower prices for Vytorin.
- 6.84 The new requested lower prices and the sponsor’s revised estimated cost to Government of maintaining the compliance advice (and as a consequence maintaining a higher price for Vytorin, than the sum of its component products), are provided in the table below.

MSD proposed new prices for Vytorin with estimated Government savings

| Strength (eze-simva) | Sum of Component prices | Current Vytorin Price (Ex man) | New proposed Vytorin Price (ex man) | Scripts/year | Estimated Commonwealth savings of compliance advice (ex man) | Cost of Maintaining Compliance Advice |
|----------------------|-------------------------|--------------------------------|-------------------------------------|--------------|--|---------------------------------------|
| 10- 10 | | | | | | |
| 10- 20 | | | | | | |
| 10- 40 | | | | | | |
| 10- 80 | | | | | | |
| | | | | Total | \$10 - \$20 million | Less than \$10 million |

7 PBAC Outcome

- 7.1 In considering this matter, the PBAC noted that since it gave advice for Vytorin under subsection 101(4AC) of the Act in 2008, potential new alternative therapies to Vytorin have been PBS listed, or been recommended for listing and the CMWG report has become available. Additionally, new information has become available that informs the clinical importance of any difference in compliance, which was a key area of uncertainty for the PBAC in 2008 and which is required to be addressed under Question 5 in the methodology developed by the CMWG.
- 7.2 The PBAC agreed with the submission that ezetimibe taken concomitantly with a statin is an alternative therapy to Vytorin. The PBAC also considered that pharmaceutical items containing the drugs: atorvastatin with ezetimibe and ezetimibe with rosuvastatin also constitute relevant alternative therapies, as these products contain ezetimibe in combination with a HmG Co-A reductase inhibitor (statin). Both the 10% Medicare sample analyses and the commissioned market survey included in

the sponsor's submission suggest that patients switch to Vytorin from statins other than simvastatin, with the most frequently reported statin being atorvastatin. This suggests that prescribers are willing to consider switching between statins. It appears likely that patients, especially those with previous experience on atorvastatin, would be switched to the atorvastatin and ezetimibe combination should Vytorin be delisted (particularly given the saving of one co-payment). This observation is also consistent with past PBAC views on the interchangeability of the three ezetimibe-statin combination drugs.

- 7.3 The PBAC acknowledged the PSCR comment that it is not possible to conduct adherence and persistence studies on the PBS data available for the recently listed atorvastatin with ezetimibe combination products due to the limited time that these products have been available, and that the rosuvastatin with ezetimibe combination products will only be PBS listed in early 2015. However, the PBAC considered that the availability of these combination products on the PBS did mean that in the future Vytorin users could switch to these products, particularly those who are concerned about the cost of an additional co-payment and/or have prior experience with other statins.
- 7.4 The PBAC accepted that statin monotherapy is not an alternative therapy.
- 7.5 The PBAC noted that the submission claimed that, based on the 304-patient MPR subgroup of Cohort 1 of the Vytorin Compliance Study IV, patients switching from concomitant therapy with ezetimibe and a statin to Vytorin experienced a 14% improvement in MPR versus the statin component and a 6% improvement versus the ezetimibe component, based on the differences in mean MPRs. Of the 304 patients in this subgroup, 51% (156 patients) were claimed to have experienced an improvement in MPR of greater than 10%. Further, a larger improvement among patients aged 65 years and older was claimed, with 63% (73 patients) of these older patients experiencing an improvement of greater than 10% in MPR after switching from concomitant therapy to Vytorin. The submission claimed that when compliance was further examined by measuring the differences in mean CMG in a 500-patient subgroup of Cohort 1, patients switching from concomitant therapy to Vytorin experienced an 11% improvement in CMG versus the statin component and a 4% improvement versus the ezetimibe component.
- 7.6 The PBAC further noted the submission's claim that the demonstration of an improvement in compliance in 156 patients in the 304-patient subgroup of Cohort 1 met the requirement in subsection 101(4AC) of an improvement in compliance in some patients. The PBAC noted that, were it to accept this claim, then the 156 patients represented around 1% of the total number of patients who were dispensed Vytorin (at start or finish) in Cohort 2 (n=15,830) of the 10% Medicare sample.
- 7.7 However the methodological concerns highlighted during the evaluation and by DUSC meant that PBAC could not be satisfied that the analyses presented by the submission were sufficiently robust to provide a reliable basis for the PBAC to accept the claim of an improvement in compliance in some patients. These methodological concerns included time-dependent bias, possible differences in application of methods pre- and post-Vytorin, and that the compliance measures were assessed in

different groups. These issues were further exacerbated by the limited statistical testing and sensitivity analyses conducted in the submission.

