Ezetimibe with simvastatin utilisation analysis

Drug utilisation sub-committee (DUSC)

October 2014

Abstract

Purpose

To compare the predicted versus actual use of ezetimibe with simvastatin (Vytorin®) following the extension to listing from 1 December 2012 for the 10/10 and 10/20 strengths for patients inadequately controlled on the maximum tolerated dose of a statin. The listing was not expected to result in any additional patients being treated as the free combination of ezetimibe and simvastatin 10 mg or 20 mg could be used if this was the maximum tolerated dose of simvastatin. The analysis was undertaken in the context of the complete PBS and RPBS ezetimibe market as patients may move between ezetimibe plain and fixed dose combination (FDC) presentations.

Date of listing on PBS

The extension to the listing of the 10-10 and 10-20 strengths of ezetimibe with simvastatin FDC products was effective from 1 December 2012.

The full PBS listing history of ezetimibe and its combination products is provided in Appendix A.

Data Source / methodology

Prescription data from the Department of Human Services pharmacy claims database and the DUSC database.

Key Findings

- The number of new patients commencing ezetimibe in any presentation is steady, with approximately 38,000 new patients each year. The number of prevalent patients on ezetimibe is increasing over time, and the majority of use is ezetimibe added to a statin.

- The submission assumed that the requested change would not result in any additional patients being treated. Rather, the 10-10 mg and 10-20 mg FDCs were expected to

replace the concomitant use of ezetimibe and simvastatin. This has not been the case. Twelve months after the extension to listing:

- the number of patients taking ezetimibe + simvastatin 10 mg or 20 mg (as the concomitant agents or in a fixed dose combination) increased from 9,800 to 12,872; and
- an additional 3,096 people were on the 10-10 and 10-20 FDC forms, but only 24 fewer patients were on the concomitant agents. Therefore the FDC did not substitute for the concomitant agents.

- Analysis of the streamlined authority code data indicates that ezetimibe as add on to a statin, in patients inadequately controlled on the maximum tolerated dose of a statin, is contributing the most to overall use.

Purpose of analysis

To compare the predicted versus actual use of ezetimibe with simvastatin (Vytorin®) following the extension to listing from 1 December 2012 of the 10/10 and 10/20 strengths for patients inadequately controlled on the maximum tolerated dose of a statin. The listing was not expected to result in any additional patients being treated as the free combination of ezetimibe and simvastatin 10 mg or 20 mg could be used if this was the maximum tolerated dose of simvastatin. The analysis is undertaken in the context of the complete PBS and RPBS ezetimibe market as patients may move between ezetimibe plain and fixed dose combination (FDC) presentations.

Background

Pharmacology

Ezetimibe is a lipid modifying agent that inhibits the intestinal absorption of cholesterol and related plant sterols.[1]

Simvastatin is a HMG-CoA reductase inhibitor.[2]

Therapeutic Goods Administration (TGA) approved indications[1,2]

Ezetimibe

- Primary Hypercholesterolaemia: alone, or with an HMG-CoA reductase inhibitor (statin), as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia.

- Homozygous Familial Hypercholesterolaemia (HoFH): with a statin. Patients may also receive adjunctive treatments (e.g., LDL apheresis).

- Homozygous Sitosterolaemia (Phytosterolaemia): for the reduction of elevated sitosterol and campesterol levels.

[1] Ezetrol (ezetimibe). Australian Approved Product Information. Sydney: Merck, Sharp & Dohme (Australia) Pty Limited. Approved 23 June 2003, most recent update 24 November 2014. Available from < www.ebs.tga.gov.au>. Accessed 31 July 2014 and 14 January 2015.
[2] Vytorin (ezetimibe and simvastatin). Australian Approved Product Information. Sydney: Merck, Sharp & Dohme (Australia) Pty Limited. Approved 7 January 2005, most recent update 24 November 2014. Available from <www.ebs.tga.gov.au>. Accessed 31 July 2014 and 14 january 2015.

Ezetimibe with simvastatin

- Primary Hypercholesterolaemia: 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:
  - Patients not appropriately controlled with a statin or ezetimibe alone
  - Patients already treated with a statin and ezetimibe.

- Homozygous Familial Hypercholesterolaemia (HoFH). Patients may also receive adjunctive treatments (e.g., LDL apheresis).

Dosage and administration[1,2]

The recommended dose of ezetimibe is 10 mg once daily, used alone or with a statin.

The patient should be on an appropriate lipid-lowering diet and should continue on this diet during treatment.

The dose of simvastatin in ezetimibe with simvastatin is individualised. See the full product information for details.

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from the TGA (Product Information) and the TGA (Consumer Medicines Information).

Clinical situation

The Guidelines for the Management of Absolute Cardiovascular Disease Risk[3] and the Therapeutic Guidelines[4] recommend that statins should be used as first-line therapy. If LDL C levels are not sufficiently reduced on maximally tolerated doses of statin, one or more of ezetimibe, bile acid binding resin or nicotinic acid can be added. Where statins cannot be tolerated at all ezetimibe, or one or more of ezetimibe, bile acid resin or nicotinic acid can be used. Fibrates such as gemfibrozil are not recommended for add on to statin therapy because of increased risk of myositis.

The Guidelines for the Management of Absolute Cardiovascular Disease Risk[3] recommend lipid targets as following in table 1.

Table 1: Lipid targets

Lipid target	Target level
Total cholesterol	< 4.0 mmol/L
HDL-C	≥ 1.0 mmol/L

[3] National Vascular Disease Prevention Alliance. Guidelines for the management of absolute cardiovascular disease risk. 2012.
[4] Expert Group for Cardiovascular. Therapeutic Guidelines; Cardiovascular. Version 6(2). Melbourne: Therapeutic Guidelines Ltd. Available from < http://www.tg.org.au/>.Accessed 31 July 2014.

Lipid target	Target level
LDL-C	< 2.0 mmol/L
Non HDL-C	< 2.5 mmol/L
TG	< 2.0 mmol/L

Current guidelines from the American College of Cardiology and the American Heart Association[5] no longer recommend prescribing additional cholesterol-lowering drugs, such as ezetimibe, to patients who do not reach targets with statins alone, as reduction in heart attack or stroke risk has not been demonstrated.

PBS listing details (as at 1 August 2014)

The details of the PBS listing of ezetimibe and ezetimibe with simvastatin are shown in table 2.

Table 2: PBS listing of ezetimibe and ezetimibe with simvastatin

Item	Name, form & strength, pack size	Max. quant.	Repeats	DPMQ	Brand name and manufacturer
8757X	EZETIMIBE 10mg tablet, 30	1	5	$71.31	Ezetrol® Merck Sharpe & Dohme (Australia) Pty Ltd
9483D	EZETIMIBE 10mg + SIMVASTATIN 10mg tablet, 30	1	5	$89.13	Vytorin® Merck Sharpe & Dohme (Australia) Pty Ltd
9484E	EZETIMIBE 10mg + SIMVASTATIN 20mg tablet, 30	1	5	$96.93	Vytorin® Merck Sharpe & Dohme (Australia) Pty Ltd
8881K	EZETIMIBE 10mg + SIMVASTATIN 40mg tablet, 30	1	5	$108.19	Vytorin® Merck Sharpe & Dohme (Australia) Pty Ltd
8882L	EZETIMIBE 10mg + SIMVASTATIN 80mg tablet, 30	1	5	$124.31	Vytorin® Merck Sharpe & Dohme (Australia) Pty Ltd

Source: August 2014 PBS Schedule

[5] Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA Guideline on the treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2013; Published online before print November 12, 2013, doi: 10.1161/01.cir.0000437738.63853.7a.

Abridged restriction

Ezetimibe and ezetimibe with simvastatin are listed as Authority required (streamlined) pharmaceutical benefits for patients who meet certain criteria. The full restriction wording is available from the PBS website.

Abridged restrictions are provided below with the current streamlined authority codes in brackets. The 12 month predicted versus actual analysis relates to the 'patients inadequately controlled with maximum tolerated dose of a statin' indications.

Ezetimibe

- Treatment of hypercholesterolaemia, in conjunction with dietary therapy and exercise, for co-administration with an HMG CoA reductase inhibitor (statin) in patients whose cholesterol levels are **inadequately controlled with a statin** and who have coronary heart disease (3724), diabetes mellitus (3725), peripheral vascular disease (3726), heterozygous familial hypercholesterolaemia (3727), symptomatic cerebrovascular disease (3728), family history of coronary heart disease (3729), hypertension (3730), are contraindicated to a statin (1989), or where treatment with a statin must be discontinued or reduced because the patient developed a clinically important product related adverse event during treatment with a statin (3731).
- **homozygous sitosterolaemia** (1991).
- patients with **homozygous familial hypercholesterolaemia** who are eligible for PBS-subsidised lipid lowering medication (according to the criteria set out in the General Statement for Lipid Lowering Drugs), in combination with a statin (2438).

Ezetimibe with simvastatin

- Treatment of hypercholesterolaemia, in conjunction with dietary therapy and exercise, in patients whose cholesterol levels are **inadequately controlled with a statin** and who have coronary heart disease (4068), diabetes mellitus (4085), peripheral vascular disease (4086), heterozygous familial hypercholesterolaemia (4069), symptomatic cerebrovascular disease (4096), family history of coronary heart disease (4120), hypertension (4121), or where the patient has developed a clinically important product related adverse event during treatment with a statin necessitating a reduction in the statin dose (4147).
- **homozygous familial hypercholesterolaemia** who are eligible for PBS-subsidised lipid lowering medication (according to the criteria set out in the General Statement for Lipid Lowering Drugs) (4097)

Inadequate control with a statin is defined as follows:

(1) where the patient falls into a category for which the General Statement for Lipid-Lowering Drugs includes an initial cholesterol threshold for PBS-subsidy (i.e. a patient not in a very high risk category), a cholesterol level in excess of that threshold after at least 3 months of treatment at a maximum tolerated dose of a statin, in conjunction with dietary therapy and exercise; or

(2) where the patient falls into a category for which the General Statement for Lipid-Lowering Drugs allows PBS-subsidised treatment with a statin at any cholesterol level (i.e. a very high risk category patient), a cholesterol level in excess of 4 mmol per L after at least 3 months of treatment at a maximum tolerated dose of a statin, in conjunction with dietary therapy and exercise.

A clinically important product-related adverse event is defined as follows:

(i) Severe myalgia (muscle symptoms without creatine kinase elevation) which is proven to be temporally associated with statin treatment; or

(ii) Myositis (clinically important creatine kinase elevation, with or without muscle symptoms) demonstrated by results twice the upper limit of normal on a single reading or a rising pattern on consecutive measurements and which is unexplained by other causes; or

(iii) Unexplained, persistent elevations of serum transaminases (greater than three times the upper limit of normal) during treatment with a statin

The general statement for lipid lowering drugs is available from the PBS website.

Nurse practitioners can prescribe ezetimibe and its combinations as continuing therapy only, where the treatment of, and prescribing of medicine for, a patients has been initiated by a medical practitioner.

Dates of listing on PBS

The extension to the listing of the 10-10 and 10-20 strengths of ezetimibe with simvastatin FDC products was effective from 1 December 2012.

The full PBS listing history of ezetimibe and its combination products is provided in Appendix A. Current PBS listing details are available from the PBS website.

Relevant aspects of the PBAC consideration

At the July 2012 meeting the PBAC recommended the extension to the listing of the 10 mg-10 mg and 10 mg-20 mg ezetimibe with simvastatin fixed dose combination strengths to include the additional indication of treatment, in conjunction with dietary therapy and exercise, in patients whose cholesterol levels are inadequately controlled with an HMG CoA reductase inhibitor (statin) and who meet certain criteria. The PBAC recommended the extension of listing as requested in order to remove inequities for those patients whose maximum tolerated dose of simvastatin was 10 mg or 20 mg per day.

The submission assumed that the requested change would not result in any additional patients being treated. Rather, the 10-10 mg and 10-20 mg FDCs would replace the concomitant use of ezetimibe and simvastatin. The percent of concomitant ezetimibe and simvastatin 10 and 20 mg prescriptions predicted to be replaced by the equivalent FDC was 57 % in Year 1 increasing to 71 % in Year 5. Growth was predicted to be only due to

population growth. A small incremental cost to government for patients switching from free combination of ezetimibe and simvastatin 10 or 20 mg to the FDC was expected as result of the loss of a co-payment and the Section 101(4AC) advice.

Table 3 below summarises the number of the prescriptions and associated costs expected to result from the proposed change to the restriction:

Table 3: Impact of proposed restriction wording change for VYTORIN 10/10 and 10/20 mg

	Year 1	Year 2	Year 3	Year 4	Year 5
VYTORIN 10/10 & 10/20 scripts	4,497	4,831	5,172	5,522	5,879
DPMQ	$418,533	$449,592	$481,379	$513,897	$547,148
DPMQ less average patients co-pay	$360,843	$387,620	$415,026	$443,062	$471,730
Incremental cost to government*	$11,880	$12,762	$13,664	$14,587	$15,531

Source: Minor submission to the July 2012 PBAC

The Outcome from the July 2012 PBAC is published on the PBS website.

There have been many changes and additions to PBS listings for ezetimibe products and other lipid modifying agents over the past decade. As these are important to interpreting changes in utilisation, the PBS listing history and relevant aspects of PBAC consideration are provided in Appendices A and B.

Previous reviews by the DUSC

The DUSC last reviewed the utilisation of ezetimibe and ezetimibe with simvastatin FDC in September 2007. The DUSC noted that the overall use of ezetimibe and ezetimibe with simvastatin together had been consistently less than predicted. The lower use of the FDC was mostly because where patients required coadministered statin and ezetimibe there was greater use of other concomitant statins (e.g. atorvastatin) rather than switching to the ezetimibe/simvastatin combination product.

The DUSC has also provided advice for major submissions considered by the PBAC in November 2008 (assessment of ezetimibe with simvastatin FDC compliance advantage) and in July 2012 (requested listing of atorvastatin/ezetimibe co-pack).

Methods

The number of prescriptions, patient category and government expenditure for lipid modifying therapies was extracted from the DUSC database from January 2003 to April 2014 inclusive. Data were extracted based on the date of prescription supply and so there may be small differences compared with publicly available Department of Human Services (DHS) Medicare date of processing data.

The DUSC database combines data on PBS/RPBS prescriptions submitted to the DHS Medicare for payment of a subsidy by the Government, with an estimate of under general copayment prescriptions based on dispensing data from a sample of pharmacies to the end of March 2012, replaced by actual under copayment data from DHS Medicare from 1 April 2012. The DUSC database also includes an estimate of private prescriptions based on dispensing data from a sample of pharmacies to August 2012.

The number of patients treated was determined by counting the number of individual de-identified personal identification numbers (PINs) in the PBS/RPBS data for the specified time period. New (initiating) patients were defined as those who did not have a PBS or RPBS prescription supplied for any ezetimibe product since ezetimibe was first listed (1 August 2004). The prevalent treated population was a count of individual PINs with at least one script supplied in the specified time period.

Indications for use were determined from the streamlined authority code nominated by the prescriber when prescribing a PBS benefit, recorded by the pharmacist upon supply, and captured in the DHS Medicare prescription database. Streamlined codes were extracted for all original prescriptions.

Deidentified individual patient prescription data were used to examine lipid lowering therapies co administered with ezetimibe products. The analyses imputed drug regimens for the prevalent treated population since ezetimibe was first available (August 2004). The methodology is fully described in Appendix C.

All ezetimibe products are priced above the general patient copayment, however some other lipid lowering therapies are priced below the general copayment. Therefore patient level analysis using a concessional cohort was considered necessary because under copayment prescription data was not available in the dataset prior to April 2012, and because it is understood that the private prescription market for statins has increased over the last 1-2 years due to generic competition. Both of these factors would contribute to an underestimation of lipid modifying therapies for general patients. However, to allay concerns that the concessional cohort may not be sufficiently representative of the entire PBS ezetimibe population the same analysis was undertaken for all patients. Both analyses are provided in this report. As there was minimal difference between the concessional and full population, the discussion and key findings focus on the full PBS population.

