Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Ezetimibe and Rosuvastatin

Proprietary Product Name: Rosuzet/Ezalo

Sponsor: Merck Sharp & Dohme (Australia) Pty Limited

Date of CER:
First round: 27 February 2014
Second round: 19 June 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
ADR(s)	Adverse drug reaction(s)
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
ApoB	Apolipoprotein B
ARTG	Australian Register of Therapeutic Goods
AST	Aspartate aminotransferase
AUC0-∞	Area under the concentration-time curve from time zero to infinity (extrapolated)
AUC0-t	Area under the concentration-time curve from time zero to time of last non-zero concentration
BMI	Body mass index
CAD	Coronary artery disease
CCDS	Company core data sheet
CE	CETP-mediated cholesteryl ester
CI	Confidence interval
CK	Creatine kinase
CLcr	Creatinine clearance
Cmax	Maximum observed concentration
CMI	Consumer Medicine Information
CPMP	Committee for Propriety Medicinal Products
ECG	Electrocardiogram
EMA	European Medicines Agency
FDC	Fixed dose combination
FH	Familial hypercholesterolaemia

Abbreviation	Meaning
GCP	Good clinical practice
HCP(s)	Health care provider(s)
HDL-C	High density lipoprotein cholesterol
HeFH	Heterozygous Familial Hypercholesterolaemia
HoFH	Homozygous Familial Hypercholesterolaemia
hsCRP	High sensitivity C-reactive protein
ICH	International conference on harmonization
IQR	Interquartile range
Kel	Elimination rate constant
LC/MS/MS	Liquid Chromatography/ Mass Spectroscopy/ Mass Spectroscopy
LDL/LDL-C	Low density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
LLD	Lipid-lowering drug
LLQ	Lower limit of quantification
LQCT	The sampling time of the last quantifiable concentration used to estimate the Kel
MMP-9	Matrix metalloproteinase -9 (MMP-9)
NCEP ATP III	National Cholesterol Education Program Adult Treatment Panel III
NPC1L1	Niemann-Pick C1-Like 1
PAD	Peripheral artery disease
PBS	Pharmaceutical Benefits Scheme
PCSK 9	Proprotein convertase subtilising/kein type 9
PI	Product information
PK	Pharmacokinetic
PSUR	Periodic Safety Update Report

Abbreviation	Meaning
TC	Total cholesterol
TEAE(s)	Treatment-emergent adverse event(s)
TGA	Therapeutic Goods Administration
TIMP-1	Tissue inhibitor of metalloproteinase -1
TLIN	The time point where In-linear Kel calculation begins
Tmax	Time of observed Cmax
$T_{1/2}$	Elimination half-life
ULN	Upper limit of normal
VLDL	Very low density lipoprotein

1. Introduction

This is a Category 1, type submission to register a new fixed dose combination tablet. This is a hybrid submission containing literature and two bioequivalence studies. The sponsor indicates that the dossier is supported by clinical and non-clinical data included in an earlier submission (PM-2012-03419-1-3) to register an ezetimibe and rosuvastatin (as calcium) composite pack.

The proposed fixed dose combination tablet contains ezetimibe and rosuvastatin (as calcium). Ezetimibe is in the class of lipid-modifying compounds that inhibit the intestinal absorption of cholesterol and related plant sterols.(1) Ezetimibe targets the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is responsible for the intestinal uptake of cholesterol and phytosterols.(1)

Rosuvastatin (as calcium) is a member of the statin drug class (2). It is a synthetic competitive inhibitor of HMG-CoA reductase, the enzyme which converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol (3). Rosuvastatin enhances the uptake and catabolism of LDL and it inhibits the synthesis of very low density lipoprotein (VLDL) in the liver. (3)

The approved indications for Ezetrol (ezetimibe) are:

> ***"Primary Hypercholesterolaemia***
>
> *EZETROL administered alone, or with an HMG-CoA reductase inhibitor (statin), is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia.*
>
> ***Homozygous Familial Hypercholesterolaemia (HoFH)***
>
> *EZETROL, administered with a statin, is indicated for patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis).*
>
> *Homozygous Sitosterolaemia (Phytosterolaemia)*
>
> *EZETROL is indicated for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolaemia." (1)*

The approved indications for MSD rosuvastatin (rosuvastatin (as calcium)) are the same as the approved indications for Crestor (4), the innovator rosuvastatin:

"MSD ROSUVASTATIN should be used as an adjunct to diet when the response to diet and exercise is inadequate.

Prevention of Cardiovascular Events

MSD ROSUVASTATIN is indicated for prevention of major cardiovascular events in men ≥50 years old and women ≥60 years old with no clinically evident cardiovascular disease but with at least two conventional risk factors for cardiovascular disease (hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease). MSD ROSUVASTATIN is indicated to:

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

In patients with hypercholesterolaemia

MSD ROSUVASTATIN is indicated for the treatment of hypercholesterolaemia (including familial hypercholesterolaemia).

Prior to initiating therapy with MSD ROSUVASTATIN, secondary causes of hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemias, obstructive liver disease, other drug therapy, alcoholism) should be identified and treated." (3)

The proposed indications for the ezetimibe and rosuvastatin (as calcium) fixed dose combination are:

"Primary Hypercholesterolaemia

ROSUZET/EZALO 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 rosuvastatin or ezetimibe alone; or*
- *already treated with rosuvastatin and ezetimibe.*

Homozygous Familial Hypercholesterolaemia (HoFH)

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

> **Comment**: Ezetrol can be administered with a statin for the treatment of primary hypercholesterolaemia (1) and is indicated for patients with HoFH when administered with a statin (1). Therefore, the co-administration of ezetimibe and a statin is already approved in the proposed indications.
>
> For the fixed-dose combination tablets, the proposed indication for the treatment of primary hypercholesterolaemia specifies that use is appropriate in patients who are not appropriately controlled on monotherapy or who are already being treated with both ezetimibe and rosuvastatin, indicating that the patient should not be initiated with concomitant ezetimibe and rosuvastatin treatment. In the Ezetrol PI, the indication for the treatment of primary hypercholesterolaemia suggests that Ezetrol and a statin could be initiated concomitantly (1).
>
> The proposed indications for the fixed dose combination tablets do not include Homozygous Sitosterolaemia (Phytosterolaemia), as only ezetimibe is approved for use in this condition, nor does it include prevention of cardiac events, which is an indication only approved for rosuvastatin (as calcium).

The proposed indications for the fixed-dose combination tablets are consistent with the indications approved for the Rosuzet composite pack (5) and Ezalo composite pack (6). It is indicated in the DOSAGE AND ADMINISTRATION section of the PI for the Rosuzet/Ezalo composite pack that the combination product is not indicated for first-line use. This statement should be added to the DOSAGE AND ADMINISTRATION section of the PI for the Rosuzet/Ezalo fixed dose combination tablets.

2. Clinical rationale

The sponsor's rationale for the proposed fixed dose combination of ezetimibe and rosuvastatin (as calcium) is that these two medicines have different, complementary, mechanisms of action to lower low density lipoprotein cholesterol (LDL-C) levels. Both medicines are approved as an adjunctive therapy to diet for hypercholesterolaemia. The sponsor indicates that the fixed dose combination tablet provides both ezetimibe and rosuvastatin in one tablet for once daily dosing, which will be simpler to administer for the patients who require both ezetimibe and rosuvastatin, and may assist adherence to treatment. The fixed dose combination tablet will also be simpler for the prescriber as he/she will prescribe one medicinal product rather than two separate products. The availability of the fixed dose combination tablet will also provide another option to administer ezetimibe and rosuvastatin. The sponsor proposes four tablet strengths of the fixed dose combination tablet to enable titration of the dose of rosuvastatin. The sponsor highlights that concomitant use of ezetimibe and rosuvastatin is already prescribed in clinical practice based on Pharmaceutical Benefits Scheme (PBS) claims data.

The sponsor indicates that the co-administration of ezetimibe and rosuvastatin meets the criteria for a fixed dose combination in the EMA Guideline on Clinical Development of Fixed Combination Medicinal Products, in that it provides an improvement in benefit/risk due to a level of efficacy above the one achievable by a single substance with an acceptable safety profile. The sponsor highlights that the justification for the proposed fixed dose combination tablet was approved by the TGA on 17 May 2013.

Comment: The primary benefit of the fixed dose combination tablet over the co-administration of the mono-therapies is convenience for the patient. The advantages and disadvantages of the co-administration of ezetimibe and rosuvastatin were evaluated in the submission to register the ezetimibe and rosuvastatin (Rosuzet/Ezalo) composite pack (PM-2012-03419-1-3) and all four dose strengths proposed were approved. The TGA-adopted "Guideline on Clinical Development of Fixed Combination Medicinal Products" (7) was also applicable to the ezetimibe and rosuvastatin composite pack. Specific safety information was added to the PIs regarding the composite pack containing ezetimibe 10 mg and rosuvastatin 40 mg.

2.1. Guidance

The sponsor requested advice from the TGA with regard to this submission. In particular, the sponsor sought:

- review and acceptance of the justification for a new fixed dose combination product containing ezetimibe and rosuvastatin
- review and acceptance of the proposed literature-based submission strategy and inclusion/exclusion criteria
- advice on the combination of new data from the updated literature search with data previously submitted in the application to register the ezetimibe and rosuvastatin composite pack

- review and acceptance of regulatory strategy for demonstrating bioequivalence between multiple strengths of the fixed dose combination tablets and the co-administration of the individual medications

The TGA found the justification for the new fixed dose combination product containing of ezetimibe and rosuvastatin to be acceptable. The proposed updated literature search strategy was found to be acceptable.

The TGA requested that the sponsor address the clinical criteria in Section 4 of Appendix 15 of ARGPM for bioequivalence in relation to the sponsor's proposal not to submit bioequivalence studies for two of the proposed strengths of fixed dose combination tablet.

The TGA identified, in the planning letter, specific issues to be addressed by the sponsor in the submission dossier:

- the sponsor was requested to confirm whether or not the application relied in part on population PK studies
- the sponsor was requested to provided a comprehensive table of contents which includes the contents of Modules 1 and 2
- the sponsor was requested to include an RMP in the submission.

Comment: The sponsor has addressed issues raised by the TGA in the planning letter.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The clinical dossier consisted of both previously submitted clinical data and new clinical data. The submission contained the following clinical information:

Module 5 (35 volumes)

- Two bioequivalence studies Study P417 and Study P425
- One clinical pharmacology study (Study P03317) that provided pharmacokinetic data and pharmacodynamic data. This study has previously been evaluated by the TGA as it was included in submission PM-2012-03419-1-3, the application to register a new composite pack for ezetimibe and rosuvastatin.
- The synopsis and appendices of one clinical safety and efficacy study (Study P139V1). This study has previously been evaluated by the TGA as it was included in submission PM-2012-03419-1-3, the application to register a new composite pack for ezetimibe and rosuvastatin.
- 75 datasets identified from two systematic reviews of the literature, of which 46 efficacy and safety datasets, derived from 63 publications, were identified in a previous review for submission PM-2012-03419-1-3 (and previously evaluated). The remaining 29 new safety and efficacy datasets were derived from 30 publications identified in the updated literature review (out of 35 datasets with ezetimibe and rosuvastatin co-administration identified, 33 of which were new.)
- Periodic Safety Update Report (PSUR) Addendum Report for ezetimibe for the period 17 April 2012 to 16 April 2013
- Clinical studies from the original application to register Ezetrol (Application No. 99/3917/3) – provided on a separate DVD.
- Literature references (Module 5.4)

Module 1

- Application letter, application form, draft Australian PI and CMI documents for Rosuzet and Ezalo, literature-based submission documents, compliance with meetings and pre-submission processes, overseas regulatory status, summary of biopharmaceutic studies, biowaiver justification, Risk Management Plan (RMP).

Module 2

- Clinical Overview and Clinical Summary.

> **Comment**: The sponsor has previously undertaken a literature search to identify publications relating to the co-administration of ezetimibe and rosuvastatin. The publications identified were included in submission PM-2012-03419-1-3, the application to register an ezetimibe and rosuvastatin composite pack. For this current application, the sponsor undertook a second search using the same search strategy but using a date limit covering the period 2012 to 22 April 2013. The previous search covered publication dates up to 2012. For both searches, the databases searched were EMBASE, PubMed, Clinicaltrials.gov, Toxline, Merck Sharp & Dohme's internal database (Clinical Literature Information Centre). The TGA approved the sponsor's search strategy and the updated search. New publications were identified from the second search. Publications previously submitted to the TGA were referred to and considered in this submission but were not formally re-evaluated. The publications identified in the searches included full articles, abstracts, posters and information on ClinicalTrials.gov.

3.2. Paediatric data

The sponsor has not included data in this submission to support the use of the proposed product in the paediatric population.

> **Comment**: The draft PIs for Rosuzet fixed dose combination tablets and Ezalo fixed dose combination tablets state that the respective products are not recommended for use in children.
>
> There were subjects aged less than 18 years of age in a number of the new publications identified in the updated literature search for this submission (12-16).

3.3. Good clinical practice

The sponsor states in each of the Clinical Study Reports for Study P425 and Study P417, respectively, that the study was conducted in compliance with Good Clinical Practice (ICH-GCP). In each of the Clinical Study Reports, it is indicated that the clinical protocol was approved by an institutional ethics committee and the research was undertaken in accordance with clinical research guidelines established by the basic principles defined in the EU Directive 2001/20/EC and the principles in the Declaration of Helsinki. Informed consent was obtained.

> **Comment**: Steps undertaken to comply with the principles of good clinical practice were not specified in all of the newly-identified publications submitted to support this product.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each pharmacokinetic topic.

Table 1. Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	Primary objectives
PK in healthy adults	Bioequivalence† - Single dose	Study P417	The two primary objectives were: to evaluate, under fasting conditions, the single dose pharmacokinetic profile (AUC0-t and Cmax) of un-conjugated ezetimibe and total ezetimibe after oral administration of a single dose of the test formulation (fixed dose combination of rosuvastatin calcium + ezetimibe, 40/10 mg tablet) and reference formulations (co-administration of Crestor (rosuvastatin calcium) 40 mg with Ezetrol (ezetimibe) 10 mg as individual tablets) to evaluate, under fasting conditions, the single dose pharmacokinetic profile (AUC0-t and Cmax) of rosuvastatin after oral administration of a single dose of the test formulation (fixed dose combination of rosuvastatin calcium + ezetimibe 40/10 mg tablet) and reference formulations (co-administration of Crestor (rosuvastatin calcium) 40 mg and Ezetrol (ezetimibe) 10 mg as individual tablets).
		Study P425	The two primary objectives were: to evaluate, under fasting conditions, the single dose pharmacokinetic profile (AUC0-t and Cmax) of un-conjugated ezetimibe and total ezetimibe after oral administration of a single dose of the test formulation (fixed dose combination of rosuvastatin calcium + ezetimibe, 5/10 mg tablet) and reference formulations (co-administration of Crestor (rosuvastatin calcium) 5mg with Ezetrol (ezetimibe) 10 mg as individual tablets) to evaluate, under fasting conditions, the single dose pharmacokinetic profile (AUC0-t and Cmax) of rosuvastatin after oral administration of a single dose of the test formulation (fixed dose combination of rosuvastatin calcium + ezetimibe 5/10 mg tablet) and reference formulations (co-administration of Crestor (rosuvastatin calcium) 5mg and Ezetrol (ezetimibe) 10 mg as individual tablets).

† Bioequivalence of different formulations.

4.2. Summary of pharmacokinetics

Two new pharmacokinetic studies were included in this submission, Study P417 and Study P425. These studies were single dose bioequivalence studies comparing the highest and lowest strengths of the proposed fixed dose combination tablets with co-administration of the mono-components.

The pharmacokinetic properties of the mono-components of the fixed dose combination tablets, ezetimibe and rosuvastatin are described in the respective Australian product information documents for Ezetrol (1) and MSD Rosuvastatin (3). The pharmacokinetics results of Study P03317, a 14 day study evaluating the effects of ezetimibe 10 mg and rosuvastatin 10 mg, either alone or in combination, in hypercholesterolaemic subjects, are described in the product information for the ezetimibe composite pack and rosuvastatin composite pack (5, 6).