- 7.8 The PBAC noted that the submission also estimated persistence in patients receiving Vytorin or the two pill regimen of a statin and ezetimibe in Cohort 2 (n=16,594) using a Kaplan Meier analysis. Patients were included in Cohort 2 if they were dispensed a prescription for Vytorin or ezetimibe as a single agent (Ezetrol). Based on this analysis, the submission claimed that the 'bottom 50% of patients, in relation to persistence, gain an additional ten months when treated with Vytorin versus a concomitant ezetimibe and a statin'.
- 7.9 The PBAC agreed with DUSC that the persistence analysis which was undertaken where patients were allocated to groups according to whether their last prescription was for Vytorin or concomitant ezetimibe and statin, is likely to be subject to survivor bias favouring Vytorin. As the extent of this bias cannot be assessed from the submission, the PBAC agreed with DUSC that the analysis cannot be relied upon to inform the compliance claim.
- 7.10 The PBAC considered the evidence provided by the submission in response to Question 5 of the CMWG framework, namely whether any compliance benefit associated with Vytorin is sufficient to affect health outcomes (e.g. MI, mortality) in the appropriate Australian patients. The PBAC noted that, in measuring the effect of compliance on health outcomes, the key points made in the CMWG report are that: ideally studies should include both measures of compliance and health outcomes; the association between compliance and a medicine (claiming superior compliance) must be established before any effect on clinical outcomes can be directly attributed to that particular form of medicine; and the quality of the measurement of compliance affects the estimate of the association between compliance and treatment on health outcomes.
- 7.11 The PBAC was not satisfied that there was a significant improvement in compliance that could translate to a significant (clinically relevant) increase in health outcomes because:
- (a) The PBAC was not satisfied that there is a significant improvement in compliance in some patients that can be attributed to the combination items of Vytorin over their alternative therapies because of methodological concerns raised above. The CMWG report notes that an association between compliance and an intervention must be shown before any effect on clinical outcomes can be attributed to the intervention.
 - (b) The submission does not provide evidence to verify the claim that that MPR >80% for Vytorin is associated with significantly greater reduction in LDL and reduced cardiovascular events compared to an MPR <80%, so the selection of this cut-off for inclusion in the MPR and CMG subgroup analyses is arbitrary.
 - (c) The clinical significance of an improvement in MPR >10% has not been established.
 - (d) No evidence is presented in the submission measuring health outcomes for the Vytorin or for the nominated alternative therapies (ezetimibe and a statin). The information presented in the submission is limited to the association between statin compliance and health outcomes. The PBAC noted that the IMPROVE-IT trial is due to report in 2014. This trial investigates health outcomes for Vytorin over statin monotherapy.

- 7.12 Overall, the PBAC concluded on the basis of all the information available to it that it was no longer satisfied that the combination item Vytorin provides for some patients a significant improvement in patient compliance over the alternative therapy of concomitant ezetimibe with a statin.
- 7.13 Additionally, as no evidence was presented to establish improved compliance with Vytorin compared to atorvastatin with ezetimibe or ezetimibe with rosuvastatin, the PBAC was not satisfied that Vytorin provides a significant improvement for some patients in patient compliance over those alternative therapies.
- 7.14 The submission did not contend and the PBAC was not satisfied, that therapy involving Vytorin provides, for some patients, as significant improvement in efficacy, or reduction in toxicity, over alternative therapies.
- 7.15 The PBAC noted the sponsor's requested lower prices in the pre-PBAC response, but considered that the negotiation of an appropriate price for Vytorin following PBAC's consideration of this submission was a matter for the Minister.

Outcome:

The PBAC advised the Minister that it was no longer satisfied as to the matters required by subsection 101(4AC) of the Act in relation to the following combination items: ezetimibe with simvastatin, tablets, 10 mg – 10 mg, 10 mg – 20 mg, 10 mg – 40 mg and 10 mg – 80 mg, oral.

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

The sponsor disagrees with the decision from the PBAC. The sponsor believes that the submission provides the best possible evidence available to meet the CMWG and s101(4AC) requirements i.e. MSD believes that Vytorin provides, for some patients, a significant improvement in patient compliance over alternate therapies. MSD does not believe there is sufficient evidence to overturn the PBAC's previous decision.