The lipid modifying therapy market included in this report includes statins (C10AA), ezetimibe (C10AX09), simvastatin in combination with ezetimibe (C10BA02), atorvastatin in combination with amlodipine (C10BX03), simvastatin in combination with sitagliptin (A10BH51), fibrates (C10AB), bile acid sequestrants (C10AC) and nicotinic acid and derivatives (C10AD).

Data manipulation was undertaken using SAS.

Results

Analysis of drug utilisation

Patients

Figure 1 shows the number of patients who initiated to any PBS subsidised ezetimibe product for the first time between August 2004 and March 2014.

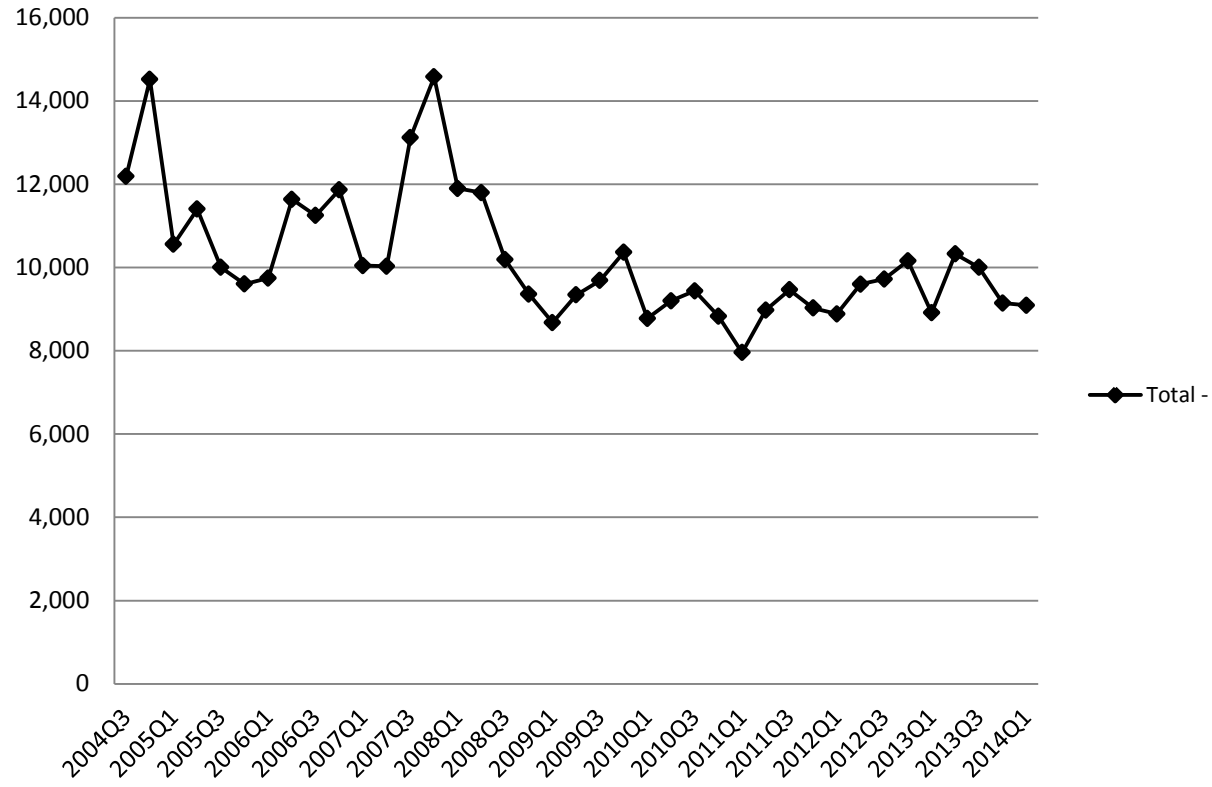

Figure 1: Total number of patients initiating to ezetimibe in any presentation

Over the last 5 years the number of patients initiating ezetimibe, in any presentation, has been fairly steady with about 35,000-38,000 new patients each year. The DUSC noted that there had been a decline in the number of patients initiating ezetimibe during 2008 and considered that a contributing factor may have been publication of the ENHANCE study. The ENHANCE study compared the use of simvastatin alone against simvastatin plus ezetimibe among patients with familial hypercholesterolemia and found no beneficial effect on progression of atherosclerosis. The DUSC considered that although the ENHANCE trial was conducted in only a subset of the PBS population eligible for ezetimibe (familial hypercholesterolaemia) that the release of study results likely impacted on utilisation of

ezetimibe in Australia as it had elsewhere in the world.[6,7] The DUSC considered that the results on the IMPROVE-IT study once available will influence future utilisation of ezetimibe in Australia.

There was no apparent increase in the number of patients commencing ezetimibe overall in the 12 months following the extended listing of the 10-10 and 10-20 FDC presentations.

A further breakdown for patients initiating ezetimibe for the first time, by the specific ezetimibe presentation of the first prescription, is shown in Figure 2.

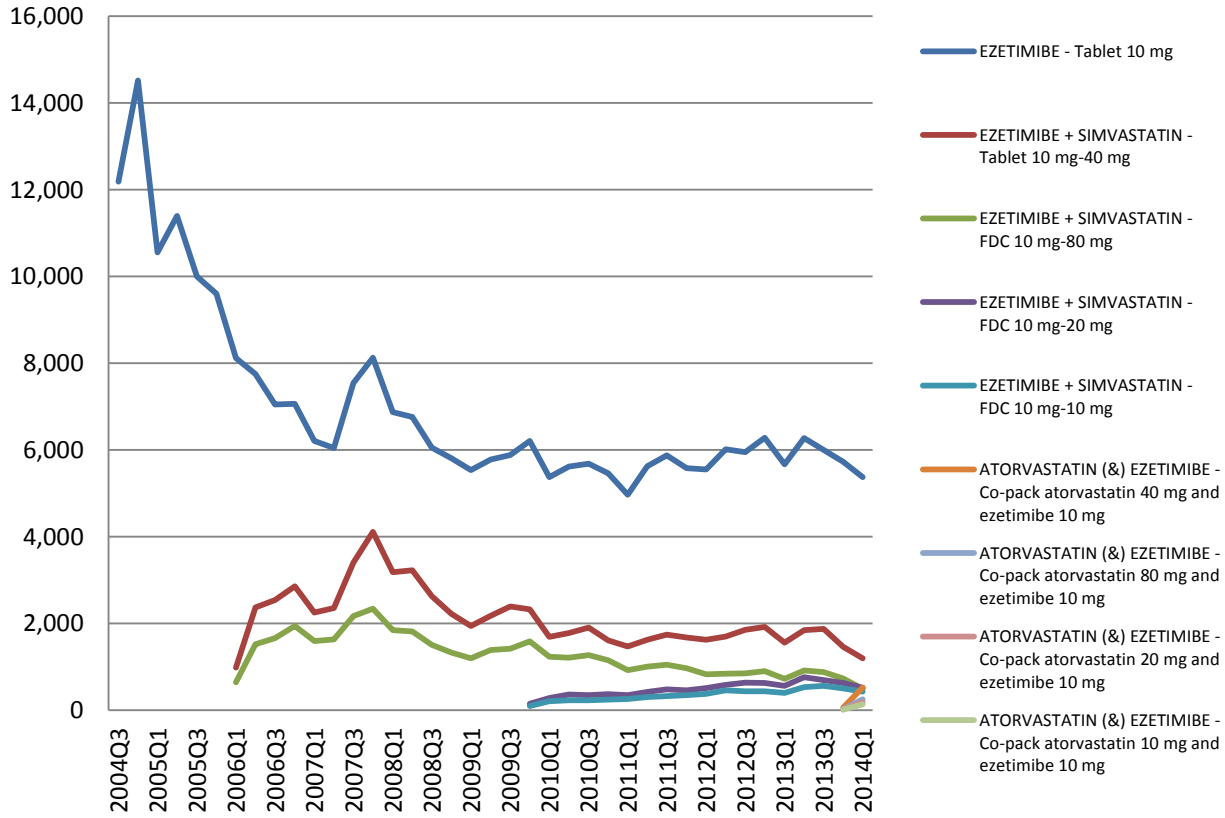

Figure 2: Number of patients initiating to ezetimibe, by product and strength.

Most patients initiate on the plain ezetimibe presentation. A proportion of these will use ezetimibe as monotherapy while some will be in combination with other lipid modifying agents (see co administration analysis later in this report). Some patients initiate ezetimibe in a FDC or co-pack presentation and this proportion has remained steady over recent times (38.9 % in 2010, 38.3 % in 2013). Presumably initiation on ezetimibe in a FDC or co-pack would be as add on therapy after a statin.

[6] Lu L, Krumholz HM, Tu JV, Ross JS, Ko DT, Jackevicius CA. Impact of the ENHANCE trial on the use of ezetimibe in the United States and Canada. Am Heart J. 2014;167(5):683-689. doi:10.1016/j.ahj.2014.01.014.
[7] Ross JS, Frazee SG, Garavaglia SB, Levin R, Novshadian H, Jackevicius CA, et. Al. Trends in Use of Ezetimibe After the ENHANCE Trial, 2007 Through 2010. JAMA InternMed. 2014;174(9):1486-1493. doi:10.1001/jamainternmed.2014.3404.

The number of patients initiating ezetimibe on the 10-10 and 10-20 FDC is comparatively low but has been increasing over time. There was a further increase in the 12 months after the extension to listing for the 10-10 and 10-20 presentations.

While the number of patients initiating ezetimibe is relatively stable (see Figure 1), the number of patients on treatment (prevalent patients) is rising as shown in Figure 3 (total ezetimibe, any presentation) and Figure 4 (by product and strength). At the end of 2013 over 200,000 patients were on treatment with ezetimibe. The Sponsor in the pre-subcommittee response (PSCR p1, p6) suggested the 'DUSC findings that the number of prevalent patients on ezetimibe is increasing over time supports MSD's claim of a compliance benefit associated with Vytorin'. The DUSC considered that the analysis shows that a lot of people continue on therapy with ezetimibe, in the same way that people continue on statin therapy, but that this doesn't support a claim of comparative improved compliance over alternative therapies.

The proportions of patients on the 10-40 and 10-80 presentations of the FDC are similar. The number of patients on the 10-10 and 10-20 presentations is comparatively much lower, but is growing.

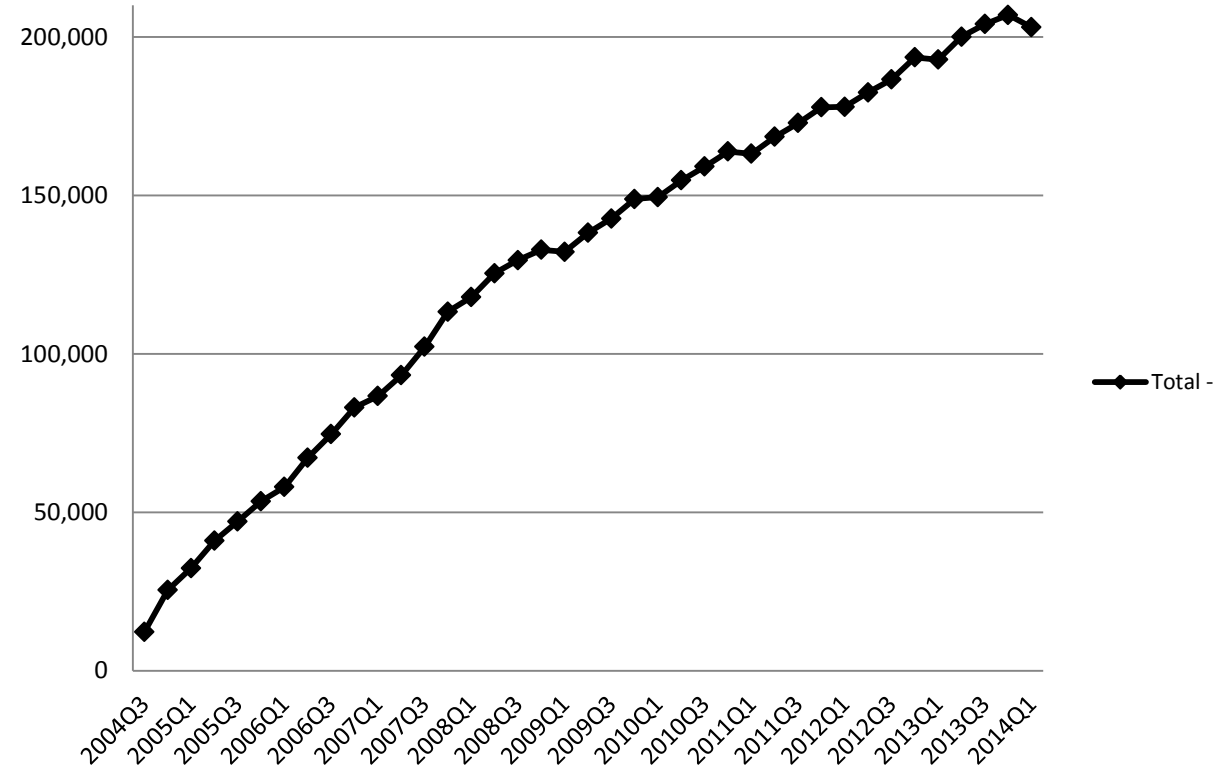

Figure 3: Number of prevalent patients on any ezetimibe product

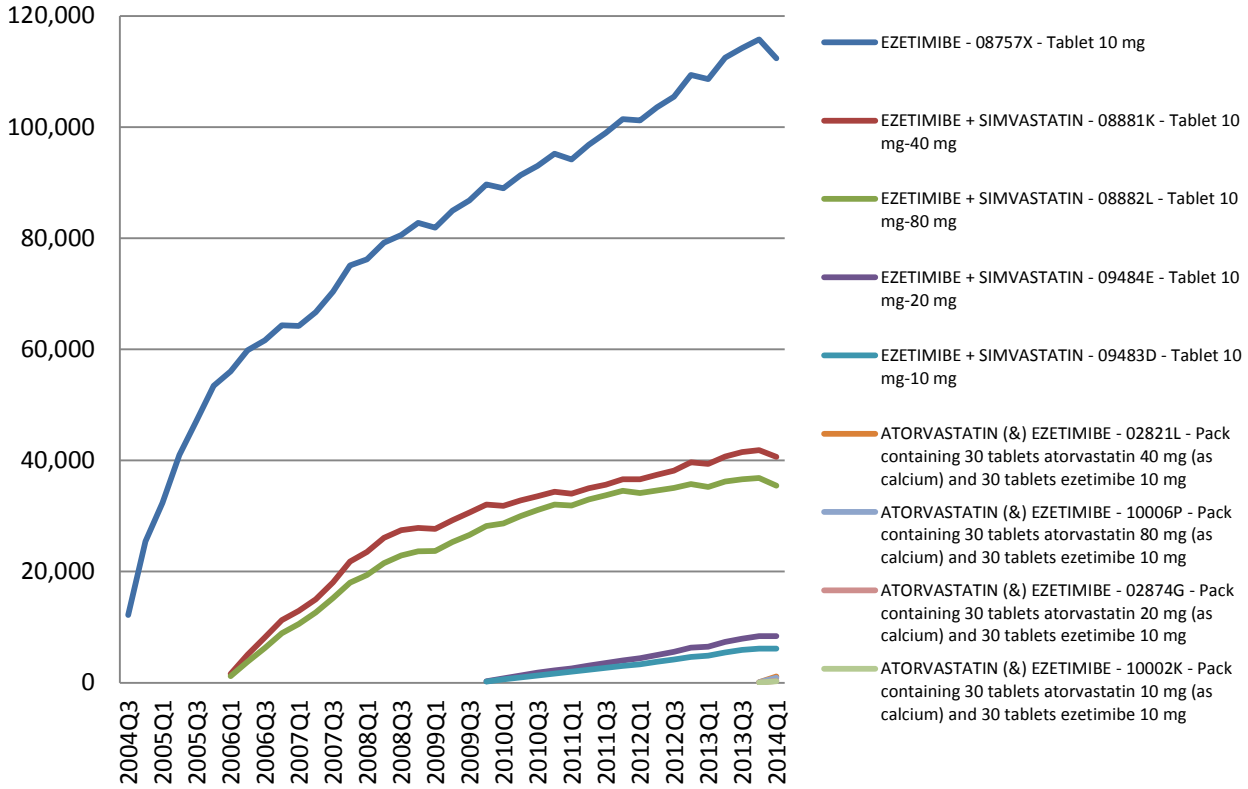

Figure 4: Number of prevalent patients on ezetimibe, by product and strength.

