



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for ezetimibe and ezetimibe/simvastatin

Proprietary Product Name: Ezetrol and Vytorin

Sponsor: Merck Sharp & Dohme Australia Pty
Ltd

June 2017

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Common abbreviations

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
ACS	acute coronary syndrome
AE	adverse event
ALT	alanine aminotransferase
ARR	absolute risk reduction
ARTG	Australian Register of Therapeutic Goods
AST	aspartate aminotransferase
AUC	area under the plasma drug concentration-time curve
BP	blood pressure
CABG	coronary artery bypass grafting
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
CK	creatinine kinase
CK-MB	creatinine kinase, MB Fraction
CKD	chronic kidney disease
C _{max}	maximum serum concentration of drug
CMI	Consumer Medicine Information
CrCl	creatinine clearance
CSR	clinical study report
CTT	Cholesterol Treatment Trialists
CV	cardiovascular
ECG	electrocardiogram
EMA	European Medicines Agency
ESRD	end stage renal disease

Abbreviation	Meaning
FDC	fixed dose combination
FDA	Food and Drug Administration (US)
HDL	high-density-lipoprotein
HDL-C	high-density-lipoprotein cholesterol
HeFH	Heterozygous Familial Hypercholesterolaemia
HoFH	Homozygous Familial Hypercholesterolaemia
HR	hazard ratio
hs-CRP	high sensitivity C-Reactive Protein
IMNM	immune-mediated necrotising myopathy
ITT	Intention-to-Treat
KM	Kaplan-Meier
LDL	low-density-lipoprotein
LDL-C	low-density-lipoprotein cholesterol
MAE	major atherosclerotic event
MI	myocardial infarction
MVE	major vascular event
NNT	Number Needed to Treat
NSTE	non-ST segment elevation
NSTEMI	non-ST segment elevation myocardial infarction
PCI	percutaneous coronary intervention
PD	pharmacodynamic(s)
PI	Product Information
PK	pharmacokinetic(s)
RMP	Risk Management Plan
RRR	relative risk reduction
SAE	serious adverse event

Abbreviation	Meaning
SHARP	Study of Heart and Renal Protection
SmPC	Summary of Product Characteristics
STEMI	ST-elevation myocardial infarction
Tmax	time taken to reach the maximum concentration (Cmax)
UA	unstable angina

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Extension of indications
<i>Decision:</i>	Approved
<i>Date of initial decision:</i>	11 August 2016
<i>Date of final decision:</i>	17 January 2017
<i>Date of entry onto ARTG</i>	20 January 2017
<i>Active ingredients:</i>	Ezetimibe and ezetimibe/simvastatin
<i>Product names:</i>	Ezetrol and Vytorin
<i>Sponsor's name and address:</i>	Merck Sharp & Dohme (Australia) Pty Limited Locked Bag 2234 North Ryde NSW 1670
<i>Dose form:</i>	Capsule
<i>Strengths:</i>	Ezetrol: 10 mg ezetimibe Vytorin: 10 mg ezetimibe with 10 mg simvastatin (Vytorin 10/10), 20 mg simvastatin (Vytorin 10/20), 40 mg simvastatin (Vytorin 10/40) or 80 mg simvastatin (Vytorin 10/80)
<i>Container:</i>	Blister packs
<i>Pack sizes:</i>	Ezetrol: 5, 10 and 30 Vytorin: 5, 10 and 30
<i>Approved therapeutic use:</i>	Ezetrol: Adults (≥ 18 Years) Prevention of Cardiovascular Disease: Ezetrol, is indicated for administration in combination with the maximum tolerated dose of a statin with proven cardiovascular benefit in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS) in need of additional lowering of LDL-C in the expectation of a modest further reduction in the risk of cardiovascular events following at least one year of therapy (see Clinical Trials). Vytorin: Adults (≥ 18 Years) Prevention of Cardiovascular Disease: Vytorin is indicated in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS) taking their maximum tolerated dose of simvastatin and in need of additional lowering of LDL-C in the expectation of a modest further reduction in the risk of

cardiovascular events following at least one year of therapy (see Clinical Trials).

<i>Route of administration:</i>	Oral
<i>Dosage:</i>	Recommended: Ezetrol: 10 mg once daily Vytorin: 10/10 mg/daily to 10/80 mg/daily
<i>ARTG numbers:</i>	91161, 98100, 98111, 98115, 98117

Product background

This AusPAR describes two submissions by Merck Sharp & Dohme (Australia) Pty Limited for extension of indications: Ezetrol (PM-2015-01524-1-3) containing ezetimibe, and Vytorin (PM-2015-01545-1-3) containing a fixed dose combination (FDC) of ezetimibe/simvastatin. As the data submitted in both dossiers was identical, and TGA's Delegate of the Secretary who considered the dossiers prepared one overview report considered by the Advisory Committee on Prescription Medicines (ACPM), these two submissions have been combined into a single AusPAR.

Ezetimibe is in a class of lipid modifying compounds that inhibit the intestinal absorption of cholesterol and related plant sterols. Ezetimibe has a mechanism of action that differs from other classes of cholesterol reducing compounds (for example, statins, bile acid sequestrants [resins], fibric acid derivatives, and plant sterols).

Ezetrol was approved by TGA in 2003 for use in homozygous familial hypercholesterolaemia and homozygous sitosterolaemia and primary hypercholesterolaemia.

According to the Australian Therapeutic Guidelines, statins are first line therapy with hyperlipidemia due primarily to elevation of low-density-lipoprotein (LDL). If the target LDL is not reached, ezetimibe, bile acid resins, nicotinic acid and fibrates are used as second line agents.

The rationale for the use of combination therapy with ezetimibe and a statin comes from the established link between lowering LDL and reducing cardiovascular (CV) events, and the limitations in achieving low LDL levels in some patients with statin therapy. Ezetimibe, through selectively inhibiting intestinal absorption of cholesterol and related phytosterols via NPC1L1, offers a complementary mechanism of action to that of statin therapy.

The approved indications for Ezetrol at time of this submission were:

Adults (≥ 18 Years)

- § **Primary Hypercholesterolaemia:** Ezetrol administered alone, or with an HMG CoA reductase inhibitor (statin), is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia.
- § **Homozygous Familial Hypercholesterolaemia (HoFH):** Ezetrol, administered with a statin, is indicated for patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis).
- § **Homozygous Sitosterolaemia (Phytosterolaemia):** Ezetrol is indicated for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolaemia.

Children and Adolescents 10-17 Years (pubertal status: boys Tanner Stage II and above and girls who are at least one year post-menarche)

- § **Heterozygous Familial Hypercholesterolaemia (HeFH):** Ezetrol co-administered with simvastatin (doses up to 40 mg) is indicated as an adjunctive therapy to diet in adolescent patients (10-17 years old) with heterozygous familial hypercholesterolaemia 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):** Ezetrol co-administered with simvastatin (doses up to 40 mg) is indicated in adolescent patients (10-17 years old) with HoFH. Patients may also receive adjunctive treatments (e.g. LDL apheresis)

The proposed (additional) indications for Ezetrol are:

Adults (≥ 18 Years)

- § **Prevention of Cardiovascular Disease:** Ezetrol, administered with a statin, is indicated to reduce the risk of cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalisation for unstable angina, or need for revascularisation) in patients with coronary heart disease (CHD).

Vytorin (ezetimibe/simvastatin) is a lipid lowering product that selectively inhibits the intestinal absorption of cholesterol and related plant sterols and inhibits the endogenous synthesis of cholesterol. The approved indications for Vytorin at time of this submission were:

Adults (≥ 18 Years)

- § **Primary Hypercholesterolaemia:** Vytorin is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia where use of a combination product is appropriate:
- § Patients not appropriately controlled with a statin or ezetimibe alone
 - § Patients already treated with a statin and ezetimibe.
- § **Homozygous Familial Hypercholesterolaemia (HoFH):** Vytorin is indicated in patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis).

Children and Adolescents 10-17 Years (pubertal status: boys Tanner Stage II and above and girls who are at least one year post-menarche)

- § **Heterozygous Familial Hypercholesterolaemia (HeFH):** Vytorin is indicated as adjunctive therapy to diet in adolescent patients (10-17 years old) with heterozygous familial hypercholesterolaemia 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):** Vytorin is indicated in adolescent patients (10-17 years old) with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis).

The proposed (additional) indications for Vytorin are:

Adults (≥ 18 Years)

§ **Prevention of Cardiovascular Disease:** *Vytorin is indicated to reduce the risk of cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalisation for unstable angina, or need for revascularisation) in patients with coronary heart disease (CHD).*

The following dosage forms and strengths are currently registered:

- Ezetrol 10 mg white-to-off white capsule shaped tablets available in blister packs of 5, 10 and 30.
- Vytorin is available as white to off-white, capsule shaped, biconvex compressed tablets containing 10 mg of ezetimibe with 10 mg of simvastatin (Vytorin 10/10), 20 mg of simvastatin (Vytorin 10/20), 40 mg of simvastatin (Vytorin 10/40) or 80 mg of simvastatin (Vytorin 10/80). Each of these formulations is available in blister packs of 5, 10 and 30.

No new dosage forms or strengths are proposed for Ezetrol or Vytorin.

Regulatory status

At time of submission to TGA, marketing applications for ezetimibe and ezetimibe/simvastatin tablets for the prevention of CV disease had been submitted in the US (not approved) and EU (approved). Similar applications were planned for Switzerland and Singapore. At time of initial decision, TGA was unable to obtain US reports to establish the reasons for the decision.

In the EU, Vytorin is marketed as Inegy.

The wording of the indication in the UK is:

Ezetrol is indicated to reduce the risk of cardiovascular events (see section 5.1) in patients with coronary heart disease and a history of acute coronary syndrome when added to ongoing statin therapy or initiated concomitantly with a statin.

Inegy (Vytorin) is indicated to reduce the risk of cardiovascular events (see section 5.1) in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS), either previously treated with a statin or not.

Other lipid lowering medicines on the Australian Register of Therapeutic Goods (ARTG) that have been approved for a reduction in CV events at time of the current submission are shown in Table 1.

Table 1: Lipid lowering medicines on the ARTG approved for a reduction in CV events.

Simvastatin	Zocor is indicated in patients at high risk of CHD (with or without hypercholesterolaemia) including patients with diabetes, history of stroke or other cerebrovascular disease, peripheral vessel disease, or with existing CHD to reduce the risk of cardiovascular death, major cardiovascular events including stroke, and hospitalisation due to angina pectoris. These effects do not replace the need to independently control known causes of cardiovascular mortality and morbidity such as hypertension, diabetes and smoking.
Atorvastatin	Atorvastatin is indicated in hypertensive patients with multiple risk factors for coronary heart disease (CHD) which may include diabetes, history of stroke or other cerebrovascular disease, peripheral vascular disease or existing asymptomatic CHD (see CLINICAL TRIALS) to reduce the risk of non-fatal myocardial infarction and non-fatal stroke. These effects do not replace the need to independently control known causes of cardiovascular mortality and morbidity such as hypertension, diabetes and smoking.
Rosuvastatin	Rosuvastatin is indicated for prevention of major cardiovascular events in men ≥ 50 years old and women ≥ 60 years old with no clinically evident cardiovascular disease but with at least two conventional risk factors for cardiovascular disease (hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease). Rosuvastatin is indicated to: <ul style="list-style-type: none"> · Reduce the risk of nonfatal myocardial infarction · Reduce the risk of nonfatal stroke · Reduce the risk of coronary artery revascularisation procedures.

Product Information

The approved Product Information (PI) documents current at the time this AusPAR was prepared can be found as Attachments 1 and 2. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Quality findings

There was no new data submitted.

III. Nonclinical findings

There was no new data submitted.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 3.

Introduction

This submission is for the registration of a new indication for both ezetimibe (Ezetrol) and the FDC of ezetimibe/simvastatin (Vytorin).

Clinical rationale

High LDL-C is a major risk factor for CHD. The effectiveness of LDL-C lowering therapy for reducing the risk of coronary events in patients with and without CHD is firmly established. The Cholesterol Treatment Trialists' (CTT) meta-analysis of data from 26

large, randomised, double blind, placebo controlled studies shows that statin therapy reduces CV risk by about 20% per 1 mmol/L (39.7 mg/dL) LDL-C reduction.¹ The proportional reduction in major vascular events (MVEs) was observed to be generally consistent across several subgroups, including age, gender, baseline lipids, diabetics, and various other demographic characteristics, and was generally consistent for all statins studied. The magnitude of the proportional reduction has been found to be directly proportional to the absolute LDL-C reduction achieved, down to LDL-C levels at least as low as 70 mg/dL (1.8 mmol/L).² The treatment effect observed during the first year of therapy was approximately one-half that seen after the first year. Despite the availability of statins, lipid lowering CV outcome trials show that many at-risk subjects are still having CV events, and a significant proportion of the CHD population fails to achieve adequate LDL-C lowering.³ The sponsor states that this residual risk represents a significant unmet medical need and the development of improved pharmacologic therapies for risk reduction in subjects with CHD is essential.

Ezetimibe is an azetidinone inhibitor which selectively inhibits the intestinal absorption of cholesterol and related phytosterols via an interaction with NPC1L1. Ezetimibe therapy offers a unique and complementary mechanism of action which yields incremental LDL-C reductions when combined with statins. An extensive preclinical and clinical program has been conducted with ezetimibe alone and in combination with statins. When ezetimibe 10 mg/d is added to ongoing statin therapy, an average reduction in LDL-C of up to 25% relative to the on-statin baseline has been observed in pooled analyses of clinical trials.⁴ The magnitude of the observed reductions with ezetimibe on top of statins is generally independent of statin type, potency/dose and patient characteristics. Recent research has shown that naturally occurring NPC1L1 genetic variants associated with reduced plasma LDL cholesterol levels are associated with a reduced risk of CHD,⁵ suggesting that ezetimibe mediated LDL-C lowering should reduce CV risk.

Ezetimibe was approved in the United States in October 2002, in the Reference Member State for the EU (Germany) in October 2002, and subsequently in numerous countries for use as monotherapy or in co-administration with statins in primary hypercholesterolemia. Ezetimibe plus statin co-administration is also indicated for treatment of HoFH and as monotherapy in the treatment of patients with homozygous sitosterolemia.

Based on the results from the large IMPROVE-IT study, the sponsor is seeking an indication for ezetimibe (when used with a statin) and ezetimibe/simvastatin to reduce the risk of CV events in patients with CHD. Although IMPROVE-IT studied patients presenting with ACS, used simvastatin as the background statin and entered patients with

¹ Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet* 376: 1670-81 (2010).

² Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet* 376: 1670-81 (2010); ESC guidelines of CV prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts. *Eur Heart J*. 33: 1635-1701 (2012).

³ Waters DD, et al. Lipid Treatment Assessment Project 2: A Multinational Survey to Evaluate the Proportion of Patients Achieving Low-Density Lipoprotein Cholesterol Goals. *Circulation* 120: 28-34 (2009); Santos RD, et al. A comparison of non-HDL and LDL cholesterol goal attainment in a large, multinational patient population: the Lipid Treatment Assessment Project 2. *Atherosclerosis* 224: 150-153 (2012); Karalis DG, et al. Use of Lipid-Lowering Medications and the Likelihood of Achieving Optimal LDL-Cholesterol Goals in Coronary Artery Disease Patients. *Cholesterol* 2012: 861924; Steinberg BA, et al. Nine-year trends in achievement of risk factor goals in the US and European outpatients with cardiovascular disease. *Am Heart J*. 156: 719-727 (2008).

⁴ Morrone D, et al. Lipid-altering efficacy of ezetimibe plus statin and statin monotherapy and identification of factors associated with treatment response: A pooled analysis of over 21,000 subjects from 27 clinical trials. *Atherosclerosis* 223: 251-261 (2012).

⁵ Myocardial Infarction Genetics Consortium. Inactivating mutations in NPC1L1 and protection from coronary heart disease. *NEJM* 371: 2072-82 (2014).

defined LDL-C levels, the sponsor believes that the results support conclusions that apply to patients with chronic CHD, those receiving any statin, and to subjects with a broad range of LDL-C levels.

Contents of the clinical dossier

The submission contained the following clinical information:

- No clinical pharmacology studies
- No population pharmacokinetic analyses
- One pivotal efficacy/safety study: IMPROVE-IT
- No dose finding or other efficacy/safety studies
- No pooled analyses, meta-analyses, Integrated Summary of Efficacy, Integrated Summary of Safety, etcetera
- Post-marketing safety analysis was provided.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

The IMPROVE-IT study was conducted in conformance with Good Clinical Practice (GCP) standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Evaluator comment: Throughout the trial, study sites noted to have GCP non-compliance issues were reviewed by GCP compliance committee. A total of 24 sites were reported to this committee, of which there were 7 where serious GCP non-compliance issues were noted. Because IMPROVE IT was a large, event driven trial, the principle of Intention-to-Treat was followed and no subject's data were excluded from the efficacy analyses on the basis of GCP violations.

Pharmacokinetics

No new pharmacokinetic studies were provided in the current dossier.

Pharmacodynamics

No new pharmacodynamic studies were provided in this submission. The pharmacodynamics of ezetimibe and ezetimibe/simvastatin FDC are well documented due to their approved use for other indications.

Dosage selection for the pivotal studies

No new data was provided.

Efficacy

Studies providing efficacy data

Pivotal efficacy study P04103 (IMPROVE-IT)

- Indication: Adults (≥ 18 Years) Prevention of Cardiovascular Disease to reduce the risk of cardiovascular events (cardiovascular death, nonfatal MI, nonfatal stroke, hospitalisation for unstable angina, or need for revascularisation) in patients with coronary heart disease (CHD).

P04103 was a Phase IIIb, multicentre, randomised, double blind, active controlled study.

The primary objective of this study was to evaluate the clinical benefit of ezetimibe/simvastatin combination compared with simvastatin in stabilised ACS subjects defined as the reduction in the risk of the occurrence of the composite endpoint of CV death, major coronary events and non-fatal stroke. Major coronary events included non-fatal MI, documented UA that required admission into a hospital and all coronary revascularisation with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) occurring at least 30 days after randomised treatment assignment.

The secondary objectives were to evaluate the clinical benefit of ezetimibe/simvastatin combination compared with simvastatin in stabilised ACS subjects on the occurrence of the following supportive composite endpoints (change from primary endpoint noted in bold):

- composite endpoint of **death due to any cause**, major coronary events or non-fatal stroke.
- composite endpoint of **death due to coronary heart disease** (CHD death), non-fatal MI, and **urgent coronary revascularisation** (either PCI or CABG occurring at least 30 days after randomisation);
- composite endpoint of CV death, non-fatal MI, documented UA that requires admission into a hospital, **all revascularisation (including both coronary and non-coronary)** occurring at least 30 days after randomisation, and non-fatal stroke.

The tertiary objectives were to evaluate the clinical benefit of ezetimibe/simvastatin combination compared with simvastatin in stabilised ACS subjects on each of the following endpoints analysed individually: death from any cause, CHD death, CV death, MI, documented UA that requires admission into a hospital, all coronary revascularisation with either PCI or CABG occurring at least 30 days after randomisation, urgent coronary revascularisation with either PCI or CABG (occurring at least 30 days after randomisation, all revascularisation (including both coronary and non-coronary) occurring at least 30 days after randomisation, stroke, any CV event leading to admission into a hospital, and CHF that requires hospitalisation occurring at least 30 days after randomisation. Other tertiary objectives were to evaluate the proportion of subjects achieving reductions in LDL-C and high sensitivity-C-reactive protein (hs-CRP)⁶ and to evaluate the potential relationship between the risk of occurrence of any primary endpoint event and the concentrations of LDL-C and hs-CRP following 1 month and 4 months of treatment with ezetimibe/simvastatin combination or simvastatin. Safety and tolerability of ezetimibe/simvastatin combination compared with simvastatin was also evaluated.

The study was conducted in 18,144 subjects with stabilised high risk ACS who were enrolled within 10 days of hospitalisation for either a non-ST segment elevation (NSTE) or

⁶ To evaluate the percentage of subjects achieving endpoint concentrations of LDL-C of <70 mg/dL (<1.8 mmol/L) and hs-CRP of <2.0 mg/L following 1 month and 4 months of treatment with ezetimibe/simvastatin combination compared with simvastatin.

unstable angina (UA) or Non-ST Elevation Myocardial Infarction (NSTEMI) or ST-elevation Myocardial Infarction (STEMI). After randomisation, subjects were to have clinical visits at the end of Month 1 and Month 4, and every 4 months, thereafter. Subjects who discontinued from study therapy were generally followed by phone visit at the same visit schedule as subjects remaining on drug. All subjects, including subjects who discontinued from treatment, were monitored for suspected clinical endpoint event until the termination of the trial. The trial was specified to end after all subjects had been followed for a minimum of 2.5 years and a primary endpoint event had been documented in at least 5250 subjects. All subjects, including subjects who discontinued treatment, were to be monitored for clinical endpoint events until the termination of the study. An independent Clinical Events Committee (CEC) reviewed and adjudicated each suspected clinical endpoint event and was blinded to treatment. Suspected clinical endpoint events included death from any cause, MI, UA, all revascularisation (including both coronary and non-coronary), stroke, any CV event leading to hospitalisation, and congestive heart failure (CHF) requiring hospitalisation occurring at least 30 days after randomisation. In addition, the CEC adjudicated instances of malignancies and instances of unexplained myalgia based on pre-specified review criteria. An independent Data Safety Monitoring Board (DSMB) evaluated safety findings at regular intervals, and efficacy findings at specified interim analyses. An independent LDL-C Monitoring Committee (LMC) periodically reviewed the achieved LDL-C results by treatment group during the recruiting phase of the trial and advised the Executive Committee regarding potential need to increase the targeted number of primary endpoint events in order to preserve study power (if the difference in median LDL-C between treatment groups was less than anticipated).

The study was conducted from 26 October 2005 to 4 May 2015 at 1400 centres of which 1147 allocated subjects to study treatment: 24 trial centres were in Argentina, 10 in Australia, 16 in Austria, 19 in Belgium, 33 in Brazil, 64 in Canada, 9 in Chile, 19 in Colombia, 23 in Czech republic, 19 in Denmark, 4 in Ecuador, 2 in Estonia, 17 in Finland, 28 in France, 55 in Germany, 2 in Hong Kong, 15 in Hungary, 23 in India, 25 in Israel, 69 in Italy, 4 in Malaysia, 40 in Netherlands, 8 in New Zealand, 20 in Norway, 13 in Peru, 30 in Poland, 13 in Portugal, 2 in Singapore, 13 in Slovakia, 17 in South Africa, 12 in South Korea, 38 in Spain, 24 in Sweden, 13 in Switzerland, 6 in Taiwan, 7 in Turkey, 16 in Ukraine, 36 in UK, and 359 in the US.

Evaluator's conclusions on efficacy

IMPROVE-IT was a Phase IIIb, multicentre, randomised, double blind, active controlled study in 18,144 subjects with stabilised ACS which evaluated the clinical benefit of ezetimibe/simvastatin combination (n = 9067) compared with simvastatin monotherapy (n = 9077). This study enrolled subjects presenting with ACS with relatively low baseline LDL-C values as it was considered unethical to study patients not already at optimal LDL-C goal, per 2004 NCEP ATP III guidelines.⁷ All patients included in the IMPROVE-IT study were high-risk subjects with ACS from one of three categories according to the diagnosis of the qualifying event:

- Subjects with a diagnosis of NSTEMI or UA from the Early ACS trial;
- Subjects with a diagnosis of STEMI;
- Subjects with a diagnosis of NSTEMI or UA.

⁷ National Cholesterol Education Program, National Heart Lung and Blood Institute, National Institutes of Health. Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. NIH publication no. 02-5215.

The criteria for entry into the IMPROVE-IT trial stipulated enrolment within 10 days of a subject's qualifying ACS event. ACS guidelines define the acute period as the period during hospitalisation, followed by a subacute period extending from discharge to approximately 3 months. After 3 months, patients are considered to have entered the chronic phase of their disease. The risk for recurrent events appears generally consistent over a prolonged period of follow up beginning at around 3 months, as has been observed in other studies such as ISIS2.⁸ Subjects presenting with ACS were chosen for this study because of their relatively high event rate which facilitated having study power to detect the risk reduction anticipated for patients in the LDL-C range studied. Minimum follow-up of 2.5 years also assured that the ACS subjects had transitioned to a phase of chronic CHD. The prolonged follow-up treatment period of IMPROVE-IT allowed for the evaluation of the persistence of benefit of the study therapy and included longer term follow-up to assess the effects of ezetimibe during the chronic and more stable phase of CHD. A prior study (PROVE-IT)⁹ had demonstrated that reductions in CV events attributable to LDL-C reductions achieved through chronic statin therapy in a population presenting with ACS was of a similar magnitude to that seen in 'stable' CHD populations. Thus, IMPROVE-IT was designed as a study assessing the efficacy of the additional LDL-C reduction from ezetimibe in subjects with CHD presenting with ACS.

Compared to simvastatin monotherapy, treatment with ezetimibe/simvastatin reduced the rate of the first occurrence of the primary composite endpoint of CV death, non-fatal MI, documented unstable angina that requires admission into a hospital, coronary revascularisation with either PCI or CABG occurring at least 30 days after randomisation, or non-fatal stroke. The primary endpoint occurred in 2,572 of 9,067 subjects (7 yr KM rate 32.72 %) in the ezetimibe/simvastatin group and 2,742 of 9,077 subjects (7 yr KM rate 34.67 %) in the simvastatin monotherapy group in the protocol-defined ITT population (HR 0.936, 95% CI 0.887-0.988; $p = 0.016$), corresponding to a relative risk reduction of 6.4%. This modest risk reduction following ezetimibe/simvastatin combination compared to simvastatin monotherapy was mainly driven by a reduction in risk of non-fatal MI and non-fatal stroke both as individual events as well as components of the composite endpoint. However, no differences were noted between the treatment groups in the rate of unstable angina requiring hospitalisation, or all coronary revascularisation with PCI or CABG (> 30 days after randomisation) whether as components of the composite endpoint or as individual events.

Treatment with ezetimibe/simvastatin was associated with a reduction in the rate of total stroke (HR 0.857, 95% CI 0.734-1.001, $p = 0.052$) compared with simvastatin monotherapy mainly driven by significant reduction in the incidence of non-haemorrhagic (that is, ischemic stroke and stroke of undetermined type) compared to simvastatin monotherapy (HR 0.793, 95% CI 0.670-0.939; $p = 0.007$). Although not significantly different, it is important to note that more subjects allocated to ezetimibe/simvastatin suffered a haemorrhagic stroke: 59 (0.65%) versus 43 (0.47%) in the simvastatin monotherapy group, of which 28 and 11, respectively, were fatal (HR 1.377, 95% CI 0.930-2.040; $p = 0.110$). A similar imbalance for haemorrhagic stroke has been reported in previous statin studies.¹⁰

The secondary composite endpoints focused on coronary events and provide additional clinically relevant information that supports the findings in the primary composite

⁸ Baigent C, et al. ISIS-2: 10 year survival among patients with suspected acute myocardial infarction in randomised comparison of intravenous streptokinase, oral aspirin, both, or neither. *BMJ* 316: 1337-1343 (1998).

⁹ Cannon CP, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *NEJM* 350: 1495-1504 (2004).

¹⁰ Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet* 376: 1670-1681 (2010).

endpoint. The results were also consistent across the 4 exploratory composite endpoints studied, including a 9.9% reduction in the risk of the composite endpoint of CV death, non-fatal MI and non-fatal stroke (HR 0.901, 95% CI 0.841-0.965; $p = 0.003$). Given the number of discontinuations from study therapy, and the limited information related to lipid values for those who discontinued study therapy, pre-specified on-treatment analyses were also conducted. The on-treatment analyses were consistent with the results in the protocol-defined ITT population further supporting the finding that ezetimibe added to a statin resulted in reduction in cardiovascular events. However, on-treatment analyses should be interpreted with caution as they represent a non-randomised comparison.

The CHMP guidelines state that:

to provide supportive information, and to ensure reliable interpretation, analysis of each separate component of the composite should be presented. For overall mortality and cardiovascular mortality both confidence intervals and point estimates are relevant for assessment and any point estimate considerably in favour of the comparator is a matter of concern.

With regard to the individual components of the primary composite endpoint, the rates for non-fatal MI and non-fatal stroke were reduced in the ezetimibe/simvastatin compared with simvastatin monotherapy groups. The rates of CV death, CHD death, and death from any cause either as components of the composite or as individual events were similar between the treatment groups. However, patients in the ezetimibe/simvastatin group were at higher risk of experiencing fatal stroke (HR: Ez/Sim: Sim = 1.217) and haemorrhagic stroke (HR = 1.377), although interpretation was limited by wide confidence intervals.

The consistency of the treatment effect for the primary endpoint was generally consistent across 20 pre-specified subgroups (including race, region, smoking status, prior PCI, prior stroke, statin experience and baseline LDL-C quartiles) with the vast majority of the HR point estimates favouring ezetimibe/simvastatin with broadly overlapping confidence intervals. Although these analyses suffer from limited power and absence of multiplicity control, the results are consistent with the results in the overall cohort studied. It is important to note that majority (75%) of patients enrolled in the study were males, but the benefit in terms of reduction in the primary efficacy endpoint was lesser in males with 95% CIs including unity. The relative risk reduction in primary efficacy endpoint appears to be slightly greater in the female patient population.

At year 1 (in subjects who had laboratory evaluations completed), the LS mean difference in LDL-C levels achieved was 16.8 mg/dl (0.44 mmol/L, $p < 0.001$) representing a 23% further lowering of LDL-C by ezetimibe relative to the LDL-C on simvastatin monotherapy with similar reduction observed over the entire trial (averaging all LDL-C values obtained over time). However, measurement of lipid values was not required after a subject permanently discontinued study therapy, therefore excluding subjects who had discontinued study drug prematurely. When imputing LDL-C values for subjects with no blood sample collected at 1 year using baseline levels, the between-group LDL-C difference was still 12.7 mg/dl (0.33 mmol/L). It is important to note that prior to the institution of Amendment #5, subjects with LDL-C >79 mg/dL (>2.0 mmol/L) based on protocol specified criteria were to have their simvastatin dose increased to 80 mg in a blinded manner. The use of simvastatin 80 mg was not balanced between the 2 groups with 6.2% and 27.0% in the ezetimibe/simvastatin and simvastatin groups, respectively, receiving simvastatin 80 mg sometime during the trial. Thus, the difference in LDL-C between the treatment groups would be expected to be smaller than that generally attributed to the addition of ezetimibe to a statin at a given dose. The observed changes and between-group differences in other lipids and apolipoproteins were also consistent with the known effects of simvastatin and ezetimibe from previous studies. Specifically, treatment with ezetimibe produced additional reductions in non-HDL-C and apolipoprotein B compared with

simvastatin monotherapy, with a more modest additional reduction in TG. HDL-C was slightly increased by addition of ezetimibe, with no significant between-group difference in apolipoprotein AI.

Relevance of IMPROVE-IT results for patients with chronic CHD

The IMPROVE-IT results showed that the benefit with ezetimibe began to emerge after one year of treatment, and continued over the ensuing years of the trial. Given that the benefit of further LDL-C lowering with ezetimibe occurred predominantly after 1 year strongly suggests that its benefits are not associated with events immediately surrounding the acute ACS event. Furthermore, an analysis of total events (first and recurrent events) demonstrated that subjects in the ezetimibe/simvastatin group had a reduced hazard for total events for the primary and secondary composite endpoints compared to subjects in the simvastatin group. Although this analysis has limitations due to the inherent bias that may be introduced with a non-randomised comparison, the results support the durability of the treatment benefit of ezetimibe/simvastatin beyond the prevention of the first event, which is an important clinical benefit for high-risk subjects.

Relevance of IMPROVE-IT results in patients with higher LDL-C levels

The 2010 CTT meta-analysis, including data from 26 lipid lowering statin trials and 170,000 subjects, demonstrated a strong relationship between the absolute degree of LDL-C lowering and proportional decrease in CV disease risk across a broad range of LDL-C levels and patient characteristics.¹¹ This relationship also holds for ezetimibe where the proportional change in LDL-C with ezetimibe is independent of baseline LDL-C levels¹² (PI for Ezetimibe). The CTT meta-analysis reported a 22% CV risk reduction per mmol/L LDL-C lowering. Therefore at higher baseline LDL-C levels, statins produce larger absolute changes in LDL-C and, as shown in the CTT meta-analysis, greater cardiovascular risk reduction. Although the IMPROVE IT study enrolled patients with lower LDL-C levels, the results of IMPROVE IT should be relevant to patients whose LDL-C levels are not well controlled on a statin and, based on the larger absolute LDL-C change observed in these patients, one would expect the CV benefits to be even greater.

Relevance of IMPROVE-IT results to patients treated with any statin

Ezetimibe targets NPC1L1, largely in the small intestine to inhibit intestinal cholesterol absorption. Statins inhibit HMGCoA reductase to decrease hepatic cholesterol synthesis. These mechanisms are complementary, and when ezetimibe and statins are administered together, help block potential compensatory increases in cholesterol absorption or cholesterol synthesis. These two complementary mechanisms also share a final common pathway that lowers LDL-C via the up-regulation of hepatic LDL receptors.

Ezetimibe supports a consistent proportional additive decrease in LDL-C levels when added to or co-administered with any statin. A pooled analysis from 27 lipid lowering trials including over 21,000 subjects showed that ezetimibe has a consistent additive lipid lowering effect when added to different statins, different doses of a statin, and statins of varying potency, and across a diverse patient population and this is reinforced by the fact

¹¹ Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet* 376: 1670-1681 (2010); Cholesterol Treatment Trialists' (CTT) Collaboration. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 380: 581-590 (2012).

¹² Morrone D, et al. Lipid-altering efficacy of ezetimibe plus statin and statin monotherapy and identification of factors associated with treatment response: A pooled analysis of over 21,000 subjects from 27 clinical trials. *Atherosclerosis* 223: 251-261 (2012).

that ezetimibe is approved for lipid lowering with all statins.¹³ All approved statins also have a similar safety profile, and the safety profile of ezetimibe is similar when administered with all statins (PI for Ezetimibe). Statin related CV outcomes benefit is associated with the degree of statin mediated LDL-C lowering and does not vary for different statins.¹⁴ The sponsors claim that that these observations support the conclusion that co-administration of ezetimibe with an inhibitor of HMG CoA reductase (any statin) will have additive benefit on CV risk reduction, and that this incremental benefit is expected to be similar with co-administration of other statins which are already shown to be effective in reducing the risk of CV events.

The clinical information relating to the consistent lipid lowering of ezetimibe when administered with or added to a statin is also consistent with information relating to persons with both NPC1L1 and HMGCoA reductase LDL-C lowering genetic variants. In such individuals, the observed LDL-C lowering is consistent with the sum of the LDL-C lowering associated with each genetic variant individually. This mimics the clinical situation when ezetimibe is given with a statin, and the observation that the LDL-C lowering mediated each by ezetimibe and statins is also additive. The CV risk reduction associated with presence of both NPC1L1 and HMGCoA reductase genetic variants is similarly additive. This is consistent with the IMPROVE-IT result which demonstrated that co-administration of ezetimibe with an inhibitor of HMG CoA reductase will have additive benefit on CV risk reduction. However, genetic testing for these variants was not done in the IMPROVE-IT study.

To determine whether larger reductions in LDL cholesterol safely produce further reductions in major vascular events, several trials have compared more intensive versus standard statin regimens.¹⁵ Although their results tend to suggest further benefit,¹⁶ only two had significant results for their primary outcome.¹⁷ The results of the IMPROVE IT study provide some evidence that the additional LDL-C reduction associated with addition of ezetimibe to simvastatin is translated into additive benefit on CV risk reduction, although the clinical relevance of the modest 6.4% relative risk reduction is not clear.

Although IMPROVE-IT studied patients presenting with ACS, used only simvastatin as the background statin, and entered patients with LDL-C levels, the sponsors have provided information to justify that the modest benefits observed in terms of reduction of CV events may apply to patients with chronic CHD, those receiving any statin and to subjects with a

¹³ Morrone D, et al. Lipid-altering efficacy of ezetimibe plus statin and statin monotherapy and identification of factors associated with treatment response: A pooled analysis of over 21,000 subjects from 27 clinical trials. *Atherosclerosis* 223: 251-261 (2012).

¹⁴ Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet* 376: 1670-1681 (2010); Baigent C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 366: 1267-1278 (2005); European Association for Cardiovascular Prevention & Rehabilitation, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J*. 32: 1769-818 (2011).

¹⁵ Cannon CP, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *NEJM* 350: 1495-1504 (2004); LaRosa JC, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *NEJM* 352: 1425-1435 (2005); Pedersen TR, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomised controlled trial. *JAMA* 294: 2437-2445 (2005); de Lemos JA, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA* 292: 1307-1316 (2004); Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group, et al. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial. *Lancet* 376: 1658-1669 (2010).

¹⁶ Cannon CP, et al. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. *J Am Coll Cardiol*. 48: 438-445 (2006).

¹⁷ Cannon CP, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *NEJM* 350: 1495-1504 (2004); LaRosa JC, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *NEJM* 352: 1425-1435 (2005).

broad range of LDL-C levels. However, there were limitations in the submission which preclude any definite conclusions regarding efficacy of ezetimibe (Ezetrol) when used with a statin and ezetimibe/simvastatin (Vytorin) for the proposed indication to reduce the risk of CV events (CV death, non-fatal myocardial infarction, non-fatal stroke, hospitalisation for UA, or need for revascularisation) in patients with CHD.

