



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for ezetimibe and atorvastatin

Proprietary Product Name: Atozet / Zeteze

Sponsor: Merck Sharp & Dohme (Australia) Pty
Limited

July 2017

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Common abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ACS	Acute coronary syndrome
AE	Adverse event
AESI	Adverse event of special interest
AMI	Acute myocardial infarction
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ARR	Absolute risk reduction
ARTG	Australian Register of Therapeutic Goods
CABG	Coronary artery bypass graft
CHD	Coronary heart disease
CK	Creatine kinase
CK-MB	Creatine kinase-MB fraction
CMI	Consumer Medicines Information
CSR	Clinical Study Report
CTT	Cholesterol Treatment Trialists
CVD	Cardiovascular disease
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EU SPC	European Union Summary of Product Characteristics
HeFH	Heterozygous Familial Hypercholesterolaemia
HMG-CoA	hydroxymethylglutaryl coenzyme A
HoFH	Homozygous Familial Hypercholesterolaemia
hs-CRP	High sensitivity C-reactive protein
ITT	Intention to treat
LDL-C	Low density lipoprotein cholesterol

Abbreviation	Meaning
LMC	LDL-C Monitoring Committee
MI	Myocardial infarction
NNT	Number needed to treat
NPC1L1	Niemann-Pick C1-Like transporter
NSTE-ACS	Non-ST Segment Elevation Acute Coronary Syndrome
NSTEMI	Non-ST Segment Elevation Myocardial Infarction
PCI	Percutaneous coronary intervention
PI	Product information
RMP	Risk Management Plan
RRR	Relative risk reduction
SAE	Serious adverse event
SMQ	Standardised MedDRA query
STEMI	ST-Elevation Myocardial Infarction
TG	Triglycerides
TIA	Transient ischaemic attack
TRAE	Treatment related adverse event
UA	Unstable angina
USPI	United States Prescribing Information

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Extension of indications
<i>Decision:</i>	Approved
<i>Date of decision:</i>	19 May 2017
<i>Date of entry onto ARTG</i>	24 May 2017
<i>Active ingredients:</i>	Ezetimibe and atorvastatin
<i>Product names:</i>	Atozet/Zeteze
<i>Sponsor's name and address:</i>	Merck Sharp & Dohme (Australia) Pty Limited Locked Bag 2234 North Ryde NSW 1670
<i>Dose form:</i>	Film-coated tablet
<i>Strengths:</i>	Ezetimibe/atorvastatin 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg
<i>Container:</i>	Blister pack
<i>Pack sizes:</i>	10 and 30 film coated tablets
<i>Approved therapeutic use:</i>	Prevention of Cardiovascular Disease Atozet/Zeteze is indicated in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS) taking their maximum tolerated dose of atorvastatin 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>	Dosage range of ezetimibe/atorvastatin 10/10 mg to 10/80 mg as a single daily dose. The recommended starting dose is 10/10 mg or 10/20 mg once daily, and can be administered at any time of the day, with or without food.
<i>ARTG numbers:</i>	216956, 216957, 216958, 216959, 216960, 216961, 216962, 216963

Product background

This AusPAR describes the application by Merck Sharp & Dohme (Australia) Pty Limited (MSD) to extend the indications for Atozet/Zeteze (ezetimibe and atorvastatin) tablets to include the following indication:

Prevention of Cardiovascular Disease

Atozet/Zeteze is indicated to reduce the risk of cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, or need for revascularization) in patients with coronary heart disease (CHD).

At time of submission, this application related to two previous submissions: the sponsor made an application for an Extension of Indications for Ezetrol (ezetimibe, submission, PM-2015-01524-1-3) and Vytorin (ezetimibe/simvastatin fixed dose combination, submission PM-2015-01525-1-3) based on the outcomes of the IMPROVE-IT study, a Phase IIIb multicentre, multinational, double blind randomised controlled study of 18,144 adult patients presenting with an acute coronary syndrome (ACS) event that compared ezetimibe 10 mg and simvastatin 40 mg or 80 mg with simvastatin at the same doses alone. Protocol changes resulted in most patients taking simvastatin at 40 mg daily dosing in each arm of the study. The primary composite outcome was a combination of cardiovascular death, non-fatal MI, documented unstable angina requiring hospitalisation, all coronary revascularisation \geq 30 days after the index event and non-fatal stroke.

The current approved indications for the combination product Atozet/Zeteze are:

Primary Hypercholesterolaemia

Atozet is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia where use of a combination product is appropriate in those patients:

- § *not appropriately controlled with atorvastatin or ezetimibe alone; or*
- § *already treated with atorvastatin and ezetimibe*

Homozygous Familial Hypercholesterolaemia (HoFH)

Atozet is indicated in patients with HoFH. Patients may also receive adjunctive treatments (e.g. LDL apheresis).

As outlined in the AusPAR for Atozet/Zeteze,¹ ezetimibe inhibits the intestinal absorption of cholesterol and atorvastatin is a synthetic lipid lowering agent. Ezetimibe targets the sterol transporter, Niemann-Pick C1-Like (NPC1L1), which is responsible for the intestinal uptake of cholesterol and phytosterols. The current approved indications for ezetimibe are:

Adults (\geq 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)

¹ Dated 7 August 2015, published 25 August 2015.

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)

Atorvastatin inhibits hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, the rate limiting enzyme that converts 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. The current approved indications of Lipitor (atorvastatin) are:

Lipitor is indicated as an adjunct to diet for the treatment of patients with hypercholesterolaemia.

Prior to initiating therapy with atorvastatin, secondary causes of hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemias, obstructive liver disease, other drug therapy, and alcoholism) should be identified and treated.

Lipitor 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, Prevention of Cardiovascular Disease) 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. as an adjunct to diet for the treatment of patients with hypercholesterolaemia.

No new dosage forms or strengths are proposed for Atozet or Zeteze.

No changes to the dosage and administration instructions have been proposed but the sponsor has introduced a new heading in this section in relation to the proposed indication. The proposed heading would indicate that the general dosage instructions relate to the existing primary hypercholesterolaemia and the proposed CHD indications. The separate dosage instructions for patients with HoFH and special patient populations remain unchanged. The current dosage instructions in this section are:

Atozet can be administered within the dosage range of 10/10 mg to 10/80 mg as a single daily dose. The recommended starting dose of Atozet is 10/10 mg or 10/20 mg once daily. Atozet can be administered at any time of the day, with or without food. Therapy should be individualised according to the target lipid levels, the recommended goal of therapy, and the patient's response. After initiation and/or upon titration of Atozet, lipid levels should be re-analysed within 2 or more weeks and dosage adjusted according to the patient's response.

The proposed heading would indicate that doses within the range of 10/10 mg to 10/80 mg as a single daily dose would be efficacious for the prevention of cardiovascular events.

Regulatory status

As of 15 March 2017, marketing applications for ezetimibe/atorvastatin tablets for prevention of cardiovascular disease have been submitted worldwide as detailed below in Table 1.

Table 1: International regulatory status for ezetimibe/atorvastatin as of 15 March 2017.

Country / region	Submission date	Status	Approved indications
US	Not planned	n/a	n/a
EU (DCP)	8 May 2015	Approved, 5 Feb 2016	Prevention of Cardiovascular Events [TRADEMARK] is indicated to reduce the risk of cardiovascular events in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS), either previously treated with a statin or not.
Canada	Not planned	n/a	n/a
Switzerland	15 Dec 2015	Under review	
Netherlands	Refer to EU above	Approved, 15 Mar 2016	
Sweden	Refer to EU above	Approved, 25 Feb 2016	
UK	Refer to EU above	Approved, 16 Feb 2016	
New Zealand	Not planned	n/a	n/a
Singapore	26 May 2016	Under review	

As of 15 March 2017, marketing applications for ezetimibe/atorvastatin tablets for cardiovascular risk reduction have not been deferred, withdrawn or rejected in any country.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. 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 requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

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 2.

Introduction

Information on the condition being treated

According to the Australian Institute of Health and Welfare (AIHW) National Mortality Database, cardiovascular disease (CVD) is the leading cause of death in Australia and was the underlying cause of death in 43,946 Australian deaths in 2012 (30% of all deaths). CVD was an associated cause of death in a further 37,558 deaths. In 2012, CHD was the underlying cause in 20,046 deaths (or 14% of all deaths), accounting for more deaths than any other single disease in Australia. Approximately half of CHD deaths (9,286) resulted from acute myocardial infarction (AMI).

Risk factors for CVD include overweight and obesity, physical inactivity, poor diet, tobacco smoking, excessive alcohol consumption, high blood pressure and high cholesterol. The AIHW estimates that in 2011-2012, 63% of adults had dyslipidaemia.

Current treatment options

There are a number of treatment options available for dyslipidaemia including statins, bile acid binding resins, fibrates, ezetimibe, nicotinic acid and omega-3 ethyl esters. It should be noted that not all drugs in each class carry the same indications. There are several registered statins available in Australia including atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin. Ezetimibe is approved for use in combination with a statin for several of the listed indications. Ezetimibe is available as a combination product in Australia in combination with simvastatin, atorvastatin or rosuvastatin. Several statins have indications that relate to the prevention of cardiovascular events. Rosuvastatin, atorvastatin and simvastatin each have indications relating to the prevention of cardiovascular events. However, it should be noted that each statin has different indications.

Rosuvastatin (trade name: Crestor) has the following indication of relevance to the submission:

Prevention of Cardiovascular Events

Crestor 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). Crestor is indicated to:

- § *Reduce the risk of nonfatal myocardial infarction*
- § *Reduce the risk of nonfatal stroke*
- § *Reduce the risk of coronary artery revascularisation procedures.*

Simvastatin (trade name: Zocor) has the following indication of relevance to the submission:

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.

Clinical rationale

The sponsor states that the IMPROVE-IT study demonstrated that the addition of ezetimibe to simvastatin reduced the risk of CV events in subjects with CHD beyond that produced by simvastatin alone. Based on the results from study, the sponsor is seeking an indication for ezetimibe (when used with a statin), ezetimibe/simvastatin, and ezetimibe/atorvastatin to reduce the risk of CV events in patients with CHD. The Sponsor argues that although IMPROVE-IT studied patients presenting with ACS, used simvastatin as the background statin, and entered patients with defined LDL-C levels the conclusions apply to patients with chronic CHD, those receiving any statin, and to subjects with a broad range of LDL-C levels.