Overall prescription utilisation

The total number of prescriptions for lipid modifying therapies is shown in Figure 5.

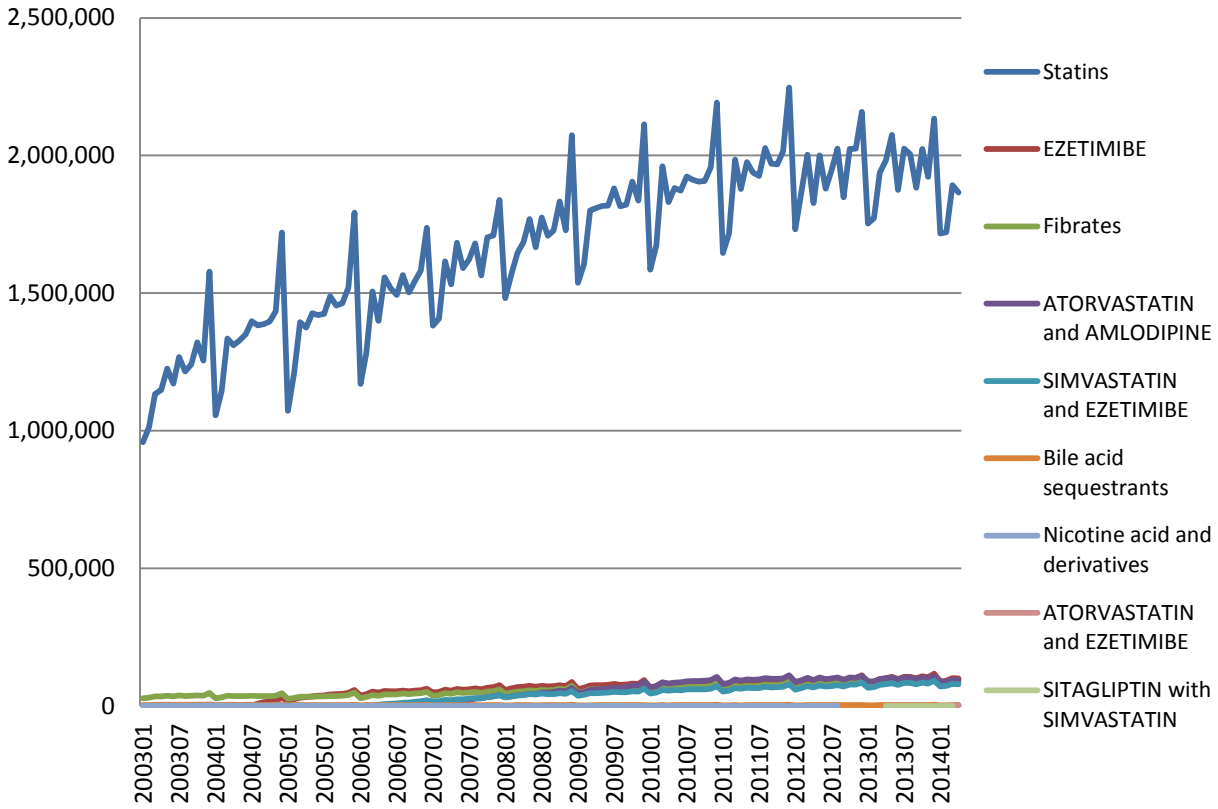

Figure 5: Total number of lipid modifying prescriptions (PBS/RPBS subsidised, undercopayment and private) by drug group supplied from January 2003 to April 2014.

Source: DUSC database, extracted 20 August 2014.

Note: estimate of private prescriptions available to August 2012.

The number of prescriptions for lipid lowering therapies has increased steadily over the last 10 years, although there is an apparent plateau in statin prescriptions in the most recent 1-2 years. This may be due to private prescription of statins in the general patient population.

Figure 6 shows the same data as Figure 5 with plain statins excluded so that the trends in the other drug groups are more visible. Similarly, trends in the utilisation of ezetimibe and its combinations can be more readily seen in Figure 7.

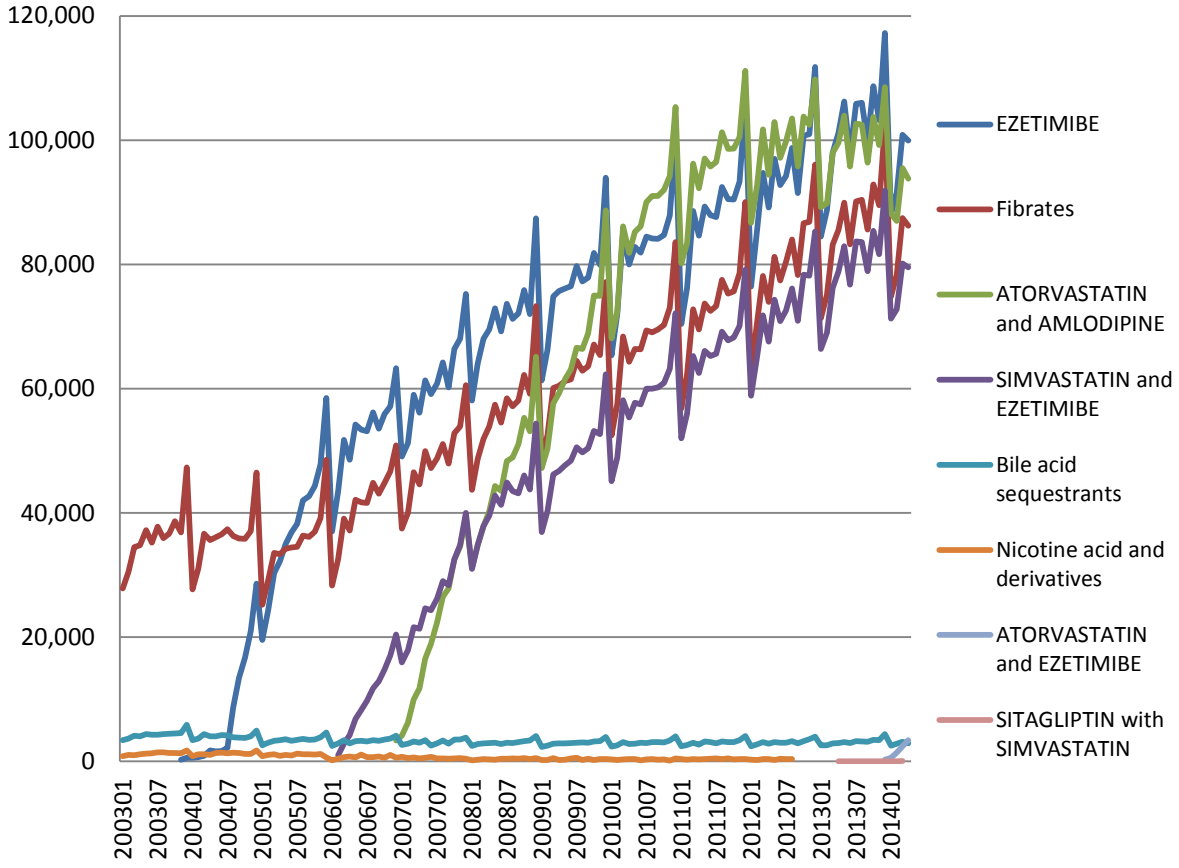

Figure 6: Total number of lipid modifying prescriptions (PBS/RPBS subsidised, undercopayment and private, excluding statins) by drug group supplied from January 2003 to April 2014.

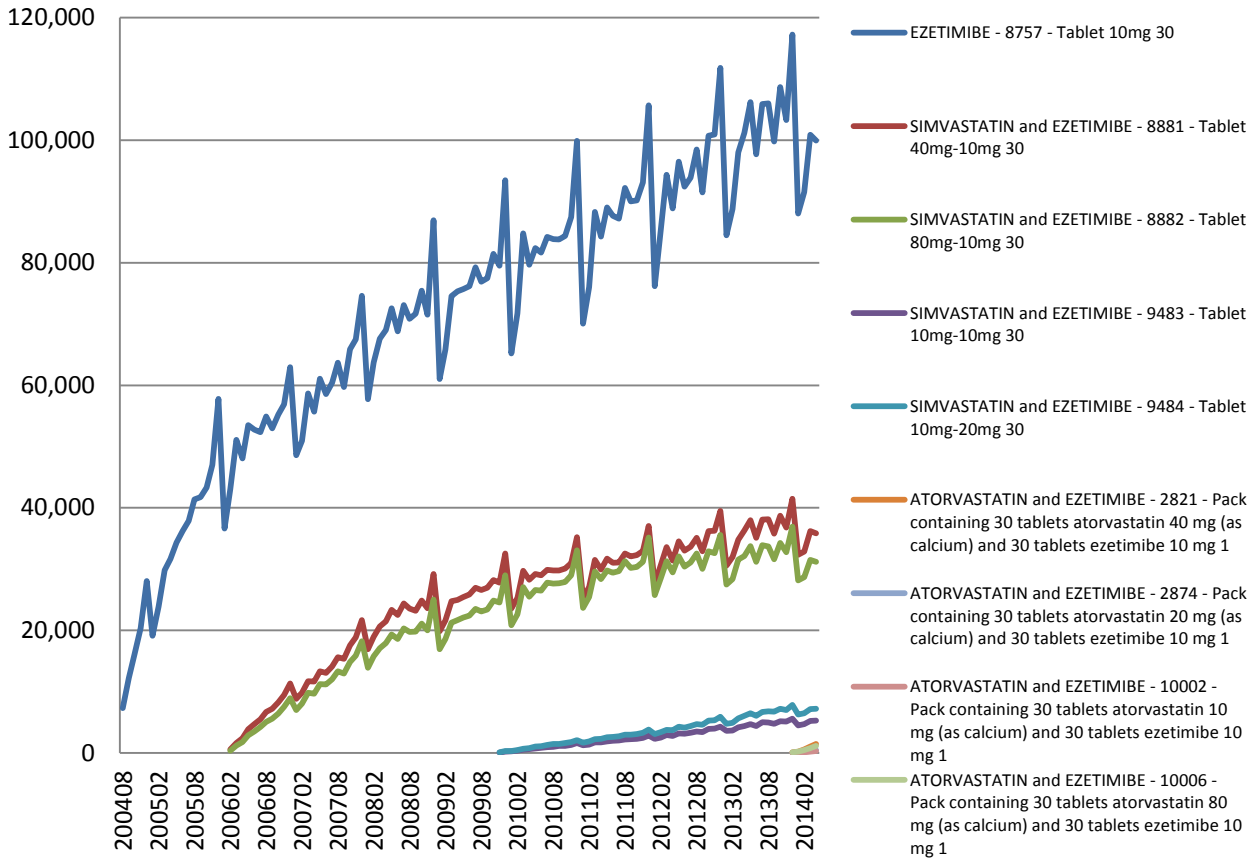

Figure 7: Number of ezetimibe (single agent and FDC with simvastatin by strength) prescriptions from January 2003 to April 2014.

(PBS/RPBS subsidised and undercopayment. Private excluded to simplify the figure and the script numbers were not significant)

Trends in the number of prescriptions supplied are similar to trends in the number of patients on treatment. There is no clear inflexion point for the 10-10 and 10-20 ezetimibe-simvastatin FDC following the extension to listing on 1 December 2012.

The rate of growth for ezetimibe and ezetimibe with simvastatin has been higher than the rate of growth for the whole lipid modifying class (Table 4).

Table 4: Prescription volume[#] for lipid lowering therapies

	Drug	Form & Strength	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
All ezetimibe products	EZETIMIBE			84,164[a]	444,090	620,497	725,263	848,970	916,691	988,940	1,053,740	1,130,983	1,217,084
	SIMVASTATIN and EZETIMIBE	10mg-10mg							299[c]	10,506	24,097	39,260	55,666
		10mg-20mg							444[c]	14,152	32,278	52,626	76,238
		40mg-10mg				61,794[b]	171,657	272,828	311,715	350,869	374,617	404,523	435,660
		80mg-10mg				47,694[b]	144,229	228,668	271,500	322,129	354,159	372,379	387,624
	SIMVASTATIN and EZETIMIBE Total						109,488	315,886	501,496	583,958	697,656	785,151	868,788
All ezetimibe products Total				84,164	444,090	729,985	1,041,149	1,350,466	1,500,649	1,686,596	1,838,891	1,999,771	2,172,272
Other lipid modifying therapies			15,006,368	16,715,670	17,476,654	18,359,894	20,147,690	21,870,491	23,249,942	24,437,686	25,295,683	25,405,793	25,656,130
All lipid modifying therapies			15,006,368	16,799,834	17,920,744	19,089,879	21,188,839	23,220,957	24,750,591	26,124,282	27,134,574	27,405,564	27,828,402

[#] All PBS/RPBS prescriptions including undercopayment (survey data until March 2012, actual from April 2012). Private prescriptions are excluded. Data is date of supply.
First listed from [a]1 August 2004. [b]1 February 2006, [c]1 November 2009.

Table 5: Growth in prescription volume[#] (% from previous year) for lipid lowering therapies.

	Drug	Form & Strength	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
All ezetimibe products	EZETIMIBE				428%[a]	40%	17%	17%	8%	8%	7%	7%	8%
	SIMVASTATIN and EZETIMIBE	10mg-10mg								3414%[c]	129%	63%	42%
		10mg-20mg								3087%[c]	128%	63%	45%
		40mg-10mg					178%[b]	59%	14%	13%	7%	8%	8%
		80mg-10mg					202%[b]	59%	19%	19%	10%	5%	4%
	SIMVASTATIN and EZETIMIBE Total						189%	59%	16%	19%	13%	11%	10%
All ezetimibe products Total					428%	64%	43%	30%	11%	12%	9%	9%	9%
Other lipid modifying therapies				11%	5%	5%	10%	9%	6%	5%	4%	0%	1%
All lipid modifying therapies				12%	7%	7%	11%	10%	7%	6%	4%	1%	2%

[#] All PBS/RPBS prescriptions including undercopayment (survey data until March 2012, actual from April 2012). Private prescriptions are excluded.
First listed from [a]1 August 2004. [b]1 February 2006, [c]1 November 2009.

The 10-10 and 10-20 FDC products were first listed in November 2009. Utilisation of these lower strengths has been growing at a much faster rate than the 10-40 and 10-80 strengths. To assess whether the use of ezetimibe with simvastatin 10 or 20 mg has increased overall (given concomitantly or given as the FDC) an analysis of individual patient drug regimens is provided later in this report.

Figure 8 shows the contribution of the FDC presentation to total use of ezetimibe over time. After rapid initial uptake in the first few years, the market share of the FDC has risen slowly in recent years. This may be due to the higher market share for other statins and addition of the plain form of ezetimibe to these statins. In 2013, 44 % of ezetimibe prescriptions were for the FDC.