Limitations of efficacy data

- Overall, the results from the IMPROVE-IT pivotal study do not support all of the components of the proposed indication:
 - CV death: ezetimibe/simvastatin did not show any reduction in CV or overall mortality
 - non-fatal MI: ezetimibe/simvastatin showed significant reduction in non-fatal MI
 - non-fatal stroke: ezetimibe/simvastatin showed significant reduction in nonfatal stroke but this was limited to non-haemorrhagic stroke but this is similar to stroke findings with other statins¹⁸
 - hospitalisation for unstable angina: ezetimibe/simvastatin did not show any reduction in hospitalisation for unstable angina, although interpretation was limited by very low event rates in both treatment groups.
 - need for revascularisation: this is very generalised term and not justified as the primary composite endpoint in the pivotal IMPROVE IT study specifically includes 'all coronary revascularisation with either PCI or CABG occurring at least 30 days after randomisation'. Furthermore, this component of the composite primary endpoint failed to show any clear benefits with ezetimibe/simvastatin compared to simvastatin alone.
- The ARR and NNT following combination treatment with ezetimibe/simvastatin compared to simvastatin monotherapy was not provided in the IMPROVE-IT study report. The absolute reduction of risk (ARR or NNT) is very important as it would be useful to determine the clinical relevance of the RRR since RRR does not take the baseline level of risk of the subjects into consideration. This is especially important as the sample size was changed from an original size of 10,000 subjects to up to 18,000 subjects because the primary endpoint event rate was lower than anticipated in the original design. It is important to determine the actual clinical benefit following the modest 6.4% relative risk reduction (RRR) in the primary composite endpoint and information on the ARR and NNT would provide clarification on this issue.
- The number of subjects who at some point had their dose of simvastatin increased from 40 to 80 mg per day was greater in the simvastatin group compared to the ezetimibe/simvastatin group (6.2% in the ezetimibe/simvastatin and 27.0% in the simvastatin monotherapy group) and the sponsors have stated that this would give a more conservative estimate of benefit of ezetimibe/simvastatin and hence this sensitivity analysis was conducted censoring subjects at time of up-titration of simvastatin dose. However, results of this sensitivity actually were a cause for concern due to greater number of events in the ezetimibe/simvastatin group (2461/9067, 27.14%) compared with simvastatin alone (2205/9077, 24.29%) including a higher incidence of CV death, non-fatal MI, UA requiring hospitalisation and coronary revascularisation (PCI or CABG).

¹⁸ Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet* 376: 1670-1681 (2010).

- Efficacy and safety of the ezetimibe in combination with simvastatin dose > 40 mg was not adequately evaluated. Majority of the patients received 40 mg simvastatin and exposure to the higher dose of 80 mg simvastatin was limited especially in the ezetimibe/simvastatin group. Overall, only 561 patients of the 9067 patients in the ezetimibe/simvastatin group received 80 mg simvastatin at any time during the study. However, it is important to note that 229 of these 561 patients were down-titrated to 40 mg during the study (due to protocol amendment #5 or other reasons). Hence, only 332 patients received the 80 mg dose of simvastatin in the ezetimibe/simvastatin group for the duration of the study.

Safety

Studies providing safety data

In the pivotal IMPROVE-IT study, the following safety data were collected: laboratory tests (including liver function tests and CK levels), physical examinations, adverse events (AEs) and clinic evaluations. General AEs were recorded at each visit. Serious AEs (SAEs) were recorded within 1 working day of the investigator learning of the event. Suspected clinical endpoint events, including death, were exempt from being reported as SAEs (as per the IMPROVE-IT protocol). The protocol also specified that monitoring and recording of AEs (including SAEs) was only required if they occurred 30 days or less following permanent discontinuation of study drug. In addition to the protocol defined ITT approach, the selected safety parameters of SAEs, CEC-reviewed myopathy/ rhabdomyolysis, hepatic ALT/AST elevations, and CK elevations were also analysed¹⁹ as follows.

AEs were summarised by frequency of occurrence. No statistical inferential analysis of safety data was planned except for the following parameters of interest, for which point estimates, 95% CIs, and p-values for the differences in incidences between the treatment groups are provided using the Miettinen and Nurminen method: myopathy, rhabdomyolysis, cholecystectomy, AEs reflective of gallbladder disease, and ALT and/or AST elevations >3xULN. Cancer and cancer-related death were analysed using a Cox proportional hazards model with treatment as a covariate. Inferential analysis of cancer or cancer related death AEs was not specified in the study protocol, but was added to the SAP due to the interest raised by the findings of the SEAS study. Additionally, other relevant AESI were reviewed and summarised including new onset diabetes, pancreatitis, acute renal failure, interstitial lung disease, hypersensitivity reactions, and haemorrhagic stroke. The Medical Dictionary of Regulatory Activities (MedDRA) Version 17.0 was used in reporting of all AEs.

Patient exposure

IMPROVE-IT study

The mean duration of exposure was 1389 days in the ezetimibe/simvastatin group and 1427 days in the simvastatin group. A total of 5710 subjects were on treatment for at least 72 months. For the first 6 years of the trial, IMPROVE-IT called for compliant subjects in either treatment group who had LDL-C >79 mg/dL (2.0 mmol/L) on two consecutive measurements to have their dose of simvastatin increased from the initial 40 mg per day to 80 mg per day in a blinded manner. With amendment #5 to the protocol, subjects who had been receiving simvastatin 80 mg for less than a year or who required taking the

¹⁹ Analysis similar to the protocol-defined ITT approach in the SAP, but excluding subjects who never took study drug. Analysis similar to the protocol-defined ITT approach in the SAP, but excluding subjects who never took study drug and limited to the time period when subjects are on-treatment up to and including 30 days after the last dose of study drug.

potentially interacting drugs ranolazine or amlodipine, had their simvastatin dose returned to 40 mg per day. As expected, the numbers of subjects who at some point had their dose of simvastatin increased from 40 to 80 mg per day was greater in the simvastatin group compared to the ezetimibe/simvastatin group (27% versus 6.2%). With protocol amendment #5, a greater proportion of subjects in the simvastatin monotherapy group were down-titrated from simvastatin 80 mg to simvastatin 40 mg (8.7% versus 2.5%). Compliance was >85% in over 86% of the patients with similar compliance rates in both treatment groups.

Comments: Overall, only 561 patients of the 9067 patients in the ezetimibe/simvastatin group received 80mg simvastatin at any time during the study. However, it is important to note that 229 of these 561 patients were down-titrated to 40mg during the study (due to protocol amendment #5 or other reasons). Hence, only 332 patients received the 80mg dose of simvastatin in the ezetimibe/ simvastatin group.

Safety issues with the potential for major regulatory impact

Liver toxicity

All narratives for deaths in the IMPROVE-IT study adjudicated by the CEC into the category of “Other” or “Unknown” were searched to determine if they contained text that may indicate death caused by liver failure such as the terms ‘hepatic’ or ‘liver’. This evaluation was not pre-specified and was carried out after database lock. All narratives containing these terms were then reviewed by a Merck physician to determine if the death could be attributed to a hepatic cause. This review revealed 14 deaths related to hepatic causes (9 subjects in the ezetimibe/simvastatin group and 5 in the simvastatin group). Of the 9 subjects in the ezetimibe/simvastatin group with a hepatic cause of death, 5 cases were related to non-alcoholic cirrhosis. For one [information redacted] patient, death occurred within 30 days of permanent discontinuation of study therapy who developed a surgical wound infection post CABG and subsequently ‘oedematous ascetic syndrome caused by hepatic cirrhosis.’ The investigator considered the liver failure which resulted in death unlikely related to study drug. The remainder of the deaths due to non-alcoholic cirrhosis occurred between 1 and 5 years after discontinuation of study therapy. For one subject who also had an event meeting the biochemical criteria for DILI, death occurred nearly 2 years after study drug was discontinued. The CEC reported liver failure as cause of death for a [information redacted] diabetic smoker patient²⁰ who withdrew consent during the trial. In both of these cases, death occurred more than 1 year after permanent discontinuation of study therapy. In 4 of the 5 subject deaths in the simvastatin treatment group, nonalcoholic steatohepatitis was a contributing factor and 1 was related to cirrhosis.²¹

AEs related to hepatitis included preferred terms of ‘chronic hepatitis’, drug induced liver injury’, ‘hepatic failure’, ‘hepatocellular injury’, ‘hepatitis’, and ‘hepatitis acute’. These terms were not pre-specified and cases of hepatitis were not adjudicated. There were no meaningful differences in the occurrence of these events between treatment groups.

A total of 49 subjects met the biochemical criteria for potential DILI²² with similar incidence in both groups; 26/8027 (0.3%) in the ezetimibe/simvastatin group and

²⁰ This subject had withdrawn consent to participate in the study and the only available information related to his death was listed in the civil death registry which reported “severe liver failure” as cause of death.

²¹ For a [information redacted] patient with a history of hypertension death due to hepatorenal syndrome occurred within 2 months of discontinuation of the study therapy. The investigator reported the hepatorenal syndrome as unrelated to study drug. In the remainder of the subjects, death occurred greater than 1 year after the subjects had stopped study therapy.

²² To identify possible DILI cases, laboratory tests that were performed in conjunction with the annual safety panel, together with any local laboratory tests performed in relation to reported AEs were screened. Specifically, the following post baseline laboratory test results derived from the same blood sample or from

23/8068 (0.3%) in the simvastatin group. However, the criteria for Hy's Law (meeting biochemical criteria referenced above and no alternative cause identified) were only met in 3 cases (an alternative explanation for the elevated transaminase level was identified and Hy's Law was not met for all the other cases). These 3 cases are described in detail below:

- a [information redacted] patient (ezetimibe/simvastatin 40 mg) with elevated bilirubin on randomisation who was hospitalised with elevated transaminases and weakness approximately one month later, was diagnosed with an MI one week later and subsequently died.
- a [information redacted] patient (ezetimibe/simvastatin 40 mg) on aspirin and beta blocker who developed transaminase elevations approximately 1.5 years after randomisation when she presented with weakness, malaise and anaemia. Study drug was stopped, she underwent colonoscopy (details not available) and transaminase elevations resolved.
- a [information redacted] patient (simvastatin 40 mg) developed transaminase elevations approximately one month after randomisation to simvastatin 40 mg. Medications included aspirin and beta blocker and one year following study drug discontinuation, the subject presented with cholelithiasis and pancreatitis and underwent cholecystectomy.

Haematological toxicity

None.

Serious skin reactions

None.

Cardiovascular safety

None.

Unwanted immunological events

None.

Post marketing data

Ezetrol

The MAH reviewed cumulatively more than 12 years of post-marketing data (from 2002 through 30 November 2014) for 8 events of interest with the use of ezetimibe (rhabdomyolysis/ myopathy; malignancies; gallbladder disorders; interstitial lung disease; haemorrhagic stroke; pancreatitis; acute renal failure; hypersensitivity). A cumulative search of the company global pharmacovigilance database through 30 November 2014 was performed for all medically confirmed spontaneous reports, including literature cases, and cases received from regulatory agencies reported with the use of ezetimibe coded with at least one preferred term (PT) from the standardised MedDRA queries (SMQs) (version 17.1) and only narrow terms were included in the search.

Over this period of time, an estimated 12,702,461,463 tablets have been distributed with an estimated 34,801,264 patient-treatment years of use of ezetimibe. This review was

combinations of blood samples collected on the same study day constituted the criteria used to screen for potential DILI cases: ALT and/or AST activity $\geq 3 \times$ ULN; AND total bilirubin concentration $\geq 2 \times$ ULN; AND alkaline phosphatase concentration $< 2 \times$ ULN. In order to be considered a DILI case, the subject would need to meet the biochemical criteria listed above without an alternate cause for the laboratory abnormalities. Cases meeting these criteria were not adjudicated.

conducted using all reports received in the global safety database because the population studied in IMPROVE-IT could not be isolated in the post-approval reports.

Rhabdomyolysis/myopathy

A total of 662 cases were retrieved that included 642 medically confirmed (666 events, 463 serious and 203 non-serious) and 20 consumer reports (23 events- 13 serious and 10 non-serious).²³ Of the 463 serious events, the three most often reported events were rhabdomyolysis (395 events), myopathy (55 events) and myoglobin blood increased (6 events). Of the 203 non-serious events, there were 181 events of myopathy, 14 events of myoglobin blood increased, 6 events of rhabdomyolysis and 2 events of myoglobin urine increased. Patients were reported to be recovered or recovering in 336 cases (including 6 reports with sequelae), patients did not recover in 58 cases and the outcome was unknown in 248 reports. Of the 642 medically confirmed reports, there were 7 cases with a fatal outcome. Five of the seven cases with a fatal outcome involved patients with comorbid conditions and reported the use of statins as secondary suspect medications. The remaining two cases lacked sufficient information to allow for medical assessment. One of the 20 non-medically confirmed cases reported a fatal outcome;²⁴ six patients were noted to be recovered or recovering, while 6 patients did not recover; the outcome was unknown in the remaining 8 reports.

Malignancies

A total of 121 cases were retrieved that included both medically confirmed (100) and consumer reports (21). Of these 121 cases, 100 reports containing 114 events within the SMQ were received from health care professionals (98 serious and 2 non-serious) with breast cancer (11 events), neoplasm malignant (11 events) and pancreatic cancer (10 events) reported most frequently. A fatal outcome due to malignancy or complications associated with metastatic disease progression was reported in 11 cases; 24 patients did not recover, 12 were noted to be recovered or recovering and the outcome was unknown in 55 reports. Of the 21 reports received from consumers, 20 were serious and 1 was non-serious; neoplasm malignant (4 events), colon cancer (4 events) and breast cancer (3 events) were the most commonly reported serious events. A fatal outcome due to malignancy was reported in 2 cases; 4 patients did not recover, 6 patients were noted to be recovered or recovering, and the outcome was unknown in the remaining 9 cases.

Gallbladder disorders

A total of 304 cases were retrieved that included 266 medically confirmed reports of which 150 were serious (most common were cholelithiasis [44 events], jaundice [21], and blood bilirubin increased [17]) and 116 were non-serious (blood bilirubin increased [48], cholelithiasis [41], and jaundice [26] were most common); six reports had fatal outcome, 104 patients recovered or were recovering, 30 patients did not recover and the outcome was unknown for 133 cases. Of the 38 consumer reports 25 were serious and 13 were non-serious (cholelithiasis and cholecystitis most common); one report had a fatal outcome, 11 patients were recovered or recovering, 7 patients did not recover and the outcome was not provided in the remaining 20 cases.

²³ There were 13 serious events reported, 11 events of rhabdomyolysis and 2 events of myopathy. There were 10 non-serious events; myopathy (8 events) and myoglobin blood increased (2 events).

²⁴ This case concerned a [information redacted] patient with reported liver disease (8 years) and diabetes (3-4) years that was placed on therapy with ezetimibe and developed rhabdomyolysis, kidney failure and removal of her gallbladder. Concomitant therapy included omeprazole, lactulose, neomycin, levothyroxine Na, calcium carbonate, furosemide, colesvelam hydrochloride and venlafaxine hydrochloride. Therapy with ezetimibe was discontinued and the patient died several months later.

Interstitial lung disease

A total of 27 cases were retrieved that included 26 medically confirmed (19 serious and 7 non-serious) and 1 consumer report. There were no reports with a fatal outcome; 12 patients were recovered or recovering (one with sequelae), 7 patients did not recover and the outcome was not provided in the remaining 8 cases.

Haemorrhagic stroke

A total of 51 cases were retrieved that included 41 medically confirmed (40 serious and 1 non-serious). There were four reports with a fatal outcome, 16 patients were recovered or recovering, 2 patients were not recovered and the outcome was unknown in the remaining 19 cases. All 10 consumer reports were serious; one report with a fatal outcome. The outcome was reported as recovering in one case; recovered with sequelae in one case; not recovered in 2 cases and unknown in the remaining 5 cases.

Pancreatitis

A total of 321 cases were retrieved that included 300 medically confirmed reports (291 serious and 9 non-serious); 4 reports had a fatal outcome; outcome was reported as recovered in 119 cases, recovering in 36 cases, recovered with sequelae in 4 cases; not recovered in 21 cases and, unknown in 121 cases. All 21 consumer reports were serious; none of the reports had a fatal outcome, outcome was reported as recovered in 10 cases, recovering in 2 cases, not recovered in one case; and unknown in the remaining 8 cases.

Acute renal failure

A total of 185 cases were retrieved that included 173 medically confirmed reports (159 serious and 14 non-serious); 10 reports with a fatal outcome. Outcome was reported as recovered in 62 cases, recovering in 21 cases; recovered with sequelae in 2 cases; not recovered in 13 cases and unknown in 65 cases. Of the 12 consumer reports, 7 were serious and 5 were non-serious; fatal outcome for one case, 1 each recovered and recovering, 2 not recovered and unknown in the remaining 6 cases.

Hypersensitivity

A total of 2,303 cases were retrieved that included 1896 medically confirmed reports (367 serious and 1529 non-serious) with rash, angioedema, urticarial and hypersensitivity reported most commonly. There were five reports with a fatal outcome. The outcome was reported as recovered in 937 cases, recovering in 213 cases; recovered with sequelae in 5 cases; not recovered in 163 cases, and unknown in 732 cases. Of the 407 consumer reports, 41 were serious and 366 were non-serious with rash, hypersensitivity, urticarial reported most frequently; no fatal outcome for any reports, outcome was reported as recovered in 90 cases, recovering in 63 cases; not recovered in 132 cases and unknown in 137 cases.

Comments: Overall, review of more than 12 years of marketed data did not reveal new safety issues or emerging information about a change in the known characteristics of the risks of ezetimibe. These events/conditions are adequately and accurately described in the Ezetrol label.

Vytorin

The MAH reviewed cumulatively more than 10 years of post-marketing data (from 2004 through 30 Nov 2014) for each of the 8 events of interest²⁵ with the use of ezetimibe/simvastatin. Over this period of time, an estimated 10,768,170,172 tablets have been distributed with an estimated 29,501,836 patient-treatment years of use of ezetimibe/simvastatin. This review was conducted using all reports received in the global

²⁵ Rhabdomyolysis/myopathy; malignancies; gallbladder disorders; interstitial lung disease; haemorrhagic stroke; pancreatitis; acute renal failure; hypersensitivity.

safety database as the population studied in IMPROVE-IT could not be isolated in the post approval reports.

Rhabdomyolysis/myopathy

A total of 702 cases were retrieved that included 681 medically confirmed reports (591 serious and 101 non-serious); rhabdomyolysis, myopathy and myoglobin blood increased were reported most frequently. Of the 681 medically confirmed reports, 7 cases had a fatal outcome, patients were reported to be recovered or recovering in 386 reports (including 4 reports with sequelae), patients did not recover in 61 cases and the outcome was unknown in 230 reports. Of the 21 consumer reports, 10 were serious and 11 were non-serious (rhabdomyolysis, myopathy and myoglobin blood increased most common). None of the 21 non-medically confirmed cases reported a fatal outcome; 11 patients were noted to be recovered or recovering, while 6 patients did not recover and outcome was unknown in the remaining 4 reports.

Malignancies

A total of 113 cases were retrieved that included 91 medically confirmed (all serious). A fatal outcome due to malignancy was reported in 6 cases, 24 patients did not recover, 10 were noted to be recovered or recovering and the outcome was unknown in the remaining 51 reports. Of the 22 consumer reports (all serious), fatal outcome due to malignancy was reported in 3 cases, 4 patients did not recover, 2 patients were noted to have recovered and the outcome was unknown for the remaining 13 reports. Neoplasm malignant, breast cancer and lung neoplasm malignant were most commonly reported (for both medically confirmed and consumer reports).

Gallbladder disorders

A total of 174 cases were retrieved that included 143 medically confirmed reports (80 serious and 63 non-serious) and cholelithiasis, cholecystitis, jaundice and blood bilirubin increased were reported most commonly. There were 2 reports with a fatal outcome, 75 patients recovered or were recovering; 21 patients did not recover; and the outcome was unknown for the remaining 77 reports. Of the 31 consumer reports, 17 were serious and 14 non-serious; there were no reports with a fatal outcome, 9 patients were recovered or recovering; 11 patients did not recover; and the outcome was not provided in the remaining 13 reports.

Interstitial lung disease

A total of 17 cases were retrieved that included 14 medically confirmed (9 serious and 5 non-serious). There were 2 reports with a fatal outcome,²⁶ 2 patients recovered or were recovering, 2 patients did not recover, and outcome was unknown in 8 cases. Of the 3 consumer reports (all non-serious), there was no fatal outcome, 2 were reported as not recovered and remaining case was unknown.

Haemorrhagic stroke

A total of 87 cases were retrieved that included 31 medically confirmed (all serious); there were no reports with a fatal outcome, 10 patients were considered recovered or recovering (two with sequelae), 4 patients did not recover and the outcome was unknown in the remaining 20 reports. Of the 56 consumer reports (all serious), there were no cases with a fatal outcome, 1 patient recovered and the outcome was unknown in the other 55 reports.

²⁶ One of which was being treated with methotrexate, which confounded the report. The second patient, who had a history of diffuse systemic sclerosis, interstitial interstitial lung disease (ILD) and renal insufficiency, had possible active ILD in the upper lobe and chronic fibrotic changes in multiple lobes prior to succumbing to her illness.

Pancreatitis

A total of 152 cases were retrieved that included 144 medically confirmed reports (all serious) of whom 2 reports had a fatal outcome; 95 patients were considered recovered or recovering and 9 patients did not recover. Of the 8 consumer reports (all serious), none had a fatal outcome, 3 patients were considered recovered or recovering and 3 patients did not recover, while outcome was unknown in two reports.

Acute renal failure

A total of 198 cases were retrieved that included 182 medically confirmed reports (172 serious and 10 non-serious) and 5 reports with a fatal outcome;²⁷ 98 patients recovered or were recovering (one with sequelae), 17 did not recover and outcome was unknown in the remaining 62 reports. Of the 16 consumer reports (12 serious and 4 non-serious), one had a fatal outcome (insufficient information received from the consumer did not allow for an assessment); 6 patients were recovered or recovering (one with sequelae), 4 patients did not recover and the outcome was unknown in the remaining 5 reports.

Hypersensitivity

A total of 1236 cases were retrieved that included 906 medically confirmed reports (169 serious and 737 non-serious) with rash, angioedema, urticarial and hypersensitivity reported most commonly. There were no reports with a fatal outcome, 493 patients were recovered or recovering (including one with sequelae), 79 patients did not recover and the outcome in the remaining 355 cases was unknown. In 56 cases, drug hypersensitivity was listed as a concurrent condition. Of the 330 consumer reports (25 serious and 305 non-serious), none had a fatal outcome; 120 patients were considered recovered or recovering (including two with sequelae), 132 patients did not recover and the outcome was unknown in the remaining 87 cases. In 77 cases, drug hypersensitivity or drug intolerance was listed as a concurrent condition.

Comments: The post-marketing report for Vytorin represents a review of the safety information in a group of patients reporting AEs who received ezetimibe/simvastatin for any indication. No new safety issue or emerging information about a change in the known characteristics of the risks of ezetimibe/simvastatin was revealed. These events/conditions are adequately and accurately described in the Vytorin label.

Evaluator's conclusions on safety

Safety for proposed indication of CV prevention in patients with CHD

In the IMPROVE-IT study, involving 18,144 patients treated with either ezetimibe/simvastatin 10/40 mg (n = 9067; of whom 6% were uptitrated to ezetimibe/simvastatin 10/80 mg) or simvastatin 40 mg (n = 9077; of whom 27% were uptitrated to simvastatin 80 mg), the safety profiles were similar during a median follow-up period of 6.0 years. The overall safety profile of ezetimibe/simvastatin in IMPROVE-IT is consistent with the known safety profile as described in the product labels and no unexpected, important adverse effects were observed during the study. There were no meaningful differences between the treatment groups in clinical adverse events, including those reported as serious. There were also no meaningful differences in discontinuations due to clinical adverse experiences between the two treatment groups. All deaths were adjudicated by the CEC and classified as to whether or not they were considered attributable to CV disease. Of the 18,144 subjects in the ITT population, 2446 (13.48%) died during the course of the study: 1215 (13.40%) and 1231 (13.56%) in the

²⁷ Rhabdomyolysis was reported as the cause of death in four reports and the fifth report did not contain sufficient information for a medical assessment.

ezetimibe/simvastatin and simvastatin groups, respectively with no meaningful differences noted between the treatment groups in CV or Non-CV deaths.

More subjects in the ezetimibe/simvastatin group experienced a haemorrhagic stroke than in the simvastatin group, but the number of haemorrhagic strokes was relatively small in both treatment groups, and the HR for all strokes suggests an overall benefit for the ezetimibe/simvastatin group. This result of a benefit for overall strokes, but a smaller increase in risk for haemorrhagic strokes is consistent with the stroke data from the CTT meta-analysis of statin based lipid lowering trials.

In both the ITT analysis and on-treatment analysis, which censored events that occurred > 30 days after the last dose of study therapy, there were no clinically meaningful differences between treatment groups with respect to the incidence of pre-defined AESI. The following were the incidence rates in the ITT population: CEC determined myopathy/rhabdomyolysis (0.3% in both treatment group), CEC determined myopathy (ezetimibe/simvastatin versus simvastatin: 0.2% versus 0.1%); rhabdomyolysis (0.1% versus 0.2%), defined elevations in CK above pre-specified limits (0.7% in both treatment groups; elevated CK with symptoms (0.3% in both treatment groups), defined elevations in AST and/or ALT (2.5% versus 2.3%), gallbladder-related AEs (3.1% versus 3.5%) and cholecystectomy (1.5% in both treatment groups).

Over the course of the IMPROVE-IT trial, there were 1607 (17.7%) subjects who experienced myalgia (muscle pain, tenderness or weakness without myopathy) in the ezetimibe/simvastatin group compared with 1564 (17.2%) subjects in the simvastatin group. The rate of AEs with the preferred term of myalgia was also similar between the treatment groups (10.68% in the ezetimibe/simvastatin group and 10.08% in the simvastatin group). Additionally, AEs with the preferred term of myalgia led to discontinuation in 209 (2.31%) subjects in the ezetimibe/simvastatin group and 201 (2.21%) subjects in the simvastatin monotherapy group. The sponsors suggest that the similar incidence of myalgia in the ezetimibe/simvastatin and simvastatin monotherapy groups indicate no contribution from ezetimibe towards this common AE associated with statin therapy. However, it is important to note that there were more patients on the higher dose of simvastatin (80 mg) in the monotherapy group which may also imply that although more patients in the combination treatment group were on the lower dose of simvastatin (40 mg), the incidence of myalgia was similar in the two treatment groups suggesting a potential contributory role of ezetimibe. Exposure adjusted rate of unexplained myalgia was not provided in the CSR.

With regard to hepatic safety analyses, there were no clinically meaningful differences between treatment groups, and no data suggestive of previously unknown significant hepatic toxicity related to treatment assignment. The incidence of death due to hepatic causes was relatively low and several of these occurred well after study drug had been discontinued. No pattern for hepatic death or potential DILI cases suggesting a clinically relevant difference between treatment groups was evident. The rate of subjects with consecutive ALT and/or AST values $\geq 3xULN$ was similar between the treatment groups. The rate of gallbladder AEs was generally similar between the treatment groups.

Following the prior SEAS trial, in which an imbalance was observed in the incidence of cancer and cancer-related mortality between the ezetimibe/simvastatin and the placebo treatment groups, closer monitoring and adjudication of all potential malignancies (cancers) and neoplasms was implemented. The resulting incidences of adjudicated new cancers or death due to cancer did not differ between the ezetimibe/simvastatin and simvastatin treatment groups.

Safety analyses were also conducted for AEs of interest not specified in the protocol that were noted to be risks potentially associated with ezetimibe or the statins during the course of the trial. There were no clinically meaningful differences between treatment

groups with regard to the number of subjects classified with new onset diabetes [ezetimibe/simvastatin versus simvastatin 650 (7.2%) versus 659 (7.3%)]. In addition, no clinically meaningful differences between treatment groups were noted in pancreatitis AEs [57 (0.63%) versus 58 (0.64%)], acute renal failure [259 (2.86%) versus 235 (2.59%)], interstitial lung disease related AEs [34 (0.37%) versus 40 (0.44%)] or hypersensitivity reaction related AEs [735 (8.11%) versus 748 (8.24%)]. The safety analyses show no evidence of an imbalance in the incidence of these additional adverse events of special interest. Overall, rates of diabetes and acute renal failure were generally consistent with those seen in the literature on statins.

In order to assess changes in renal function over time in subjects enrolled in the IMPROVE-IT trial, summary statistics for change from baseline in creatinine clearance (ml/min) were calculated using the Cockcroft-Gault Equation and no clinically meaningful changes were noted over the course of the study in either treatment group at any point in time. Additional analyses of creatinine clearance over time were also performed by categories of LDL-C level at the time of qualifying event (<70 mg/dL [<1.81 mmol/L], 70 to 100 mg/dL [1.81 to 2.59 mmol/L], >100 mg/dL [>2.59 mmol/L]) with the higher LDL-C groups exhibiting slightly greater creatinine clearance at baseline. However, there was a considerable amount of variability around the point estimates. The changes in creatinine clearance between the two treatment groups were similar within the three LDL-C categories over the course of the study. Overall, no clinically meaningful changes in renal function were noted in any of the baseline LDL-C categories examined, or between the treatment groups in IMPROVE-IT.

The post-marketing report for Ezetrol and Vytorin represents a review of the safety information in a group of patients reporting AEs who received ezetimibe/simvastatin for any indication over the 10-12 years of marketing since initial registration. No new safety issue or emerging information about a change in the known characteristics of the risks of ezetimibe/simvastatin was revealed. These events/conditions are adequately and accurately described in the Ezetrol and Vytorin labels.

The overall safety and tolerability of ezetimibe/simvastatin in IMPROVE-IT revealed no new safety findings and was consistent with current ezetimibe/simvastatin product labelling.

First round benefit-risk assessment

Ezetrol

- ***For indication: "Prevention of Cardiovascular Disease: Ezetrol, administered with a statin, is indicated to reduce the risk of cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalisation for unstable angina or need for revascularisation) in patients with coronary heart disease (CHD)."***

First round assessment of benefits

The benefits of Ezetrol (when used with any statin) in the proposed usage for CV prevention in patients with CHD are:

- Ezetimibe is an azetidinone inhibitor which selectively inhibits the intestinal absorption of cholesterol and related phytosterols via an interaction with NPC1L1. Ezetimibe therapy offers a unique and complementary mechanism of action which yields incremental LDL-C reductions when combined with statins.

- The database supporting this indication is considerable with a study population of 18,144 subjects with CHD presenting with ACS and median clinical follow-up of 71.4 months (mean = 64.7 months) in the pivotal IMPROVE IT study.
- Treatment with ezetimibe/simvastatin resulted in a 6.4% RRR in the primary composite efficacy endpoint (CV death, non-fatal MI, documented UA requiring hospitalisation, all coronary revascularisation and non-fatal stroke) compared to treatment with simvastatin monotherapy (Hazard Ratio [HR] 0.936; 95% CI 0.887-0.988; p = 0.016).
- The effect of ezetimibe/simvastatin relative to simvastatin monotherapy on the primary composite endpoint was generally consistent across the subgroups, including sex, age, race, medical history of diabetes mellitus, baseline lipid levels, prior statin therapy, prior stroke, hypertension and region (US/non-US). The HRs of the subgroups was almost all less than one, and the confidence intervals were broadly overlapping.
- Given that the benefits of CV event reduction following additional LDL-C lowering with ezetimibe occurred predominantly after 1 year strongly suggests that its benefits are not associated with events immediately surrounding the acute ACS event. Furthermore, an analysis of total events (first and recurrent events) demonstrated that subjects in the ezetimibe/simvastatin group had a reduced hazard for total events for the primary and secondary composite endpoints compared to subjects in the simvastatin group. Although this analysis has limitations due to the inherent bias that may be introduced with a non-randomised comparison, the results support the durability of the treatment benefit of ezetimibe/simvastatin beyond the prevention of the first event, which is an important clinical benefit for high-risk subjects.
- The overall safety and tolerability of ezetimibe/simvastatin in IMPROVE-IT revealed no new safety findings related to study therapy and was consistent with current ezetimibe/simvastatin product labelling.

First round assessment of risks

The risks of Ezetrol (when used with any statin) in the proposed usage for CV prevention in patients with CHD are:

- The absolute risk reduction (ARR) and Number Need to Treat (NNT) to get the modest 6.4% RRR in CV events was not provided in the submission.
- The RRR in the primary composite endpoint appears to be mainly driven by reduction in non-fatal MI and non-fatal stroke (mainly non-haemorrhagic stroke). There was no reduction in risk of CV death, hospitalisation for UA or need for revascularisation although these are included in the proposed indication.
- The proposed indication mentions ‘need for revascularisations’ which implies coronary and non-coronary revascularisation. This is not justified as the primary composite endpoint in the pivotal IMPROVE IT study specifically includes ‘all coronary revascularisation with either PCI or CABG occurring at least 30 days after randomisation’.
- Although it is expected that the additional LDL-C lowering with ezetimibe with any statin would further reduce the risk of CV disease, the incremental CV benefits of ezetimibe on top of other newer statins has not been directly assessed.
- The incidence of myalgia (muscle pain, tenderness or weakness without myopathy) was 17.7% and 17.2% in ezetimibe/simvastatin and simvastatin groups, respectively with myalgia leading to discontinuation in 2.31% and 2.21% of patients, respectively. The sponsors suggest that the similar incidence of myalgia in the ezetimibe/simvastatin and simvastatin monotherapy groups indicate no contribution from ezetimibe towards this common AE associated with statin therapy. However, it is

important to note that there were more patients on the higher dose of simvastatin (80 mg) in the monotherapy group which may also imply that although more patients in the combination treatment group were on the lower dose of simvastatin (40 mg), the incidence of myalgia was similar in the two treatment groups suggesting a potential contributory role of ezetimibe. Exposure-adjusted rate of unexplained myalgia was not provided in the CSR.

- Increased risk of haemorrhagic stroke.
- Risk of rhabdomyolysis/ myopathy, malignancies; gallbladder disorders, pancreatitis and interstitial lung disease, acute renal failure and hypersensitivity.

First round assessment of benefit-risk balance

The proposed indication is as follows: “Prevention of Cardiovascular Disease: Ezetrol, **administered with a statin**, is indicated to reduce the risk of cardiovascular events (**cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalisation for unstable angina or need for revascularisation**) in patients with coronary heart disease (CHD).”

Ezetimibe is an azetidinone inhibitor which selectively inhibits the intestinal absorption of cholesterol and related phytosterols via an interaction with NPC1L1 and it offers a unique and complementary mechanism of action which yields incremental LDL-C reductions when combined with statins. An extensive preclinical and clinical program has been conducted with ezetimibe alone and in combination with statins. When ezetimibe 10 mg/d is added to ongoing statin therapy, an average reduction in LDL-C of up to 25% relative to the on-statin baseline has been observed in pooled analyses of clinical trials.²⁸ The magnitude of the observed reductions with ezetimibe on top of statins is generally independent of statin type, potency and dose, and patient characteristics.²⁹ Furthermore, ezetimibe is approved for lipid lowering with all statins. All approved statins also have a similar safety profile, and the safety profile of ezetimibe is similar when administered with all statins.

After a heart attack, treatment with a statin is first line, evidence based management. Some of the largest studies ever conducted in medicine have demonstrated that statins decrease further heart attacks and save lives. The Heart Foundation recommends that all individuals who have had a heart attack or who have a diagnosis of CHD receive lipid lowering therapy, namely statins. This recommendation is strongly supported by other main health organisations. Since 1994, large, multicentre trials including more than 170,000 people have shown that people taking statins to lower their LDL-C have fewer major coronary events (non-fatal heart attack or death from CHD):

- Major coronary events are reduced by a quarter (24%)
- 1 in 5 coronary deaths are prevented (that is, 20% reduction)
- Death from any-cause is reduced by 10%

²⁸ Morrone D, et al. Lipid-altering efficacy of ezetimibe plus statin and statin monotherapy and identification of factors associated with treatment response: A pooled analysis of over 21,000 subjects from 27 clinical trials. *Atherosclerosis* 223: 251-261 (2012).

²⁹ Davidson MH, et al; Ezetimibe co-administered with simvastatin in patients with primary hypercholesterolemia. *J Am Coll Cardiol.* 40: 2125-2134 (2002); Kerzner B, et al. Efficacy and safety of ezetimibe co-administered with lovastatin in primary hypercholesterolemia. *Am J Cardiol.* 91: 418-424 (2003); Melani L, et al. Efficacy and safety of ezetimibe coadministered with pravastatin in primary hypercholesterolemia: a prospective randomised, double-blind trial. *Eur Heart J.* 24: 717-728 (2003); Ballantyne CM, et al: Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective randomised, double-blind trial. *Circulation* 107: 2409-2415 (2003).

- Coronary artery surgery and coronary angioplasty is reduced by a quarter (25%) and nearly a third (28%), respectively.³⁰

The benefits can be seen with every 1.0 mmol/L reduction in LDL cholesterol. The most recent Cholesterol Treatment Trialists' Collaboration (CTT) meta-analysis of 26 trials involving approximately 170,000 people confirmed this benefit seen with every 1.0 mmol/L reduction in LDL cholesterol.³¹ A meta-analysis involving 13 individual trials and in excess of 91,000 patients showed that treating 255 patients with a statin for 4 years led to the prevention of 5.4 CV events and one extra case of diabetes.³²

At the time IMPROVE-IT was initiated, the benefit of statin-mediated lipid lowering was well established, but the impact of incremental LDL-C reductions through the addition of lipid lowering therapies to background statin therapy on CV patient outcomes had not been demonstrated. While IMPROVE-IT was underway, other large-scale evaluations (ACCORD, FIELD, AIM-HIGH, Dalcetrapib Outcomes, and HPS2-THRIVE) of incremental clinical benefit of additional lipid lowering therapy on top of statins had negative primary endpoint results.³³ The drugs included in these studies (fibrates, niacin and a CETP inhibitor) were not primarily LDL-C lowering drugs and had other unique properties that may have contributed to their failure. Some in the scientific community also theorised that these add-on therapies had not shown benefit as the subjects' lipids in these trials were already well controlled with statin therapy.³⁴ In any event, this raised questions if add-on therapy to statins could be beneficial and even questions relating to the LDL-C hypothesis itself.