4.2.1. Pharmacokinetics in healthy subjects

4.2.1.1. Absorption

4.2.1.1.1. Sites and mechanisms of absorption

· **Ezetimibe**

Ezetimibe is absorbed rapidly after oral administration and is extensively conjugated to a phenolic glucuronide, ezetimibe-glucuronide, which is pharmacologically active (1). Mean maximum plasma concentrations (Cmax) occurred within 4 to 12 hours or ezetimibe and occurred within 1 to 2 hours for ezetimibe-glucuronide (1).

· **Rosuvastatin**

Rosuvastatin is absorbed linearly over the dose range (3). Peak plasma levels of rosuvastatin occur five hours after dose administration (3). The half-life is 19 hours and there is no increase in half-life when the dose is increased. There is minimal accumulation of rosuvastatin on once daily dosing (3).

4.2.1.2. Bioavailability

4.2.1.2.1. Absolute bioavailability

· **Ezetimibe**

As ezetimibe is virtually insoluble in aqueous media suitable for injection, its absolute bioavailability cannot be determined (1).

· **Rosuvastatin**

The absolute bioavailability of rosuvastatin is 20% (3).

4.2.1.2.2. Bioavailability and bioequivalence studies

In study P417, comparing the test product, rosuvastatin calcium + ezetimibe 40/10 mg fixed dose combination tablet, with the reference, co-administration of Crestor (rosuvastatin calcium) 40 mg tablet and Ezetrol (ezetimibe) 10 mg tablet, the 90% confidence intervals of the geometric mean ratios of the test and reference products for AUC0-t for rosuvastatin, ezetimibe (unconjugated) and total ezetimibe were all within 80.00% to 125.00%, the pre-defined range of bioequivalence (Geometric mean ratio (%) [90%CI] Unconjugated ezetimibe AUC0-t 101.07 90%CI [95.24, 107.25]; total ezetimibe (ezetimibe +ezetimibe glucuronide) AUC0-t 95.65 90%CI [90.92, 100.62]; Rosuvastatin AUC0-t 100.36 90%CI [95.83, 105.12]). The lower limit of the 90% confidence interval of the geometric mean ratios of the test and reference product for Cmax of total ezetimibe was below 80% (Cmax 80.84 90%CI [74.90, 87.25]). For unconjugated ezetimibe and rosuvastatin, the 90% confidence intervals of the geometric mean ratios of the test and reference products for Cmax were within 80.00% to 125.00%. (Unconjugated

ezetimibe Cmax 93.55 90%CI [86.14, 101.60]; Rosuvastatin Cmax 100.89 90%CI [94.47, 107.75]).

In Study P425, comparing the test product, rosuvastatin calcium + ezetimibe 5/10 mg fixed dose combination tablet, with the reference, co-administration of Crestor (rosuvastatin calcium) 5 mg tablet and Ezetrol (ezetimibe) 10 mg tablet, the 90% confidence intervals of the geometric mean ratios of the test and reference products for AUC0-t and Cmax for rosuvastatin, ezetimibe (unconjugated) and total ezetimibe were all within 80.00% to 125.00%, the pre-defined range of bioequivalence (Geometric mean ratio (%) [90%CI] Unconjugated ezetimibe AUC0-t 105.43 90%CI [99.93, 111.22]; Cmax 103.32 90%CI [94.26, 113.25]; Total ezetimibe (ezetimibe +ezetimibe glucuronide) AUC0-t 104.42 90%CI [99.43, 109.66]; Cmax 96.24 90%CI [89.61, 103.35]; Rosuvastatin AUC0-t 104.04 90%CI [98.43, 109.96]; Cmax 98.95 90%CI [92.69, 105.62]).

4.2.1.2.3. Influence of food

· **Ezetimibe**

The oral bioavailability of ezetimibe, when administered as Ezetrol 10 mg tablets, was not affected by the concomitant administration of high fat and non-fat meals (1).

· **Rosuvastatin**

Rosuvastatin may be administered with or without food (3).

4.2.1.2.4. Dose proportionality

· **Ezetimibe**

No substantial deviation from dose proportionality is reported for doses between 5 mg and 20 mg (17).

· **Rosuvastatin**

Absorption increases linearly over the dose range. (3)

4.2.1.2.5. Bioavailability during multiple-dosing

· **Ezetimibe**

In a 14 day multiple dose study, using 10 mg daily, in patients with moderate hepatic insufficiency (Child-Pugh score 7-9) the mean AUC for total ezetimibe was increased approximately four fold, compared to healthy subjects, on Day 1 and Day 14 (1).

· **Rosuvastatin**

Minimal accumulation occurs on repeated once daily dosing (3).

4.2.1.2.6. Effect of administration timing

· **Ezetimibe**

Ezetimibe can be administered at any time of the day (1).

· **Rosuvastatin**

Rosuvastatin can be administered at any time of the day (3).

4.2.1.3. Distribution

4.2.1.3.1. Volume of distribution

· **Ezetimibe**

Ezetimibe is 99.7% bound to human plasma proteins and ezetimibe-glucuronide is 88 to 92% bound to human plasma proteins (1).

· **Rosuvastatin**

At steady state, the volume of distribution is approximately 134 litres (3). Rosuvastatin is approximately 90% bound to plasma proteins, mainly albumin. (3)

4.2.1.4. Metabolism

· **Ezetimibe**

Ezetimibe is primarily metabolised in the small intestine and liver via glucuronide conjugation (1). It is excreted in the bile (1). Of total ezetimibe in the plasma, ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected, ezetimibe constitutes approximately 10 to 20% and ezetimibe-glucuronide 80 to 90% of the total drug in plasma, respectively (1). Ezetimibe and ezetimibe-glucuronide both have a half-life of approximately 22 hours (1).

· **Rosuvastatin**

Rosuvastatin is not extensively metabolised (3). The major metabolite, N-desmethyl rosuvastatin, is formed principally by cytochrome P450 2C9 (3). Based on in vitro studies, N-desmethyl rosuvastatin has approximately one-sixth to one-half of the HMG-CoA reductase inhibitory activity of rosuvastatin (3). Greater than 90% of active plasma HMG-CoA reductase inhibitory activity overall is accounted for by rosuvastatin (3).

4.2.1.4.1. Metabolites identified in humans: Active metabolites

· **Ezetimibe**

The metabolite of ezetimibe, ezetimibe-glucuronide, is pharmacologically active (1).

· **Rosuvastatin**

The major metabolite of rosuvastatin is N-desmethyl rosuvastatin, which is formed principally by cytochrome P450 2C9 (3). N-desmethyl rosuvastatin is pharmacologically active (3). It has been demonstrated in in vitro studies that this metabolite has approximately one-sixth to one-half the HMG-CoA reductase inhibitors activity of the parent compound, rosuvastatin (3).

4.2.1.5. Excretion:

4.2.1.5.1. Routes and mechanisms of excretion

· **Ezetimibe**

Following oral administration of 14 C-ezetimibe (20 mg) to human subjects, over a 10 day period approximately 78% of the administered radioactivity was recovered in the faeces and 11% in the urine (1).

· **Rosuvastatin**

Approximately 10% of rosuvastatin is metabolised (3). Approximately 90% of rosuvastatin is eliminated unchanged in the faeces and the rest is excreted in the urine (3).

4.2.2. Pharmacokinetics in the target population

The pharmacokinetics of ezetimibe and rosuvastatin, following administration of ezetimibe 10 mg and rosuvastatin 10 mg alone and in combination, in untreated healthy hypercholesterolaemic subjects were described in Study P03317, a phase 1 pharmacodynamic study. A secondary objective of this study was to evaluate the potential for a pharmacokinetic drug interaction between ezetimibe and rosuvastatin.

> **Comment**: Study P03317 was evaluated as part of the application for the registration of the ezetimibe and rosuvastatin composite pack (Submission PM2012-03419-1-3). The results of the evaluation of the pharmacokinetic interaction are described in Section 4.2.4.1 below.

4.2.3. Pharmacokinetics in other special populations

4.2.3.1. Pharmacokinetics in subjects with impaired hepatic function

· **Ezetimibe**

After a single 10mg dose of ezetimibe, the mean AUC for total ezetimibe was increased, compared to healthy subjects, approximately 1.7-fold in patients with mild hepatic impairment (Child-Pugh score 5 to 6) (1). In a 14 day multiple dose study, using 10 mg daily, in patients with moderate hepatic insufficiency (Child-Pugh score 7-9) the mean AUC for total ezetimibe was increased approximately four fold, compared to healthy subjects, on Day 1 and Day 14 (1).

· **Rosuvastatin**

In a pharmacokinetic evaluation in subjects with varying degrees of hepatic impairment, two subjects with severe hepatic impairment (Child-Pugh scores of 8 and 9) had an increase in systemic exposure to rosuvastatin that was at least two fold higher than subjects with lower Child-Pugh scores (3).

4.2.3.2. Pharmacokinetics in subjects with impaired renal function

· **Ezetimibe**

The mean AUC values for total ezetimibe was increased approximately 1.5-fold, compared to healthy subjects (n=9), in patients with severe renal disease (n=8; mean CrCl ≤30 mL/min/1.73 m^2) after a single 10 mg dose of ezetimibe (1).

· **Rosuvastatin**

In a pharmacokinetic evaluation in subjects with varying degrees of renal impairment, subjects with severe renal impairment, defined as creatinine clearance less than 30 mL/min/1.73 m^2, had a three fold increase in plasma concentration compared with healthy volunteers (3).

4.2.3.3. Pharmacokinetics according to age

4.2.3.3.1. Paediatric patients

· **Ezetimibe**

There are no pharmacokinetic differences between adolescents and adults based on total ezetimibe. Pharmacokinetic data are unavailable for the paediatric population under 10 years of age (1).

· **Rosuvastatin**

There appears to be no information on the pharmacokinetics specifically in paediatric patients in the Australian PI for MSD rosuvastatin but it is indicated that age had no clinically relevant effect on the pharmacokinetics of rosuvastatin (3).

4.2.3.3.2. Geriatric patients

· **Ezetimibe**

Compared to the young (18 to 45 years), plasma concentrations for total ezetimibe are approximately 2-fold higher in the elderly (≥65years) (1).

· **Rosuvastatin**

Age had no clinically relevant effect on the pharmacokinetics of rosuvastatin (3).

4.2.3.4. Pharmacokinetics related to genetic factors

4.2.3.4.1. Gender

· **Ezetimibe**

Plasma concentrations for total ezetimibe are slightly higher (<20%) in women than in men (1).

· **Rosuvastatin**

Gender had no clinically relevant effect on the pharmacokinetics of rosuvastatin (3).

4.2.3.4.2. Race

· **Ezetimibe**

There were no pharmacokinetic differences between Blacks and Caucasians, based on a meta-analysis of pharmacokinetic studies (1).

· **Rosuvastatin**

In a large pharmacokinetic study undertaken in the US, Asian subjects had an approximately 2 fold elevation in median exposure (AUC and Cmax) compared to a Caucasian control group (3). A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic and Black of Afro-Caribbean groups (3).

4.2.4. Pharmacokinetic interactions

4.2.4.1. Pharmacokinetic interactions demonstrated in human studies

· **Ezetimibe**

Based on pre-clinical studies, ezetimibe does not induce cytochrome P450 drug metabolising enzymes (1). No clinically significant pharmacokinetic interactions were observed when ezetimibe was co-administered with other statins (atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin) (1). Drug-drug interactions have been reported with cholestyramine, cyslosporin, fenofibrate and gemfibrozil (1). Co-administration of ezetimibe and antacids decreased the absorption rate of ezetimibe but it is not considered clinically significant (1). Increased International Normalised Ratio has been reported post-marketing in patients who had Ezetrol added to warfarin or fluindione (1). Most of the patients were on other medications also.

· **Rosuvastatin**

Drug-drug interactions have been reported between rosuvastatin and warfarin, cyclosporin, fusidic acid, gemfibrozil, protease inhibitors, oral contraceptives and antacids (3).

· **Ezetimibe administered with rosuvastatin**

Study P03317 was a phase 1 pharmacodynamic study, the secondary objective of which was to evaluate the potential for a pharmacokinetic drug interaction between ezetimibe and rosuvastatin. The following summary is in the product information for Rosuzet composite pack (5) and Ezalo composite pack (6):

> "In a pilot four period parallel design study of healthy hypercholesterolemic patients, primarily designed to evaluate the short term LDL lowering effects of ezetimibe 10 mg, rosuvastatin 10 mg, ezetimibe 10 mg plus rosuvastatin 10 mg, and placebo, the pharmacokinetics of the compounds were also evaluated. The pharmacokinetic results from this study indicate that co-administration of ezetimibe 10 mg and rosuvastatin 10 mg would not result in the pharmacokinetics of either drug being significantly altered during co-administration compared to monotherapy.
>
> This small, parallel groups study showed that there was no effect on the AUC or Cmax of ezetimibe, total ezetimibe (ezetimibe + conjugated ezetimibe) or rosuvastatin when

ezetimibe 10 mg was co-administered with rosuvastatin 10 mg compared with ezetimibe 10 mg alone or rosuvastatin 10 mg alone. The mean AUC for ezetimibe and total ezetimibe were similar between ezetimibe + rosuvastatin versus ezetimibe alone (97% [90% CI 70–133%] and 113% [90% CI 89–143%] respectively). The mean Cmax for ezetimibe and total ezetimibe were similar between ezetimibe + rosuvastatin versus ezetimibe alone (104% [90% CI 69–158%] and 118% [90% CI 83–170%] respectively). There was a small increase in the mean AUC and Cmax for rosuvastatin during rosuvastatin and ezetimibe co-administration compared to rosuvastatin alone (119% [90% CI 87-162%] and 117% [90% CI 84-163%] respectively).

Although no pharmacokinetic studies of ezetimibe and rosuvastatin co-administration have been conducted in patients at increased risk of rosuvastatin exposure such as hepatic or renal impairment, there is the potential for increased exposure to rosuvastatin in patients receiving this combination."

4.3. Evaluator's overall conclusions on pharmacokinetics

The pharmacokinetics of ezetimibe and rosuvastatin as individual mono-components have been previously established. In this submission, two bioequivalence studies were submitted comparing the proposed fixed dose combination tablet, at the lowest and highest strengths, with administration of the mono-components. In Study P425, comparing the test product, rosuvastatin calcium + ezetimibe 5/10 mg fixed dose combination tablet, the lowest strength proposed, with the reference, co-administration of Crestor (rosuvastatin calcium) 5 mg tablet and Ezetrol (ezetimibe) 10 mg tablet, the 90% confidence intervals of the geometric mean ratios of the test and reference products for AUC0-t and Cmax for rosuvastatin, ezetimibe (unconjugated) and total ezetimibe were all within the pre-defined range of bioequivalence (80.00% to 125.00%). In Study P417, comparing the test product, rosuvastatin calcium + ezetimibe 40/10 mg fixed dose combination tablet, the highest strength proposed, with the reference, co-administration of Crestor (rosuvastatin calcium) 40 mg tablet and Ezetrol (ezetimibe) 10 mg tablet, the 90% confidence intervals of the geometric mean ratios of the test and reference products for AUC0-t for rosuvastatin, ezetimibe (unconjugated) and total ezetimibe were all within 80.00% to 125.00% as were the 90% confidence intervals of the geometric mean ratios of the test and reference products for Cmax for unconjugated ezetimibe and rosuvastatin. Although the lower limit of the 90% confidence interval of the geometric mean ratio of the test and reference product for Cmax of total ezetimibe was below 80% (Cmax 80.84 90%CI [74.90, 87.25]), this is unlikely to be of major concern from a clinical perspective as the 90% confidence interval of the geometric mean ratio of the test and reference product for AUC0-t of total ezetimibe, and the AUC0-t and Cmax of the parent compound, ezetimibe (unconjugated), were within the bioequivalence range.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

No new pharmacodynamic studies were included in the submission.

The clinical study report for Study P03317, a 14 day pharmacodynamic study evaluating the effects of ezetimibe 10 mg and rosuvastatin 10 mg, either alone or in combination, in hypercholesterolaemic subjects, was included in the submission. Study P03317 was evaluated as part of the application for the registration of the ezetimibe rosuvastatin composite pack (Submission PM2012-03419-1-3). The primary objective of the study was to evaluate the pharmacodynamic effects and safety of the co-administration of ezetimibe and rosuvastatin.