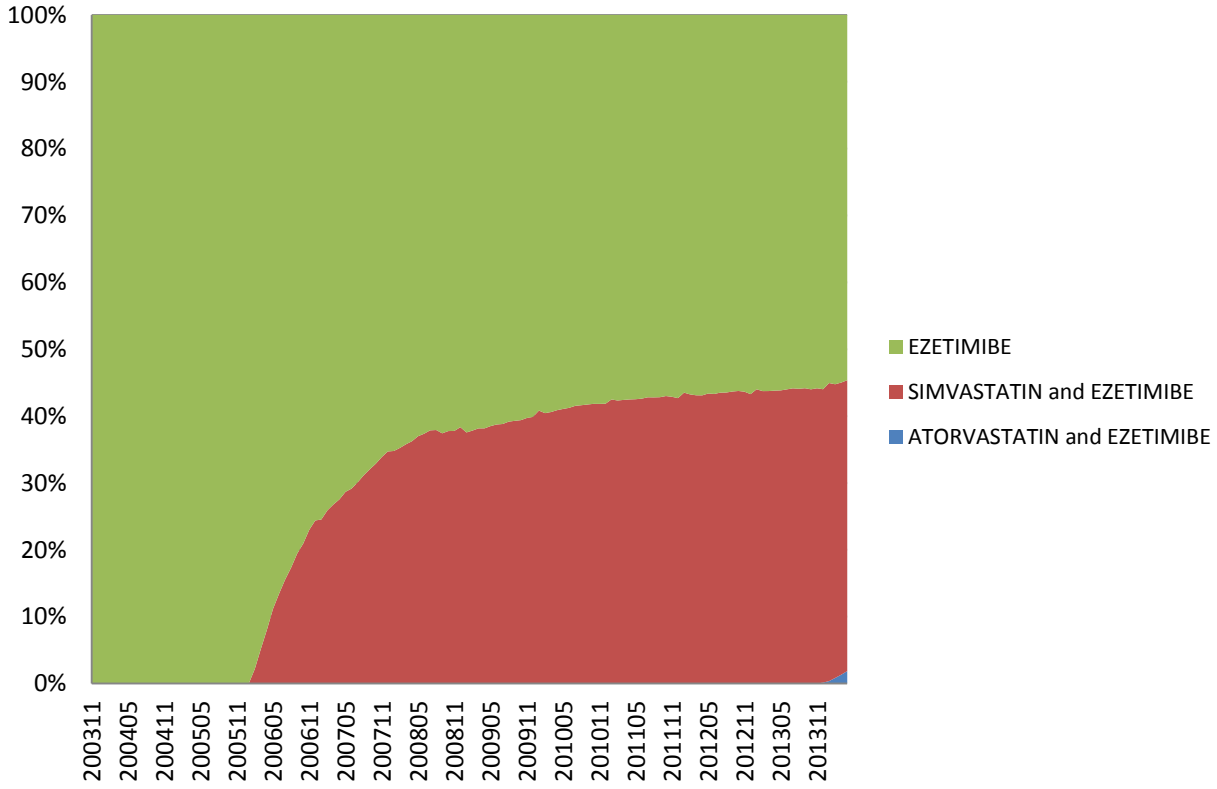

Figure 8: FDC and plain ezetimibe products grouped as a percentage of total prescriptions

Utilisation by patient category

Figure 9 shows the annual utilisation of ezetimibe (in any presentation) by patient category. All ezetimibe products are priced above the general patient copayment.

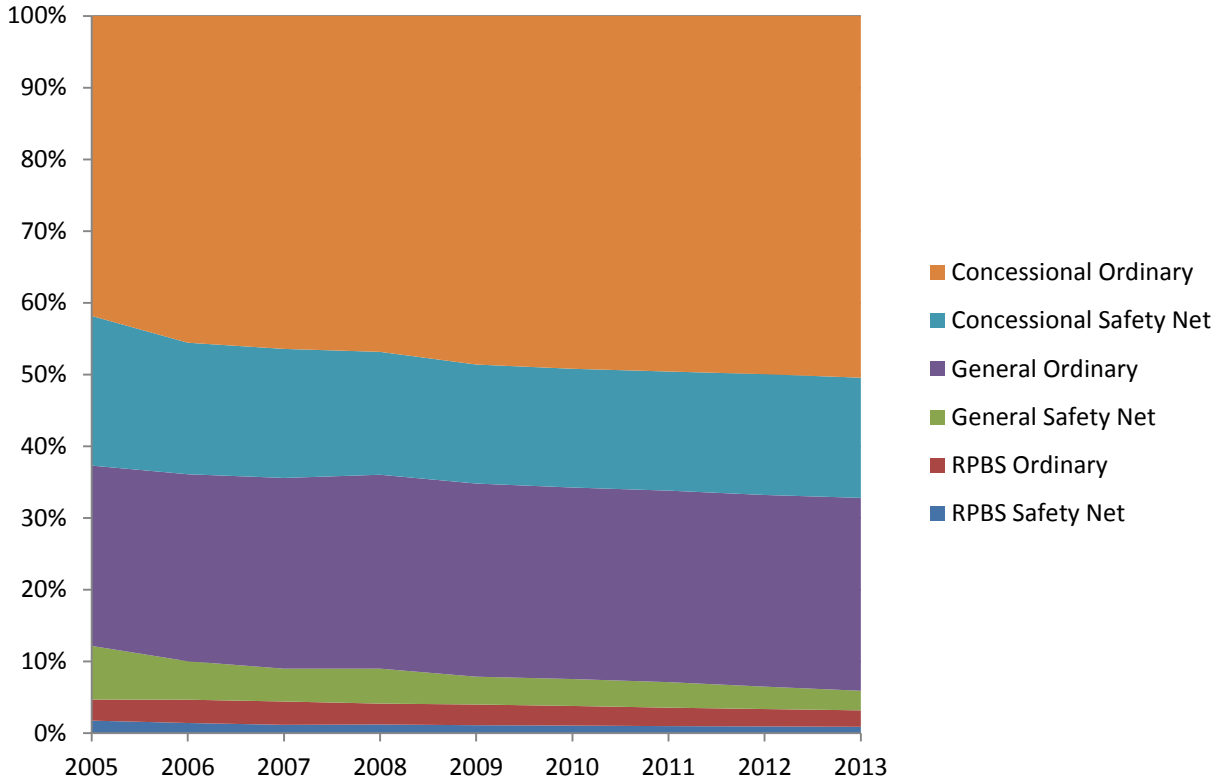

Figure 9: Percent of ezetimibe (any presentation) prescriptions by patient category

Concessional prescriptions, including concessional Safety Net and RPBS, comprise the majority of prescriptions for ezetimibe products (approximately 70 %) and this proportion has remained steady over time.

Figure 10 shows the annual utilisation of all lipid modifying therapies by patient category. The number of lipid lowering therapies priced below the general patient copayment has increased over time, and so a coinciding increase in undercopayment prescriptions is evident. The declining proportion of general prescriptions in the last 1-2 years may be due to increasing provision of some lipid modifying therapies on private prescription. The data illustrates why a concessional only cohort was compared for patient level analyses, as lipid lowering therapies may be missing from the prescription histories of general patients.

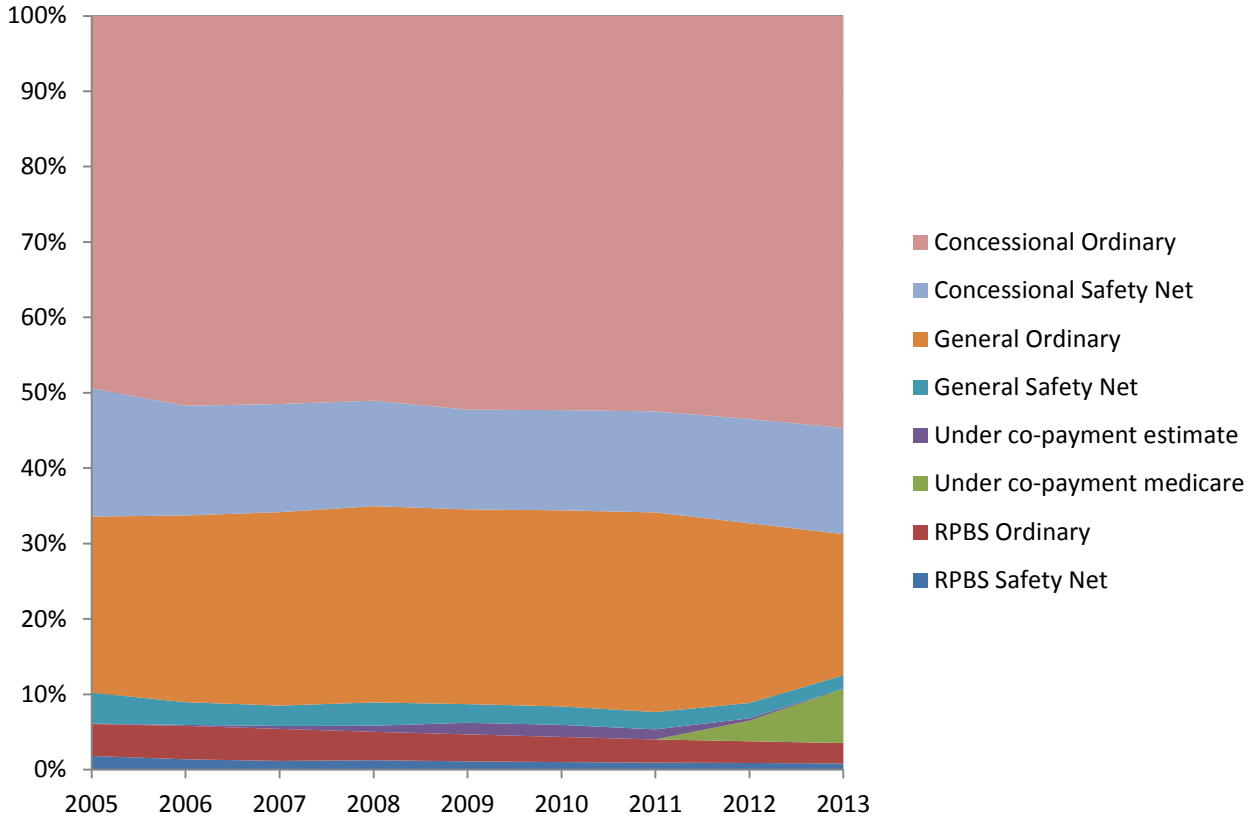

Figure 10: Percent of lipid modifying therapy prescriptions by patient category.

Streamlined codes for indication

The number of original prescriptions supplied of ezetimibe single agent and FDC by the streamlined authority code (as selected by the prescriber and entered by the pharmacist) is shown in Figures 11 and 12 respectively.

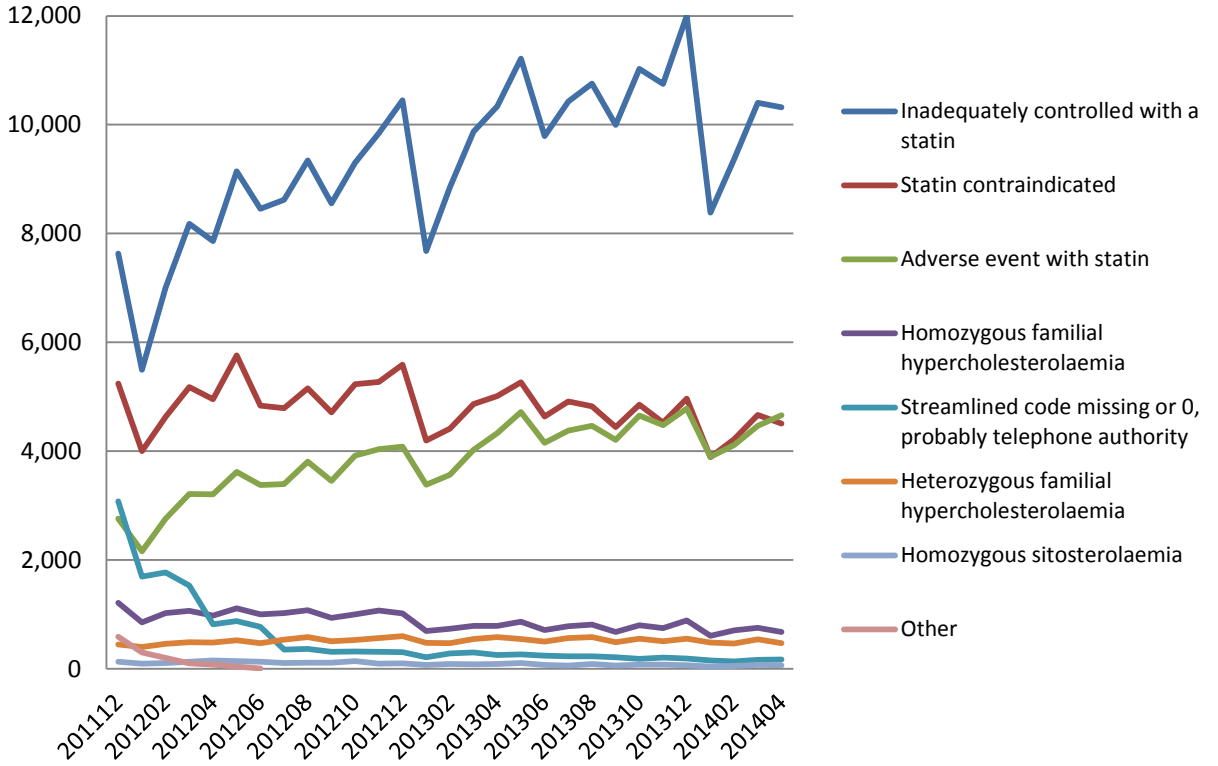

Figure 11: Original prescriptions for ezetimibe by restriction.

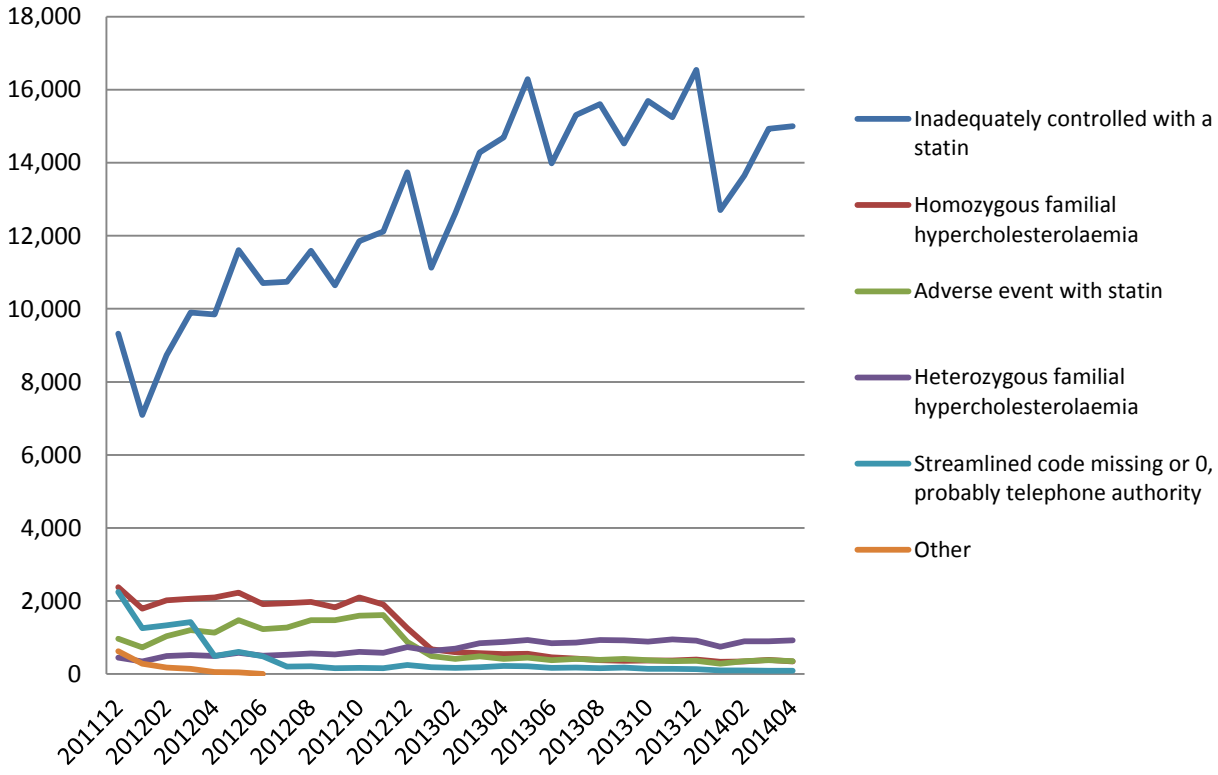

Figure 12: Original prescriptions for ezetimibe FDC with simvastatin by restriction.

