

1 May 2017

EZETIMIBE REVIEW

ANALYSIS OF UTILISATION DATA

Health Technology Assessment Team



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Review of the current utilisation of PBS-listed ezetimibe and ezetimibe combination products

In November 2013, the PBAC expressed concern that the listing of ezetimibe with statin co-packs and combination products on the PBS may direct use away from optimal dose titration of statins. The terms of reference (ToR) for the post-market review of ezetimibe therefore included the following:

ToR 1, as approved by the Minister for Health, involves a review of current utilisation of PBS-listed ezetimibe and ezetimibe combination products.

An analysis of unit record level PBS data was conducted in 2016 to identify people first dispensed ezetimibe alone or in combination with a statin or other non-statin lipid lowering therapy (LLT) during the period April 2014 to March 2015. This analysis was conducted in a sample of the complete PBS dataset (including under co-payment prescriptions) for all lipid lowering medicines (ATC C10) dispensed between April 2012 and March 2016. This utilisation analysis was presented in the draft ezetimibe post market review Report available at (<http://www.pbs.gov.au/reviews/ezetimibe-review-files/draft-ezetimibe-post-market-review-report.pdf>). The aim of this study was to answer the following research question:

“Is ezetimibe being prescribed on the PBS in accordance with the PBS restrictions for ezetimibe, which require up-titration of statins to maximally tolerated doses before initiation of treatment with ezetimibe?”¹

Ezetimibe is PBS-listed for use:

- (i) as monotherapy among those who are contraindicated for statin therapy, among those necessitating withdrawal of statin therapy as a result of statin-related adverse events and in patients with homozygous sitosterolaemia; and
- (ii) in combination with the maximum tolerated dose of statin when cholesterol levels are in excess of defined thresholds.

The Drug Utilisation Sub-Committee (DUSC) of the PBAC reviewed the results of this initial study in February 2017 and requested an additional analysis using the same dataset be conducted to more comprehensively answer the above research question. The DUSC’s view was that not all utilisation pre- and post- ezetimibe initiation had been linked at the individual patient level and that this was likely to have underestimated the number of patients who were not using ezetimibe in accordance with the restriction.

The DUSC also questioned some of the definitions of ezetimibe monotherapy and ezetimibe combination therapy used in the initial data analysis (December 2016). These definitions were refined/simplified as explained in Section 2.1 and Section 2.4 and prompted some limited changes to the algorithm used for calculating the proportion of patients meeting the defined criteria. **Application of the alternative definitions and the revised algorithm in the additional analysis (March 2017) of the same PBS dataset produced results that are not identical to the results reported in the initial study (refer to Appendix B, Tables B.3 and B.4).**

¹ Q1 was designed with limitations of the PBS utilisation data in mind rather than the precise words of ezetimibe restriction

1. Data description

The Department provided the PBS data on 14 September 2016. The data was extracted for all medicines listed under ATC C10 for the dates of supply of ezetimibe from 1 April 2012 to 31 March 2016 (including the actual dispensing dates up to 31 July 2016). *This PBS dataset is complete as it includes all under co-payment prescriptions (i.e., the dispensed statins that are priced under the general co-payment threshold are included).* The dataset does not contain prescriptions written as private scripts or samples given to patients by doctors. The original 111,561,966 records were split into two datasets: patient details and item details. Tables A.1a and A.1b in Appendix A list the variables in the two datasets and their description. The two datasets were subsequently merged in order to add the ATC5 codes to the corresponding item codes.

Further modifications included:

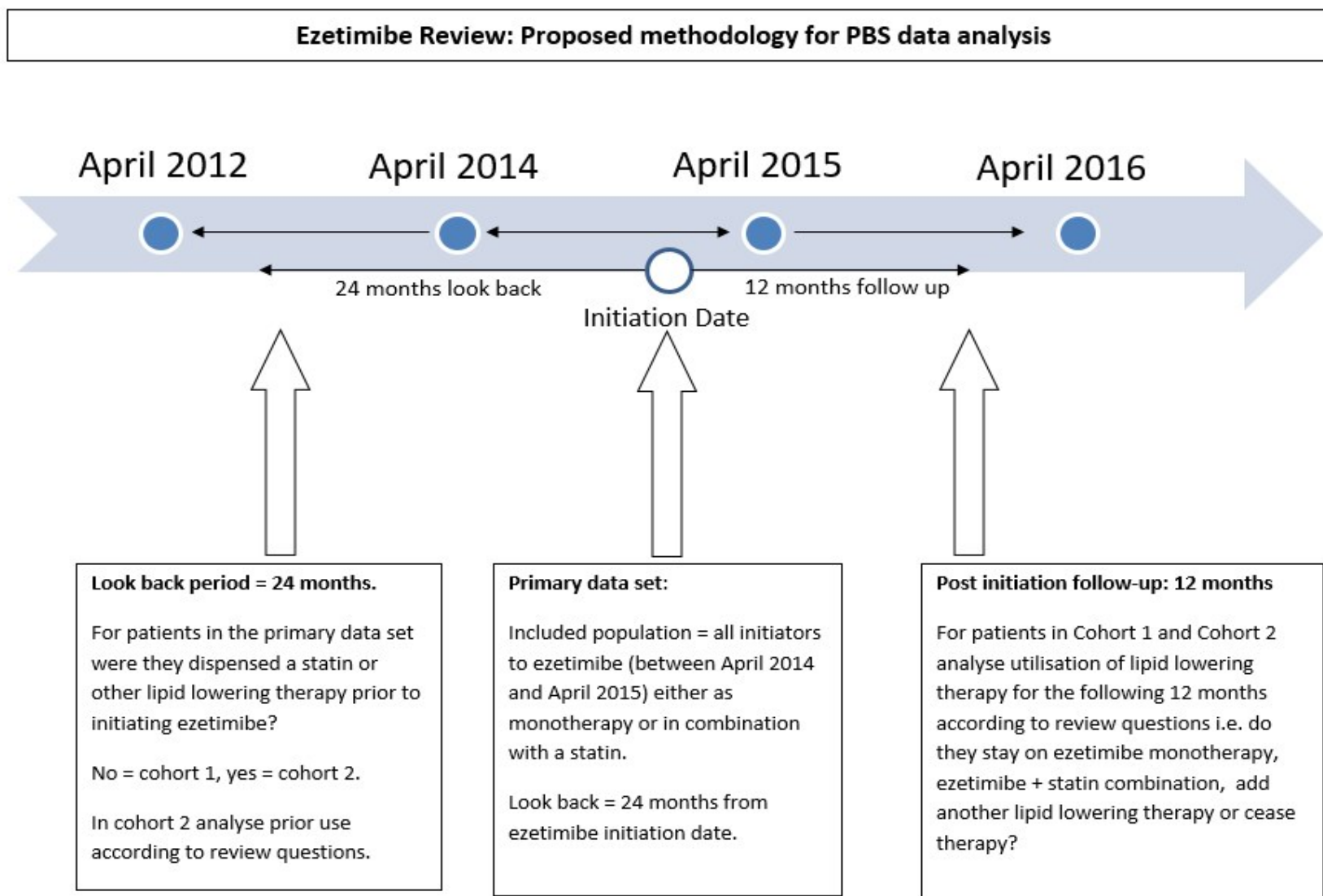
- Deleting the records corresponding to patients who were prescribed ezetimibe or ezetimibe combination prior to 1 April 2014 (N=13,155,888 records or 11.8%);
- Deleting the duplicates that involve the same drug of the same strength dispensed to the same patient on the same day. Although the actual reason for such occurrences (up to 30 identical supplies could occur simultaneously and without section 24) is unclear, it was assumed that the removal of the duplicates (N=2,842,332 or 2.9%) would not affect results of the analysis.

The final total number of records available for the primary analysis is 95,563,746 prescription records for 45,645 patients initiating treatment with ezetimibe (i.e. prescriptions for patients who were first dispensed ezetimibe or ezetimibe combination between 1 April 2014 and 31 March 2015). In the sensitivity analysis the number of ezetimibe initiator patients (i.e. patients who were first dispensed ezetimibe or ezetimibe combination between 1 April 2015 and 31 March 2016) was 54,599. The records were sorted by the supply date. The supply date was also used in assigning other criteria in the course of data analysis (e.g. the period of continuous treatment).

The primary dataset is subdivided into Cohort 1 and Cohort 2. Cohort 1 included patients who were not dispensed a statin or other lipid lowering therapy (LLT) prior to initiating ezetimibe in the period from 1 April 2014 to 31 March 2015 (base year for the primary analysis); Cohort 2 included patients who were dispensed a statin or other LLT prior to initiating ezetimibe in the base year.

Figure 1.1 illustrates the definitions for the primary dataset, Cohort 1 and Cohort 2.

Figure 1.1 Definition of the cohorts and approach to the data analysis



2. Method of data analysis

Figure 1.1 also illustrates the approach to the initial (December 2016) data analysis. Looking back from the exact date of the first ezetimibe dispensed to each patient in the base year of 1 April 2014 to 31 March 2015, we have investigated the prior 24 month history of statin and non-statin prescriptions dispensed to this patient (i.e. the same time interval of 24 months applied to history of LLT for each patient).

The additional (March 2017) analysis included the same study population as in the 2016 ezetimibe utilisation report i.e., people who received their first prescription for ezetimibe between 1 April 2014 and 31 March 2015. Initiators to ezetimibe were further categorised into the following two cohorts, those with:

- no history of statin or non-statin LLT in the 24 months prior to ezetimibe initiation (**Cohort 1**); and
- a history of statin or non-statin LLT in the 24 months prior to ezetimibe initiation (**Cohort 2**).

Additional analyses of sub-groups of those in Cohort 2 were also conducted (see below).

2.1. History of LLT prior to ezetimibe initiation – initial analysis (December 2016)

By definition, Cohort 1 does not have any history of statin or LLT dispensed in previous 24 months.

For the patients from Cohort 2 the following research questions were investigated in relation to history of statin use:

1. The mean number of prior statin prescriptions dispensed per person;
2. The mean number of prior non-statin LLTs prescriptions dispensed per person;
3. Distribution of patients across the number of statin prescriptions dispensed prior to ezetimibe initiation;
4. Number/proportion of patients receiving a continuous statin treatment prior to the first filled ezetimibe prescription (*see Clarification Note 1 below*)
5. For those with two or more statin prescriptions dispensed, the number/proportion of patients who :
 - did not experience an adjustment in statin dose or potency²;
 - experienced up- or down-titration of statin (including adjusting the dose or switching to another statin of higher or lower potency²);
6. Detailed analysis of the instances of up- and down titrations either in terms of statin dose or potency observed over 24 months prior to ezetimibe initiation.

Clarification Note 1: The following 2-step **definition of continuous use of statin** applied:

- a) All patients who have filled a minimum of three statin prescriptions within 6 months of ezetimibe initiation were classified as having received continuous treatment;
- b) A proportion of patients with 1 or 2 prescriptions within 6 months of ezetimibe initiation was also assumed to be in continuous treatment if the first (or the only) of these two prescriptions was the very first time the statin was dispensed to the patient. In other words, both filled statin prescriptions should fall within 6 months of ezetimibe initiation and no statin prescriptions were filled in the 6 month period prior to ezetimibe initiation.

² For the allocation of statins into potency categories see and Tables A1a, A1b, A1c and Table A.2 in Appendix A.

This definition of continuous use of statin was not used in the additional (March 2017) analysis, however the mutually exclusive groups were defined for patients with at least one statin prescription dispensed in the 6 months prior to ezetimibe initiation, as explained in section 2.4.

Clarification Note 2: definition of treatment termination (ceasing statin therapy). Conversely, the patients who had no statin prescription filled within 6 months prior to ezetimibe initiation are assumed to have ceased the background statin treatment. *Definition of treatment termination effectively remained unchanged in the additional analysis, but was clarified in relation to the time of the previous use of statin. Patients were considered ceasing statin therapy if they received statin in the 24 months prior, but did not have any statin prescriptions dispensed in the 6 months immediately prior to initiating ezetimibe.*

Similarly, for the post-ezetimibe analysis the patients who had no LLT prescription filled within the time interval from the 6th to the end of the 12th month are assumed to have ceased a LLT treatment. *This definition was not used in the additional analysis.*

Clarification Note 3: Co-administered therapy at time of ezetimibe initiation occurred if a dispensed ezetimibe prescription was followed by a dispensed LLT on the same or within the next 30 days or preceded by LLT prescription within the previous 30 days.

In the additional analysis this definition was replaced with the “initiation to ezetimibe”, and “initiation to combination ezetimibe and statin (or other LLT)” as explained in section 2.4.

Clarification Note 4: For the purposes of this Review **up- or (down-) titration of statin** is viewed as either switching to the higher (lower) dose of statin or to the more (less) potent statin. Table A.2 in Appendix A shows the allocation of particular brands/doses of statin to the corresponding potency category.

Definition of up- or (down-) titration of statin remained unchanged in the additional analysis.

Clarification Note 5. Definition of a “patient instance”. For each patient in Cohort 2, every occasion involving a statin adjustment either in terms of increasing/decreasing a dose of the same statin or switching to another statin of a different potency is counted as a separate “patient instance”.

Patient instances were not used in the additional analysis.