Comment: Three publications that were identified in the first literature search, to support the registration of the ezetimibe and rosuvastatin composite pack, relate to Study P03317 (19-21).

5.2. Summary of pharmacodynamics

The pharmacodynamic properties of ezetimibe and rosuvastatin calcium are described in the respective Australian product information documents for Ezetrol (1) and MSD rosuvastatin (3).

5.2.1. Mechanism of action

· **Ezetimibe**

Ezetimibe inhibits the intestinal absorption of cholesterol, resulting in a reduced amount of cholesterol being delivered to the liver (1).

· **Rosuvastatin**

Rosuvastatin is a synthetic competitive inhibitor of HMG-CoA reductase, the enzyme that converts a precursor of cholesterol (3). Rosuvastatin decreases VLDL and LDL particles by increasing the number of hepatic LDL receptors on the cell surface, which enhances the uptake and catabolism of LDL, and through inhibition of the synthesis of VLDL in the liver (3).

· **Ezetimibe administered with a statin**

As statins reduce cholesterol synthesis in the liver and ezetimibe inhibits absorption of cholesterol, their different mechanisms of reducing cholesterol are complementary (1).

5.3. Primary pharmacodynamic effects

5.3.1. Mechanism of action

· **Ezetimibe**

Ezetrol inhibited intestinal cholesterol absorption by 54%, compared with placebo, in a two week clinical study of 18 hypercholesterolaemic patients (1).

· **Rosuvastatin**

In patients with hypercholesterolaemia and mixed dislipidaemia, rosuvastatin reduces total-C, LDL-C, ApoB, non HDL-C and TG and increases HDL-C (3).

· **Ezetimibe administered with a statin**

Ezetrol administered with a statin in patients with hypercholesterolaemia, reduces total cholesterol, LDL-C, ApoB and TG, and increases HDL-C, beyond either treatment alone (1).

The following is an extract from the Clinical Evaluation Report for the Rosuzet/Ezalo Composite Pack (Submission PM2012-03419-1-3) (17) in relation to the pharmacodynamic results of Study P03317:

> "The co-administration of ezetimibe 10mg + rosuvastatin 10mg resulted in a statistically significant average % change from baseline to endpoint of -16.4% in LDL-C compared with rosuvastatin 10mg alone, -44.6% compared with ezetimibe alone and -59.1% compared with placebo."

5.3.2. Genetic-, gender- and age-related differences in pharmacodynamic response

· **Ezetimibe**

The reduction in LDL-C is comparable between patients aged 65 years and older and subjects aged 18 to 45 years treated with ezetimibe, and between men and women treated with ezetimibe (1).

- **Rosuvastatin**

Based on the clinical trial program, rosuvastatin is effective regardless of age, gender and race (3).

5.4. Evaluator's overall conclusions on pharmacodynamics

No new pharmacodynamic studies were included in the submission. The pharmacodynamic effects of co-administered ezetimibe and rosuvastatin were established in the application for the registration of the ezetimibe and rosuvastatin composite pack (Submission PM2012-03419-1-3).

6. Dosage selection for the pivotal studies

No new pivotal studies were included in this submission.

A pivotal study, Study P139V1, was evaluated as part of the application for the registration of the ezetimibe and rosuvastatin composite pack (Submission PM2012-03419-1-3). The dosage of rosuvastatin (5 mg or 10 mg) administered during the open-label run-in period was based on the patient's risk category, current statin therapy and LDL-C value within the previous 12 weeks. During the six week double-blind treatment period, patients starting on rosuvastatin 5 mg during the run-in period were randomised to rosuvastatin 5 mg + ezetimibe 10 mg or rosuvastatin 10 mg, and patients starting on rosuvastatin 10 mg during the run-in period were randomised to rosuvastatin 10 mg + ezetimibe 10 mg or rosuvastatin 20 mg.

7. Clinical efficacy

7.1. Studies providing efficacy data

No new clinical study reports of efficacy studies are included in this submission. New publications describing efficacy studies, identified in the updated literature search, are included in the submission.

The sponsor indicates that evidence establishing efficacy for ezetimibe co-administered with rosuvastatin is based on the original approval of ezetimibe as monotherapy and co-administered with statins (99/3917/3), Study P03317, Study P139V1, and publications (including abstracts). The bioequivalence studies included in this submission provide a bridge between the efficacy and safety of the co-administration of ezetimibe and rosuvastatin as mono-components and the proposed fixed dose combination tablet which is the subject of this application.

> **Comment**: The application for the ezetimibe and rosuvastatin composite pack (Submission PM2012-03419-1-3) has been approved by the TGA which indicates that the evidence to support the efficacy of concomitant administration of ezetimibe 10 mg and rosuvastatin 5 mg, 10 mg, 20 mg, 40 mg is acceptable.
>
> Based on the information in the table of clinical studies previously submitted to the TGA as part of the original ezetimibe marketing application, none of the studies were evaluating ezetimibe in combination with rosuvastatin. A number of the studies submitted evaluated ezetimibe in combination with other statins, specifically atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin and cerivastatin. These studies were not re-evaluated. Efficacy results from controlled clinical studies in which Ezetrol was administered as monotherapy, or co-administered with a statin, are summarised in the Clinical Trials section of the Ezetrol PI (1).

LDL-C levels are expressed in mmol/L in Australia. Many of the literature publications included in this submission use the units mg/dL. To convert to mmol/L, values in mg/dL can be divided by 38.7 (22). Therefore, an LDL-C of 100 mg/dL is equivalent to 2.6 mmol/L and 70 mg/dL is equivalent to 1.8 mmol/L.

7.2. Primary hypercholesterolemia and homozygous familial hypercholesterolemia

7.2.1. Ezetimibe plus rosuvastatin (with or without other lipid-lowering treatment)

7.2.1.1. Clinical studies

7.2.1.1.1. Study P139V1

Study P139V1 was evaluated as part of the application for the registration of the ezetimibe rosuvastatin composite pack (Submission PM2012-03419-1-3). It was the pivotal study evaluating the effects of the addition of ezetimibe to rosuvastatin compared with doubling the dose of rosuvastatin (18). The synopsis and appendices of this study were included in this current submission. The following information is from the Australian PI for Rosuzet composite pack (5) and Ezalo composite pack (6):

> "In a multicentre, randomised, double-blind, 6 week-active comparator study (P139V1), 440 subjects (272 male and 168 female) at moderately high/high risk of coronary heart disease with LDL cholesterol levels failing to reach their NCEP ATPIII goal (< 2.6 mmol/L or <1.8mmol/L depending on baseline characteristics) were stratified to treatment with rosuvastatin 5mg or 10 mg for 4-5 weeks. Patients were then randomised to either doubling of their rosuvastatin dose (10 mg or 20 mg) or to add ezetimibe 10 mg to their rosuvastatin (5 or 10 mg) therapy.
>
> Patients were 32 to 79 years of age with a mean baseline LDL-C of 2.69 mmol/L in the rosuvastatin (5 or 10 mg) + ezetimibe 10 mg group and 2.60 mmol/L in the rosuvastatin (10 or 20 mg) group. The majority of patients were white (76.8%) and the majority (67.5%) were high risk for CHD with atherosclerotic vascular disease (AVD). Overall, the mean duration of hypercholesterolemia was 9.2 years.
>
> The primary endpoint was percent change from baseline in LDL-C at Week 6 based on full analysis set population (all randomised patients excluding those who failed to receive at least one dose of study treatment or had lack of baseline data). The addition of ezetimibe 10 mg to rosuvastatin (5 mg or 10 mg) achieved significantly greater LDL-C reductions compared to doubling the initial dose of rosuvastatin (10 mg or 20 mg) ($p < 0.001$). The LS mean percent change in LDL-C from baseline to the study end was -20.96% when ezetimibe 10 mg was added to rosuvastatin and –5.71% when the original rosuvastatin dose was doubled (data pooled across the rosuvastatin 5 mg and 10 mg strata). The LS mean treatment difference was -15.25% with a 95% CI (-19.89, -10.60) (Table 2).

Table 2: Study P139V1 - Analysis of Percent Change from Baseline in LDL-Cholesterol (mg/dL) at Study Endpoint After 6 Weeks of Treatment

Treatment	N	Baseline (mg/dl) Mean ± SD	Endpoint (mg/dl) Mean ± SD	LS mean (95% CI)	Difference in LS Mean (95% CI)	P value
Overall						
ezetimibe 10mg + rosuvastatin (5 or 10mg)	219	103.90 ± 25.39	80.73 ± 32.28	-20.96 (-24.28, - 17.64)	-15.25 (-19.89, -10.60)	< 0.001
Rosuvastatin (10 or 20mg)	217	100.20 ± 24.44	92.88 ± 26.52	-5.71 (-9.05, -2.38)		
Stratum I						
ezetimibe 10mg + rosuvastatin 5 mg	98	106.74 ± 23.54	85.89 ± 31.37	-17.92 (-22.69, -13.15)	-12.31 (-18.95, -5.67)	<0.001
Rosuvastatin 10 mg	96	102.42 ± 23.41	95.36 ± 23.27	-5.61 (-10.43, -0.79)		
Stratum II						
ezetimibe 10mg + rosuvastatin 10mg	121	101.60 ± 26.67	76.79 ± 32.59	-23.74 (-28.34, -19.14)	-17.46 (-23.92, -10.99)	<0.001
Rosuvastatin 20mg	121	98.44 ± 25.18	90.90 ± 28.78	-6.28 (-10.88, -1.69)		

The secondary endpoints were percent change from baseline in other lipid and lipoprotein parameters and percent change from baseline in LDL-C at Week 6. Ezetimibe 10 mg added to on-going rosuvastatin therapy (5 or 10 mg) significantly lowered total-cholesterol, non-HDL-C and Apo B, compared with doubling of the rosuvastatin dose ($p < 0.001$) and resulted in a significantly greater proportion of patients reaching their LDL-C goal compared with doubling the baseline dose of rosuvastatin (10 mg or 20 mg) (59.4% vs. 30.9%, adjusted odds ratio = 4.5 with a 95% CI of (2.9, 6.9); $p < 0.001$). LDL-C treatment goals were < 1.8 mmol/L for patients at high risk for CHD with AVD and < 2.6 mmol/L for patients at moderately high risk and high risk for CHD without AVD)."

7.2.1.2. Literature

Comment: The literature submitted to support the application for the Rosuzet/Ezalo composite pack was re-submitted to support this current application. Extracts from the Clinical Evaluation Report for the Rosuzet/Ezalo Composite Pack (Submission PM2012-03419-1-3) (18) that relate to the evaluation of the efficacy of the co-administration of ezetimibe and rosuvastatin based on the published literature submitted have been considered. The publications in Submission PM2012-03419-1-3 were reviewed by the evaluator in relation to their proposed application[1]. Groupings included comparison of monotherapy to combination therapy, addition of ezetimibe to rosuvastatin, addition of ezetimibe to rosuvastatin compared to doubling or titrating the dose of rosuvastatin and addition of ezetimibe to rosuvastatin compared to addition of ezetimibe to other statins. Of note, there were three publications related to the randomised, double-blind parallel group Study P139V1, described in Section 7.2.1.1 above (23-25). Information from Study P139V1 and two studies described in the published literature identified in the first literature search, EXPLORER (26-30) and GRAVITY (31-33), are included in the respective PIs for the Rosuzet Composite pack (5) and Ezalo Composite pack (6).

An updated literature search based on the same search strategy used to identify relevant literature for the application for ezetimibe and rosuvastatin composite pack, but date limited to the period 2012 to a date in 2013, was undertaken by the sponsor.

[1] These are referenced by a number in square brackets and the full citation is given in section 15.2.

7.2.1.2.1. Extract of the review of the literature in Submission PM2012-03419-1-3

- Comparison of monotherapy (either rosuvastatin or ezetimibe) to combination therapy (rosuvastatin and ezetimibe):

The following information is an extract from the Clinical Evaluation Report for the Rosuzet/Ezalo Composite Pack (Submission PM2012-03419-1-3) (18):

> "Evidence for this was provided in 4 studies – the P139V1, EXPLORER study (Ballantyne 2007) [8], Kouvelos 2013 [9] and Sawayama (ESSENTIAL) 2010 [10]. Overall, the combined therapy reduced LDL-C more than either ezetimibe or rosuvastatin monotherapy and (when data was available) more in the combination group reached LDL-C targets than either monotherapy alone."

- Addition of ezetimibe to rosuvastatin

The following information is an extract from the Clinical Evaluation Report for the Rosuzet/Ezalo Composite Pack (Submission PM2012-03419-1-3) (18):

> "There were six studies (Inoue 2010) [14], Leibovitz 2006 abstract) [15], Madrigal 2007 [16], Ose 2005 abstract [17], Stein 2005 [18], Stein 2007[19], Fras 2008 [20] that examined the effect of adding ezetimibe to rosuvastatin. Overall the reduction in LDL-C when ezetimibe 10mg was added to rosuvastatin was between 10.6 and 70%."

- Addition of ezetimibe to rosuvastatin compared to doubling or titrating the dose of rosuvastatin

The following information is an extract from the Clinical Evaluation Report for the Rosuzet/Ezalo Composite Pack (Submission PM2012-03419-1-3) (18):

> "In general, addition of ezetimibe to rosuvastatin reduced LDL-C numerically more than doubling or titrating the dose of rosuvastatin. This was demonstrated in the pivotal P139V1 study, Okada 2011 [26, 27] and Yamagishi 2010 [28]."

- Addition of ezetimibe to rosuvastatin compared to addition of ezetimibe to other statin

The following information is an extract from the Clinical Evaluation Report for the Rosuzet/Ezalo Composite Pack (Submission PM2012-03419-1-3) (18):

> "There were 12 studies that studied the effect of the addition of rosuvastatin compared to the addition of ezetimibe to other statins (Okada 2011, Sharma 2008, Boufidou 2007-abstract Styliadis 2007-abstract, Tripoten 2010-abstract, Zubareva 2010-abstract, Foody 2011-abstract, Madrigal 2007, GRAVITY 2007, Fras 2008, Teramoto 2012, Inoue 2010)"

7.2.1.2.2. Review of the new literature identified in the updated literature search

The updated literature search identified the following new articles that referred specifically to co-administration of ezetimibe and rosuvastatin, with or without other lipid-lowering treatment.

- **Randomised, controlled studies**

Yamazaki 2013 (34)

This article described an exploratory, multi-centre, prospective, open-label, randomised, parallel group pilot study undertaken in Japan. It is reported that the study protocol was approved by a hospital ethics committee. The study was undertaken according to the Declaration of Helsinki.

Subjects (n=46) had high-risk coronary artery disease (CAD) and LDL-C and hs-CRP levels of >70 mg/dL and >1.0 mg/L, respectively, that were not improved by 4 weeks of rosuvastatin treatment (2.5 mg/day). Subjects were males and females with a median age of 73 years (range

42-84 years) who had undergone percutaneous coronary intervention for CAD. Subjects were randomly assigned to receive 10 mg of rosuvastatin (R10, n = 24) or 2.5 mg/day of rosuvastatin combined with 10 mg/day of ezetimibe (R2.5/E10, n = 22) for 12 weeks. The primary endpoint was a change from baseline after 12 weeks in high sensitive C-reactive protein (hs-CRP). There were numerous secondary endpoints including change in level of LDL-C. Fasting blood samples were collected at baseline, 4, 8 and 12 weeks. For LDL-C, there was a decrease in LDL-C at 4, 8 and 12 weeks, compared with baseline, in both treatment groups. The decreases from baseline at 12 weeks were similar in the R2.5/E10 (-21.9±14.4 mg/dL, 25.4% decrease) and R10 group (-20.3±15.3 mg/dL, 23.3% decrease). At 12 weeks, mean hs-CRP had decreased in both treatment groups from baseline. In both treatment groups mean IL-6, TNF- α and PTX3 values were similar at baseline and 12 weeks.

> **Comment**: This study was exploratory and the primary endpoint was change in hs-CRP. It was not powered for the comparison between the groups of LDL-C. The treatments compared were ezetimibe 10 mg and rosuvastatin 2.5 mg compared with rosuvastatin monotherapy at a dose four times higher (10 mg) than in the combination group.