Figures 11 and 12 show the vast majority of original prescriptions for ezetimibe plain and FDC are for use in patients whose cholesterol levels are inadequately controlled on a statin. Utilisation for this indication is growing.

Ezetimibe Treatment Patterns

Co-administration analysis

Figures 13 and 14 show the 20 most common ezetimibe containing regimens for concessional only and all patients on ezetimibe, respectively.

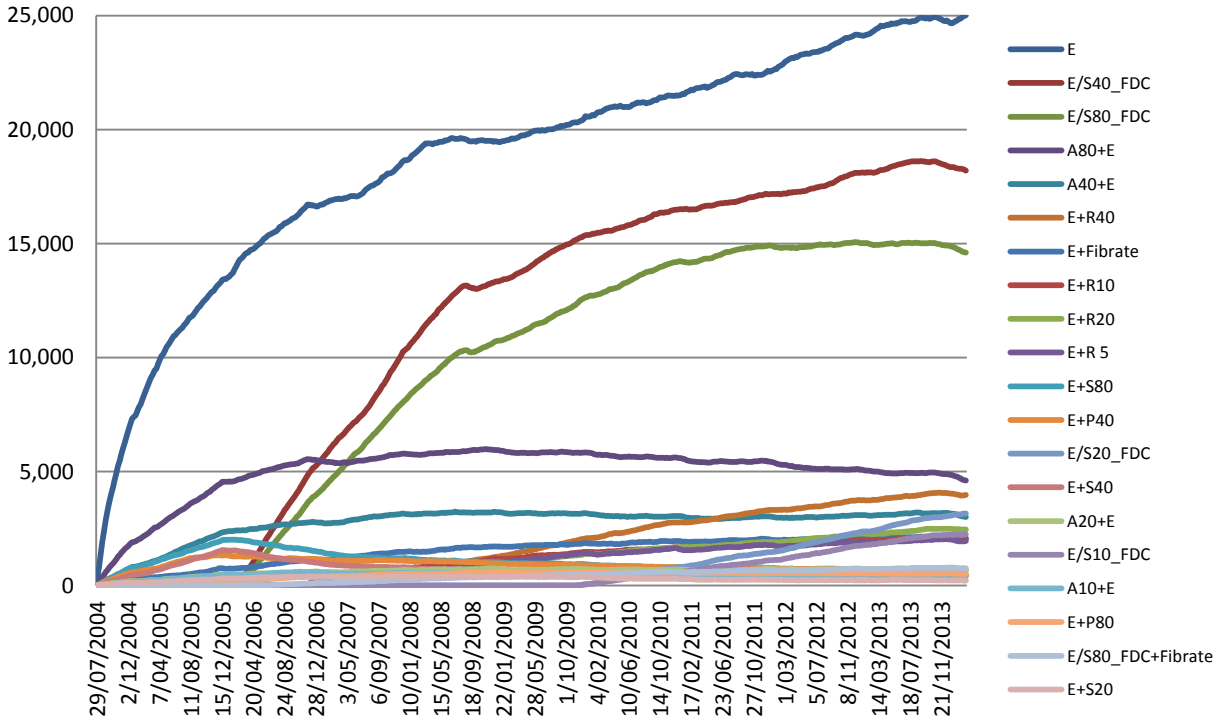

Figure 13: Twenty most common ezetimibe regimens (concessional cohort)

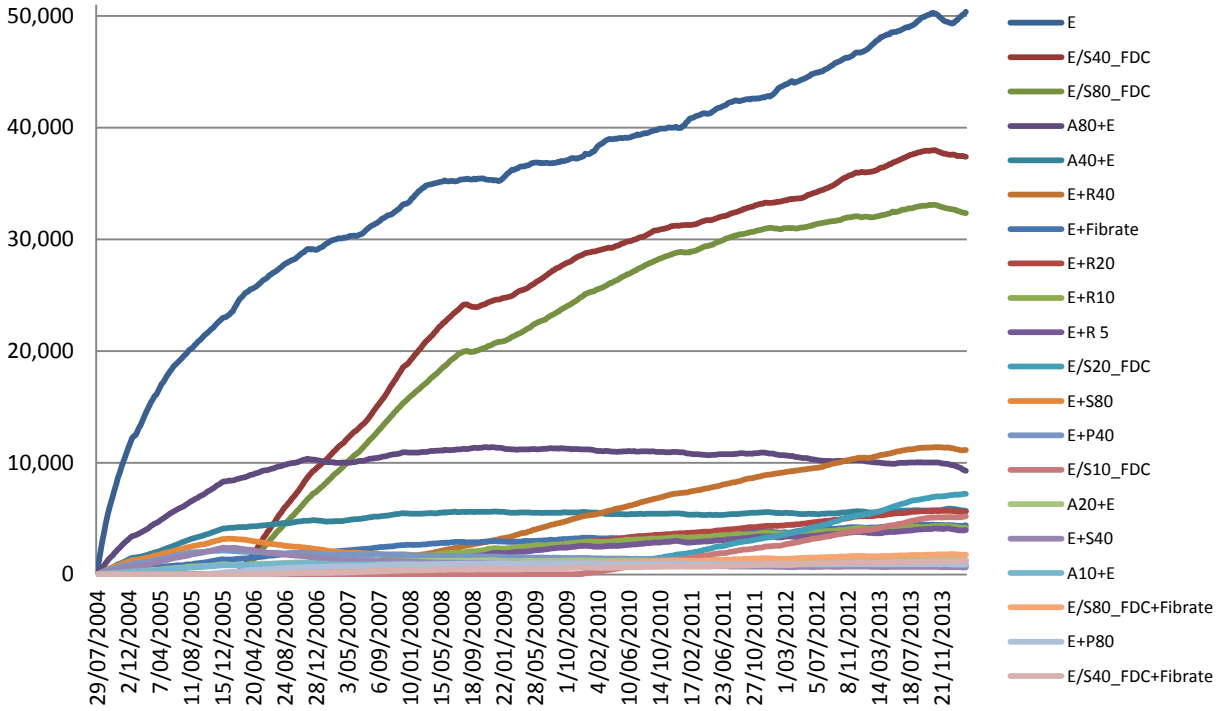

Figure 14: Twenty most common ezetimibe regimens (all patients)

Ezetimibe monotherapy is the most common individual regimen and this has remained the case over time. It is more common that ezetimibe is used in combination with a statin. The general trends are similar between the concessional and total population, even noting that undercopayment prescriptions may be missing for general patients. Tables 6 and 7 provide more details at four time points in the above figures: approximately one year prior to the extended listing (24/11/2011); immediately prior to the extension to listing (29/11/2012); approximately one year after the extension to listing (28/11/2013) and a recent time point (27/2/2014) for the concessional and full cohorts, respectively.

Table 6: Ezetimibe containing regimens at several points in time (concessional only patients)

	Week starting	24/11/2011	24/11/2011	29/11/2012	29/11/2012	28/11/2013	28/11/2013	27/02/2014	27/02/2014
Therapy Type	Drug regimen	Patients	%	Patients	%	Patients	%	Patients	%
Ezetimibe monotherapy	**E**	**22,398**	**26.0%**	**24,097**	**26.3%**	**24,766**	**26.1%**	**25,011**	**26.6%**
Ezetimibe with any statin	E+S 5	70	0.1%	72	0.1%	71	0.1%	76	0.1%
Ezetimibe with any statin	E+S10	210	0.2%	190	0.2%	174	0.2%	164	0.2%
Ezetimibe with any statin	E/S10 FDC	1,043	1.2%	1,718	1.9%	2,218	2.3%	2,250	2.4%

	Week starting	24/11/ 2011	24/11/ 2011	29/11/ 2012	29/11/ 2012	28/11/ 2013	28/11/ 2013	27/02/ 2014	27/02/ 2014
Ezetimibe with any statin	E+S20	257	0.3%	236	0.3%	230	0.2%	216	0.2%
Ezetimibe with any statin	E/S20 FDC	1,411	1.6%	2,287	2.5%	3,024	3.2%	3,156	3.4%
Ezetimibe with any statin	E+S40	502	0.6%	469	0.5%	424	0.4%	403	0.4%
Ezetimibe with any statin	E/S40 FDC	17,122	19.8%	18,056	19.7%	18,463	19.4%	18,205	19.4%
Ezetimibe with any statin	E+S80	697	0.8%	595	0.6%	516	0.5%	485	0.5%
Ezetimibe with any statin	E/S80 FDC	14,876	17.2%	15,042	16.4%	14,932	15.7%	14,599	15.5%
Ezetimibe with any statin	A10+E	479	0.6%	494	0.5%	479	0.5%	446	0.5%
Ezetimibe with any statin	A20+E	723	0.8%	715	0.8%	752	0.8%	717	0.8%
Ezetimibe with any statin	A40+E	3,028	3.5%	3,082	3.4%	3,185	3.4%	3,009	3.2%
Ezetimibe with any statin	A80+E	5,477	6.3%	5,098	5.6%	4,892	5.1%	4,602	4.9%
Ezetimibe with any statin	E+R 5	1,774	2.1%	1,909	2.1%	2,026	2.1%	1,952	2.1%
Ezetimibe with any statin	E+R10	1,821	2.1%	1,952	2.1%	2,118	2.2%	2,051	2.2%
Ezetimibe with any statin	E+R20	1,894	2.2%	2,255	2.5%	2,491	2.6%	2,466	2.6%
Ezetimibe with any statin	E+R40	3,263	3.8%	3,725	4.1%	4,062	4.3%	3,969	4.2%
Ezetimibe with any statin	E+P10	192	0.2%	193	0.2%	212	0.2%	207	0.2%
Ezetimibe with any statin	E+P20	239	0.3%	250	0.3%	268	0.3%	260	0.3%
Ezetimibe with any statin	E+P40	771	0.9%	733	0.8%	684	0.7%	657	0.7%

	Week starting	24/11/2011	24/11/2011	29/11/2012	29/11/2012	28/11/2013	28/11/2013	27/02/2014	27/02/2014
Ezetimibe with any statin	E+P80	540	0.6%	531	0.6%	529	0.6%	513	0.5%
Ezetimibe with any statin	E+F20	75	0.1%	84	0.1%	84	0.1%	83	0.1%
Ezetimibe with any statin	E+F40	127	0.1%	125	0.1%	117	0.1%	106	0.1%
Ezetimibe with any statin	E+F80	164	0.2%	172	0.2%	185	0.2%	178	0.2%
Ezetimibe with any statin - Total		**56,755**	**65.8%**	**59,983**	**65.4%**	**62,136**	**65.4%**	**60,770**	**64.7%**
Ezetimibe with other lipid modifying therapy		**7,154**	**8.3%**	**7,570**	**8.3%**	**8,097**	**8.5%**	**8,108**	**8.6%**
Total		**86,307**	**100.0%**	**91,650**	**100.0%**	**94,999**	**100.0%**	**93,889**	**100.0%**

Note: S = simvastatin, A=atorvastatin; F=fluvastatin; P=pravastatin; R=rosuvastatin; E=ezetimibe

* includes atorvastatin/amlodipine FDC; simvastatin/sitagliptin FDC; fibrates, bile acid sequestrants; nicotinic acid derivatives

Table 7: Ezetimibe containing regimens at several points in time (all patients)

	Week starting	24/11/2011	24/11/2011	29/11/2012	29/11/2012	28/11/2013	28/11/2013	27/02/2014	27/02/2014
Therapy Type	Drug regimen	Patients	%	Patients	%	Patients	%	Patients	%
Ezetimibe monotherapy	**E**	**42,664**	**24.9%**	**46,472**	**24.9%**	**49,598**	**24.9%**	**50,356**	**25.4%**
Ezetimibe with any statin	E+S 5	111	0.1%	139	0.1%	129	0.1%	135	0.1%
Ezetimibe with any statin	E+S10	288	0.2%	336	0.2%	330	0.2%	312	0.2%
Ezetimibe with any statin	E/S10 FDC	2,419	1.4%	3,846	2.1%	5,123	2.6%	5,216	2.6%
Ezetimibe with any statin	E+S20	387	0.2%	413	0.2%	395	0.2%	378	0.2%
Ezetimibe with any statin	E/S20 FDC	3,207	1.9%	5,205	2.8%	7,024	3.5%	7,222	3.6%
Ezetimibe with any statin	E+S40	724	0.4%	714	0.4%	675	0.3%	642	0.3%

	Week starting	24/11/2011	24/11/2011	29/11/2012	29/11/2012	28/11/2013	28/11/2013	27/02/2014	27/02/2014
Ezetimibe with any statin	E/S40 FDC	33,162	19.4%	35,813	19.2%	37,666	18.9%	37,380	18.9%
Ezetimibe with any statin	E+S80	1,033	0.6%	912	0.5%	805	0.4%	750	0.4%
Ezetimibe with any statin	E/S80 FDC	30,859	18.0%	32,016	17.1%	32,854	16.5%	32,346	16.3%
Ezetimibe with any statin	A10+E	904	0.5%	914	0.5%	935	0.5%	876	0.4%
Ezetimibe with any statin	A20+E	1,241	0.7%	1,260	0.7%	1,343	0.7%	1,330	0.7%
Ezetimibe with any statin	A40+E	5,569	3.3%	5,642	3.0%	5,831	2.9%	5,695	2.9%
Ezetimibe with any statin	A80+E	10,910	6.4%	10,227	5.5%	9,946	5.0%	9,280	4.7%
Ezetimibe with any statin	E+R 5	3,396	2.0%	3,797	2.0%	4,085	2.1%	3,981	2.0%
Ezetimibe with any statin	E+R10	3,703	2.2%	4,097	2.2%	4,331	2.2%	4,178	2.1%
Ezetimibe with any statin	E+R20	4,310	2.5%	5,155	2.8%	5,718	2.9%	5,636	2.8%
Ezetimibe with any statin	E+R40	8,811	5.1%	10,345	5.5%	11,364	5.7%	11,142	5.6%
Ezetimibe with any statin	E+P10	299	0.2%	414	0.2%	471	0.2%	476	0.2%
Ezetimibe with any statin	E+P20	357	0.2%	485	0.3%	535	0.3%	509	0.3%
Ezetimibe with any statin	E+P40	1,313	0.8%	1,288	0.7%	1,262	0.6%	1,232	0.6%
Ezetimibe with any statin	E+P80	946	0.6%	950	0.5%	939	0.5%	912	0.5%
Ezetimibe with any statin	E+F20	118	0.1%	164	0.1%	167	0.1%	164	0.1%
Ezetimibe with any statin	E+F40	177	0.1%	201	0.1%	194	0.1%	187	0.1%
Ezetimibe	E+F80	358	0.2%	361	0.2%	394	0.2%	382	0.2%

	Week starting	24/11/2011	24/11/2011	29/11/2012	29/11/2012	28/11/2013	28/11/2013	27/02/2014	27/02/2014
with any statin									
Ezetimibe with any statin - Total		**114,602**	**66.9%**	**124,694**	**66.8%**	**132,516**	**66.6%**	**130,361**	**65.8%**
Ezetimibe with other lipid modifying therapy*		**13,914**	**8.1%**	**15,533**	**8.3%**	**16,791**	**8.4%**	**17,435**	**8.8%**
Total		**171,180**	**100.0%**	**186,699**	**100.0%**	**198,905**	**100.0%**	**198,152**	**100.0%**

Note: S = simvastatin, A=atorvastatin; F=fluvastatin; P=pravastatin; R=rosuvastatin; E=ezetimibe
* includes atorvastatin/amlodipine FDC; simvastatin/sitagliptin FDC; fibrates, bile acid sequestrants; nicotinic acid derivatives

There is little change in regimens over the time period shown.