Figure 2.1 “Pre-Ezetimibe Initiation Decision Matrix” illustrates the algorithm for decision analysis on identifying ezetimibe prescribing practices that may fall outside the PBS restrictions.

Figure 2.1 Pre-Ezetimibe Initiation Decision Matrix

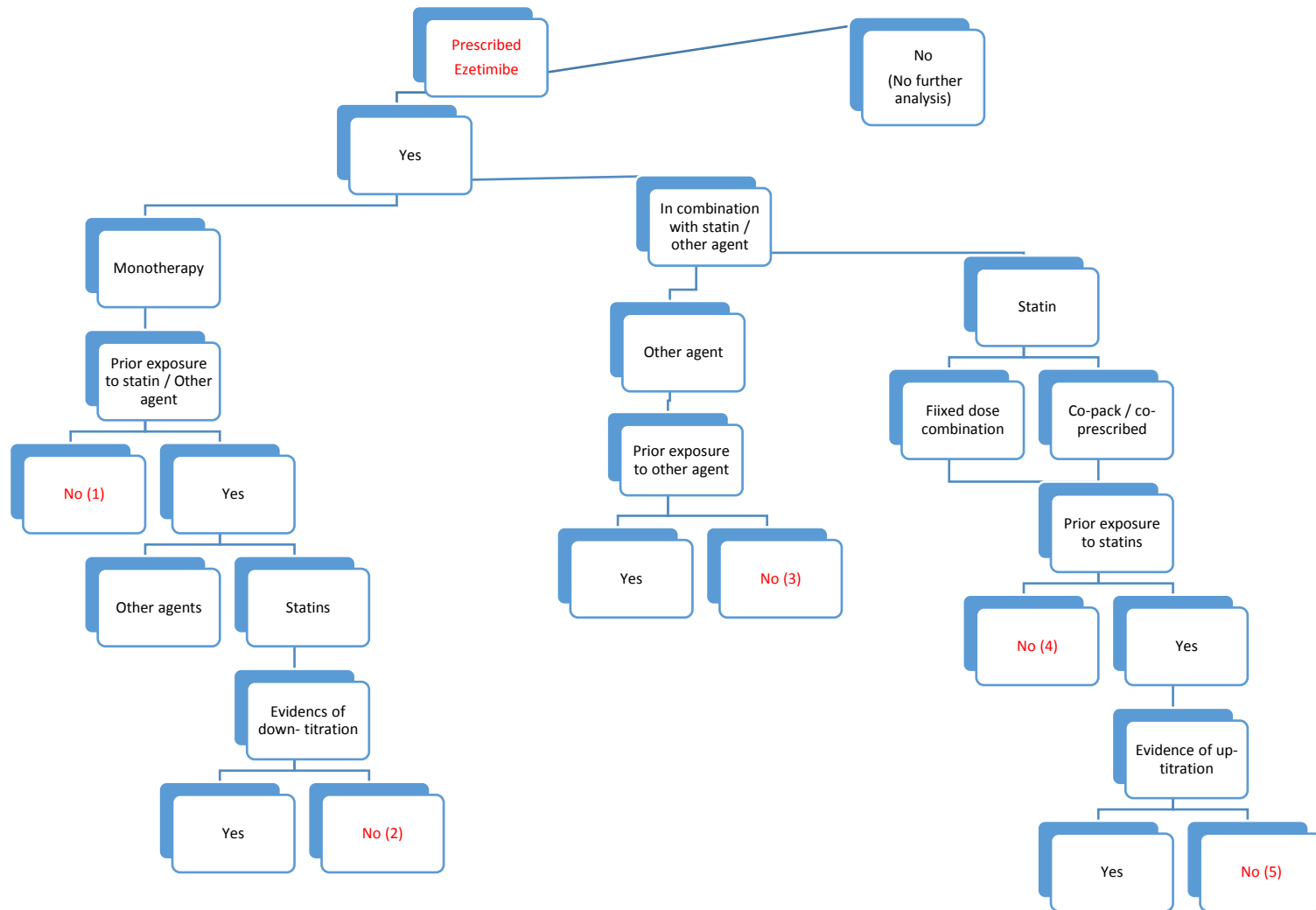


Figure 2.1 “Pre-Ezetimibe Initiation Decision Matrix” is applicable only to the analysis of 24 months of LLT and inclusive of the decision to initiate on ezetimibe. The following point represents prescription dispensing pattern that is likely to indicate ezetimibe prescribing that is outside the PBS restrictions:

- Statin naïve patients (Cohort1) who were initiated on ezetimibe in combination with statin (No (4) in Figure 2.1);

The following points in Figure 2.1 include ezetimibe prescribing that are potentially non-compliant with the PBS restriction, however there is insufficient information in the PBS data to determine the extent of the non-compliance with certainty.

- Statin naïve patients (Cohort 1) initiated on ezetimibe monotherapy (No (1) in Figure 2.1);
- Patients in Cohort 2 who were subsequently initiated on ezetimibe monotherapy, without any evidence of a prior statin down-titration (No (2) in Figure 2.1).
- Patients in Cohort 2 who were subsequently initiated on ezetimibe/statin combination without any evidence of a prior statin up-titration (No (5) in Figure 2.1).
- Patients in Cohort 2 initiated on ezetimibe/non-statin combination without any evidence of a prior exposure to the non-statin (No (3) in Figure 2.1).

2.2. History of LLT post ezetimibe treatment

Looking forward from the base year of April 2014 - April 2015, we have investigated the history of statin and other LLT supplied to the patients post ezetimibe initiation.

For Cohort 1 we calculated number/proportion of patients who:

1. Did not change treatment regimen following ezetimibe initiation: i.e. stayed on the initially prescribed ezetimibe monotherapy or ezetimibe in combination with statin or ezetimibe in combination with non-statin LLT;
2. Started on ezetimibe monotherapy but later switched to ezetimibe combination with a non-statin;
3. Started on combination ezetimibe + statin therapy (fixed dose combination (FDC) or co-administered³) and later switched to monotherapy with a statin;
4. Started on combination ezetimibe + statin therapy (FDC or co-administered³) and later switched to monotherapy with a non-statin;
5. Started on combination ezetimibe + statin therapy and later switched to monotherapy with ezetimibe;
6. Terminated treatment with all LLTs⁴.

For Cohort 2 we calculated number/proportion of patients who:

1. Did not change the ezetimibe treatment since the first prescription by the type of therapy: monotherapy or ezetimibe in combination with statin or non-statin LLT (FDC or co-administered³);
2. Started on ezetimibe monotherapy but later switched to ezetimibe combination therapy with a statin (FDC or co-administered³);
3. Started on ezetimibe monotherapy but later switched to ezetimibe combination with a non-statin (FDC or co-administered³);

³ Co-administered therapy was defined in Clarification Note 3.

⁴ Defined as no supply of any LLT for at least 6 months, see Clarification Note 2.

4. Started on ezetimibe monotherapy but later switched to statin as monotherapy;
5. Started on ezetimibe monotherapy but later switched to a non-statin LLT as monotherapy;
6. Started on combination ezetimibe + statin therapy (FDC or co-administered) and later switched to monotherapy with statin;
7. Started on combination ezetimibe + statin therapy (FDC or co-administered) and later switched to monotherapy with a non-statin;
8. Started on combination ezetimibe + statin therapy (FDC or co-administered) and later switched to monotherapy with ezetimibe;
9. Terminated treatment with any LLT (i.e. no supply of any LLT for at least 6 months).

2.3. Linking the pre- and post-ezetimibe history of statin use (December 2016).

Identification of patients in Cohort 2 in whom statin therapy was up-titrated at the time of, or after, initiation of ezetimibe

By looking back to the last prescribed statin and comparing statin potency and dose before and after initiation of ezetimibe, we were able to identify patients in whom any statin up-titration (either in terms of potency or a dose) had occurred either at the time of ezetimibe initiation or at any time during 12 month after ezetimibe initiation.

For Cohort 2 we calculated number/proportion of patients who:

1. Initiated on ezetimibe + statin therapy (FDC or co-administered monotherapy) where a statin component was more intensive (either in terms of potency or a dose) in comparison to the last statin treatment received prior to ezetimibe initiation.
2. At any time during the 12 month following ezetimibe initiation were dispensed a statin either as monotherapy or in combination with ezetimibe (FDC or co-administered monotherapy) where a statin component was more intensive (either in terms of potency or a dose) in comparison to the last statin treatment received prior to ezetimibe initiation.

2.4. Method of additional data analysis (March 2017)

The approach for the additional analysis of PBS prescription data replicates and expands on the approach described in Section 2.3 above “Linking the pre- and post-ezetimibe history of statin use” by identifying patients in Cohort 2 in whom statin therapy was up-titrated at the time of, or after, initiation of ezetimibe. This approach allows for an estimation of the use of ezetimibe on the PBS, which is inconsistent with its restriction.

DUSC suggested that the following three groups could be more accurately identified in PBS data:

- those initiating ezetimibe in accordance with the PBS restriction (**green**);
- those initiating ezetimibe in a manner that is not consistent with the PBS restriction (**red**);
and
- the remainder for whom compliance with the PBS restriction is unknown (**orange**).

The tables representing the decision matrix for classifying patients into these three groups (**red**, **green** and **orange**) according to the history of dispensing of lipid lowering medicines before and after initiating ezetimibe are presented in Appendix B. These tables were presented to the Ezetimibe Reference Group on 17 March 2017, to seek additional clinical input and agreement on the colour coding of each cell in the decision matrix. All coloured cells include discrete patient numbers from Cohort 1 and Cohort 2.

The following refined definitions were used in the additional analysis:

Initiation to ezetimibe: individuals dispensed their first prescription for ezetimibe or a fixed-dose combination (FDC) containing ezetimibe between 1 April 2014 and 31 March 2015 in the dataset i.e., the first dispensing for a minimum of two years from April 2012 onwards in the complete PBS dataset.

Initiation to combination ezetimibe and statin (or other LLT): individuals dispensed a statin or other LLT on the same day or within the following 30 days of the ezetimibe initiation date.

Among patients in Cohort 2, prior use of lipid lowering therapy was categorised into eight groups, defined in Table 2.1.

Table 2.1: Definitions of lipid lowering use prior to ezetimibe initiation (applicable to Cohort 2)

Ceasing statin therapy	Received statin in the 24 months prior, but did not have any statin prescriptions dispensed in the 6 months immediately prior to initiating ezetimibe
Patients with at least one statin prescription dispensed in the 6 months prior to ezetimibe initiation	
Mutually exclusive groups	Down-titrated statin only or on the lowest statin dose
	Up-titrated statin <u>only</u> , but not to the highest statin dose
	Last dose of statin before ezetimibe initiation was the highest dose of statin (including those who were up-titrated to the highest dose)
	Stayed on the same dose of statin which was neither the highest nor the lowest dose of statin
Both up- and down- titrated statin (excluding those who were on the highest dose and lowest dose prior to initiation)	
Patients with prior non-statin LLT only	Over the 24 months prior to ezetimibe initiation, no statin prescriptions were dispensed, but at least one non-statin LLT prescription was dispensed

The additional analysis of the 12 month post-ezetimibe LLT use was primarily focused on patients described in Table 2.2. However, no analysis of the full 12 months post-ezetimibe was conducted on those in Cohort 1 who were initiated on ezetimibe + statin (all considered to be use outside of the restriction) or ezetimibe + non-statin LLT (all considered to be use within the restriction) were conducted. Although there is a possibility that among those who initiated therapy with ezetimibe + non-statin LLT may have added a statin over the following 12 months (which would represent use of ezetimibe outside of the restriction), this population of 40 patients represents less than 0.1% of the entire population (N=45,645) and their exclusion from this further analysis would have minimal effect.

Table 2.2: Definitions of lipid lowering use after ezetimibe initiation for both Cohort 1 and 2

Cohort	Status at initiation and follow – up of 365 days
Cohort 1	Initiate and remain on ezetimibe monotherapy
	Initiate ezetimibe in combination with a statin or later add or switch to therapy involving a statin
	Initiate ezetimibe in combination with or later add/switch a non-statin LLT
Cohort 2	Initiate and remain on ezetimibe monotherapy (ie, receive no other LLT)
	Initiate ezetimibe in combination with statin at higher intensity* or later add/ switch to statin at higher intensity*
	Initiate ezetimibe in combination with statin at same intensity** or later add/ switch to statin at same intensity**
	Initiate ezetimibe in combination with statin at lower intensity*** or later add/ switch to statin at lower intensity***

Initiate and remain on ezetimibe in combination with other non-statin LLT or, add/switch to other LLT

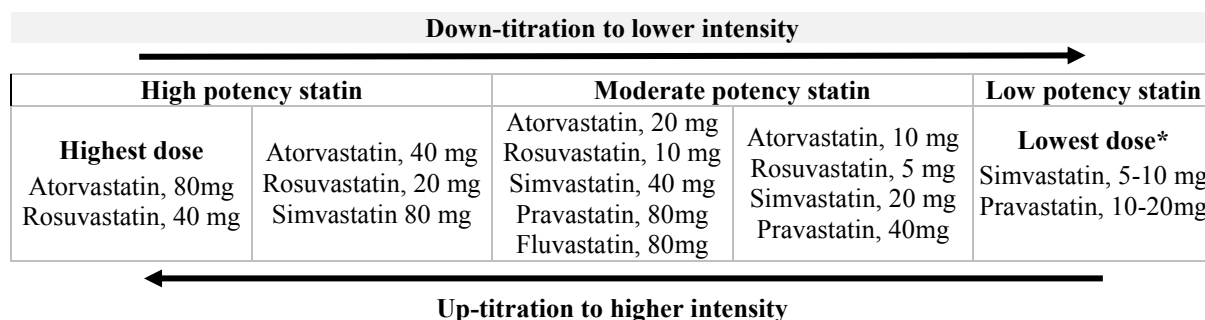
* If any statin prescriptions post ezetimibe initiation (365 days) at higher intensity than last statin strength dispensed before starting ezetimibe

** Patients with the highest intensity in all statins prescribed in post-ezetimibe period being equal in intensity to the last pre-ezetimibe statin

*** If all statin prescriptions post ezetimibe initiation at a lower intensity than the last statin pre-ezetimibe statin prescription

References to the highest and lowest statin doses and changes resulting from up or down titration of statins described in Table 2 are defined in Figure 2.2.