Johns 2012 (35)

This was an abstract that described a prospective, randomised, open-label pilot study of 12 weeks duration. The objective of the study was to determine whether HIV-positive patients not reaching lipid treatment targets with rosuvastatin 10 mg would show greater improvement with the addition of ezetimibe to their rosuvastatin therapy compared with patients treated with an increased dose of rosuvastatin (20 mg). Subjects were eligible for the study if their apolipoprotein B (apoB) was >0.80 g/l despite therapy with rosuvastatin 10 mg daily for a minimum of 3 months. The primary endpoint was the difference in apoB change from baseline to week 12 between the treatment groups. Secondary outcomes included between group differences in changes in other lipid parameters. Forty three subjects completed the study (Rosuvastatin + ezetimibe (n=23), Rosuvastatin 20 mg (n=20)). The majority of subjects were male (90.6%) and Caucasian (81.4%) and the average age was 56.7 years. Significant improvements in apoB were seen within both treatment groups from baseline to Week 12 but the difference between the groups was not statistically significant. Changes from baseline to week 12 in total cholesterol were -1.00 mmol/L in the rosuvastatin 10 mg + ezetimibe 10 mg group and -0.51 mmol/L in the rosuvastatin 20 mg group. Triglycerides decreased in the rosuvastatin 10 mg + ezetimibe 10 mg group (-0.63 mmol/L) but increased in the rosuvastatin 20 mg group (+0.04 mmol/L).

> **Comment**: LDL-C changes were not specified in this study. ApoB is not usually considered a primary outcome for studies assessing the efficacy of drug(s) on hypercholesterolaemia (36).

- **Time series**

Kawashiri 2012 (37)

This article described a prospective, open, randomised study, in Japanese patients with heterozygous familial hypercholesterolaemia (FH) with single LDL receptor gene mutations. Subjects (n=17; 12 males, 5 females; mean±SD age 63.9 ± 7.4 years) met clinical diagnostic criteria for heterozygous FH and were heterozygous with a confirmed LDL receptor gene mutation. The study protocol was approved by two hospital ethics committees and written informed consent was obtained from study subjects. The primary objective of the study was to investigate the efficacy and safety of co-administering rosuvastatin 20 mg/day, ezetimibe 10 mg/day and granulated colestimide 3.62 g/day. A comparison of lipid parameters and safety between rosuvastatin 20 mg/day and combination therapy with rosuvastatin 10 mg/day and ezetimibe 10 mg/day was a secondary endpoint. There was a washout period of lipid-lowering agents before entry into the study and subjects were placed on a specific diet. Subjects were divided into two groups by an envelope method for the secondary endpoint – group 1 -

rosuvastatin 20 mg/day, group 2 - rosuvastatin 10 mg/day co-administered with ezetimibe 10 mg/day. There were three different phases in the study. All subjects received 4 weeks of rosuvastatin 5 mg/day treatment then 4 weeks of rosuvastatin 10 mg/day. In group 1, the dose was then increased to 20 mg/day for 8 weeks (phase 1) after which subjects in this group received ezetimibe 10 mg/day added to rosuvastatin 20 mg/day for 8 weeks and in group 2 the dose of rosuvastatin was increased to 20 mg/day for 8 weeks (phase 2). In phase 3, subjects in both groups were given, in addition to the treatment that they were receiving in phase 2, granulated colestimide 3.62 g twice daily for 8 weeks. The primary endpoints were changes in lipid parameters, including LDL-C, after concomitant rosuvastatin 20 mg/day, ezetimibe 10 mg/day and granulated colestimide 3.62 g/day, and the safety of the combined therapy. Secondary endpoints included a comparison of lipid parameters and safety between rosuvastatin 20 mg/day and rosuvastatin 10 mg/day co-administered with ezetimibe 10 mg/day. Compared with baseline, LDL-C decreased by -54.1% after administration of rosuvastatin 20 mg/day for 8 weeks and by -61.1% following treatment with rosuvastatin 10 mg/day co-administered with ezetimibe 10 mg/day for 8 weeks. Further smaller decreases in LDL-C levels were seen in both groups following administration of 8 weeks of rosuvastatin 20 mg/day and ezetimibe 10 mg /day in both groups in phase 2.

> **Comment**: The comparison of the lipid parameters and safety between rosuvastatin 20 mg/day and combination therapy with rosuvastatin 10 mg/day and ezetimibe 10 mg/day was a secondary endpoint in this study. Subjects were allocated using the envelope method which could possibly result in selection bias (38). The number of subjects was very small (n=17) and it is reported that there were apparent differences, due to chance, between the groups in relation to mean age, gender distribution and baseline lipid levels.

Blaha 2013 (39)

This prospective study investigated mean platelet volume after extracorporeal LDL cholesterol elimination. Subjects were 7 men and 5 women with familial hypercholesterolaemia in the Czech republic. Ten subjects were receiving high dose statins in combination with ezetimibe (10 mg daily). Six subjects were on rosuvastatin (maximally tolerated dose). Subjects had been regularly treated with LDL- apheresis or rheohemapheresis.

> **Comment**: It is not indicated which of the subjects in this study were on both ezetimibe and rosuvastatin. This study does not appear to specifically relate to the efficacy and safety of ezetimibe in combination with rosuvastatin. No safety data are included in the article.

Chiou 2010 (40)

The objective of the study described in this article was to investigate patients with familial hypercholesterolaemia using molecular diagnostic methods and to compare abnormalities in small mutation and large DNA rearrangement subgroups. Subjects were Taiwanese.

For four weeks, subjects (n=102) were on the diet recommended by the National Cholesterol Education Program Adult Treatment Panel III therapeutic lifestyle changes then followed a titration protocol until their LDL-C was less than 100 mg/dL. The four titration steps were rosuvastatin 10 mg/day for 4 weeks, rosuvastatin 20 mg/day for 4 weeks, rosuvastatin 20 mg/day co-administered with ezetimibe 10 mg/day for 4 weeks and rosuvastatin 40 mg/day co-administered with ezetimibe 10 mg/day for 4 weeks. Probands were divided into five subgroups based on the molecular diagnosis. The cumulative percentage of subjects who reached the goal of LDL-C ≤ 100 mg/dL in response to each of the four titration steps was lower in the subgroups with abnormal MLPA results, nonsense mutations, or frameshift mutations compared with the subgroups with undetected or mis-sense mutations.

Luknar 2012 (41)

This article describes an open-label, non-controlled, study in a single study centre. The objective of the study was to evaluate, in heart transplant recipients, the safety of rosuvastatin and its influence on blood lipids. Subjects (n=16; 11 males, median age 57 years, range 36-60 years) had had an inadequate hypolipidaemic response to fluvastatin 80 mg. All subjects were receiving a combined immunosuppressive regimen and one subject was receiving ezetimibe as well as fluvastatin. Fluvastatin was ceased and subjects received open-label rosuvastatin 10 mg/day. Following the initiation of rosuvastatin 10 mg, mean LDL-C decreased from 3.69±0.76 mmol/L at baseline to 2.93±0.76 mmol/L after a median of 12 weeks.

> **Comment**: The effect of rosuvastatin in combination with ezetimibe on lipid levels in the single subject who was receiving this combination is not presented.

- **Observational studies**

Graesdal 2012 (13)

This article describes retrospective case reports of seven patients in Norway receiving treatment for homozygous familial hypercholesterolemia. The aim of the study was to assess the seven patients treated with LDL apheresis with respect to their quality of life, clinical and laboratory assessments and cardiovascular status. The study was approved by an ethics committee and was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Written informed consent was obtained. For two subjects, their co-medication included rosuvastatin 40 mg daily and ezetimibe 10 mg daily. In these two patients, the mean post-apheresis LDL was lower than the mean pre-apheresis LDL, based on measurements taken in the year prior to the study. (patient 1 pre-apheresis mean LDL 5.5 mmol/L (min 3.1 – max 8.0), post apheresis mean LDL 2.2 mmol/L (min 1.0 – max 3.8), patient 2 pre-apheresis mean LDL 4.6 mmol/L (min 4.3 – max 5.1), post apheresis mean LDL 1.3 mmol/L (min 1.1 – max 1.6)).

> **Comment**: These retrospective case reports are low level evidence.

Nenseter 2013 (14)

This article is related to that by Graesdal et al (13). The study was undertaken in Norway and subjects included the same seven patients with homozygous familial hypercholesterolemia being treated with LDL apheresis. Two of these subjects were on rosuvastatin 40 mg daily and ezetimibe 10 mg daily. The aim of this study was to examine matrix metalloproteinase -9 (MMP-9) and tissue inhibitor of metalloproteinase -1 (TIMP-1) and cellular mRNA levels in patients with homozygous familial hypercholesterolemia (n=7), in comparison with age- and sex- matched patients with heterozygous familial hypercholesterolemia (n=6) and healthy subjects (n=7) and to test if three consecutive once weekly LDL apheresis sessions in the patients with homozygous familial hypercholesterolemia had short-term effects on MMP-9 and TIMP-1 in serum and peripheral blood mononuclear cells. Subjects with heterozygous familial hypercholesterolemia were on atorvastatin or simvastatin and three of the six also received concomitant ezetimibe. The study was approved by an ethics committee and written informed consent was obtained from subjects.

> **Comment**: There were no specific efficacy results related to the concomitant use of rosuvastatin and ezetimibe with LDL apheresis reported in the article.

Al-Hinai 2013 (16)

This article describes a case report of a 9 year old female with homozygous familial hypercholesterolemia due to a low-density lipoprotein receptor (LDLR) gene mutation. The patient was treated with rosuvastatin 10 mg and ezetimibe 10 mg which reduced the LDL-C from 22.1 mmol/L to 20.0 mmol/L (9.5% decrease). Direct adsorption of lipoprotein apheresis was subsequently commenced.

Comment: Only one dose strength of rosuvastatin was used. The dose frequencies of rosuvastatin 10 mg and ezetimibe 10 mg are not described.

Hanton 2013 (42)

This article describes case reports of eight patients with suspected familial hypercholesterolaemia with proprotein convertase subtilising/kein type 9 (PCSK 9) gene mutations. The patients were from a number of clinics in the UK. Two of the eight patients received treatment with ezetimibe concomitantly with rosuvastatin. One patient who was on rosuvastatin 40 mg with ezetimibe 10 mg treatment had a reduction in total cholesterol to 7.5 mmol/L compared with 15.0 mmol/L when not on medication. A second patient was started on weekly LDL- apheresis combined with rosuvastatin 40 mg daily and ezetimibe 10 mg daily because of refractory hyperlipidemia despite maximum doses of combination lipid regulating therapy.

Comment: Little detail was provided about each of the patients. The dose frequencies of rosuvastatin 40 mg and ezetimibe 10 mg are not described for one of the subjects. It appears that the first patient had a LDL-C value of 5.8 mmol/L while on rosuvastatin and ezetimibe treatment and that his LDL-C was 12.3 mmol/L before starting on cholesterol-lowering treatment.

Lee 2013 (43)

This article describes a case report of a 61 year old male with high density lipoprotein deficiency who had apolipoprotein A-I sequencing which revealed a novel mutation. His medications included rosuvastatin 40 mg/day and ezetimibe 10 mg/day.

Comment: There was no information in this article that specifically related to the efficacy and safety of rosuvastatin in combination with ezetimibe. The case was also on other lipid-lowering treatments.

Li 2012 (44)

This article describes a case report. A 57 year old female with familial combined hyperlipidemia and a personal and family history suggestive of mitochondrial disease received concomitant treatment with 5 mg rosuvastatin once a week and 10 mg ezetimibe once daily. After four weeks of concomitant therapy, LDL-C had decreased 27.3%, from 3.88 mmol/L to 2.82 mmol/L. The subject's younger sister, who also had familial combined hyperlipidemia and had been diagnosed with possible mitochondrial disease, received the same rosuvastatin and ezetimibe treatment regimen. She had a 33.2% reduction in LDL-C (3.19 mmol/L to 2.13 mmol/L).

Comment: The dosage regimen described in this case report is not consistent with that proposed for the ezetimibe and rosuvastatin fixed dose combination tablet as rosuvastatin was only administered once a week.

Orsoni 2012 (45)

This article describes an observational study. The objective of the study was to evaluate the consequences of LDL apheresis on the efficacy of the reverse cholesterol transport pathway in patients with familial hypercholesterolemia. The study subjects were patients with FH undergoing LDL apheresis every two to three weeks. All the patients were receiving a statin in combination with ezetimibe, of whom one was receiving rosuvastatin with ezetimibe (rosuvastatin 20 mg once daily and ezetimibe 10 mg once daily). Patients were on stable treatment for three months before blood sampling was undertaken to assess the ability of HDL particles to mediate free cholesterol efflux from macrophages, CETP-mediated cholesteryl ester (CE) transfer from HDL to apoB-containing lipoproteins and hepatic HDL–CE delivery. The study was approved by the hospital's Human Subjects Review Committee. Written informed consent was obtained. It is reported that LDL apheresis reduced CETP-mediated CE transfer from HDL to LDL.

Comment: This study does not appear to have direct relevance to the application. There were no efficacy and safety results specific to the use of rosuvastatin in combination with ezetimibe.

Young 2012 (46)

This article describes a case report regarding a 48 year old woman who had preserved left ventricular ejection fraction. The woman's concurrent medical conditions were with hyperlipidemia, obesity, diabetes, poorly controlled hypertension, a small pericardial effusion, chronic obstructive pulmonary disease and sleep apnoea. She was receiving multiple medications including ezetimibe 10 mg once daily and rosuvastatin once daily. She had symptoms of lightheadedness and shortness of breath and was hospitalised. The patient was still on rosuvastatin and ezetimibe when discharged from hospital.

Comment: There were no efficacy and safety results specific to the use rosuvastatin in combination with ezetimibe.

7.2.2. Ezetimibe plus any statin (with or without other lipid-lowering treatment)

7.2.2.1. Clinical studies

Comment: Ezetrol (ezetimibe) is already indicated for the treatment of patients with primary (heterozygous familial and non-familial) hypercholesterolaemia administered alone or with a statin, as adjunctive therapy to diet, and for the treatment of patients with homozygous familial hypercholesterolaemia administered with a statin (1). The original application to register ezetimibe (Application No. 99/3917/3) contained clinical studies to support the co-administration of Ezetrol with a statin. These studies have been previously evaluated. The information in the dossier for Application No. 99/3917/3 provided in this submission was used as a reference. None of the studies in Application No. 99/3917/3 related to the addition of rosuvastatin to ezetimibe treatment.

The following information is from the Australian PI for Ezetrol (1):

"EZETROL Initiated Concurrently with a Statin

In four, multicentre, double-blind, placebo-controlled, 12-week trials, in 1187 patients with hypercholesterolaemia, EZETROL 10 mg was administered alone or with various doses of atorvastatin, simvastatin, pravastatin, or lovastatin. The greatest LDL-C reducing effect is seen with the lowest dose of each statin, with only a further 2-9% incremental reduction in LDL-C with each doubling of the dose. Comparatively, adding 10mg of EZETROL to a given dose of a statin is shown to achieve a greater reduction in LDL-C than that achieved with statin dose doubling.

Table 3: Mean Absolute and Percent Change from Baseline in Plasma Concentration of Calculated LDL-C for EZETROL Administered with Statins

	Atorvastatin Study Abs[a] (Pct[b])	Simvastatin Study Abs[a] (Pct[b])	Pravastatin Study Abs[a] (Pct[b])	Lovastatin Study Abs[a] (Pct[b])
Placebo	0.20 (+4%)	-0.08 (-1%)	-0.03 (-1%)	0.00 (0%)
EZETROL	-0.92 (-20%)	-0.92 (-19%)	-0.91 (-20%)	-0.86 (-19%)
10 mg statin	-1.76 (-37%)	-1.25 (-27%)	-0.96 (-21%)	-0.94 (-20%)
EZETROL + 10 mg statin	-2.46 (-53%)	-2.10 (-46%)	-1.55 (-34%)	-1.56 (-34%)
20 mg statin	-1.91 (-42%)	-1.74 (-36%)	-1.10 (-23%)	-1.18 (-26%)
EZETROL + 20 mg statin	-2.59 (-54%)	-2.16 (-46%)	-1.82 (-40%)	-1.87 (-41%)
40 mg statin	-2.09 (-45%)	-1.75 (-38%)	-1.43 (-31%)	-1.44 (-30%)
EZETROL + 40 mg statin	-2.69 (-56%)	-2.55 (-56%)	-1.97 (-42%)	-2.15 (-46%)
80 mg statin	-2.57 (-54%)	-2.11 (-45%)	-	-
EZETROL + 80 mg statin	-2.93 (-61%)	-2.64 (-58%)	-	-
Pooled data: All statin doses	-2.08 (-44%)	-1.71 (-36%)	-1.16 (-25%)	-1.19 (-25%)
Pooled data: All EZETROL + statin doses	-2.67 (-56%)	-2.36 (-51%)	-1.78 (-39%)	-1.86 (-40%)

[a] Mean absolute change from baseline, expressed as mmol/L
[b] Mean percent change from baseline

In a pooled analysis of all EZETROL + statin doses, EZETROL had a beneficial effect on total-C, Apo B, TG, and HDL-C (Table 4).