Approximately 26 % and 25 % of regimens were for ezetimibe as monotherapy in the concessional and full populations, respectively. The marginally smaller ezetimibe monotherapy use in the full population could possibly be due to concomitant private prescription of statin.

At the most recent time point, 65.8 % of patients were taking ezetimibe with a statin (either concomitantly with a plain statin or in a FDC). The most common statin containing regimens were the 10-40 and 10-80 ezetimibe with simvastatin FDCs, noting that a small proportion of patients (less than 0.5 %) were also taking this regimen as the concomitant tablets. The next most common statin regimens involve ezetimibe with concomitant rosuvastatin 40 mg or atorvastatin 80 mg. Total use of ezetimibe with a statin may be underestimated in this analysis because ezetimibe coadministered with the FDC of amlodipine and atorvastatin is captured in the 'other lipid modifying therapies' category. The impact will be small as less than 5 % of statin prescriptions are prescribed in this form.

The shaded cells in Tables 6 and 7 represent the regimens of most relevance for the predicted versus actual analysis. The July 2012 submission to the PBAC assumed that the change would not result in any additional patients being treated. Rather, the 10/10 and 10/20 mg FDCs would replace the concomitant use of ezetimibe and simvastatin. The percent of concomitant ezetimibe and simvastatin 10 and 20 mg prescriptions predicted to be replaced by the equivalent FDC was 57 % in Year 1 increasing to 71 % in Year 5. The data in Table 5 indicates that 3,072 more patients were on a regimen of ezetimibe + 10 mg or 20 mg simvastatin in 12 months after the extension to listing (i.e. 9,800 patients at 29/11/2012 and 12,872 patients at 28/11/2013). This is an increase of 31 % over the previous year.

Analysis of expenditure

PBS/RPBS expenditure for lipid modifying therapies is shown in Table 8. Although the number of lipid modifying prescriptions has increased, overall expenditure has declined in recent years due to price reductions for some statins. The total PBS/RPBS expenditure for ezetimibe and ezetimibe with simvastatin has continued to increase over time, with expenditure of $ 165.9 million in 2013.

Table 8: R/PBS expenditure ($ millions, date of supply)

	Drug	Form & Strength	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
All ezetimibe products	EZETIMIBE			$ 5.4	$ 27.5	$ 37.5	$ 43.1	$ 50.5	$ 54.4	$ 58.8	$ 62.3	$ 66.5	$ 71.3
	SIMVASTATIN and EZETIMIBE	Tablet 10mg-10mg							$ .02	$ .8	$ 1.8	$ 2.9	$ 4.1
		Tablet 10mg-20mg							$ .04	$ 1.2	$ 2.6	$ 4.3	$ 6.2
		Tablet 40mg-10mg				$ 7.5	$ 19.5	$ 27.9	$ 29.8	$ 33.6	$ 35.8	$ 38.5	$ 41.4
		Tablet 80mg-10mg				$ 7.1	$ 19.8	$ 27.7	$ 30.2	$ 35.9	$ 39.4	$ 41.3	$ 42.9
	SIMVASTATIN and EZETIMIBE Total						$ 14.7	$ 39.3	$ 55.6	$ 60.1	$ 71.5	$ 79.6	$ 87.
All ezetimibe products Total				$ 5.4	$ 27.5	$ 52.2	$ 82.3	$ 106.1	$ 114.5	$ 130.3	$ 141.9	$ 153.5	$ 165.9
Other lipid modifying therapies			$ 847.2	$ 961.8	$ 962.1	$ 977.9	$ 1030.2	$ 1087.	$ 1168.	$ 1241.9	$ 1280.2	$ 1060.3	$ 783.3
All lipid modifying therapies			$ 847.2	$ 967.3	$ 989.5	$ 1030.1	$ 1112.5	$ 1193.1	$ 1282.6	$ 1372.2	$ 1422.1	$ 1213.8	$ 949.2

Discussion

Following the listing of the 10-10 and 10-20 ezetimibe with simvastatin FDCs as add on therapy in patients who cannot tolerate a higher dose of statin, the number of patients on these products increased but there was not a corresponding decrease in the number of people on concomitant ezetimibe and simvastatin 10 or 20 mg. This is contrary to the submission assumption. The PSCR (p2-3) notes that Vytorin patients are not only sourced from concomitant ezetimibe and simvastatin. The DUSC agrees that this is the case and is appropriate, but noted that the report compares predicted and actual use based on the approach taken in the submission. It appears that the submission included only the pool of patients taking ezetimibe and simvastatin, although as this was hardcoded in the submission spreadsheet and could not be verified.

Although the rate of growth has slowed in recent years, there continues to be an increase in the utilisation of ezetimibe and ezetimibe with simvastatin over time. This is evident from the prevalent patient count, and the prescription volume and expenditure analyses.

Analysis of the streamlined authority data indicates that ezetimibe as add on to a statin, in patients inadequately controlled on the maximum tolerated dose of a statin, is contributing the most to overall use. This is also evident in the co-administration analysis where at least 65 % of patients are using ezetimibe in combination with a statin. The DUSC questioned whether patients are trialling maximum tolerated doses of a statin prior to commencing on the FDC product, as required for the PBS subsidy for hypercholesterolaemia, but noted that utilisation data alone would not be able to quantify this. Use of ezetimibe added to statins may reflect Australian guidelines which currently recommend treating to target cholesterol levels.[3,4] However, there remains a lack of clinical endpoint data for ezetimibe. The IMPROVE-IT study designed to assess clinical benefit (defined as the reduction in the risk of the occurrence of the composite endpoint of CV death, major coronary events, and stroke) of ezetimibe with simvastatin compared to simvastatin alone in subjects with acute coronary syndrome, commenced in October 2005. The estimated primary completion date (final data collection date for primary outcome measure) according to ClinialTrials.gov is September 2014. The outcomes of the IMPROVE-IT study may influence utilisation of ezetimibe in Australia in the future.

Following consideration of these analyses at the October 2014 meeting of the DUSC, the results of the IMPROVE-IT study were presented at the American Heart Association Scientific Sessions in November 2014, however the full results of the IMPROVE-IT study were not published at this time.

DUSC actions

The DUSC requested that the report be provided to the PBAC.

Context for analysis

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

Sponsor comment

Merck Sharp & Dohme (Australia) Pty Limited: The sponsor considers that the illustrated growth of ezetimibe and low dose Vytorin (10/10 and 10/20mg) is in-line with historical growth and that Fig 6 shows this is similar to other lipid modifying prescriptions. The sponsor considers that clinicians prescribe these products in appropriate patients not at target LDL-C levels.

Appendix A

PBS listings/changes to listings for lipid modifying agents including ezetimibe and ezetimibe with simvastatin

Table A.1: Major changes to PBS listings of lipid modifying agents

Date	Drug (Item)	Description of addition/amended listing
Aug 04	Ezetimibe 10mg (8757X)	New Authority required listing for: • Patients with a contraindication or adverse reaction to a statin such that statins cannot be taken, • Homozygous sitosterolaemia; homozygous familial hypercholesterolaemia in combination with a statin, • Co-administration with a statin when cholesterol levels are inadequately controlled with a statin* in patients with: (a) coronary heart disease; or (b) diabetes mellitus
Dec 05	Nicotinic acid (1687T)	Deleted from PBS
Feb 06	Ezetimibe + simvastatin FDC 10mg-40mg (8881K) 10mg-80mg (8882L)	New Authority required listing for patients whose cholesterol levels are inadequately controlled with a statin* and have: (a) coronary heart disease; or (b) diabetes mellitus and for patients with homozygous familial hypercholesterolaemia in combination with a statin
Apr 06	Ezetimibe 10mg (8757X) and ezetimibe + simvastatin FDC 10mg-40mg (8881K) 10mg-80mg (8882L)	Additional indication for co-administration with a statin when cholesterol levels are inadequately controlled with a statin* in patients with: (a) peripheral vascular disease, or (b) heterozygous familial hypercholesterolaemia
Aug 06	Fenofibrate, existing items 67mg capsule (8721B) 160mg tablet (8722C) replaced with 48mg capsule (9022W) 145mg tablet (9023X)	New fenofibrate items listed under the Restricted benefit listing for use in patients who meet the criteria set out in the General Statement for Lipid Lowering Drugs. The new lower and higher dose items are bioequivalent to the existing lower and higher dose items under low fat fed conditions (TGA). The pre-existing items are phased out and are deleted from December 2006 PBS listing.
Oct 06	Statins, fenofibrate, gemfibrozil.	Revised General statement for lipid lowering drugs
Oct 06	Ezetimibe 10mg (8757X) and ezetimibe + simvastatin FDC 10mg-40mg (8881K) 10mg-80mg (8882L)	Additional indication for co-administration with a statin when cholesterol levels are inadequately controlled with a statin* in patients with (a) cerebrovascular disease which has become symptomatic Also increased use due to the change in definition of patients whose cholesterol levels are inadequately controlled with a statin (in revised General statement for lipid lowering drugs).
Dec 06	Amlodipine with atorvastatin various strength tablets (9049G, 9050H, 9051J, 9052K, 9053L, 9054M, 9055N, 9056P).	New restricted benefit listing for patients with hypertension and/or angina and who meet the criteria in the General Statement for Lipid-Lowering drugs.
Dec 06	Rosuvastatin 5mg(9042X), 10mg(9043Y), 20mg(9044B), 40mg(9045C)	New restricted benefit listing for use in patients who meet the criteria in the General Statement for Lipid Lowering Drugs

Date	Drug (Item)	Description of addition/amended listing
Aug 07	Ezetimibe 10mg (8757X)	Additional indication for co-administration with a statin when cholesterol levels are inadequately controlled with a statin* in patients with: (a) family history of coronary heart disease, or (b) hypertension; and for patients where statin treatment has to be reduced to 20mg or less per day due to adverse reaction.
Aug 07	Ezetimibe + simvastatin FDC 10mg-40mg (8881K) 10mg-80mg (8882L)	Additional indication for co-administration with a statin when cholesterol levels are inadequately controlled with a statin* in patients with: (a) family history of coronary heart disease, or (b) hypertension
Nov 09	Ezetimibe + simvastatin FDC 10mg-10mg (9483D) 10mg-20mg (9484E)	Listing of lower strengths for patients with homozygous familial hypercholesterolaemia who are eligible for PBS subsidised lipid lowering therapy; and for patients eligible for statins where treatment with a statin must be reduced to a dose of 20mg or less per day, because the patient developed a clinically important adverse event during treatment with a statin.
Jul 11	Ezetimibe 10mg Ezetimibe + simvastatin FDC 10mg-10mg (9483D) 10mg-20mg (9484E)	Amend restriction not to specify a particular dose of a statin i.e. remove the daily dose statement of 'to a dose of 20mg or less', and amend wording to specify the 'the ezetimibe component' rather than 'ezetimibe'
Dec 12	Ezetimibe + simvastatin FDC 10mg-10mg (9483D) 10mg-20mg (9484E)	Extend listing for the 10-10 and 10-20 FDC for patients inadequately controlled on the maximum tolerated dose of a statin.
Dec 13	Atorvastatin + ezetimibe composite pack 10mg-10mg (10002K) 20mg-10mg (2874G) 40mg-10mg (2821L) 80mg-10mg (10006P)	Listed for hypercholesterolaemia in patients inadequately controlled on a statin with (a) coronary heart disease; or (b) diabetes mellitus (c) homozygous familial hypercholesterolaemia (d) peripheral vascular disease (e) heterozygous familial hypercholesterolaemia (f) family history of coronary heart disease (g) hypertension (h) symptomatic cerebrovascular disease, or (i) has developed a clinically important product-related adverse event during treatment.
Listed Apr 13 Deleted Apr 14	Sitagliptin with simvastatin 100 mg–10 mg (2391W) 100 mg–20 mg (2377D) 100 mg–40 mg (2383K)	Listed for type 2 diabetes and hypercholesterolaemia for patients who meet the criteria in the General Statement for Lipid Lowering Drugs and when used in combination with metformin or a sulfonylurea in patients contraindicated or intolerant to the combination of metformin and a sulfonylurea

* The definition of when cholesterol levels are inadequately controlled with a statin changed when the "General statement for lipid lowering drugs" was revised in October 2006.

Appendix B

Summary of PBAC consideration and predicted utilisation of ezetimibe and ezetimibe with simvastatin

Table B.1: Summary of PBAC consideration and predicted utilisation of ezetimibe and ezetimibe with simvastatin

PBAC Meeting **Product**	**PBAC consideration and recommendation**
June 2003 **Ezetimibe**	Authority required listing recommended for • patients eligible for subsidised lipid lowering medication but when statins are unsuitable (contraindicated or the patient developed a clinically important product related adverse event during treatment with a statin) • co-administration with statins in patients eligible for subsidised lipid lowering medication, with coronary heart disease and/or diabetes mellitus, when the patient is above NHF target lipid levels. • patients with homozygous sitosterolemia. • with statins for patients eligible for subsidised lipid lowering medication with homozygous familial hypercholesterolaemia. The recommendation for patients where statins are inappropriate was on the basis of pricing being related to the extent of LDL cholesterol reduction with ezetimibe compared to statins. The submission presented eight randomised trials that examined lipid-modifying effect rather than the clinical end-points. The submission only presented preliminary economic evaluations in respect to where statins are inappropriate. PBAC did not accept the claim of cost effectiveness at the requested price, particularly in the absence of any clinical endpoint data showing improved outcomes in terms of mortality or cardiovascular events. For homozygous sitosterolaemia and homozygous familial hypercholesterolaemia, listing was recommended on the basis that the benefits of treatment outweigh the risks and costs of long-term use.
September 2003 **Ezetimibe**	The PBAC agreed to rescind its previous advice that the price of ezetimibe should be based on a 'frame of reference' approach with statins for those patients who are intolerant of statins. The cost-minimisation submission was based on an indirect comparison of ezetimibe and cholestyramine using placebo as the common comparator. Two ezetimibe trials and seven studies of cholestyramine were included as primary evidence of which the endpoint examined was difference in estimated LDL-C reduction between active and placebo arms from baseline. There was no significant difference in LDL-C reduction between ezetimibe and cholestyramine. Dose equivalence: ezetimibe 10mg ≡ cholestyramine 17.2g
December 2003 **Ezetimibe**	Extension to listing for co-administration with 40mg or greater of a statin in patients with: • CHD and/or diabetes whose cholesterol levels remain inadequately controlled The submission presented one pivotal trial to examine the efficacy and safety of ezetimibe in patients with existing CHD or multiple cardiovascular risk factors with primary hypercholesterolaemia which was not controlled with statins. Three supportive studies compared efficacy and safety of ezetimibe versus statin therapy. An updated preliminary economic evaluation was presented as well as a modelled economic