The question to be answered is whether the additional reduction in LDL-C following treatment with ezetimibe in combination with a statin translates into a clinically relevant benefit in terms of prevention of CV events. IMPROVE-IT was the first study to actually evaluate this and the database supporting this indication was considerable with a study population of 18,144 subjects with CHD presenting with ACS and median clinical follow-up of 71.4 months (mean = 64.7 months). Over the course of the study, the ezetimibe/simvastatin treatment group achieved an additional mean reduction in LDL-C of 14.2 mg/dL (0.367mmol/L) or 15.9% (95% CI: 16.7 to 15.2, p<0.001) relative to the simvastatin treatment group. The primary composite endpoint showed a modest 6.4% RRR with ezetimibe/simvastatin compared to treatment with simvastatin monotherapy (HR 0.936; 95% CI: 0.887 - 0.988; p = 0.016). The ARR and NNT was not provided in the CSR for IMPROVE-IT limiting interpretation of the true clinical relevance of the modest 6.4% RRR following additional ezetimibe therapy in patients with CHD. The ARR and NNT is very important since RRR does not take the baseline level of risk of the subjects into consideration. This is especially important as the sample size was changed from an original size of 10,000 subjects to up to 18,000 subjects because the primary endpoint

³⁰ Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet* 376: 1670-1681 (2010).

³¹ Cholesterol Treatment Trialists' (CTT) Collaboration. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 380: 581-590 (2012).

³² Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet* 376: 1670-1681 (2010).

³³ The ACCORD study group. Effects of combination lipid therapy in Type 2 Diabetes Mellitus. *NEJM* 362: 1563-1574 (2010); LaRosa JC, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *NEJM* 352: 1425-1435 (2005); Guyton JR, et al. Relationship of lipoproteins to cardiovascular events: the AIM-HIGH Trial (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes). *J Am Coll Cardiol*. 62: 1580-1584 (2013); Schwartz GC, et al. Effects of Dalcetrapib in patients with recent Acute Coronary Syndrome. *NEJM* 367: 2089-2099 (2012); HPS2-THRIVE Collaboration group. Effects of extended-release Niacin with Laropiprant in High-risk patients. *NEJM* 371: 203-212 (2014).

³⁴ Tariq SM, et al. HDL Hypothesis: Where do we stand now? *Curr Atheroscler Rep*. 16: 398 (2014).

event rate was lower than anticipated in the original design. When only the RRR is used to describe an effect of treatment, it concentrates only on the people who will die or experience the serious CV event and ignores all of the people who will be unaffected. Therefore, using a description for the treatment that ignores the much larger chance that they will be in the group that survives regardless of the treatment (while still being subjected to the potential harms and side effects of the treatment) is very misleading. This needs to be provided in order to determine the true clinical benefit of adding ezetimibe to a statin for prevention of CV events in patients with CHD.

Overall, analysis of the individual CV event categories did not show any benefit in rates of death from any cause, CV death, CHD, fatal MI, fatal stroke, UA requiring hospitalisation or all coronary revascularisation with PCI or CABG (> 30 days after randomisation). Clear benefit of simvastatin/ezetimibe treatment over simvastatin monotherapy was only observed for non-fatal MI, non-fatal (non-haemorrhagic) stroke. The risk of haemorrhagic stroke appears to increase with simvastatin/ezetimibe treatment.

In 2011, FDA implemented changes to simvastatin labelling based on findings from large clinical trials and other databases that suggested risk of serious muscle toxicity with simvastatin 80 mg is greater than that seen with certain newer statins that produce similar or greater LDL-C lowering. Due to this FDA communication, there was a protocol amendment which limited the number of patients receiving 80 mg simvastatin in the IMPROVE-IT study. The sponsors suggest that the similar incidence of myalgia (muscle pain, tenderness and weakness without myopathy) in the ezetimibe/simvastatin and simvastatin monotherapy groups indicate no contribution from ezetimibe towards this common AE associated with statin therapy. However, there were more patients on the higher dose of simvastatin (80 mg) in the monotherapy group which may also imply that although more patients in the ezetimibe/simvastatin combination treatment group were on the lower dose of simvastatin (40 mg), the incidence of myalgia was similar in the two treatment groups suggesting a potential contributory role of ezetimibe.

The proposed indication mentions 'need for revascularisations' which implies coronary and non-coronary revascularisation. This is not justified as the primary composite endpoint in the pivotal IMPROVE IT study specifically includes 'all coronary revascularisation with either PCI or CABG occurring at least 30 days after randomisation'

The proposed indication states that ezetimibe 10mg could be used with 'any statin' but the only data available is from the IMPROVE-IT study which used only simvastatin and there is no evidence to support administration of ezetimibe 10mg with simvastatin doses >40mg.

While it is accepted that the CV prevention benefits of ezetimibe with a statin are related to its LDL-C lowering capacity, this has not been directly assessed for any of the newer statins.

Furthermore, it is important to stress that for incremental CV event reduction in patients with CHD, ezetimibe 10 mg may only be administered with a statin with proven CV benefit (statins which have already received approval for indication of CV prevention in patients with CHD).

While it is accepted that the CV prevention benefits of ezetimibe with a statin are related to its LDL-C lowering capacity, the evidence from the IMPROVE-IT study is that the incremental LDL-C reduction observed by adding ezetimibe 10 mg to simvastatin 40 mg only translated into a modest 6.4% RRR in CV events.

Overall, the benefit risk balance of Ezetrol (used with any statin) for the proposed usage is unfavourable.

Vytorin

- ***For indication: “Prevention of Cardiovascular Disease: Vytorin is indicated to reduce the risk of cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalisation for unstable angina or need for revascularisation) in patients with coronary heart disease (CHD).”***

First round assessment of benefits

The benefits of Vytorin in the proposed usage for CV prevention in patients with CHD are:

- Ezetimibe is an azetidinone inhibitor which selectively inhibits the intestinal absorption of cholesterol and related phytosterols via an interaction with NPC1L1. Ezetimibe therapy offers a unique and complementary mechanism of action which yields incremental LDL-C reductions when combined with statins.
- The database supporting this indication is considerable with a study population of 18,144 subjects with CHD presenting with ACS and median clinical follow-up of 71.4 months (mean = 64.7 months) in the pivotal IMPROVE-IT study.
- Treatment with ezetimibe/simvastatin resulted in a 6.4% RRR in the primary composite efficacy endpoint (CV death, non-fatal MI, documented UA requiring hospitalisation, all coronary revascularisation and non-fatal stroke) compared to treatment with simvastatin monotherapy (HR 0.936; 95% CI: 0.887-0.988; p = 0.016).
- The effect of ezetimibe/simvastatin relative to simvastatin monotherapy on the primary composite endpoint was generally consistent across the subgroups, including sex, age, race, medical history of diabetes mellitus, baseline lipid levels, prior statin therapy, prior stroke, hypertension and region (US/non-US). The HRs of the subgroups was almost all less than one, and the confidence intervals were broadly overlapping.
- Given that the benefits of CV event reduction following additional LDL-C lowering with ezetimibe occurred predominantly after 1 year strongly suggests that its benefits are not associated with events immediately surrounding the acute ACS event. Furthermore, an analysis of total events (first and recurrent events) demonstrated that subjects in the ezetimibe/simvastatin group had a reduced hazard for total events for the primary and secondary composite endpoints compared to subjects in the simvastatin group. Although this analysis has limitations due the inherent bias that may be introduced with a non-randomised comparison, the results support the durability of the treatment benefit of ezetimibe/simvastatin beyond the prevention of the first event, which is an important clinical benefit for high-risk subjects.
- The overall safety and tolerability of ezetimibe/simvastatin in IMPROVE-IT revealed no new safety findings related to study therapy, and was consistent with current ezetimibe/simvastatin product labelling.

First round assessment of risks

The risks of Vytorin in in the proposed usage for CV prevention in patients with CHD are:

- The ARR and NNT to get the modest 6.4% RRR in CV events was not provided in the submission.
- The RRR in the primary composite endpoint appears to be mainly driven by reduction in non-fatal MI and non-fatal stroke (mainly non-haemorrhagic stroke). There was no reduction in risk of CV death, hospitalisation for UA or need for revascularisation although these are included in the proposed indication. Furthermore, the primary composite endpoint in the pivotal IMPROVE IT study specifically includes ‘all coronary revascularisation with either PCI or CABG occurring at least 30 days after randomisation’ while the proposed indication is generalised and mentions ‘need for revascularisations’.

- The incidence of myalgia (muscle pain, tenderness or weakness without myopathy) was 17.7% and 17.2% in ezetimibe/simvastatin and simvastatin groups, respectively with myalgia leading to discontinuation in 2.31% and 2.21% of patients, respectively. The sponsors suggest that the similar incidence of myalgia in the ezetimibe/simvastatin and simvastatin monotherapy groups indicate no contribution from ezetimibe towards this common AE associated with statin therapy. However, it is important to note that there were more patients on the higher dose of simvastatin (80 mg) in the monotherapy group which may also imply that although more patients in the combination treatment group were on the lower dose of simvastatin (40mg), the incidence of myalgia was similar in the two treatment groups suggesting a potential contributory role of ezetimibe. Exposure adjusted rate of unexplained myalgia was not provided in the CSR.
- Increased risk of haemorrhagic stroke.
- Risk of rhabdomyolysis/myopathy, malignancies; gallbladder disorders, pancreatitis and interstitial lung disease, acute renal failure and hypersensitivity.

First round assessment of benefit-risk balance

The proposed indication is as follows: “Prevention of Cardiovascular Disease: Ezetrol, **administered with a statin**, is indicated to reduce the risk of cardiovascular events (**cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalisation for unstable angina or need for revascularisation**) in patients with coronary heart disease (CHD).”

Ezetimibe is an azetidinone inhibitor which selectively inhibits the intestinal absorption of cholesterol and related phytosterols via an interaction with NPC1L1 and it offers a unique and complementary mechanism of action which yields incremental LDL-C reductions when combined with statins. An extensive preclinical and clinical program has been conducted with ezetimibe alone and in combination with statins. When ezetimibe 10 mg/d is added to ongoing statin therapy, an average reduction in LDL-C of up to 25% relative to the on-statin baseline has been observed in pooled analyses of clinical trials.³⁵ The magnitude of the observed reductions with ezetimibe on top of statins is generally independent of statin type, potency and dose, and patient characteristics.³⁶ Furthermore, ezetimibe is approved for lipid lowering with all statins.

At the time IMPROVE-IT was initiated, the benefit of statin-mediated lipid lowering was well established. After a heart attack, treatment with a statin is first-line, evidence-based management. Some of the largest studies ever conducted in medicine have demonstrated that statins decrease further heart attacks and save lives. The Heart Foundation recommends that all individuals who have had a heart attack or who have a diagnosis of CHD receive lipid lowering therapy, namely statins. This recommendation is strongly supported by other peak health organisations. Since 1994, large, multicentre trials including more than 170,000 people have shown that people taking statins to lower their LDL-C have fewer major coronary events (non-fatal heart attack or death from CHD):

- Major coronary events are reduced by a quarter (24%)

³⁵ Morrone D, et al. Lipid-altering efficacy of ezetimibe plus statin and statin monotherapy and identification of factors associated with treatment response: A pooled analysis of over 21,000 subjects from 27 clinical trials. *Atherosclerosis* 223: 251-261 (2012).

³⁶ Davidson MH, et al; Ezetimibe co-administered with simvastatin in patients with primary hypercholesterolemia. *J Am Coll Cardiol.* 40: 2125-2134 (2002); Kerzner B, et al. Efficacy and safety of ezetimibe co-administered with lovastatin in primary hypercholesterolemia. *Am J Cardiol.* 91: 418-424 (2003); Melani L, et al. Efficacy and safety of ezetimibe coadministered with pravastatin in primary hypercholesterolemia: a prospective randomised, double-blind trial. *Eur Heart J.* 24: 717-728 (2003); Ballantyne CM, et al: Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective randomised, double-blind trial. *Circulation* 107: 2409-2415 (2003).

- 1 in 5 coronary deaths are prevented (that is, 20% reduction)
- Death from any-cause is reduced by 10%
- Coronary artery surgery and coronary angioplasty is reduced by a quarter (25%) and nearly a third (28%), respectively.³⁷

The benefits can be seen with every 1.0 mmol/L reduction in LDL cholesterol. The most recent Cholesterol Treatment Trialists' Collaboration (CTT) meta-analysis of 26 trials involving approximately 170,000 people confirmed this benefit seen with every 1.0 mmol/L reduction in LDL cholesterol.³⁸ A meta-analysis involving 13 individual trials and in excess of 91,000 patients showed that treating 255 patients with a statin for 4 years led to the prevention of 5.4 CV events and one extra case of diabetes.³⁹

However, the impact of incremental LDL-C reductions through the addition of lipid-lowering therapies to background statin therapy on CV patient outcomes had not been demonstrated. While IMPROVE-IT was underway, other large-scale evaluations (ACCORD, FIELD, AIM-HIGH, Dalcetrapib Outcomes, and HPS2-THRIVE) of incremental clinical benefit of additional lipid lowering therapy on top of statins had negative primary endpoint results.⁴⁰ The drugs included in these studies (fibrates, niacin and a CETP inhibitor) were not primarily LDL-C lowering drugs and had other unique properties that may have contributed to their failure. Some in the scientific community also theorised that these add-on therapies had not shown benefit as the subjects' lipids in these trials were already well controlled with statin therapy.⁴¹ In any event, this raised questions if add-on therapy to statins could be beneficial and even questions relating to the LDL-C hypothesis itself.

The question to be answered is whether the additional reduction in LDL-C following treatment with ezetimibe in combination with a statin translates into a clinically relevant benefit in terms of prevention of CV events. IMPROVE-IT was the first study to actually evaluate this and the database supporting this indication was considerable with a study population of 18,144 subjects with CHD presenting with ACS and median clinical follow-up of 71.4 months (mean = 64.7 months). Over the course of the study, the ezetimibe/simvastatin treatment group achieved an additional mean reduction in LDL-C of 14.2 mg/dL (0.367 mmol/L) or 15.9% (95% CI: 16.7 to 15.2, $p < 0.001$) relative to the simvastatin treatment group. The primary composite endpoint showed a modest 6.4% RRR with ezetimibe/simvastatin compared to treatment with simvastatin monotherapy (HR 0.936; 95% CI: 0.887-0.988; $p = 0.016$). The ARR and NNT was not provided in the CSR for IMPROVE-IT limiting interpretation of the true clinical relevance of the modest 6.4% RRR following additional ezetimibe therapy in patients with CHD. The ARR and NNT is very important since RRR does not take the baseline level of risk of the subjects into

³⁷ Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet* 376: 1670-1681 (2010).

³⁸ Cholesterol Treatment Trialists' (CTT) Collaboration. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 380: 581-590 (2012).

³⁹ Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet* 376: 1670-1681 (2010).

⁴⁰ The ACCORD study group. Effects of combination lipid therapy in Type 2 Diabetes Mellitus. *NEJM* 362: 1563-1574 (2010); LaRosa JC, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *NEJM* 352: 1425-1435 (2005); Guyton JR, et al. Relationship of lipoproteins to cardiovascular events: the AIM-HIGH Trial (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes). *J Am Coll Cardiol*. 62: 1580-1584 (2013); Schwartz GC, et al. Effects of Dalcetrapib in patients with recent Acute Coronary Syndrome. *NEJM* 367: 2089-2099 (2012); HPS2-THRIVE Collaboration group. Effects of extended-release Niacin with Laropiprant in High-risk patients. *NEJM* 371: 203-212 (2014).

⁴¹ Tariq SM, et al. HDL Hypothesis: Where do we stand now? *Curr Atheroscler Rep*. 16: 398 (2014).

consideration. This is especially important as the sample size was changed from an original size of 10,000 subjects to up to 18,000 subjects because the primary endpoint event rate was lower than anticipated in the original design. When only the RRR is used to describe an effect of treatment, it concentrates only on the people who will die or experience the serious CV event and ignores all of the people who will be unaffected. Therefore using a description for the treatment that ignores the much larger chance that they will be in the group that survives regardless of the treatment (while still being subjected to the potential harms and side effects of the treatment) is very misleading. This needs to be provided in order to determine the true clinical benefit of adding ezetimibe to a statin for prevention of CV events in patients with CHD.

Overall, analysis of the individual CV event categories did not show any benefit in rates of death from any cause, CV death, CHD, fatal MI, fatal stroke, UA requiring hospitalisation or all coronary revascularisation with PCI or CABG (> 30 days after randomisation). Clear benefit of simvastatin/ezetimibe treatment over simvastatin monotherapy was only observed for non-fatal MI, non-fatal (non-haemorrhagic) stroke. The risk of haemorrhagic stroke appears to increase with simvastatin/ezetimibe treatment.

The proposed indication mentions 'need for revascularisations' which implies coronary and non-coronary revascularisation. This is not justified as the primary composite endpoint in the pivotal IMPROVE IT study specifically includes 'all coronary revascularisation with either PCI or CABG occurring at least 30 days after randomisation'.

In 2011, FDA implemented changes to simvastatin labelling based on findings from large clinical trials and other databases that suggested risk of serious muscle toxicity with simvastatin 80mg is greater than that seen with certain newer statins that produce similar or greater LDL-C lowering. Due to this FDA communication, there was a protocol amendment which limited the number of patients receiving 80 mg simvastatin in the IMPROVE-IT study. The sponsors suggest that the similar incidence of myalgia (muscle pain, tenderness and weakness without myopathy) in the ezetimibe/simvastatin and simvastatin monotherapy groups indicate no contribution from ezetimibe towards this common AE associated with statin therapy. However, there were more patients on the higher dose of simvastatin (80 mg) in the monotherapy group which may also imply that although more patients in the ezetimibe/simvastatin combination treatment group were on the lower dose of simvastatin (40 mg), the incidence of myalgia was similar in the two treatment groups suggesting a potential contributory role of ezetimibe.

While it is accepted that the CV prevention benefits of ezetimibe with a statin are related to its LDL-C lowering capacity, the evidence from the IMPROVE-IT study is that the incremental LDL-C reduction observed by adding ezetimibe 10 mg to simvastatin 40 mg only translated into a modest 6.4% RRR in CV events. There is no evidence that the benefit-risk profile would be favourable at simvastatin doses >40 mg.

Overall, the benefit risk balance of Vytorin for the proposed usage is unfavourable.

First round recommendation regarding authorisation

Ezetrol

It is recommended that submission for registration of Ezetrol for the proposed indication of "Prevention of Cardiovascular Disease: Ezetrol, administered with a statin, is indicated to reduce the risk of cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalisation for unstable angina or need for revascularisation) in patients with coronary heart disease (CHD)" be rejected at this stage. The main reasons for the rejection are:

- Lack of information on ARR and NNT to determine the true clinical relevance of the modest 6.4% RRR in CV events observed with ezetimibe/simvastatin compared to simvastatin monotherapy in patients with CHD in the IMPROVE-IT study.
- The proposed indication mentions ‘need for revascularisations’ which implies coronary and non-coronary revascularisation. This is not justified as the primary composite endpoint in the pivotal IMPROVE IT study specifically includes ‘all coronary revascularisation with either PCI or CABG occurring at least 30 days after randomisation’.

Vytorin

It is recommended that submission for registration of Vytorin for the proposed indication of “Prevention of Cardiovascular Disease: Vytorin is indicated to reduce the risk of cardiovascular events (cardiovascular death, nonfatal MI, nonfatal stroke, hospitalisation for UA, or need for revascularisation) in patients with coronary heart disease (CHD)” be rejected at this stage. The main reasons for the rejection are:

- Lack of information on ARR and NNT to determine the true clinical relevance of the modest 6.4% RRR in CV events observed with ezetimibe/simvastatin compared to simvastatin monotherapy in patients with CHD in the IMPROVE-IT study.
- The proposed indication mentions ‘need for revascularisations’ which implies coronary and non-coronary revascularisation. This is not justified as the primary composite endpoint in the pivotal IMPROVE IT study specifically includes ‘all coronary revascularisation with either PCI or CABG occurring at least 30 days after randomisation’.

Clinical questions

Pharmacokinetics

None.

Pharmacodynamics

None.

Efficacy

Question 1

In the CSR of the IMPROVE-IT study, listing of subjects with the major protocol deviations was provided but summary tables were not provided. Listing of individual subjects with majority protocol deviations was provided but summary tables were not provided. Could the sponsor please provide the summary tables to confirm if the incidence of these protocol deviations was similar in the two treatment groups?

Question 2

The CSR states that the sensitivity analysis of the primary composite endpoint censoring subjects at the time of simvastatin up-titration showed that the results were generally consistent (Table 2). This statement by the sponsors in the CSR is inaccurate since the results in the table actually show a greater number of events in the ezetimibe/simvastatin group (2461/9067, 27.14%) compared with simvastatin alone (2205/9077, 24.29%) including a higher incidence of CV death, non-fatal MI, UA requiring hospitalisation and coronary revascularisation (PCI or CABG) in the ezetimibe/simvastatin group compared

with the simvastatin monotherapy group (Table 2). The number of subjects who at some point had their dose of simvastatin increased from 40 to 80 mg per day was greater in the simvastatin group compared to the ezetimibe/simvastatin group (6.2% in the ezetimibe/simvastatin and 27.0% in the simvastatin monotherapy group) and the sponsors have stated that this would give a more conservative estimate of benefit of ezetimibe/ simvastatin and hence this sensitivity analysis was conducted censoring subjects at time of up-titration of simvastatin dose. Hence, the observation regarding a higher incidence of overall events and the individual components of the composite endpoint in the ezetimibe/ simvastatin group is of concern. Could the sponsors clarify this issue?

Table 2: IMPROVE-IT study – sensitivity analysis of primary composite endpoint: subjects censored at time of titration: CV death, MCE, or non-fatal stroke (protocol-defined ITT population).

	EZ-Simva (N=9067)				Simva (N=9077)				Treatment Comparison	
	n	(%) ²	Annual % ³	KM% (95% CI) ⁴	n	(%) ²	Annual % ³	KM% (95% CI) ⁴	HR (95% CI) ⁵	p-Value ⁵
Primary Composite Endpoint	2461	(27.14)	6.43	32.35 (31.23, 33.50)	2205	(24.29)	7.22	33.78 (32.50, 35.09)	0.949 (0.896, 1.006)	0.077
Cardiovascular death	323	(3.58)			260	(2.86)				
Non-fatal MI	746	(8.23)			721	(7.94)				
Documented UA requiring hospitalization	111	(1.22)			90	(0.99)				
All coronary revascularization with PCI or CABG ≥ 30 days	1108	(12.22)			949	(10.45)				
Non-fatal stroke	171	(1.89)			185	(2.04)				

If a subject has multiple events only the first event contributing to the composite endpoint is counted in the component row of the table.
¹ Major Coronary Event = Non-fatal MI, documented UA requiring hospitalization, or coronary revascularization with PCI or CABG ≥ 30 days after randomization.
² Crude number of events (n) and percentage (%).
³ Annual% = total events / time at risk in years.
⁴ Kaplan-Meier estimate and confidence interval at 7 years.
⁵ Hazard ratio (EZ/Simva vs. Simva), confidence interval, and p-Value from Cox proportional hazard model with covariates of the stratification factors (EARLY ACS trial chronic prescription lipid-lowering experience, and high-risk ACS diagnosis) and treatment.
N = Number of subjects in protocol-defined ITT population.

Question 3

The ARR and NNT following combination treatment with ezetimibe/simvastatin compared to simvastatin monotherapy was not provided in the IMPROVE-IT study report. This is important to determine the actual clinical benefit following the modest 6.4% RRR in the primary composite endpoint and the sponsors are requested to provide this information.

Question 4

The proposed indication mentions 'need for revascularisations' which implies coronary and non-coronary revascularisation. This is not justified as the primary composite endpoint in the pivotal IMPROVE IT study specifically includes 'all coronary revascularisation with either PCI or CABG occurring at least 30 days after randomisation'. Can the sponsors please provide justification for using the generalised term 'need for revascularisations' in the proposed indication?

Question 5

Could the endpoints in the pivotal IMPROVE-IT be considered competing events? Is the Cox PH model the best way of analysing data with co-dependent variables?

Safety

Question 6

The sponsors suggest that the similar incidence of myalgia in the ezetimibe/simvastatin and simvastatin monotherapy groups in the IMPROVE-IT study indicate no contribution from ezetimibe towards this common AE associated with statin therapy. However, it is important to note that there were more patients on the higher dose of simvastatin (80 mg) in the monotherapy group which may also imply that although more patients in the combination treatment group were on the lower dose of simvastatin (40 mg), the

incidence of myalgia was similar in the two treatment groups suggesting a potential contributory role of ezetimibe. Due to the imbalance in use of simvastatin 80 mg in the two treatment groups, an exposure-adjusted rate of unexplained myalgia would have helped in interpretation of role of ezetimibe in myalgia. However, this was not provided in the CSR. Could the sponsor conduct an exposure-adjusted analysis of myalgia and provide the results for evaluation?

Second round evaluation

Details of sponsor's responses to clinical questions and evaluator's subsequent comments are contained in Attachment 3.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of responses to clinical questions and other information submitted by the sponsors, the benefits of Ezetrol/Vytorin in proposed use for prevention of CV disease remain unchanged from those identified in the first round.

Second round assessment of risks

After consideration of responses to clinical questions and other information submitted by the sponsors, the risks of Ezetrol/Vytorin in proposed uses are as follows.

The risks of Ezetrol in the proposed usage for CV prevention in patients with CHD are:

- The modest 6.4% RRR in the primary composite endpoint appears to be mainly driven by reduction in non-fatal MI and non-fatal stroke (mainly non-haemorrhagic stroke). There was no reduction in risk of non-CV and CV deaths, hospitalisation for UA and need for revascularisation although these are included in the proposed indication.
- Patients in the ezetimibe/simvastatin group were at higher risk of experiencing fatal stroke (HR: ezetimibe/simvastatin: simvastatin = 1.217) and haemorrhagic stroke (HR = 1.377); the NNH (Number needed to harm) was not provided.
- Although it is expected that the additional LDL-C lowering with ezetimibe with any statin would further reduce the risk of CV disease, the incremental CV benefits of ezetimibe on top of other newer statins has not been directly assessed.
- Risk of rhabdomyolysis/myopathy, malignancies; gallbladder disorders, pancreatitis and interstitial lung disease, acute renal failure and hypersensitivity.

The risks of Vytorin in the proposed usage for CV prevention in patients with CHD are:

- The modest 6.4% RRR in the primary composite endpoint appears to be mainly driven by reduction in non-fatal MI and non-fatal stroke (mainly non-haemorrhagic stroke). There was no reduction in risk of non-CV and CV deaths, hospitalisation for UA and need for revascularisation although these are included in the proposed indication.
- Patients in the ezetimibe/simvastatin group were at higher risk of experiencing fatal stroke (HR: ezetimibe/simvastatin: simvastatin = 1.217) and haemorrhagic stroke (HR = 1.377); the NNH (number needed to harm) was not provided
- Risk of rhabdomyolysis/myopathy, malignancies; gallbladder disorders, pancreatitis and interstitial lung disease, acute renal failure and hypersensitivity.

Second round assessment of benefit-risk balance

After consideration of responses to clinical questions and other information submitted by the sponsors, the benefit-risk profile of Ezetrol (with a statin) and Vytorin remain unfavourable for the proposed indication of 'Prevention of cardiovascular disease to reduce the risk of cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalisation for unstable angina, or need for **coronary** revascularisation), in patients with coronary heart disease (CHD).'

Second round recommendation regarding authorisation

Ezetrol

In response to the first round clinical evaluation report, the sponsor has modified the proposed indication to the following:

Adults (>18 years)

*Prevention of Cardiovascular Disease: Ezetrol, administered with a statin **with proven cardiovascular benefit**, is indicated to reduce the risk of cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, or need for **coronary** revascularisation), in patients with coronary heart disease (CHD).*

After review of the Section 31 response, it is still recommended that submission for registration of Ezetrol for the indication of prevention of major CV events in patients with CHD be rejected. The main reason for the rejection is:

- The additional reduction in LDL-C achieved due to ezetimibe add-on treatment was translated into a modest 6.4% RRR in composite primary endpoint with ezetimibe/simvastatin compared to simvastatin alone. The proposed indication states that Ezetrol with a statin reduces the risk of CV events (CV death, nonfatal MI, nonfatal stroke, hospitalisation for UA, or need for coronary revascularisation), in patients with CHD. However, clear benefits were only observed in terms of reduced risk of nonfatal MI and nonfatal stroke. There was no clear reduction in CV death, hospitalisation due to UA and need for coronary revascularisation (incidence in the ezetimibe/simvastatin was similar to or slightly higher than that in the simvastatin group) and there appears to be an increased risk of haemorrhagic stroke and fatal stroke.

Although a stand-alone indication for CV prevention is not acceptable, it is acknowledged that the IMPROVE-IT trial has provided vast clinical data in over 18,000 patients evaluating CV prevention role of ezetimibe when used in combination with simvastatin. Hence, the information regarding results of the IMPROVE-IT trial could still be retained (with appropriate caveats regarding effects on CV death, hospitalisation due to UA and need for coronary revascularisation and increased risk of fatal/haemorrhagic stroke) in the 'Clinical trials' section of the proposed PI for Ezetrol as discussed.

Vytorin

In response to the first round clinical evaluation report, the sponsor has modified the proposed indication to the following:

Adults (>18 years)

Prevention of Cardiovascular Disease: Vytorin is indicated to reduce the risk of cardiovascular events (cardiovascular death, nonfatal myocardial infarction,

nonfatal stroke, hospitalization for unstable angina, or need for coronary revascularisation), in patients with coronary heart disease (CHD).

After review of the Section 31 response, it is still recommended that submission for registration of Vytorin for the above indication be rejected. The main reason for the rejection is:

- The additional reduction in LDL-C achieved due to ezetimibe add-on treatment was translated into a modest 6.4% RRR in composite primary endpoint with ezetimibe/simvastatin compared to simvastatin alone. The proposed indication states that Vytorin reduces the risk of CV events (CV death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for UA, or need for coronary revascularisation), in patients with CHD. However, clear benefits were only observed in terms of reduced risk of nonfatal MI and non-fatal stroke. There was no clear reduction in CV death, hospitalisation due to UA and need for coronary revascularisation (incidence in the ezetimibe/simvastatin was similar to or slightly higher than that in the simvastatin group) and there appears to be an increased risk of haemorrhagic stroke and fatal stroke.

Although a stand-alone indication for CV prevention is not acceptable, it is acknowledged that the IMPROVE-IT trial has provided vast clinical data in over 18,000 patients evaluating CV prevention role of ezetimibe when used in combination with simvastatin. Hence, the information regarding results of the IMPROVE-IT trial could still be retained (with appropriate caveats regarding effects on CV death, hospitalisation due to UA and need for coronary revascularisation and increased risk of fatal/haemorrhagic stroke) in the 'Clinical trials' section of the proposed PI for Ezetrol as discussed.

V. Pharmacovigilance findings

The sponsor submitted EU-RMP Version 3.0 (dated 24 March 2015, DLP 23 January 2015) with Australian Specific Annex (ASA) Version 2.1 (dated 6 July 2015), which was reviewed by the RMP evaluator.

Ezetrol: risk management plan

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 3.

Table 3: Ongoing safety concerns.

Important identified risks	Rhabdomyolysis/Myopathy
	Abnormal liver function
	Hypersensitivity
Important potential risks	Cholecystitis/Cholelithiasis
	Pancreatitis
Missing information	Exposure during pregnancy and lactation
	Limited clinical trial experience in children 10-17 years old beyond 1 year and in children 6-10 years old beyond 12 weeks. No clinical trial experience in children less than 6 years of age.

RMP reviewer comment

Notwithstanding to the evaluation of the nonclinical and clinical aspects of the Safety Specification, the summary of safety concerns is considered acceptable in the context of this application.

However, it is noted that previous versions of the RMP included drug interactions as an important identified risk. This included interactions with:

- Warfarin, another coumarin anticoagulant, or fluindione
- Cyclosporine

The sponsor should provide justification to clarify their removal from the summary.

Pharmacovigilance plan

In the EU-RMP, the sponsor proposes routine pharmacovigilance for the identified/potential risks and missing information presented in the Summary of Safety Concerns (see above).

Table 4: Ongoing safety concerns.

Safety concern	Planned action(s)
Important identified risks	
Rhabdomyolysis/Myopathy	Routine pharmacovigilance Enhanced pharmacovigilance in children
Abnormal Liver Function	Routine pharmacovigilance Enhanced pharmacovigilance in children
Hypersensitivity	Routine pharmacovigilance
Important potential risks	
Cholecystitis/Cholelithiasis	Routine pharmacovigilance
Pancreatitis	Routine pharmacovigilance
Missing information	
Exposure during pregnancy and lactation	Routine pharmacovigilance
Limited clinical trial experience in children 10-17 years old beyond 1 year and in children 6-10 years old beyond 12 weeks. No clinical trial experience in children less than 6 years of age.	Routine pharmacovigilance Enhanced pharmacovigilance in children

The sponsor notes the following justifications for no additional pharmacovigilance for the missing information items:

- Routine pharmacovigilance for exposure during pregnancy and lactation has been performed for over 10 years since first marketing approval of ezetimibe, and these pharmacovigilance activities will continue.
- Pharmacovigilance of paediatric adverse event reports has been performed since first marketing approval of ezetimibe was obtained. This pharmacovigilance activity of the paediatric age group (≤ 18 years) will continue.

There are no additional pharmacovigilance activities proposed for Australia (ASA Version 2.1, 6 July 2015).

RMP reviewer comment

There is no definite objection to the pharmacovigilance plan proposed by the sponsor in the context of this application. It is noted that the sponsor has proposed 'enhanced pharmacovigilance in children' for the safety concerns of rhabdomyolysis/myopathy, abnormal liver function, and missing paediatric information. The sponsor should provide further details on the proposed 'enhanced' activities.

Risk minimisation activities

The sponsor proposes routine risk minimisation activities (that is, PI labelling) for all identified/potential safety concerns and missing information.

The proposed risk minimisation activities are discussed further.

RMP reviewer comment

The sponsor's conclusions with regards to proposed risk minimisation activities are considered acceptable in the context of this submission.

Reconciliation of issues outlined in the RMP report

The following section summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the TGA RMP reviewer, and the RMP reviewer's evaluation of the sponsor's responses.

Recommendation #1 in RMP evaluation report

Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated Section 31 request and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.

Sponsor response

The Scientific Evaluation Branch at TGA has advised that they have reviewed the nonclinical specifications section of the RMP and believe that they are an adequate summary of the nonclinical findings and their potential clinical relevance.

The clinical evaluator has concluded that the safety specification in the draft risk management plan (RMP version 3.0) is satisfactory. There are no additional considerations to be addressed from the clinical evaluation report.

The ASA to the RMP will be revised following finalisation of the PI.

Evaluator's comment

The sponsor's response is noted.

However, the first comment regarding the nonclinical evaluation is inaccurate as a nonclinical evaluation report was not performed for this submission.

The updated version of the ASA will need to be provided to TGA in order to advise the RMP condition(s) of registration.⁴²

Recommendation #2 in RMP evaluation report

Specific drug interactions were included as important identified risks in the Summary of Safety Concerns of previous RMPs (drug interactions included that with warfarin, flumidione, cyclosporin). The sponsor should provide justification for their removal from the current Summary of Safety Concerns.

Sponsor response

The MAH confirms that previous versions of the RMP have included these risks in varying sections. The RMP has been updated to include the following two drug interactions as important identified risks:

- Interaction with warfarin, another coumarin anticoagulant or flumidione
- Interaction with ciclosporin

⁴² The sponsor later clarified that their earlier response was a verbatim reproduction of communication received from TGA when clarification of the RMP recommendation for nonclinical evaluation was sought.

Evaluator's comment

An updated RMP reflective of these changes was not submitted as part of the Section 31 response.

The updated version of the RMP will need to be provided to TGA in order to advise the RMP condition(s) of registration.

Recommendation #3 in RMP evaluation report

The sponsor has proposed 'enhanced pharmacovigilance in children' for the safety concerns of rhabdomyolysis/myopathy, abnormal liver function, and missing paediatric information. The sponsor should provide further details on the proposed 'enhanced' activities.

Sponsor response

For the important identified risk of rhabdomyolysis/myopathy, enhanced pharmacovigilance in children consists of the following activities:

- Events of rhabdomyolysis/myopathy and related muscle events will be reviewed and evaluated in all children (under 18 years of age).
- Post-marketing reports of these muscle events in children will be comprehensively detailed in the Periodic Safety Update Reports.

For the important identified risk of abnormal liver function, enhanced pharmacovigilance in children consists of the following activities:

- Events of abnormal liver function and related hepatic events will be reviewed and evaluated in all children (under 18 year of age).
- Post-marketing reports of these hepatic events in children will be comprehensively detailed in the Periodic Safety Update Reports.

For the missing paediatric information, enhanced pharmacovigilance in children consists of the following activities:

- Monitoring and evaluating safety and effectiveness of ezetimibe in all children less than 18 years of age.
- Post-marketing reports of therapy with ezetimibe given to children will be detailed in the Periodic Safety Update Reports including adverse drug reactions related to growth and maturation (Tanner stages) and rare, unexpected events (for example, cancer-related adverse drug reactions).
- A review of published literature reports where the subject of the article includes ezetimibe-treated patients less than 18 years of age will be done.