Table 4: Pooled Analysis of Absolute and Percent Change from Baseline in Total-C, ApoB, TG, and HDL-C

	Total-C Abs[a] (Pct[b])	Apo B Abs[c] (Pct[b])	TG Abs[d] (Pct[e])	HDL-C Abs[a] (Pct[b])
EZETROL + Atorvastatin	-2.86 (-41%)	-0.78 (-45%)	-0.55 (-33%)	0.09 (+7%)
Atorvastatin alone	-2.24 (-32%)	-0.61 (-36%)	-0.40 (-24%)	0.05 (+4%)
EZETROL + Simvastatin	-2.49 (-37%)	-0.69 (-41%)	-0.53 (-29%)	0.11 (+9%)
Simvastatin alone	-1.78 (-26%)	-0.51 (-30%)	-0.32 (-20%)	0.09 (+7%)
EZETROL + Pravastatin	-1.86 (-27%)	-0.51 (-30%)	-0.36 (-21%)	0.10 (+8%)
Pravastatin alone	-1.17 (-17%)	-0.35 (-20%)	-0.26 (-14%)	0.08 (+7%)
EZETROL + Lovastatin	-1.96 (-29%)	-0.57 (-33%)	-0.44 (-25%)	0.10 (+9%)
Lovastatin alone	-1.25 (-18%)	-0.36 (-21%)	-0.21 (-12%)	0.04 (+4%)

[a] Mean absolute change from baseline, expressed as mmol/L
[b] Mean percent change from baseline
[c] Mean absolute change from baseline, expressed as g/L
[d] Median absolute change from baseline, expressed as mmol/L
[e] Median percent change from baseline

EZETROL Added to On-going Statin Therapy

In a multicentre, double-blind, placebo-controlled, 8-week study, 769 patients with hypercholesterolaemia already receiving statin monotherapy and not at National Cholesterol Education Program (NCEP) LDL-C goal (2.59 to 4.14 mmol/L, depending on baseline characteristics) were randomised to receive either EZETROL 10 mg or placebo in addition to their on-going statin therapy.

Among statin-treated patients not at LDL-C goal at baseline (~82 %), LDL-C goal at study endpoint was achieved by 72% and 19% of patients randomised to EZETROL and placebo, respectively.

EZETROL, added to on-going statin therapy, significantly lowered total-C, LDL-C, Apo B, and TG and increased HDL-C, compared with placebo (Table 5). LDL-C reductions were consistent across all statins.

Table 5: Response to Addition of EZETROL to On-going Statin Therapya in Patients with Hypercholesterolaemia (Absolute and Percent Change from Baseline)

	N	Total-C Abs[b] (Pct[c])	LDL-C Abs[b] (Pct[c])	Apo B Abs[d] (Pct[c])	TG Abs[e] (Pct[f])	HDL-C Abs[b] (Pct[c])
On-going Statin +Placebo	390	-0.16 (-2%)	-0.16 (-4%)	-0.05 (-3%)	-0.05 (-3%)	0.00 (+1%)
On-going Statin +EZETROL	379	-0.99 (-17%)	-0.92 (-25%)	-0.27 (-19%)	-0.19 (-14%)	0.03 (+3%)

[a] Percentages of patients receiving each statin: 40% atorvastatin, 31% simvastatin, 29% others (pravastatin, fluvastatin, cerivastatin, lovastatin)
[b] Mean absolute change from baseline, expressed as mmol/L
[c] Mean percent change from baseline
[d] Mean absolute change from baseline, expressed as g/L
[e] Median absolute change from baseline, expressed as mmol/L
[f] Median percent change from baseline

EZETROL or placebo added to statin therapy reduced median C-reactive protein by 10 % or 0 % from baseline, respectively.

In a multicentre, double-blind, 14 week study, 621 patients with hypercholesterolaemia receiving atorvastatin 10 mg daily with an LDL-C > 3.36 mmol/L were randomised to receive atorvastatin 20 mg or EZETROL 10 mg added to atorvastatin 10 mg therapy. The atorvastatin dose could be titrated up to 80 mg in the atorvastatin arm and up to 40 mg in the EZETROL plus atorvastatin co-administration arm, based on patients not attaining LDL-C goal (< 2.59 mmol/L). The mean baseline LDL-C was 4.84 mmol/L and approximately 60% of the patients had heterozygous familial hypercholesterolaemia (HeFH). At study end, there was a significant difference in attainment of LDL-C goal between patients in the EZETROL co-administration arm (22%) and patients on atorvastatin monotherapy (7%). At week 4, there was a significant difference in LDL-C reductions between co-administration patients (24%; EZETROL + atorvastatin 10 mg) and monotherapy patients (9 %; atorvastatin 20 mg). In the sub-group of patients with HeFH, similar results for LDL-C goal attainment and LDL-C reductions were achieved.

In a similarly designed study in 100 patients with hypercholesterolaemia receiving simvastatin 20 mg and not at LDL-C goal, the addition of EZETROL 10 mg to simvastatin titration compared to titration of simvastatin alone produced similar advantages to those observed in the atorvastatin study described above. For example, significant differences in LDL-C goal attainment (27% for EZETROL + simvastatin vs. 3% for simvastatin alone) and LDL-C reductions (24% for EZETROL + simvastatin vs. 11% for simvastatin alone) were achieved."

"Homozygous Familial Hypercholesterolaemia (HoFH)

A study was conducted to assess the efficacy of EZETROL in the treatment of HoFH. This double-blind, randomised, 12-week study enrolled 50 patients with a clinical and/or genotypic diagnosis of HoFH, with or without concomitant LDL apheresis, already receiving atorvastatin or simvastatin (40mg). Patients were randomised to one of three treatment groups, atorvastatin or simvastatin (80mg), EZETROL 10mg administered with atorvastatin or simvastatin (40mg), or EZETROL 10mg administered with atorvastatin or simvastatin (80mg). Results are shown in Table 6. EZETROL, administered with atorvastatin (40 or 80mg) or simvastatin (40 or 80mg), significantly reduced LDL-C compared with increasing the dose of simvastatin or atorvastatin monotherapy from 40 to 80mg.

Table 6: Mean Response to EZETROL in Patients with HoFH (Mean Absolute and Percent Change from Baseline)

Treatment (Daily Dose)	N	LDL-C Abs[a] (Pct[b])
Atorvastatin (80 mg) or Simvastatin (80 mg)	17	-0.51 (-7%)
EZETROL + Atorvastatin (40, 80 mg) or Simvastatin (40, 80 mg)	33	-1.76 (-21%)
Sub-group analysis: EZETROL + Atorvastatin (80 mg) or Simvastatin (80 mg)	17	-2.00 (-27%)

[a] Mean absolute change from baseline, expressed as mmol/L
[b] Mean percent change from baseline

”

7.2.2.2. Literature

Comment: Please refer to the comment under Section 7.2.1.2.

The updated literature search identified the following new articles that referred to co-administration of ezetimibe and any statin, including rosuvastatin.

7.2.2.2.1. Randomised controlled trials

- **Okada 2012 (47)**

This article described a randomised trial with an observation period of 52 weeks. Institutional Review Boards of participating hospitals approved the protocol. Written informed consent was obtained from subjects. The objective of this study was to assess the mechanism of long-term LDL-C lowering effect of ezetimibe plus a statin. Subjects (n=200) had coronary artery disease and LDL-C levels of ≥ 70 mg/dL after treatment with atorvastatin 10 mg/day or rosuvastatin 2.5 mg/day. Subjects were randomised to received ezetimibe 10 mg/day plus a statin (n=100) or a double dose of statin (atorvastatin 20 mg /day or rosuvastatin 5.0 mg/day) (n=100). Fifty subjects withdrew from the study (ezetimibe+ statin group: patient request n=19, adverse effect n=3; double-dose statin group: patient request n=25; adverse effect n=3). One hundred and fifty subjects were followed for 52 weeks (ezetimibe+ statin group (n=78); double-dose statin group (n=72)). Fasting blood samples were collected for LDL-C levels at baseline, 12 weeks and 52 weeks. At 12 weeks the LDL-C was 83.2 ± 17.9 mg/dL in the ezetimibe + statin group compared with 92.3 ± 20.9 mg/dL in the double-dose statin group ($p<0.01$). From baseline to 12 weeks, there was a greater decrease in LDL-C level in the ezetimibe + statin group compared with the double-dose statin group (-28.7 ±19.7 mg/dL vs -16.5 ±17.0 mg/dL, $p<0.01$). At 52 weeks the LDL-C was 83.1 ± 20.3 mg/dL in the ezetimibe + statin group compared with 96.8 ± 21.6 mg/dL in the double-dose statin group ($p<0.01$) and a greater proportion of subjects in the double-dose statin group had a LDL-C level higher than baseline value compared with the ezetimibe+ statin group (31.9% vs 9.0%, $p<0.01$). The percentage decrease in LDL-C from baseline at Week 52 was 25.7% in the ezetimibe + statin group and 11.4% in the double-dose statin group. Campesterol, a cholesterol absorption marker, and lathosterol, a cholesterol synthesis marker and plasma PCSK9 concentrations were also measured.

Comment: The results did not differentiate between the two statins, atorvastatin and rosuvastatin.

- **Okada 2012 (48)**

This was a poster that described a randomised study. Subjects (n=146) had coronary artery disease and LDL-C levels of ≥ 70 mg/dL after treatment with atorvastatin 10 mg/day or rosuvastatin 2.5 mg/day. Subjects were randomised to received ezetimibe 10 mg/day plus a

statin (E/S) (n=75) or a double dose of statin (D/S) (n=71). Subjects were followed for 52 weeks. From baseline to 12 weeks, there was a greater decrease in LDL-C level in the E/S group compared with the D/S group (-28 ±19 mg/dL vs -17 ±17 mg/dL, p<0.01). In the E/S group, the LDL-C level at 12 weeks had increased by 1mg/dL at Week 52 but in the D/S group, the LDL-C had increased at Week 52 by 5 mg/dL.

Campesterol, a cholesterol absorption marker, and lathosterol, a cholesterol synthesis marker and plasma PCSK9 concentrations were also measured.

> **Comment**: This publication appears to relate to the same study as that described in the article by Okada at al (47). The results were not specific for rosuvastatin as the atorvastatin and rosuvastatin data were analysed together.

· **Giugliano 2012 (49)**

This article described a phase 2, multi-centre dose-ranging, randomised, double-blind, placebo-controlled study that assessed the efficacy, safety and tolerability of AMG 145, a human monoclonal IgG2 antibody against proprotein convertase subtilisin/kexin type 9 (PCSK9), which binds LDL receptors, targeting them for degradation. Subjects had hypercholesterolaemia and were on a statin. The primary endpoint was the percentage change in LDL-C concentration from baseline after 12 weeks. Use of ezetimibe and/or a statin were permitted during this study.

> **Comment**: This study is not specifically related to the efficacy of the co-administration of ezetimibe with rosuvastatin. LDL-C results for those subjects in the placebo groups who received ezetimibe plus rosuvastatin, if any, are not presented.

· **Raal 2012 (50)**

This article described a phase 2, multi-centre, double-blind, randomised, placebo-controlled, dose- ranging study that assessed the efficacy and safety of AMG 145, a human monoclonal IgG2 antibody against proprotein convertase subtilisin/kexin type 9 (PCSK9). Subjects had heterozygous familial hypercholesterolemia. The primary end point was percentage change from baseline in LDL-C at week 12.

> **Comment**: This study is not specifically related to the efficacy of the co-administration of ezetimibe with rosuvastatin. Use of ezetimibe and/or a statin were permitted during this study. It is not indicated in the article which patients in the placebo group were receiving both ezetimibe and rosuvastatin.

· **Stein 2012 (51)**

This article described a phase 2, multi-centre, randomised, placebo-controlled study assessing the efficacy and safety of various doses and dosing intervals of a monoclonal antibody to PCSK9 (REGN727), added to statins to further lower LDL-C in patients with heterozygous familial hypercholesterolaemia. The treatment period was 12 weeks in duration. Subjects were adults with LDL concentrations of 2.6 mmol/L or higher who were on a stable diet and statin dose, with or without ezetimibe. Subjects were randomised to one of four different doses and dosing intervals of REGN727 or placebo. The primary endpoint was mean per cent reduction in LDL-C from baseline at week 12. There were 15-16 patients randomised to each treatment group. The study was undertaken in accordance with the Declaration of Helsinki, the Committee for Proprietary Medicinal Products (CPMP) guidelines and the ethics principles of good clinical practice. Fifteen subjects were allocated to receive placebo every two weeks, all of whom received it. In the placebo group, all subjects were on a statin and 73% were also on ezetimibe.

> **Comment**: It is not indicated in the article which patients in the placebo group were receiving both ezetimibe and rosuvastatin so it is not possible to draw specific conclusions regarding the safety and efficacy of ezetimibe + rosuvastatin from this study. The subjects were receiving a statin + placebo, a statin + ezetimibe + placebo, or a statin+/- ezetimibe + one of the doses and dosage regimens for REGN727.

· **Sullivan 2012 (52)**

The objective of the study described in this article was to assess the efficacy and tolerability of AMG 145, a human monoclonal antibody to PCSK9, in patients with statin intolerance due to muscle-related side effects. All patients had intolerance to one or more statins because of muscle related events. The study was a randomised, double-blind, placebo and ezetimibe controlled dose ranging study of 12 weeks duration. Patients were randomized to one of five treatment groups: AMG145 alone at doses of 280 mg, 350 mg, or 420 mg; AMG145 at 420 mg plus 10 mg of ezetimibe; or 10 mg of ezetimibe plus placebo. AMG145 or placebo was administered subcutaneously every 4 weeks. Ezetimibe was administered once daily and was not blinded. Patients could receive stable doses of statins less than or equal to a specified weekly maximum. The primary end point was percentage change from baseline to week 12 in ultracentrifugation-measured LDL cholesterol. At baseline, 16% of patients used statins. In the placebo/ezetimibe treatment group (n=33) the least–squares mean percentage change in LDL-C from baseline to week 12 was -14.8% (95%CI[-22.6%,-7.0%]).

> **Comment**: Specific results were not presented for the patients who were on a statin or another lipid lowering drug at baseline and who were randomised to ezetimibe plus placebo.

7.2.2.2.2. Time series

· **Tamaki 2012 (53)**

This article describes a prospective study that was undertaken in Japan. The aim of the study was to examine the clinical effects of ezetimibe, including its effects on atherosclerotic markers. Subjects were outpatients with hypercholesterolemia who had not achieved serum LDL-C levels recommended in the Japan Atherosclerosis Society 2007 guidelines despite ezetimibe monotherapy with diet and exercise or ezetimibe in combination with statin therapy for at least 4 weeks. Ethics Committee approval was obtained. Patients were treated with 10 mg ezetimibe once a day for 12 weeks during which time other anti-hyperlipidemic, anti-hypertensive and anti-diabetic medications were continued without dosage modification. Of 112 patients in the study, for 17 patients, treatment with ezetimibe combined with a statin was initiated. Of these 17 patients, 16 completed the 12 weeks of treatment, of whom rosuvastatin was administered prior to the administration of ezetimibe in 4 patients. After 12 weeks of combined therapy of ezetimibe with a statin (n=16), LDL-C had decreased from a baseline level of 157.1±7.8 mg/dL to 120.0± 8.7 mg/dL. For ezetimibe monotherapy (n=75)), LDL-C decreased from a baseline level of 159.3±2.5 mg/dL to 130.6± 2.7 mg/dL.

> **Comment**: The dose of rosuvastatin is not specified in those patients who received it. No primary endpoint appears to have been specified in this study.