	evaluation. The model extrapolated results from lipid levels, to risk of fatal and non-fatal CHD events, and on to the final outcome of patient survival. Endpoint TC:HDL ratios were calculated for the ezetimibe and comparator arms in the model. A Markov process was then used to model total health care costs and life expectancy, with and without ezetimibe therapy. Although there were residual uncertainties over the modelling, the PBAC recommended listing on the basis of acceptable cost-effectiveness. A particular matter that the PBAC wished to continue to monitor is the extent to which future randomised trials reporting major cardiovascular outcomes where cholesterol therapy is titrated to achieve reductions to target levels demonstrate further reductions in major cardiovascular endpoints beyond that achieved with non-titrated therapy or monotherapy.
March 2005 **Ezetimibe + simvastatin FDC 10/40 and 10/80**	Recommended authority required listing of FDC ezetimibe and simvastatin (10/40mg and 10/80mg) on a cost-minimisation basis compared to the sum of the corresponding strengths of the individual components. The price for the simvastatin component of the combination tablet will be maintained at the same price as that of simvastatin.
July 2005 **Ezetimibe + simvastatin FDC 10/40 and 10/80**	The PBAC recommended that the previously recommended restriction for ezetimibe with simvastatin be amended to allow for patients with coronary heart disease or diabetes mellitus who were inadequately controlled after three months treatment at a daily dose 40 mg or greater of any statin to commence treatment on Vytorin® (ezetimibe with simvastatin).
July 2005 **Atorvastatin**	Change in therapeutic group
November 2005 **Ezetimibe (and extended to ezetimibe + simvastatin)**	Recommended the addition of two indications to the current listing for ezetimibe for peripheral vascular disease and heterozygous familial hypercholesterolaemia on the basis of acceptable cost effectiveness The submission included the two key trials that were previously considered at the June and December 2003 PBAC meetings. Seven supportive trials comparing ezetimibe co-administered with statins with statins alone in adults with CHD and/or diabetes and/or CHD-risk equivalents over 6 to 24 weeks were also presented. The modelled economic evaluation presented also adopted a cost-effectiveness approach, using a Markov state transition model with four health states which extrapolates trial-based changes in total cholesterol and HDL-C to life-years gained. PBAC did not recommend for CVD because the general statement for lipid lowering drugs current at the time did not include this patient group, but this group could be included if and when changes to general statement occurred.
October 2006	Revisions to the General Statement for lipid lowering drugs
November 2006 **Ezetimibe (and extended to ezetimibe + simvastatin)**	Extension to the current authority listing to the treatment of patients with hypertension, an family history of coronary heart disease **(Part A)** and high dose statin intolerance **(Part B)** **Part A:** The submission presented a meta-analysis of six trials where ezetimibe was compared with placebo as add-on therapy to a statin in patients who primarily have established CHD or who are CHD risk equivalent. Two modelled economic evaluation were presented – one for patients with hypercholesterolaemia and hypertension and the other for patients with hypercholesterolaemia and family history of CHD. The type of model was a decision analytic model with Markov process which extrapolates trial-based changes in total cholesterol and HDL-C to life-years gained over 70 years; **Part B:** The submission provided a meta-analysis of the same six trials used in part A. A modelled economic evaluation was presented. The type of model was a decision analytic

	model with Markov process which extrapolated trial-based changes in total cholesterol and HDL-C to life-years gained over 70 years. The PBAC indicated that any future applications for extensions to the listing of ezetimibe either as monotherapy or in combination with simvastatin must be accompanied by a comparison against a therapeutic strategy where the dose of statin is increased or a switch to a more potent (on a mg per mg basis) statin is made. These strategies are increasingly being used in clinical practice and are therefore appropriate additional comparators to placebo.
November 2006 **Ezetimibe + simvastatin 10-10 FDC**	PBAC rejected an application to list new strength (10mg – 10mg) on grounds of unclear clinical need and unnecessary proliferation of dose forms. There was also a lack of evidence that patients were at a lower risk of side effects with this combination than with a 10mg dose or higher of a more potent statin. The PBAC noted that a patient was more likely to be switched to a 10mg dose of a more potent statin than to require the introduction of ezetimibe and that this was clinically appropriate.
March 2008 **Ezetimibe + simvastatin FDC**	Advice under section 101(4AC) deferred to seek clarification of some inconsistencies in the data set presented.
April 2008 **Ezetimibe + simvastatin FDC**	Advice under section 101(4AC) rejected. The combination item does not provide for some patients: • a significant improvement in patient compliance with therapy; or • a significant improvement in efficacy; or • a significant reduction in toxicity over the alternative therapies identified above. With respect to whether or not Vytorin therapy provides an improvement in efficacy over the alternative therapies in some patients, the PBAC did not accept that the submission's claimed linear relationship between compliance and efficacy had been adequately demonstrated, considering instead that the relationship is more likely to be sigmoidal.
November 2008 **Ezetimibe + simvastatin FDC**	The resubmission presented a new analysis (Vytorin® Compliance Study II, unpublished) based on an extract from an updated 1:10 random sample of PBS de-identified patient identification numbers (PINs). Individual PINs were followed for 12 months post initiation for ezetimibe or ezetimibe/simvastatin FDC to capture all 'in scope' statin and ezetimibe/simvastatin FDC prescriptions. Assessment of compliance was demonstrated through analysis of the Medication Possession Ratio (MPR). Overall the DUSC committee considered that the Vytorin Compliance Study II presented in the resubmission did not provide sufficient evidence to demonstrate a significant compliance advantage for patients taking Vytorin versus the individual components taken concomitantly in the context of chronic treatment of hypercholesterolaemia. DUSC considered that the difference in MPR in the comparator cohort (.81 versus 0.91 respectively) could not be attributed to the benefits of the combination item alone. While the MPR was higher, persistence to any therapy was lower in the Vytorin group and error rates of inappropriate concurrent combinations due to the availability of Vytorin apparent in both groups. The PBAC advised the Minister and the PBPA under section 101(4AC) of the *National Health Act* that the submission 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 clinical importance for treated patients of this compliance benefit remains uncertain.
March 2009 **Ezetimibe + simvastatin FDC**	PBAC rejected listing of 10/20mg strength as a second line treatment in patients whose cholesterol levels are inadequately controlled with a statin daily dose of 20mg or greater on the basis of a lack of clinical need, given the availability of statins to provide a similar health benefit, that in terms of cost-effectiveness evaluation the listing would provide currently available benefits at a higher cost, and the listing would place an additional significant

	financial burden on the PBS.
July 2009 **Ezetimibe + simvastatin FDC**	PBAC recommended an authority required listing of FDC ezetimibe and simvastatin (10/10mg and 10/20mg) on a cost-minimisation basis compared with the individual tablets given concomitantly for reasons of financial equity for those patients unable to tolerate high doses of a statin and who require additional lipid-lowering treatment.
Nov 2009 **Ezetimibe +/- simvastatin**	Reject request to change from Authority required (streamlined) to restricted benefit as the more restrictive classification remained appropriate for these products.
Nov 2010 **Ezetimibe**	Recommended restriction be amended to not specify a particular dose of a statin. This option allowed ezetimibe to be added as clinically appropriate while continuing to support uptitration of statins as the first line treatment of hypercholesterolaemia. Despite considerable deficiencies in both clinical and economic data presented, the PBAC considered that such a change was also consistent with clinical practice and quality use of medicine and represented acceptable, if somewhat uncertain, cost effectiveness in this patient group with inadequate cholesterol control. This recommendation was reaffirmed at the March 2011 meeting.
March 2012 **Ezetimibe +/- simvastatin**	Reject extension to listing for primary prevention of major cardiovascular events in patients with moderate to severe chronic kidney disease and who do not fall into a category for which the General Statement for Lipid Lowering Drugs allows PBS subsidised treatment with a statin, on the basis of an inappropriate clinical management algorithm and high and unacceptable cost-effectiveness.
July 2012 **Ezetimibe + simvastatin 10-10 and 10-20**	PBAC recommended the extension to the listing of the 10 mg-10 mg and 10 mg-20 mg ezetimibe with simvastatin fixed dose combination strengths to include the additional indication of treatment, in conjunction with dietary therapy and exercise, in patients whose cholesterol levels are inadequately controlled with an HMG CoA reductase inhibitor (statin) and who meet certain criteria. The PBAC recommended the extension of listing as requested in order to remove inequities for those patients whose maximum tolerated dose of simvastatin was 10 mg or 20 mg per day.
July 2012 **Atorvastatin + ezetimibe co-pack**	To request an Authority Required (Streamlined) listing for the treatment, in conjunction with dietary therapy and exercise, for co-administration with a HMG CoA reductase inhibitor (statin) in patients whose cholesterol levels are inadequately controlled with a statin and who meet certain criteria. The PBAC rejected the application because of concerns over the labelling and packaging of the co-pack and because the superiority in terms of efficacy and safety over the fixed dose combination ezetimibe and simvastatin has not been demonstrated.
Nov 2012 **Atorvastatin + ezetimibe co-pack**	To request an Authority Required (STREAMLINED) listing for the treatment, in conjunction with dietary therapy and exercise, for co-administration of ezetimibe with an HMG CoA reductase inhibitor (statin) in patients whose cholesterol levels are inadequately controlled with a statin and who meet certain criteria or who have homozygous familial hypercholesterolaemia. The PBAC rejected the submission on the basis that the co-pack provided no demonstrated clinical or convenience advantage to consumers, the potential increase in cost to Government and the lack of evidence that the composite combination pack would be used appropriately.
July 2013 **Atorvastatin +**	The PBAC recommended an Authority required (Streamlined) listing of ezetimibe and atorvastatin co-pack for hypercholesterolaemia in combination with dietary therapy and exercise where cholesterol levels are inadequately controlled by a statin and patients have

ezetimibe co-pack	hypertension, CHD (or a family history), diabetes, PVD, heterozygous familial hypercholesterolaemia or CVD, on a cost-minimisation basis with the corresponding doses of the components (ezetimibe and atorvastatin) given concomitantly. However, the PBAC remained of the view that there was no compelling clinical need for the co-pack product, and remained concerned that it might direct use inappropriate from adequate titration of statins given alone. The PBAC had previously accepted the corresponding doses of the components (ezetimibe and atorvastatin) given concomitantly, as well as ezetimibe/simvastatin fixed-dose combination (FDC) were the appropriate comparators. The PBAC accepted the claim that the ezetimibe+atorvastatin co-pack is equivalent in terms of comparative effectiveness and safety with the co‑administration of the components; and has similar efficacy and safety to ezetimibe/simvastatin FDC at therapeutically equivalent doses (non-inferiority). The PBAC recalled that at its November 2008 meeting, it advised the Minister under subsection 101(4AC) of the National Health Act 1953 and the Pharmaceutical Benefits Pricing Authority (PBPA) that ezetimibe and simvastatin FDC had a significant improvement in compliance over its alternative therapies for some patients, at the time of listing, was ezetimibe administered concomitantly with simvastatin. The PBAC recalled also that this advice was given before the finalisation of the Compliance to Medicines Working Group report, and that the criteria of that report had therefore not been used to assess the compliance claims for that product as they have for all compliance claims since. The PBAC considered that the impending PBS listing of ezetimibe and atorvastatin co-pack would allow the co-pack to be considered as an alternative therapy to the ezetimibe and simvastatin FDC. The PBAC therefore considered that the basis of its previous advice to the Minister under subsection 101(4AC) for the ezetimibe and simvastatin FDC will need to be reviewed, given that the new alternative therapy will be available. The PBAC therefore invited the sponsor of the ezetimibe and simvastatin FDC to submit data in support of its continued claim of compliance benefit and 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 Compliance to Medicines Working Group Report to the PBAC. The PBAC noted that the sponsor of ezetimibe and atorvastatin had withdrawn its claims of compliance benefit under subsection 101(4AC) of the National Health Act 1953 from its second submission in November 2012. The PBAC recommended, under section 101 (3BA) of the National Health Act, that ezetimibe and atorvastatin co-pack should be treated as interchangeable on an individual patient basis with ezetimibe and simvastatin FDC.
Nov 2013 **Ezetimibe and rosuvastatin co-pack**	The PBAC recommended Authority required (Streamlined) listing of ezetimibe + rosuvastatin co-pack for hypercholesterolaemia in combination with dietary therapy and exercise where cholesterol levels are inadequately controlled by a statin and patients have hypertension, coronary heart disease (or a family history), diabetes, peripheral vascular disease, heterozygous familial hypercholesterolaemia or cerebrovascular disease. The PBAC considered that the cost-effectiveness of the combination drug ezetimibe+ rosuvastatin would be acceptable if it were cost-minimised against the combination drug atorvastatin+ezetimibe, with a relativity of rosuvastatin:atorvastatin of 1:2.2. As was the case in their considerations of the ezetimibe + atorvastatin co-pack, the PBAC were of the view that there was no compelling clinical need for co-pack products, and remained concerned that it might inappropriately direct use away from adequate titration of

	statins given alone. The PBAC agreed that the components (co administered) and the ezetimibe/simvastatin FDC were both relevant comparators. The Committee also considered that the ezetimibe+atorvastatin co-pack (recommended at the July 2013 PBAC meeting) was a relevant comparator. The PBAC accepted the claim that the ezetimibe+rosuvastatin co-pack is equivalent in terms of comparative effectiveness and safety with the co administration of the components; and has similar efficacy and safety to ezetimibe/simvastatin FDC at therapeutically equivalent doses (non-inferiority), and noted that no claim was made in the submission against the ezetimibe + atorvastatin co-pack. The PBAC noted that the pre-PBAC Response offered a reduced price, such that the price of the ezetimibe + rosuvastatin co-pack was no higher than the price of the ezetimibe + atorvastatin co-pack, at a relativity of 1:2.5 for the statin component. Although not accepting the relativity proposed by the sponsor, the PBAC considered this approach was appropriate, as if treatment with the combination ezetimibe + rosuvastatin was substantially more costly than an alternative therapy or alternative therapies, the PBAC could only recommend listing of the combination if it is satisfied that the combination provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies. The alternative therapies in this case include the combination atorvastatin + ezetimibe. The Committee noted that the sponsor's proposed relativity of rosuvastin:atorvastatin of 1:2.5 reflected the relative ex-manufacturer prices of the two statins at the time rosuvastatin was listed. However this does not take account of the reference price driven price reductions (WAMTC) which have been applied to rosuvastatin since listing. When those are taken into account a relativity of 1:2.2 is appropriate (based on the approved ex-manufacture prices of the two drugs in November 2013). The PBAC noted that, in contrast to the statins, there are no patient relevant outcome data for ezetimibe. However, the largest contribution to the price of the combination is from the ezetimibe component. The PBAC further noted that in the 12 months to 30 June 2012, Government expenditure on ezetimibe and the combination, ezetimibe + simvastatin, under the PBS was $60.5 million and $78.3 million respectively. The PBAC formed the view that the Minister may wish to consider requesting the PBAC to undertake a review of, and subsequently provide advice to the Minister regarding, the cost-effectiveness of ezetimibe, taking into account the latest available evidence and best practice. In accordance with subsection 101(3BA) of the National Health Act 1953, the PBAC advised the Minister that it is of the opinion that, on the basis of the material available to it at its November 2013 meeting, ezetimibe + rosuvastatin co-pack should be treated as interchangeable on an individual patient basis with the ezetimibe + atorvastatin co-pack, and with the ezetimibe and simvastatin FDC.
March 2014 **Atorvastatin + ezetimibe co-pack**	The minor submission requested the PBAC reconsider their advice from the July 2013 meeting that Atozet should be treated as interchangeable with Vytorin on an individual patient basis. The PBAC considered that the current minor submission did not evidence to support a claim that atorvastatin + ezetimibe is superior to simvastatin + ezetimibe, and reaffirmed its recommendation of July 2013 that, under section 101 (3BA) of the National Health Act, ezetimibe + atorvastatin co-pack should be treated as interchangeable on an individual patient basis with ezetimibe + simvastatin FDC.

July 2014 **Ezetimibe + rosuvastatin FDC**	The PBAC recommended an Authority Required (Streamlined) listing of ezetimibe + rosuvastatin FDC for hypercholesterolaemia in combination with dietary therapy and exercise where cholesterol levels are inadequately controlled by a statin and patients have hypertension, coronary heart disease (or a family history), diabetes, peripheral vascular disease, heterozygous familial hypercholesterolaemia or cerebrovascular disease. The PBAC was satisfied that ezetimibe + rosuvastatin FDC is equivalent to the ezetimibe + rosuvastatin co-pack in terms of efficacy and safety. The Committee accepted the relativity of rosuvastatin:atorvastatin of 1:2.2 and agreed that the price of the FDC should be the same as the price for the co-pack, noting that the co-pack listing has not proceeded and the price will now need to be recalculated as a result of price disclosure. The PBAC reiterated its views from November 2013, that in contrast to the statins, there are no patient relevant outcome data for ezetimibe. However, the largest contribution to the price of the combination is from the ezetimibe component. The PBAC reiterated its view that the Minister may wish to consider requesting the PBAC to undertake a review of, and subsequently provide advice to the Minister regarding, the cost-effectiveness of ezetimibe, taking into account the latest available evidence and best practice.