Evaluator's comment

The sponsor's response is noted and is acceptable from a RMP perspective.

These details should be provided in the updated versions of the RMP and ASA.

Summary of recommendations

It is considered that the sponsor's response to the TGA S31 Request has not adequately addressed all of the issues identified in the RMP evaluation report. There are outstanding issues (see below).

Outstanding issues*Issues in relation to the RMP*

The sponsor has proposed changes to the Safety Specification of the RMP and details of the ASA.

These revised documents are required to propose the RMP conditions of registration (that is, referral to version control identifiers).

Comments on the safety specification of the RMP*Clinical evaluation report*

The clinical evaluator concluded that “The Safety Specification in the draft RMP (version 3.0) is satisfactory. The safety specifications identified by the sponsors in the RMP are consistent with the adverse event/safety profile from the clinical trial data.”

Nonclinical evaluation report

There was no nonclinical evaluation undertaken for this application.

Key changes to the updated RMP

There was no updated RMP submitted with the Section 31 response.

Suggested wording for conditions of registration*RMP*

Wording for the RMP conditions of registration cannot be provided at this time as the sponsor has proposed updates to the RMP and ASA.

The EU RMP (Version 3.0, dated 24 March 2015, DLP 23 January 2015), with ASA (Version 2.1, dated 6 July 2015) is to be revised to the satisfaction of the TGA (see outstanding issues above).

Vytorin: risk management plan**Safety specification**

The sponsor provided a summary of ongoing safety concerns which are shown at Table 5.

Table 5: Ongoing safety concerns.

Important identified risks	Rhabdomyolysis/Myopathy
	Abnormal liver function
	Hypersensitivity
Important potential risks	Pancreatitis
	Cholecystitis/Cholelithiasis
	Interstitial lung disease
	Simvastatin hypersensitivity syndrome
	New onset diabetes/impaired glucose metabolism
Missing information	Haemorrhagic stroke
	Exposure during pregnancy and lactation
	Use in children (Limited clinical trial experience in children 10-17 years of age. No clinical trial experience in children less than 10 years of age).

RMP reviewer comment

Notwithstanding to the evaluation of the non-clinical and clinical aspects of the Safety Specification, the summary of safety concerns is considered acceptable in the context of

this application. The following advice, specific to the simvastatin component, is noted in the PI, but no revisions to the summary are considered necessary:

- There is advice in the PI relating to neurological effects reported with simvastatin. This includes cases of peripheral neuropathy and paraesthesia.
- The PI includes the following advice for simvastatin (statins in general):
 - There have been very rare reports of immune-mediated necrotising myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment: muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents (see PRECAUTIONS, Myopathy/Rhabdomyolysis)...

However, it is noted that previous versions of the RMP included drug interactions as an important identified risk. This included interactions with:

- Warfarin; another coumarin anticoagulant, or fluindione
- Cyclosporine
- Potent CYP3A4 Inhibitors, including itraconazole; telithromycin; ketoconazole, erythromycin, HIV protease inhibitors and nefazodone
- Fusidic acid
- Grapefruit juice
- Diltiazem, verapamil, and amlodipine
- Fibrates
- Niacin (≥ 1 g/day)
- Danazol
- Amiodarone

'Increased Hb1Ac and FSG' was also considered an important potential risk.

While these specific items may be captured in the broader identified and potential risks in the Summary of Safety Concerns, the sponsor should provide justification to clarify their removal from the Summary.

Pharmacovigilance plan

In the EU-RMP, the sponsor proposes routine pharmacovigilance for the identified/potential risks and missing information presented in the Summary of Safety Concerns (see above).

Table 6: Ongoing safety concerns.

Safety concern	Planned action(s)
<i>Important identified risks</i>	
Rhabdomyolysis/Myopathy	Routine pharmacovigilance
Abnormal Liver Function	Routine pharmacovigilance
Hypersensitivity	Routine pharmacovigilance
<i>Important potential risks</i>	
Pancreatitis	Routine pharmacovigilance
Cholecystitis/Cholelithiasis	Routine pharmacovigilance
Interstitial Lung Disease	Routine pharmacovigilance
Simvastatin hypersensitivity syndrome	Routine pharmacovigilance
New onset diabetes/impaired glucose metabolism	Routine pharmacovigilance
Haemorrhagic stroke	Routine pharmacovigilance
<i>Missing information</i>	
Exposure during pregnancy and lactation	Routine pharmacovigilance
Use in children (limited clinical trial experience in children 10–17 years of age. No clinical trial experience in children less than 10 years of age).	Routine pharmacovigilance

There are no additional pharmacovigilance activities proposed for Australia (ASA Version 2.1, 6 July 2015).

RMP reviewer comment

There is no definite objection to the pharmacovigilance plan proposed by the sponsor in the context of this application. There is significant clinical history with the ezetimibe and simvastatin components of Vytorin.

Risk minimisation activities

The sponsor proposes routine risk minimisation activities (that is, PI labelling) for all identified/potential safety concerns and missing information.

The proposed risk minimisation activities are discussed further.

RMP reviewer comment

The sponsor's conclusions with regards to proposed risk minimisation activities are considered acceptable in the context of this submission.

Reconciliation of issues outlined in the RMP report

The following section summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the TGA RMP reviewer, and the RMP reviewer's evaluation of the sponsor's responses.

Recommendation #1 in RMP evaluation report

Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated Section 31 request and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.

Sponsor response

The Scientific Evaluation Branch at TGA has advised that they have reviewed the nonclinical specifications section of the RMP and believe that they are an adequate summary of the nonclinical findings and their potential clinical relevance.

The clinical evaluator has concluded that the safety specification in the draft risk management plan (RMP version 2.0) is satisfactory. There are no additional considerations to be addressed from the Clinical Evaluation Report.

The ASA to the RMP will be revised following finalisation of the PI.

Evaluator's comment

The sponsor's response is noted.

However, the first comment regarding the nonclinical evaluation is inaccurate as a nonclinical evaluation report was not performed for this submission.

The updated version of the ASA will need to be provided to TGA in order to advise the RMP condition(s) of registration.⁴³

Recommendation #2 in RMP evaluation report

Specific drug interactions and increased Hb1Ac/FSG were included as important identified and potential risks, respectively, in the Summary of Safety Concerns of previous RMPs (drug interactions included that with warfarin, fluindione, cyclosporin, potent CYP3A4 inhibitors [including itraconazole, telithromycin, ketoconazole, erythromycin, HIV protease inhibitors, nefazodone], fusidic acid, grapefruit juice, diltiazem, verapamil, amlodipine, fibrates, niacin (≥ 1 g/day), danazol, amiodarone). While the adverse outcomes of these specific interactions may be captured in broader identified and potential risks, the sponsor should provide justification for their removal from the current Summary of Safety Concerns.

Sponsor response

The sponsor confirms that previous versions of the RMP have included these risks in varying sections. The RMP has been updated to include the following two drug interactions as important identified risks:

- Interaction with warfarin, another coumarin anticoagulant or fluindione
- Interaction with ciclosporin

The remaining drug interactions relate to the increased rate of rhabdomyolysis due to increased plasma level of statin. The risk of rhabdomyolysis and these drug-drug interactions are considered to be covered under the important identified risk "Rhabdomyolysis/myopathy" and are thus not repeated within this section.

Evaluator's comment

An updated RMP reflective of these changes was not submitted as part of the Section 31 response.

The updated version of the RMP will need to be provided to TGA in order to advise the RMP condition(s) of registration.

Summary of recommendations

It is considered that the sponsor's response to the TGA Section 31 Request has adequately addressed all of the issues identified in the RMP evaluation report. However, there remains an outstanding issue (see below).

⁴³ The sponsor later clarified that their earlier response was a verbatim reproduction of communication received from TGA when clarification of the RMP recommendation for nonclinical evaluation was sought.

Outstanding issues*Issues in relation to the RMP*

The sponsor has proposed changes to the Safety Specification of the RMP (and therefore also details of the ASA).

These revised documents are required to propose the RMP conditions of registration (i.e. referral to version control identifiers).

Comments on the safety specification of the RMP*Clinical evaluation report*

The Clinical Evaluator concluded that “The Safety Specification in the draft RMP (version 2.0) is satisfactory. The safety specifications identified by the sponsors in the RMP are consistent with the adverse event/safety profile from the clinical trial data.”

Nonclinical evaluation report

A nonclinical evaluation was not undertaken for this application.

Key changes to the updated RMP

No updated RMP was provided with the Section 31 response.

Suggested wording for conditions of registration*RMP*

Wording for the RMP conditions of registration cannot be provided at this time as the sponsor has proposed updates to the RMP/ASA.

The EU RMP (Version 2.0, dated 24 March 2015, DLP 23 January 2015), with ASA (Version 2.1, dated 6 July 2015) is to be revised to the satisfaction of TGA.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate’s overview and recommendations:

Quality

There was no new data submitted.

Nonclinical

There was no new data submitted.

Clinical**Efficacy**

The evidence for the indication of CV benefits was derived largely from a single pivotal study: the IMPROVE-IT study (published in the NEJM 2015).⁴⁴ Some supportive evidence was provided in the SHARP study. The SEAS study and ENHANCE study had been evaluated previously and are included in the PI.

⁴⁴ Cannon CP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *NEJM* 372: 2387-2397 (2015).

Study design

This was a Phase IIIb, multicentre, randomised, double blind, active (both arms received simvastatin) and placebo (one arm received ezetimibe, the other placebo) controlled trial.

Objective: To determine the efficacy and safety of ezetimibe in combination with simvastatin in stabilised patients with ACS.

Efficacy endpoints:

- Primary Efficacy Endpoint: A composite of CV death, major coronary event (non-fatal MI, UA needing admission to hospital, all coronary revascularisation with either PCI or CABG occurring at least 30 days after randomisation) and non-fatal stroke.
- Secondary Efficacy endpoints:
 - Composite death from any cause, major coronary event, non-fatal stroke
 - Composite endpoint of death due to CHD, non-fatal MI and urgent coronary revascularisation
 - Composite of CV death, non-fatal MI, UA requiring admission to hospital, all revascularisation, non-fatal stroke
- Tertiary: Components of the composite measures and subgroups, reductions in LDL-C and CRP.

Efficacy was analysed using ITT.

The study was designed with a sample size of 10,000 patients and the assumption that the expected 15 mg/dL (0.39 mmol/L) difference in LDL-C between treatment groups would translate into a 10% reduction in events in 2 years. However, the sample size was changed after 2.5 years to 18,000 subjects as the event rate was lower than anticipated.

Patients

Entry criteria were age > 50 years presenting with NSTEMI, STEMI, or hospitalised for UA. The study included patients with mild-moderate renal failure but excluded those with CrCl < 30 ml/min.

Table 7: Study entry criteria.

	EZ/Sim 9067	Simva 9077	Total 18144
Male	6842 (75.5%)	6886 (75.9%)	13782 (75.7%)
Age	63.6 ± 9.7	63.6 ± 9.8	63.0 ± 9.8
≥ 65 years	44.4%	43.5%	43.9%
≥ 75 years	15.1%	15.7%	15.4%
BMI	28.3 ± 5.2	28.3 ± 5.2	28.3 ± 5.2
ACS diagnosis			
NSTEMI	47.4%	46.9%	47.2%
Unstable angina	24%	24.4%	24.2%
STEMI	28.5%	28.7%	28.6%
Medical history			
History of angina	41.1%	41%	41%
Previous MI	21.2%	20.7%	21%
Hypertension	61.5%	61.2%	61.4%
Diabetes	27.1%	27.3%	27.2%
CrCl < 60ml/min	17.9%	18%	18%

Overall, 64% were naïve to lipid lowering therapy at baseline. Statin use accounted for almost all of those on lipid lowering agents at baseline. The mean LDL-C at the time of randomisation was 2.1 mmol/L.

Intervention

Patients were randomised 1:1 to ezetimibe/simvastatin 10/40 mg and simvastatin 40 mg. Initially, the patients were able to have their dose titrated up to 80 mg of simvastatin if their LDL-C remained over 2.0 mmol/L. The protocol was later amended after an increased risk of myopathy associated with high statin doses was identified in another study.

Participant flow

A total of 18,144 subjects were randomised into the study. The protocol defined ITT population included 9,067 subjects in the ezetimibe/simvastatin group and 9,077 subjects in the simvastatin monotherapy group. Overall, 13,728 (75.7%) subjects completed the study. Overall, around 10% of patients in the study discontinued due to adverse events and these were equally balanced between the two treatment groups. A total of 8,462 (46.6%) completed on study drug and 5,108 (28%) completed off study drug. A total of 1932 subjects died before their final visit, which includes deaths that occurred within 4 months of an office or telephone visit.

Primary efficacy endpoint

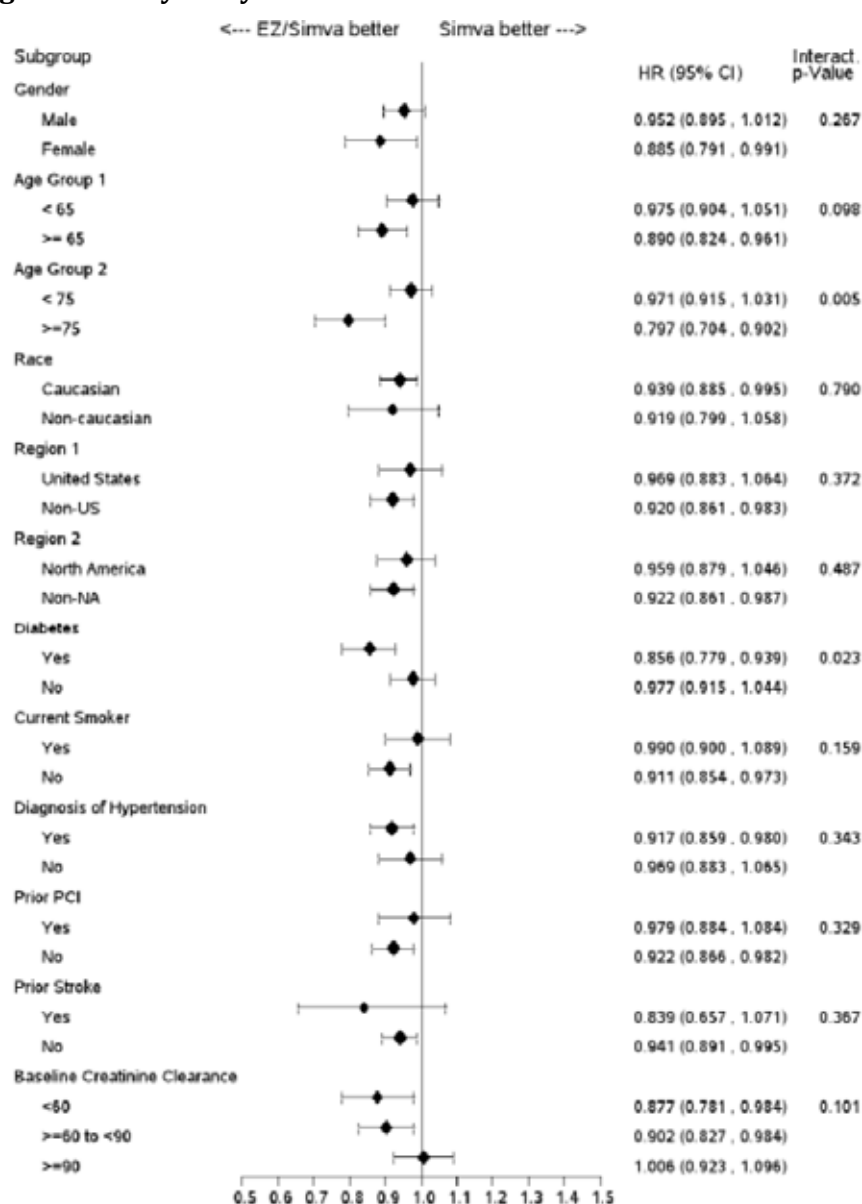
The primary efficacy endpoint was the occurrence of the composite endpoint CV death, major coronary events and non-fatal stroke. Treatment with ezetimibe/simvastatin resulted in a 6.4% RRR in the primary efficacy endpoint compared to treatment with simvastatin monotherapy (HR 0.936; 95% CI 0.887-0.988; p = 0.016).

Table 8: Study entry criteria.

endpoint	Ez/Simz N=9067	Simvastatin N=9077	Absolute Risk Difference	Number Needed to treat
Primary composite	2572 (28.4%)	2742 (30.2%)	1.95%	51
CV death	342 (3.77%)	319 (3.51%)	-0.21%	476
Non fatal MI	782 (8.62%)	902 (9.94%)	0.78%	128
UA requiring hospitalization	117 (1.29%)	107 (1.18%)	0.09%	1111
All coronary revascularisation	1153 (12.72)	1175 (12.94)	0.22%	454
Non fatal stroke	178 (1.96)	239 (2.63)	0.67%	149

Note: 6.2% of patients in the simvastatin/ezetimibe group compared to 27% of patients in the simvastatin group had their dose of simvastatin increased from 40 mg to 80 mg.

The CV benefits emerged 1 year after treatment.

Figure 1: Study entry criteria.

Secondary and tertiary efficacy endpoints

Hochberg's procedure was used to control alpha at 0.05 for tests of the secondary hypotheses. The secondary analyses were performed only if the primary analysis was statistically significant. Analyses of all tertiary and exploratory variables were intended to be supportive of the primary and secondary endpoints with no additional multiplicity adjustments.

Ezetimibe/simvastatin reduced the incidence of the composite endpoint of death due to all causes, major coronary events and non-fatal stroke (7-year Kaplan-Meier [KM] rate for ezetimibe/simvastatin versus simvastatin 38.6% versus 40.25%; HR = 0.95, 95% CI: 0.90-1.0; p = 0.035).

Ezetimibe/simvastatin reduced the incidence of the composite endpoint of death due to CHD, non-fatal MI and urgent coronary revascularisation with either PCI or CABG occurring at least 30 days after randomisation (7-year KM rate: 17.5% versus 18.9%; HR = 0.91, 95% CI: 0.85-0.98; p = 0.016).

Ezetimibe/simvastatin reduced the incidence of the composite endpoint of CV death, nonfatal MI, documented UA that requires admission into a hospital, all revascularisation

(including both coronary and non-coronary) occurring at least 30 days after randomisation and non-fatal stroke (7-year KM rate: 34.5% versus 36.2%; HR = 0.95, 95% CI: 0.90-1.0; p = 0.035).

The rates of death from any cause, CV death, or CHD death were similar between the treatment groups. No differences were noted between the treatment groups in UA requiring hospitalisation or all coronary revascularisation with PCI or CABG (> 30 days after randomisation). Treatment with ezetimibe/simvastatin was shown to reduce the rate of MI (fatal or non-fatal) with a HR of 0.87 (95% CI: 0.80 -0.95; p=0.002) but this was driven mainly by reduction in non-fatal MI (7-year KM rate for non-fatal MI was 12.8% in the ezetimibe/simvastatin group compared to 14.4% in the simvastatin monotherapy group; HR 0.87, 95% 0.8-0.95; p = 0.002) while the rate of fatal MI was low and similar between the treatment groups.

Treatment with ezetimibe/simvastatin was shown to reduce the incidence of stroke (fatal or non-fatal) (296 of 9,067 subjects in the ezetimibe/simvastatin group compared to 345 of 9,077 in the simvastatin group; HR = 0.86, 95% CI: 0.7-1.0; p = 0.052), but this reduction in stroke events was mainly driven by reduction in non-fatal stroke (7 year KM rate for nonfatal stroke was 3.49% versus 4.24%; HR 0.80 95% CI : 0.68 - 0.95; p = 0.010). The rate of fatal stroke was low and similar between the treatment groups. The rate of non-haemorrhagic stroke or unknown stroke was reduced in the ezetimibe/simvastatin group (7-year KM rate: 3.48% versus 4.23%; HR = 0.793, 95% CI: 0.670 - 0.939; p = 0.007). However, the incidence of haemorrhagic stroke was higher in the ezetimibe/simvastatin group compared to in the simvastatin monotherapy group (HR 1.38, 95% CI: 0.93-2.04; p = 0.110).

On-treatment analyses were pre-specified and performed on the primary composite endpoint and key secondary composite endpoints. Results for the primary composite endpoint with events censored at 30 days after the date of permanent discontinuation of study drug supported the findings in the protocol defined ITT population and a 7.60% reduction in risk for the primary composite endpoint was observed (HR 0.924; 0.868-0.983, p = 0.012).

A total of 5,314 subjects had at least 1 primary endpoint event, 2307 subjects had at least 2 events, 965 subjects had at least 3 events and 453 subjects had at least 4 events.⁴⁵ The risk reduction in the primary endpoint of ezetimibe/simvastatin compared to simvastatin was consistent (p = 0.688) across the 1st, 2nd, 3rd, and 4th events and was associated with an average risk reduction of 6.6% (HR = 0.934; 95% CI: 0.89-0.99; p = 0.013).

Other efficacy endpoints

Lipid,⁴⁶ Lipoproteins, Apolipoproteins and hs-CRP

The LS mean LDL-C at the time of the qualifying event was 2.43 mmol/L in both treatment groups. LDL-C lowering was observed at 1 month and was generally sustained over the duration of follow-up. The corresponding LS mean LDL-C levels at 1 year were 1.4 mmol/L in the ezetimibe/simvastatin group versus 1.86 mmol/L in the simvastatin group, representing a 0.434 mmol/L between group difference (95% CI -17.5 to 16.0; p<0.001).

The proportion of subjects that achieved LDL-C <1.81 mmol/L and hs-CRP <2 mg/L was significantly greater in the ezetimibe/simvastatin compared to the simvastatin monotherapy group at 1 month (50.6% versus 30.5%) and 4 months (53.4% versus 29.9%).

⁴⁵ The analysis uses up to the 4th event per subject since only a small number of subjects had more than 4 events.

⁴⁶ During the trial, subjects were requested to fast for 12 hours prior to scheduled blood work, however, blood was collected regardless of the fasting state of the subject in the event that they failed to fast.

Relationship of LDL-C reduction to outcomes treatment benefit

In the 2010 cholesterol treatment trialist meta-analysis,⁴⁷ lowering of LDL-C by 22% after 1 year resulted in a 22% reduction in MVEs.

The HR for clinical benefit per mmol of LDL-C reduction with ezetimibe in IMPROVE-IT was 0.80, which is consistent with the HR (0.78) observed with statins in the meta-analysis performed by the CTT in 2010.⁴⁸ However, it is unclear how this was calculated.

Delegate's comments

The clinical outcome endpoints in the pivotal submitted study (IMPROVE-IT) were objective and clinically relevant and generally complied with the TGA adopted CHMP guidelines for evaluation of medicinal products for CV disease prevention.⁴⁹ However, it is important to note that the TGA adopted guidelines for composite endpoints in trials of CV disease prevention mentions that:

All-cause mortality is preferred over CV mortality as primary endpoint or as one component of the primary endpoint. CV mortality if objectively and conservatively defined may also be acceptable and may be more sensitive to detect differences in non-inferiority approaches. Sufficient confidence regarding overall mortality and non-CV mortality is necessary in this case. Composite endpoints may be appropriate if they include hard clinical events such as non-fatal MI, stroke. However, including in the composite, components which have markedly different weight in term of clinical benefit is discouraged. An example is the combination in the primary composite endpoint of fatal events and clinician decision outcomes such as hospitalisation, coronary revascularisation, amputation, use of rescue therapy, hospitalisation for heart failure. In such a case, the statistical significance of the primary composite endpoint is often driven by the clinician-decision outcome component, presenting further challenges for the interpretation of the study overall results. The more clearly components of a composite endpoint directly refer to the disease process, the less there is problem of interpretation.

The IMPROVE-IT trial did not look at all-cause mortality. The composite endpoint included hospitalisation for angina and revascularisation which may have been driven by clinician decisions.

The evaluator was satisfied that the results of the IMPROVE-IT study were relevant to patients with chronic CHD as the benefits with ezetimibe were seen after 1 year of therapy and were persistent over the 7 years of the study.

The evaluator was satisfied that the results of the IMPROVE-IT trial were also relevant to subjects with higher LDL levels as there was a strong relationship between the absolute degree of LDL lowering and proportionate decrease in CV disease risk across a broad range of LDL levels in the CTT. Studies with ezetimibe have shown that the proportional change in LDL-C with ezetimibe is independent of baseline LDL-C.

The evaluator was unsure if the results of the IMPROVE-IT study could be extrapolated for use with other statins. It was noted that a pooled analysis from 27 lipid lowering trials involving over 21,000 subjects showed that ezetimibe has a consistent additive lipid lowering effect when added to different statins, different doses of statins, statins of

⁴⁷ Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet* 376: 1670-1681 (2010).

⁴⁸ Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet* 376: 1670-1681 (2010).

⁴⁹ European Medicines Agency, "Guideline on the evaluation of medicinal products for cardiovascular disease prevention (EMA/CHMP/EWP/311890/2007)", 25 September 2008.

varying potency. Ezetimibe is approved for lipid lowering with all statins. However to allow an indication for use with all statins would also infer use with statins that are not yet approved for use and with no data to support that use.

Supportive studies

The simvastatin and ezetimibe in aortic stenosis study (SEAS)

The results of the large (1873 patients followed up for a mean of 52.2 months) randomised SEAS trial demonstrated that **ezetimibe/simvastatin 10/40 mg daily is not associated with a reduction in the primary composite endpoint of CV death, aortic valve replacement surgery, nonfatal MI, CHF from AS progression, CABG, PCI, hospitalised unstable angina and non-haemorrhagic stroke**. However, there was a significant reduction in the incidence of atherosclerotic adverse events in the ezetimibe/simvastatin arm compared with placebo (15.7% versus 20.1%, $p = 0.02$), which has been demonstrated in other trials of statins as well.

SHARP

This was a Phase V, double blind, placebo controlled, multicentre study conducted at 380 centres in 18 countries from August 2003 to August 2010. The primary objective was to assess the effects of lowering LDL-C with combined ezetimibe 10 mg and simvastatin 20 mg daily (ezetimibe/simvastatin 10/20 mg) versus placebo on the time to a first MVE (defined as non-fatal MI or cardiac death, non-fatal or fatal stroke, or any revascularisation excluding dialysis access procedure) in about 9,000 patients with CKD (6,000 pre-dialysis and 3,000 on dialysis at randomisation). The secondary objective was to assess the effects of ezetimibe/simvastatin 10/20 mg on: progression to ESRD (among pre-dialysis patients); various causes of death; major cardiac events (defined as non-fatal MI or cardiac death); stroke (both overall and subtypes); hospitalisation for angina and to assess the effects of major vascular effects among particular subgroups of patients.

The study was underpowered, as the mean LDL reduction at the midpoint of the trial was less than anticipated. The study design was also updated due to a higher incidence of non-coronary events and haemorrhagic stroke.

Patients were randomised 4:4:1 to receive ezetimibe/simvastatin:placebo:simvastatin. Compared to placebo (749/4,191), ezetimibe/simvastatin (639/ 4193) reduced the risk of MVE by 16% (RR 0.84, 95% CI 0.75- 0.93, $p = 0.001$). The risk ratio of ezetimibe/simvastatin 10/20 mg versus placebo on the components of MVE in all patients including those originally allocated to simvastatin was 0.85, 95% CI: 0.77-0.94, $p = 0.0012$. Patients randomised to ezetimibe/simvastatin had a non-significant 10% lower risk for major cardiac events (cardiac death and non-fatal MI), a significant 19% risk reduction for total stroke and a significant 21% risk reduction ($p = 0.0036$) for any revascularisation procedure (including coronary or non-coronary angioplasty or grafting, and non-traumatic amputation, but excluding vascular access surgery for dialysis) compared to placebo. There was no comparison performed between those on simvastatin alone compared to other treatments.

There was no significant difference in the risk of progression of CKD.

ENHANCE

The ENHANCE trial was a randomised study aimed at studying the effect of ezetimibe on top of simvastatin versus simvastatin on carotid intima-media thickness in 720 patients with heterozygous familial hypercholesterolemia. **Despite achieving a significant differential reduction in LDL-C, no regression in carotid intima-media thickness was observed at the end of the 2-year follow-up period.**

Safety

IMPROVE IT study

- Suspected clinical endpoint events were not reported as SAE
- Mean duration of exposure was 1389 days in the simvastatin/ezetimibe group and 1427 in the simvastatin group
- Compliance was over 85% with similar compliance rates in both groups
- The incidence of all AEs (ezetimibe/simvastatin versus simvastatin alone: 85.6% versus 85.4%)
- Overall, 4818 (26.55%) patients experienced at least one treatment related AE (ezetimibe/simvastatin versus simvastatin alone: 26.8% versus 26.3%).
- There were 7289 (40.2%) subjects who experienced at least one SAE; 3640 (40.1%) in the ezetimibe/simvastatin group and 3649 (40.2%) in the simvastatin group. The most common SAEs were neoplasms (benign and malignant) musculoskeletal disorders and infections/ infestations with similar incidence in the treatment groups
- There were no new safety concerns
- Overall, the incidence of elevations in ALT and AST with or without bilirubin elevations was generally similar between the ezetimibe/simvastatin and simvastatin treatment groups across the different range of elevations. The incidence of discontinuations was slightly higher in the ezetimibe/simvastatin group compared to the simvastatin group due to ALT increased (0.23% versus 0.08%) and AST increased (0.19% versus 0.06%).
- There was little change in serum creatine kinase (CK)⁵⁰ from baseline over time and no apparent difference in change from baseline in CK between the treatment groups
- The rates of muscle related events, especially the more severe events, were generally similar between the two treatment groups. The combined endpoint of myopathy/rhabdomyolysis occurred in 0.3% of subjects in both treatment groups. There was no meaningful difference between the groups in the incidence of CEC reported rhabdomyolysis (ezetimibe/simvastatin versus simvastatin: 0.1% versus 0.2%) and myopathy (0.2% versus 0.1%).
- In the ITT analysis, there were 59 haemorrhagic strokes in the ezetimibe/simvastatin group and 43 in the simvastatin group. At 7 years, the KM estimates were 0.77% in the ezetimibe/simvastatin group and 0.59% in the simvastatin group (HR 1.377; 0.930-2.040; p = 0.110). In the on-treatment analysis which censored events occurring beyond 30 days after the date of permanent discontinuation of study drug, there were 32 haemorrhagic stroke events in the ezetimibe/simvastatin group compared with 34 in the simvastatin group. These findings suggest that a large proportion of the haemorrhagic stroke events occurring in subjects allocated to ezetimibe/simvastatin occurred after the subjects had discontinued study therapy.

SHARP study

- 9438 patients were followed during the first year of the study
- Mean duration of follow up was 4.9 years

⁵⁰ Serum CK was measured at baseline and at regularly scheduled visits after the initiation of Amendment 5. Prior to Amendment 5 (June 22, 2011), CK was only routinely measured at baseline or when a subject reported unexplained muscle symptoms.

- Compliance declined over the course of the study; at 20-25 months of follow-up, 68% of patients allocated to ezetimibe/simvastatin and 67% of patients allocated to placebo were taking >80%, while at 44-49 months, compliance had fallen to 60% and 56%, respectively.
- Only AE that were serious or led to treatment discontinuation were recorded
- During the overall study period, of 33 patients with suspected serious adverse reactions (SSARs), 20 (0.4%) patients were allocated to ezetimibe/simvastatin 10/20 mg and 13 (0.3%) patients were allocated to placebo. The most common SSARs were CK elevations >10x ULN, which were observed in 7 patients allocated to ezetimibe/simvastatin 10/20 mg and 4 patients allocated to placebo
- The numbers of deaths overall and of deaths due to non-vascular causes collectively were not significantly different in patients allocated to ezetimibe/simvastatin versus placebo. There were no significant differences between the ezetimibe/simvastatin and placebo groups in mortality from specific non-CHD or non-vascular causes, including cancer
- CK elevation is more common in patients with renal failure. There was no pattern suggestive of increased myopathy or rhabdomyolysis.

The clinical evaluator recommended **rejection** for a number of reasons.

RMP evaluation

The prevalence of CHD is estimated to be around 6.5% among those > 20 years.

Table 9: Ongoing Safety Concerns for ezetimibe.

Important identified risks	Rhabdomyolysis/Myopathy
	Abnormal liver function
	Hypersensitivity
Important potential risks	Cholecystitis/Cholelithiasis
	Pancreatitis
Missing information	Exposure during pregnancy and lactation
	Limited clinical trial experience in children 10–17 years old beyond 1 year and in children 6-10 years old beyond 12 weeks. No clinical trial experience in children less than 6 years of age.

Routine pharmacovigilance for most risks will continue. Enhanced pharmacovigilance in children will continue.

The sponsor has agreed to include the drug interactions with warfarin, other coumarin anticoagulants, fludione and cyclosporin however will need to submit an updated RMP.

Table 10: Ongoing Safety Concerns for ezetimibe/simvastatin.

Important identified risks	Rhabdomyolysis/Myopathy
	Abnormal liver function
	Hypersensitivity
Important potential risks	Cholecystitis/Cholelithiasis
	Pancreatitis
	Interstitial lung disease
	Simvastatin hypersensitivity syndrome
	New onset diabetes/impaired glucose metabolism
	Haemorrhagic stroke
Missing information	Exposure during pregnancy and lactation
	Limited clinical trial experience in children 10–17 years old beyond 1 year and in children 6-10 years old beyond 12 weeks. No clinical trial experience in children less than 6 years of age.

Routine pharmacovigilance for most risks will continue. Enhanced pharmacovigilance in children will continue.

The sponsor has agreed to include the drug interactions with warfarin, other coumarin anticoagulants, flucloxacillin and cyclosporin however will need to submit an updated RMP.

Discussion

- Is a separate indication needed?

The aim of any lipid lowering therapy is to reduce the risk of CV events. Ezetimibe is currently indicated for the management of primary and familial hypercholesterolaemia. The proposed new indication would therefore also cover for patients with CHD who do not have hypercholesterolaemia.

- Is the evidence robust?

This is a major concern of the Delegate, particularly in view of the relatively small ARR, confidence intervals approaching 1, lack of supporting evidence from other trials, and significant difference in only some of the components of the composite endpoint (that is, if there was a real difference in coronary artery disease, why were the benefits only significant for non-fatal MI and not for UA, vascularisation procedures, and CV death?)

EMA guidelines for the use of one pivotal study state:

the minimal requirement is generally one controlled study with statistically compelling and clinically relevant results.

The IMPROVE-IT study was a large, randomised study with follow up for around 6 years. The use of a composite outcome increases the statistical power. However, could the statistical significance of the primary outcome be virtue of the large size of the study and very large patient population? It is noted that the upper confidence intervals approach unity (or cross unity for some components and subgroups); thus, the statistical significance could be due to chance. There was a statistically significant reduction in non-fatal MI but not in related events such as UA, revascularisation or CV death.

Other large-scale trials ACCORD, FIELD, AIM-HIGH, Dalcetrapib Outcomes, and HPS2-THRIVE failed to find a clinical benefit for the addition of fibrates, niacin and a CETP inhibitors on top of statins. These drugs are not primarily LDL-C lowering drugs and had other properties that may have contributed to their failure.

- Are the differences in CV events clinically significant?

Clinical significance is a difficult concept to define. In this study it is highlighted by having a composite endpoint. The study was not powered to determine the individual components of the endpoint.

The RRR of 6.4% was below the anticipated RRR of 10% that the sponsor used in the power calculations.

In the IMPROVE IT study, there was no overall benefit in all-cause mortality or CV mortality. These are the preferred endpoints in studies of CV prevention.

The ARR seen was small (around 2% overall), and this was in a high risk population (post acute coronary event and with a high proportion having diabetes and hypertension). The ARR in the sponsor's proposed indications 'CHD' is likely to be less.

- How does ezetimibe compare with other medicines and strategies used for CV prevention?

After an acute coronary event, treatment with a statin is first line, evidence based management. Since 1994, large, multicentre trials including more than 170,000 people have shown that people taking statins to lower their LDL-C have fewer major coronary events (non-fatal heart attack or death from CHD):

- Major coronary events are reduced by a quarter (24%)
- 1 in 5 coronary deaths are prevented (that is, 20% reduction)
- Death from any-cause is reduced by 10%
- Coronary artery surgery and coronary angioplasty is reduced by a quarter (25%) and nearly a third (28%), respectively.⁵¹

The benefits can be seen with every 1.0 mmol/L reduction in LDL cholesterol. A meta-analysis involving 13 individual trials and in excess of 91,000 patients showed that treating 255 patients with a statin for 4 years led to the prevention of 5.4 CV events and one extra case of diabetes.⁵² The addition of ezetimibe would potentially add 6% to the reduction on major coronary event.

Aspirin lead to a 22% reduction in the risk of subsequent vascular events.

Smoking cessation leads to a reduction in relative risk of mortality to 0.64.

Weight loss of around 5 kg leads to a 4 mmHg reduction in blood pressure (BP) and 40% reduced risk of stroke and MI, and 50% reduction in risk of diabetes.

- Are the indications an accurate reflection of the findings from the IMPROVE-IT study?

Apart from the concerns about the robustness of the study results and clinical significance of the findings, the Delegate is concerned that several key words in the indications may not be an accurate reflection of the efficacy gains in the IMPROVE-IT study.

- Use with any statin is not appropriate. The evidence demonstrated is with simvastatin only.
- The phrase 'cardiovascular events' is a composite endpoint and is misleading as the study did not show benefit in all components.

⁵¹ Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet* 376: 1670-1681 (2010).

⁵² Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet* 376: 1670-1681 (2010).

- The proposed population with CHD is not the same as those enrolled in the trial and the benefits seen may be less in this group. The clinical trial population used patients with an ACS, and of these around 30% had diabetes.
- Are the CV benefits seen due to a lowering of LDL or an independent effect of ezetimibe?