Figure 2.2: Definitions applied in this analysis for “highest” and “lowest” dose statins and movement from higher to lower (or lower to higher) intensities and doses assumed to the “same” across statins



As defined in Table 5 of Stone et al 2013⁵, the “lowest” dose aggregates two strengths of simvastatin (5mg and 10 mg) and two strengths of pravastatin (10 and 20mg).

3. Results of the additional analysis (March 2017)

Of the 45,645 patients who were first dispensed ezetimibe between 1 April 2014 and 31 March 2015, 6,938 patients were represented in Cohort 1 (had no history of LLT in the 24 months prior to ezetimibe initiation) and 38,707 patients were represented in Cohort 2 (had a history of LLT in the 24 months prior to ezetimibe initiation).

Table 3.1 presents the results of the analysis of Cohort 1 (those with no history of statin use in the 24 months prior to ezetimibe initiation). Cells shaded in green represent treatment regimens in accordance with, cells shaded in red represent treatment regimens not in accordance with, and orange cells represent treatment regimens of unknown accordance with the PBS ezetimibe restrictions. The numbers of patients in some categories have changed given new definitions were applied in the current compared with previous analyses (see Table B.3 Appendix B for further explanation).

Table 3.1: Use of treatments over the 12 months after ezetimibe initiation among patients in Cohort 1 (patients initiating ezetimibe with no prior dispensing of any lipid lowering therapy in 24 months prior to ezetimibe initiation; N=6,938)

LLT in Prior 24 months	Post-ezetimibe LLT (followed for 12 months)		
	stay on ezetimibe monotherapy	start/add/switch to a statin	switch or add other LLT*
No LLT	N=3,148 (45.4%)	N=3,647 (52.6%)	N=143 (2.0%)

LLT = lipid lowering therapy *non-statin

⁵ Stone NJ, et al (2014). 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*, 129 [Suppl 2]: S1-S45.

*

In Cohort 1, 3,148 patients initiated on monotherapy and stayed on monotherapy for the next 12 months. This number includes patients with a single ezetimibe prescription. There is insufficient evidence to establish compliance with the PBS restriction in this subgroup of Cohort 1 patients. A further 3,647 patients initiated ezetimibe and received a statin in the following 12 months (red group). The remaining 143 patients in Cohort 1 initiated ezetimibe and were dispensed only other non-statin LLT in the following 12 months (green group).

Table 3.2 presents the results of the analysis of Cohort 2 patients initiated on ezetimibe monotherapy, or in combination with a statin or a non-statin LLT (those with a history of statin use in the 24 months prior to ezetimibe initiation).

Compliance with ezetimibe restrictions requires consideration of the nature of both pre and post-ezetimibe statin status. In considering continuing treatment with ezetimibe over the 12 months after an initial ezetimibe prescription, of those in Cohort 2 (those with a history of statin use in the 24 months prior to ezetimibe initiation), a total of 4,713 patients in were considered to be in violation of, and 21,243 were considered to be initiated and continued use according to the PBS restrictions. It was unclear whether the remaining 12,751 patients were treated in compliance with the PBS restrictions.

Of the 45,645 patients included in this analysis (Cohorts 1 and 2):

- 143 + 21,243 = 21,386 (46.9%) were treated in a manner that was in accordance with the PBS restriction for ezetimibe;
- 3,647 + 4,713 = 8,360 (18.4%) were treated in a manner that was not in accordance with the PBS restriction for ezetimibe; and
- 3,148 + 12,751 = 15,899 (34.8%) were treated in a manner in which accordance with the PBS restriction for ezetimibe is unknown.

Table 3.2: Use of treatments over the 12 months after ezetimibe initiation among patients in Cohort 2 according to subgroups; N=38,707

Pre Ezetimibe LLT	N	Post-ezetimibe LLT (followed for 12 months)				
		stay on ezetimibe monotherapy ^a	start/add/switch statin to higher dose ^{*,b}	start/add/switch statin to same dose ^{**b}	start/add/switch statin to lower dose ^{***b}	start/stay/add other LLT only ^c
Ceased statin more than 6 months prior ezetimibe	7,327	3,327 (45.4%)	615 (8.4%)	1,545 (21.1%)	1,587 (21.7%)	253 (3.5%)
Down titrated statin or on lowest dose	2,837	912 (32.1%)	601 (21.2%)	1,022 (36.0%)	222 (7.8%)	80 (2.8%)
Up titrated statin (but not on highest)	2,401	306 (12.7%)	258 (10.7%)	1,285 (53.5%)	515 (21.4%)	37 (1.5%)
On highest dose of statin	6,986	245 (3.5%)	N/A	4,930 (70.6%)	1,778 (25.5%)	33 (0.5%)
Stayed on same dose of statin	15,616	3,147 (20.2%)	1,787 (11.4%)	8,022 (51.4%)	2,463 (15.8%)	197 (1.3%)
Up and down titrated statin	2,633	331 (12.6%)	517 (19.6%)	1,320 (50.1%)	425 (16.1%)	40 (1.5%)
All other LLT (no statin)	907	303 (33.4%)	384 (42.3%)			220 (24.3%)

N/A= not applicable, LLT = lipid lowering therapy

Grey cells pre ezetimibe indicate that at least one statin prescription was dispensed in the 6 months prior to starting ezetimibe

* If any statin scripts post ezetimibe initiation (365 days) at higher dose than last statin strength dispensed before starting ezetimibe

** Patients with the highest intensity in all statins prescribed in post-ezetimibe period being equal in intensity to the last pre-ezetimibe statin

*** If all statin scripts post ezetimibe initiation at a lower dose than the last statin pre-ezetimibe statin script

^a only relevant to those initiating ezetimibe monotherapy

^b applies to all initiators (ezetimibe monotherapy, ezetimibe + statin combination or ezetimibe + non-statin LLT) combination. For those initiating on ezetimibe + statin combination, this may represent the single initiating statin intensity

^c only relevant to those initiating ezetimibe monotherapy and ezetimibe + non-statin LLT combination therapy

4. Results of the initial analysis (December 2016)

Presentation of the results is organised according to the approach outlined in Figure 1.1, beginning with the history of LLT prior to ezetimibe initiation (either as monotherapy or in combination with other LLT) followed by the history of LLT over the 12 months after the first ezetimibe prescription.

Table 4.1 describes the sample of the population that was selected for the analysis of ezetimibe utilisation data.

Table 4.1 Summary of the population first prescribed ezetimibe in the base year

	Number of patients	Mean number (SD) of statin prescriptions dispensed prior to ezetimibe initiation	Mean number (SD) of non-statin prescriptions dispensed prior to ezetimibe initiation
Cohort 1	6,938 (15%)	0	0
Cohort 2	38,707 (85%)	Mean: 13.49±8.425 Median (IQR): 14 (6-21)	Mean: 0.98±3.966 Median (IQR): 0 (0-0)
Total	45,645 (100%)	-	-

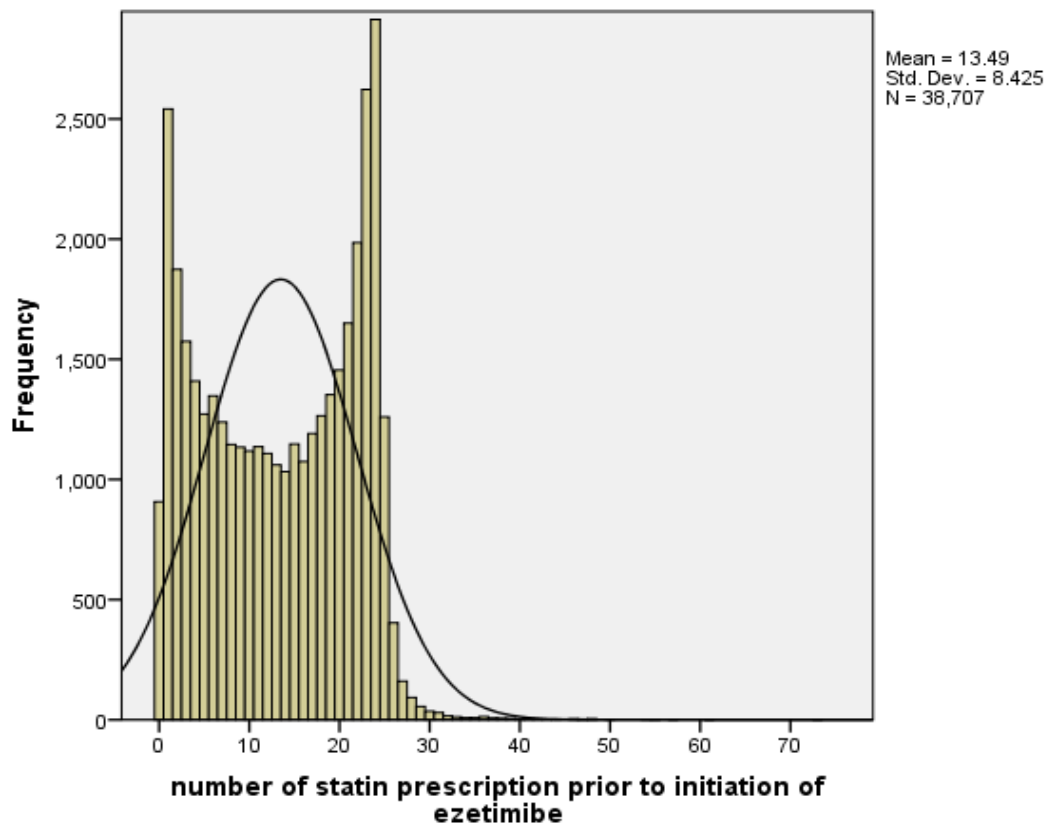
SD=standard deviation; IQR=interquartile range

Cohort 1 included 6,938 patients who represented 15% of the total 45,645 patients initiated on ezetimibe in the base year. For cohort 2, the mean number of dispensed statin prescriptions in the 2 years preceding the first ezetimibe supply was 13.5 (SD=8.4). The mean number of dispensed non-statin lipid lowering prescriptions in cohort 2 in the 2 years preceding the first ezetimibe supply was about one but the distribution was significantly skewed.

4.1. History of LLT prior to ezetimibe initiation

Figure 4.1.1 shows the distribution of Cohort 2 patients across the number of statin prescriptions dispensed over the period of 24 months prior to ezetimibe initiation.

Figure 4.1.1 distribution of Cohort 2 patients across the number of statin prescriptions



The distribution in Figure 4.1.1 is demonstrably opposite of normal with two peaks at the opposite ends: one representing the regular monthly use of a statin clustering around 24 filled prescriptions over 2 years and another representing only a limited number of filled prescriptions over the same period of time. The majority of the population is fairly evenly distributed around the median of 14 prescriptions. A small proportion of patients (N=907, 2.3%) with zero statin prescriptions met the criteria of Cohort 2 due to a non-statin LLT dispensed to them in 2 years preceding ezetimibe initiation.

Table 4.1.1 shows the distribution of Cohort 2 patients across the number of dispensed statin prescriptions over the 6 months preceding ezetimibe initiation.

Table 4.1.1 distribution of Cohort 2 patients across the number of dispensed statin prescriptions

Number of statin prescriptions dispensed in 6 months prior to ezetimibe initiation	Number/Proportion of patients
<i>New to statin therapy</i>	
One-two statin prescriptions dispensed*	1,883 (4.9%)
<i>≥ 3 Prior statin script dispensed</i>	
Three statin prescriptions dispensed	3,707 (9.6%)
Four statin prescriptions dispensed	4,010 (10.3%)
Five statin prescriptions dispensed	6,275 (16.2%)
Six statin prescriptions dispensed	6,537 (16.9%)
>six statin prescriptions dispensed	1,834 (4.7%)
Sub-total	24,246 (57.7%)
<i>< 3 Prior statin script dispensed</i>	
Less than three prescriptions dispensed**	14,461 (37.4%)
Total	38,707 (100%)

* includes only patients who first started on a statin within 6 months prior to ezetimibe initiation. See Clarification Note 1 on p.3 for the detailed definition.