· **Cuchel 2013 (54)**

This article described a Phase 3, single-arm, open-label, multi-centre, study. The study was approved by the review board of each institution or the ethics committee. The aim of the study was to assess the efficacy and safety of the lomitapide, a microsomal triglyceride transfer protein inhibitor, in adults with homozygous familial hypercholesterolaemia. The primary efficacy endpoint was percent change from baseline in LDL concentration at the maximum tolerated dose of lomitapide after 26 weeks of treatment. Of 31 patients who entered the run-in period for the study, 29 were enrolled in the efficacy phase and 23 patients completed the 26 week efficacy phase and the 52 week safety phase. During the run in period, which was at least 6 weeks in duration, patients were initiated on concomitant lipid-lowering therapies and were stabilised on a low fat diet. Lomitapide was then initiated and dose titrated at intervals up to 60 mg day or until an individually determined maximum dose was achieved based on safety and tolerability. At baseline, twenty-two of the patients were being treated with statins, primarily rosuvastatin or atorvastatin, and ezetimibe.

Comment: The results of this study are not specifically related to the efficacy of concomitant administration of ezetimibe and rosuvastatin, or another statin, as all subjects also received lomitapide.

· **Kolovou 2012 (12)**

This article describes an open, prospective, uncontrolled clinical study undertaken in one centre. The aim of the study was to investigate changes in plasma lipids and lipoproteins and cardiovascular events after LDL apheresis in children and adults who had total cholesterol (TC) values resistant to hypolipidemic treatment. Written informed consent was obtained. Patients were treated with maximum doses of one of the statins plus ezetimibe and/or colesevelam and/or fenofibrate and with a low fat diet. LDL apheresis frequency was adjusted individually. Five patients had homozygous familial hypercholesterolemia, 10 patients had hypercholesterolemia (familial or non familial) and six patients had mixed dyslipidemia. Patients (n=21) had a mean age of 41± 14 years. Ninety percent of patients (n=19) were on statins at baseline and 48% (n=10) were receiving ezetimibe. Mean follow-up was for 47±23 months (range 9-81 months).

Comment: It is not indicated if Ethics Committee approval was obtained. The results for all patients were presented together. The changes in LDL-C for the patients with homozygous familial hypercholesterolemia who were receiving ezetimibe concomitantly with rosuvastatin, or another statin, plus LDL apheresis were not presented.

· **Tobaru 2013 (55)**

This article describes an exploratory, prospective, uncontrolled study. The study received Ethics Committee approval. Subjects were patients with hypercholesterolaemia and coronary artery disease who had not achieved the Japan Atherosclerosis Society 2007 guidelines target cholesterol level (LDL-C <100 mg/dL) despite at least 4 weeks of treatment with statin monotherapy. Subjects with familial hypercholesterolemia and secondary or drug-induced hypercholesterolemia were excluded. Subjects received 12 weeks treatment with ezetimibe 10 mg daily concomitantly with the statin that they had been receiving prior to the study. Subjects also received guidance regarding diet and exercise. Concomitant drugs were not discontinued and dosages were not changed. The primary endpoint was the rate of achieving the target LDL-C level. Of the 35 subjects, 13 were receiving rosuvastatin treatment (mean dose 4.6 ±2.0 mg/day) at baseline.

At 4 weeks, the rate of achieving the target LDL-C level was 70.8% (n=17) and 65.4% (n=17) at 12 weeks. The mean LCL-C values were lower at Week 4 ((n=26) 87.2±26.9 mg/dL) and at Week 12 ((n=29) 94.6±30.4 mg/dL) compared with baseline ((n=32) 121.3±29.4 mg/dL).

Comment: The efficacy results were not presented for ezetimibe in combination with a specific statin.

7.2.2.2.3. Observational studies

· **Desai 2012 (56)**

This was an abstract. Claims from a nationwide health insurer were used to evaluate the trends in statin prescribing in a cohort of 24,218 patients with acute myocardial infarction hospitalised in the period July 2006 to December 2010.

Comment: This publication did not pertain to the efficacy of ezetimibe in combination with a statin.

· **Karalis 2012 (57)**

This article described a retrospective analysis of outpatient electronic health records at one study site in the USA, a cardiology sub-speciality practice. Patients with coronary artery disease

who had been seen at one of the outpatient clinics over a 12 month period from September 2008 to September 2009, and who had a recent lipid profile in their record, were identified. The aim of the study was to determine if underutilisation of lipid-lowering therapy in patients with coronary artery disease in clinical practice was one barrier to achieving an LDL-cholesterol of <70 mg/dL. There were 9,950 patients who met the study criteria. Fourteen percent of patients (n=1378) received a combination of a statin and ezetimibe. Of those patients who were receiving a statin plus another lipid-lowering medication, 276 were on more than one non-statin lipid lowering drug. A higher proportion of patients treated with a statin and ezetimibe attained an LDL-cholesterol of <70 mg/dL compared with patients treated with a statin alone (41% vs 37%, p=0.01).

> **Comment**: The results presented were for any statin of any dose in combination with ezetimibe. Patients receiving rosuvastatin and ezetimibe, if there were any, may also have been receiving other non-statin lipid lowering drugs also.

- **Park 2012 (58)**

This article describes a prospective, cross sectional, multi-centre survey conducted in eight Asian countries. The primary objective of the study was to determine the proportion of patients on lipid-lowering therapy attaining LDL-C goals as defined by the updated 2004 NCEP ATP III guidelines. Subjects were patients with hypercholesterolaemia aged 18 years or older, with two or more cardiovascular risk factors as defined by the updated 2004 NCEP ATP III guidelines who had been on lipid-lowering treatment for at least three months and stable medication for at least 6 weeks. The study protocol was approved by the participating centres' Investigational Review Board and Ethics Committee. The study was conducted in accordance with good clinical research practice and conformed to guidelines of the Declaration of Helsinki. Patients provided written informed consent. The physician and patient filled out questionnaires. A fasting blood sample was taken to determine blood glucose and lipid concentrations. The primary endpoint was the proportion of patients on lipid-lowering treatment achieving their therapeutic LDL-C goals, overall and by country. LDL-C goal attainment according to lipid lowering drug type was an additional endpoint. Indications for lipid lowering therapy were secondary prevention (50.8%, n=3615), primary prevention (47.6%, n = 3385) and familial hypercholesterolemia (1.6%, n=112). There were 7,281 patients in the per-protocol population, of whom 9.2% (n=671) were on combination therapy. It is reported that most of the combination therapies consisted of a statin plus another drug. The attainment of LDL-C goals was more likely for patients on rosuvastatin monotherapy compared with combination therapy (combination therapy versus rosuvastatin monotherapy: odds ratio 0.68 95%CI[0.51, 0.91]).

> **Comment**: Specific physicians were invited to participate in the study and the physicians invited patients to participate. This may have led to a selection bias. Combination therapy was not further specified for those patients receiving it.

- **Pereg 2012 (59)**

This article describes a review of information in the computerised database of a health maintenance organisation in Israel. The study population was residents of a district in Israel who were medically insured by the health maintenance organisation and who were 18 years of age or older without a history of coronary artery disease (CAD), cerebral artery disease or peripheral artery disease (PAD) who underwent first coronary or peripheral vascular intervention during the period 1 January 2004 to 31 December 2010 and who had at least one full lipid profile available six months or more after the intervention. The aim of the study was to compare the lipid-lowering treatment characteristics and the attainment of LDL-C targets in patients after first coronary or peripheral vascular intervention. The percentage of patients treated with atorvastatin, rosuvastatin, ezetimibe or niacin was also examined. The study was approved by the institutional ethics committee. Primary endpoints were the percentage of patients who achieved the LDL-C goal of <100 mg/dL and the percentage of patients who

achieved the LDL-C goal of <70 mg/dL. Small proportions of patients were on rosuvastatin following first coronary or peripheral vascular intervention (PAD (n=1626) 3.5%, CAD (n=7512), 5.4%) and even smaller proportions of patients were on ezetimibe (PAD 1.4%, CAD 1.8%). LDL-C targets were attained by a higher proportion of patients with CAD compared with PAD after first coronary or peripheral vascular intervention.

> **Comment**: It is not specified if any of the patients were taking both rosuvastatin and ezetimibe. Only patients with lipid profiles were included this may have resulted in selection bias. The accuracy and completeness of the database for any given patient relied on the patient's physician who was responsible for updating the data.

- **Pittman 2012 (60)**

This article described a retrospective analysis using an integrated pharmacy and medical claims database. The study objective was to determine if non-adherence to statins is associated with subsequent intensification of lipid therapy in patients who were previously on a stable statin dose. The data from the claims database was de-identified. The data were for approximately 13 million patients enrolled in 450 health plans in the United States. Study subjects were patients aged 8 to 62 years of age as of 1 January 2009, were continuously enrolled in the health plan for at least 27 months during the period 1 April 2008 and 31 December 2010. The analysis included patients who, during the period 1 January to 31 December 2009, had received a stable dose of a statin for at least 180 days. There was a follow-up period of 360 days after the patient had been on a stable stain dose for the required period (the index date). A stable dose was defined as the patient having had at least two claims for the same drug and dose or an equivalent dose of a different statin during the 180 day period. The patient could not have any claims for ezetimibe during this period. Patients on statin therapy for at least 12 months before the index date, and who had had at least one additional statin claim during the follow-up period, were selected. Treatment intensification was defined as the addition of ezetimibe or a prescription of a statin with an increased daily dose equivalent in the 360 days after the statin index date. Non-adherence to a statin, defined as proportion of days covered of less than 80%, was a predictor of dose escalation.

> **Comment**: This publication did not pertain to the efficacy of ezetimibe in combination with a statin.

- **Seed 2012 (61)**

This article described a national audit of the management of familial hypercholesterolemia (FH) undertaken in England, Wales, Scotland and Northern Ireland between April and September 2010. Participating lipid clinics were asked to select cases from the first 40 consecutive cases with a diagnosis of FH visiting the clinic during the audit period. Cases were required to have attended outpatients for at least three clinic appointments. No patient-identifiable data were collected. There were 2,324 audited patients, of whom 86% were on a statin, a third receiving rosuvastatin, and 40% were receiving ezetimibe. The median [interquartile range (IQR)] LDL-C value for patients on treatment was 3.3 mmol/L [2.6-4.3]. In comparison, the median [IQR] LDL-C value pre-treatment was 6.1 [5.3-7.3] mmol/L.

> **Comment**: There were no efficacy results presented specific to ezetimibe in combination with a statin.

- **Senarante 2012(62)**

This article described a prospective case series. The aim of the study was to compare the LDL-C reductions achieved with statins and the LDL-C reductions achieved with ezetimibe adjunct therapy. Study subjects were 109 consecutive patients attending a cardiac rehabilitation program in one hospital over a 3.5 year period who received statin monotherapy followed by ezetimibe adjunct therapy. The statin was titrated to a moderate/high dose. Ezetimibe 10 mg daily was added to the statin therapy in patients who did not reach target levels of less than 78

mg/dL (2.0 mmol/L). All patients received diet and lifestyle counselling initially and as required at the time of up titration of the statin and addition of ezetimibe. Informed consent for the data collection and analysis was not obtained as the establishment and maintenance of the database into which the patients' data were being entered were considered part of the organisation's clinical practice to ensure quality care. A lipid profile was obtained for each patient before the start of statin therapy, 4 to 6 weeks after statin therapy was initiated and following the addition of ezetimibe therapy. The mean ± SEM LDL level decreased from baseline (168.7 ± 3.6 mg/dL) to a greater extent following treatment with a statin with ezetimibe adjunct therapy (74.2 ± 2.2 mg/dL) than on a statin alone (104.2 ± 2.6 mg/dL). The mean reduction in LDL level was 37±1% on statin therapy and with the addition of ezetimibe the LDL level was reduced a further 28 ±1%. In patients who had a high percent LDL-C reduction with statins, the percent LDL-C reduction by the addition of ezetimibe was lower and vice versa.

> **Comment**: The results were not presented for specific statins administered with and without ezetimibe.

- **Toth 2012 (15)**

This article describes a longitudinal retrospective cohort analysis of the changes in prescription patterns for ezetimibe/simvastatin, ezetimibe plus statin and statin therapies. The prescription changes were identified in a health database containing de-identified patient prescription data. Two cohorts were used for the periods that related to the reporting of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial. For each cohort there was a six month identification phase for baseline therapy and a six month follow-up therapy phase. The analysis included patients who had been receiving ezetimibe/simvastatin, ezetimibe plus statin therapies and statin monotherapy if they had filled at least one prescription for a lipid lowering therapy in the identification period, filled at least one prescription for ezetimibe/simvastatin, ezetimibe or a statin during the identification or follow-up period, and met other criteria. A higher proportion of patients receiving ezetimibe/simvastatin and ezetimibe plus statin therapies switched to statin monotherapy during the six month period after the results of the ENHANCE trial were reported compared with the six months before the results were reported.

> **Comment**: The results of this study relate to prescribing and do not pertain to the efficacy of ezetimibe in combination with a statin.

- **Querton 2012 (63)**

This article describes a cross sectional study. The study population was consecutive adult outpatients who had type 2 diabetes who were receiving follow-up at a diabetes centre in one hospital in Belgium during the period October 2009 to October 2010 and who had a LDL-C <70 mg/dL.

The objectives of the study were to determine, in patients with type two diabetes treated with statins with on-statin LDL-C <70 mg/dL, firstly, the proportion who met the following: LDL-C<70 mg/dL, non-high density lipoprotein cholesterol <100 mg/dL, apoB<80 g /dL, and secondly the variables associated with target attainment and non-attainment.

The study population (n=118) was split into two groups according to whether or not they met the non-HDL-C and apoB targets. Of the 118 patients, 5% were treated with a statin in combination with ezetimibe. Of the patients who were at the goal for the three parameters, LDL-C, non-HDL-C and apoB targets (n=79), 5.1% were on a statin plus ezetimibe. For those patients only at goal for LDL-C (n=39), 2.7% were on a statin plus ezetimibe.

> **Comment**: There were no efficacy results specific to the use of rosuvastatin in combination with ezetimibe.

7.3. Analyses performed across trials (pooled analyses and meta-analyses)

No new analyses performed across trials were submitted in this application.

7.4. Evaluator's conclusions on clinical efficacy for primary hypercholesterolaemia and homozygous familial hypercholesterolaemia

No confirmatory clinical efficacy trials, comparing the proposed fixed dose combination with the mono-components, are included in the submission. However, the application for the registration of the ezetimibe and rosuvastatin composite pack (Submission PM2012-03419-1-3), in the same indications as those proposed for the fixed dose combination tablet, has been approved by the TGA, which indicates that the evidence to support the efficacy of concomitant administration of ezetimibe 10 mg and rosuvastatin 5 mg, 10 mg, 20 mg, 40 mg is acceptable. The evidence provided to support the efficacy of the fixed dose combination tablet is the same as the evidence provided to support the efficacy of the ezetimibe and rosuvastatin composite pack plus additional publications identified in the updated literature review. The bioequivalence studies for the lowest and highest dose strengths of the proposed fixed dose combination tablet, and the biowaiver justification for the intermediate strengths, support the therapeutic equivalence of the concomitant administration of ezetimibe and rosuvastatin and the proposed fixed dose combination.

The evidence presented to support the fixed dose combination tablets relates primarily to a surrogate marker, LDL-C, rather than a clinical outcome, cardiovascular morbidity and mortality. The use of LDL-C as a surrogate endpoint is acceptable as it has been established in epidemiologic studies that cardiovascular morbidity and mortality vary directly with the level of LDL-C (and total cholesterol) (1) and intervention studies have shown that lowering LDL-C and TG, or raising HDL-C, has benefits on mortality and cardiovascular event rates (3). The guideline "Note for guidance on treatment of lipid disorders" (36) indicates that reduction in LDL-C cholesterol is the primary endpoint to support an indication of hypercholesterolaemia for a lipid-lowering drug and that reduction in LDL-C with respect to NCEP standards can be a secondary endpoint.