The aim of any lipid lowering therapy is to reduce a risk factor for CV events, not merely to lower the LDL value. The results of the IMPROVE-IT study are expected, or put another way if a study showed that a lipid lowering agent did not show a CV benefit, one would question the validity of the lipid lowering effects or use of LDL as a surrogate endpoint.

There was no comparison of the use of ezetimibe/simvastatin with high dose statin or more potent statin or other lipid lowering agent. It was not clear if the benefits were due to treating to a lower LDL target or adding ezetimibe.

The CTT was a meta-analysis of individual participant data from RCT involving at least 1000 participants and at least 2 years duration of more versus less intensive statin regimes (5 trials; 39,612 individuals; median follow up 5.1 years) and statin versus control (21 trials; 129,526 individuals; median follow up 4.8 years). For each trial, the average risk reduction and average risk reduction per 1.0 mmol/L LDL cholesterol was calculated.

For the trials of more versus less intensive statin therapy, the weighted mean further reduction in LDL cholesterol at 1 year was 0.51mmol/L. Compared with less intensive regimens, more intensive regimens produced a 15% (95% CI 11-18%, p<0.001) further reduction in vascular events. There were significant reductions in coronary death or non-fatal MI of 13 % (95% CI 7-19%, p< 0.001), coronary revascularisation of 19% (95% CI 15-24) and ischemic stroke 16% (95% CI 5-26), p = 0.005). In the trials of statin versus control, there was a mean reduction of LDL of 1.07 mmol/L and risk reduction of CV events of 22% (95% CI 19-24). Across all 26 trials, all-cause mortality was reduced by 10% per 1.0 mmol/L LDL reduction (95% CI 0.87-0.93), largely reflecting a reduction in deaths due to coronary artery disease (RR 0.80, 95% CI 0.74-0.87) and other cardiac causes (RR 0.89, 95% CI 0.81-0.98) with no significant effect on death due to stroke or other vascular events.

Although it is not possible to make a direct comparison between the results of the CTT and IMPROVE-IT, it would appear that the effects of ezetimibe are due to the LDL lowering effect. And that the RRR of ezetimibe with simvastatin is less than with intensive statin therapy.

- Safety

The safety profile of ezetimibe has been previously described. There was an imbalance in the number of haemorrhagic strokes among patients treated with ezetimibe in the IMPROVE-IT study. A similar imbalance for haemorrhagic stroke was also identified in the intensive statin therapy group of the CTT.

Question for sponsor

Please supply a copy of the final letter from the FDA outlining the reasons for rejection.

Summary of issues

- Although the aim of treatment of hyperlipidaemia is to prevent CV events, the prevention of CV events is not currently covered by any of the stated indications;
- The evidence behind the proposed change in indications is on the basis of a **single** large multicentre randomised controlled trial:: the IMPROVE-IT study;

- The population proposed in the indications (all adults with CHD) do not meet that studied in the IMPROVE-IT study (adults after ACS);
- The absolute (2%) and relative risk (6%) reduction in the composite endpoints in the IMPROVE-IT study were small;
- Not all components of the composite endpoint showed a statistically significant reduction in relative risk;
- The IMPROVE-IT study evaluated the use of ezetimibe with simvastatin; however, the sponsor proposes to include all statins in the indication.

Proposed action

The Delegate's proposed plan of action is to **reject** the application to extend the indication of ezetimibe and ezetimibe/simvastatin for use in the prevention of CV events. The main reason rejection is that efficacy is not satisfactorily established (see details above). It would be acceptable to include the results of the IMPROVE-IT study in the PI, with some minor amendments as described below. The RMP needs revising to include the drug interactions which appear to be missing in the versions included with this application.

Request for ACPM advice

1. Is the single pivotal study robust enough to ensure efficacy?
2. Are the benefits in CV risk reduction large enough warrant this indication?
3. Is it reasonable to extrapolate benefits when used in combination with all statins or should the indication be restricted to simvastatin?
4. Is it reasonable to extrapolate the use in all patients with CHD when the study population in the IMPROVE-IT study were a high risk group?
5. Were the benefits seen due to a lowering of LDL (and therefore may be seen with other drugs) or due to ezetimibe? And does this matter for the new indication?
6. Is the imbalance in the number of haemorrhagic strokes between the ezetimibe and ezetimibe/simvastatin groups a concern?

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

MSD does not concur with the Delegate's conclusion that the applications to extend the indications should be rejected on the basis that efficacy is not satisfactorily established. The clinical significance of the IMPROVE-IT study is strongly endorsed by leading experts in the fields of lipidology and CV medicine. MSD provides with this response supporting statements from several key scientific leaders discussing the relevance of these findings to their clinical practice.

MSD is disappointed that the Delegate has not accepted the recommendations of the clinical evaluator on several of the issues that have been raised in the Delegate's request for ACPM advice, notably the applicability of the findings from the IMPROVE-IT study in CHD patients presenting with ACS to patients in the non-acute phase of CHD; to all statins with proven CV risk benefit.

In addition, MSD highlights that several issues raised in the Delegate's overview were not matters on which questions were raised during the Section 31 request for information,

meaning that MSD has not had a reasonable opportunity to address these issues during the evaluation:

- whether it is appropriate to include all CHD patients in the indication or only those in the ACS phase of CHD;
- whether the phrase CV events is misleading given the study did not show benefit in all components of the composite endpoint;
- concerns around the robustness of the statistical significance of the primary outcome of the study; and
- questions around a speculated alternative mechanism of action for ezetimibe.

Additionally, the Delegate has compared the risk reduction seen in IMPROVE-IT to various other interventions recognized as being effective in reducing CV risk (aspirin, weight loss, etcetera). MSD considers that it is not reasonable to imply comparability of the relative risk benefit of different interventions in different populations, with different background risk and background therapies, and that were completed in different eras in this way.

MSD provides the following comments on the Delegate's request for ACPM advice.

Are the benefits in cardiovascular risk reduction large enough to warrant this indication?

MSD contends that while the RRR in the primary endpoint in the IMPROVE-IT study appears to confer a 'modest' benefit from the addition of ezetimibe to simvastatin, the benefit observed in IMPROVE-IT is entirely consistent with the current level of knowledge related to lipid lowering therapy and expected CV benefit and risk reduction, and is supportive of an indication involving reduction in CV risk.

IMPROVE-IT enrolled patients whose LDL-C levels were comparable to the treatment targets of current CV risk management guidelines (that is, under current guidelines, many of these patients would not be considered to have hypercholesterolaemia). This low LDL-C entry criterion limited the degree of LDL-C lowering that could be achieved, along with the potential related CV risk reduction. The 6.4% RRR is expected when considering the patient population studied, baseline LDL-C levels, the observed LDL-C reduction, and comparison to the CV risk reduction observed with statin.

In order to assess the IMPROVE-IT results and allow for appropriate comparison with the benefits of LDL-C lowering with statins in the CTT meta-analyses (CTT), the analysis and imputation methods employed in CTT were utilized. Based on these calculations, IMPROVE-IT showed ezetimibe was associated with a HR 0.80 per mmol/L LDL-C lowering, very comparable to the HR observed with statins (0.78 per mmol/L LDL-C lowering).⁵³ In comparing ezetimibe's CV benefit to that of statins it is important to understand that such comparisons require adjustment for LDL-C change. For example, higher intensity statins by virtue of their greater impact on LDL-C reduction have greater unadjusted CV benefit than lower intensity statins; however, the benefit for statins as a whole is generally uniform when adjusting for LDL-C change. The findings from IMPROVE-IT demonstrate that the reduction in CV risk was comparable to that observed with statins for the same LDL-C reduction; to expect a larger risk reduction in IMPROVE-IT would require ezetimibe to have benefits that go beyond its effect on LDL-C and beyond the risk reduction expected with statin therapy with an equivalent degree of LDL-C lowering.

Ezetimibe's CV risk benefit when used with a statin is consistent with the known complementary and additive mechanisms of action of ezetimibe and statins with respect to lipid lowering. In addition, recent genetic research conducted in persons with both

⁵³ Cannon CP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *NEJM* 372: 2387-2397 (2015).

NPC1L1 and HMG-CoA reductase LDL-C lowering genetic variants is consistent with and confirms the additive benefit of ezetimibe and statins, targeting NPC1L1 and HMG-CoA reductase respectively, on CV risk reduction observed in IMPROVE-IT.⁵⁴

In real world clinical practice, ezetimibe is generally used to address the unmet medical need of at-risk patients whose LDL-C levels are not well controlled (that is, not at their LDL-C target) on statin therapy and thus have higher baseline LDL-C levels when initiated on ezetimibe than those enrolled in IMPROVE-IT. Given that ezetimibe and statins have consistent proportional LDL-C lowering that is generally independent of baseline LDL-C, the anticipated absolute LDL-C reduction with the addition of ezetimibe in these “real world” patients with higher baseline LDL-C levels would be greater than observed in IMPROVE-IT. Subsequently, the anticipated CV risk reduction in these patients would be greater as well.

As discussed above, the 6.4% risk reduction for the primary endpoint seen in IMPROVE -IT is entirely consistent with what would be expected based on the CTT meta-analysis. The exploratory MAE composite endpoint (MACE, CV death, non-fatal MI, and non-fatal stroke) was associated with 9.9% risk reduction (HR 0.901; 95% CI 0.841-0.965) in the ezetimibe/simvastatin group compared to simvastatin alone. In addition, there was a 20.6% risk reduction in non-haemorrhagic stroke (HR 0.794; 95% CI 0.670-0.943, $p = 0.008$) and 12.9% risk reduction in non-fatal myocardial infarction (HR 0.871; 95% CI 0.798-0.950, $p = 0.002$) with ezetimibe/simvastatin. Overall these results relating to “hard clinical events” are of significant importance to patients and clinicians, and further confirm the relevance of the IMPROVE-IT findings.

Although IMPROVE IT did not demonstrate a mortality benefit, the study was not powered to detect a small difference in mortality, as doing so would have required an unreasonably large trial. The mortality findings in IMPROVE-IT are consistent with previously conducted trials which evaluated high dose/high intensity versus lower dose/lower intensity statin therapy and did not show a reduction in mortality. Despite the lack of mortality benefit, the therapeutic benefit of high intensity statin therapy is widely endorsed in expert panel recommendations.

Importantly, given the well-established safety profile of ezetimibe co-administered with a statin, the CV risk reduction benefit provided by ezetimibe add-on therapy comes with minimal added risk for the patient.

Is the single pivotal study robust enough to ensure efficacy?

IMPROVE-IT is the first trial to demonstrate that ezetimibe/simvastatin provides incremental benefit in reducing the primary composite endpoint of CV death, MCE, and non-fatal stroke compared with simvastatin alone (HR 0.936; 95% CI 0.887-0.988; $p = 0.016$) and as noted above the benefit was seen in the clinically important endpoints of MI and non-haemorrhagic stroke. This clinically relevant and scientifically expected result is supported by a considerable database of 18,144 subjects with 5314 primary endpoint events. The median clinical follow-up achieved during the trial was 71.4 months (mean = 64.7 months) resulting in a total of 97,822 patient-years of follow-up. Ezetimibe has a broad experience in clinical studies enrolling over 37,000 subjects, and a post marketing experience of more than 36 million patient years.

Ezetimibe has a well-defined mechanism of action through the upregulation of LDL receptors that is complementary and additive to statins with respect to lipid lowering.

⁵⁴ Stitzel NO, et al. Inactivating mutations in NPC1L1 and protection from coronary heart disease. *NEJM* 371: 2072-82 (2014); Ference BA, et al. Effect of naturally random allocation to lower low-density lipoprotein cholesterol on the risk of coronary heart disease mediated by polymorphisms in NPC1L1, HMGCR, or both - a 2 x 2 factorial mendelian randomization study. *J Am Coll Cardiol.* 65: 1552-61 (2015).

Additionally, recent genetic research confirms the additive benefit of ezetimibe and statins on CV risk reduction.

Given the positive results of the IMPROVE-IT trial and its consistency with the totality of available data noted above (that is, CTT meta-analysis, ezetimibe + statin clinical database, known ezetimibe and statin mechanisms of action, and genetic studies) conducting another long-term CV outcome trial to evaluate the question would be impractical and its equipoise may be questioned by Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs).

Is the imbalance in the number of haemorrhagic strokes between the ezetimibe and ezetimibe/simvastatin groups a concern?

Overall, fewer subjects in the ezetimibe/simvastatin treatment group experienced stroke events compared to the simvastatin monotherapy group; (fatal or non-fatal HR 0.857, 95% CI 0.734-1.001; $p = 0.052$, non-fatal stroke HR 0.802 95% CI 0.678-0.949; $p = 0.010$). In the protocol specified ITT population more subjects treated with ezetimibe/simvastatin suffered a haemorrhagic stroke compared with the simvastatin only group (59 events [7-yr KM 0.77%] in the ezetimibe/simvastatin group and 43 events [7-yr KM 0.59%] in the simvastatin group) (HR 1.377; 95% CI 0.930-2.040; $p = 0.110$). Given the low rate of these events, wide confidence intervals and other issues noted below, it is difficult to draw any concrete conclusions in regards to the risk of haemorrhagic stroke. In addition, the imbalance in haemorrhagic stroke is no longer evident when events are censored at 30 days after study drug discontinuation. In this on-treatment analysis, there were 32 subjects (7-yr KM 0.58%) with haemorrhagic stroke in the ezetimibe/simvastatin group and 34 subjects (7-yr KM 0.59%) with haemorrhagic stroke in the simvastatin group (HR 0.937; 95% CI 0.578-1.519, $p = 0.793$).

A similar imbalance in haemorrhagic stroke events has been reported in previous statin studies, and as highlighted in the CTT meta-analyses, this imbalance is off-set by the benefit seen in preventing the much more frequently occurring non-haemorrhagic stroke. Despite the imbalance in haemorrhagic stroke events noted in statin clinical trials, statin use continues to be widespread and endorsed by current treatment guidelines, indicating that in the clinical setting the benefit is seen to outweigh the risk.

In the broader ezetimibe development program, there is no suggestion of an increased risk of haemorrhagic stroke associated with ezetimibe use. Considering the information described above, haemorrhagic stroke remains an important potential risk in the EU ezetimibe/simvastatin RMP. MSD will perform routine pharmacovigilance of haemorrhagic stroke through the monitoring and evaluation of reports of haemorrhagic stroke and related events reported in patients treated with ezetimibe/simvastatin. Appropriate measures (such as updating of the PI) will be taken if new information is obtained that alters the risk/benefit profile of ezetimibe/simvastatin.

Is it reasonable to extrapolate benefits when use in combination with all statins or should the indication be restricted to simvastatin?

MSD believes that the information base relating to lipid lowering in general and with ezetimibe, and the results of IMPROVE-IT support the expectation of CV risk reduction for ezetimibe add-on therapy when used with all statins with proven outcomes benefit.

While the clinical evaluator has concluded that 'the incremental CV benefits of ezetimibe on top of other newer statins has not been directly assessed', they have made this statement in the context that:

...it is expected that the additional LDL-C lowering with ezetimibe with any statin would further reduce the risk of CV disease.

In addition, in the clinical evaluator's conclusions on clinical efficacy, the evaluator notes that:

Although IMPROVE-IT studied patients presenting with acute coronary syndrome (ACS), used only simvastatin as the background statin, and entered patients with LDL-C levels, the sponsors have provided information to justify that the modest benefits observed in terms of reduction of CV events may apply to patients with chronic CHD, those receiving any statin and to subjects with a broad range of LDL-C levels.

In the Section 31 request for these applications, the clinical evaluator noted that:

It is important to stress that ezetimibe 10 mg should be administered with a 'statin with proven cardiovascular benefit', that is, only with statins which are already approved for prevention of CV events in patients with CHD.

MSD concurs with the clinical evaluators view that the benefits of ezetimibe added on to simvastatin will also occur when ezetimibe is added to another statin, which has demonstrated a beneficial effect on CV risks, and as such proposed the inclusion of this in the indication statement for Ezetrol in the Section 31 response. Therefore, MSD has addressed the Delegate's comment that:

...to allow an indication for use with all statins would also infer use with statins that are not yet approved for use and with no data to support that use.

An additional important piece of information to consider when assessing the implications of the IMPROVE-IT result relates to the complementary and additive mechanism of action of ezetimibe and statins via the upregulation of LDL receptors. Statin equivalence and the consistent benefit of ezetimibe add-on therapy with all statins are endorsed in current European guidelines for the management of dyslipidaemias.⁵⁵ Furthermore, based on the results of the IMPROVE-IT trial, the 2015 ESC Guidelines for the Management of NSTEMI-ACS Patients and 2016 ACC Expert Consensus Decision Pathway recommend the use of add-on ezetimibe therapy when additional LDL-C lowering is needed with all statins.⁵⁶

The safety profile of ezetimibe administered with atorvastatin and rosuvastatin, as well as with other statins with proven CV benefit, is well established. The benefit of adding ezetimibe is inferred from the available scientific information and guideline recommendations developed with the consensus of key scientific leaders. MSD believes that limiting the use of ezetimibe in this indication to patients taking simvastatin is inconsistent with current clinical practice, is not warranted on the basis that an outcomes study has not been conducted on every member of the statin class co-administered with ezetimibe, and potentially prevents patients from accessing the most appropriate treatment to prevent CV morbidity.

Is it reasonable to extrapolate the use in all patients with CHD when the study population in the IMPROVE-IT study were a high risk group?

MSD concurs with the clinical evaluator's view:

Relevance of IMPROVE-IT results for patients with Chronic CHD

The IMPROVE-IT results showed that the benefit with ezetimibe began to emerge after one year of treatment, and continued over the ensuing years of the trial. Given that the benefit of further LDL-C lowering with ezetimibe occurred predominantly after 1 year strongly suggests that its benefits are not associated with events immediately surrounding the acute ACS event. Furthermore, an analysis of total

⁵⁵ Reiner Z, et al. ESC/EAS guidelines for the management of dyslipidaemias. *Eur Heart J*. 32: 1769-818 (2011).

⁵⁶ Roffi M, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 37: 267-315 (2016); Lloyd-Jones DM, et al. 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statins Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol*. 68: 92-125 (2016).

events (first and recurrent events) demonstrated that subjects in the ezetimibe/simvastatin group had a reduced hazard for total events for the primary and secondary composite endpoints compared to subjects in the simvastatin group. Although this analysis has limitations due to the inherent bias that may be introduced with a non-randomised comparison, the results support the durability of the treatment benefit of ezetimibe/simvastatin beyond the prevention of the first event, which is an important clinical benefit for high-risk subjects.

A stabilized ACS population was selected for study in IMPROVE-IT, because this represents a high-risk population, with high event rates (to support event accrual), and because PROVE-IT⁵⁷ had demonstrated that statin therapy could reduce CV risk in an ACS population. ACS can be considered as the initial clinical event on a continuum of the natural history of CHD with patients moving into the more chronic phase of the disease over time. The risk of subsequent CV events following an ACS event can be divided into two phases. During the acute phase of an ACS, the risk of a recurrent CV event is very high. However, as time passes, the acute syndrome transitions into a chronic phase where the risk for recurrent events is high but generally appears constant over a prolonged follow up period. In order to evaluate whether ezetimibe provides incremental benefit starting soon after an ACS event, and also throughout the transition to and in the chronic stable phase of ischemic heart disease, IMPROVE-IT was specifically designed to include longer term follow-up. All participants in IMPROVE-IT were pre-specified to be followed for at least 2.5 years. Since the trial was also event driven and required more than 5000 events to complete, the last patient randomised actually had the potential for 4 years of follow up and the median follow-up in the entire cohort was approximately 6 years in order to accrue the necessary number of events.

Thus, the population in IMPROVE IT was followed through both phases of the disease and the study therefore provides evidence of the drugs benefit in the CHD population overall irrespective of disease phase. IMPROVE-IT provides unequivocal data demonstrating the incremental benefit of ezetimibe on top of statins in decreasing CV risk in patients with CHD following the ACS period and into a period of chronic CHD.

Were the benefits seen due to a lowering of LDL (and therefore may be seen with other drugs) or due to ezetimibe? And does this matter for the new indication?

IMPROVE-IT clearly demonstrates that lowering LDL-C with ezetimibe results in CV benefit and, as discussed above, the CV risk reduction observed with LDL -C lowering by ezetimibe is consistent with the benefit that would be expected with a similar degree of statin mediated LDL-C lowering. Any suggestion of an alternate mechanism of action is speculative, and is not supported by the evidence.

Conclusion

MSD maintains that the results of the IMPROVE-IT study confirm the clinical relevance of ezetimibe therapy in the reduction of CV risk in patients with CHD. The findings support an indication which will provide an additional option for prescribers in managing patients who are unable to achieve the desired results on statin therapy.

However, should the ACPM advise that it is not reasonable to extrapolate the use to all patients with CHD, MSD would like to request consideration of a modified indication, consistent with that approved for these applications in the EU:

Ezetrol

§ Prevention of Cardiovascular Events

⁵⁷ Cannon CP, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *NEJM* 350: 1495-1504 (2004).

Ezetrol is indicated to reduce the risk of cardiovascular events (see section 5.1) in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS) when added to ongoing statin therapy or initiated concomitantly with a statin.

Vytorin

§ *Prevention of Cardiovascular Events*

Vytorin is indicated to reduce the risk of cardiovascular events (see section 5.1) in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS), either previously treated with a statin or not.

Should the ACPM advise that it is not reasonable to extend the indication to include all CV events from the primary composite endpoint of the study, MSD is willing to consider further modification of the indication.

Question for sponsor

- *“Please supply a copy of the final letter from the FDA outlining the reasons for rejection.”*

On 12 February 2016, FDA issued a Complete Response Letter following review of Merck’s Zetia and Vytorin supplemental new drug applications (sNDA). The FDA action letter confirmed that Merck would not get an approval as a recommended action for the Zetia and Vytorin sNDAs based on IMPROVE-IT. The FDA indicated that the results are not adequately statistically persuasive to support the proposed claim on the basis of a single trial. Merck would need to generate additional evidence that would independently substantiate that ezetimibe reduces the risk of CV events by conducting another adequate and well controlled trial. The team is diligently in post action discussions about the next steps.

Advisory Committee considerations

The ACPM, having considered the evaluations and the Delegate’s overview, as well as the sponsor’s response to these documents, resolved to recommend the following to the TGA Delegate of the Secretary.

- Ezetrol (ezetimibe): PM-2015-01524-1-3

The ACPM, taking into account the submitted evidence of pharmaceutical quality, safety and efficacy agreed with the Delegate that Ezetrol tablet containing 10 mg of ezetimibe has an overall negative benefit-risk profile for the proposed indication.

- Vytorin (ezetimibe/simvastatin): PM-2015-01525-1-3

The ACPM, taking into account the submitted evidence of pharmaceutical quality, safety and efficacy agreed with the Delegate that Vytorin tablet containing ezetimibe 10 mg/ simvastatin FDC 40 mg and ezetimibe 10 mg/ simvastatin FDC 80 mg has an overall negative benefit-risk profile for the proposed indication.

In making these recommendations, the ACPM:

- Was of the view that efficacy (clinically meaningful benefit) had not been satisfactorily established in the proposed indication.
- Advised that the clinical meaningfulness of the efficacy data submitted was uncertain because of the small size of the effect, the proposed translation to a wider population than that studied and the inconsistent effect within the composite primary endpoint chosen for investigation (CV events).
- Noted there was no overall benefit in all-cause mortality or CV mortality which are better clinically meaningful and reliable endpoints.

- Advised that the results of the single clinical trial were not robust enough to support the extension of indication on the basis of a single trial.
- Noted that the RRR of 6.4% was below the anticipated RRR of 10% that the sponsor used in the power calculations.
- Was concerned that the ARR seen in the high risk population (post-acute coronary event and with a high proportion having diabetes and hypertension) was small (around 2% overall) and the RRR in a lower risk population as proposed in the indications was likely to be even smaller.
- Was of the view that the population with CHD in the proposed indication is not the same as those enrolled in the trial and the benefits seen may be less in this group as the clinical trial population used patients with an ACS.
- Noted that there was no comparison of the use of ezetimibe/simvastatin with a high dose statin, more potent statins or other lipid lowering agents.
- Noted that the benefits were probably due to treating to a lower LDL target.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

- ***(Q1) Is the single pivotal study robust enough to ensure efficacy?***

The ACPM noted that the FDA indicated that the results of the IMPROVE-IT study were not adequately statistically persuasive to support the proposed claim on the basis of a single trial. The ACPM also noted that the EMA guidelines for the use of one pivotal study state the minimal requirement is generally one controlled study with statistically compelling and clinically relevant results.

The ACPM was of the view that the use of a composite outcome increased the statistical power and it seemed likely that the large size of the study and very large patient population contributed to the statistical significance of the primary outcome.

Therefore, the ACPM advised that although efficacy is proven for the lipid lowering effect the data submitted in support of the clinical endpoint are not sufficiently robust to predict a reliable translation to a meaningful outcome benefit for patients.

- ***(Q2) Are the benefits in cardiovascular risk reduction large enough warrant this indication?***

The ACPM noted the relatively small absolute risk ratio in a high risk population (post acute coronary event and with a high proportion having diabetes and hypertension). The ACPM was of the view that the ARR in the sponsor's proposed indications CHD is likely to be less.

The ACPM also noted that the confidence intervals were approaching one, there was lack of supporting evidence from other trials, and there was a significant difference in only some of the components of the composite endpoints.

The ACPM was of the view that there was no overall benefit in all-cause mortality or CV mortality. The ACPM noted that these are the preferred endpoints in studies of CV prevention. In addition the RRR of 6.4% was below the anticipated RRR of 10% that the sponsor used in the power calculations.

The ACPM noted that the population with CHD in the proposed indication is not the same as those enrolled in the clinical trial group group which used patients with an ACS.

Therefore, the ACPM advised that the indication requested is not supported by the data submitted.

- ***(Q3) Is it reasonable to extrapolate benefits when used in combination with all statins or should the indication be restricted to simvastatin?***

Ezetimibe is available for additional LDL lowering in conjunction with a statin currently. It is unknown whether the endpoints in IMPROVE-IT would translate to other statin ezetimibe combinations.

- ***(Q4) Is it reasonable to extrapolate the use in all patients with CHD when the study population in the IMPROVE-IT study were a high risk group?***

The ACPM noted that the evaluator was satisfied that the results of the IMPROVE-IT study were relevant to patients with chronic CHD as the benefits with ezetimibe were seen after 1 year of therapy and were persistent over the 7 years of the study. However, the ACPM was of the view that it was not reasonable to impute meaningful clinical relevance from these results for a wider population, particularly when the study population was in patients with ACS.

- ***(Q5) Were the benefits seen due to a lowering of LDL (and therefore may be seen with other drugs) or due to ezetimibe? And does this matter for the new indication?***

The ACPM was of the view that the demonstrated benefit is most likely due to LDL-C reduction but noted that this is not a critical consideration for this submission.

- ***(Q6) Is the imbalance in the number of haemorrhagic strokes between the ezetimibe and ezetimibe/simvastatin groups a concern?***

The ACPM noted that more subjects in the ezetimibe/simvastatin group experienced a haemorrhagic stroke than in the simvastatin group, but the number of haemorrhagic strokes was relatively small in both treatment groups. In addition, the HR for all strokes suggests an overall benefit for the ezetimibe/simvastatin group. This result of a benefit for overall strokes, but a smaller increase in risk for haemorrhagic strokes is consistent with the stroke data from the Cholesterol Treatment Trialists' (CTT) meta-analysis of statin based lipid lowering trials.

The ACPM advised that this event is appropriately specified in the RMP.

- ***The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.***

The ACPM expressed concern about the increased myopathy risk with Vytorin 10/80. The ACPM was of the view that clinical consideration should be given to a different statin, rather than increasing simvastatin to 80 mg in the FDC product.

Initial outcome

Based on a review of quality, safety and efficacy, TGA rejected the registration of the applications made as part of one submission to extend the registered indications for ezetimibe (PM-2015-1524-1-3) and the FDC ezetimibe/simvastatin (PM-2015-01525-1-3) in relation to the existing registered therapeutic goods:

- Ezetrol: ezetimibe 10 mg tablet blister pack (ARTG R 91161); and
- Vytorin FDC: ezetimibe and simvastatin 10/10mg, 10/20mg, 10/ 40mg and 10/80mg tablet blister pack (ARTG R 98100, 98111, 98115 and 98117).

This decision relates to these proposed indications:

- Ezetrol for the proposed indication:

Adults (≥ 18 Years)

Prevention of Cardiovascular Disease: Ezetrol, administered with a statin, is indicated to reduce the risk of cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalisation for unstable angina, or need for revascularisation) in patients with coronary heart disease (CHD).

- Vytorin FDC for the proposed indication:

Adults (≥ 18 Years)

Prevention of Cardiovascular Disease: Vytorin is indicated to reduce the risk of cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalisation for unstable angina, or need for revascularisation) in patients with coronary heart disease (CHD).

Reasons for the decision

In relation to both of these decisions, the TGA Delegate of the Secretary is not satisfied that efficacy of the goods have been satisfactorily established for the purpose for which they are proposed to be used.

The reasons for the decisions are set out below.

Background

Ezetrol was considered by the Australian Drug Evaluation Committee (ADEC) at its 227th and 228th meetings in April and June 2003, respectively. It was included on the ARTG in June 2003. Vytorin was included on the ARTG in January 2005.

A pre-submission meeting was held in February 2015 between TGA and MSD to discuss the current submission to extend the use of Ezetimibe for CV protection in combination with a statin. The issues of use with other statins, use in CHD rather than ACS, and others were raised. In July 2015, the sponsor submitted two applications for Ezetrol and Vytorin FDC. As the applications propose similar changes and relate to the same data, it is appropriate and convenient to consider and discuss the applications together in this notice.

The use of ezetimibe for CV prevention has been approved EMA in February 2016 with the following indication:

Ezetrol is indicated to reduce the risk of cardiovascular events (see section 5.1) in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS) when added to ongoing statin therapy or initiated concomitantly with a statin.

In their pre ACPM response, the sponsor informed the TGA that:

On February 12, 2016, the Food and Drug Administration (FDA) issued a Complete Response Letter following review of Merck's Zetia (NDA 021445/S-038) and Vytorin (NDA 021687/S-054) supplemental new drug applications (sNDA).

The FDA action letter confirmed that the sponsor would not get an approval as a recommended action for the Zetia and Vytorin sNDAs based on IMPROVE-IT. FDA indicated that the results are not adequately statistically persuasive to support the proposed claim on the basis of a single trial. TGA informally requested a copy of the complete response letter, however this was not provided.

The applications for the use of Ezetrol and Vytorin for CV prevention were considered by the ACPM in June 2016. The main ground for rejection was that efficacy was not clearly established.

Material considered

In making these decisions, the Delegate of the Secretary took into account the following material:

- Cover letter from the sponsor dated 6 July 2015
- TGA clinical evaluation reports (first round dated November 2015 and second round dated April 2016)
- Delegate's 'request for ACPM advice' dated June 2016
- Sponsor's pre ACPM response
- Minutes of the ACPM June 2016
- Minutes of ADEC 227 and 228 in 2003
- Sponsor post ACPM response dated July 2016
- RMP dated April 2016

Overseas Data was also taken into consideration:

- FDA Centre for drug evaluation and research: summary minutes of the endocrinologic and metabolic drug advisory committee meeting, December 2015
- European variation reports dated February 2016, supplied by the sponsor

Literature references were also considered:

- Cannon CP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *NEJM* 372: 2387-2397 (2015) (including editorials);
- CTT collaboration. Efficacy and safety of more intensive lipid lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet* 376: 1670-1681 (2010);
- Cannon CP, et al. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. *J Am Coll Cardiol.* 48: 438-445 (2006)
- Cannon CP, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *NEJM* 350: 1495-1504 (2004);
- EMA/CHMP/748108/2013: Guideline on clinical investigation of medicinal products in the treatment of lipid disorders;
- EMA/CHMP/EWP/311890/2007: Guideline on the evaluation of medicinal products for cardiovascular disease prevention;
- CPMP/EWP/2330/99: Points to consider on application with meta-analysis or single pivotal study;
- ACC/AHA Prevention Guideline: 2013 ACC/AHA Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. *Circulation* 129 (suppl 2): S1-S45 (2014);
- Piepoli MF, et al. European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J.* 37: 2315-2381 (2016);
- National Vascular Disease Prevention Alliance: Guidelines for the management of absolute cardiovascular disease risk (2012).

Findings on material questions of fact

The Delegate of the Secretary makes the following findings based on the material identified above.

IMPROVE-IT Study

The study which formed the basis of this submission was the IMPROVE-IT study. This was an investigator initiated superiority study designed to determine the safety and efficacy of ezetimibe in combination with simvastatin in stabilised patients with ACS. It was a multicentre, randomised, double blind, active and placebo controlled trial. The main efficacy endpoint was a composite of CV death, major coronary event (non-fatal MI, UA needing admission to hospital, all coronary revascularisation) and non-fatal stroke. Secondary endpoints included other composite measures.

The study was designed with a sample size of 10,000 patients on the assumption that there would be a 0.39 mmol/L difference in LDL-C between groups that would translate to a 10% reduction in events over 2 years. However, the sample size was increased as the event rate was lower than anticipated.

The patients enrolled in the study were of high CV risk, including 41% with a history of angina, 21% with a history of MI, 61% with hypertension, 27% with diabetes, and 18% with moderate renal impairment. The baseline lipid level was 2.43mmol/L.

After 7 years, the primary composite endpoint was reached in 28.4% of the ezetimibe/simvastatin group and 30.2% of the simvastatin group. This calculates to be a RRR of 6.4%, ARR of 1.95%. The ARR in the components of the endpoint were numerically small, but favoured ezetimibe/simvastatin except UA. There was no statistically significant difference in CV or all-cause mortality. Further details of the study are available in the dossier and clinical evaluation report.

There were no new safety concerns. The rate of myopathy was similar between the two groups, which was surprising as more patients in the simvastatin group received high dose simvastatin which has a known association with myopathy. Numerically, there were more haemorrhagic strokes in the ezetimibe/simvastatin group but no increased risk of stroke overall. An increased rate of haemorrhagic stroke has also been observed with other LDL lowering drugs and is included in the RMP.

Other investigator initiated studies

- **SHARP:** The aim of this study was to assess the LDL lowering effect of ezetimibe 10mg and simvastatin 20mg versus placebo in patients with CKD. This study showed beneficial effects of the combination therapy in terms of a reduced rate of MVEs, however, there was insufficient data to determine if there was a beneficial effect of ezetimibe over simvastatin alone.
- **ENHANCE:** The aim of this study was to determine if ezetimibe had additional benefits over simvastatin on carotid intima thickness in patients with heterozygous familial hypercholesterolemia. Despite achieving significant reductions in LDL-C, no regression in carotid intima thickness was observed after 2 years.

Recommendation from the clinical evaluator

The clinical evaluator recommended rejection of the proposed indications for Ezetrol and Vytorin for the prevention of CV events for the following reasons:

- The RRR in the primary endpoint was modest. There was no reduction in non-CV or CV deaths.
- There was a higher risk of fatal and haemorrhagic stroke in the group treated with ezetimibe/simvastatin group than the simvastatin group alone.

- The term 'need for revascularisation' in the indication was not supported by the clinical trials.
- There is a risk of rhabdomyolysis/myopathy, malignancies; gallbladder disorders, pancreatitis, interstitial lung disease, acute renal failure and hypersensitivity.
- There was no information about the incremental effect of ezetimibe on other statins.

Recommendation from ACPM

The ACPM, taking into account the submitted evidence of pharmaceutical quality, safety and efficacy, agrees that Ezetrol and Vytorin had an overall negative benefit-risk profile for the proposed indications. In making this recommendation, the ACPM:

- was of the view that efficacy (clinically meaningful benefit) had not been satisfactorily established in the proposed indication;
- advised that the clinical meaningfulness of the efficacy data submitted was uncertain because of the small size of the effect, the proposed translation to a wider population than that studied and the inconsistent effect within the composite primary endpoint chosen for investigation (CV events);
- noted there was no overall benefit in all-cause mortality or CV mortality which are better clinically meaningful and reliable endpoints;
- advised that the results of the single clinical trial were not robust enough to support the extension of indication on the basis of a single trial;
- noted that the RRR of 6.4% was below the anticipated RRR of 10% that the sponsor used in the power calculations;
- was concerned that the ARR seen in the high risk population (post-acute coronary event and with a high proportion having diabetes and hypertension) was small (around 2% overall) and the RRR in a lower risk population as proposed in the indications was likely to be even smaller;
- was of the view that the population with CHD in the proposed indication is not the same as those enrolled in the trial and the benefits seen may be less in this group as the clinical trial population used patients with an ACS;
- noted that there was no comparison of the use of ezetimibe/simvastatin with a high dose statin, more potent statins or other lipid lowering agents; and
- noted that the benefits were probably due to treating to a lower LDL target.

Advice from EMA guidelines

EMA guidelines provide the following advice in relation to both pivotal trials and CV prevention:⁵⁸

In cases where the confirmatory evidence is provided by one pivotal study, this study will have to be exceptionally compelling and in the regulatory evaluation special attention will be paid to:

§ *Internal validity*

§ *External validity*

§ *Clinical relevance: the estimated size of benefit must be large enough to be clinically valuable*

⁵⁸ European Medicines Agency, "Points to consider on application with 1. Meta-analyses; 2. One pivotal study (CPMP/EWP/2330/99)", 31 May 2001.