**Have also had at least one dose of statin dispensed in period 6 -24 months prior to index ezetimibe

More than a third of all patients (14,461 or 37.4%) filled less than 3 prescriptions during the 6 months prior to first ezetimibe prescription. Although it could be argued that some of these patients may not have been optimally treated with statins prior to commencing treatment with ezetimibe, there are insufficient details to conclude it with certainty. This subgroup excludes the small proportion of patients (1,883 or 4.9%) who, albeit only having 1-2 statin prescriptions filled, were only recently initiated on a statin (i.e. all the filled statin prescriptions over the 24 month period fall within 6 months of ezetimibe initiation). Therefore, from the results shown in Table 4.1.1 it follows that most patients (24,246 or 62.6%) met the criteria for continuous use of a statin adopted for the Review. Figure 4.1.2 illustrates the results for these patients.

Figure 4.1.2 distribution of Cohort 2 patients who were in a continuous treatment at the time of ezetimibe initiation across the number of dispensed statin prescriptions

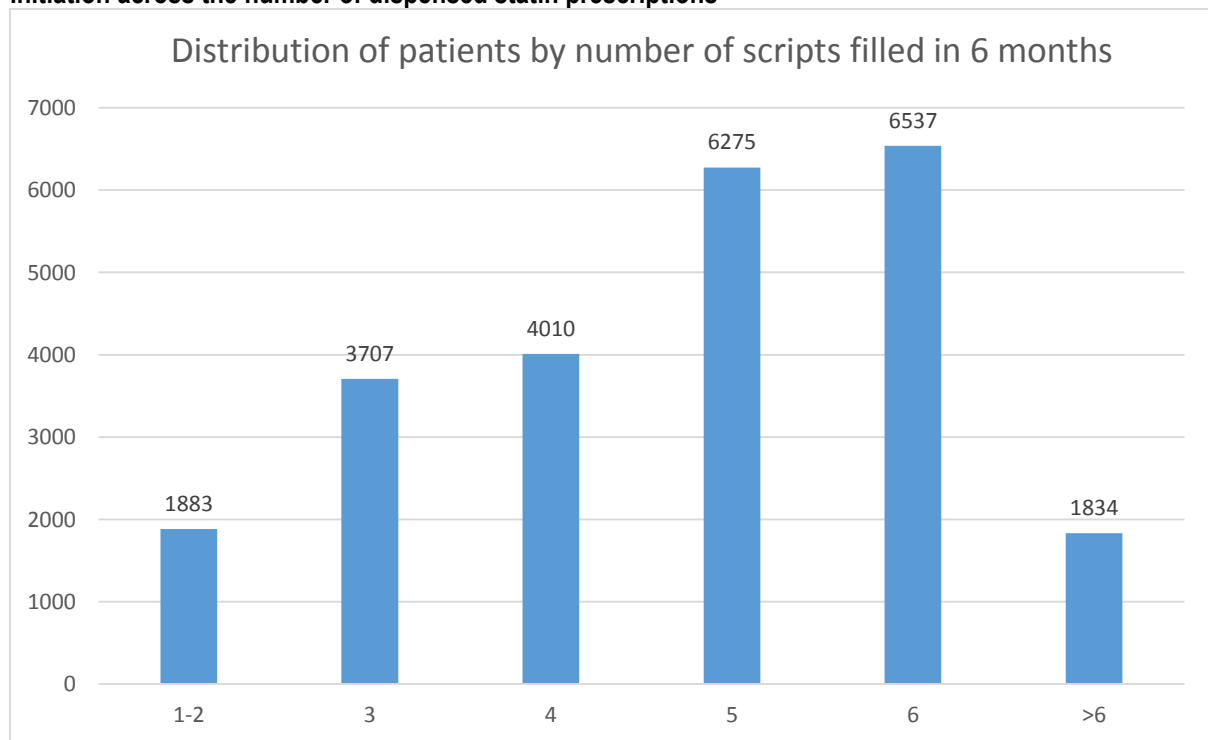


Table 4.1.2 shows the total number of Cohort 2 patients who experienced up- or down-titration of the statin prior to ezetimibe initiation or remained on the initial dose. Up- or down-titration was defined as switching to more (or less) potent statin either in terms of a dose or intensity of a drug. (Table A.2 in Appendix A shows the potency categories assigned to each statin observed in the 95,563,746 records of the dataset).

Table 4.1.2 Proportion of the total Cohort 2 patients in each of the categories of the 24-month pre-ezetimibe history of LLT

	Remained on non-statin LLT*	Remained on the same statin dose or potency	Up-titration only of statin dose or potency	Down-titration only of statin dose or potency	Both up- and down-titration of statin dose or potency
Total number of patients (N=38,707)	907 (2.3%)	26,676 (68.9%)	4,525 (11.7%)	2,707 (7.0%)	3,892 (10.1%)

*the dose change in non-statin LLT was not examined

A small proportion of patients (2.3%) had only a non-statin LLT prior to the first ezetimibe prescription. Majority (26,676 or 68.9%) of patients remained on the same dose of statin throughout the period of 24 months. This number includes the patients who had only one supply of a statin during the 24 month period and those already on the highest dose of statin. Table 4.1.3 shows details on the same statin dose prescribed to these patients.

Table 4.1.3 Remained on the same dose or potency of statin prior to ezetimibe initiation (N=26,676)

Potency of statin		Number of patients (%)
<i>Low-intensity statin</i>		<i>649 (2.4%)</i>
Moderate-intensity statin	Lower dose	4,301 (16.1%)
	Higher dose	8,202 (30.7%)
<i>Moderate intensity statin (subtotal)</i>		<i>12,503 (46.9%)</i>
High-intensity statin	Lower dose	8,180 (30.7%)
	Higher dose	5,344 (20.0%)
<i>High intensity statin (subtotal)</i>		<i>13,524 (50.7%)</i>

Of all patients (N=26,676) who filled prescriptions for the same dose or potency of statin during the period of up to 24-months before ezetimibe initiation, only a small proportion (649 or 2.4%) were dispensed a low-intensity statin. Around 47% of patients were dispensed a moderate intensity statin with either lower (4,301 or 16.1%) or higher dose (8,202 or 30.7%). A half of the patients who remained on the same dose of statin (13,524 or 50.7%) were dispensed a high intensity statin and stayed on the same dose prior to initiation of ezetimibe treatment. This includes 20.0% (N=5,344) of patients who were dispensed the highest dose of a high-intensity statin at some point in time preceding initiation of ezetimibe treatment. **When considering use of statins prior to initiation of ezetimibe, there is insufficient evidence to establish whether the maximum tolerated dose of statin was administered prior to initiation of ezetimibe in patients other than those who were prescribed the higher dose of the highest intensity statin.**

Table 4.1.2 shows that there were 4,525 (11.7%) patients who had experienced at least one up-titration of a statin dose and no down-titrations and 2,707 (7.0%) patients who experienced at least one down-titration of a statin dose and no up-titrations. A separate category of 3,892 (10.1%) patients had been prescribed at least one up-titrated statin and at least one down-titrated statin in terms of either dose or potency.

Table 4.1.4 provides greater detail about these patients (from Table 4.1.2: N=4,525+2,707+3,892 =11,124 or 28.8%) who had at least two statin prescriptions dispensed prior to ezetimibe initiation and experienced up- or down- titration of the statin either in terms of dose or potency. Multiple counting of the patients who experienced more than one occasion of statin adjustment was allowed and resulted in the total number of patient instances (N_{PIS}) of 22,364. (*The concept of patient instances is explained in Clarification Note 5 in the Methods section*).

Table 4.1.4 Number of patient instances (N_{PIS} =22,364) in each of the categories of statin adjustment during the 24-months of pre-ezetimibe statin prescription history in Cohort 2.

Up-titrating					Down-titrating					Total number of occasions involving statin adjustment (patient instances)
Low to moderate intensity	Low to high intensity	Moderate to high intensity	Lower dose to higher dose within moderate intensity	Lower dose to higher dose within high intensity	Moderate to low intensity	High to low intensity	High to moderate intensity	Higher dose to lower dose within moderate intensity	Higher dose to lower dose within high intensity	
762 (3.4%)	95 (0.4%)	6,064 (27.1%)	2,502 (11.2%)	3,292 (14.7%)	911 (4.1%)	237 (1.1%)	4,552 (20.4%)	2,122 (9.5%)	1,827 (8.2%)	22,364 (100%)

Table 4.1.4 indicates that in the period of up to 24 months prior to ezetimibe initiation there was a mean of 2.01 statin adjustments per patient (22,364/11,124), which included 1.14 occasions of statin up-titration (SD=1.37; Range 0-22) and 0.87 occasions of down-titration (SD=1.34; range 0-21). (*The numbers only apply to the patients who experienced at least one adjustment*).

Most of the up-titrating occasions (N_{PIS} =6,064 or 27.1%) involved up-titration from a moderate to high intensity statin. The second most frequently occurred up-titration involved increasing the dose within the high intensity category of statins (N_{PIS} =3,292 or 14.7%). Conversely, more than twenty percent of all patient instances (N_{PIS} =4,552 or 20.4%) involved replacing a high potency statin with the moderate potency statin. ***There is insufficient evidence to draw a conclusion on whether down-titrating was associated with adverse events experienced by patients.***

4.2. History of LLT post ezetimibe initiation

Table 4.2.1 shows the number of prescriptions dispensed to patients in Cohort 1 and Cohort 2 in the 12 months of post-initiation with ezetimibe.

Table 4.2.1 Summary of the population first prescribed ezetimibe in the base year

	Number of patients	Mean number (SD) of LLT prescriptions (i.e. ezetimibe, statin and non-statin) in the 12 month after ezetimibe initiation
Cohort 1	6,938 (15%)	Mean: 6.25±5.15 Median (IQR): 5.00 (1-11)
Cohort 2	38,707 (85%)	Mean: 11.43±6.16 Median (IQR): 12.00 (8-13)
Total	45,645 (100%)	-

SD=standard deviation; IQR=interquartile range

In the 12 months after initiation of ezetimibe treatment, mean number of prescriptions pertaining to all lipid lowering treatments (including statin, non-statin and ezetimibe) were 6.25 (SD=5.15) and 11.43 (SD=6.16) for Cohort 1 and Cohort 2 respectively. The difference in mean numbers of the

dispensed LLT between cohorts 1 and 2 was statistically significant ($p < 0.0001$). However, the following factors should be taken into consideration:

- a) the proportion of patients on co-prescribed therapy (as opposed to monotherapy of FDC) was higher in Cohort 2 (see Table 3.2.3 below).
- b) the proportion of patients who were initiated on ezetimibe monotherapy but subsequently switched to ezetimibe and statin combination therapy was higher in Cohort 2 (see Table 3.2.5 below).
- c) duration of continuous treatment also affects the mean number of prescription. The proportion of patients who discontinued LLT was much higher in Cohort 1 than in Cohort 2 (see Section 4.5 for details).

Table 4.2.2 shows the number and proportion of Cohort 1 patients across the number of dispensed LLT prescriptions in the 12 months post-ezetimibe initiation.

Table 4.2.2 distribution of Cohort 1 patients across the number of LLT prescriptions

Number of scripts	Number of patients	Proportion of patients
1	1,740	25.1%
2	774	11.2%
3	469	6.8%
4	357	5.1%
5	332	4.8%
6	359	5.2%
7	262	3.8%
8	275	4.0%
9	244	3.5%
10	300	4.3%
11	372	5.4%
12	619	8.9%
≥13	835	12.0%
Total	6,938	100%

About a quarter of patients in Cohort 1 (1,740 or 25.1%) did not fill another ezetimibe or any other LLT prescription (i.e. the first script of ezetimibe as a monotherapy or in combination was the only LLT prescription filled in the 12 months following ezetimibe initiation). In addition, 18.0% (11.2% + 6.8%) filled only one or two LLT prescriptions in the post-ezetimibe period, while a similar proportion of 20.9% (8.9% + 12.0%) patients received an LLT treatment monthly. The remaining patients were fairly evenly distributed across the number of LLT prescription, which ranged from 4 to 11 (including the first ezetimibe script). Figure 4.2.1 graphically illustrates the distribution of Cohort 1 patients across the number of dispensed LLT prescriptions presented in Table 4.2.2.