In the pre-submission overview, the sponsor argues that the results of IMPROVE-IT are generalizable to statins due to the demonstrated effect of statins on cardiovascular outcomes, the demonstrated additive effect of ezetimibe on LDL lowering with statins and the demonstrated relationship between LDL-C lowering and reduction in cardiovascular risk across all statins. The sponsor states that ezetimibe supports a consistent proportional additive decrease in LDL-C levels when added to or co-administered with any statin. In pooled analyses of clinical trials, a 25% relative reduction in LDL-C is observed when ezetimibe is added to ongoing statin therapy, an observation generally independent of statin type, potency and dose, and patient characteristics.

The sponsor states that in January 2015, in a pre-submission consultation with the German Federal Institute for Drugs and Medical Devices (BfArM), the BfArM concurred that the incremental benefit exhibited with ezetimibe was seen as a group effect and could be applied to all statins.

The Cholesterol Treatment Trialists' (CTT) meta-analysis from 26 large, randomised, double-blind, placebo-controlled studies is reported to have shown that statin therapy reduces cardiovascular risk by about 20% per 1 mmol/L LDL-C reduction. The relationship of reduction in LDL-C to reduction in CV events observed in IMPROVE-IT is reported to be consistent with the CTT findings. The sponsor states that the findings of an additive effect of NPC1L1 and HMGCoA reductase genetic variants on LDL lowering and the additive CV risk reduction associated with presence of both NPC1L1 and HMGCoA reductase genetic variants is consistent with the IMPROVE-IT result demonstrating the additive outcomes benefit of ezetimibe and simvastatin, targeting NPC1L1 and HMGCoA reductase, respectively. The sponsor concludes that co-administration of ezetimibe with an inhibitor of HMG CoA reductase will have additive benefit on CV risk reduction.

Guidance

The following guidance documents are of relevance to this submission:

- Australian Regulatory Guidelines for Prescription Medicines (ARGPM);
- Form for providing product information for a restricted medicine or other medicine in relation to which the Secretary requires product information to be provided;
- Guideline on clinical investigation of medicinal products in the treatment of lipid disorders EMA/CHMP/748108/2013;
- Guideline on the Evaluation of Medicinal Products for Cardiovascular Disease Prevention EMEA/CHMP/EWP/311890/2007;

- Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study CPMP/EWP/2330/99; and
- Questions and Answers Document on the Clinical Development of Fixed Combinations of Drugs Belonging to Different Therapeutic Classes in the Field of Cardiovascular Treatment and Prevention CHMP/EWP/191583/2005.

Contents of the clinical dossier

The submission contained the following clinical information:

- One efficacy and safety study: IMPROVE-IT
- An analysis of post market safety including CIOMS reports for various adverse events (AEs)
- 147 literature references

Paediatric data

The submission did not include paediatric data.

Good clinical practice

The IMPROVE-IT CSR states that the trial 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. The report states that throughout the trial, study sites noted to have GCP non-compliance issues were reviewed at 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. The report indicates that 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 included in the submission.

Pharmacodynamics

No new pharmacodynamics studies were included in the submission.

Dosage selection for the pivotal studies

The Clinical Study Report for the pivotal study IMPROVE-IT states that all subjects were to be dosed with study drug in the evening, consistent with the ezetimibe/simvastatin combination label and simvastatin label. The sponsor is applying to have the proposed indication applied to Atozet products with a range of strengths for the atorvastatin component (10-80 mg).

Efficacy

Studies providing efficacy data

The sponsor has not provided any clinical data that directly support the proposed indication for Atozet.

The sponsor has relied on clinical data provided in one efficacy study, Study P04103 (IMPROVE-IT), to support the proposed indication. The IMPROVE-IT study examined the efficacy of ezetimibe/simvastatin compared to simvastatin monotherapy in high risk patients with ACS. The sponsor argues that although IMPROVE-IT studied patients presenting with ACS, used simvastatin as the background statin and entered patients with defined LDL-C levels, the results provide sufficient information to support the application of the conclusions to patients with chronic CHD, those receiving any statin and to patients with a broad range of LDL-C levels. TGA has evaluated this study in submissions PM-2015-01524-1-3 and PM-2015-01525-1-3, but is yet² to finalise a decision about approval of the requested extension of indication.

The sponsor has relied on extrapolation of these data to support its requested extension of indication for Atozet.

Study P04103 (IMPROVE IT)

Study P04103 (IMPROVE-IT) was a multicentre, randomised, double blind, active control, Phase IIIb trial comparing the efficacy of ezetimibe plus simvastatin and simvastatin monotherapy in high risk subjects with stabilised ACS. The trial had 1147 centres that allocated subjects to study treatments in 39 countries.

The primary objective of the study was to evaluate the clinical benefit of ezetimibe/simvastatin combination compared with simvastatin in stabilized 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 unstable angina (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 randomized treatment assignment.

The study had three secondary objectives evaluating the clinical benefit of ezetimibe/simvastatin combination compared with simvastatin in stabilized ACS subjects on the following composite endpoints:

- Death due to any cause, major coronary events, or non-fatal stroke.
- Death due to CHD, non-fatal MI, and urgent coronary revascularization (either PCI or CABG occurring at least 30 days after randomisation).
- CV death, non-fatal myocardial infarction (MI), documented UA that requires admission into a hospital, all revascularisation (including both coronary and non-coronary) occurring at least 30 days after randomization, and non-fatal stroke.

The study the following tertiary objectives:

- 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

² At the time of the writing of this clinical evaluation report.

- 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 revascularization (including both coronary and non-coronary) occurring at least 30 days after randomisation
- stroke
- any cardiovascular event leading to admission into a hospital
- CHF that requires hospitalisation occurring at least 30 days after randomisation
- To evaluate the proportion of subjects achieving reductions in LDL-C and hs-CRP:
 - 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.
 - To evaluate the potential relationship between the risk of occurrence of any primary endpoint event and the concentrations of LDL-C and high sensitivity-C-reactive protein (hs-CRP) following 1 month and 4 months of treatment with ezetimibe/simvastatin combination or simvastatin.
- To evaluate the safety and tolerability of ezetimibe/simvastatin combination compared with simvastatin.

The study included the additional pre-specified exploratory analyses:

- Composite of CV death, non-fatal MI, and non-fatal Stroke
- Composite of coronary death, MI, and coronary revascularization
- Composite of CHD Death or Non-fatal MI
- Composite of Cardiovascular Death or Non-fatal MI

Other efficacy studies

There were 147 literature references. These articles were not individually analysed as this was not a literature based submission. References were checked for consistency with the results reported in the submission where relevant.

Evaluator's conclusions on efficacy

The sponsor has not submitted any data to support the efficacy of atorvastatin with ezetimibe for the proposed indication but has relied on the clinical evidence that relates to simvastatin. The sponsor has requested the same indication requested for simvastatin/ezetimibe and ezetimibe in submissions PM-2015-01524-1-3 and PM-2015-01525-1-3 be extrapolated to Atozet products. The sponsor has relied heavily on the similar mechanism of action of statins to support the extrapolation of results from the IMPROVE-IT study to Atozet. A comparison of the efficacy of simvastatin and atorvastatin in lowering cardiovascular event rates has not been included in the submission. It is therefore difficult to confirm that the outcome would be similar if atorvastatin were substituted for simvastatin. While statins have the same mechanism of action, they have

different efficacy and safety profiles as demonstrated by the difference in approved indications and adverse event profiles. The statin cerivastatin was withdrawn from sale worldwide due to concerns that severe muscle effects were more common with cerivastatin than other statins. Due to these differences in efficacy and safety it is not possible to extrapolate the results from one study involving one statin to all statins. It is important that the claims for each statin be assessed individually.

The TGA adopted EU guideline (Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study CPMP/EWP/2330/99) states that where confirmatory evidence is provided by one pivotal study only:

In the exceptional event of a submission with only one pivotal study, this has to be particularly compelling with respect to internal and external validity, clinical relevance, statistical significance, data quality and internal consistency.

The IMPROVE-IT study did not examine the effect of ezetimibe/atorvastatin on cardiovascular risk and therefore does not meet the external validity criteria as the results cannot be generalised to a different statin. The clinical relevance of the observed benefit is unclear as the number needed to treat has not been stated and the study population has been selected to exclude patients with LDL-C levels above a certain threshold and those who were not responsive to treatment. In addition, the subgroup analysis did not identify a significant reduction in the occurrence of the primary composite endpoint with ezetimibe/simvastatin therapy for male patients despite a high proportion of male patients included in the study. This may indicate a lack of internal consistency. In conclusion, the criteria outlined in the EU guidelines regarding the submission of a single pivotal study have not been met and the results of the IMPROVE-IT study are not considered compelling.

The sponsor has proposed that the new indication be applied to all strengths of Atozet without providing a supporting justification. The strength of atorvastatin in Atozet products range between 10-80 mg and the proposed dosage instructions for this indication imply that Atozet is efficacious at preventing cardiovascular events across the entire dosage range. However, no data has been submitted to support the efficacy of any dose of atorvastatin with ezetimibe in preventing cardiovascular events. In the IMPROVE-IT study patients were commenced on 40mg simvastatin and were uptitrated to 80mg as required regardless of whether they were on ezetimibe. Changes to the simvastatin prescribing information, prompted dose restrictions on simvastatin as outlined in Protocol Amendment 5 to IMPROVE-IT. No additional subjects were to have their simvastatin dose increased to 80 mg and subjects taking the simvastatin dose of 80 mg for less than 12 months were to have their dose decreased to 40 mg. As a result, the majority of the study participants received either ezetimibe or ezetimibe and simvastatin 40 mg and only a small proportion of the study population received the 80 mg simvastatin dose. It is therefore difficult to extrapolate the results of the study to other doses of simvastatin and then further extrapolate to all doses of atorvastatin. The effect of the various combinations on cardiovascular outcome is potentially related to LDL-C levels but it has not been demonstrated that a higher statin dose has any further incremental benefit in cardiovascular outcome. In addition, there is the potential that a higher statin dose could increase adverse events or lead to a higher drop-out rate that could offset any potential cardiovascular benefit in this population. It is possible that at the lower atorvastatin doses (for example, 10 mg) the effect of Atozet on the risk of cardiovascular events is not clinically or statistically significant. Therefore, the effect on cardiovascular outcome cannot be extrapolated to all strengths of the ezetimibe/simvastatin combination product and then to all strengths of the Atozet products.