§ *The degree of statistical significance: statistical evidence considerably stronger that $p < 0.05$ is usually required. (see point 9 below)*

§ *Internal consistency: similar effects in different sub-populations.*

For CV disease prevention:⁵⁹

Composite outcomes, including fatal and non-fatal CVD events, in which multiple endpoints are combined, are frequently used as primary outcome measures in randomised trials to reflect a number of outcomes that are of clinical importance and to increase statistical efficiency when event rates are low. Composite endpoints may be appropriate in trials of CV disease prevention when including hard clinical events (e.g. nonfatal MI, stroke). However, including in the composite, components which have a markedly different weight in term of clinical benefit is discouraged. An example is the combination in the primary composite endpoint of fatal events and clinician decision outcomes: hospitalisation, coronary revascularisation, amputation, use of rescue therapy, hospitalisation for heart failure. If a composite primary endpoint is used, generally its separate components are secondary or tertiary endpoints, which are analysed separately if clinically meaningful and validated.

To provide supportive information, and to ensure reliable interpretation, analyses of each separate component of the composite should be presented. For overall mortality and CV mortality both confidence intervals and point estimate are relevant for assessment. Any point estimate considerably in favour of the comparator is a matter of concern.

European Guidelines for CV Prevention 2016

The European Guidelines for CV prevention state (on page 48) that ezetimibe is indicated as combination therapy with statins in selected patients when a specific goal is not reached with the maximum tolerated dose of statin. It states (on page 47) that the use of ezetimibe with simvastatin has demonstrated that this combination of therapy gives results in line with the cholesterol treatment trialists.

There is some uncertainty in the area of cardiology if lipid lowering drugs should be used for patients at risk of future CV events, or to target a specific LDL level. Evidence from trials has suggested that lowering LDL C to < 1.8 mmol/L is associated with a lower risk of recurrent CV events.

The reasons for the Delegate of the Secretary's decision

The reason for the Delegate of the Secretary's decision with respect to the two applications is that efficacy is not satisfactorily established for the proposed indications. These decisions are made in the context of the use of a medication for the prevention of a common disease where there are a number of approved and efficacious treatment alternatives. In this setting, a new medicine would need to have robust evidence of efficacy against an appropriate comparator with minimal risks. In addition, Ezetrol is currently listed on the ARTG and not registering this new indication would not limit the availability of this medicine. The same argument applies with respect to Vytorin.

The sponsor's main evidence in support of the proposed indications came from a single large pivotal study. The Delegate of the Secretary has the following concerns about accepting the results of the study to support these indications.

⁵⁹ European Medicines Agency, "Guideline on the evaluation of medicinal products for cardiovascular disease prevention (EMA/CHMP/EWP/311890/2007)", 25 September 2008.

The results are not clinically meaningful

To justify the use of a medication to be used in an asymptomatic person with an unknown future risk of an event, there must be good evidence that the medication will work. In the IMPROVE-IT trial, the risk of the primary composite endpoint was around 30% over 7 years and the use of ezetimibe over simvastatin reduced the risk of an event by around 2%. This is a very small improvement in the event rate. Fifty subjects would be needed to be treated for 7 years to prevent 1 composite event. Even more subjects need to be treated to prevent a component of the composite endpoint. The Delegate of the Secretary accepts that an assessment of a clinically meaningful benefit may be subjective; however, the Delegate of the Secretary's view is supported by the clinical evaluator, the ACPM, and the sponsor's own experts who stated the effects of the IMPROVE-IT study were 'modest'.

The statistical significance was not robust

There was less difference between the events in treatment groups than anticipated. The revised sample size was based on data from the Cholesterol Treatment Trialists' meta-analysis and a meta-analysis of the four intensive versus standard dose statin trials where a reduction of 15 mg/dL difference in LDL between groups would lead to a 9.375% RRR. The final result of primary endpoint in the IMPROVE-IT study was a RRR of 6.4% despite a reduction in LDL-C of 0.39 mmol/L. This would suggest that ezetimibe did not have the magnitude of effect that the investigators had anticipated when they designed the trial, and is less efficacious than more intensive statin therapy.

The overall event rate for the primary endpoint (in both groups) was lower than expected in the trial. This resulted in more subjects needed to be recruited to adequately power the study. The confidence intervals in the clinical trial were narrow, indicative of the large sample size, and approached 1, signifying there is a 5% chance there was no statistically significant difference.

There were a number of outcomes evaluated, leading to the risk of a positive event due to multiplicity.

The use of a composite endpoint can be useful to increase the power of a study where the risk of individual outcomes is low, but does have problems of its own. The study was not powered for the components of the primary endpoints, and therefore one cannot be certain about the interpretation of these. Although the risk of primary composite endpoint was reduced, there was an increased risk of the components 'CV death' and 'documented UA' requiring hospitalisation. Overall, there was no change in the risk of stroke however there was an increased risk of fatal and haemorrhagic stroke. These discrepancies also put doubt over the validity of the composite endpoint.

There are concerns about the external validity

The proposed indication 'CHD' includes a wider population than in the study who had an ACS. Patients who have had an acute coronary event are at higher risk than those with more stable coronary artery disease. Risk reduction in patients with lower baseline risk is likely to be lower. The EMA and external experts were also of the view that its use should be considered in patients with ACS.

There was a discrepancy among efficacy of ezetimibe on the different sorts of markers of CV events (that is, reduction in non-fatal MI and revascularisation but increased CV death and documented UA, and small decreased risk of stroke but increased risk of fatal and haemorrhagic stroke). The Delegate of the Secretary would expect these all be in the same direction as they share similar pathophysiology. Although there will be some variability around any endpoint, the Delegate of the Secretary would expect that if the use of ezetimibe in addition to simvastatin had significant effect on coronary artery disease all measures of this would improve.

This clinical trial attempted to establish whether the use of ezetimibe/simvastatin was superior to simvastatin alone. There was no comparison to other mechanisms to lower LDL such as higher dose statin, a more potent statin or other drugs which lower LDL.

Use in the combination with simvastatin or all statins

There is no evidence of the efficacy for CV prevention with statins other than simvastatin: the Delegate of the Secretary is aware that ezetimibe is indicated for use with other statins as a treatment for hyperlipidemia and do not dispute the efficacy in this regard. However its use with other statins for the prevention of CV events has not been tested. The available statins have different potency, and the additional efficacy of Ezetimibe over these other statins for the prevention of CV events is unknown. A number of studies have demonstrated the benefits of high versus low dose statins, and more potent statins. The 2013 ACC/AHA guidelines describe the different potencies of the statins.⁶⁰

Use in the Australian context

The Australian Guidelines for CV risk reduction recommend the use of a risk calculator which does not include previous coronary artery disease, but does include age, sex, smoking, lipids, and blood pressure. A total assessment CV risk (REACH) was provided in the IMPROVE-IT study in the subgroup analysis, but there was very little difference in outcome between quartiles. The 2016 European CVD Prevention Guidelines also recommend a targeted approach to individual CV risk. The proposed indications are out of line with these guidelines. The Delegate of the Secretary would accept an indication out of line with an approved guideline if there was sufficient evidence to support it; however, this is not the case with current applications for Ezetrol and Vytorin.

The Delegate of the Secretary acknowledges the opinions of numerous experts that the sponsor submitted with their response to the notice issued under Section 31 (although notes that at least one of these may have a conflict of interest as they were an investigator in the IMPROVE-IT study; the others potential conflicts are unknown). These doctors were cardiologists and a general practitioner and were of the opinion that the IMPROVE-IT trial showed 'modest' benefits in the prevention of CV events. They had a consistent view that ezetimibe had a role in the management of patients after an ACS where optimal LDL levels could not be achieved with a statin alone due to intolerance or lack of efficacy. This view is also shared in the SAHMRI Lipid management after ACS consensus statement. The Delegate of the Secretary accepts ezetimibe may have a role for this subgroup of patients, but this is a different indication to that proposed.

Conclusion

The Delegate of the Secretary's view is supported by the clinical evaluator and is consistent with advice of the ACPM. In addition, the advice from the experts solicited by the sponsor did not support the proposed indication.

Accordingly, for the reasons set out above, the Delegate of the Secretary has decided not to register the products with the proposed indications because the efficacy has not been satisfactorily established for the purposes for which they are to be used.

Section 60 review

Following the initial decision described above, the sponsor sought a review under the provisions of Section 60 of the Act.

⁶⁰ Stone NJ, 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. *J Am Coll Cardiol.* 63(25 Pt B): 2889-2934 (2014).

Outcome

Ezetrol

Concerning the application to register ezetimibe (Ezetrol), pursuant to Section 60 of the Act, the Delegate of the Minister for the review has decided to set aside the initial decision to refuse registration and substitute in its place a decision to register ezetimibe (Ezetrol) 10 mg tablets for the following additional indication:

Adults (≥ 18 years)

Prevention of Cardiovascular Disease: *Ezetrol is indicated for administration in combination with the maximum tolerated dose of a statin with proven cardiovascular benefit in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS) in need of additional lowering of LDL-C in the expectation of a modest further reduction in the risk of cardiovascular events following at least one year of therapy (see Clinical Trials).*

The Delegate of the Minister notes that the sponsor requested this indication in its email dated 5 January 2017.

In making this decision, the Delegate of the Minister is mindful of the provisions of Section 25AA (1) and (1A) of the Act.

The Delegate of the Minister is prepared to register the product for the additional indication above on the basis that the Clinical Trials section of the PI will include the wording, figure and table set out below in the annexure to this decision letter, which should be read as part of this decision letter.

Vytorin

Concerning the application to register the FDC ezetimibe/simvastatin (Vytorin) 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg tablets, pursuant to Section 60 of the Act, the Delegate of the Minister has decided to set aside the initial decision to refuse registration and substitute in its place a decision to approve the following additional indication for Vytorin tablets:

Adults (≥ 18 years)

Prevention of Cardiovascular Disease: *Vytorin is indicated in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS) taking their maximum tolerated dose of simvastatin and in need of additional lowering of LDL-C in the expectation of a modest further reduction in the risk of cardiovascular events following at least one year of therapy (see Clinical Trials).*

The Delegate of the Minister notes that the sponsor requested this indication in its email dated 5 January 2017.

In making this decision, the Delegate of the Minister is mindful of the provisions of Section 25AA (1) and (1A) of the Act.

The Delegate of the Minister is prepared to register the product for the additional indication above on the basis that the Clinical Trials section of the PI will include the wording, figure and table set out below in the annexure to this decision letter, which should be read as part of this decision letter.

Transcript of the reasons for the Delegate of the Minister's substituted decision

Findings of fact

In July 2015, MSD submitted an application to register Ezetrol 10mg tablets for the following extended indication:

Adults (≥ 18 Years)

Prevention of Cardiovascular Disease: Ezetrol, administered with a statin, is indicated to reduce the risk of cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalisation for unstable angina, or need for revascularisation) in patients with coronary heart disease (CHD).

At the same time, MSD also submitted an application to register Vytorin 10 mg ezetimibe/10 mg simvastatin, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg combination tablets for the following additional indication:

Adults (≥ 18 Years)

Prevention of Cardiovascular Disease: Vytorin is indicated to reduce the risk of cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalisation for unstable angina, or need for revascularisation) in patients with coronary heart disease (CHD).

At that time of submission, these products were included on the ARTG for essentially identical indications as for Ezetrol, with minor wording differences to take into account that Vytorin is a FDC product.

The submitted clinical data supporting the proposed extension of indications relied principally on the results of the IMPROVE-IT clinical trial. The results of this trial had been published in the *NEJM*.⁶¹ The applications also included the report of the SHARP clinical trial referred to as Study #044. The submission also included a number of published papers, three of which have been referred to frequently in discussion of this application and the sponsor's Request for Review:

- Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. *Lancet* 366: 1267-1278 (2005);
- Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet* 376: 1670-1681 (2010); and
- Cholesterol Treatment Trialists' (CTT) Collaboration. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 380: 581-590 (2012).

Applications to extend the indications were approved in the EU in February 2016. The applications were processed through the Mutual Recognition Procedure with the German Regulatory Agency (BfArM) as the Reference Member State. The relevant approved indication for Ezetrol in Europe as reflected in the Summary of Product Characteristics (SmPC) is:

Prevention of Cardiovascular Events

Ezetrol is indicated to reduce the risk of cardiovascular events (see section 5.1) in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS) when added to ongoing statin therapy or initiated concomitantly with a statin.

The relevant approved indication in Europe for Vytorin (marketed in the EU as Inegy) as reflected in the SmPC is:

Prevention of Cardiovascular Events

⁶¹ Cannon CP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *NEJM* 372: 2387-2397 (2015).

Inegy is indicated to reduce the risk of cardiovascular events (see section 5.1) in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS), either previously treated with a statin or not.

An application in the US to extend the indication for ezetimibe tablets to CV risk reduction was rejected. Two rounds of clinical evaluation were undertaken by TGA. The second round evaluation took into account the sponsor's responses to the first round report including clinical questions in that report.

In April 2016, the sponsor submitted a response document to the second round clinical evaluation report with a heading "Clinical Relevance of IMPROVE-IT Findings". In that document, the sponsor addressed the clinical significance of "a modest 6.4% RRR", challenged the accuracy of the clinical evaluation report concerning HRs for "deaths from all causes, CV death, non-CV deaths, unknown deaths", and commented on "an increased risk of haemorrhagic stroke and fatal stroke".

In May 2016, the Delegate of the Secretary sought the advice of the ACPM concerning both applications for extension of indications. The Delegate of the Secretary sought specific advice about six matters. The Delegate of the Secretary indicated that her proposed plan of action was

to reject the application to extend the indication of ezetimibe and ezetimibe/simvastatin for use in the prevention of CV events. The main reason for rejection is that efficacy is not satisfactorily established (see details above). It would be acceptable to include the results of the IMPROVE-IT study in the product information, with some minor amendments as described below. The RMP needs revising to include the drug interactions which appear to be missing in the versions included with this application.

In May 2016, the sponsor provided a pre-ACPM response. The sponsor stated that it did not concur with the Delegate of the Secretary's conclusion that the applications to extend the indications should be rejected on the basis that efficacy is not satisfactorily established. In addition to addressing the matters on which the Delegate of the Secretary had sought the advice of the ACPM, the sponsor raised the possibility of amended indications in the following terms:

However, should the ACPM advise that it is not reasonable to extrapolate the use to all patients with CHD, MSD would like to request consideration of a modified indication, consistent with that approved for these applications in the EU:

§ *Ezetrol:*

Prevention of Cardiovascular Events

Ezetrol is indicated to reduce the risk of cardiovascular events (see section 5.1) in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS) when added to ongoing statin therapy or initiated concomitantly with a statin.

§ *Vytorin:*

Prevention of Cardiovascular Events

Vytorin is indicated to reduce the risk of cardiovascular events (see section 5.1) in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS), either previously treated with a statin or not.

Should the ACPM advise that it is not reasonable to extend the indication to include all CV events from the primary composite endpoint of the study, MSD is willing to consider further modification of the indication.

At its meeting held in June 2016, the ACPM considered the applications to extend the indications. The resolutions are outlined above.

In July 2016, the sponsor provided a response to the ACPM minutes. In summary, the sponsor did not concur with the resolution that the application has an overall negative benefit-risk profile for the proposed indication. The sponsor maintained, as detailed in all previous responses (including the pre-ACPM Response, Appendix 1) to TGA, that the results of the IMPROVE-IT study confirm the clinical relevance of ezetimibe therapy in the reduction of CV risk in patients with CHD. The sponsor noted that it had provided supporting statements from several leading experts in the fields of lipidology and CV medicine with the pre-ACPM Response. The sponsor stated that it would appreciate the delegate's consideration of the clinical expert statements provided.

The sponsor pointed out that, specifically, the following issues have been addressed by the experts:

- Clinical meaningfulness of the efficacy data provided from IMPROVE-IT;
- Extrapolation to all statins.

In August 2016, a copy of the Delegate of the Secretary's Section 25 decision letter was forwarded to the sponsor.

After the lodgement of the Section 60 request for review and the Delegate of the Minister's consideration of the documentation, the Delegate of the Minister informed the sponsor that they were not minded to register the additional indications proposed in the request for review. The Delegate of the Minister invited the sponsor to consider seeking a different indication, which they indicated they were minded to register.

There followed an exchange of emails during December 2016 and January 2017.

On 5 January 2017, as reflected in the sponsor's emails, the sponsor now sought registration for the following additional indications:

§ Ezetrol

Adults (≥ 18 years)

Prevention of Cardiovascular Disease: Ezetrol is indicated for administration in combination with the maximum tolerated dose of a statin with proven cardiovascular benefit in patients with CHD and a history of ACS in need of additional lowering of LDL-C in the expectation of a modest further reduction in the risk of cardiovascular events following at least one year of therapy (see Clinical Trials).

§ Vytorin

Adults (≥ 18 years)

Prevention of Cardiovascular Disease: Vytorin is indicated in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS) taking their maximum tolerated dose of simvastatin and in need of additional lowering of LDL-C in the expectation of a modest further reduction in the risk of cardiovascular events following at least one year of therapy (see Clinical Trials).

The sponsor also indicated that the PI documents would include the wordings, Figure⁶² and Table⁶³ as reflected in the exchange of emails.

⁶² See Figure 2 in this AusPAR.

⁶³ See Table 11 in this AusPAR.

The Delegate of the Minister's consideration of the sponsor's submission

The Delegate of the Minister deals in turn with each of the matters raised in the sponsor's Request for Reconsideration. The sponsor's letter seeking review contends that the Delegate of the Secretary:

- Did not consider the indication sought (as amended during the evaluation)
- Did not consider all material available to her including the CTT meta-analysis, expert opinions, and a pooled analysis of 27 clinical studies comparing ezetimibe plus statin to statin monotherapy
- Relied on factual findings that were not correct in relation to the pivotal clinical study (IMPROVE-IT), other investigator initiated studies, recommendations from the clinical evaluator and the ACPM, EMA Guidelines on use of a single pivotal study and CV Prevention, and clinical guidelines on lipid lowering
- Relied on reasons that do not have foundation in the materials available when questioning the clinical and statistical significance of the results of IMPROVE-IT, the relevance of findings regarding the components of the composite primary endpoint and the use of ezetimibe for CV disease prevention with statins other than simvastatin.
- Relied on reasons that do not support the decision in relation to the assessment of efficacy, the degree of statistical significance of the results, external validity of the study findings and consistency of the proposed indication with current treatment guidelines.

The Delegate of the Minister deals in turn with each of the matters raised by the sponsor. The Delegate of the Minister has italicised information taken from the sponsor's Request.

Sponsor's request

(a) The Delegate of the Secretary did not consider the indication sought (as amended during the evaluation)

Delegate of the Minister's response

The Delegate of the Minister notes that revisions were made to the indications throughout the evaluation process and in the Section 60 material. The Delegate of the Minister acknowledges that the Delegate of the Secretary did not make their decision in relation to the revised indications sought at the time of the decision. The Delegate of the Minister indicates that they are making their decision in relation to the most recent iterations of the proposed indications (that is, the indications proposed in the Section 60 material).

Sponsor's request

(b) The Delegate of the Secretary did not consider all material available to her including the CTT meta-analysis, expert opinions, and a pooled analysis of 27 clinical studies comparing ezetimibe plus statin to statin monotherapy. The nature of these materials is described in more details in paragraphs 6.1 to 6.3 of the sponsor's letter seeking review:

6.1 CTT Meta-Analysis

Efficacy and Safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials

This document is included in the list of materials considered, however the Delegate has not placed sufficient weight on the findings of this meta-analysis in reaching the initial decision.

The meta-analysis was provided as a reference to the initial application (Module 5.4: 03TK50) and is discussed at length in the clinical overview (Module 2.5).

This material contradicts the reasons for the Delegate's decision and supports the correct and preferable decision. The importance of the meta-analysis in underpinning the relevance of the clinical effects observed in IMPROVE-IT, explaining the consistency of the reduction in CV risk with the observed reduction in LDL-C, and in supporting the generalizability of the results observed with simvastatin to other statins is further discussed in Sections 8.1, 8.2 and 8.5 of this document.

The relevance of this document is explained by Professor [information redacted] in their second report:

For a proper understanding of the effect statins have in treating or preventing CV disease, reference needs to be made to the published results of the meta-analyses carried out by CTT, as set out in the following articles:

- § *'The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials' Lancet. 2012; 380(9841): 581-590.*
- § *'Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials' Lancet. 2010; 376(9753): 1670-1681.*
- § *'Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins' Lancet. 2005; 366(9493):1267-1278.*

The CTT meta-analyses have drawn a very clear correlation between reduction in LDL-C and reduced risk of MVEs down to LDL-C levels of <1.8 mmol/L with no evidence of any threshold within the range studied. This linear correlation was also reported to be applicable across the patient population, irrespective of age, sex, baseline LDL-C or previous vascular disease (see 'The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials' Lancet. 2012; 380(9841): 581-590, 585). The IMPROVE-IT results are entirely consistent with the linear correlation demonstrated by the CTT meta-analyses. That is, the results show that the LDL-C hypothesis is supported by the LDL-C reductions achieved by ezetimibe. In addition, the observed trend from the CTT meta-analyses between the reduced risk of MVEs and lower LDL-C level continues down to LDL-C levels of 1.4 mmol/L.

Delegate of the Minister's response

The Delegate of the Minister acknowledges that the three *Lancet* publications (2005; 2010; 2012) were included in the references in the sponsor's submission of July 2015. The Delegate of the Minister notes that the authors of the 2012 paper (meta-analysis of individual data from 27 randomised trials) concluded that:

In individuals with 5-year risk of MVEs lower than 10%, each 1 mmol/L reduction in LDL cholesterol produced an absolute reduction in MVEs of about 11 per 1000 over 5 years.

The Delegate of the Minister notes that this meta-analysis included results of studies of six different statins including one that is not registered in Australia (lovastatin). The paper does not report separately the pooled effects of each of those six individual statins. The paper reports analyses of:

MVEs, major coronary events (defined as non-fatal myocardial infarction or coronary death), stroke (subdivided by type), coronary revascularisation procedures, cancers, and cause-specific mortality.

It does not report an analysis congruent with the primary objective of the IMPROVE-IT trial (the clinical benefit of ezetimibe/simvastatin combination compared with simvastatin

in stabilised ACS subjects defined as the reduction in the risk of the occurrence of the composite endpoint of CV death, major coronary events, and non-fatal stroke. Major coronary events included

non-fatal MI, documented UA that required admission into a hospital, and all coronary revascularization with either percutaneous coronary intervention (PCI) or CABG occurring at least 30 days after randomized treatment assignment.

The paper does not report any results involving the combined use of a statin with ezetimibe. The Delegate of the Minister accepts that the results of the IMPROVE-IT trial showing reductions in risk of some CV events are generally consistent with the results of the CTT analyses. The published papers do not constitute evaluable evidence to support the efficacy of combinations of ezetimibe and a statin, but do constitute supportive evidence.

Sponsor's request

6.2 Expert Opinions

In reaching the initial decision, the Delegate has failed to consider the entirety of the expert testimony from 4 key scientific leaders in the field of lipidology and cardiology. These statements were provided by MSD in its pre-ACPM response (May 2016) and referenced again in its post-ACPM response submitted July 2016.

The Delegate acknowledges these statements and is of the view that the expert assessment of the effects of IMPROVE-IT as modest is supportive of the reason that 'The results are not clinically meaningful'.

The expert statements support the correct and preferable decision by discussing the place of ezetimibe treatment in patients with a history of ACS, an indication offered by MSD in its pre-ACPM response, but not considered by the ACPM or the Delegate.

The statements contradict the Delegate's reason that the modest benefit observed is not clinically significant. The experts view is that ezetimibe is not intended to replace statins, but to complement them in patients who are unable to reach target LDL-C levels on their maximally tolerated statin dose. In this context, a modest improvement in LDL-C, and in CV outcomes, on top of the improvement achieved by a statin, addresses a treatment gap that currently exists, and is therefore clinically significant.

Professor [information redacted] explains, in their second report, the correct understanding of the term 'modest' as it was used in the expert statements:

The IMPROVE-IT study demonstrated that, even in patients with already low low-density lipoprotein cholesterol (LDL-C) levels, effecting a further reduction in LDL-C using ezetimibe provided an additional benefit in terms of reduced risk of adverse CV events. Because of the very significant number of patients in the population with Chronic Heart Disease (CHD) and at a high risk of having a CV event such as those with a history of ACS, the benefit shown is quite large in population terms, and in terms of the prevention of CV events that can be achieved.

An immediate change of practice by almost all practitioners would generally occur where a 15% relative benefit is demonstrated. However a drug that is shown to deliver a relative benefit lower than 15% can still be clinically meaningful. This is especially where the benefit produced is shown to be additive to that from existing treatments. The results demonstrated by the IMPROVE-IT study might be described by some as 'modest' because they do not show that a revolutionary change in the way patients are treated is needed, but that does not mean that the improvements shown are not of clinical significance and overall importance.

Further discussion of the support offered by these experts for the proposed indication is included in Section 5.4 of this document.

Delegate of the Minister's response

The Delegate of the Minister has reviewed the Expert Statements and the SAHMRI Consensus Advice. It is important to note that these statements express opinions and do not constitute evaluable evidence. That said, the Delegate of the Minister has taken into account the opinions of these experts that the results of the IMPROVE-IT trial are both statistically and clinically significant with an ARR of 2% and a RRR of 6% in the primary outcome measure in patients with a history of ACS. Two experts describe the magnitude of the event reduction as modest.

6.3 Pooled analysis of ezetimibe studies: Lipid-altering efficacy of ezetimibe plus statin and statin monotherapy and identification of factors associated with treatment response: a pooled analysis of over 21,000 subjects from 27 clinical trials

In reaching the conclusion that there is no evidence of the efficacy of ezetimibe for CV prevention with statins other than simvastatin, the Delegate has failed to consider the evidence from this analysis that ezetimibe provides a consistent proportional additive decrease in LDL-C levels with any statin at any statin dose (on average 23% relative to on-statin baseline). In considering this and the finding that the results of IMPROVE-IT are consistent with the CTT meta-analysis, it is possible to infer that ezetimibe would also provide a constant proportional additive decrease on CV events.

Further discussion of the generalizability of the results of IMPROVE-IT to statins other than simvastatin can be found in Section 8.4 of this document.

Delegate of the Minister's response

See response under 6.1 above.

Sponsor's request

(c) The Delegate of the Secretary relied on factual findings that were not correct in relation to the pivotal clinical study (IMPROVE-IT), other investigator initiated studies, recommendations from the clinical evaluator and the ACPM, EMA Guidelines on use of a single pivotal study and CV Prevention, and clinical guidelines on lipid lowering. The nature of the claimed instances is described in paragraphs 7.1 to 7.6 of the sponsor's letter seeking review:

7.1 IMPROVE-IT study

The Delegate's decision was affected by her erroneous statements that:

- § the rate of myopathy in the ezetimibe/simvastatin group was surprising; and*
- § there was an increased risk of fatal and haemorrhagic stroke associated with ezetimibe add-on treatment.*

The Delegate stated that:

The rate of myopathy was similar between the two groups, which was surprising as more patients in the Simvastatin group received high dose simvastatin which has a known association with myopathy.

The similar rate of myopathy between the two groups is not surprising. The risk of myopathy associated with ezetimibe use is described in the Product Information for Ezetrol (as available online on the Australian Register of Therapeutic Goods, ARTG ID: 91161). Myopathy is a known adverse reaction to lipid lowering drugs, and has been reported rarely in post-marketing use of ezetimibe monotherapy. Given that patients in the ezetimibe/simvastatin group in IMPROVE-IT experienced greater lipid lowering, it is not unexpected to see cases of myopathy associated with such very low

LDL-C levels. In the case of the proposed patient population, the risk of myopathy is consistent with what is already known about ezetimibe, and is far outweighed by the decreased risk of CV events.

The Delegate further stated that:

Numerically, there were more haemorrhagic strokes in the ezetimibe/simvastatin group but no increased risk of stroke overall

and

...there was an increased risk of fatal and haemorrhagic stroke.

In IMPROVE-IT, treatment with ezetimibe was associated with a substantial reduction in stroke. This was driven by a reduction in ischemic stroke. In IMPROVE-IT the numbers of patients experiencing haemorrhagic stroke were small overall (59 and 43 events in the ezetimibe/simvastatin and simvastatin groups respectively) and conclusions cannot be drawn from this data regarding increases in risk of haemorrhagic stroke due to the small incidence of events and the fact that the difference was not statistically significant ($p = 0.110$). Notably, the imbalance in haemorrhagic strokes in IMPROVE-IT was not present when assessing the results for those who remained on study treatment and within 30 days of study drug discontinuation.

These results are similar to stroke related results from the Cholesterol Treatment Trialists' (CTT) meta-analyses of statin CV outcomes trials. Any imbalance is off-set by the benefit seen in preventing the much more frequently occurring non-haemorrhagic stroke, particularly in the ACS population from the proposed indication, who are at high risk of recurrent events.

Professor [information redacted] provides the proper explanation of the occurrence of adverse events in IMPROVE-IT in their second report:

The IMPROVE-IT trial did not show any meaningful increases in adverse effects caused by the addition of ezetimibe to simvastatin treatment. While there were numerically more incidences of fatal and haemorrhagic stroke in the group of patients treated with ezetimibe, this increase was not statistically significant and the incidence of these events was low in both groups.

The IMPROVE-IT study does not show, or provide any basis for believing, that ezetimibe increases the risk of haemorrhagic stroke or of fatal stroke in general, or of other adverse events.

It should be noted that the Cholesterol Treatment Trialists' (CTT) Collaborators meta-analyses of statin studies (discussed below) have shown that reduction of LDL-C can lead to an increased frequency of haemorrhagic stroke. However, given the low overall frequency of these strokes, the much greater incidence rate of other adverse CV events, and the significant overall lowering of risk of adverse CV events achievable through lowering LDL-C, the benefits of LDL-C lowering in patients with need of additional lowering of LDL-C levels markedly outweigh the risks.

Further, the reported overall incidence of adverse effects in patients receiving ezetimibe monotherapy is the same as that in patients receiving placebo treatment. This is set out in the 'Adverse Effects' section of the current Product Information sheet on the Australian Register of Therapeutic Goods for Ezetrol (ARTG ID: 91161).

As the Delegate correctly stated in the decision, 'there were no new safety concerns' shown for the ezetimibe/simvastatin group compared to the simvastatin control

group. IMPROVE-IT did not show any new risks associated with ezetimibe treatment as an add-on to statin treatment.

Delegate of the Minister's response

The Delegate of the Minister notes that the ACPM advised that:

Safety

The ACPM noted that overall, 4818 (26.55%) patients experienced at least one treatment-related adverse event (AE) (Ezetimibe/ Simvastatin versus Simvastatin alone: 26.8% versus 26.3%).

There were 7289 (40.2%) subjects who experienced at least one serious adverse event (SAE); 3640 (40.1%) in the ezetimibe/simvastatin group and 3649 (40.2%) in the simvastatin group. The most common SAEs were neoplasms (benign and malignant) musculoskeletal disorders and infections/ infestations with similar incidence in the treatment groups. The risk of myopathy related events was similar in the two groups, given that more patients in the simvastatin monotherapy group had higher dose of statin, there was concern that ezetimibe may also be a risk factor for myopathy.

The ACPM noted that no new safety concerns were identified.

and that

The ACPM noted that more subjects in the ezetimibe/simvastatin group experienced a haemorrhagic stroke than in the simvastatin group, but the number of haemorrhagic strokes was relatively small in both treatment groups. In addition, the hazard ratio (HR) for all strokes suggests an overall benefit for the ezetimibe/simvastatin group. This result of a benefit for overall strokes, but a smaller increase in risk for haemorrhagic strokes is consistent with the stroke data from the Cholesterol Treatment Trialists' (CTT) metaanalysis of statin based lipid lowering trials.

The ACPM advised that this event is appropriately specified in the Risk Management Plan (RMP).

Sponsor's request

7.2 Other Investigator Initiated Studies

The Delegate has referred to and relied on findings from other investigator initiated studies. In deciding these studies were relevant to the matters before her, the Delegate has made errors in understanding these studies.

(a) SHARP

In reference to the SHARP trial (Module 5.4: 03RJ73), the Delegate said:

SHARP: The aim of this study was to assess the LDL lowering effect of Ezetimibe 10mg and Simvastatin 20mg versus placebo in patients with CKD. This study showed beneficial effects of the combination therapy in terms of a reduced rate of MVEs, however, there was insufficient data to determine if there was a beneficial effect of Ezetimibe over Simvastatin alone.

The correct factual finding is that the results from the SHARP study are not of relevance to the assessment of the proposed indications. The correct factual finding is also that, as the SHARP study was not designed to determine if there was a beneficial effect to ezetimibe/simvastatin treatment over simvastatin therapy in terms of 'a reduced rate of MVEs', it cannot be sensibly concluded that the data from the SHARP study is insufficient to determine whether this benefit existed. Instead it can only be concluded that this was not a matter investigated by the SHARP study.

First, the SHARP study looked at patients with no known history of myocardial infarction or coronary revascularisation, and who had CKD. This patient population differs from the patient population studied in IMPROVE-IT, and those patients to which the proposed indications relate: "patients with coronary heart disease (CHD), with a history of acute coronary syndrome (ACS)". Consequently the SHARP study did not provide data or findings relevant to the proposed indications.

Second, the fact that the incremental benefit of ezetimibe was not determined in SHARP was a function of the study design, and not the result of insufficient data. In SHARP the outcomes benefit of ezetimibe/simvastatin was compared to placebo, therefore it was not possible to determine the incremental effect of ezetimibe from this study.

(b) ENHANCE

In reference to the ENHANCE study (Module 5.4: 03RCY3), the Delegate said:

ENHANCE: The aim of this study was to determine if ezetimibe has additional benefits over simvastatin on carotid intima thickness in patients with heterozygous familial hypercholesterolemia. Despite achieving significant reductions in LDL-C, no regression in carotid intima thickness was observed after 2 years.

The correct factual finding is that the results from the ENHANCE study are not relevant to an assessment of the proposed indications.

This study is not relevant to the current application because carotid intima thickness (cIMT) is not a validated surrogate endpoint for assessing the effects of a therapy on CV disease. In fact, this technique is seldom used now to evaluate drug efficacy (Module 5.4: 03RLCF, 03RLCG, 043X62), hence the results of this study are not comparable to the results of IMPROVE-IT.

Further, there were methodological problems with this study that led to possible confounding of the results, due to significant lipid lowering therapy prior to study initiation.

(c) Summary

These studies neither support nor conflict the incremental efficacy of ezetimibe observed in IMPROVE-IT and hence do not contain findings of material fact that are relevant to the decision.

Delegate of the Minister's response

The Delegate of the Minister notes that the expert opined that:

As supportive evidence, the SHARP study found significant CV event rate reduction in patients with chronic renal failure, who are generally considered to be at high CV risk, treated with simvastatin and ezetimibe compared with simvastatin alone.

The Delegate of the Minister has based their decision on the results of the IMPROVE-IT trial.

Sponsor's request

7.3 Recommendation from the clinical evaluator

The Delegate said one of the reasons the clinical evaluator recommended rejection of the proposed indications was that:

The term 'need for revascularisation' in the indication was not supported by the clinical trials.

This is false. The proposed indications include the words 'need for coronary revascularisation' (emphasis added) and not the words 'need for revascularisation', as explained in Section 5.1, as a direct response to this concern in the first round clinical evaluation report. This issue was not listed in the reasons for rejection of the proposed indication in the second round clinical evaluation.

The clinical evaluator also included a question in the Section 31 request, seeking a justification for the inclusion of the term need for revascularisation, when the primary outcome for IMPROVE-IT included only coronary revascularisation.

In their Section 31 response, MSD agreed with the clinical evaluator's view that the term 'revascularisation' did not reflect the primary outcome of the study, and amended the proposed indication to include only coronary revascularisation. The clinical evaluator was satisfied with this response, and this matter was not listed as a reason for rejection in the second round recommendation regarding authorisation.

Hence, this was not a correct factual finding at the time of the Delegate's decision, and is therefore not a basis for rejection of the application. The indications proposed at the time of the Delegate's decision included the words 'need for coronary revascularisation', consistent with the primary efficacy outcome for IMPROVE-IT.

Delegate of the Minister's response

The Delegate of the Minister accepts that earlier modifications of the proposed indication and the indication proposed in the sponsor's Request for Review include the term "coronary revascularisation". The Delegate of the Minister accepts that "coronary revascularisation" is the appropriate wording.

Sponsor's request

7.4 Recommendation from ACPM

The Delegate relied upon findings made by the ACPM which are incorrect.

(a) Appropriateness of end points

The ACPM said, and the Delegate repeated in their decision, that:

there was no overall benefit in all-cause mortality or CV mortality which are better clinically meaningful and reliable endpoints.

There is no basis for the conclusion that mortality endpoints are better clinically meaningful and reliable endpoints than those used in IMPROVE-IT, or that all-cause mortality and CV mortality are the preferred endpoints in studies of CV prevention.

These findings of the ACPM and Delegate arose because of an erroneous interpretation of the CHMP Guideline on the Evaluation of Products for Cardiovascular Disease Prevention (2008).⁶⁴

In the Delegate's request for ACPM's Advice, the Delegate provided the ACPM with the following information, which affected the ACPM's recommendation:

The clinical outcome endpoints in the pivotal submitted study (IMPROVE-IT) were objective and clinically relevant and generally complied with the TGA adopted CHMP guidelines for evaluation of medicinal products for cardiovascular disease prevention (2008).⁶⁵ However, it is important to note

⁶⁴ European Medicines Agency, "Guideline on the evaluation of medicinal products for cardiovascular disease prevention (EMA/CHMP/EWP/311890/2007)", 25 September 2008.

⁶⁵ European Medicines Agency, "Guideline on the evaluation of medicinal products for cardiovascular disease prevention (EMA/CHMP/EWP/311890/2007)", 25 September 2008.

that the TGA adopted guidelines for composite endpoints in trials of CV disease prevention mentions that:

All-cause mortality is preferred over CV mortality as primary endpoint or as one component of the primary endpoint. CV mortality if objectively and conservatively defined may also be acceptable and may be more sensitive to detect differences in non-inferiority approaches.