Figure 4.2.1 distribution of Cohort 1 patients across the number of dispensed LLT prescriptions

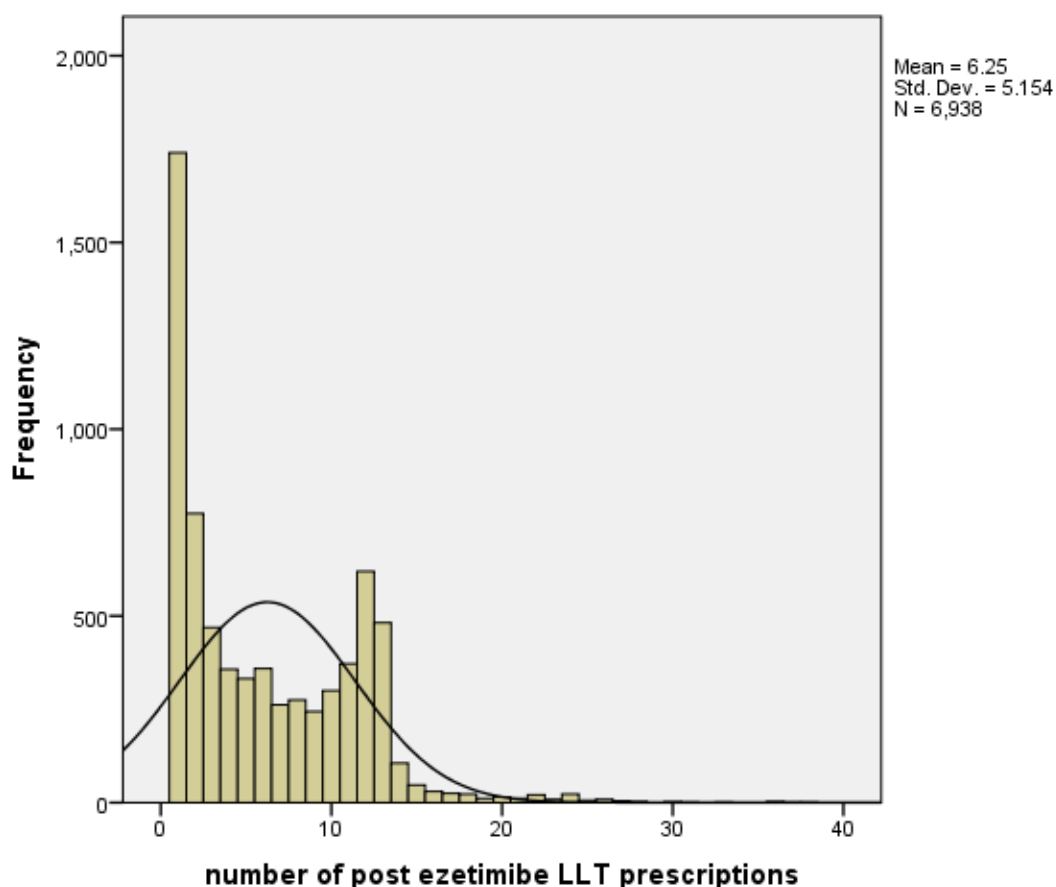


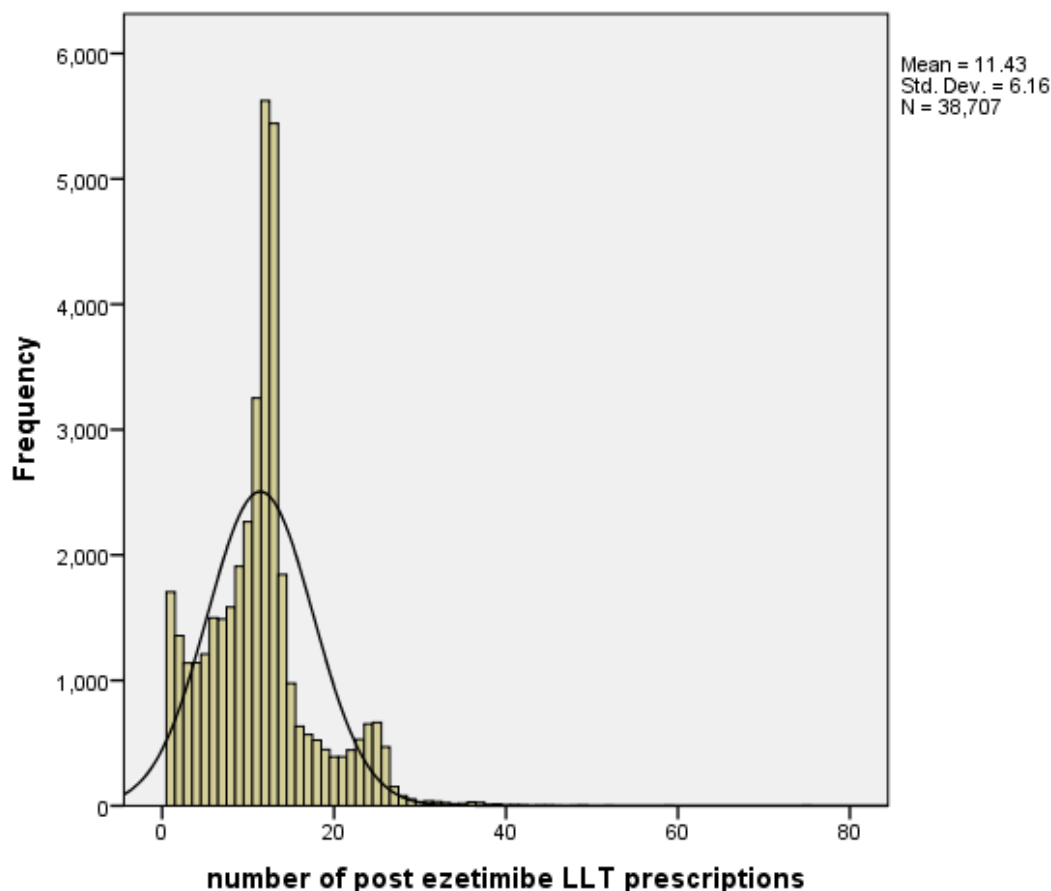
Table 4.2.3 shows the number and proportion of Cohort 2 patients across the number of dispensed LLT prescriptions in the 12 months post-ezetimibe initiation.

Table 4.2.3 distribution of Cohort 2 patients across the number of LLT prescriptions

Number of scripts	Number of patients	Proportion of patients
1	1,705	4.4%
2-4	3,636	9.5%
5-9	7,690	19.9%
10-14	18,427	47.6%
15-19	3,150	8.1%
20-24	2,408	6.2%
25-29	1,420	3.7%
>30	271	0.7%
Total	38,707	100%

Only 4.4% (N=1,705) of Cohort 2 patients did not fill another ezetimibe or any other LLT prescription in the 12 months following ezetimibe initiation, this is much less than the equivalent proportion in Cohort 1. About half of Cohort 2 patients (18,427 or 47.6%) obtained at least 10 LLT prescriptions over 12 months. In addition, almost 20% (7,690 or 19.9%) filled between 5 and 9 prescriptions over the same time interval. Figure 4.2.2 graphically illustrates the distribution of Cohort 2 patients across the number of dispensed LLT prescriptions presented in Table 4.2.3.

Figure 4.2.2 distribution of Cohort 2 patients across the number of dispensed LLT prescriptions



Remarkably, in Cohort 2 the pattern of LLT utilisation in the post-ezetimibe period is a reversed pattern of LLT utilisation in the pre-ezetimibe period that was resolutely opposite of normal distribution.

Research questions on LLT utilisation in the period of post-ezetimibe initiation begin with the data on distribution of patients across ezetimibe initiation categories. Table 4.2.4 shows proportions of patients initiated on ezetimibe monotherapy or a combination with statin or non-statin LLT.

Table 4.2.4 number of patients initiated on ezetimibe monotherapy or ezetimibe combination therapy

Ezetimibe-based LLT	Number of patients (%)	
	Cohort 1	Cohort 2
Patients initiated on ezetimibe monotherapy	3,698 (53.3%)	10,424 (26.9%)
Patients initiated on ezetimibe and statin/non-statin combination therapy		
○ Ezetimibe and statin (free pill combination)	358 (5.2%)	9,523 (24.6%)
○ Ezetimibe and statin (fixed dose combination)	2,822 (40.7%)	17,983 (46.5%)
○ Ezetimibe and non-statin combination	60 (0.9%)	777 (2.0%)
<i>Subtotal</i>	3,240 (46.7%)	28,283 (73.1%)
Total	6,938 (100%)	38,707 (100%)

More than a half (53.3%) of patients in Cohort 1 were initiated on ezetimibe monotherapy. According to the definition of co-administered therapy (Clarification Note 3 in Method section), this

means that no other LLT was dispensed within the next 30 days. The proportion of patients in Cohort 1 who were initiated on ezetimibe monotherapy is twice the proportion of Cohort 2 patients (26.9%) who were initiated on ezetimibe monotherapy after some history of lipid-lowering drugs, predominately, a statin. In both cohorts a large proportion of patients were initiated on ezetimibe and statin combination either as FDC (40.7% and 46.5%) or as a free pill combination (5.2% and 24.6%) in Cohort 1 and Cohort 2 respectively. The proportion of patients receiving a free pill combination was much higher in Cohort 2 than in Cohort 1. ***In Cohort 1 initiation on ezetimibe in combination with a statin would likely indicate use that is not in accordance with the PBS restrictions (see more in Discussion section).*** Since the definition of a free pill co-administration assumes that a statin or non-statin prescription was dispensed with the next 30 days of ezetimibe dispensing, these proportions may be overestimates, because it was not possible to distinguish an occasion of a therapy switch from the a free pill co-administration. However, with respect to Cohort 1, that would still indicate a likely violation of the PBS restrictions, if ezetimibe monotherapy is replaced with a statin monotherapy. In both cohorts the proportion of patients who were initiated on ezetimibe in combination with a non-statin LLT was small (0.9% and 2.0% respectively) and was not subjected to further scrutiny.

Table 4.2.5 presents a limited analysis of the changes in LLT observed in Cohort 1 and Cohort 2 post-ezetimibe initiation. Results are aggregated by the initiation status. Patients needed to have at least 2 prescriptions filled to be considered for the potential therapy switch. If no switch of therapy was observed in 12 months, a patient was included in the “remained on the initially assigned therapy” category whether a monotherapy or a combination. Table 4.2.5 shows the first switch of therapy; if the patient had more than one switch, they were included in the category “experienced more than one switch of therapies”. In this analysis the changes in both the dose and potency of a statin were ignored (See Table 4.2.6 for some additional analysis).

Table 4.2.5 proportion of patients with changes according to ezetimibe initiation status

	Cohort 1	Cohort 2
Initiated on ezetimibe monotherapy		
○ Remained on ezetimibe monotherapy	2,155 (58.3%)	6,061 (58.1%)
○ Switched to statin monotherapy	181 (4.9%)	815 (7.8%)
○ Switched to non-statin monotherapy	43 (1.2%)	151 (1.4%)
○ Switched to ezetimibe and statin combination therapy	133 (3.6%)	932 (8.9%)
○ Experienced more than one switch of therapies*	1,186 (32.1%)	2,465 (23.6%)
<i>Total (%)</i>	<i>N=3,698 (100%)</i>	<i>N=10,424 (100%)</i>
Initiated on ezetimibe and statin combination therapy		
○ Remained on ezetimibe plus statin combination therapy	1,985 (62.4%)	17,134 (62.3%)
○ Switched to statin monotherapy	245 (7.7%)	3,576 (13.0%)
○ Switched to ezetimibe monotherapy	45 (1.4%)	1,703 (6.2%)
○ Experienced more than one switch of therapies*	905 (28.5%)	5,093 (18.5%)
<i>Total (%)</i>	<i>N=3,180 (100%)</i>	<i>N=27,506 (100%)</i>
Initiated on ezetimibe and non-statin combination therapy		
○ Not applicable**	<i>N=60 (100%)</i>	<i>N=777 (100%)</i>
Grand Total	N=6,938	N=38,707

*Assuming one switch per month, the maximum possible number of combinations of switches over 12 month is equal to 3072; although the actual number of observed combinations is likely to be much smaller, the disaggregated analysis would still go beyond the reasonable timeframe or page limit.

**changes within this category of patients were not analysed

More than a half of patients (58.3% and 58.1% for Cohort 1 and Cohort 2 respectively) who were initiated on ezetimibe monotherapy remained on the monotherapy for the next 12 months. In a small proportion of patients the first switch from ezetimibe monotherapy was to a statin

monotherapy (4.9% and 7.8% for Cohort 1 and Cohort 2 respectively). Likewise, in a small proportion of patients ezetimibe monotherapy was altered by adding a statin either as a FDC or as a free pill (3.6% and 8.9% in Cohort 1 and Cohort 2 respectively). The remaining patients in both cohorts experienced more than one switch of therapy. ***In Cohort 1, of those who initiated ezetimibe monotherapy, 314 (181+133 or 8.5%) patients went on to switch to statin monotherapy or add statin to ezetimibe would likely indicate ezetimibe prescribing practice that is not in accordance with the PBS restrictions.***

A large and almost equal proportion of patients (62.4% and 62.3% in Cohort 1 and Cohort 2 respectively) who first started on ezetimibe in combination with statin continued on this combination therapy in the post-ezetimibe period. A small proportion of patients (1.4% and 6.2% in Cohort 1 and Cohort 2 respectively) experienced the first change of therapy by switching from ezetimibe combination to ezetimibe monotherapy. A higher proportion of patients (7.7% and 13.0% in Cohort 1 and Cohort 2 respectively) switched from ezetimibe combination to statin monotherapy.

A significant proportion of patients (ranging from 23.6% to 32.1% across the Cohorts and initiation status) had more than one switch after ezetimibe initiation (e.g. changing from ezetimibe monotherapy to ezetimibe and statin combination therapy, and then dropping ezetimibe in favour of a statin monotherapy). The number of possible combinations was too large to describe in detail, and would likely to have produced only a limited additional value. Therefore, a different approach to post-ezetimibe statin up-titrating history was undertaken to investigate prescription practices in Cohort 2 that may not be consistent with the PBS restrictions.

4.3. Linking the pre- and post-ezetimibe history of statin use. Identifying the patients in Cohort 2 in whom statin therapy was up-titrated at the time of, or after, initiation of ezetimibe

For each subgroup of patients from Cohort 2 as defined in Table 4.2.5 by their ezetimibe initiation status and the first therapy switch, we calculated the proportion of patients who, over the 12 months post-ezetimibe period, experienced an up-titration of statin which was more intensive (either in terms of potency or a dose) in comparison to the last statin treatment received prior to ezetimibe initiation. Table 4.3.6 shows the results.