The IMPROVE-IT study excluded patients with LDL-C levels above a certain threshold and patients who did not achieve adequate LDL-C control were withdrawn from the study. The criteria for withdrawal based on LDL-C levels were modified as part of Protocol

Amendment 5. A total of 149 patients were withdrawn due to LDL-C levels. While it would not be ethical to continue ineffective treatment, these limitations on the study population may have introduced bias by selecting the patients most likely to respond to treatment and therefore reduce the generalizability of the study.

The result for the primary composite endpoint found a modest relative risk reduction in the primary efficacy endpoint compared to treatment with simvastatin monotherapy. However, the results were not suggestive of a reduction in the risk across all the composite endpoints. The rates of CV death and documented UA requiring hospitalisation were slightly higher in the ezetimibe/simvastatin group compared to the simvastatin monotherapy group. The benefits observed for the composite primary efficacy outcome appear to be due to reductions in non-fatal MI and non-fatal stroke.

Safety

Studies providing safety data

Pivotal studies that assessed safety as the sole primary outcome

No studies were submitted that assessed safety as the sole primary outcome.

Pivotal and/or main efficacy studies

The IMPROVE-IT study was designed to evaluate the safety and tolerability of ezetimibe/simvastatin combination compared with simvastatin. This study did not include patients taking atorvastatin or ezetimibe/atorvastatin.

Safety variables assessed included safety laboratory tests (including liver function tests and CK levels), physical examinations, adverse events, and clinic evaluations. Safety analyses were based on the ITT population. The protocol did not require the reporting of AEs that occurred more than 30 days after permanent discontinuation of the study drug unless they were considered AEs of special interest. The study included an analysis of all AEs, treatment related AEs, serious adverse events (SAEs), AEs leading to discontinuation of treatment and the following AEs of Special Interest:

- Defined increases in AST, ALT;
- Defined increases in CK;
- All AEs reflective of gallbladder-disease;
- All cholecystectomies;
- All occurrences of myopathy and rhabdomyolysis; and
- Cancer.

Select safety parameters were also analysed excluding study patients who never took study drug and excluding study subjects who never took the drug and limited to the 30 day time period after the last dose of study drug.

Other studies

No other safety studies were included in the submission, but the sponsor has provided a review of cumulative post-marketing data from 2013 to 31 December 2014 for the following eight events of interest with the use of the ezetimibe/atorvastatin combination:

- Rhabdomyolysis/myopathy;
- Malignancies;
- Gallbladder disorders;

- Interstitial lung disease;
- Haemorrhagic stroke;
- Pancreatitis;
- Acute renal failure; and
- Hypersensitivity.

Patient exposure

No patients were exposed to ezetimibe/atorvastatin or atorvastatin during the IMPROVE-IT study. The median duration of exposure for the ezetimibe/simvastatin and simvastatin groups was 1389 and 1427 days respectively. A total of 5710 subjects were on treatment for at least 72 months.

A total of 1989 patients had their dose of simvastatin titrated to 80 mg (332 in the ezetimibe/simvastatin group and 1657 in the simvastatin monotherapy group). A total of 1018 patients receiving 80 mg of simvastatin had their dose titrated back down to 40mg (229 in the ezetimibe/simvastatin group and 789 in the simvastatin group). The mean duration of exposure to the 80mg simvastatin dose was 38.0 months (30.3 in the ezetimibe/simvastatin group and 39.8 in the simvastatin group).

Safety issues with the potential for major regulatory impact

Liver function and liver toxicity

Adverse event of special interest (AESI) related to liver function and liver toxicity included defined increases in AST, ALT and all cholecystectomies.

At screening, subjects with active liver disease or persistent unexplained serum transaminase elevations ($\geq 2 \times$ ULN) were ineligible for the study. Subjects with transient increases in serum transaminases due to the index MI were eligible for the study.

Per protocol, ALT and AST testing was performed at screening/randomization, Month 1, Month 4, Month 8, Month 16, annually and at study completion/early discontinuation. Total bilirubin and alkaline phosphatase were evaluated only at the screening/randomization visit, the annual visit, and at the time of study completion/early discontinuation.

If a subject was found to have an ALT and/or AST measurement $\geq 3 \times$ ULN believed to be related to study drug, then the subject was to have repeat laboratories performed within 1 week. If the same transaminase activity was $\geq 3 \times$ ULN on two consecutive occasions, the study medication was interrupted. Investigative sites were instructed to repeat the subject's laboratory tests approximately every 2 weeks until the transaminase activity decreased to $< 2 \times$ ULN, at which time study drug could be restarted at the discretion of the investigator, following discussion with the sponsor's clinical monitor. A subject who had a second episode of two consecutive observations of transaminase activity $\geq 3 \times$ ULN believed to be related to study drug was to be discontinued from study medication, but would be monitored for any clinical endpoint event until the termination of the trial.

There were 14 deaths related to hepatic causes (9 subjects in the ezetimibe/simvastatin group and 5 in the simvastatin group). Limited information is available relating to these cases. Most available laboratory information does not provide evidence of serious liver injury. Only one case from the ezetimibe/simvastatin group met the laboratory criteria to be considered a potential DILI case. Of the 9 subjects in the ezetimibe/simvastatin group with a hepatic cause of death, 5 cases were related to non-alcoholic cirrhosis. One death occurred within 30 days of permanent discontinuation of study therapy. This patient

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.

Alcoholic cirrhosis was listed as the cause of death for one case and hepatitis B carrier status and alcohol abuse contributed to liver failure in another case. In two cases where the patient had withdrawn consent to participate in the study the cause of death was listed as liver failure. In both these cases the death occurred more than one year after permanent discontinuation of study therapy. In 4 of the 5 subject deaths in the simvastatin treatment group, non-alcoholic steatohepatitis was a contributing factor and one death was related to cirrhosis.

A total of 49 subjects, 26/8027 (0.3%) in the ezetimibe/simvastatin group and 23/8068 (0.3%) in the simvastatin group, met the biochemical criteria for potential DILI. An alternative explanation for the elevated transaminase level was identified for all but 3 cases. Limited clinical information was available for these three patients. Two of the subjects received ezetimibe/simvastatin. One subject was a patient with elevated bilirubin on randomisation who was hospitalized with elevated transaminases and weakness approximately one month later. He was diagnosed with an MI one week later and subsequently died. The other subject was a patient on aspirin and beta blocker who developed transaminase elevations approximately 1.5 years after randomisation and presented with weakness, malaise and anaemia. The study drug was stopped and she underwent colonoscopy and transaminase elevations resolved. One subject was assigned to treatment with simvastatin 40mg. This subject was a patient who developed transaminase elevations approximately one month after randomisation. Medications included aspirin and beta blocker and one year following study drug discontinuation, the subject presented with cholelithiasis and pancreatitis and underwent cholecystectomy.

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 largest numbers of elevations occurred during the first 4 months of treatment, dropped and remained fairly constant over the rest of the first year and then dropped further in the subsequent years. There was no apparent difference in the time course between treatment groups.

Approximately 17% of randomised subjects were up-titrated to simvastatin 80mg during the trial (27% in the simvastatin treatment group, and 6% in the ezetimibe/simvastatin treatment group). Given the imbalance in the treatment groups for those uptitrated to simvastatin 80 mg, exposure-adjusted analyses for instances of ALT/AST elevations > 3X ULN consecutive were also conducted. This assessment was not randomised but the exposure adjusted rate of consecutive ALT or AST $\geq 3 \times$ ULN was similar between the treatment groups in subjects taking simvastatin at a dose of 40 mg. Comparisons at the 80 mg dose are limited by the lesser use and thus the smaller number of cases in the ezetimibe/simvastatin group, however the risk appeared similar between the treatment groups.

Standardized MedDRA Queries (SMQs) were used to identify the preferred terms that were representative of gallbladder related events. The rate of gallbladder adverse events was generally similar between the treatment groups (3.11% versus 3.54% in the ezetimibe/simvastatin and simvastatin groups, respectively). A similar number of patients in each treatment arm experienced 'cholecystectomy hospitalisation' (133 in the ezetimibe/simvastatin group versus 134 in the group and in the simvastatin group).

Renal function and renal toxicity

No clinically meaningful changes in creatinine clearance were noted over the course of the study in either treatment group. In addition, there was no apparent difference in creatinine clearance between the treatment groups 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, 70 to 100 mg/dL, >100 mg/dL). Creatinine clearance at baseline was slightly different between the three groups examined, with the higher LDL-C groups exhibiting slightly greater creatinine clearance at baseline. However, there was a lot of variability around the point estimates. In any of the three LDL-C categories, there were no differences in creatinine clearance between the two treatment groups and no apparent change in creatinine clearance over time. Thus, no clinically meaningful changes in renal function were noted in any of the baseline LDL-C categories examined.

Other clinical chemistry

There was little change in CK from baseline over time and no apparent difference in change from baseline in CK between the treatment groups.

Haematology and haematological toxicity

The CSR does not discuss changes in the haematology laboratory parameters observed in the IMPROVE-IT study. The table of AEs with an incidence of $\geq 2\%$ in one or more treatment groups indicates that the incidence of anaemia was slightly higher in the ezetimibe/simvastatin group (3.92% versus 3.60%).

Other laboratory tests

Rhabdomyolysis

The rate of the AESI of myopathy/rhabdomyolysis was similar between the treatment groups (0.3% in each treatment group). In the ITT population, there were 13 subjects (0.1%) in the ezetimibe/simvastatin group that developed rhabdomyolysis compared to 18 subjects (0.2%) in the simvastatin group. In the on-treatment analysis there were 12 subjects who experienced rhabdomyolysis in the ezetimibe/simvastatin group and 18 in the simvastatin monotherapy group. Of the 12 patients in the ezetimibe/simvastatin group, 9 patients experienced rhabdomyolysis with renal involvement and one subject was taking the 80 mg simvastatin dose and five subjects were taking concomitant therapies that may have contributed to the rhabdomyolysis and renal impairment. In two other subjects there were alternate explanations or contributing factors such as a fall or accidental overdose of study drug. Alternate aetiology was not described for two patients: one patient with onset of muscle pain and rhabdomyolysis within one month of starting study drug, and another patient with diabetic nephropathy whose event occurred one week following discontinuation of study drug due to elevated CK. The subject was not placed on haemodialysis and died 15 days later due to end stage renal disease.