Sufficient confidence regarding overall mortality and non-CV mortality is necessary in this case. Composite endpoints may be appropriate if they include hard clinical events such as non-fatal MI, stroke. However, including in the composite, components which have markedly different weight in term of clinical benefit is discouraged. An example is the combination in the primary composite endpoint of fatal events and clinician decision outcomes such as hospitalisation, coronary revascularisation, amputation, use of rescue therapy, hospitalisation for heart failure. In such a case, the statistical significance of the primary composite endpoint is often driven by the clinician-decision outcome component, presenting further challenges for the interpretation of the study overall results. The more clearly components of a composite endpoint directly refer to the disease process, the less there is problem of interpretation.

The IMPROVE IT trial did not look at all-cause mortality. The composite endpoint included hospitalisation for angina and revascularisation which may have been driven by clinician decisions.

As the above extract makes plain, this guideline makes clear that CV outcome endpoints other than mortality are acceptable provided they can be justified as being objective and clinically relevant.

Further, the clinical evaluator was of the view that the components of the primary endpoint were directly related to the coronary heart disease and hence the primary outcome was acceptable and consistent with those used for other major studies examining the effect of treatment of statins for CV prevention.

Even if reference is made to only "hard clinical events" (as that term is used in the CHMP Guideline), IMPROVE-IT still shows a statistically and clinically significant improvement in outcomes for patients in the ezetimibe/simvastatin group when compared to the simvastatin group. As outlined above, an exploratory endpoint in IMPROVE-IT was the composite of CV death, non-fatal MI and non-fatal stroke (MACE endpoint). There was a 9.9% reduction in the risk of MACE in the ezetimibe/simvastatin group (HR 0.901; 95% CI 0.841-0.965, $p = 0.003$)

Contrary to the ACPM's statement, the guideline does not stipulate that mortality measures are 'better clinically meaningful' or 'preferred', but that they are generally acceptable.

Although all-cause and CV mortality may be acceptable measures of CV disease prevention, it is not always practical to use these endpoints, and the CHMP Guideline acknowledges this.

Conducting a trial powered on mortality raises significant practical considerations. For example, to power an IMPROVE-IT like study to detect a 10% treatment effect (note-this would be a large treatment effect) the study would need to enrol 60,000 subjects and follow for 10 years (assuming a 5.8% event rate at 7 years in the simvastatin only group). This raises ethical considerations as to whether it is in the interests of patients to answer this clinical question when there is sufficient other

information available that is supportive of the link between lowering LDL-C and improvement in CV outcomes (see Section 7.5(c)).

Further, in defining a primary endpoint, or a component of a composite primary endpoint, the guideline expresses a preference for all-cause mortality over CV mortality, due to the difficulties in objectively defining CV mortality. The guideline does not state that mortality outcomes are the preferred outcomes in general. In trials such as IMPROVE-IT, CV mortality is a better indicator of the effect of the treatment on the disease process. Given the age and overall health of the population, when considering all-cause mortality any treatment effect is likely to be diluted by causes of death not related to CV events.

The findings of IMPROVE-IT with regard to mortality outcomes are consistent with:

- § findings of other studies in lipid-lowering medicines (high dose/high intensity versus lower dose/lower intensity statin trials e.g. PROVE-IT, TNT, IDEAL (Module 5.4: 03PQH9, 03QW0W and 03QNK9, respectively)) which generally show similar risk for mortality between treatment groups, and
- § the requirements of the CHMP guideline for CV prevention (“For overall mortality and CV mortality both confidence intervals and point estimates are relevant for assessment and any point estimate considerably in favour of the comparator is a matter of concern”) in that, for mortality endpoints all point estimates are approaching 1, confidence intervals all include 1, and p-values are at least 0.499 or greater, indicating there is no statistically significant difference in the rates of death (see Section 4).

Additionally, IMPROVE-IT was not designed to assess the potential benefit of incremental LDL-C reductions on mortality endpoints alone (see Section 7.1).

Delegate of the Minister’s response

The ACPM is an independent group of medical experts. The Delegate of the Minister has noted that they recorded that:

The ACPM noted that there was no overall benefit in all-cause mortality or CV mortality which are better clinically meaningful and reliable endpoints.

The Delegate of the Minister has noted also that it is not always practical to use these endpoints, and that the CHMP Guideline on the Evaluation of Products for Cardiovascular Disease Prevention (2008)⁶⁶ acknowledges this. It is factually correct to state as in the European SmPC section 5.1 that:

Total mortality was unchanged in this high risk group (see Table 1).

Table 1 in that SmPC⁶⁷ indicates that CV mortality and rates of UA requiring hospitalisation and all coronary revascularisation were also unchanged. Importantly, the Delegate of the Minister has not accepted the implied requirement for a reduction in all-cause mortality or CV mortality as a reason for rejection of the sponsor’s application.

Sponsor’s request

Wrong indications considered

The Delegate relied on a recommendation from the ACPM that was not relevant because the indications sought had been amended to address the ACPM’s recommendation.

⁶⁶ European Medicines Agency, “Guideline on the evaluation of medicinal products for cardiovascular disease prevention (EMA/CHMP/EWP/311890/2007)”, 25 September 2008.

⁶⁷ Noted as Table 11 in this AusPAR.

The proposed indications which the ACPM considered, and made a recommendation in relation to, did not include the words "with a history of acute coronary syndrome (ACS)" which are included in the correct proposed indications.

Refer to Section 5 for details of changes to the proposed indication during the evaluation.

The ACPM stated that it noted the sponsor requested consideration of modified indications, which included these words:

if the ACPM considered that it was not reasonable to extrapolate the use to all patients with coronary heart disease (CHD).

However, the ACPM then only said it:

was of the view that the population with CHD in the proposed indication is not the same as those enrolled in the trial and the benefits seen may be less in this group as the clinical trial population used patients with an acute coronary syndrome (ACS).

The ACPM failed to consider or express an opinion on the amended proposed indications, which included the words "with a history of acute coronary syndrome (ACS)".

Had the Delegate considered the correct indications, the concerns of the ACPM around extrapolation to a perceived broader population would not have been a material consideration in the decision. The question of whether efficacy has been established would have centred on the population with ACS, which has been shown to receive a statistically, and clinically, significant benefit as per the proposed indication. Further discussion of the statistical and clinical significance of the study outcomes is included in Sections 7.5(a)(i), 8.1 and 8.2.

Delegate of the Minister's response

See my response at (a) above, viz: "the Delegate did not consider the indication sought (as amended during the evaluation)."

Sponsor's request

7.5 Advice from EMA Guidelines

The Delegate of the Secretary relied on two EMA Guidelines, concerning Pivotal Trials (CPMP/EWP/2330/99)⁶⁸ and CV Prevention (EMEA/CHMP/EWP/311890/2007).⁶⁹

The Delegate failed to properly consider and apply the Guidelines as a whole, and this led to the Delegate erroneously coming to the conclusion that IMPROVE-IT failed to satisfy the requirements needed for approval of the proposed indications.

(a) EMA Guideline on One Pivotal Study (CPMP/EWP/2330/99)⁷⁰

The Delegate summarised the guidance provided by the EMA document, Points to Consider on Application with 1. Meta-Analyses 2. One Pivotal Study (CPMP/EWP/2330/99), regarding the prerequisites to be satisfied where one pivotal study is relied upon, as follows:

⁶⁸ European Medicines Agency, "Points to consider on application with 1. Meta-analyses; 2. One pivotal study (CPMP/EWP/2330/99)", 31 May 2001.

⁶⁹ European Medicines Agency, "Guideline on the evaluation of medicinal products for cardiovascular disease prevention (EMEA/CHMP/EWP/311890/2007)", 25 September 2008.

⁷⁰ European Medicines Agency, "Points to consider on application with 1. Meta-analyses; 2. One pivotal study (CPMP/EWP/2330/99)", 31 May 2001.

In cases where the confirmatory evidence is provided by one pivotal study, this study will have to be exceptionally compelling and in the regulatory evaluation special attention will be paid to:

- § *Internal validity*
- § *External validity*
- § *Clinical relevance: the estimated size of benefit must be large enough to be clinically valuable*
- § *The degree of statistical significance: statistical evidence considerably stronger than $p < 0.05$ is usually required.*
- § *Internal consistency: similar effects in different sub-populations.*

The Delegate then expressed concern regarding some of these factors in relation to the proposed indications. The Delegate failed to properly apply the prerequisites from this Guideline. The correct understanding is that the results of IMPROVE-IT satisfy each of the prerequisite factors, and the Guideline supports a decision in favour of granting the proposed indications.

By considering all aspects of the guidance the Delegate would have placed the correct emphasis on the primary results of the study and the totality of evidence supporting the proposed indication, leading to a favourable assessment of the efficacy of the ezetimibe/simvastatin combination in the proposed indication.

(i) The degree of statistical significance

The Delegate said that statistical evidence considerably stronger than $p < 0.05$ is usually required. The Delegate failed to consider the following portion of the Guideline:

- § *The degree of statistical significance. Statistical evidence considerably stronger than $p < 0.05$ is usually required, **accompanied by precise estimates of treatment effects, i.e. narrow confidence intervals. The required degree of significance will depend on factors such as the therapeutic indication, the primary endpoint, the amount of supportive data and whether the alternative analyses demonstrating consistency are pre-specified.***

The missing commentary on the degree of statistical significance provides additional context to the statement reproduced in the Delegate's decision, which is relevant to the findings from IMPROVE-IT. According to the Guideline, in addition to the p-value, there are other factors that are important in determining the level of support for the proposed indication offered by a single clinical study.

- § *Therapeutic indication: the proposed indication is reflected in the population enrolled in the study, and represents an unmet medical need. See Sections 5.4, 6.2 and 8.1 of this document for further details.*
- § *Primary endpoint: the primary endpoint chosen for IMPROVE-IT is reflective of the disease process (atherosclerosis and sequelae). The outcome shows an incremental benefit on important CV outcomes in a population where demonstrating such a benefit is difficult (as discussed further in Section 7.4(a) and 8.1).*
- § *Amount of supporting data: as discussed below, there is an extensive body of supporting data to validate the results of IMPROVE-IT.*
- § *Alternative analyses demonstrating consistency: as discussed, the primary and secondary outcomes, which were pre-specified in the statistical analysis plan, are*

all statistically significant, and consistently show a benefit of ezetimibe/simvastatin over simvastatin monotherapy.

When these factors are taken into account, the correct decision is that the results of IMPROVE-IT satisfy the requirement for substantial statistical significance.

(ii) Internal consistency

The Delegate failed to properly consider and apply the following guidance from the Guideline regarding internal consistency.

§ *Internal consistency*

Similar effects demonstrated in different pre-specified sub- populations. All important endpoints showing similar findings.

There is strong internal consistency in IMPROVE-IT. In addition to the consistency of the results in the pre-specified primary and secondary outcomes, subgroup analyses of the primary composite endpoint showed that the effect of ezetimibe/simvastatin relative to simvastatin monotherapy was generally consistent across subgroups. Although the study was not powered to adequately assess subgroup differences, the fact this finding is consistent with other important endpoints is supportive of the conclusion that the benefit of ezetimibe was demonstrated in the pre-specified sub-populations.

(iii) Plausibility of the hypothesis

The Delegate failed to properly consider and apply the following prerequisite from the Guideline:

§ *The plausibility of the hypothesis tested*

The hypothesis tested, that in stabilised high-risk ACS subjects, the administration of ezetimibe/simvastatin combination compared with simvastatin monotherapy will reduce the incidence of the primary composite endpoint, is highly plausible, as demonstrated by:

- § *the established understanding of the correlation between LDL-C lowering and CV risk reduction; and*
- § *what is known about the additive effect of ezetimibe when administered with a statin. These matters are discussed further in Sections 6.1, 6.3, 7.6, 8.1 and 8.5 of this document.*

(b) EMA Guideline on CV Prevention (EMEA/CHMP/EWP/311890/2007)⁷¹

The Delegate set out the guidance provided by the EMA Guideline on the Evaluation of Medicinal Products for Cardiovascular Disease Prevention as follows:

- § *Composite outcomes, including fatal and non-fatal CVD events, in which multiple endpoints are combined, are frequently used as primary outcome measures in randomised trials to reflect a number of outcomes that are of clinical importance and to increase statistical efficiency when event rates are low. Composite endpoints may be appropriate in trials of CV disease prevention when including hard clinical events (e.g. nonfatal MI, stroke). However, including in the composite, components which have a markedly different weight in term of clinical benefit is discouraged. An example is the combination in the primary composite endpoint of fatal events and clinician decision outcomes: hospitalisation, coronary revascularisation, amputation, use of rescue therapy,*

⁷¹ European Medicines Agency, "Guideline on the evaluation of medicinal products for cardiovascular disease prevention (EMEA/CHMP/EWP/311890/2007)", 25 September 2008.

hospitalisation for heart failure. If a composite primary endpoint is used, generally its separate components are secondary or tertiary endpoints, which are analysed separately if clinically meaningful and validated.

- § *Provide supportive information, and to ensure reliable interpretation, analyses of each separate component of the composite should be presented. For overall mortality and CV mortality both confidence intervals and point estimate are relevant for assessment. Any point estimate considerably in favour of the comparator is a matter of concern.*

The Delegate then said that:

The use of a composite endpoint can be useful to increase the power of a study where the risk of individual outcomes is low, but does have problems of its own. The study was not powered for the components of the primary endpoints, and therefore one cannot be certain about the interpretation of these.

The Delegate's decision was influenced by the finding that the primary composite endpoint was not on its own a reliable basis for making a decision in support of the proposed indications.

As explained below, the preferable finding is that the primary composite endpoint of IMPROVE-IT is a reliable and sufficient basis for making a decision in favour of the granting of the proposed indications.

The advice from this Guideline, as taken and applied by the Delegate, excludes the following relevant contextual information:

Clinical outcome endpoints should be objective and clinically relevant...A clinical event is most likely to be suitable if there are accepted specific criteria for its definition and can be objectively established (e.g. MI, ACS, stroke). Other events, like transient ischaemic attack, silent MI or stable angina pectoris are less likely to be objectively defined. Therefore, clinically relevant justifications should be provided when using them as components of a composite primary endpoint...

*An example is the combination in the primary composite endpoint of fatal events and clinician decision outcomes: hospitalisation, coronary revascularisation, amputation, use of rescue therapy, hospitalisation for heart failure. **In such case, the statistical significance of the primary composite endpoint is often driven by the clinician- decision outcome component, presenting further challenges for the interpretation of the study overall results. The more clearly components of a composite endpoint directly refer to the disease process, the less there is any problem of interpretation (emphasis added)***

Although, as stated in the excerpt reproduced in the initial decision letter, including in the composite, components which have a markedly different weight in term of clinical benefit is discouraged', the missing information provides additional context around the selection of the components of a composite endpoint. Consideration of this context is important to assessing the relevance of the chosen endpoint to the proposed indication.

Whilst it is true that, for example, non-fatal MI or stroke may be outcome measures that are considered 'hard clinical endpoints', the Guideline does not explicitly preclude the use of other components in the primary endpoint provided these are also directly related to the atherosclerotic process, and are objectively measured.

The components of the primary outcome are directly related to the atherosclerotic process which results in CHD and ACS, and the endpoint is consistent with those used for other major studies examining the effect of the treatment of statins for CV prevention. The clinical evaluator concurred with this.

It is true that the composite endpoint includes hospitalization for angina and revascularization which may be driven by clinician decisions. However, documented UA requiring hospitalisation was adjudicated by an independent Clinical Events Committee (CEC). Each suspected endpoint was reviewed by the committee, who were blinded to treatment. The aim of the CEC was to define and adjudicate primary endpoints in a consistent and unbiased manner throughout the entire course of the study. Two committee members reviewed each suspected endpoint against pre-defined criteria, including supporting documentation, to determine whether the event had been correctly identified as an endpoint. In this way, individual clinician judgement was mitigated for all adjudicated endpoints, including those classed as 'clinician decision' endpoints.

*Coronary revascularisation was not adjudicated by the CEC, but was clearly defined in the study protocol (Module 5.3.5.1: P04103, Synopsis Table 1): **Coronary Revascularisation** occurring at least 30 days post randomization – All PCI and CABG performed >30 days after randomization will be counted as an endpoint event.*

Hence, the inclusion of UA and coronary revascularization as components of the endpoint is justified in that these are directly related to the disease process, and were objectively defined and, in the case of UA, evaluated for validity by the CEC prior to inclusion as primary endpoints.

Had the Delegate considered these additional aspects of the guidance, this would have enabled the Delegate to:

- § *appreciate the relevance of the primary endpoint to the proposed indication, and*
- § *understand the role of the CEC in ensuring all endpoints included in the study results were objectively defined and identified,*

and hence, to accept the relevance of all components of the composite endpoint, whether considered 'hard clinical' or 'clinician decision' under other circumstances.

(c) Other relevant guidance

The following additional guidance, not relied on by the Delegate in her reasons, is relevant in this instance:

The ICH Note for Guidance on Statistical Principles for Clinical Trials (CPMP/ICH/363/96)⁷² considers that 'in some circumstances the weight of evidence from a single confirmatory trial may be sufficient'.

MSD contends that this is one such circumstance based on the totality of evidence supporting the proposed revised indications in addition to the positive results of IMPROVE-IT:

- § *LDL-C as an accepted biomarker and therapeutic target for reducing CHD risk*
- § *Genetic studies supporting CV risk reduction related to polymorphisms in NPC1L1, the target of ezetimibe (Module 5.4:043P2F).*
- § *Corroborating evidence from ezetimibe related lipid-lowering trials and information related to ezetimibe and statin mechanism of action (MOA)*

⁷² European Medicines Agency, "ICH Topic E 9 Statistical Principles for Clinical Trials, Step 5: Note for guidance on statistical principles for clinical trials (CPMP/ICH/363/96)", September 1998.

(discussed in Module 2.5 and provided in Module 5.4: 03XSQL, 03PGGL, 03PJ6X, 03PGGP, 03PHZ3)

- § Evidence supporting the similarity of the CV risk reduction benefit provided per mmol/L LDL-C lowering by ezetimibe and statins (see Section 8.1).

7.6 Accepted LDL-C targets

In the context of discussing the 2016 EU Guidelines on cardiovascular disease prevention⁷³ in clinical practice, the Delegate asserted that:

There is some uncertainty in the area of cardiology if lipid lowering drugs should be used for patients at risk of future CV events, or to target a specific LDL level.

The clinical guidelines listed in the decision contradict this assertion. These major therapeutic guidelines acknowledge that reduction in LDL-C is inextricably linked to the risk of future CV events:

- § ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce ASCVD Risk:⁷⁴ the guideline acknowledges that:

Decades of research have demonstrated an association between high levels of low-density lipoprotein cholesterol (LDL-C) and an increased risk of atherosclerotic cardiovascular disease (ASCVD)...

Whilst the guideline does not nominate specific LDL-C targets it does advocate the use of high, moderate or low intensity statin regimes based on underlying risk factors which includes elevated LDL-C in all groups except those with clinical ASCVD. The intensity of the statin regime chosen is based upon its average ability to lower LDL-C (Table 3). Higher baseline risk, including higher baseline LDL-C, requires greater LDL-C reduction.

- § 2016 EU Guidelines on cardiovascular disease prevention in clinical practice:⁷⁵ the guideline states that:

The evidence that reducing plasma LDL-C reduces CVD risk is unequivocal.

This guideline advocates treating to an LDL-C target of ≤ 1.8 mmol/L for prevention of recurrent CV events and in other very-high-risk subjects (section 3a.7.10).

- § NVDPA guidelines for the management of absolute cardiovascular disease risk 2012:⁷⁶ this guideline for primary prevention of CVD acknowledges that ‘the results of epidemiological studies, as well as trials with clinical endpoints, confirm that a reduction in LDL-C must be of primary concern in the prevention of CVD.’ An LDL-C target of < 2.0 mmol/L is advocated for adults ≥ 45 years without known history of CVD.

What is common to all these guidelines is the acknowledgement that lowering LDL-C is linked to the risk of future CV events. The strategy by which the guidelines recommend reduction in LDL-C as one of the components of reducing future risk may

⁷³ European Medicines Agency, “Guideline on the evaluation of medicinal products for cardiovascular disease prevention (EMA/CHMP/EWP/311890/2007)”, 25 September 2008.

⁷⁴ Stone NJ, 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. *J Am Coll Cardiol.* 63(25 Pt B): 2889-2934 (2014).

⁷⁵ European Medicines Agency, “Guideline on the evaluation of medicinal products for cardiovascular disease prevention (EMA/CHMP/EWP/311890/2007)”, 25 September 2008.

⁷⁶ National Vascular Disease Prevention Alliance, “Guidelines for the management of absolute cardiovascular disease risk”, 2012.

vary slightly (i.e. some target a % reduction in LDL-C based on average intensity of statin regime and others include a specific LDL-C target), but the ultimate aim is consistent: reduce LDL-C to reduce the risk of future CV events.

Further, the optimal modern approach to the use of LDL-C targets was explained in the expert's second report:

The 2016 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice,⁷⁷ which take into account the IMPROVE-IT results, explain optimal LDL-C management practice. These recommend that for patients with very high CV risk, the target is both a 50% reduction in LDL-C, and an LDL-C level which is less than 1.8 mmol/L. For example, if a patient has an LDL-C level of 2.6mmol/L and suffers a heart attack, the target will be to reduce his/her LDL-C level to at least 1.3mmol/L. These patients may have levels of LDL-C that would previously have been seen as not problematic (ie. they may have reached target of 1.8 mmol/L) and the purpose of the extra LDL-C lowering target is not to treat hypercholesterolaemia, but to reduce their CV risk. Many patients fail to reach their target LDL-C level through statin therapy alone.

Ezetimibe will be a very valuable tool for treating such patients and assisting them with reaching or coming closer to their target LDL-C levels, and hence for prevention of further CV disease.

Delegate of the Minister's response

The Delegate of the Minister has noted the various criticisms. As the Delegate of the Minister proposes a decision based on their own review of the submitted results of the IMPROVE-IT trial and because their decision deals largely or completely with those criticisms, the Delegate of the Minister does not find it necessary to respond further about each point.

Sponsor's Request

(d) The Delegate of the Secretary relied on reasons that do not have foundation in the materials available when questioning the clinical and statistical significance of the results of IMPROVE-IT, the relevance of findings regarding the components of the composite primary endpoint and the use of ezetimibe for CV disease prevention with statins other than simvastatin. The nature of those reasons is described in more detail in paragraphs 8.1 to 8.5 of the sponsor's letter seeking review:

8.1 The materials state that the results are clinically meaningful

The Delegate did not properly understand the clinical outcome demonstrated by IMPROVE-IT. The Delegate said:

In the IMPROVE IT trial, the risk of the primary composite endpoint was around 30% over 7 years and the use of ezetimibe over simvastatin reduced the risk of an event by around 2%. This is a very small improvement in the event rate. Fifty subjects would be needed to be treated for 7 years to prevent 1 composite event. Even more subjects need to be treated to prevent a component of the composite endpoint.

In fact IMPROVE-IT demonstrated that one in fifty patients treated with ezetimibe/simvastatin, that would otherwise have experienced at least one of the composite events making up the primary composite endpoint, would not experience any of the events for seven years.

⁷⁷ European Medicines Agency, "Guideline on the evaluation of medicinal products for cardiovascular disease prevention (EMA/CHMP/EWP/311890/2007)", 25 September 2008.

As explained by Professor [information redacted] in their second report:

The relative and absolute improvements in the composite endpoints for the treatment group in the IMPROVE-IT study are conservative measures of the actual benefits achieved by treatment with ezetimibe....the number of patients that would experience a clinically significant benefit is higher.

The primary composite outcome of IMPROVE-IT only took into account the first occurrence of any of the components of the composite. Contrary to the statement of the Delegate, the ARR in the primary composite endpoint is not a measure of how many subjects would be needed to be treated to prevent one occurrence of any of the composite events.

Further, the reasons acknowledge the existence of a treatment effect in stating:

This is a very small improvement in the event rate.

Additionally, the Delegate in her request for ACPM advice acknowledged that:

the aim of any lipid lowering therapy is to reduce the risk factor for CV events' and that 'the rationale for the use of combination therapy with ezetimibe and a statin comes from the established link between lowering LDL and reducing CV events, and the limitations in achieving low LDL levels in some patients with statin therapy.

The Delegate goes on to say that the results of the IMPROVE-IT study are expected, or to put it another way if a study showed that a lipid lowering agent did not show a CV benefit, one would question the validity of the lipid lowering effects or the use of LDL as a surrogate endpoint.

Hence the Delegate acknowledges that IMPROVE-IT did show a benefit in the proposed indication.

The reasons also state that the Delegate's views are supported by the clinical evaluator, the ACPM, and the sponsor's own experts who stated the effects of IMPROVE-IT were 'modest'. The acceptance of a 'modest' effect is inconsistent with the assertion that the results are not clinically meaningful (see discussion of meaning of 'modest' in Section 6.2). The treatment in question, ezetimibe and simvastatin, did demonstrate a clinical benefit as compared to the comparator, simvastatin monotherapy. Subjects did experience fewer adverse CV outcomes on the combination. The magnitude of the effect is consistent with current knowledge around the relationship between LDL-C reduction and CV risk reduction (Module 5.4: 03TK50, 043P2P, 03QW0C) and is the minimally expected benefit in clinical practice, given the higher baseline LDL-C in many real-life patients. In the overall context of prevention of CV events in post-ACS patients it is significant, and supportive of the proposed indication.

A clear endorsement of the clinically meaningful nature of the results of IMPROVE-IT is the clinical use of ezetimibe, as explained in the expert's second report:

Since the release of the IMPROVE-IT study, use of ezetimibe as a treatment for patients with elevated CV risk, who are in need of additional lowering of LDL-C levels, is becoming an increasingly common clinical practice.

High LDL-C is a major risk factor for CHD. The effectiveness of LDL-C lowering therapy for reducing the risk of coronary events in patients with and without CHD is firmly established, and underpins current guidelines for lipid lowering as a component of CV risk reduction. Central to the assessment of the clinical significance of the results of IMPROVE-IT is the understanding that the effect of ezetimibe on CV risk reduction is attributable to its LDL-C lowering capacity and that, as highlighted by the Delegate, the results of IMPROVE-IT are 'expected'.

The relevant facts to consider in establishing the clinical significance of the results of IMPROVE-IT are as follows:

§ Findings from the 2010 CTT meta-analysis (Module 5.4: 03RCP0):

- Magnitude of LDL-C reduction is directly proportional to the absolute LDL-C reduction across a broad range of LDL-C levels, down to levels at least as low as 1.8 mmol/L.
- CTT reported a 22% risk reduction per mmol/L of LDL-C lowering for the CTT major vascular endpoint (CTT-MVE: CHD death, non-fatal MI, coronary revascularization that occurred \geq 30 days after randomization and stroke).
- At higher baseline LDL-C levels, statins produced larger absolute changes in LDL-C and therefore greater risk reduction
- The benefits for statins were generally consistent when adjusted for LDL-C change i.e. large reductions in LDL-C produce larger risk reduction; small reductions in LDL-C produce smaller risk reductions, and the per mmol change is constant regardless of the baseline LDL-C.

§ Findings from IMPROVE-IT:

- The entry criteria for IMPROVE-IT meant that baseline LDL-C at the time of the qualifying ACS event was low in relation to the overall cohort represented by the proposed indication (LS mean 2.43 mmol/L in both treatment arms) which limited the amount of LDL-C lowering that was possible.
- Since the active comparator was simvastatin 40 mg, a moderately intensive statin regimen, this also limited the absolute incremental LDL-C lowering able to be achieved by ezetimibe.
- Hence, the LS mean difference in LDL-C between the groups at 1 year was 0.43 mmol/L (95% CI -0.45, -0.41; $p < 0.001$) (Module 5.3.5.1: P04103 – 14.5 Table 14- 11).

§ Comparison of the IMPROVE-IT results to the CTT findings (Module 5.3.5.1: Section 11.1.6.4):

- Relationship between LDL-C reduction and outcomes treatment benefit observed in IMPROVE-IT was assessed through analysis of observed reductions in CV events per 1 mmol/L reduction in LDL-C.
- This analysis was carried out for a composite outcome consistent with that used in the CTT analysis (CTT Major Vascular Endpoint: CHD death, non-fatal MI, coronary revascularisation \geq 30 days after randomisation and stroke).
- The HR for clinical benefits per mmol/L reduction in LDL-C with ezetimibe in IMPROVE-IT was 0.80 (i.e. 20% CV risk reduction per mmol/L LDL-C lowering, consistent with the 22% risk reduction per mmol/L LDL-C reduction observed in the CTT).
- This shows that, for an equivalent reduction in LDL-C, the outcomes treatment benefit seen with ezetimibe is consistent to that seen with statins.

§ Knowledge about the effects of ezetimibe:

- *The proportional change in LDL-C with ezetimibe has been shown to be independent of Baseline LDL-C levels (Module 5.4: 04434Q, 03XSQL) i.e. at higher baseline levels, the addition of ezetimibe results in larger absolute changes in LDL-C.*

§ *Clinical expert opinion on the ACS patient population:*

- *Expert [information redacted]: ‘It should be noted that 30% of patients with ACS do not reach the target of 1.8 mmol/L on high dose statins.’*
- *Expert [information redacted]: ‘in Australian clinical practice, it is noted that observational data (Baker IDI Cholesterol Crossroads 2011) shows generally patients on treatment have LDL levels above goals (@ 2.6 mmol/L versus a goal of <2.0 mmol/L) representing 70% of the total treatment-group...’*

In clinical practice, ezetimibe is generally used for patients whose LDL-C levels are not well controlled (i.e. not at their LDL-C target) on the maximum tolerated dose of a statin (see Sections 5.4 and 9.6). Many of these patients are likely to have higher LDL-C levels when initiated on ezetimibe than those enrolled in IMPROVE-IT. Given that, as established in Section 6.3, ezetimibe and statins have consistent proportional LDL-C lowering that is generally independent of baseline LDL-C, the anticipated absolute LDL-C reduction with addition of ezetimibe in these ‘real world’ patients with higher baseline LDL-C levels would be greater than observed in IMPROVE-IT. Subsequently, the anticipated CV risk reduction in these patients would be greater as well.

Hence, the clinical benefit observed in the study population of ACS patients, who would be considered in clinical practice to have well controlled LDL-C at the time of their presenting event, was the anticipated benefit based on the LDL-C difference observed. For the remaining patients, who do not have well controlled LDL-C at the time of presentation with ACS, despite treatment with the maximum tolerated dose of statins, as per the current treatment guidelines, the clinical benefit from the addition of ezetimibe would be expected to be greater, in proportion to the additional LDL-C reduction they will be able to achieve.

Delegate of the Minister’s response

In reaching their decision, the Delegate of the Minister has accepted that the primary outcome result and several secondary outcome results were statistically significant. The Delegate of the Minister thinks that the additional benefit in the primary outcome (ARR of 2% and a RRR of 6%) in patients with a history of ACS is a small additional clinical benefit. The Delegate of the Minister has accepted the word “modest” as used by two of the sponsor’s experts as a reasonable description of the clinical benefit. The Delegate of the Minister thinks that individual medical practitioners will vary in their view of the extent to which the benefit is clinically meaningful in their individual patients and this supports the need for a specific unambiguous Indication and clear unambiguous information in the PI.

Sponsor’s request

8.2 The materials support the statistical significance of the results

The Delegate’s reasons misunderstand the relationship between the 6.4% RRR observed in the study and the 9.375% RRR used for the power calculations for the study, concluding that this means that ‘ezetimibe did not have the magnitude of effect that the investigators had anticipated when they designed the trial, and is less efficacious than more intensive statin therapy.’

Although the RRR was smaller than anticipated in the power calculation, it should be noted that at the time IMPROVE-IT was initiated, the relationship between LDL-C lowering and CV risk reduction had not been quantified to the extent achieved by the CTT meta-analysis. The 9.375% RRR chosen for the power calculations was based on the best knowledge available at the time.

The 6.4% RRR observed in IMPROVE-IT is consistent with data from the CTT meta-analyses which, as previously discussed, established the relationship between LDL-C lowering by statins and the reduction in CV events (22% risk reduction per mmol/L LDL-C reduction).

The relationship between LDL-C reduction and CV risk reduction with ezetimibe has been shown, through IMPROVE-IT, to be consistent with that between LDL-C reduction and CV risk reduction with statins observed in CTT (20% risk reduction per mmol/L LDL-C reduction).

Hence, the reason given that the RRR observed in IMPROVE-IT being smaller than the RRR used in the power calculations means that ezetimibe is less efficacious than more intensive statin therapy is incorrect. The RRR observed in IMPROVE-IT is equivalent to the RRR that would be expected for statin therapy given the equivalent LDL-C reduction.

The statement in the reasons that 'the confidence intervals in the trial were narrow, indicative of the large sample size, and approached 1 – signifying there is a 5% chance there was not statistically significant difference' overestimate the probability that the findings of IMPROVE-IT are due to chance.

The p-value for the primary composite endpoint was 0.016, indicating that the probability of observing a treatment effect as great or greater than what was actually observed, given that there was truly no treatment difference, was 1.6%, not 5%, which was well-within the accepted level of error. The observed treatment effect, when adjusted for LDL-C lowering, was consistent with what was predicted by CTT meta-analysis.

Delegate of the Minister's response

The Delegate of the Minister thinks that it is not inappropriate to note that a result of a clinical study has fallen short of the predicted result on which power calculations were based. That said, the Delegate of the Minister accepts that the result of the primary outcome was statistically significant as were a number of secondary outcome measures.

Sponsor's request

8.3 The materials indicate that the results are not adversely impacted by multiplicity IMPROVE-IT had a single primary efficacy endpoint with a single comparison defined in the primary hypothesis. Therefore, there was no need to adjust for multiplicity for the primary hypothesis, other than accounting for the interim analyses, which was achieved through the use of a pre-specified alpha-spending function. The three secondary hypotheses were to be tested only if the primary hypothesis was statistically significant and were controlled for multiplicity by the use of Hochberg's method.

Analyses of all tertiary and exploratory variables were intended to be supportive of the primary and secondary endpoints and therefore no multiplicity adjustment was applied to these endpoints.

Delegate of the Minister's response

The Delegate of the Minister accepts that the issue of multiplicity was addressed appropriately.

Sponsor's request

8.4 The materials indicate that the composite primary endpoint showed statistically significant benefit

The reasons misunderstand the role of composite endpoints and focus on the components of the endpoint, concluding that 'although the risk of the primary composite endpoint was reduced, there was an increased risk of the components 'CV death' and 'documented unstable angina requiring hospitalization. Overall there was no change in the risk of stroke however there was an increased risk of fatal and haemorrhagic stroke. These discrepancies also put doubt over the reliability of the study results'.

Powering the study on the individual components of the endpoint would have required an unreasonably large study (as previous illustrated in this document). IMPROVE-IT was powered to assess a difference in the primary endpoint and was underpowered to assess differences in the individual components of the composite primary endpoint, therefore it is difficult to assess the potential benefit, or lack of benefit, on individual components of the endpoint.

The individual components of the endpoint were appropriately analysed as tertiary endpoints of the study (see section 7.5(b)).

Table 11: HRs for individual endpoints.

Endpoint	HR (95% CI)	p-Value
CV death	1.000 (0.887, 1.127)	0.997
Non-fatal MI	0.871 (0.798, 0.950)	0.002
Documented UA requiring hospitalization	1.059 (0.846, 1.326)	0.618
All coronary revasc. with PCI or CABG \geq 30 days after rand.	0.947 (0.886, 1.012)	0.107
Non-fatal stroke	0.802 (0.678, 0.949)	0.010

Contrary to the Delegate's assertion, it cannot be concluded that there was an increased risk of CV death and documented UA, since the point estimates for the HRs for these endpoints is almost unity, with 1.0 (no difference) being well within the 95% confidence intervals. At best it could be concluded that there was no evidence of difference in these components, however as previously discussed, the study was not powered to enable firm conclusions about the individual components to be drawn.

With regard to the risk of stroke, this is discussed in 7.1 of this document.

Viewed as a whole, the composite primary endpoint did show that there was a statistically significant benefit of treatment with ezetimibe/simvastatin over simvastatin monotherapy. Analyses of the individual components of the composite endpoint are supportive, but firm conclusions cannot be drawn. What can be seen is that although not all components of the endpoint showed a statistically significant benefit for ezetimibe/simvastatin, none showed a benefit for simvastatin monotherapy (confidence intervals for CV death, UA and coronary revasc. all included 1.0).

Consistent with the EMA Guidance on the use of a single pivotal study, the IMPROVE-IT results demonstrated a consistent benefit in both the primary and secondary efficacy outcomes. The overall trend is in favour of the combination:

Table 12: HRs for primary and secondary endpoints.

<i>Endpoint</i>	<i>HR (95% CI)</i>	<i>p-Value</i>
Primary efficacy endpoint		
<i>CV death, major coronary events (non-fatal MI, documented UA requiring hospitalization, all coronary revasc., non-fatal stroke)</i>	<i>0.936 (0.887, 0.988)</i>	<i>0.016</i>
Secondary Endpoints		
<i>Death due to any cause, major coronary events, non-fatal stroke</i>	<i>0.948 (0.903, 0.996)</i>	<i>0.035</i>
<i>Death due to CHD, non-fatal MI, urgent coronary revasc.</i>	<i>0.912 (0.847, 0.983)</i>	<i>0.016</i>
<i>CV death, non-fatal MI, documented UA, all revasc., non-fatal stroke</i>	<i>0.945 (0.897, 0.996)</i>	<i>0.035</i>

Hence, the reliance of the reasons on how:

- § *the components of the composite endpoint,*
- § *the relationship between the RRR used in the power calculation and that observed in the study, and*
- § *the acceptable probability that the findings of IMPROVE-IT are due to chance*

relate to the statistical significance of the study findings does not provide a full and accurate assessment of the external validity of the study results (see also Section 9.3).