No additional high level studies were identified in the updated literature search to support the registration of the fixed dose combination tablet in the proposed indications. None of the studies described were confirmatory randomised double-blind, controlled studies analysed by intention to treat, or systematic reviews of randomised controlled trials. Therefore, the evidence that is provided in the publications is potentially affected by sources of bias and confounding. Of the newly identified publications that described randomised controlled trials, there were none that had a primary endpoint of LDL-C reduction and for which the primary objective was to evaluate the efficacy of the concomitant use of ezetimibe and rosuvastatin compared with either mono-component.

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

- Efficacy study -Study P139V1 (previously evaluated)
- PD study -Study P03317 (previously evaluated)
- Bioequivalence studies –Study P417 and Study P425 (new)
- Literature (identified for this submission and previously identified for Submission PM2012-03419-1-3)

- Ezetimibe studies in registration dossier (previously evaluated)
- PSUR Addendum Report for ezetimibe (new)

No new safety studies were included in the submission.

> **Comment**: The safety profiles of the mono-components of the proposed fixed dose combination tablet, ezetimibe and rosuvastatin, are described in the respective product information document for Ezetrol (1) and MSD rosuvastatin (3). Specific safety issues identified with the co-administration of ezetimibe and rosuvastatin are included in the PIs for the Rosuzet composite pack and Ezalo composite pack (5, 6).
>
> The studies in the registration dossier for Ezetrol were not related to treatment with ezetimibe in combination with rosuvastatin specifically. As the studies in the registration dossier for Ezetrol have already been evaluated, pertinent safety data would have been included in the PI for Ezetrol (1), the PIs for the Rosuzet composite pack and Ezalo composite pack (5, 6) and the draft PIs for the proposed fixed dose combination tablets.

8.1.1. Pivotal efficacy studies

8.1.1.1. Study P139V1

Study P139V1 was evaluated as part of the application for the registration of the ezetimibe rosuvastatin composite pack (Submission PM2012-03419-1-3). The following information is an extract from the Clinical Evaluation Report for the Rosuzet/Ezalo Composite Pack (Submission PM2012-03419-1-3) (18):

"In the pivotal efficacy study P139V1 the following safety data were collected:

General adverse events (AEs) were assessed by physical examination, ECG, vital signs, AE assessment and blood tests - hematology, blood chemistry, urinalysis CK, ALT, AST. The All Patients as Treated population was used for safety in this study – consisting of all randomised patients who received at least one dose of study treatment.

The analysis of safety followed a 3 –tiered approach

- Tier 1 – Including gastrointestinal related AEs, gallbladder-related AEs, allergic reaction or rash AEs, hepatitis-related AEs, elevations in ALT/AST ≥ 3 x ULN, elevations in CK ≥ 10 x ULN, elevations in CPK ≥ 10 x ULN with muscle symptoms and elevations in CPK ≥ 10 x ULN with drug-related muscle symptoms.
- Tier 2 – one or more AEs, drugs related AEs, serious AEs, discontinuations due to an AE
- Tier 3 was everything else

AEs of particular interest, including laboratory measurements of ALT/AST and CPK were assessed by laboratory tests.

Laboratory tests, including AST, ALT, CPK and urinalysis, were performed at Visits 1,3,4. Other tests included serum glucose, ALP, bicarbonate, urea, chloride, creatine kinase, creatinine, GGT, sodium, potassium, uric acid, bilirubin, TSH. Hematology collected at Visits 2,3,5 – blood hemoglobin, white cell count, platelets, red cell count, blood haematocrit. Urinalysis for blood, protein, glucose, creatinine and pH measured at Visits 1,3,4."

8.1.2. Dose-response and non-pivotal efficacy studies

No dose-response studies or non-pivotal efficacy studies providing safety data were included in the submission.

> **Comment**: Study P139V1, a pivotal efficacy study, provided safety data in relation to two doses of rosuvastatin administered alone and two doses of rosuvastatin administered with ezetimibe.

8.1.3. Other studies evaluable for safety only

There were no studies evaluable for safety only.

8.1.4. Other studies

8.1.4.1. Clinical pharmacology studies

8.1.4.1.1. Study P03317

Study P03317, a phase I study, was evaluated as part of the application for the registration of the ezetimibe and rosuvastatin composite pack (Submission PM2012-03419-1-3). The primary objective was to evaluate the pharmacodynamic effects and safety of the co-administration of ezetimibe and rosuvastatin in healthy hyperchloesterolaemic subjects. Subjects were questioned/and or examined for evidence of adverse events throughout the study. Haematology, blood chemistry and urinalysis were assessed at screening, Day -1 and Day 15 (follow-up). In addition, a liver and skeletal muscle chemistry panel was undertaken prior to treatment administration on Days 3, 7, 10 and 14. Vital signs were measured on each of the treatment days, prior to treatment administration, and on Day 15. Physical examinations were performed at screening and on Day 15. ECGs were undertaken at screening only.

8.1.4.1.2. Study P417

Study P417 was a bioequivalence study comparing fixed dose combination ezetimibe 10 mg + rosuvastatin 40 mg and co-administration of the mono-components. Adverse events were monitored during the screening period, throughout the study and post-study, vital signs were measured pre-dose and at 2, 8, 12 and 24 hours (± 30 minutes) post-dose in each period, hematology and creatine kinase were assessed at Day 0 of Period 1, ALT and AST were assessed on Day 4 of Period I and Day 1 of Period II (Day 11) and haematology, biochemistry and urine analysis were assessed on Day 4 of Period II (Day 15 of the study). Wellbeing was assessed at check-in, vital recording, check-out and at ambulatory blood sample collection.

8.1.4.1.3. Study P425

Study P425 was a bioequivalence study comparing fixed dose combination ezetimibe 10 mg + rosuvastatin 5 mg and co-administration of the mono-components. Adverse events were monitored during the screening period, throughout the study and post-study, vital signs were measured pre-dose and at 2, 8, 12 and 24 hours (± 30 minutes) post-dose in each period, hematology and creatine kinase were assessed at Day 0 of Period 1, ALT and AST were assessed on Day 4 of Period I and Day 1 of Period II (Day 11 of the study) and haematology , biochemistry and urine analysis were assessed on Day 4 of Period II (Day 15 of the study). Wellbeing was assessed at check-in, vital recording, check-out and at ambulatory blood sample collection.

8.2. Literature

A number of the studies described in the published articles identified in the literature review to support the application for the registration of the ezetimibe rosuvastatin composite pack (Submission PM2012-03419-1-3), and the updated literature search to support the current application for the fixed dose combination, provided safety data.

8.3. Pivotal studies that assessed safety as a primary outcome

There were no pivotal studies of ezetimibe administered in combination with rosuvastatin in which safety was assessed as the primary outcome.

8.4. Patient exposure

In this current submission, patient exposure to ezetimibe administered with rosuvastatin is based on Study P03317, Study P139V1 and literature publications including peer-reviewed publications, abstracts and trials registered on the website clinicaltrials.gov.

The sponsor indicates that 2,409 patients, overall, have been exposed to the combination of ezetimibe and rosuvastatin, based on studies/datasets in which the number of subjects exposed was clearly identifiable. The range of exposure is reported to be 2 to 73 weeks and the median duration of exposure is reported to be 8 to 10 weeks. Overall, regardless of the indication for treatment, 194 patients were exposed for 52 weeks or more. In combination with ezetimibe 10 mg, the doses of rosuvastatin were reported to have ranged between 2.5 mg and 40 mg with one patient taking 60 mg. The dose of ezetimibe administered was reported to have almost always been 10 mg. One literature publication, identified for Submission PM2012-03419-1-3, reported administration of a fixed dose ezetimibe 10 mg and rosuvastatin 10 mg tablet Sharma et al (64). The formulation of the fixed dose ezetimibe and rosuvastatin tablet used is unknown. Over one third of the patients were reported to have received, in combination with ezetimibe, a dose of rosuvastatin that was either not specified or titrated during the study.

Overall, the majority of subjects exposed were adults. The ages ranged from children up to 89 years. Both males and females were exposed. The published literature from which exposure was derived included studies of different designs including both interventional and observational studies. In the published literature identified by the sponsor, subjects generally had hypercholesterolaemia, a proportion of whom also had cardiovascular disease. The specific type of hypercholesterolaemia was heterozygous familial hypercholesterolaemia and homozygous familial hypercholesterolaemia in some of the studies. Two studies were in HIV-positive patients with dislipidemia.

Of the 194 patients exposed to the combination for 52 weeks or more, the majority (65%; n=126) were exposed to ezetimibe in combination with rosuvastatin 10 mg and for 67 of the remaining 68 patients the dose of rosuvastatin was not specified.

The information in the following table is the sponsor's summary of the overall extent of exposure from all studies with clearly distinguishable co-administration of ezetimibe and rosuvastatin.

Table 7: Summary of overall extent of exposure from all studies with clearly distinguishable co-administration of ezetimibe and rosuvastatin

Duration weeks	Eze + Rosuva 2.5	Eze + Rosuva 5	Eze + Rosuva 10	Eze + Rosuva 20	Eze + Rosuva 40	Eze + Rosuva dose not specified	Total Eze + Rosuva	Percentage
2			12				12	0.5%
4						37	37	1.5%
6		99	373	204	255	268	1199	49.8%
8 to 10			21			306	327	13.6%
12 to 24	152	54	24	1	145	235	611	25.4%
26	17					12	29	1.2%
52 or more	1		126			67	194	8.1%
	170	153	556	205	400	925	2409	
Percentage	7.1%	6.4%	23.1%	8.5%	16.6%	38.4%		

Copied from Submission PM-2013-02434-1-3. Module 2. 2.5 Clinical Overview Update.

In six publications that were identified in the updated search, the number of patients exposed to ezetimibe administered with rosuvastatin could be estimated by the sponsor resulting in

estimated numbers of patients exposed for certain durations that are higher than those in the above table. Based on the sponsor's estimation, approximately 267 patients were exposed to at least 52 weeks of ezetimibe with rosuvastatin.

Comment: The application to register the Rosuzet/Ezalo composite pack was approved by the TGA for indications identical to those proposed in the current application, based on a smaller number of patients with clearly distinguishable exposure to the combination for 52 weeks or more.

In this submission, in which a greater total number of patients have been exposed to the co-administration of ezetimibe and rosuvastatin, 194 patients overall were exposed to ezetimibe administered with rosuvastatin for 52 weeks or more. This is acceptable based on the guidelines 3CCC6a "Clinical Investigation of Medicinal Products for Long-term Use" (65). A breakdown of exposure by duration and dose in patients with primary hypercholesterolaemia and homozygous familial hypercholesterolaemia, respectively, is not provided. Exposure to the "add on" and replacement components, respectively, for the primary hypercholesterolaemia indication are not specified. Nonetheless, use of ezetimibe and rosuvastatin concomitantly in the treatment of primary hypercholesterolaemia for both the "add on" and replacement components of the indication are already approved as is the use of ezetimibe and rosuvastatin concomitantly in the treatment of homozygous familial hypercholesterolaemia. Therefore, extent of exposure in the proposed indications is considered acceptable. It is noted that the sponsor provided a detailed reckoning and breakdown of the numbers of subjects exposed to add on therapy in each indication in the Pre-ACPM response for Submission PM-2012-03419-1-3.

With regard to the proposed doses, for only the ezetimibe 10 mg/rosuvastatin 10 mg dose has there been exposure of more than 100 patients for 52 or more weeks. Serious adverse events that occur at low frequencies may not have been identified based on the exposure to date. Statements have been included in the Australian PIs for Rosuzet composite pack (5) and Ezalo composite pack (6) regarding the limited clinical data on the long term effects of co-administering ezetimibe and rosuvastatin. It is recommended that the same information is included in the draft PIs.

8.5. Adverse events

8.5.1. All adverse events (irrespective of relationship to study treatment)

8.5.1.1. Pivotal studies

8.5.1.1.1. Study P139V1

The following is an extract from the Clinical Evaluation Report for the Rosuzet/Ezalo Composite Pack (Submission PM2012-03419-1-3) (18):

"Overall the safety profile between the groups was comparable i.e. between rosuvastatin 5 or 10mg + ezetimibe and rosuvastatin 10 or 20mg. Specifically there was no differences between these groups in gastrointestinal-related, allergic reactions or rashes, and hepatic–related clinical adverse reactions, percentages of patients with ALT ≥ 3xULN and CPK ≥ 10x ULN. There were no ALT ≥ 3xULN and CPK ≥ 10x ULN associated with muscle symptoms and gallbladder related events."

Comment: Safety related data from this study is included in the ADVERSE EFFECTS section of the Australian PIs for the Rosuzet composite pack (5) and Ezalo composite pack (6). It is recommended that this information is included in the draft PIs for the fixed dose combination tablets.

8.5.1.2. Other studies

8.5.1.2.1. Study P03317

The following is an extract from the Clinical Evaluation Report for the Rosuzet/Ezalo Composite Pack (Submission PM2012-03419-1-3) (18):

> "The occurrence of AEs was similar across the 4 treatment groups. There were reports of myalgia but classified as not likely to be related to treatment and were not associated with increased CPK concentrations. One patient in the combination rosuvastatin 10mg/ezetimibe 10mg group had an ALT concentration of 81 at study end. On closer examination it can be seen that the ALT increased every week during the study, and resolved on ceasing the drug at the completion of the study,"

8.5.1.2.2. Study P417

Seven subjects experienced 16 treatment-emergent adverse events (TEAEs). The TEAEs were mild to moderate intensity.

Thirteen of the sixteen TEAEs were considered to have emerged from a single treatment.

Five subjects had alanine aminotransferase increased and aspartate aminotransferase increased, three following treatment with the fixed dose combination tablets and two following the co-administration of single doses of Ezetrol 10 mg and Crestor 40 mg. The remaining two subjects were reported with vomiting, and toothache and pyrexia, respectively.

The remaining three AEs were considered to have emerged from both formulations. The three AEs considered to have emerged from both formulations were reported in one subject. The AEs were musculoskeletal pain, aspartate aminotransferase increased and blood creatine phosphokinase increased.

8.5.1.2.3. Study P425

The proportions of subjects with at least one treatment-emergent adverse event (TEAE) were low following administration of both the test and reference products (test 5.1% (n=3); reference 3.5% (n=2)). Nine adverse events were reported or observed for seven subjects during the study. Six of the adverse events were considered to have emerged from single treatments, two from both formulations and one was not considered to have emerged from any of the treatments.

All adverse events were mild to moderate intensity.

Two subjects had laboratory abnormalities reported as adverse events described in Section 8.6. The only other TEAE following the reference treatment, co-administration of single doses of Crestor 5 mg and Ezetrol 10 mg, was diarrhoea (n=2). Other TEAEs following the test treatment, rosuvastatin calcium + ezetimibe 5 mg/10 mg fixed dose combination tablet, were headache (n=1) and hordeolum (n=1).

8.5.1.3. Literature

The sponsor reports that 27 studies of ezetimibe and rosuvastatin co-administration were identified in the original literature review and 20 studies in the updated review reported safety data.

> **Comment**: Safety data were not reported in all of the new publications identified for this submission. An extract from the Clinical Evaluation Report for the Rosuzet/Ezalo Composite Pack (Submission PM2012-03419-1-3) (18) in relation to adverse effects reported in the published literature identified in the original literature review is shown in Section 8.6. These adverse effects relate mainly to laboratory parameters.

Of the new literature identified in the updated literature search, the following safety data were reported in subjects/patients receiving ezetimibe concomitantly with rosuvastatin or another statin.

8.5.1.3.1. Randomised controlled studies

· **Okada 2012 (47)**

This article described a randomised trial with an observation period of 52 weeks. The objective of this study was to assess the mechanism of long-term LDL-C lowering effect of ezetimibe plus a statin. Subjects (n=200) had coronary artery disease and LDL-C levels of ≥ 70 mg/dL after treatment with atorvastatin 10 mg/day or rosuvastatin 2.5 mg/day. Subjects were randomised to received ezetimibe 10 mg/day plus a statin (n=100) or a double dose of statin (atorvastatin 20 mg /day or rosuvastatin 5.0 mg/day) (n=100). Fifty subjects withdrew from the study (ezetimibe+ statin group: patient request n=19, adverse effect n=3; double-dose statin group: patient request n=25; adverse effect n=3).

Comment: The results did not differentiate between the two statins, atorvastatin and rosuvastatin.

No information on adverse effects reported during this study was included in the article.