Of the 9 subjects with an event of rhabdomyolysis associated with renal involvement receiving simvastatin monotherapy, 4 subjects received the 40 mg dose and 5 subjects received the 80 mg dose. There were contributing factors of alternate explanations for 7 subjects. One patient received 80 mg of simvastatin for 1.6 years prior to the event; they were diagnosed with idiopathic pulmonary fibrosis and a secondary diagnosis of right lobar pneumonia was made at the time of the rhabdomyolysis event. The subject recovered from the rhabdomyolysis approximately 16 days after ceasing the study drug but was hospitalised 12 days later and experienced progressive respiratory insufficiency and persistent fever; they later had a cardiac and respiratory arrest and died. The adjudicated cause of death was severe respiratory insufficiency.

There were 3 subjects in the ezetimibe/simvastatin and 9 subjects in the simvastatin monotherapy groups who had Clinical Events Committee (CEC) reported events of rhabdomyolysis without renal involvement. The 3 subjects in the ezetimibe/simvastatin group were both receiving ezetimibe/simvastatin 40 mg at the time of the event. In two of the subjects, the event of rhabdomyolysis occurred within approximately one month from the start of study drug. In these cases, study drug was permanently discontinued and the event resolved.

There were 9 subjects with the event of rhabdomyolysis without renal involvement in the simvastatin monotherapy arm, 4 were receiving simvastatin 40 mg and 5 were receiving simvastatin 80 mg at the time of the event. All subjects permanently discontinued study therapy and recovered from the event. Among the subjects on simvastatin monotherapy, 5 were found to have contributing factors or alternate explanations which might have contributed to these events.

Myopathy

There were 13 cases of myopathy in patients in the ezetimibe/simvastatin group and 9 in the simvastatin group. One subject in the ezetimibe/simvastatin group was receiving 80mg simvastatin compared to 5 in the simvastatin group.

Myalgia without myopathy

A total of 3,171 cases of unexplained myalgia were reported by the investigators during IMPROVE-IT. Excluding the cases that were adjudicated as meeting the criteria for myopathy or rhabdomyolysis (56 [0.3%]), the remaining cases potentially represent unexplained myalgia in subjects taking statins. Over the course of the IMPROVE-IT trial, there were 1607 (17.7%) subjects who experienced this type of myalgia in the ezetimibe/simvastatin group compared with 1564 (17.2%) subjects in the simvastatin group. This result is reported to indicate no contribution from ezetimibe to the incidence of this AE. The rate of AEs with the preferred term of myalgia was similar between the treatment groups (10.68% in the ezetimibe/simvastatin group and 10.08% in the simvastatin group). AEs with the preferred term of myalgia led to discontinuation in 209 (2.31%) subjects in the ezetimibe/simvastatin group and 201 (2.21%) of subjects in the simvastatin monotherapy group.

Electrocardiograph findings and cardiovascular safety

The IMPROVE-IT study included ECG criteria for study inclusion, as described above, but there is little detail regarding whether follow-up ECGs were performed and if any changes in ECG were noted in the two treatment arms.

Vital signs and clinical examination findings

Change from baseline for vital signs including pulse, systolic, and diastolic blood pressure was assessed. No clinically meaningful differences were noted.

Immunogenicity and immunological events

There were no meaningful differences between the treatment groups related to hypersensitivity reaction related AEs. There were 735 (8.11%) subjects in the ezetimibe/simvastatin group and 748 (8.24%) in the simvastatin monotherapy group who had an adverse event related to hypersensitivity reactions.

Serious skin reactions

There was one report of Stevens-Johnson syndrome in the simvastatin treatment arm and two cases of erythema multiforme in the ezetimibe/simvastatin treatment arm. These cases are not discussed in detail in the CSR.

Other safety parameters

Malignancy

Investigators were required to report detailed information for any malignancy/neoplasm that was newly diagnosed after randomisation (regardless of the timing of the last dose of study drug), as well as pre-existing malignancies that worsened, relapsed, or caused a new AE after randomisation. All cases were submitted for adjudication by oncology members of the CEC. These events were classified as to whether or not they were malignant, site of origin, extent of disease involvement, and relationship to vital status.

The analysis of CEC adjudicated new cancers and death due to cancer found that the overall incidence of new cancers or death due to cancer did not meaningfully differ between the treatment groups as the associated hazard ratios for these endpoints were all near 1.0 (range 0.993-1.032).

New onset diabetes

Approximately 7.2% of subjects were either reported or deduced to have developed diabetes over the course of the trial. No clinically meaningful differences between treatment groups were noted; there were 650 (7.2%) subjects with New Onset Diabetes in the ezetimibe/simvastatin group and 659 (7.3%) in the simvastatin group.

Pancreatitis

No clinically meaningful differences between treatment groups in specific pancreatitis related adverse experiences were noted; there were 57 (0.63%) subjects with an AE of pancreatitis in the ezetimibe/simvastatin group and 58 (0.64%) in the simvastatin group.

Acute renal failure

There were no meaningful differences between treatment groups in specific renal failure related adverse experiences. There were 259 (2.86%) subjects with acute renal failure in the ezetimibe/simvastatin group versus 235 (2.59%) in the simvastatin group.

Interstitial lung disease

No meaningful differences between the treatment groups related to interstitial lung disease were identified. There were 34 (0.37%) subjects in the ezetimibe/simvastatin group and 40 (0.44%) in the simvastatin group who had an adverse event related to interstitial lung disease.

Haemorrhagic stroke

In the ITT analysis, there were 59 haemorrhagic strokes in the ezetimibe/simvastatin group and 43 in the simvastatin group, with an annualized rate of 0.12 and 0.09, respectively. 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. The sponsor states that these findings indicate that a large proportion of the haemorrhagic stroke events occurring in subjects allocated to ezetimibe/simvastatin occurred after the subjects had discontinued study therapy.

Post marketing data

The sponsor estimates the post market exposure for ezetimibe/atorvastatin from 2013 to 31 December 2014 to be 16,422,093 tablets distributed with an estimated 44,992 patient-treatment years of use of ezetimibe/atorvastatin.

The sponsor has provided an analysis of post market reports for eight adverse events of interest. A cumulative search of the company global pharmacovigilance database through 31 December 2014 was performed for all medically confirmed spontaneous reports including literature cases and cases from regulatory agencies with at least one preferred term from the standardised MedDRA queries (SMQ). Only narrow terms were included in the search. A separate search was run to retrieve consumer reports.

Evaluator's conclusions on safety

The safety results of the IMPROVE-IT study were evaluated in submissions PM-2015-01524-1-3 and PM-2015-01525-1-3. The overall safety profile for ezetimibe/simvastatin in the IMPROVE-IT study is consistent with the known safety profile for this combination therapy.

As outlined above, the IMPROVE-IT study did not include ezetimibe/atorvastatin therapy in either treatment arm. As a result, the safety results from this study cannot readily be extrapolated to the Atozet therapy.

The results of the analysis of post-market experience did not identify any new safety issues or significantly alter the expected frequency of known adverse events associated with Atozet therapy. However, it should be noted that the search strategy only identified patients treated with ezetimibe/atorvastatin and did not include cases where patients were treated with ezetimibe or atorvastatin alone.

First round benefit-risk assessment

First round assessment of benefits

Table 2 shows a summary of the first round assessment of benefits.

Table 2: First round assessment of benefits.

Indication: Prevention of Cardiovascular Disease	
Atozet/Zeteze is indicated to reduce the risk of cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, or need for revascularization) in patients with coronary heart disease (CHD).	
Benefits	Strengths and Uncertainties
Theoretical reduction in cardiovascular events	The sponsor has stated that treatment with ezetimibe/simvastatin resulted in a 6.4% relative risk reduction (RRR) in the primary composite efficacy endpoint (cardiovascular 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). However, the incidence of several of the composite endpoints was actually higher in the ezetimibe/simvastatin treatment arm and the clinical significance of a relative risk reduction of 6.4% has not been clearly demonstrated. Critically, the results of the IMPROVE-IT study relate to a different statin and cannot be extrapolated to all other statins at all doses.

First round assessment of risks

Table 3 shows a summary of the first round assessment of risks.

Table 3: First round assessment of risks.

Risks	Strengths and Uncertainties
The lack of direct evidence to support the efficacy and safety of Atozet for the proposed indication	The efficacy of ezetimibe/atorvastatin was not evaluated in the IMPROVE IT study. No clinical data to support the efficacy or safety of Atozet in the prevention of cardiovascular events has been presented in the submission.
Insufficient justification to support reliance on indirect evidence for the proposed indication	The justification to extrapolate the results of the IMPROVE-IT study to other statins is not sufficiently robust to support the proposed indication for Atozet. The clinical relevance of the results of the IMPROVE-IT study has not been clearly demonstrated. Not all statins have the same efficacy and safety profiles and the results of the IMPROVE-IT study cannot be readily extrapolated to all statins. In addition, the study examined only one dose combination but the Sponsor wishes to extrapolate the results to all the available dose combinations for Atozet.
The efficacy across all dosage strengths has not been demonstrated	The proposed indication implies that Atozet reduces the risk of cardiovascular events at all dosage strengths but the vast majority of patients in the IMPROVE-IT received the ezetimibe/simvastatin 10/40 mg. It has not been demonstrated that other doses of simvastatin would provide a similar benefit. It has not been demonstrated that any strength of Atozet would provide a similar benefit. This is not appropriate as alternate dosage regimens may be associated with a worse safety profile or a non-significant impact on cardiovascular events.
One pivotal study	Only one pivotal study has been included in the submission and it is not considered sufficiently compelling to support the proposed indication.
The clinical significance of the IMPROVE-IT study results has not been clearly defined	The submission has not discussed the absolute risk reduction and NNT to allow the assessment of the clinical relevance of the 6.4% relative risk reduction in CV events observed with ezetimibe/simvastatin compared to simvastatin monotherapy in patients with CHD in the IMPROVE-IT study.
Higher rates of CV death and documented UA requiring hospitalisation in the ezetimibe/simvastatin arm	The result for the primary composite endpoint found a 6.4% relative risk reduction in the primary efficacy endpoint compared to treatment with simvastatin monotherapy. However, the results were not suggestive of a reduction in the risk of all the composite endpoints. There was a slightly higher rate of CV death and documented UA requiring hospitalisation in the ezetimibe/simvastatin group compared to the simvastatin monotherapy group. The benefits observed for the composite primary efficacy outcome appear to be due to reductions in non-fatal MI and non-fatal stroke.