The reasons do not consider the statistical significance of the benefit observed in the primary composite endpoint, for which the study was powered, nor the internal consistency of the primary and secondary composite endpoints with other endpoints evaluated in the study (see also Section 4).

Delegate of the Minister's response

The Delegate of the Minister accepts that composite endpoints are commonly used in the study of treatments of CV diseases. The Delegate of the Minister accepts that by the usual criteria of a p value less than 0.05 and 95% CI not crossing 1.00 the primary efficacy endpoint has been shown to be statistically significant. The Delegate of the Minister also accepts that several secondary endpoints have been shown to be statistically significant by those criteria.

Sponsor's request

8.5 The materials provide evidence to support the use of ezetimibe with statins other than simvastatin

The reasoning of the Delegate on this point was influenced by her erroneous understanding of the reasons given by the clinical evaluator. The Delegate stated that the reasons given by the clinical evaluator for their recommended rejection included that:

There was no information about the incremental effect of Ezetimibe on other statins.

This reflected the first round clinical evaluation report, in which the clinical evaluator said:

Furthermore, it is important to stress that for incremental CV event reduction in patients with CHD, ezetimibe 10mg may only be administered with a statin with proven CV benefit (statin which have already received approval for indication of CV prevention in patients with CHD)

Following the amendments referred to in section 5, the clinical evaluator did not raise this objection in their second round evaluation report, instead stating that:

The modified indication for Ezetrol addresses the evaluator's query.

Further, additional support for the applicability of the findings from IMPROVE-IT to statins other than simvastatin is available including:

- § *Ezetimibe mechanism of action: Ezetimibe targets NPC1L1, largely in the small intestine to inhibit intestinal cholesterol absorption. Statins inhibit HMGCoA reductase to decrease hepatic cholesterol synthesis. These mechanisms are complementary, and when ezetimibe and statins are administered together, help block potential compensatory increases in cholesterol absorption or cholesterol synthesis. These two complementary mechanisms also share a final common pathway that lowers LDL-C via the up-regulation of hepatic LDL receptors (see Australian Product Information as available online on the Australian Register of Therapeutic Goods, ARTG ID: 91161).*
- § *CTT Analysis: The CTT meta-analysis demonstrated that the simvastatin effect related to CV outcomes is equivalent to the effect with other statins, thus supporting the extrapolation of IMPROVE-IT results to other statins (Module 5.4: 03TK50).*
- § *The pooled analysis from 27 lipid lowering trials including over 21,000 subjects (Module 5.4: 03XSQL) showing that ezetimibe has a consistent additive lipid lowering effect when added to different statins, different doses of a statin, and statins of varying potency, and across a diverse patient population.*
- § *Endorsement from regulatory agencies that the additive effect of ezetimibe is independent of the statin type or dose through the approved indications and dosage information for Ezetrol (see Australian Product Information as available online on the Australian Register of Therapeutic Goods, ARTG ID: 91161, US Prescribing Information, European Summary of Product Characteristics)*

Supportive information from studies involving people with naturally occurring genetic mutations in NPC1L1 and HMGCoA reductase variants showing that:

- § *the observed LDL-C lowering in patients with NPC1L1 variants is associated with a reduced risk of CHD, suggesting that ezetimibe mediated LDL-C lowering should reduce CV risk, (Module 5.4: 043P2F) and*
- § *in patients with both NPC1L1 and HMGCoA reductase variants, the associated LDL-C reduction is additive, as is the observed CV risk reduction (see Attachment 3). This mimics the clinical situation when ezetimibe is given with a statin.*

The following statement of Professor [information redacted] in their second round report:

...the results of the IMPROVE-IT study can be logically extrapolated to demonstrate the efficacy of ezetimibe with any statin with proven CV benefit. Where a patient treated with a statin has a need of additional lowering of LDL-C, ezetimibe can be used to further lower their LDL-C, and this will also lead to the statistically significant and clinically meaningful reduction in risk of CV events demonstrated by the IMPROVE-IT study.

As discussed in Section 8.1, ezetimibe is used in clinical practice to provide additional LDL-C lowering when this cannot be achieved using the maximum tolerated dose of a statin. The key scientific leaders who provided testimony with the pre-ACPM response concurred that this would be the expected use for ezetimibe in reducing the risk of subsequent events in ACS patients (section 5.4). Ezetimibe is used to enable patients to reach, or more closely approach, the LDL-C target that is agreed to optimally reduce the risk that an ACS patient will have an additional CV event (see Attachment 4 and expert statements provided with pre-ACPM response).

The Delegate's concern that:

to allow an indication for use with all statins would also infer use with statins that are not yet approved for use and with no data to support that use

is not supported by the EU Guideline on the clinical investigation of medicinal products for the treatment of lipid disorders,⁷⁸ nor by any information about potential new statin candidates currently in development.

The EU lipids guideline, in discussing the choice of efficacy endpoints demonstrating prevention of CV morbidity and mortality (4.1.1), states:

HMG-CoA reductase inhibitors have accrued considerable evidence demonstrating reduction of CV events (including stroke) and overall mortality in patients with CV risk factors, irrespective of their LDL-C levels.

and

The requirement of clinical studies showing beneficial outcome on morbidity and mortality during registration largely depends on the mechanism of action and the pharmacological class of the medicinal product and the target population. Such studies are not foreseen for the registration of a new HMGCoA reductase inhibitor.

The TGA's own adopted guideline does not foresee the necessity for new statins, should any arise, to conduct studies with mortality and morbidity outcomes to receive approval for an indication for the prevention of CV outcomes. Therefore, if a new statin was to obtain approval in Australia for an LDL-C lowering indication, the guideline would support the use of that statin for reduction in CV risk.

Additionally, MSD is not aware of any new statins being investigated, either for an LDL-lowering indication, or some novel indication. Even discounting the EU lipids guideline position, the likelihood a new statins being approved in the future is remote. Hence the concerns expressed by the Delegate around possible future statins do not carry sufficient weight to be a reason for rejection of the application.

⁷⁸ European Medicines Agency, "Guideline on clinical investigation of medicinal products in the treatment of lipid disorders (EMA/CHMP/748108/2013, Rev. 3)", 23 June 2016.

Delegate of the Minister's response

The Delegate of the Minister is of the opinion that the body of available information suggests that it is likely that the combination of ezetimibe with a statin registered in Australia (a statin with proven CV benefit) would achieve similar clinical outcomes to those reported for combinations of ezetimibe and simvastatin in the IMPROVE-IT trial. It is important that prescribers are aware that this is an assumption as an IMPROVE-IT like study has not been conducted with any of the other statins registered in Australia. It is for that reason that the words:

The incremental benefit is expected to be similar with co-administration of other statins shown to be effective in reducing the risk of cardiovascular events but this has not been demonstrated in studies similar to IMPROVE-IT

are to be included in the PI documents.

Sponsor's request

(e) The Delegate of the Secretary relied on reasons that do not support the decision in relation to the assessment of efficacy, the degree of statistical significance of the results, external validity of the study findings and consistency of the proposed indication with current treatment guidelines. The nature of those matters is described in more detail in paragraphs 9.1 to 9.6 of the sponsor's letter seeking review:

9.1 The Delegate of the Secretary applied the wrong test, requiring more than satisfactorily establishing efficacy

In their decision, the Delegate accepts that "ezetimibe has a role in the management of patients after an ACS where optimal LDL levels could not be achieved with a statin alone due to intolerance or lack of efficacy". However, in rejecting the registration for the sought indications, she states that efficacy is not satisfactorily established apparently on the basis that she questions the degree of efficacy stating that there registering the indications "would need...robust evidence of efficacy against an appropriate comparator with minimal risks".

This raises two issues. The first relates to whether the statutory test for efficacy has been met where the degree of efficacy is considered to be "small or modest". The second relates to the view that the efficacy must be found to be "clinically meaningful" in order for efficacy to be satisfactorily established in accordance with s25(1)(d) of the Act.

The statutory test of efficacy under Section 25(1)(d) of the Act does not require the efficacy of a drug to be equivalent, for example, to the market leader (the "Gold Standard"). As long as there is a measurable degree of efficacy, as has been found here for the indications sought, the statutory test has been satisfied.

Section 25(1)(d) relevantly requires that the quality, safety and efficacy of the drug: be assessed in relation to the purpose for which it is to be used (i.e. the proposed indications); and that the quality, safety and efficacy be satisfactorily established.

An application may be made for registration of a drug for the treatment of any medical condition. There is no limit or restriction in the Therapeutic Goods Act 1989 concerning the medical condition that may be targeted. The choice is one for the sponsor of the drug and it is not open to the decision makers under the Therapeutic Goods Act 1989 to refuse registration solely upon the basis of the targeted medical condition or to compulsorily redefine the scope of the application lodged.

Once these criteria are satisfied (and assuming all other statutory requirements are satisfied) there is no statutory justification for the Secretary or the Minister to refuse registration.

Registration is not a discretionary decision by the Secretary or Minister. The role of the Secretary and the Minister is to determine whether they are satisfied on the quality, safety and efficacy issues, at which point there is no residual power or discretion for the Secretary or Minister to withhold registration.

The Act does not specify the level of efficacy that a drug is required to achieve to satisfy section 25(1)(d) beyond saying that it need only be such a level as to satisfy the purpose for which it is to be used (the proposed indication).

In Re Eli Lilly Australia P/L and Minister for Health and Family Services (No2) [1999] AATA 565; (1999) 56 ALD 541, Deputy President McMahon dealt with and rejected the Minister's argument that a drug may be denied registration because its efficacy was only modest:

This is not sufficient. Even if they were so, the test would still be whether the changes effected by the proposed therapy are efficacious in serving the intended indication. They may serve it well or they may serve it indifferently. Some products are "wonder drugs"; others have a more common place effect. So long as they produce what they claim to do, then we do not see it as part of our function to give marks in accordance with the excellence of results... (p553 para 38).

See also Minister for Health and Aged Care v Pharmacia & Upjohn P/L [2000] FCA 1278; (2000) 63 ALD 160 where Beaumont J upheld a decision of the Administrative Appeals Tribunal in Re Pharmacia & Upjohn and Minister [2000] AATA 72; (2000) 58 ALD 285 which itself affirmed the above principle; and see Re Searle and Minister for Health and Family Services (1997) 25 AAR 295; (1997) 47 ALD 333 at 336 para 8 to the same effect.

The purpose of requiring efficacy as a criterion in Section 25(1)(d) is to ensure that the public is not misled into using a product which does not, in an overall sense, achieve the effects it claims, even if the drug is not the most efficacious drug on the market, and even if the drug is only efficacious for a sub-set of an indicated patient group.

If the TGA adopts a policy equivalent to the "gold standard" approach then such a policy is unlawful and not binding (Drake v Minister for Immigration and Ethnic Affairs (No.2) [1979] AATA 179; (1979) 2 ALD 634; Re Control Investments P/L and ABC (1981) 59 FLR 257; BHP Direct Reduced Iron P/L v Chief Officer, Australian Customs Service [1998] FCA 1346). It is an error of law on the part of the decision maker to simply and inflexibly apply such a policy without giving a "proper, genuine and realistic consideration" of the merits of the individual case (section (1)(e) and 2(f) Administrative Decisions (Judicial Review) Act 1977; Mendoza v Minister for Immigration, Local Government and Ethnic Affairs (1991) 31 FCR 405; Croft v Minister for Health (1983) 66 FLR 196; Hindi v Minister for Immigration (1988) 20 FCR 1; Robobatini v Minister for Immigration and Multicultural Affairs [1999] FCA 1238; (1999) 90 FCR 583).

The evaluation of the clinical data in this case is unequivocal in that ezetimibe boasts a distinctly measurable degree of efficacy. While the Delegate and the ACPM described the effect as "small" the clinical evaluator describes it as "modest". With either of these views MSD contends that the statutory test has been met.

The requirement imposed by the Delegate claims that not only must efficacy be demonstrated by statistically significant data it must also be clinically significant or meaningful. The suggestion that "not registering this new indication would not limit the availability of this medicine" suggests that the use of the medicines for the indications sought is already within the registrations sought. The only basis on which

this appears to be doubted in the reasons is the incorrect assertion that the results are not clinically meaningful. The Delegate's own assessment is that this "may be subjective". In seeking to obtain support for this the Delegate contends that "the clinical evaluator, the ACPM and the sponsor's own experts...stated the effects of the IMPROVE-IT study were 'modest". For the reasons set out in section 6.2, this misunderstands what is meant by modest. It requires more than satisfactorily establishing efficacy and represents the substitution of the statutory test with a different subjective test of whether the results of the supporting study are clinically significant or meaningful.

The reasons in fact disclose that the Delegate has found that efficacy has been established albeit at a modest level. In circumstances where the Delegate has also found that there are no new safety concerns, this should support registration.

Delegate of the Minister's response

The Delegate of the Minister proposes to approve each of the two products for a separate indication, albeit in each case quite detailed and specific. It follows that the Delegate of the Minister has satisfied themselves that the balance of benefits and risks is positive for the indication they have found. The Delegate of the Minister has not required evidence of a "wonder drug" or required the products to reach a "gold standard".

Sponsor's request

9.2 The failure of IMPROVE-IT to provide robust statistical significance, when considered with the totality of the evidence, is not sufficient, to refuse to register the proposed indications

The statistical significance and clinical relevance of IMPROVE-IT are explained in Sections 7.5(a)(i), 8.1, 8.2 and 8.4.

Delegate of the Minister's response

See my response to 8.4 above.

Sponsor's request

9.3 Concerns about external validity do not consider the indications actually sought and misunderstand the primary composite endpoint

The assertion that 'the proposed indication 'CHD' includes a wider population than in the study who had an ACS' is not relevant to the indication actually sought by MSD, as discussed in Section 5.3.

Additionally, the conclusion that 'if the use of ezetimibe in addition to simvastatin had significant effect on coronary artery disease all measures of this would improve' misunderstands the function of the primary composite endpoint and the components of the endpoint in the interpretation of the study results (see Sections 4, 7.4(a) and 8.3). As discussed, the analyses of the components of the primary endpoint were tertiary endpoints of the study. Whilst these are supportive, since the study was underpowered to detect differences in the individual components, concrete conclusions cannot be drawn from the analysis. What can be said is that overall, some components favoured the combination, some showed no difference, and none favoured the comparator. Taken in the context of the overall study results, the tertiary endpoints support the positive findings of the study, and hence the proposed indication.

Delegate of the Minister's response

The Delegate of the Minister is of the opinion that an appropriately worded indication can adequately deal with the concerns expressed by the Delegate of the Secretary.

Sponsor's request

9.4 The Delegate found that IMPROVE-IT satisfactorily establishes the efficacy of ezetimibe in reducing the risk of cardiovascular events, when used with simvastatin

This reason provides no basis for refusing to register the new indication for Vytorin, since Vytorin contains the combination studied in IMPROVE-IT.

Delegate of the Minister's response

The Delegate of the Minister has not been able to confirm that the Delegate of the Secretary used the finding that:

IMPROVE-IT satisfactorily establishes the efficacy of ezetimibe in reducing the risk of cardiovascular events, when used with simvastatin

as a reason to refuse registration.

Sponsor's request

9.5 The Delegate's concerns about whether IMPROVE-IT satisfactorily establishes the efficacy of ezetimibe in reducing the risk of cardiovascular events with all statins, when considered with the totality of the evidence, is not sufficient, to refuse to register the proposed indications

As set out in Section 5, the materials provided with the application provide evidence to support the use of ezetimibe with statins other than simvastatin.

The initial concerns of the clinical evaluator were addressed by the Section 31 Response and the amended indication (see Section 5.2) and following that response, the clinical evaluator no longer considered this to be objectionable, instead stating that "The modified indication for Ezetrol addresses the evaluator's query."

Further details on the support for the use of ezetimibe with statins other than simvastatin is found in the material that was not considered by the Delegate (see Section 6.3).

Delegate of the Minister's response

See my response to 8.5.

Sponsor's request

9.6 The proposed indications are consistent with the current Australian and European Guidelines for cardiovascular risk reduction.

The proposed indication at the time of the Delegate's decision was limited to patients with CHD, with a history of ACS. This proposed use is well within both the Australia and EU Guidelines for the management of ACS patients that have been published this year, and acknowledge IMPROVE-IT in their recommendations.

Relevantly, these include:

The European Guidelines for CV Disease Prevention (2016)⁷⁹ makes the following statements:

§ *Data indicate that combination therapy with ezetimibe also brings a benefit that is in line with the Cholesterol Treatment Trialists' (CTT) Collaboration meta-*

⁷⁹ Piepoli MF, et al. European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J.* 37: 2315-2381 (2016).

analysis supporting the notion that LDL-C reduction is key to the achieved benefit independent of the approach used.

- § For non-statin treatments, selective cholesterol absorption inhibitors (e.g. ezetimibe) are not usually used as monotherapy to decrease LDL-C concentrations, unless patients are intolerant to statins. They are recommended as combination therapy with statins in selected patients when a specific goal is not reached with the maximal tolerated dose of statin.
- § Patients with dyslipidaemia, particularly those with established CVD, DM or asymptomatic high-risk individuals, may not always reach treatment goals, even with the highest tolerated statin dose. Therefore, combination treatment may be needed. It must be stressed however, that the only combination that has evidence of clinical benefit (one large RCT)* is that of statin combined with ezetimibe. Based on the relatively limited body of evidence, clinicians may restrict the use of this combination to patients at high or very high risk of CVD.'

(* The guideline references the publication of the IMPROVE-IT study)⁸⁰

Although not available at the time of the Delegate's decision, the Australian Clinical Guidelines for the Management of Acute Coronary Syndromes, published in September 2016,⁸¹ recommend the maximum tolerated dose of statins as first line therapy for post-ACS patients unless contraindicated or there is a history of intolerance. In contrast to the previous version, the 2016 guidelines recommend that ezetimibe should be considered for patients with sub-optimal LDL or statin intolerance and cites IMPROVE-IT for this recommendation.

The reliance of the reasons on the current Australian NVDPA: Guidelines for the management of absolute CV risk⁸² and the European CVD Prevention Guidelines⁸³ fails to properly consider each of these guidelines and fails to consider several other treatment guidelines that are more relevant in this case.

The NVDPA Guidelines (2012)⁸⁴ recommend a risk assessment and management algorithm for adults aged 45 years and over (or 35 years and over for Aboriginal and Torres Strait Islander adults) without known history of CVD. This risk calculator is intended to guide clinicians on the management of CVD risk in a primary prevention setting, rather than in those with established clinical CV disease. Therefore this is not the appropriate therapeutic guideline in this instance.

Other more relevant guidelines also support the proposed indications.

- § The Australian Therapeutic Guidelines recommend:
- § Hospital admission for a CV event or diagnosis of clinical CVD should prompt the commencement of statin therapy, unless contraindicated

⁸⁰ Cannon CP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *NEJM* 372: 2387-2397 (2015).

⁸¹ Chew DP, et al. National Heart Foundation of Australia & Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Management of Acute Coronary Syndromes 2016. *Heart Lung Circ.* 25: 895-951 (2016).

⁸² National Vascular Disease Prevention Alliance, "Guidelines for the management of absolute cardiovascular disease risk", 2012.

⁸³ Piepoli MF, et al. European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J.* 37: 2315-2381 (2016).

⁸⁴ National Vascular Disease Prevention Alliance, "Guidelines for the management of absolute cardiovascular disease risk", 2012.

§ *Additional drug therapy can be added to statins if target lipid levels have not been reached. Additional drug therapy includes ezetimibe.*

When discussing risk estimation the guidelines note that people who have established CVD are already known to be at higher risk of a CV event, so do not need a formal risk calculation before starting therapy.

The Australian Guidelines for Reducing Risk in Heart Disease (2012)⁸⁵ provides a framework for the management of patients with CHD. This guideline recommends the use of statin therapy in all patients with CHD (apart from in exceptional circumstances) to meet the goal of LDL-C < 1.8 mmol/L. The guideline also mentions that ezetimibe reduces LDL-C by 15-20% when given as monotherapy or when added to a statin.

Delegate of the Minister's response

It is important to note that the various guidelines express opinions and do not constitute evaluable evidence. The Delegate of the Minister notes the quotation from the European Guidelines for CV Disease Prevention (2016),⁸⁶ third dot point commencing:

§ *Patients with dyslipidaemia, particularly those with established CVD, DM or asymptomatic high-risk individuals, may not always reach treatment goals, even with the highest tolerated statin dose...*

Although the quotation does not explicitly refer to patients with CHD and a history of ACS, they would usually fall into the categories of patients at high or very high risk of CVD, to whom the Guideline recommends limitation of the combination of statin with ezetimibe.

Concerning the Australian Clinical Guidelines for the Management of Acute Coronary Syndromes, published in September 2016,⁸⁷ the Delegate of the Minister has used a variety of techniques to search the document and been unable to find the words:

ezetimibe should be considered for patients with sub-optimal LDL or statin intolerance and cites IMPROVE-IT for this recommendation.

Further, the Delegate of the Minister has been unable to find any reference to ezetimibe or any citation of Cannon and colleagues⁸⁸ in this document.

The Delegate of the Minister agrees that the 2016 guidelines state that other drugs should be added to statin therapy including when target lipid levels have not been achieved and includes ezetimibe in a list of such drugs. The document gives no consideration to the circumstances in which clinical evidence supports or limits the use of ezetimibe in combination with statin therapy. The Cannon et al. paper is not referenced.⁸⁹

⁸⁵ National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand. Reducing risk in heart disease: an expert guide to clinical practice for secondary prevention of coronary heart disease. Melbourne: National Heart Foundation of Australia, 2012.

⁸⁶ Piepoli MF, et al. European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J.* 37: 2315-2381 (2016).

⁸⁷ Chew DP, et al. National Heart Foundation of Australia & Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Management of Acute Coronary Syndromes 2016. *Heart Lung Circ.* 25: 895-951 (2016).

⁸⁸ Cannon CP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *NEJM* 372: 2387-2397 (2015).

⁸⁹ Cannon CP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *NEJM* 372: 2387-2397 (2015).

Given that the report of the IMPROVE-IT trial was published in 2015,⁹⁰ the Delegate of the Minister is of the view that less weight should be placed on reports or treatment guidelines published prior to that date.

Reasons for the Delegate of the Minister's decision

The Delegate of the Minister has noted that the IMPROVE-IT trial was conducted in subjects with stabilised high risk ACS who were enrolled within 10 days of hospitalisation for a NSTEMI, UA, NSTEMI or STEMI. Subjects were required to have an LDL-C > 50 mg/dL (1.2 mmol/L) and ≤ 125 mg/dL (≤3.2 mmol/L) at the time of presentation with ACS if they had not been taking lipid lowering therapy, or ≤100 mg/dL (≤2.6 mmol/L) if they had been receiving lipid lowering therapy.

The Delegate of the Minister accepts that the results of the IMPROVE-IT trial demonstrated a statistically significant difference favouring treatment with ezetimibe and simvastatin over treatment with simvastatin alone. That difference was an ARR of 2% and a RRR of 6% in the primary outcome measure (a composite consisting of CV death, MCE (defined as non-fatal MI, documented UA that required hospitalisation, or any coronary revascularisation procedure occurring at least 30 days after randomised treatment assignment) and non-fatal stroke. While the Delegate of the Minister has noted that there was no demonstrated overall benefit in all-cause mortality or CV mortality, the Delegate of the Minister accepts that the risk reduction may be clinically meaningful in patients with the same clinical conditions as those enrolled in the IMPROVE-IT trial, as argued by the sponsor's clinical experts. The Delegate of the Minister shares the concern expressed by the ACPM that the absolute and RRRs seen in the high risk population in the IMPROVE-IT trial may be smaller in a lower risk population and therefore does not accept that it is appropriate to generalise the results to a broader group of patients. The Delegate of the Minister has decided that the indications of Ezetrol and Vytorin should be extended provided that the results of the IMPROVE-IT trial are conveyed clearly in the Indications and other relevant parts of the approved PI documents.

Concerning the use of ezetimibe with other statins, the Delegate of the Minister has set out in the response to 8.5 above that the body of available information suggests that it is likely that the combination of ezetimibe with a statin registered in Australia (a statin with proven CV benefit) would achieve similar clinical outcomes to those reported for combinations of ezetimibe and simvastatin in the IMPROVE-IT trial.

The Delegate of the Minister thinks that it is important that prescribers are aware that this is an assumption as an IMPROVE-IT like study has not been conducted with any of the other statins registered in Australia. It is for that reason that the words:

The incremental benefit is expected to be similar with co-administration of other statins shown to be effective in reducing the risk of cardiovascular events but this has not been demonstrated in studies similar to IMPROVE-IT

is to be included in the PI documents.

Review of decision by the Administrative Appeals Tribunal

If the sponsor is dissatisfied with the Delegate's decision then, subject to the *Administrative Appeals Tribunal Act 1975*, the sponsor can make an application to the Administrative Appeals Tribunal (AAT) for a review of this decision.

⁹⁰ Cannon CP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *NEJM* 372: 2387-2397 (2015).

Annexure

(a) The PI for Ezetrol 10 mg tablets shall include in the Clinical Trials section the following words, Figure⁹¹ and Table⁹²

Prevention of Cardiovascular Events

Ezetrol in combination with simvastatin has been shown in the IMPROVE-IT trial (details below) to reduce the major CV events of non-fatal MI and stroke in patients with CHD and a history of ACS. Total mortality, CV mortality and rates of UA requiring hospitalisation and all coronary revascularisation were unchanged. There was a small increase in the rate of haemorrhagic stroke that was not statistically significant. The incremental benefit is expected to be similar with co-administration of other statins shown to be effective in reducing the risk of CV events but this has not been demonstrated in studies similar to IMPROVE-IT.

The IMPROVED Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) was a multicentre, randomised, double blind, active control study of 18,144 patients enrolled within 10 days of hospitalisation for acute coronary syndrome (ACS; either acute MI or UA). Patients had an LDL-C ≤ 125 mg/dL (≤ 3.2 mmol/L) at the time of presentation with ACS if they had not been taking lipid lowering therapy, or ≤ 100 mg/dL (≤ 2.6 mmol/L) if they had been receiving lipid lowering therapy. All patients were randomised in a 1:1 ratio to receive either ezetimibe/simvastatin 10/40 mg (n = 9,067) or simvastatin 40 mg (n = 9,077) and followed for a median of 6.0 years.

Patients had a mean age of 63.6 years; 76% were male, 84% were Caucasian, and 27% were diabetic. The average LDL-C value at the time of study qualifying event was 80 mg/dL (2.1 mmol/L) for those on lipid lowering therapy (n = 6,390) and 101 mg/dL (2.6 mmol/L) for those not on previous lipid lowering therapy (n = 11,594). Prior to the hospitalization for the qualifying ACS event, 34% of the patients were on statin therapy. At one year, the average LDL-C for patients continuing on therapy was 53.2 mg/dL (1.4 mmol/L) for the ezetimibe/simvastatin group and 69.9 mg/dL (1.8 mmol/L) for the simvastatin monotherapy group. Lipid values were generally obtained for patients who remained on study therapy.

The primary endpoint was a composite consisting of CV death, MCE (defined as non-fatal MI, documented UA that required hospitalisation, or any coronary revascularisation procedure occurring at least 30 days after randomised treatment assignment) and non-fatal stroke. The study demonstrated that treatment with ezetimibe when added to simvastatin provided incremental benefit in reducing the primary composite endpoint of CV death, MCE, and non-fatal stroke compared with simvastatin alone (RRR of 6.4%, p = 0.016). The primary endpoint occurred in 2,572 of 9,067 patients (7-year KM rate 32.72%) in the ezetimibe/simvastatin group and 2742 of 9,077 patients (7-year KM rate 34.67%) in the simvastatin alone group (see Figure 2 and Table 13 below). This incremental benefit is expected to be similar with co-administration of other statins shown to be effective in reducing the risk of CV events. Total mortality was unchanged in this high risk group.

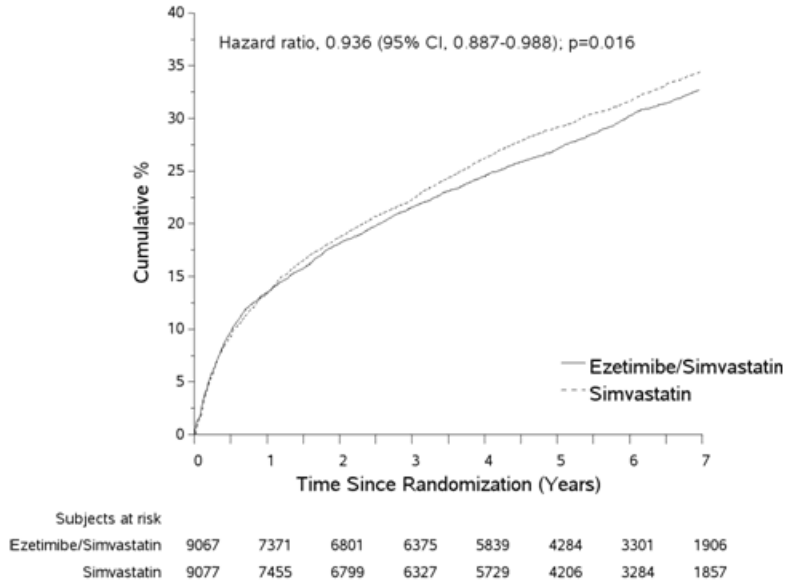
There was an overall benefit for all strokes; however, there was a small non-significant increase in haemorrhagic stroke in the ezetimibe/simvastatin group compared with simvastatin alone (see Table 13). The risk of haemorrhagic stroke for ezetimibe co-administered with higher potency statins in long term outcome studies has not been evaluated.

⁹¹ See Figure 2 in this AusPAR.

⁹² See Table 13 in this AusPAR.

The treatment effect of ezetimibe/simvastatin was generally consistent with the overall results across many subgroups, including sex, age, race, medical history of diabetes mellitus, baseline lipid levels, prior statin therapy, prior stroke, and hypertension.

Figure 2: Effects of Ezetrol and simvastatin 40 mg or 80 mg on the primary composite endpoint of CV Death, MCE, or non-fatal stroke.



This figure is titled:

Figure 1: Effect of INEGY on the Primary Composite Endpoint of Cardiovascular Death, Major Coronary Event, or Non-fatal Stroke

in section 5.1 of the current European SmPC for INEGY, but should be re-labelled to the title above.

Table 13: MCEs by treatment group in all randomised patients in IMPROVE-IT.

Outcome	INEGY 10/40 mg ^a (N=9067)		Simvastatin 40 mg ^b (N=9077)		Hazard Ratio (95% CI)	p-value
	n	K-M % ^c	n	K-M % ^c		
Primary Composite Efficacy Endpoint						
(CV death, Major Coronary Events and non-fatal stroke)	2572	32.72%	2742	34.67%	0.936 (0.887, 0.988)	0.016
Secondary Composite Efficacy Endpoints						
CHD death, nonfatal MI, urgent coronary revascularisation after 30 days	1322	17.52%	1448	18.88%	0.912 (0.847, 0.983)	0.016
MCE, non-fatal stroke, death (all causes)	3089	38.65%	3246	40.25%	0.948 (0.903, 0.996)	0.035
CV death, non-fatal MI, unstable angina requiring hospitalisation, any revascularisation, non-fatal stroke	2716	34.49%	2869	36.20%	0.945 (0.897, 0.996)	0.035
Components of Primary Composite Endpoint and Select Efficacy Endpoints (first occurrences of specified event at any time)						
Cardiovascular death	537	6.89%	538	6.84%	1.000 (0.887, 1.127)	0.997
Major Coronary Event:						
Non-fatal MI	945	12.77%	1083	14.41%	0.871 (0.798, 0.950)	0.002
Unstable angina requiring hospitalisation	156	2.06%	148	1.92%	1.059 (0.846, 1.326)	0.618
Coronary revascularisation after 30 days	1690	21.84%	1793	23.36%	0.947 (0.886, 1.012)	0.107
Non-fatal stroke	245	3.49%	305	4.24%	0.802 (0.678, 0.949)	0.010
All MI (fatal and non-fatal)	977	13.13%	1118	14.82%	0.872 (0.800, 0.950)	0.002
All stroke (fatal and non-fatal)	296	4.16%	345	4.77%	0.857 (0.734, 1.001)	0.052
Non-haemorrhagic stroke ^d	242	3.48%	305	4.23%	0.793 (0.670, 0.939)	0.007
Haemorrhagic stroke	59	0.77%	43	0.59%	1.377 (0.930, 2.040)	0.110
Death from any cause	1215	15.36%	1231	15.28%	0.989 (0.914, 1.070)	0.782

- a. 6% were uptitrated to ezetimibe/simvastatin 10/80 mg.
b. 2.7% were uptitrated to simvastatin 80 mg.
c. Kaplan-Meier estimate at 7 years.
d. includes ischemic stroke or stroke of undetermined type.

This table has the same title in section 5.1 of the current European SmPC for Inegy.

(b) The PI for Vytorin 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg fixed combination tablets shall include in the Clinical Trials section the following words, Figure⁹³ and Table⁹⁴

Prevention of Cardiovascular Events

In brief, Vytorin has been shown in the IMPROVE-IT trial to reduce some major CV events in patients with CHD and a history of ACS. Total mortality, CV mortality and rates of UA requiring hospitalisation and all coronary revascularisation were unchanged. There was a small increase in the rate of haemorrhagic stroke that was not statistically significant.

The IMPROVE-IT was a multicentre, randomised, double blind, active control study of 18,144 patients enrolled within 10 days of hospitalisation for ACS (either acute MI or UA). Patients had an LDL-C \leq 125 mg/dL (\leq 3.2 mmol/L) at the time of presentation with ACS if

⁹³ See Figure 2 in this AusPAR.

⁹⁴ See Table 13 in this AusPAR.

they had not been taking lipid lowering therapy, or ≤ 100 mg/dL (≤ 2.6 mmol/L) if they had been receiving lipid lowering therapy. All patients were randomised in a 1:1 ratio to receive either ezetimibe/simvastatin 10/40 mg (n = 9,067) or simvastatin 40 mg (n = 9,077) and followed for a median of 6.0 years.

Patients had a mean age of 63.6 years; 76% were male, 84% were Caucasian, and 27% were diabetic. The average LDL-C value at the time of study qualifying event was 80 mg/dL (2.1 mmol/L) for those on lipid-lowering therapy (n = 6,390) and 101 mg/dL (2.6 mmol/L) for those not on previous lipid-lowering therapy (n = 11,594). Prior to the hospitalisation for the qualifying ACS event, 34% of the patients were on statin therapy. At one year, the average LDL-C for patients continuing on therapy was 53.2 mg/dL (1.4 mmol/L) for the Vytorin group and 69.9 mg/dL (1.8 mmol/L) for the simvastatin monotherapy group. Lipid values were generally obtained for patients who remained on study therapy.

The primary endpoint was a composite consisting of CV death, MCE (defined as non-fatal MI, documented UA that required hospitalisation, or any coronary revascularisation procedure occurring at least 30 days after randomised treatment assignment) and non-fatal stroke. The study demonstrated that treatment with Vytorin provided incremental benefit in reducing the primary composite endpoint of CV death, MCE, and non-fatal stroke compared with simvastatin alone (RRR of 6.4%, p = 0.016). The primary endpoint occurred in 2572 of 9067 patients (7-year KM rate 32.72%) in the INEGY group and 2742 of 9077 patients (7-year KM rate 34.67%) in the simvastatin alone group (see Figure 2 and Table 13). Total mortality was unchanged in this high risk group.

There was an overall benefit for all strokes; however, there was a small non-significant increase in haemorrhagic stroke in the ezetimibe/simvastatin group compared with simvastatin alone (see Table 13). The risk of haemorrhagic stroke for ezetimibe co-administered with higher potency statins in long term outcome studies has not been evaluated.

Final outcome

Based on a review of quality, safety and efficacy, TGA approved to extend the registered indications for ezetimibe (PM-2015-1524-1-3) and the FDC ezetimibe/simvastatin (PM-2015-01525-1-3) in relation to the existing registered therapeutic goods:

- Ezetrol: ezetimibe 10 mg tablet blister pack (ARTG R 91161); and
- Vytorin FDC: ezetimibe and simvastatin 10/10mg, 10/20mg, 10/ 40mg and 10/80mg tablet blister pack (ARTG R 98100, 98111, 98115 and 98117).

The approved new indications are as follows:

- Ezetrol:

Adults (≥ 18 Years)

Prevention of Cardiovascular Disease: *Ezetrol, is indicated for administration in combination with the maximum tolerated dose of a statin with proven cardiovascular benefit in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS) in need of additional lowering of LDL-C in the expectation of a modest further reduction in the risk of cardiovascular events following at least one year of therapy (see Clinical Trials).*

- Vytorin FDC:

Adults (≥ 18 Years)

Prevention of Cardiovascular Disease: Vytorin is indicated in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS) taking their maximum tolerated dose of simvastatin and in need of additional lowering of LDL-C in the expectation of a modest further reduction in the risk of cardiovascular events following at least one year of therapy (see Clinical Trials).

Specific conditions of registration applying to these goods

- The Ezetrol EU-RMP, version 3.0, dated 24 March 2015, DLP 23 January 2015) with ASA Version 2.1 (dated 6 July 2015), included with submission PM-2015-01524-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- The Vytorin EU-RMP, version 2.0 (dated 24 March 2015, DLP 23 January 2015) with ASA Version 2.1 (dated 6 July 2015), included with submission PM-2015-01525-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachments 1 and 2. Product Information

The PI documents approved for Ezetrol and Vytorin at the time this AusPAR was published is at Attachments 1 and 2. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

Attachment 3. Extract from the Clinical Evaluation Report

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