Table 4.3.6 proportion of Cohort 2 patients who experienced post-ezetimibe up-titration of statin

Cohort 2 patients by the initiation status and the first switch of therapy (N=38,707)	Patients (%) with statin up-titrated in 12 months after ezetimibe initiation
Initiated with ezetimibe monotherapy (N=10,424)	
○ Remained on ezetimibe monotherapy (N=6,061)	0 (0%)
○ Switched to statin monotherapy (N=815)	119 (14.6%)
○ Switched to non-statin monotherapy (N=151)	0 (0%)
○ Switched to ezetimibe and statin combination therapy (N=932)	95 (10.2%)
○ Experienced more than one switch of therapies (N=2,465)	157 (6.4%)
<i>Subtotal number of patients with an up-titrated statin (%)</i>	<i>371 (3.56%)</i>
Initiated on ezetimibe and statin combination therapy (N=27,506)	
○ Remained on ezetimibe plus statin combination therapy (N=17,134)	1,940 (11.3%)
○ Switched to statin monotherapy (N=3,576)	773 (21.6%)
○ Switched to ezetimibe monotherapy (N=1,703)	42 (2.5%)
○ Experienced more than one switch of therapies (N=5,093)	637 (12.5%)
<i>Subtotal number of patients with an up-titrated statin (%)</i>	<i>3,392 (12.33%)</i>

Total number of patients with an up-titrated statin (%)	3,763 (9.72%)
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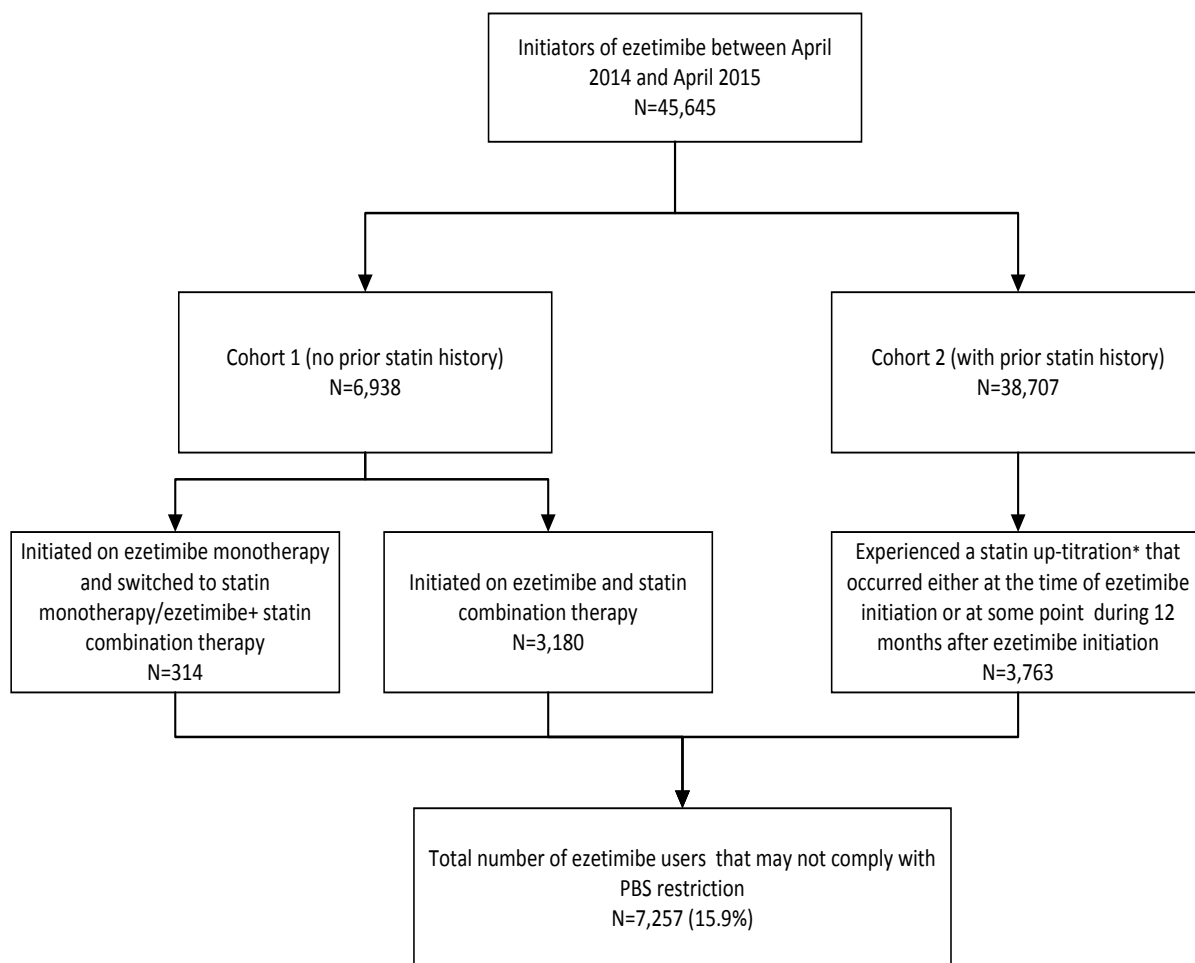
Of 10,424 Cohort 2 patients initiated on ezetimibe monotherapy, 371 or 3.56% subsequently experienced an up-titration of statin which was more intensive (either in terms of potency or a dose) in comparison to the last statin treatment received prior to ezetimibe initiation.

Of 27,506 Cohort 2 patients initiated on ezetimibe combination therapy, 3,392 or 12.33% experienced an up-titration of statin which was more intensive (either in terms of potency or a dose) in comparison to the last statin treatment received prior to ezetimibe initiation. **The were 3,763 or 9.72% out of the total Cohort 2 number of 38,707 patients, whose subsequent statin up-titration observed at some point over the 12 months of post-ezetimibe history may indicate prescription practices that are not consistent with the PBS restrictions as these patients do not appear to have been up-titrated to maximally tolerated statin prior to ezetimibe initiation.**

4.4. Estimating the total proportion of patients who were initiated on ezetimibe outside the PBS restrictions

Figure 4.4.1 summarises the results reported in Sections 4.2 and 4.3 concerning the estimated number and proportion of patients who were likely to have been initiated on ezetimibe outside the PBS restrictions.

Figure 4.4.1 proportion of patients with changes according to ezetimibe initiation status



*statin up-titration is defined as any up-titrating in terms of dose or potency.

This review’s estimate of extent of use of ezetimibe outside the PBS restrictions is somewhat higher than the estimate provided in the MSD submission (15.9% vs 11.5%). The estimates are not directly comparable due to the differences in the populations, assumptions about what constitutes “consistent with the PBS restriction” use of ezetimibe, and methods for deriving the estimates. *These are discussed in more detail in the Discussion section.*

4.5. Termination of lipid lowering treatment

The definition of cessation of LLT is given in Clarification Note 2 in the Methods section. It was stated that Cohort 2 patients who had no statin prescription filled with 6 months prior to ezetimibe initiation are assumed to have ceased the background statin treatment. The same definition of no statin prescription filled within 6 months was subsequently applied to the records observed in the post-ezetimibe period. Providing there were no prescription filled for at least from the 6th to 12th month of the 12 month post-ezetimibe period, the patient was assumed to have terminated LLT. The number includes the patients who only filled one (initial) ezetimibe prescription either in combination with another LLT or as a monotherapy. Table 4.5.1 shows the proportion of patients who ceased all LLTs according to the given definition.

Table 4.5.1 Number of patients (%) who ceased LLT by the period of cessation and a Cohort

Cohort	Period	
	6 months prior to ezetimibe initiation	at least from 6th to 12th months of the 12 month post-ezetimibe period
Cohort 2 (N=38,707)	8,234 (21.3%)	4,474 (11.6%)
Cohort 1 (N=6,938)	N/A	3,044 (43.9%)

N/A not applicable

There were 8,234 (21.3%) patients in Cohort 2 who had some history of LLT but ceased the background LLT for a period of at least 6 months before the first supply of ezetimibe. *Note, each of these 8,234 patients had been counted in Table 4.1.2 according to their individual experience with LLT prescriptions.* The termination rate in Cohort 2 patients decreases during the post-ezetimibe initiation in comparison to the period prior to the initiation (11.6% vs 21.3%). It is also evident that in the post-ezetimibe initiation period the proportion of patients who ceased all LLTs was much higher in Cohort 1 than in Cohort 2 (43.9% and 11.6% respectively).

Cohort 2 patients were further analysed to establish whether the individual tendency to terminate LLT observed before ezetimibe initiation is replicated in the 12 months of post-initiation. Table 4.5.2 shows results of comparison of termination history in Cohort 2 patients in the pre- to post-ezetimibe initiation periods.

Table 4.5.2 Cessation rate of Cohort 2 patients of the post ezetimibe period

Whether ceased LLT prior ezetimibe initiation	Number of patients ceased LLT post ezetimibe initiation and the proportion with respect to (A)
A	B
Yes = 8,234	1,963 (23.8%)
No = 30,473	2,511 (8.2%)
Total: 38,707 (100%)	N/A

N/A not applicable

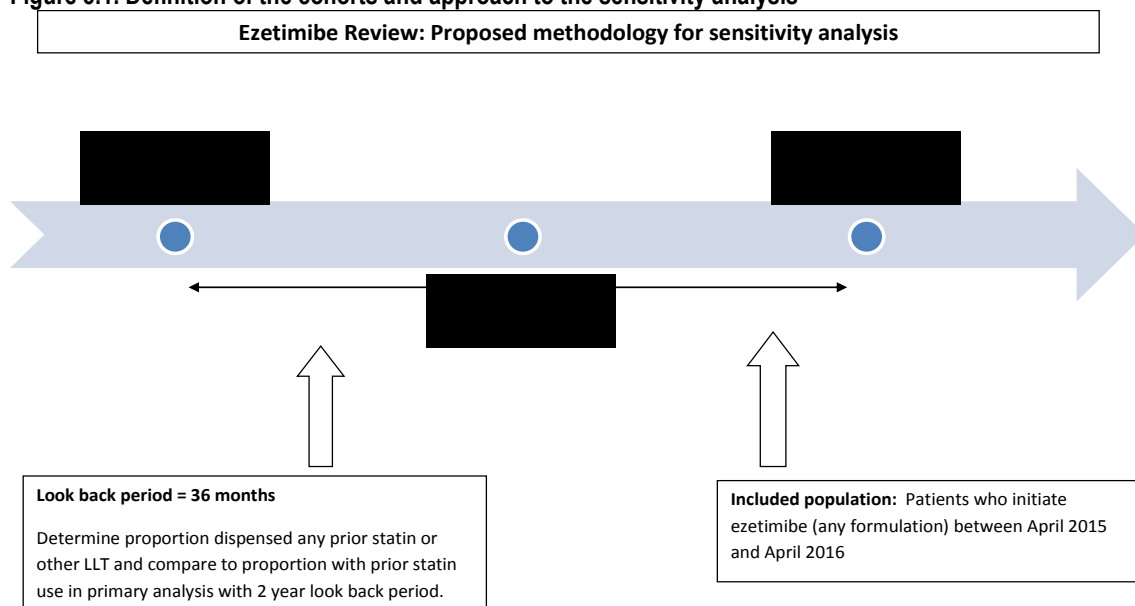
In comparison to those who did not cease LLT before starting on ezetimibe, patients who ceased LLT prior to ezetimibe initiation had a poorer LLT compliance rate during the post-ezetimibe period. In patients who ceased LLT in 6 months prior to ezetimibe treatment initiation 23.8% also terminated treatment in the post-ezetimibe period. This is almost three times higher than the equivalent proportion of 8.2% in patients without a termination history in 6 months prior to ezetimibe initiation.

5. Sensitivity analysis

5.1. Method of the sensitivity analysis

Figure 5.1 re-defines time intervals for the sensitivity analysis. Ezetimibe treatment initiators are now the patients who started ezetimibe treatment between 1st of April 2015 and 1st of April 2016 with a longer history of pre-ezetimibe LLT prescriptions covering the period of 36 months, while post-ezetimibe period is no longer included.

Figure 5.1. Definition of the cohorts and approach to the sensitivity analysis



5.2. Results of the sensitivity analysis

Table 5.2.1 shows the basic statistics about the sample of the population of 54,599 patients that were selected for the sensitivity analysis of ezetimibe utilisation data.

Table 5.2.1 Summary of the population first prescribed ezetimibe in the base year

	Number of patients	Number of prescription of statin in the past 3 years	Number of prescription of non-statin in the past 3 years
Cohort 1	6,408 (11.7%)	0	0
Cohort 2	48,191 (88.3%)	Mean: 19.52±12.642 Median: 20 (7-32) IQR	Mean: 1.33±5.637 Median: 0 (0-0) IQR
Total	54,599 (100%)	-	-

SD=standard deviation; IQR=interquartile range

There were 54,599 (6,408 in Cohort 1 and in 48,191 Cohort 2) ezetimibe initiators in 2015-2016. This represents an increase of 16% from 45,645 (6,938 in Cohort 1 and 38,707 in Cohort 2) in 2014-2015.