First round assessment of benefit-risk balance

Overall, the benefit-risk balance of Atozet and Zeteze for the proposed indication is unfavourable. No direct evidence has been submitted to support the efficacy and safety of atorvastatin combined with ezetimibe for the proposed indication. In addition, no evidence has been submitted of the efficacy and safety of all dose strength combinations of atorvastatin and ezetimibe, as requested by the sponsor, for the proposed indication.

In lieu of direct evidence, the sponsor has submitted a justification to extrapolate the efficacy and safety of simvastatin with ezetimibe to atorvastatin with ezetimibe at all dose strength combinations. This justification is based on similarity between simvastatin and atorvastatin and on a single pivotal study examining cardiovascular outcomes in patients on simvastatin and ezetimibe at a fixed dose of 40/10 mg. The IMPROVE-IT study found a modest relative risk reduction for the primary composite endpoint for ezetimibe/simvastatin when compared to simvastatin monotherapy. However, the results did not demonstrate a risk reduction across all the composite endpoints. The rates of CV death and documented UA requiring hospitalisation were slightly higher in the ezetimibe/simvastatin group compared to the simvastatin monotherapy group. The benefits observed for the composite primary efficacy outcome appear to be due to reductions in non-fatal MI and non-fatal stroke. The sponsor has not clearly demonstrated that these results can be extrapolated to Atozet therapy. In conclusion the results of the one pivotal study are not considered compelling. The justification for extrapolation is also not considered acceptable because the clinical relevance of the results have not been clearly demonstrated, not all statins have the same efficacy and safety profiles and the pivotal study examined only one dose combination, but the sponsor wishes to extrapolate the results to all the available dose combinations for Atozet.

Atozet/Zeteze is approved in Australia for the treatment of primary hypercholesterolaemia and HoFH. The proposed indication does not increase the patient population eligible to receive Atozet therapy but would extend the claims made by the sponsor to include reduction in CV events. The rejection of the proposed indication would not restrict access to this combination therapy, therefore rejection would not disadvantage patients and would have no impact on public health.

First round recommendation regarding authorisation

It is recommended that the submission to register Atozet/Zeteze for the proposed indication relating to the prevention of cardiovascular disease be rejected. The main reasons for rejection are the lack of direct evidence for Atozet for the proposed indication, the insufficient justification to support the use of indirect evidence, the extrapolation of the justification to all doses of Atozet, the inclusion of only one pivotal study that was insufficiently compelling and the questionable clinical significance of the IMPROVE-IT study results.

Clinical questions

General

1. Provide an update on the international regulatory status of the submission.
2. The application cover letter lists only the combination product and does not include the composite pack ARTG numbers. Does the sponsor intend to extend the indications for both the combination product and composite pack product?
3. What evidence is there to support the statement that the CV risk reduction associated with presence of both NPC1L1 and HMGCoA reductase genetic variants is additive?

4. Indicate which of the GCP breaches listed were considered serious breaches in the CSR.

Efficacy

5. Clarify the age range of the IMPROVE-IT study patient population and state how many patients were aged less than 50 years of age in each treatment arm.
6. Specify the NNT and the ARR for the primary composite endpoint in the IMPROVE-IT study.
7. The sensitivity analysis for the primary composite endpoint censoring subjects at the time of dose titration does not appear to be consistent with the analysis of the composite primary endpoint. The sensitivity analysis shows higher event rates in the simvastatin/ezetimibe group for each of the composite endpoints except for non-fatal stroke and a higher overall event rate for this treatment group. Clarify the source of this discrepancy and discuss how the findings impact interpretation of the results for the composite primary endpoint analysis.
8. Provide the analysis of between group change in the non-HDL-C/HDL-C ratio or identify the associated table in the submission.

Safety

9. Specify the time period covered by the post-market review of safety.

Second round evaluation

Details of sponsor's responses to clinical questions and evaluator's subsequent comments are contained in Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Atozet/Zeteze in the proposed usage are unchanged from those identified in the first round.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of Atozet/Zeteze in the proposed usage are unchanged from those identified in the first round.

Second round assessment of benefit-risk balance

The benefit-risk balance of Atozet/Zeteze (ezetimibe plus atorvastatin) given the proposed usage, is unfavourable. As described, no direct evidence has been submitted to support the efficacy and safety of atorvastatin combined with ezetimibe for the proposed indication. The sponsor has requested the indication apply to all dose strength combinations of atorvastatin and ezetimibe but no evidence has been submitted to support of the efficacy and safety of all dose strength combinations.

The sponsor has submitted a justification to extrapolate the efficacy and safety of simvastatin with ezetimibe to atorvastatin with ezetimibe at all dose strength combinations but as discussed, the results of the IMPROVE-IT study cannot be extrapolated to Atozet therapy.

The rejection of the proposed indication would not restrict access to this combination therapy, therefore rejection would not disadvantage patients and would have no impact on public health.

Second round recommendation regarding authorisation

Approval of Atozet/Zeteze (ezetimibe plus atorvastatin) is not recommended for the proposed indication:

Prevention of Cardiovascular Disease

Atozet/Zeteze is indicated to reduce the risk of cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, or need for revascularization) in patients with coronary heart disease (CHD).

After consideration of the responses to clinical questions, the benefits of Atozet/Zeteze in the proposed usage are unchanged from those identified in the first round. As stated, the main reasons for rejection are the lack of direct evidence for Atozet/Zeteze for the proposed indication, the insufficient justification to support the use of indirect evidence, the extrapolation of the justification to all doses of Atozet/Zeteze. TGA has previously determined that the IMPROVE-IT study was not sufficient evidence to support the requested extension of indication for Vytorin and Ezetrol (decision letter dated August 2016). The current submission included the same study and requested a similar extension of indication apply to all dosage strength of Atozet/Zeteze. The submission relied on extrapolation of the IMPROVE-IT study results to other statins without additional clinical data.

V. Pharmacovigilance findings

Risk management plan

The most recently evaluated EU-RMP was version 1.0 (11 September 2013) and accompanying Australian Specific Annex (ASA) (dated 13 June 2014). In support of the extended indications, the sponsor submitted EU-RMP version 4 (24 March 2015; DLP 23 January 2015) and ASA version 1.1 (7 February 2016).

The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised in Table 4.

Table 4: Ongoing safety concerns.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		R	A	R	A
Important identified risks	Muscle injury (Rhabdomyolysis/myopathy)	Ü	-	Ü	-
	Abnormal liver function (Abnormal liver function)	Ü	-	Ü	-
	Allergic reactions (Hypersensitivity)	Ü	-	Ü	-
	Drug interaction with warfarin, another coumarin anticoagulant or fludione	Ü	-	Ü	-
	Drug interaction with cyclosporin	Ü	-	Ü	-
Important potential risks	Gallbladder inflammation/gallstones (Cholecystitis/cholelithiasis)	Ü	-	Ü	-
	Pancreas inflammation (Pancreatitis)	Ü	-	Ü	-
	Stroke due to bleeding in the brain (Hemorrhagic stroke)	Ü	-	Ü	-
	Interstitial lung disease	Ü	-	Ü	-
	Diabetes (New-onset diabetes)	Ü	-	Ü	-
Missing information	Use in pregnancy and breastfeeding (Exposure during pregnancy and lactation)	Ü	-	Ü	-
	Use in children less than 18 years of age	Ü	-	Ü	-
	Use in patients with moderate or severe liver problems (Exposure in patients with moderate or severe hepatic insufficiency)	Ü	-	Ü	-
Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		R	A	R	A
Important identified risks	Muscle injury (Rhabdomyolysis/myopathy)	Ü	-	Ü	-
	Abnormal liver function (Abnormal liver function)	Ü	-	Ü	-
	Allergic reactions (Hypersensitivity)	Ü	-	Ü	-
	Drug interaction with warfarin, another coumarin anticoagulant or fludione	Ü	-	Ü	-
	Drug interaction with cyclosporin	Ü	-	Ü	-
Important potential risks	Gallbladder inflammation/gallstones (Cholecystitis/cholelithiasis)	Ü	-	Ü	-
	Pancreas inflammation (Pancreatitis)	Ü	-	Ü	-
	Stroke due to bleeding in the brain (Hemorrhagic stroke)	Ü	-	Ü	-
	Interstitial lung disease	Ü	-	Ü	-
	Diabetes (New-onset diabetes)	Ü	-	Ü	-
Missing information	Use in pregnancy and breastfeeding (Exposure during pregnancy and lactation)	Ü	-	Ü	-
	Use in children less than 18 years of age	Ü	-	Ü	-
	Use in patients with moderate or severe liver problems (Exposure in patients with moderate or severe hepatic insufficiency)	Ü	-	Ü	-

R = Routine

A = Additional

No additional pharmacovigilance or risk minimisation activities have been proposed which is consistent with the previously approved RMP. This continues to be acceptable for the proposed extension of indication.

New and outstanding recommendations

- Recommendation 1. The RMP evaluator has noted the sponsor's justification to the removal of malignancy from the list of safety concerns. It is recommended that the Delegate considers whether the removal of malignancy is justified by the safety findings from IMPROVE-IT study.
- Recommendation 2. The sponsor should provide approved version 4.2 of the EU-RMP with amended ASA to TGA.
- Recommendation 3. The sponsor should provide its pharmacovigilance plan to monitor/further characterise the newly added safety concern in the ASA.
- Recommendation 4. The sponsor should provide its risk minimisation plan to mitigate the newly added safety concern in the ASA.