Appendix C

Detailed methodology to estimate drug regimens and regimen transitions

Drug treatment regimens are estimated from prescription supply dates

The prescription data contains date of supply of each prescription, but no information on whether or not medicines should be (or were) co-administered. Thus co-administration was estimated from the data in the following way;

Step 1:

Determine the estimated medication coverage days for **each** drug or drug group.

This mainly involves detecting breaks in treatment. The outcome is the start and estimated end date for each episode of treatment for each drug or drug group.

Step 2:

Determine the estimated medication coverage days **across all** drug and drug group episodes defined in Step 1. The outcome is an estimated treatment regimen for each patient for every day in the data period.

Similar methods have been used for assessing medicine use in Australian populations.[8,9] Hallas[10] describes the method and provides references to early variants.

Figure A2.1 illustrates the method specified above. The standard coverage days (SCD) for each drug A, B & C have been shortened to 5 days to enable the figure to fit on one page. The Step 1 process results in the production of the episodes (pink bars) and the Step 2 process results in the production of the treatment regimen (blue bar). The days in this illustration are days from initiation (applicable to an incident patient analysis) but they can also be calendar days (applicable to a prevalent patient analysis).

In this illustration, a break in treatment is defined as a coverage gap of 2 or more SCDs (i.e. the patient has not received re-supply at two consecutive expected refill dates. The first gap in drug A coverage (from days -39 to -35) is not deemed to be a break in the drug A Episode 1 as the estimated gap in coverage is only 1 x SCD. The 2nd gap in drug A coverage from days -29 to -20 is deemed to be a break in treatment and the end of Episode 1 because the gap in estimated coverage is 2 x SCD.

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[8] Pratt N, Roughead EE, Ramsay E, Salter A, Ryan P 2011 "Risk of hospitalization for hip fracture and pneumonia associated with antipsychotic prescribing in the elderly: a self-controlled case-series analysis in an Australian health care claims database" Drug Saf. 34(7):567-75. doi: 10.2165/11588470-000000000-00000.

[9] Vitry AI, Roughead EE, Preiss AK, Ryan P, Ramsay EN, Gilbert AL, Caughey GE, Shakib S, Esterman A, Zhang Y, McDermott RA 2010 "Influence of comorbidities on therapeutic progression of diabetes treatment in Australian veterans: a cohort study" PLoS One. 5(11):e14024. doi: 10.1371/journal.pone.0014024.

[10] Hallas J. 2005 "Drug utilization statistics for individual-level pharmacy dispensing data" Pharmacoepidemiol Drug Saf. 14:455–463. doi: 10.1002/pds.1063

The two prescriptions for drug B supplied on day -9 are interpreted as dose escalation of drug B, if each prescription is for a different strength. The two prescriptions are deemed to be necessary to supply one SCD period and not used to extend the drug coverage period. If each prescription of drug B were for the same strength then this would be interpreted as "stockpiling" and assumed to extend the drug coverage period (see Details of Methodology below for details)

Drug C is a 3rd line agent and initiated on day 0 (by definition). The basic method imputes a short period of B+C, but a refinement of the method includes the calculation of an adjusted treatment regimen which removes short periods of overlap when it is likely that a switch has occurred before prior medicine is deemed to be fully used.

The final method for estimating the drug treatment regimen includes several refinements which are explained in below. Briefly they are:

1. Calculation of the treatment regimen on a weekly rather than daily basis.
2. Calculation of drug treatment regimen transitions – including an adjustment to allow for switching when the prior medication is not fully used.
3. Adjustment to allow for stockpiling of medication, both same-day supply and supplies on different days.
4. Change in the rules for scripts whose coverage spans the initiation data;
   - removal of stockpiling rule
5. Estimating if a patient is continuing or stopping after their last script

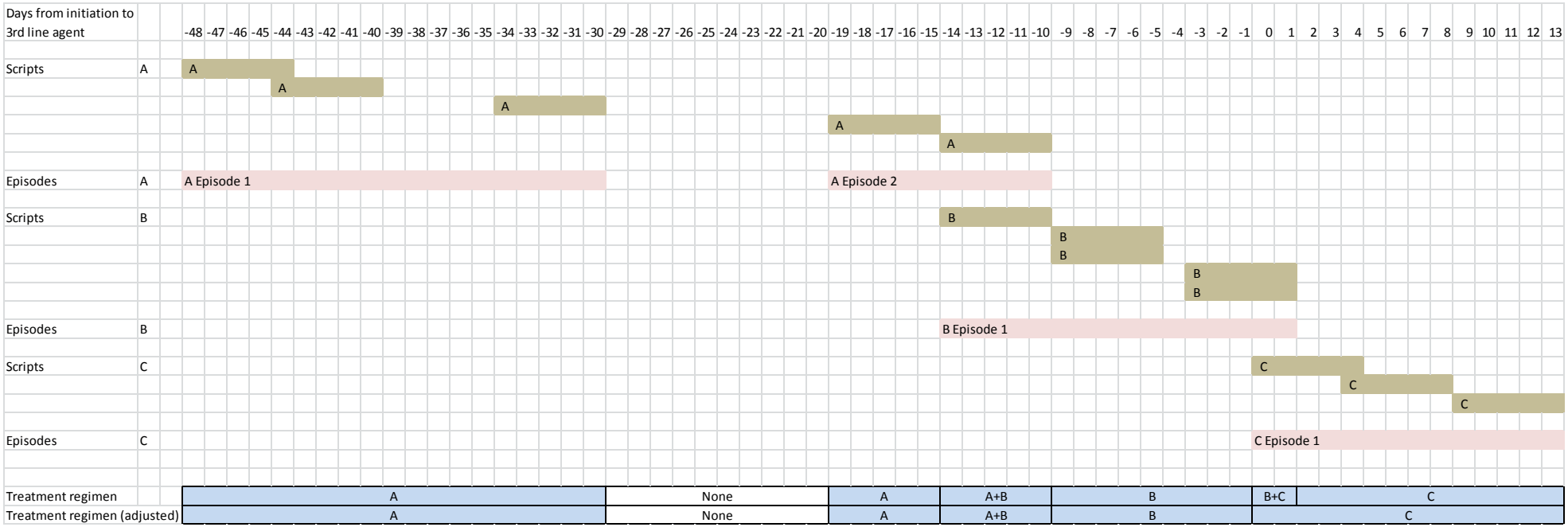

Figure C.1: Diagrammatic representation of the methodology used to determine treatment regimen

Details of Methodology

1. Calculation of the treatment regimen

Drug treatment regimens are estimated from prescription supply dates in the following way;

Step 1:

Determine the estimated medication coverage days for **each** drug or drug group.

This mainly involves detecting breaks in treatment. The outcome is the start and estimated end date for each episode for each drug or drug group.

Step 2:

Determine the estimated medication coverage days **across all** drug and drug group episodes defined in Step 1. The outcome is an estimated treatment regimen for each patient for every day in the data period.

Step 2 above was modified so that the treatment regimen was estimated on a weekly rather than daily basis. This modification was deemed necessary to keep the data volume at a manageable level. This modification means that if the a medication coverage start date falls in a particular calendar week (for prevalent patient analysis) or week since initiation (for initiation analysis) then the medication is deemed to cover that week. The same rule was applied to the medication coverage end date.

2. Drug regimen transitions - including an adjustment to allow for switching when the prior medication is not fully used

Once estimated drug regimens have been determined for every week, then transitions can be computed.

These are useful for determining patient behavior upon initiation of a drug; e.g. A→A+B (adding to existing therapy), A→B (switching) or None →A (starting therapy).

The transitions can be;

A. previous drug regimen →drug regimen at week x, or
B. drug regimen at week -1 → drug regimen at week x

Option A has the advantage that it can be calculated at any week, whereas Option B can only be calculated after initiation (i.e. from week 0). The main advantages of Option B are that it can easily be used to adjust the drug regimen in the first few weeks after initiation to allow for switching when the prior medication is not fully used. That is, if a patient switches from A to B, in the first few weeks after initiation to drug B the drug regimen may be incorrectly estimated to be A+B if the patient still has drug A "on hand" (i.e. some is unused) when drug B is initiated.

The regimen transitions are adjusted so that if a regimen transition corresponding to a switch (e.g. A→B) is detected within the first X weeks after initiation (e.g. at week Y), then all weeks between the initiation (i.e. week 0) and week Y are modified to the switch transition (i.e. A-B). This means some instances of "A→A+B" (apparent co-administration after a switch) are modified to "A→B" from week 0 to week Y (where Y ≤ X). The value of X is the 1 week + SCD (expressed in weeks) for the drug or drug group that is being substituted.

This means that if a drug A was supplied 1 day before an initiation to drug B and then there were no further supplies of drug A, then there would be apparent co-administration of A and B from week 0 to week X-1 and in week X the drug regimen would be drug B only and considered a switch. Thus the regimens from weeks 0 to X-1 would be modified to be dug B only. If a switch is first detected in week X +1 then the A script would have been supplied in week 0 (i.e. at or after initiation to drug B) and this would mean that the transition was not a switch, but an add. Thus the logic is only applied to weeks 0 to X.

A transition is considered a switch if a drug in the regimen prior to initiation (the week=-1 regimen) is not in the regimen post initiation (i.e. the week=0 regimen).

After this transition adjustment, the drug regimens can also be adjusted by using the regimen after the arrow in the adjusted regimen transition. That is, if a transition gets adjusted from A→A+B to A→B in week Y then the adjusted drug regimen for week Y changes from A+B to B. Thus even though the drug regimen is calculated first, its adjustment is dependent on both the regimen transition and adjusted regimen transition. Thus the sequence of calculations is;

1. drug regimens
2. drug regimen transitions around initiation
3. adjusted drug regimen transitions
4. adjusted drug regimens

The above adjustment process is reliant on having regard to drug initiations. If the analysis is for prevalent drug regimens only (i.e. regimens by calendar week and not relative to an initiation date) then the above adjustment is not possible. This is not a major problem as the overestimation of co-administration (e.g. A→A+B instead of A→B) is greatest in the month after initiation. In a prevalent patient analysis, patient initiations (to any and all drugs) are spread out in time (i.e. all patients do not generally initiate in the same week), and so the overestimation is also spread out over time and so minimised. In an initiating patient analysis, all over-estimations occur at the same time (as time is relative to the initiation week) and so the overestimation is significant and so needs to be adjusted for. In theory in a prevalent patient analysis, it is possible to do an initiation analysis for every drug and so find adjusted drug regimens that can then be re-expressed in calendar weeks. In practice this is too resource intensive and is unlikely to be make a significant difference to the prevalent patient drug regimens.

3. Adjustment to allow for stockpiling of medication, both same-day supply and supplies on different days

The two step methodology outlined in point 1 and refined by logic in point 2 above did not take into account the phenomenon of stockpiling. This often occurs towards the end of the calendar year when a Safety Net card holder fills prescriptions more frequently than expected, so as to stockpile the medicine and avoid a higher co-payment in the next calendar year when they lose Safety Net eligibility. Stockpiling can also occur at other times of the year. Step 1 can impute higher rates of breaks in episodes around February.is is likely to be due to the stockpiling effect and not due to genuine breaks in treatment. Thus the rule to estimate the prescription coverage end date was modified to be the greater of;

- the predicted coverage end date of the previous prescription plus the standard coverage days (SCD); and,
- the actual refill date of the previous prescription plus the SCD.

This way of calculating the prescription coverage end date takes into account medication stockpiling (i.e. early supply). The logic of the break rule remained unchanged, that is;

- a break was where a prescription was supplied 2 x SCD or more after the coverage end date of the previous prescription for the same drug or drug group.

Application of this refinement results in the reduction of the extent of seasonality in the number of breaks in episodes.

If multiple prescriptions of the same drug (but not the same strength) or drug group are supplied on the same day, it was assumed that these were necessary for the prescribed dose for the SCD and not for an extension of coverage.

If multiple prescriptions of the same drug are supplied it is generally for two different strengths to enable the prescribed dose to be administered. If two prescriptions for the same strength (as opposed to increased quantity for a single script) are supplied, the method assumes this is similar to stockpiling (i.e. sameday stockpiling) and the predicted coverage end date is extended to be the greater of;

- the predicted coverage end date of the previous prescription plus n x SCD; and,
- the actual refill date of the previous prescription plus n x SCD

where n = number of scripts on the same day.

A special case of multiple prescriptions being supplied on the same day is Regulation 24 prescriptions.

If the original and repeat prescriptions were supplied under Regulation 24 on the same day, then this was assumed to extend the coverage period (i.e. coverage period = prescriptions x SCD).

4. Change in the rules for scripts whose coverage spans the initiation data;
- removal of stockpiling rule

It was found that the stockpiling rule could result in the script coverage end date getting considerably ahead of the script supply date. This is the intent of the rule, however when a new drug B was initiated the stockpiling rules was resulting in the imputation that the new

drug B was being added to an existing drug A, when in all probability it was substituting drug A. To correct for this, the script coverage rule was changed so that if the script coverage period for a drug A script included the initiation date for drug B, then the stockpiling rule would not apply to the drug A script (i.e. its coverage would be from its supply date to the supply date + SCD). The rationale for this change is that even if patient has a lot of drug A on hand, the decision by the prescriber to initiate a new drug means that a switch could have occurred.

5. Estimating if a patient is continuing or stopping after their last script

If the last script in a patients script history is supplied within 2 x SCD of the end of the data period then the treatment is estimated to be continuing at the end of the data period (i.e. the episode coverage end date is set to the end date of the data period). Otherwise the treatment episode is estimated to have stopped and the episode coverage end date is equal to If the last script in a patients script history plus 1 x SCD.

Table C.1: Standard Coverage Days used in this analysis

Drug or Drug Group	Standard Coverage Days (i.e. Median time to re-supply by any item of the same drug or drug group)
A10	31
A20	31
A40	31
A80	31
Am10/A10_FDC	30
Am10/A20_FDC	30
Am10/A40_FDC	30
Am10/A80_FDC	31
Am5/S10_FDC	30
Am5/S20_FDC	30
Am5/S40_FDC	30
Am5/S80_FDC	31
Bile_acid	46
E	31
E/A10_Copack	33.5
E/A20_Copack	31
E/A40_Copack	32
E/A80_Copack	33
E/S10_FDC	31
E/S20_FDC	31
E/S40_FDC	31
E/S80_FDC	31
F20	29
F40	29
F80	29
Fibrate	31
Nicotinic acid	35
P10	31
P20	31
P40	31
P80	31
R 5	31
R10	31
R20	31
R40	31
S 5	31
S10	31
S20	31
S40	31
S80	31

Table C.2: Mapping of Streamlined Authority code

Adverse event with statin
3731, 3739, 4147, 4353
Heterozygous familial hypercholesterolaemia
3727, 3735, 4069
Homozygous familial hypercholesterolaemia
2431, 2438, 4097
Homozygous sitosterolaemia
1991
Inadequately controlled with a statin
3724, 3725, 3726, 3728, 3729, 3730, 3732, 3733, 3734, 3736, 3737, 3738, 4068, 4085, 4086, 4096, 4120, 4121
Other
1859, 2044, 2649, 2650, 2651, 2652, 2653, 2654, 2655, 2656, 2657, 2658, 2664, 2667, 2668, 2669, 2678, 2679, 3194, 3233, 3606
Statin contraindicated
1989
Streamlined code missing or 0, probably telephone authority
0

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The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health (DoH) has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee. The context for that information may have changed since publication.

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