The number of ezetimibe initiators without the prior history of LLT decreased by about 7.6% (530 patients) from 6,938 in 2014-2015 to 6,408 in 2015-2016. Comparing to the primary analysis, proportion of ezetimibe initiators with some previous history of LLT prescription in the preceding 36 months was higher in 2015-2016 (88.3%) than in 2014-2015 (85%). This increase in the proportion of patients who met the definition of Cohort 2 as well as the decrease in proportion of Cohort 1 patients are probably due to the longer period (36 months vs 24 months) for detecting any LLT history, but may also reflect the improvement in prescribing practices.

6. Discussion

6.1. Comparison of the proportions of statin naïve patients and patients in continuous use of statins at the time of ezetimibe initiation

The number of ezetimibe initiators without a prior history of LLT was 6,938 (15%) in 2014-2015 decreasing to 6,408 (11.7%) in 2015-2016. For the purposes of the present Review (hereafter the Deakin Review) these patients formed Cohort 1. It is possible that some of these patients were prescribed ezetimibe outside the PBS restrictions, although there is insufficient data to establish the exact proportion of such patients with certainty. There are two previously conducted PBS utilisation data analyses that involve an investigation into the history of statin use prior to initiation of ezetimibe. One was conducted in 2014 by the University of Queensland (UoQ) for the Department of Health. Another was undertaken by Merck and Co (MSD) in April 2016 and formed Section E of their submission to the Post-market Review of Ezetimibe. Table 6.1.1 briefly compares methods and characteristics of the data used for utilisation analyses in the Deakin Review and in these previous studies.

Table 6.1.1 Comparative characteristics of the PBS utilisation data analyses

Study	PBS data source	Base year (period of EZ initiation)	Time interval in relation to “prior statin use”	Criteria of comprehensive/ continuous use of statin prior to EZ initiation	Criteria for “no statin use” prior to EZ initiation	Estimated proportion of patients without history of statin use prior to EZ initiation
Ezetimibe Review 2016	Comprehensive PBS utilization data April 2012- April 2016 N=45,645	Primary analysis: one year April 2014- April 2015	24 months prior to the day of EZ initiation	Three or more filled statin prescriptions within 180 days* prior to EZ initiation	24 months prior to the day of EZ initiation	15% (Table 3 above)
University of Queensland ¹ (2014)	Study group 1a: April 2005- December 2012; PBS data limited to concessional patients N=31,612	Study group 1a: 2 years: April 2010- March 2012	April 2005 to the day of EZ initiation	At least one script within 90 days prior to EZ initiation plus three or more filled statin prescriptions within 180 days	No statin dispensed from April 2005 to the day of EZ initiation	8% (p.5 executive summary; 6.77%+1.08%=7.85% Table 8, p.41)
MSD submission to the DoH post-market EZ review 2016 ²	10% sample of a PBS concessional patient dataset from July 2010** to June 2015 N=14,808	Not applicable	Patients classified as meeting PBS criteria if a) received EZ monotherapy or b) received at least 3 scripts of statin in the previous 12 months or; c) received at least 3 scripts of statin over period longer than 12 months	No statin dispensed from January 2010 to the day of EZ initiation and assumed to have not met PBS restriction	3.3% (Table E.2.2-1 p.139)	

*patients with 1-2 statin prescriptions were included, providing a statin was first prescribed within 6 month prior to ezetimibe initiation;

**There is a discrepancy in the dates (Section E states July 2010 to June 2015; Appendix 11 states January 2010 to November 2015)

Source¹: Utilisation review of Ezetimibe. Final report prepared by the University of Queensland for the Department of Health (May 2014);

Source²: Section E (+EXCEL spreadsheet) of the MSD submission to the Department of Health (April 2016), including Appendix 11

The UoQ limited the PBS individual patient data to patients who fell under a concessional category for the entire time interval from April 2005 to December 2012. Likewise, the MSD longitudinal data analysis was conducted in a 10% sample of concessional patient prescriptions filled from January 2010 to November 2015⁶. In both cases limiting records to concessional patients was meant to

⁶ assuming the actual timeframe for ezetimibe initiation was from July 2010 to June 2015, which would explain the discrepancy in the dates in section E and Appendix 8.

ensure the completeness of the history of statin use prior to ezetimibe initiation that, should non-concessional patients be included, would be compromised by the absence of records for statin prescriptions that fell under the general co-payment threshold.

However, from April 2012 the PBS utilisation data includes all under co-payment prescriptions (e.g. statins priced under general co-payment threshold). In particular, the PBS data from April 2012 to April 2016 used by the Deakin Review contains the complete set of ATC C10 individual prescriptions filled by concessional and non-concessional patient populations. Therefore the populations in the datasets are not fully comparable as concessional patients may differ from general population with respect to clinical presentation, lifestyle and a medication adherence pattern.

Differences in the estimated proportions of patients with no prior use of statin across three sets of utilisation data may relate to one or more of the following:

- Time intervals used for assessment of the proportion of patients who had not have a recorded history of statin use prior to ezetimibe initiation vary from seven years in the UoQ report to two years (24 months) in the primary analysis of the Deakin Review;
- Numerous uncertainties in the method of PBS utilisation data analysis in the MSD submission (see Table A.3 in Appendix A).
- In particular, the estimate of 3.3% of patients initiated on ezetimibe without the prior use of a statin is likely to be an underestimate of the actual number of such patients as at least some of 4,165 (28%) patients from the entire sample who were first prescribed ezetimibe as monotherapy must have been lacking a prior statin history (e.g. due to known contraindications). The submission does not present utilisation data for these patients by their prior use of statin, but admits the double counting of the patients: once when they purchased their first ever ezetimibe script, and then again when they purchased their first ever Ezetimibe FDC script.

Effectively, due to the differences in the population and methods, the proportion of 15% statin naïve patients calculated for the Deakin Review for the primary analysis from the comprehensive PBS dataset does not have a comparable estimate in the previous analyses of the PBS utilisation data. The same applies to the proportion of 11.7% statin naïve patients estimated from the sensitivity analysis.

Differences in the estimated proportions of patients with continuous use of statin across three sets of utilisation data relate to the following:

- The UoQ definition of “comprehensive” prior statin use is more stringent than the definition of “continuous” use of statin used in the Deakin Review. The two step criteria for a “comprehensive” use includes at least one script within 90 days prior to EZ initiation plus three or more filled statin prescriptions within preceding 180 days. In the UoQ report there were 58% of the concessional patients that met this criteria (Table 8, p.41). This is comparable with 62.6% of patients (Table 4.1.1 above) who met a less strict definition of continuous use of statin in the Deakin Review that simply required three or more filled statin prescriptions within 180 days preceding initiation on ezetimibe. Removing the 4.9% of newly statin initiators who received 1 or 2 statins in the 6 months prior to ezetimibe would produce 57.7% of patients in continuous use of statin, which is very similar to the estimate from the UoQ report.
- In contrast, the MSD submission used the least strict criteria. Firstly, the length of the reference period for establishing a continuous use is twice the length used in the Deakin

Review or in UoQ report (12 months vs 6 months). Secondly, the MSD decided that the PBS restrictions were met if the patient filled at least 3 scripts of statin in the previous 12 months or even if they had filled at least 3 scripts of the same dose, but not all in the previous 12 months. *Excluding 4,165 patients first initiated on ezetimibe monotherapy, the proportion of patients who received 3 scripts of statin in the previous 12 months was 72% (calculated by the authors of the Deakin Review using EXCEL spreadsheet provided by MSD).*

- Definitions of patients' prior use of statin with regards to comprehensive/continuous or consistent with the PBS restrictions, differ across the three analyses of PBS utilisation data.

The proportion of patients of 62.6% assumed to be in continuous use of statin in the Deakin Review falls within the estimates from UoQ of 58% and MSD of 72% and most likely reflects the difference in the stringency of the criteria applied.

6.2. Uncertainties in estimating the proportions of patients who were initiated on ezetimibe outside the PBS restrictions

Although the PBS dataset used for the Deakin Review is more comprehensive than the previously analysed datasets presented in MSD submission and UoQ report, the analysis is still prone to the inherent inconsistencies and uncertainties associated with the data that was assembled for the purposes other than research. For example, the PBS prescription data is inadequate for purposes of determining whether prescribing of ezetimibe is in accordance with some aspects of the PBS restriction for ezetimibe (e.g. a patient's CHD history, ethnicity or status in terms of whether they have familial hypercholesterolaemia or have a family history of CV event or in terms of their baseline cholesterol levels). More importantly, no information on statin intolerance or existing contraindications could be extracted from the data to determine patients' eligibility for ezetimibe monotherapy. The data set contains no information on the adverse events that might have prompted a decision to down-titrate the statin dose and/or use ezetimibe as an add-on treatment. Therefore, the estimated number of patients who might have been initiated on ezetimibe outside the PBS restrictions is not free from the uncertainties.

Although the instances of up- and down titration of a statin were investigated during the pre-ezetimibe initiation period, the PBS prescription data did not provide sufficient evidence to establish whether the maximum tolerated dose of statin was administered prior to initiation of ezetimibe in patients other than those who were dispensed the higher dose of the highest intensity statin. Equally, there is insufficient evidence to draw a conclusion on whether down-titrating was associated with adverse events experienced by patients.

Equally, the Cohort 2 analysis of post-ezetimibe history could not establish with certainty whether the up-titration of statin (either in terms of potency or dose) observed at some point over the 12 month period is indicative of the maximum tolerated dose of statin not being administered prior to initiation of ezetimibe.

The PBS prescription data are prone to inconsistencies that are typical of human behaviour (e.g. some of the earlier prescriptions are filled after the date of the later prescriptions rendering the sequences of prescribed and dispensed drugs incompatible in some patients). The direction of the bias (if any) associated with this type of error is uncertain. Therefore the conclusions about non-compliance with the PBS restrictions and the calculated estimates (e.g. proportion of patients who terminated LLT) should be interpreted with caution.

7. Conclusion

- A) The absolute number of LLT naïve patients initiated on ezetimibe was 6,938 in 2014-2015 and 6,408 in 2015-2016; decrease in proportion from 15% to 11.7% is likely to relate to the difference in the observation period for detecting pre-ezetimibe LLT history (24 vs 36 months) or may reflect the improvement in prescribing practices.
- B) Of all Cohort 2 patients (N=38,707), 26,676 (68.9%) remained on the same dose of statin throughout the 24 month period prior to ezetimibe initiation. This includes 5,344 (20.0%) patients who were dispensed the highest dose of a high-intensity statin at some point in time preceding initiation of ezetimibe treatment. A smaller number of 11,124 patients (28.8%) experienced up- or down- titration of the statin either in terms of dose or potency. However, *when considering use of statins prior to initiation of ezetimibe, there was insufficient evidence to establish whether the maximum tolerated dose of statin was administered prior to initiation of ezetimibe in patients other than those who were prescribed the higher dose of the highest intensity statin. Equally, there was insufficient evidence to determine whether any down-titration of statin was related to adverse events experienced by patients.*
- C) Cohort 1 patients were different from Cohort 2 patients not just because they were statin naïve at the point of ezetimibe initiation but in other important ways, as suggested by their post-initiation history:
- More than a half (53.3%) of patients in Cohort 1 were initiated on ezetimibe monotherapy. This is twice the proportion of Cohort 2 patients (26.9%);
 - A quarter of the patients from Cohort 1 (25.1%) filled just a single ezetimibe prescription in the 12 month of post-ezetimibe observation period. In comparison, the equivalent proportion in Cohort 2 is a negligible 4.4%.
 - Cohort 1 patients who were initiated on monotherapy were more likely to experience more than one switch of LLT regimen in comparison to Cohort 2 patients
 - In spite of the treatment adjustments, the proportion of patients who ceased all LLTs was much higher in Cohort 1 than in Cohort 2 (43.9% vs 11.6%);
- D) Figure 4.4.1 shows the estimated number of patients from both Cohorts who are likely to represent ezetimibe use that is not in accordance with the PBS restrictions. Such instances were detected in the following groups:
- The proportion of Cohort 1 patients (Table 4.2.5) who were initiated on ezetimibe in combination with a statin either as a FDC N=2,822 (40.7%) or as a free pill combination N=358 (5.2%), making the total of 3,180 patients.
 - The additional proportion of patients in Cohort 1 (Table 4.2.5) in whom ezetimibe monotherapy was altered by either adding a statin N=133 (3.6%) or replaced with statin monotherapy N=181 (4.9%), making the total of 314 patients.
 - The proportion of Cohort 2 patients (Table 4.2.6) who at some point over the 12 months of post-ezetimibe history experienced an up-titration of statin which was more intensive (either in terms of potency or a dose) in comparison to the last statin treatment received prior to ezetimibe initiation N=3,763 (9.72%). *These patients do not appear to have been up-titrated to maximally tolerated statin prior to initiation of treatment with ezetimibe.*

In the initial analysis (December 2016) the total number of patients whose use of ezetimibe may not be in compliance with the PBS restriction was estimated at 7,257 or 15.9% of the total number of 45,645 patients in both Cohorts.