Wording for conditions of registration

No wording could be provided at this stage due to outstanding RMP issues to be resolved.

VI. Overall conclusion and risk/benefit assessment

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

Quality

No new quality data were provided.

Nonclinical

No new nonclinical data were provided.

Clinical

The clinical evaluator recommended rejection of the application. The main reasons for rejection were the lack of direct evidence for Atozet/Zeteze for the proposed indication, the insufficient justification to support the use of indirect evidence, and the extrapolation to all doses of Atozet.

The clinical dossier comprised:

- One efficacy and safety study: the IMPROVE-IT study;
- An analysis of post market safety including CIOMS reports for various AEs; and
- Summary documents, letter of application, PI, CMI.

Pharmacology

No new pharmacology data were provided.

Efficacy

No clinical efficacy data were provided to directly support the proposed indication.

The sponsor relied on the IMPROVE-IT study. This was a Phase IIIb multicentre, multinational, randomised, double-blind, active-controlled trial that randomised a total of

18,144 adult patients with a median age of 63.7 years (range 22-98 years) to either daily dosing with ezetimibe 10 mg in combination with simvastatin 40 mg (9067 patients) or to simvastatin 40 mg daily plus placebo (9077 patients). Patients were adults presenting with unstable angina, NSTEMI or STEMI for whom a PCI was planned for the qualifying event. Inclusion criteria were extensive. Randomisation was 1:1 for the treatment groups, stratified by participation in the EARLY-ACS trial,³ receiving chronic prescription lipid lowering therapy for > 4 weeks prior to the qualifying ACS event, and qualifying diagnosis of NSTEMI-ACS (non-ST elevation ACS) or STEMI. Chronic therapy must have been with a lipid-lowering potency equal to or less than simvastatin 40 mg daily. For lipid therapy naïve patients, LDL-C at enrolment needed to be ≥ 1.3 mmol/L and ≤ 3.2 mmol/L and total cholesterol (TC) ≤ 4.9 mmol/L and for lipid-naïve patients and LDL-C ≥ 1.3 mmol/L and ≤ 2.6 mmol/L, and TC ≤ 3.9 mmol/L for in patients already on therapy. All needed to have a fasting plasma TG ≤ 4.0 mmol/L.

Exclusion criteria were also extensive, but of note were haemodynamically unstable patients, recurrent symptoms of cardiovascular or cerebrovascular ischaemia, arrhythmia, and CABG for the qualifying event (either planned or completed), and chronic therapy with a statin of greater potency than simvastatin 40 mg daily. The simvastatin could be increased to 80 mg in a blinded manner if the LDL-C was > 2.0 mmol/L at two consecutive visits, and not attributable to poor compliance. Modification to the protocol mid-study restricted the use of simvastatin 80 mg to those that had already uptitrated to that dose for more than 12 months unless concomitantly taking amlodipine or ranolazine. For all other patients the maximum simvastatin dose remained at or was reduced to 40 mg daily. A sample size of the study was modified to 18,000 with a minimum follow-up of 2.5 years to have a 90% power to detect a 15 mg/dL (about 0.39 mmol/L) difference in LDL-C between the treatment groups that would translate to a 9.375% risk reduction (based on the outcomes of the CTT meta-analysis).

Baseline demographics were similar between the groups. In each treatment arm about 4% were aged < 50 years, and for most the qualifying event was an anterior wall STEMI. About 1/4 of patients were female, 2/3 had NSTEMI-ACS as the qualifying event, and 1/3 of subjects had prior prescription lipid lowering therapy. About 61% had a history of hypertension, 21% had a previously documented MI, 26.6% had a history of CHD, with 29.2% exhibiting disease in 3 vessels. A history of diabetes was reported by 27.2% and 20.4% of subjects were treated with antidiabetic medications. Prior to the qualifying event, 19% of subjects had a previous PCI, 9.3% had a prior CABG, and about 4% of subjects had a history of stroke.

Of the 75.7% of patients who completed the study, 46.6% completed on the study drug. The median follow-up was 6 years and the survival analysis was performed on the ITT population at 7 years.

The composite primary endpoint of cardiovascular death, non fatal MI, documented unstable angina requiring hospitalisation, all coronary revascularisation with PCI or CABG ≥ 30 days, and nonfatal stroke was as shown below.

³ The Early Glycoprotein IIb/IIIa inhibition in Non-ST Elevation Acute Coronary Syndrome study in patients with acute coronary syndromes who were assigned invasive treatment planned for the next calendar day after the index event, that compared eptifibatid prior to or after angiography.

Table 5: Composite primary endpoint ITT population at 7 years.

	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 ⁶
Primary Composite Endpoint	2572	(28.37)	6.39	32.72 (31.63, 33.85)	2742	(30.21)	6.85	34.67 (33.56, 35.81)	0.936 (0.887, 0.988)	0.016
Cardiovascular death	342	(3.77)			319	(3.51)				
Non-fatal MI	782	(8.62)			902	(9.94)				
Documented UA requiring hospitalization	117	(1.29)			107	(1.18)				
All coronary revascularization with PCI or CABG ≥ 30 days	1153	(12.72)			1175	(12.94)				
Non-fatal stroke	178	(1.96)			239	(2.63)				

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.

⁶ N = Number of subjects in protocol-defined ITT population.

There was an ARR of (KM%) 1.95% and a RRR of 6.4%. Among the components of the primary endpoint the greatest benefits were a reduction in non-fatal myocardial infarction and non-fatal stroke, although there was no overall benefit for cardiovascular death. The HR for the primary composite endpoint with events censored at 30 days after discontinuation of the study drug was 0.924 (95% CI 0.868-0.983), p = 0.012. More detail of the results of the study can be found in the clinical evaluation report. Subgroup analysis showed less favourable outcomes for those non-diabetic and <75 years of age, although the study was not specifically powered for subgroup analysis.

The safety of ezetimibe with simvastatin was similar to simvastatin alone for AEs and TRAEs, and deaths both cardiovascular and non-cardiovascular (13.5% across the study) were similar between the groups (AEs resulting in death overall 3.7%). SAEs occurred in about 40.2% of each treatment groups and most commonly were neoplasms (benign, malignant and unspecified including cysts and polyps; all neoplasia was considered a SAE) (11.82%/11.99%),⁴ infections and infestations (8.9% /8.81%), gastrointestinal disorders (7.46%/7.52%) and musculoskeletal disorders (5.8%/5.48%).

Increase in haemorrhagic stroke in the ezetimibe-simvastatin group compared with simvastatin alone (HR 1.377, 95% CI 0.93-2.04, p = 0.110) was based on relatively small numbers of events (59 versus 43).

Discontinuations due to AEs occurred in 10.6%/10.1%, due to TRAEs in 7.0%/6.8% and due to SAEs in 2.0%/1.9% of the ezetimibe-simvastatin/simvastatin alone groups, respectively. Ezetimibe did not appear to contribute significantly to the adverse effect profile of participants in the study.

An account of post-market safety reports for eight adverse events of interest (rhabdomyolysis, malignancy, gall bladder disorders, interstitial lung disease, haemorrhagic stroke, pancreatitis, acute renal failure and hypersensitivity) for patients treated with ezetimibe/atorvastatin were included in the submission and did not indicate any new safety signals for this combination of products, however this summary did not include an analysis of the safety of ezetimibe and atorvastatin alone.

⁴ New malignancies: ezetimibe-simvastatin 1.82%/year and 1.84%/year simvastatin alone.

The sponsor has provided a justification that the findings of the IMPROVE-IT study can be extrapolated to the combination of atorvastatin and ezetimibe to support its proposed new indication for Atozet, and in the response to the Round 2 clinical evaluation reports has noted the conclusions of the appeal Delegate in resolving the issues of extrapolation and dose range.

Risk management plan

The Pharmacovigilance and Special Access Branch at TGA has reviewed EU-RMP version 4.0. The sponsor intends to provide EU-RMP version 4.2 and an updated ASA prior to finalisation of this submission. The RMP evaluator referred sponsor's removal of malignancy from the Summary of Safety Concerns to the Delegate for consideration. The sponsor is encouraged to resolve any outstanding matters with the RMP team following the submission of these new documents.

Risk-benefit analysis

Delegate's considerations

The efficacy of the combination of ezetimibe and atorvastatin and the safety of the combination of these products has been established in previous submissions. Atorvastatin is indicated to reduce the risk of non-fatal myocardial infarction and nonfatal stroke in hypertensive patients with multiple risk factors for CHD but the approved indication for Atozet does not include any claims of cardiovascular benefit for the combination of ezetimibe and atorvastatin. Safety is monitored through post-market activities and no new safety concerns have been identified for this population using the combination of ezetimibe and atorvastatin from the safety data provided in the submission.

No direct evidence of the cardiovascular benefit from adding ezetimibe to atorvastatin has been presented to support the requested new indication. The sponsor's requested indication extends the population beyond the recently approved indications for Ezetrol and Vytorin that are restricted to patients with CHD and an ACS. As noted previously, these indications are based on evidence provided by a single clinical trial, the IMPROVE-IT study that demonstrated a 1.6% ARR and 6.4% RRR in cardiovascular events in patients taking ezetimibe and simvastatin compared to simvastatin alone over 7 years of therapy.

The new indication for Ezetrol allows an extrapolation of the results of the IMPROVE-IT study to all statins registered in Australia with a demonstrated cardiovascular benefit. Atorvastatin is a statin with some cardiovascular benefit, as noted by a reduction in nonfatal MI and nonfatal stroke in the currently approved indications, so it may follow that this extrapolation could extend to Atozet. The sponsor in its response to the second round clinical evaluation report *contends this conclusion supports the approval of Atozet under the same conditions as for the approval of Ezetrol since atorvastatin meets the criteria of a 'statin with proven cardiovascular benefits'*.

The new indication for Ezetrol indicates the modest benefit of adding ezetimibe to the *'maximum tolerated dose of a statin with proven cardiovascular benefit'*. There is no direct evidence to support an additional benefit from ezetimibe with the full range of doses for Atozet or the full range of doses of simvastatin, however it is difficult to contend the *'maximum tolerated dose of statin'* in the Ezetrol indication does not fit within an approved dose range of atorvastatin or that any one of the dose combinations of Atozet could not be the maximally tolerated dose for an individual patient. Therefore the approved indication for Ezetrol as it relates to statin dose could include the dose range of atorvastatin. The sponsor proposes the same dosage regimens will apply as currently approved for the currently approved combination product.

The key concern is that the sponsor is extrapolating of the findings for ezetimibe from the IMPROVE-IT study, in the absence of additional evidence of a demonstrated cardiovascular benefit for ezetimibe with atorvastatin, not only to patients with CHD and ACS but to all patients with CHD. The IMPROVE-IT study required the patients to have an ACS event as an inclusion criterion. The sponsor has not demonstrated an additional cardiovascular benefit for the combination of simvastatin and ezetimibe for all patients with CHD. The sponsor did not include studies demonstrating cardiovascular benefit for atorvastatin in the submission and has relied on previously evaluated studies that are reported in the PI for atorvastatin and Atozet. In addition, the proposed indication itemises the cardiovascular benefits based on the composite primary endpoint of the IMPROVE-IT study, including a reduction in cardiovascular mortality. The Atozet PI specifically states in the description of the ASCOT study that a statistically significant reduction in cardiovascular mortality was not seen in the atorvastatin group compared to placebo. An improvement in cardiovascular mortality with ezetimibe was not demonstrated in the IMPROVE-IT study.

Patients may already be prescribed ezetimibe and atorvastatin to achieve lower LDL-C than with a single agent and the current indication may include patients with CHD and ACS. Patients would not be disadvantaged by a restriction of the claims of benefit to align with the recently approved indication for Ezetrol.

No direct evidence has been provided for the whole population in the claimed indication and only indirect evidence has been provided of a modest benefit after prolonged therapy for the studied population with a combination of ezetimibe and simvastatin over simvastatin from a single clinical study. The sponsor's requested extension of indication as stated in the letter of application is not supported.

Data deficiencies

The prominent data deficiency is the lack of direct data for the ezetimibe atorvastatin combination product to support the claims stated in the indication. The sponsor relies on a recent submission, a study with a related but not identical statin, and a good deal of extrapolation to support its proposed indication.

Indication

The sponsor has requested an indication that is broader than the current indication for atorvastatin and for ezetimibe without substantiating supportive evidence. For the reasons outlined above the sponsor's proposed indication is not supported. Subject to the advice of the ACM the sponsor could consider alternative wording to amend the indication to align with the Ezetrol and Lipitor indications, consistent with the extrapolations implied in the Ezetrol indication.

Conditions of registration

There will be a RMP condition imposed if the submission is approved. The sponsor has indicated to the RMP team an updated RMP and ASA will be provided within the current submission.

Questions for the sponsor

- The conclusion of the Delegate is that there is insufficient evidence to support the proposed extension of indication in the submission. Please provide the sponsor's view of an alternative indication that to align the wording of the indication, including the cardiovascular outcomes claim, with that of Ezetrol and Vytorin.

Summary of issues

There is no direct clinical evidence to support the proposed indication for ezetimibe/atorvastatin.

Efficacy is extrapolated from a single study comparing ezetimibe and simvastatin with simvastatin alone in patients with an acute ACS and elevated LDL-C with a modest reduction in a composite cardiovascular outcome after 7 years of therapy.

The proposed indication also extrapolates the efficacy to a population outside the reference study.

Proposed action

The Delegate is not in a position to say, at this time, that the application for ezetimibe/atorvastatin (Atozet/Zeteze) should be approved for the requested indication.

Atozet/Zeteze 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 sponsor has requested an indication that is broader than the current indication for atorvastatin and for ezetimibe without substantiating supportive evidence.

Request for ACM advice

The committee is requested to provide advice on the following specific issues:

- 1. A number of extrapolations underpin the sponsor's proposed new indication for Atozet/Zeteze (see above). Please comment on whether the sponsor has provided sufficient justification for these extrapolations in support of its proposed indication.*
- 2. 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 acknowledges the Delegate's concerns regarding the originally proposed indication in this submission, Atozet/Zeteze is indicated to reduce the risk of CV events (CV death, nonfatal myocardial infarction, nonfatal stroke, hospitalisation for UA, or need for revascularisation) in patients with CHD), but believes that modification of the indication to align with the approved indications for Ezetrol and Vytorin for Prevention of Cardiovascular Disease addresses these concerns.

Consistent with the Delegate's request, MSD proposes the following modified indication for Atozet/Zeteze:

Prevention of Cardiovascular Disease

Atozet/Zeteze is indicated in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS) taking their maximum tolerated dose of atorvastatin 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).

MSD has also, in accordance with the Delegate's request, aligned the IMPROVE-IT clinical trial description in the Atozet/Zeteze PI with that approved in the Ezetrol PI.

In addition, MSD provides the following comments on issues presented in the Delegate's request for ACM's advice.

1. Evidence to support the proposed indication for ezetimibe/atorvastatin

The Delegate has expressed concerns regarding the applicability of the results of the IMPROVE-IT trial to Atozet given that the statin used in the trial was simvastatin:

No direct evidence of the cardiovascular benefit from adding ezetimibe to atorvastatin has been presented to support the requested new indication.

This concern was also raised during the TGA evaluation of the related extension of indication submission for Ezetrol (PM-2015-01524-1-3) and was a contributing factor in the Delegate's initial decision to not register Ezetrol for the proposed indication. However, this initial decision was overturned by TGA following MSD's appeal under Section 60 of the *Therapeutic Goods Act 1989* (dated November 2016) (Section 60 appeal). In the decision letter dated January 2017, the Section 60 reviewer voiced support for the use of ezetimibe with statins other than simvastatin:

I think 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 cardiovascular benefits) 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 this 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.

In our request for Section 60 review in relation to Ezetrol and Vytorin, MSD contended that there is a significant body of evidence to support the applicability of the findings from IMPROVE-IT to statins other than simvastatin, including:

- the ezetimibe mechanism of action;
- the Cholesterol Treatment Trialists' (CTT) meta-analyses;⁵
- a pooled analysis from 27 lipid-lowering trials;⁶
- endorsement from overseas regulatory agencies;
- information from studies with people with naturally occurring genetic mutations in NPC1L1 and HMGCoA reductase variants;⁷
- clinical expert testimony (provided for the Section 60 appeal).

The Section 60 reviewer has accepted that Ezetrol can be administered with any statin with proven CV benefits (that is, those with an approved CV prevention indication in

⁵ Cholesterol Treatment Trialists' (CTT) Collaborators, et al. 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); Cholesterol Treatment Trialists' (CTT) Collaboration, et al. 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).

⁶ 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).

⁷ Stitzel NO, et al. Inactivating mutations in NPC1L1 and protection from coronary heart disease. *N Engl J Med*. 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 × 2 factorial Mendelian randomization study. *J Am Coll Cardiol*. 65: 1552-1561 (2015); Catapano AL, Ference BA. IMPROVE-IT and genetics reaffirm the causal role of LDL in cardiovascular disease. *Atherosclerosis* 241: 498-501 (2015).

Australia), regardless of the fact that the indications for the individual statins vary in substance, provided the PI reflects the fact that the benefit is expected, but not specifically demonstrated in a clinical study like IMPROVE-IT.

MSD believes that the information base relating to lipid lowering in general and with ezetimibe, along with the results of the IMPROVE-IT trial, support the anticipated CV risk reduction for ezetimibe add-on therapy when used with all statins with proven outcomes benefit. As outlined in the Delegate's request for ACM's advice, Lipitor is currently approved for Prevention of Cardiovascular Disease as follows:

Lipitor 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 HCD (see CLINICAL TRIALS, Prevention of Cardiovascular Disease) to reduce the risk of non-fatal myocardial infarction and non-fatal stroke.

Thus, in practice, atorvastatin can be considered a statin with proven cardiovascular benefit on the basis that a beneficial effect on CV outcomes has been demonstrated in a broader population, including both those with a history of CV outcomes, and those with asymptomatic CHD, than the patients included in the proposed indication, that is, "CHD and a history of ACS taking their maximum tolerated dose of atorvastatin and in need of additional lowering of LDL-C".

However, MSD acknowledges that the proposed indication is based on indirect evidence, and hence in accordance with the requests of both the Section 60 reviewer and the Delegate, the revised PI includes the statement that "no clinical trials have been undertaken that demonstrate an improvement in cardiovascular outcome when a combination of ezetimibe and atorvastatin is used compared to atorvastatin alone". In this way, prescribers are suitably alerted to the evidence base for the proposed indication.

MSD contends that this information supports the approval of Atozet under the same conditions as for the approval of Ezetrol, since atorvastatin meets the criteria of "a statin with proven cardiovascular benefit".

The published CTT meta-analyses provide robust support for the consistent benefit of ezetimibe add-on therapy with all statins. A clinical expert provided further explanation of this in his report provided to MSD in support of the Section 60 appeal related to Ezetrol and Vytorin:

These meta-analyses show a generally linear link between reduction in LDL-C levels by statins and reduction of risk of 'major vascular events' (non-fatal myocardial infarction or coronary death, strokes, or coronary revascularisations). Significantly, this linear relationship was the same across patients treated with different statins. These meta-analyses confirm that the reduced risk of major vascular events delivered by statins is due to the lowering of LDL-C by the treatment with the statin – often referred to as the LDL-C hypothesis. They confirm that different statins work in the same manner, and there was generally no difference in benefit delivered by different statins other than that due to different levels of reduction of LDL-C.

This acceptance of statin equivalence is also observed in lipid management guidelines worldwide. The consistent benefit of ezetimibe add-on therapy with all statins is endorsed in current European guidelines for management of dyslipidaemias.⁸ Furthermore, based on the results of the IMPROVE-IT trial, the 2015 ESC Guidelines for the Management of

⁸ Catapano AL, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias: The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Atherosclerosis* 253: 281-344 (2016).

NSTE-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.⁹

Further, numerous regulatory agencies have provided endorsement of the additive effect of ezetimibe being independent of the statin type or dose through the approved indications and dosage information for Ezetrol (see Australian PI as available online for ARTG ID: 91161, USPI¹⁰, EU SPC).¹¹ MSD believes all available evidence indicates that the use of ezetimibe with all statins of proven cardiovascular benefit, including atorvastatin, can be expected to be safe and efficacious in the proposed indication.