*In the additional analysis (March 2017) the total number of patients who were treated in a manner that was not in accordance with the PBS restriction for ezetimibe was estimated at **8,360 or 18.4%** of the total number of 45,645 patients in both Cohorts. Additionally, for a further **15,899 or 34.8%** of the total 45,645 patients in both Cohorts, it was not possible to determine with certainty whether they were treated in accordance with the PBS restriction for ezetimibe.*

Appendix A (initial analysis December 2016).

Table A.1a. Patient and scripts Information

File name: PBS_EZETIMIBE_PAT_APR12toMAR16

Variables	Description	
PTNT_ID	Encrypted patient identification number	
PTNT_AGE_NUM	Patient age as at supply	
ITM_CD	Item code	
PRSCRB_DT	Date of prescription	
CNVRTD_PTNT_PSTCD	Patient postcode	
PRSCRB_ID	Encrypted prescriber identification number	
MJR_SPCLTY_GRP_CD	Prescriber major specialty group code	Description for each major specialty code can be located here: http://meteor.aihw.gov.au/content/index.phtml/itemId/607133
STRMLND_ATHRTY_CD	Streamline authority code	
SPPLY_DT	Date of supply	
PRSCRPTN_CNT	Number of prescriptions	
PTNT_SEX_CD	Patient gender	
RGLTN24_IND	Regulation 24 Indicator	Y or N
PBS_RGLTN24_ADJST_QTY	Quantity	
FRM_TYP_CD	Script type	AR = Repeat authority prescription AU = Original authority original DS = Deferred supply OR = Original prescription RE = Repeat prescription
RPT_ORDR_NMBR	Number of Repeats	
PRVS_SPPLY_NMBR	Number of times previously supplied	

Table A.1b. Item and Drug Information

File name: PBS_EZETIMIBE_ITEM_DRUG_APR12toMAR16

Variables	Description
ITM_CD	Item code
DRUG_NAME	Drug dispensed
FORM_STRENGTH	Form and strength
ATC 5	ATC level 5

Table A.1c. Item codes, drug names

Item code	Name of the Drug
02011W	simvastatin 10mg
02013Y	simvastatin 5mg
02833D	pravastatin 10 mg
02834E	pravastatin 20 mg
08023G	fluvastatin 20 mg
08024H	fluvastatin 40 mg
09234B	fluvastatin 20 mg
09237E	pravastatin 10 mg
09238F	pravastatin 20 mg
09241J	simvastatin 5mg
09242K	simvastatin 10mg
02012X	simvastatin 20mg
02584B	rosuvastatin 10 mg
02590H	rosuvastatin 5 mg
02606E	rosuvastatin 5 mg
02628H	rosuvastatin 10 mg
02863Q	fluvastatin 80 mg
03402C	rosuvastatin 5 mg
03403D	rosuvastatin 10 mg
08173E	simvastatin 40 mg
08197K	pravastatin 40 mg
08213G	atorvastatin 10 mg
08214H	atorvastatin 20 mg
08829Q	pravastatin 80 mg
09042X	rosuvastatin 5 mg
09043Y	rosuvastatin 10 mg
09230T	atorvastatin 10 mg
09231W	atorvastatin 20 mg
09235C	fluvastatin 40 mg
09236D	fluvastatin 80 mg
09239G	pravastatin 40 mg
09240H	pravastatin 80 mg
09243L	simvastatin 20mg
09244M	simvastatin 40 mg
02574L	rosuvastatin 20 mg
02594M	rosuvastatin 40 mg
02609H	rosuvastatin 20 mg
02636R	rosuvastatin 40 mg
03404E	rosuvastatin 20 mg
03405F	rosuvastatin 40 mg
08215J	atorvastatin 40 mg
08313M	simvastatin 80mg
08521L	atorvastatin 80 mg
09044B	rosuvastatin 20 mg
09045C	rosuvastatin 40 mg
09232X	atorvastatin 40 mg
09233Y	atorvastatin 80 mg
09245N	simvastatin 80mg
01224K	colestipol hydrochloride 5g, 120 sachets
01453L	gemfibrozil 600 mg
02967E	cholestyramine 4 g powder
09022W	fenofibrate 48mg, 60
09023X	fenofibrate 145mg, 30
09246P	fenofibrate 48mg, 60
09247Q	fenofibrate 145mg, 30
09248R	gemfibrozil 600 mg, 60

09249T	cholestyramine 4 g powder
09250W	colestipol hydrochloride 5g, 120 sachets
10002K	ezetimibe + atorvastatin 10 mg
10392Y	ezetimibe + atorvastatin 10 mg
02874G	ezetimibe + atorvastatin 20 mg
10393B	ezetimibe + atorvastatin 20 mg
02821L	ezetimibe + atorvastatin 40 mg
10377E	ezetimibe + atorvastatin 40 mg
10006P	ezetimibe + atorvastatin 80 mg
10376D	ezetimibe + atorvastatin 80 mg
09483D	ezetimibe +simvastatin 10 mg
08881K	ezetimibe + simvastatin 40 mg
09484E	ezetimibe +simvastatin 20 mg
08882L	ezetimibe + simvastatin 80 mg
10208G	ezetimibe + rosuvastatin 10 mg
10201X	ezetimibe + rosuvastatin 20 mg
10207F	ezetimibe + rosuvastatin 40 mg
09049G	amlodipine 5 mg + atorvastatin 10 mg
09050H	amlodipine 5 mg + atorvastatin 20 mg
09051J	amlodipine 5 mg + atorvastatin 40 mg
09052K	amlodipine 5 mg + atorvastatin 80 mg
09053L	amlodipine 10 mg + atorvastatin 10 mg
09054M	amlodipine 10 mg + atorvastatin 20 mg
09055N	amlodipine 10 mg + atorvastatin 40 mg
09056P	amlodipine 10 mg + atorvastatin 80 mg
08757X	ezetimibe 10 mg
10204C	ezetimibe + rosuvastatin 5 mg

Table A.2. Rules for assigning particular brands/doses of statin to the corresponding potency category.

Potency category [#]	Statins and the assigned category of a dose (lower vs higher)	
Low-potency statins (reduces LDL-C, on average, by <30%)	N/A	Simvastatin, 5-10 mg Pravastatin, 10-20 mg Fluvastatin 20-40 mg
Moderate-potency statins (reduces LDL-C, on average, by 30% to <50%)	Lower dose	Atorvastatin, 10 mg Rosuvastatin, 5 mg Simvastatin, 20 mg Pravastatin, 40 mg Fluvastatin, 40 mg
	Higher dose	Atorvastatin, 20 mg Rosuvastatin, 10 mg Simvastatin, 40 mg Pravastatin, 80 mg Fluvastatin 80 mg
High-potency statins (reduces LDL-C, on average, by ≥50%)	Lower dose	Atorvastatin, 40 mg Rosuvastatin, 20 mg Simvastatin 80 mg*
	Higher dose	Atorvastatin, 80mg Rosuvastatin, 40 mg

[#]The therapies were used in the RCTs reviewed by the expert panel for the 2013 ACC/AHA Guidelines.

*Discretionary decision made by the authors of the Deakin ezetimibe review

Source: Amended Table 5 from Stone 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, 2014; 129 [Suppl 2]: S1-S45.

Table A.3. Methodological uncertainties in the 2016 PBS utilisation data analysis presented by MSD

No	Nature of concern/uncertainty
1.	The report states they use date of processing PBS data for the 2010 -2015 period, but do not specifically state if they analyse cohort use according to the date of supply. The direction of effect it could have on the analysis is uncertain.
2.	Two groups were analysed independently: those that have a first script for ezetimibe (Ezetrol) Group 1; and those that have first FDC (Vytorin, Azotet, or Rosuvel); Group 2. The report acknowledges that patients <u>may be included in both groups</u> – this is likely as the majority of patients go from separate pill therapy to FDC when stable and tolerated.
3.	There is no definition of “first ever” ezetimibe or “first ever” FDC script in the dataset. i.e. there is no explicit look back period defined to identify new users of ezetimibe therapy. If patients in 2010 are included they may have only a month or two history on which to determine first script and may in fact be incorrectly categorised as new users.
4.	The report states uncertainty in the estimate of use outside the PBS restriction because some general patients were included in the data period that later became concessional. A consistent concession cohort for the period of the entire analysis should have identified by excluding those patients with any dispensing of a general script in the dataset.
5.	For all the above reasons the analysis of the proportion of patients initiating ezetimibe outside the PBS restriction is highly uncertain and is likely to be underestimated. The major contribution of this underestimate is the inclusion of the utilisation in Group 2 that have first FDC script, and this is not necessarily new use of ezetimibe.

Appendix B (additional analysis March 2017).

Table B.1: Categorisation of use among those in Cohort 1 (patients initiating ezetimibe with no prior dispensing for any lipid lowering medicine (prior 24 months))

LLT in Prior 24 months	Post-ezetimibe LLT (followed for 12 months)		
	stay on ezetimibe monotherapy	start/add/switch to a statin	switch or add other LLT*
No LLT	Orange	Red	Green

LLT = lipid lowering therapy

* non-statin

Table B.2: Categorisation of use among those in Cohort 2 (patients initiating ezetimibe who had prior dispensing of statin or other LLT in prior 24 months)

Pre Ezetimibe LLT	Post-ezetimibe LLT (followed for 12 months)				
	stay on ezetimibe monotherapy	start/add/switch to statin at higher dose*	start/add/switch to statin at same dose**	start/add/switch to statin at lower dose***	start/stay/add other LLT only
Ceased statin more than 6 months prior ezetimibe	Green	Red	Orange	Green	Green
Down titrated statin or on lowest dose	Green	Red	Green	Green	Green
Up titrated statin (but not on highest)	Red	Red	Green	Green	Orange
On highest dose of statin	Red	N/A	Green	Green	Green
Stayed on same dose of statin	Orange	Red	Orange	Green	Green
Up and down titrated statin	Green	Red	Green	Green	Green
All other LLT (no statin)	Green	Red	Red	Red	Green

N/A= not applicable, LLT = lipid lowering therapy

Grey cells pre ezetimibe indicate that at least one statin prescription was dispensed in the 6 months prior to starting ezetimibe

* If any statin scripts post ezetimibe initiation (365 days) at higher dose than last statin strength dispensed before starting ezetimibe

** Patients with the highest intensity in all statins prescribed in post-ezetimibe period being equal in intensity to the last pre-ezetimibe statin

*** If all statin scripts post ezetimibe initiation at a lower dose than the last statin pre-ezetimibe statin script

Table B.3: Explanation for the change of numbers in some categories between the previous and current analyses

	Previous analysis (2016)	Current analysis (2017)
Cohort 1		
Initiating	Ezetimibe monotherapy: N=3,698 Ezetimibe + statin: N=3,180 Ezetimibe + non-statin LLT: N=60	Ezetimibe monotherapy: N=3,701 Ezetimibe + statin: N=3,197 Ezetimibe + non-statin LLT: N=40 Combination therapy defined as statin or non-statin LLT dispensed on the same day or within 30 days after (compared with either 30 days before or 30 days after in the previous analysis) <ul style="list-style-type: none"> • decrease in those initiating combination therapy due to change in definition and resulting increase in those initiating monotherapy; • increase in those initiating statin combination therapy as new analysis included a hierarchy for statin compared with non-statin LLTs dispensed, rather than order they appeared in the utilisation data
Initiate EZ monotherapy → Stay on monotherapy	N=2,155	N=3,148 2,155 + 987 (patients who had only a single prescription on EZ; were classified as “switch not including a statin” by default previously (3,142)) + 6 patients whose statin was dispensed outside the 12 month follow-up (previously captured as switching to EZ+ statin combination) = 3,148
Initiate EZ monotherapy → Switch including a statin	N=314	N=450 314 - 6 (those who moved to “stay on ezetimibe monotherapy” (308)); + 139 (patients moving from “switch not including a statin” (447)) + 3 patients (previously classified as initiating on non-statin LLT combination moving to monotherapy and subsequently adding a statin) = 450.
Initiate EZ monotherapy → Switch including a non-statin LLT	N=1,229	N=103 1,229 – 987 (those who had a single EZ prescription dispensed (242)) – 139 (patients classified as switching to statin combination therapy as new analysis included a hierarchy for statin compared with non-statin LLTs EZ = 103

Table B.4: Ezetimibe initiation treatment status and subsequent treatments over the 12 months after ezetimibe initiation among patients in Cohort 1 (patients initiating ezetimibe with no prior dispensing of any lipid lowering therapy in 24 months prior to ezetimibe initiation; N=6,938). Results reported for the previous analysis are also presented in italicised text

	Initiated ezetimibe; then between days 31 to 365		
	stay on ezetimibe monotherapy	add a statin	add a non-statin LLT
No Prior LLT to ezetimibe initiation	Initiated ezetimibe monotherapy (N=3,701) (N=3,698)		
	N=3,148 (85.1%) <i>N=2,155 (58.3%)</i>	N=450 (12.2%) <i>N=314 (8.5%)</i>	N=103 (2.8%) <i>N=1,229 (33.2%)</i>
	Initiated ezetimibe in combination with statin (N=3,197) (N=3,180)		
	N=3,197 (100%) <i>N=3,180 (100%)</i>		
	Initiated ezetimibe in combination with non-statin LLT (N=40) (N=60)		
	N=40 (100%) <i>N=60 (100%)</i>		