2. Population stated in the proposed indication

MSD concurs that, as stated by the Delegate:

The proposed indication also extrapolates the efficacy to a population outside the reference study.

In accordance with the Delegate's request to align the wording of the Atozet indication for Prevention of Cardiovascular Disease with that of Ezetrol and Vytorin, MSD agrees to revise the indication for the Prevention of Cardiovascular Disease for Atozet to patients with CHD and a history of ACS, as specified above.

The proposed indication is, therefore, in alignment with the population seen in the reference study.

3. Proven cardiovascular benefit of Lipitor (atorvastatin) compared to Atozet (ezetimibe/atorvastatin)

The Delegate has expressed concerns that the proposed indication for Atozet is broader than the approved indication for ezetimibe and atorvastatin.

When discussing the claimed CV benefits of Atozet in comparison to the approved claims for atorvastatin, the Delegate notes:

the proposed indication itemises the cardiovascular benefits based on the composite primary endpoint of the IMPROVE-IT study, including a reduction in cardiovascular mortality. The Atozet PI specifically states in the description of the ASCOT study that a statistically significant reduction in cardiovascular mortality was not seen in the atorvastatin group compared to placebo. An improvement in cardiovascular mortality with ezetimibe was not demonstrated in the IMPROVE-IT study.

The revised indication (above) no longer itemises the CV benefits based on the composite primary endpoint of IMPROVE-IT and thus removes the contradiction in relation to specific cardiovascular benefits of atorvastatin.

MSD concurs with the Delegate's request to align the IMPROVE-IT clinical trial description in the Atozet PI with the Ezetrol PI. The approved Ezetrol text details which of the components of the composite endpoint in IMPROVE-IT achieved statistical significance, as a tertiary outcome measure in the study, and which, including mortality endpoints, did not. Thus, there is greater consistency between the proposed mortality claims from IMPROVE-IT and ASCOT.

⁹ 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).

¹⁰ U.S. Product Information for ZETIA (ezetimibe) Tablets: August 2013.

¹¹ European Summary of Product Characteristics for EZETROL (ezetimibe) Tablets: Feb 2016.

In addition, MSD has proposed a reference to the ASCOT study be added to the 'Clinical Trials' description of IMPROVE-IT to ensure clarity around the body of evidence for the cardiovascular benefits of atorvastatin.

With regard to the claimed cardiovascular benefit for ezetimibe proposed in this application, the IMPROVE-IT trial has demonstrated the contribution of ezetimibe to the reduction of cardiovascular outcomes. With respect to this indication, ezetimibe is not intended to be the primary lipid lowering therapy, but is a second line option for patients who have not reached treatment goals on their maximally tolerated dose of a statin. Hence, the IMPROVE-IT study investigates ezetimibe on combination with a statin, and the proposed indication reflects this. While the indication is broader than the approved ezetimibe indication in this sense, that is, that ezetimibe monotherapy does not have an indication for reduction in CV outcomes, this is consistent with the intended use of ezetimibe.

This is in accordance with EMA Guideline on Clinical Development of Fixed Combination Medicinal Products (CHMP/EWP/240/95 Rev.1), which states in relation to indications:

The indications claimed for a fixed combination medicinal product should be such that the presence of each active substance makes a contribution to the claimed effect or improves the overall benefit risk ratio by mitigating side effects.

At the time of registration of the Atozet fixed dose combination, evidence was not available to show that **each** active substance in Atozet (atorvastatin and ezetimibe) made a contribution to the prevention of cardiovascular disease. As a result, the Prevention of Cardiovascular disease indication in the Lipitor PI at the time was not included in the Atozet PI at registration.

However, the IMPROVE-IT trial has now proven the incremental benefit of ezetimibe add-on therapy over statin monotherapy. The contribution of ezetimibe to reduction of cardiovascular outcomes is in the context of co-administration with a statin, and this is reflected in the proposed indication.

Conclusion

MSD acknowledges the Delegate's concerns regarding the extrapolations relating to both the drug and patient population which underpin the originally proposed indication for Atozet; however, believes the proposed modification of the indication statement and clinical trial description in the Atozet PI addresses these concerns.

In addition, the body of evidence available, supported by the Section 60 reviewer's comments, suggest that the combination of ezetimibe with a statin with proven cardiovascular benefit other than simvastatin, such as atorvastatin, is likely to achieve similar clinical outcomes in this patient population.

The findings of IMPROVE-IT have been endorsed in treatment guidelines from major cardiovascular societies around the world (EU,¹² AU,¹³ US).¹⁴ While the Section 60 reviewer has noted that the various guidelines quoted express opinions and do not

¹² Piepoli MF, et al. 2016 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).

¹³ 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).

¹⁴ Lloyd-Jones DM, et al. 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin 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).

constitute evaluable evidence, these guidelines do represent an evidence based consensus from leading experts in cardiovascular medicine, and provide a framework for clinicians based on the current evidence. The consistency of recommendations incorporated into recent guidelines (EU,¹⁵ AU),¹⁶ based on the IMPROVE-IT study, and in the ACC Consensus Decision Pathway, indicate that consensus around the findings from IMPROVE-IT exists between European, US and Australian experts.

The results of the IMPROVE-IT trial have shown the efficacy of ezetimibe in Prevention of Cardiovascular Disease as add-on therapy with statins. The totality of evidence supports the consistent effect of ezetimibe when added to all statins with proven cardiovascular benefit. Together, these support an indication for second line use of ezetimibe added to atorvastatin in patients with CHD and a history of ACS who are unable to achieve the desired results on statin therapy.

Question for the sponsor

- *The conclusion of the Delegate is that there is insufficient evidence to support the proposed extension of indication in the submission. Please provide the sponsor's view of an alternative indication that to align the wording of the indication, including the cardiovascular outcomes claim, with that of Ezetrol and Vytorin.*

MSD is agreeable to consideration of an alternative indication for Prevention of Cardiovascular Disease aligned with the indications approved for Ezetrol and Vytorin, and propose the following:

Prevention of Cardiovascular Disease Atozet/Zeteze is indicated in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS) taking their maximum tolerated dose of atorvastatin 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).

Advisory Committee considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

The ACM, taking into account the submitted evidence of efficacy, safety and quality, considered Atozet/Zeteze tablet containing 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg of ezetimibe/atorvastatin to have an overall positive benefit-risk profile for the indication:

- Current indication:

Primary Hypercholesterolaemia

Atozet/Zeteze is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia where use of a combination product is appropriate in those patients:

§ *not appropriately controlled with atorvastatin or ezetimibe alone; or*

¹⁵ Piepoli MF, et al. 2016 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).

¹⁶ 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).

§ *already treated with atorvastatin and ezetimibe*

Homozygous Familial Hypercholesterolaemia (HoFH)

Atozet/Zeteze is indicated in patients with HoFH. Patients may also receive adjunctive treatments (e.g. LDL apheresis).

- Proposed extension of indication:

Atozet/Zeteze 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)

In the pre ACM response, the sponsor proposed a modification of the new indication for Atozet/Zeteze as follows:

- Modified extension of indication:

Atozet/Zeteze is indicated in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS) taking their maximum tolerated dose of atorvastatin 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 ACM provided comments on the submission taking the modified proposed indication into account.

In making this recommendation, the ACM:

- noted the recent revised indication approved by TGA for ezetimibe in January 2017;
- noted the unique subset of patients who would require this medicine; and
- noted both ezetimibe and atorvastatin as individual medicines are available on the Australian market.

Proposed conditions of registration

The ACM agreed with the Delegate on the proposed conditions of registration and advised on the inclusion of the following:

- Subject to satisfactory implementation of the RMP most recently negotiated by TGA; and
- Negotiation of the PI and CMI to the satisfaction of TGA.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

Prevention of Cardiovascular disease:

A statement in the PI and relevant sections of the CMI to address product usage including:

- § Clear statements that no clinical trials have been undertaken with atorvastatin and ezetimibe combination for the requested indication.
- § Highlight that the benefit may be smaller when ezetimibe is used in conjunction with a higher potency statin such as atorvastatin.
- § Clarification as to why Atozet is only available after maximum tolerated dose of atorvastatin has been established and a further lowering of Low-Density Lipoprotein (LDL) is still desired, for the proposed indication.

- § Inclusion of IMPROVE-IT data with clear identification that this refers to a different drug combination (ezetimibe/simvastatin).
- § Highlight that it is unlikely that many patients would require prescription of the lower dose of Atozet for the requested indication.

Specific advice

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

1. A number of extrapolations underpin the sponsor's proposed new indication for Atozet/Zeteze (see Summary of Issues, above). Please comment on whether the sponsor has provided sufficient justification for these extrapolations in support of its proposed indication.

The ACM discussed that the existing accepted indications for each component of the proposed FDC (that is, ezetimibe and atorvastatin) allow for the revised indication proposed for the FDC.

2. 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 ACM advised that this combination should only be available as a second line agent once maximum tolerated dose of atorvastatin (or equivalent statin and dose) has been established.

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Atozet/Zeteze containing ezetimibe and atorvastatin for the **new indication**:

Prevention of Cardiovascular Disease

Atozet/Zeteze is indicated in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS) taking their maximum tolerated dose of atorvastatin 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 **full indications** are now:

Prevention of Cardiovascular Disease

Atozet/Zeteze is indicated in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS) taking their maximum tolerated dose of atorvastatin 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).

Primary Hypercholesterolaemia

Atozet/Zeteze is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia where use of a combination product is appropriate in those patients:

- § *not appropriately controlled with atorvastatin or ezetimibe alone; or*
- § *already treated with atorvastatin and ezetimibe*

Homozygous Familial Hypercholesterolaemia (HoFH)

Atozet/Zeteze is indicated in patients with HoFH. Patients may also receive adjunctive treatments (e.g. LDL apheresis).

Specific conditions of registration applying to these goods

The ezetimibe/atorvastatin EU-RMP, version 4.0 dated 14 March 2015 (DLP 23 January 2015) with ASA version 1.1 dated February 2016, included with submission PM-2016-00417-1-3, and any subsequent revisions, as agreed with TGA will be implemented in Australia.

Attachment 1. Product Information

The PI approved for Atozet/Zeteze at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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