· **Yamazaki 2013 (34)**

This article described an exploratory, multi-centre, prospective, open-label, randomised, parallel group pilot study undertaken in Japan. Subjects (n=46) had high-risk coronary artery disease (CAD) and LDL-C and hs-CRP levels of >70 mg/dL and >1.0 mg/L, respectively, that were not improved by 4 weeks of rosuvastatin treatment (2.5 mg/day). Subjects were males and females with a median age of 73 years (range 42-84 years) who had undergone percutaneous coronary intervention for CAD. Subjects were randomly assigned to receive 10 mg of rosuvastatin (R10, n = 24) or 2.5 mg/day of rosuvastatin combined with 10 mg/day of ezetimibe (R2.5/E10, n = 22) for 12 weeks. Four subjects in the R10 group withdrew from the study (withdrew consent (n=1), stroke (n=1), interstitial pneumonia (n=1), eruption (n=1)). In the R2.5/E10 group, two subjects withdrew (withdrew consent (n=1), eruption (n=1)).

Comment: Other than the reasons for study discontinuation, no information on adverse effects reported during this study was included in the article.

· **Johns 2012 (35)**

Two HIV-positive patients receiving rosuvastatin 20 mg experienced mild myalgias during the 12 week study. These adverse events did not lead to study discontinuation. There were no adverse events reported in the rosuvastatin 10 mg + ezetimibe 10 mg treatment group.

· **Giugliano 2012 (49)**

This article described a phase 2, multi-centre dose- ranging study that assessed the efficacy, safety and tolerability of AMG 145. Subjects had hypercholesterolaemia and were on a statin. Use of ezetimibe and/or a statin were permitted during this study. Of the patients in the placebo groups (n=155) (placebo every 2 weeks and placebo every 4 weeks), 46% were reported with adverse events including nasopharyngitis, cough and nausea. One subject in the group receiving placebo every two weeks had an AST or ALT greater than 3 times the ULN.

Comment: Some subjects in the placebo group may have been receiving ezetimibe plus rosuvastatin but this was not specified.

· **Raal 2012 (50)**

This article described a phase 2, multi-centre, double-blind, randomised, placebo-controlled, dose-ranging study that assessed the efficacy and safety of AMG 145. Use of ezetimibe and/or a statin were permitted during this study. There were no serious adverse events in the placebo

group and no increases in transaminases more than 3 times the ULN at any post-baseline visit or creatine kinase levels more than 5 times the ULN at any post-baseline visit.

> **Comment**: Some subjects in the placebo group who had adverse events may have been receiving ezetimibe plus rosuvastatin but this was not specified.

· **Stein 2012 (51)**

This article described a phase 2, multi-centre, randomised, placebo-controlled study assessing the efficacy and safety of various doses and dosing intervals of a monoclonal antibody to PCSK9 (REGN727), added to statins to further lower LDL-C in patients with heterozygous familial hypercholesterolaemia. Subjects were randomised to one of four different doses and dosing intervals of REGN727 or placebo. In the placebo group (n=15), all subjects were on a statin and 73% were also on ezetimibe. One serious adverse event was reported in the placebo group (gastrointestinal disorder).

> **Comment**: It is not indicated in the article which patients in the placebo group were receiving both ezetimibe and rosuvastatin.

· **Sullivan 2012 (52)**

The objective of the study described in this article was to assess the efficacy and tolerability of AMG 145 in patients with statin intolerance due to muscle-related side effects. All patients had intolerance to one or more statins because of muscle related events. The study was a randomised, double-blind, placebo and ezetimibe controlled dose ranging study of 12 weeks duration. Patients were randomized to one of five treatment groups: AMG145 alone at doses of 280 mg, 350 mg, or 420 mg; AMG145 at 420 mg plus 10 mg of ezetimibe; or 10 mg of ezetimibe plus placebo. AMG145 or placebo was administered subcutaneously every 4 weeks. Ezetimibe was administered once daily and was not blinded. Patients could receive stable doses of statins less than or equal to a specified weekly maximum. Myalgia was reported in one subject (3.1%) receiving placebo/ezetimibe. The other most common treatment-emergent AEs reported by subjects in this treatment group were nasopharynitis (15.6%), nausea (3.1%) and fatigue (6.3%). One subject in this group had a CK level greater than 5 times the upper limit of normal at week 4.

> **Comment**: At baseline, 16% of patients used statins. It is not specified if any of the subjects receiving placebo and ezetimibe who had an adverse event were also on a statin.

8.5.1.3.2. Controlled trials without randomisation

· **Stein 2012 (66)**

This article described a retrospective, case-control study. The aim was to investigate the prevalence of cholelithiasis among patients treated with ezetimibe. Subjects were aged 20-85 years, had been treated with ezetimibe and statins (study group), or statins only (control group), for at least six months, and had had an abdominal ultrasound. Subjects were identified from the patient records of a health maintenance organisation is Israel from 2000 to 2009. Subjects in the study group were compared with a matched control group. The study was approved by the medical centre's ethics committee. The study group (n=25) and control group (n=168) had similar proportions of females and males, similar mean ages and age ranges and similar proportions of diabetic and hypothyroid subjects. The mean duration of ezetimibe treatment was 799 ± 379 days (range 183-1540 days). Seven subjects in the study group received ezetimibe and rosuvastatin. Cholelithiasis was reported in a comparable proportion of subjects in both groups (study group 16% (n=4); control group 20% (n=33)). In the study group, no subjects reported with cholelithiasis were reported to have received rosuvastatin and ezetimibe. Eleven subjects in the control group on rosuvastatin had cholelithiasis and one subject had gallstones.

8.5.1.3.3. Time series

· **Kawashiri 2012 (37)**

This article described a prospective, open study, in Japanese patients with heterozygous familial hypercholesterolaemia with single LDL receptor gene mutations. One subject discontinued the study while receiving ezetimibe 10 mg + rosuvastatin 20 mg/day due to myalgia without an increase in serum creatinine phosphokinase. The myalgia was reported to have disappeared after discontinuation of rosuvastatin and ezetimibe. There were no laboratory abnormalities found during the study.

· **Luknar 2012 (41)**

The safety of rosuvastatin and its influence on blood lipids was evaluated, in heart transplant recipients (n=16), in an open-label, non-controlled, study in a single study centre. All subjects were receiving a combined immunosuppressive regimen. One subject was receiving ezetimibe as well as fluvastatin. Fluvastatin was ceased and subjects received open-label rosuvastatin 10 mg/day. There were no serious adverse effects reported, no subjects were discontinued from treatment and there were no significant laboratory abnormalities. There were single reports of transient myalgia and an increase in transaminases less than 3 times ULN. An increased immunosuppressant level, described as not significant, was reported in three patients (cyclosporine (n=2), tacrolimus (n=1)). These levels required dose adjustment after the end of the study.

> **Comment**: It is not specified if the patient receiving both rosuvastatin and ezetimibe had one of the reported adverse effects. The Australian PIs for the Rosuzet composite pack (5) and Ezalo composite pack (6) include specific dosage recommendations for patients taking cyclosporin and there is information on the interactions between cyclosporin and ezetimibe and rosuvastatin, respectively, in the INTERACTIONS WITH OTHER MEDICINES sections of the PIs.

· **Cuchel 2013 (54)**

This article described a Phase 3, single-arm, open-label, multi-centre, study. The aim of the study was to assess the efficacy and safety of the lomitapide in adults with homozygous familial hypercholesterolaemia. Of 31 patients who entered the run-in period for the study, 29 were enrolled in the efficacy phase and 23 patients completed the 26 week efficacy phase and the 52 week safety phase. During the run in period, which was at least 6 weeks in duration, patients were initiated on concomitant lipid-lowering therapies and were stabilised on a low fat diet. Lomitapide was then initiated and dose titrated at intervals up to 60 mg day or until an individually determined maximum dose was achieved based on safety and tolerability. At baseline, twenty-two of the patients were being treated with statins, primarily rosuvastatin or atorvastatin, and ezetimibe. Most patients had at least one adverse event during each of the phases. No patient died during the study. Three patients discontinued the study due to gastrointestinal disorders and ceased lomitapide by Week 12. A fourth subject discontinued due to headache. Three subjects had serious adverse events assessed as unrelated, or unlikely related, to study treatment during the efficacy phase. Ten patients had ALT and/or AST level elevations more than 3 times ULN at least once during the study, four of whom had ALT increases more than 5 times the ULN and one patient had a similar elevation in AST. Of these four patients, three reported drinking quantities of alcohol that were higher than the protocol allowed. These transaminases elevations did not result in permanent treatment discontinuation. They were managed by a dose reduction or temporary interruption of the lomitapide. Elevations in bilirubin and alkaline phosphatise were not reported.

> **Comment**: For the patients who had adverse events, such as elevated levels of transaminases more than three times the ULN, it is not specified if they were on rosuvastatin and ezetimibe in addition to lomitapide.

· **Kolovou 2012 (12)**

The aim of this open, prospective, uncontrolled clinical study was to investigate changes in plasma lipids and lipoproteins and cardiovascular events after LDL apheresis in children and adults who had total cholesterol values resistant to hypolipidemic treatment. Patients (n=21) were treated with maximum doses of one of the statins plus ezetimibe and/or colesevelam and/or fenofibrate and with a low fat diet. LDL apheresis frequency was adjusted individually. Five patients had homozygous familial hypercholesterolemia, 10 patients had hypercholesterolemia (familial or non familial) and six patients had mixed dyslipidemia. Ninety percent of patients (n=19) were on statins at baseline and 48% (n=10) were receiving ezetimibe. Mean follow-up was for 47±23 months (range 9-81 months). Major adverse effects were allergic reactions and minor adverse effects were reported to include headache, dizziness and hypotensive periods. Re-challenge was negative.

> **Comment**: In relation to the adverse effects reported in the article, it is not indicated whether the patients affected were receiving rosuvastatin and ezetimibe.

· **Tamaki 2012 (53)**

This article describes a prospective study that was undertaken in Japan. The aim of the study was to examine the clinical effects of ezetimibe, including its effects on atherosclerotic markers. Subjects were outpatients with hypercholesterolemia who had not achieved serum LDL-C levels recommended in the Japan Atherosclerosis Society 2007 guidelines despite ezetimibe monotherapy with diet and exercise or ezetimibe in combination with statin therapy for at least 4 weeks. Patients were treated with 10 mg ezetimibe once a day for 12 weeks during which time other anti-hyperlipidemic, anti-hypertensive and anti-diabetic medications were continued without dosage modification. For 17 of the 112 patients in the study, treatment with ezetimibe combined with a statin was initiated. Of these 17 patients, 16 completed the 12 weeks of treatment, of whom rosuvastatin was administered prior to the administration of ezetimibe in 4 patients. Mean AST and ALT values were similar at baseline and 12 weeks in patients who received ezetimibe monotherapy (n=75) and those who received ezetimibe combined with statin therapy (n=16).

> **Comment**: No safety results were presented for ezetimibe in combination with rosuvastatin.

· **Tobaru 2013 (55)**

In this exploratory, prospective, uncontrolled study, subjects were patients with hypercholesterolemia and who had coronary artery disease who had not achieved the Japan Atherosclerosis Society 2007 guidelines target cholesterol level (LDL-C <100 mg/dL) despite at least 4 weeks of treatment with statin monotherapy. Subjects received 12 weeks treatment with ezetimibe 10 mg daily concomitantly with the statin that they had been receiving prior to the study. Subjects also received guidance regarding diet and exercise. It is reported that no problematic adverse events occurred during the period that ezetimibe was being administered. The mean creatinine phosphokinase values were higher at Week 4 (125.5±89.0 IU/L) and Week 12 (124.8±71.0 IU/L) compared with baseline (88.2±30.8 IU/L). Mean AST and ALT values were similar at Week 4 and Week 12 compared with baseline.

> **Comment**: The safety results presented were not specific to ezetimibe in combination with rosuvastatin.

8.5.1.3.4. Observational studies

· **Cziraky 2013 (67)**

This article described an observational retrospective cohort study. The objective of the study was to determine the risk of rhabdomyolysis requiring hospitalisation associated with lipid-lowering drugs. Claims data from the members of five health plans in the USA were used to

identify patients aged 18 years or older and who had received more than two statin and non-statin lipid lowering drugs during the period July 2000 to December 2004. Patients were included in the study if their first dispensed lipid-lowering drug (LLD) prescription was preceded by a six month period in which there were no dispensed LLD prescriptions. The medical records of all potential claims-based cases of hospitalised rhabdomyolysis were abstracted by two physicians, blinded to the LLD exposure status of the patient using a chart abstraction form. The medical chart abstraction phase of the study was approved by an independent Institutional Review Board. Cases of rhabdomyolysis were those that the attending physician had diagnosed at the time of hospitalisation or patients who had muscle injury at the time of hospitalisation, a creatine kinase level during hospitalisation 10 times the upper limit with signs of muscle weakness. Inception cohorts were identified for statin monotherapy and non-statin monotherapy and for combinations of non-statins with statins. Within the LLD inception cohorts, a nested case-control analysis was undertaken to estimate the risk of hospitalised rhabdomyolyis associated with the use of different LLDs. Cases had a confirmed diagnosis of rhabdomyolysis on medical record. Controls were patients receiving LLDs who did not have a diagnosis of rhabdomyolysis and who may or may not have been hospitalised. Cases and controls were matched for age, gender, region, length of follow-up and time of their first dispensed LLD prescription. There were 12 controls for each case. The rosuvastatin cohort consisted of 18,584 patients and there was one confirmed case of hospitalised rhabdomyolysis (rate (95%CI) 1.2 per 100,000 person-years (0.0-6.7). For the ezetimibe cohort (n=9,192), there were two confirmed cases of hospitalised rhabdomyolysis (rate (95%CI) 2.1 per 100,000 person-years (0.3-7.8). Compared with the reference atorvastatin monotherapy, patients receiving rosuvastatin monotherapy and ezetimibe monotherapy had an increased risk of hospitalised rhabdomyolysis (Rosuvastatin: Odds ratio 1.8 95%CI [0.3,9.4]; Ezetimibe: Odds ratio 3.9 95%CI [0.7, 22.5]).

> **Comment**: The rate of hospitalised rhabdomyolysis in patients who received ezetimibe concomitantly with rosuvastatin is not specified. Not all of the potential risk factors for rhabdomyolysis in a given patient may have been identified from the medical records. The dosage of rosuvastatin and ezetimibe monotherapies used by patients was not specified, although it is reported in the article that the average doses of statins were low.

- **Graesdal 2012 (13)**

This article describes a retrospective case review of seven patients in Norway receiving treatment for homozygous familial hypercholesterolemia. The aim of the study was to assess the seven patients treated with LDL apheresis with respect to their quality of life, clinical and laboratory assessments and cardiovascular status. For two subjects, their co-medication included rosuvastatin 40 mg daily and ezetimibe 10 mg daily. All the patents were also receiving weekly apheresis. Both subjects were reported with adverse events. One patient was reported to have had anaemia on apheresis and the second patient was reported to have had urticaria on atorvastatin treatment, hypotension on apheresis and technical difficulties with the fistula.

> **Comment**: The adverse events reported in these two subjects were not reported to have been related to ezetimibe or rosuvastatin.

- **Nenseter 2013 (14)**

This article is related to that by Graesdal et al (13).

> **Comment**: No safety data specific to the concomitant administration of ezetimibe with rosuvastatin are reported.

- **Yang 2012 (68)**

This was an abstract describing a retrospective review of cases of possible statin-related myopathy in one hospital. The objective of the study was to investigate the clinical

characteristics of patients with statin-related myopathy. Patients with a creatine phosphokinase level over 436 IU/L, and who had been prescribed any dose of statin over the period January 2004 to December 2008, were identified from laboratory and electronic case records. Rosuvastatin was prescribed in 12.3% (n=13) of patients.

> **Comment**: The abstract did not contain information required to assess possible causality such as symptom onset, rosuvastatin dose and concomitant medications in relation to the individuals who received rosuvastatin.

- **Lakey 2013 (69)**

This article describes case reports for three patients with familial hypercholesterolemia who had a clinical worsening of their Achilles tendon xanthomas after niacin, with or without a bile acid sequestrant, was added to their ongoing statin therapy. The three patients were among 236 patients with FH who attended a lipid clinic over a 19 year period. In total, 130 patients were started on niacin therapy. Of these three patients, one patient had adverse effects in their Achilles tendon xanthomas while receiving niacin and atorvastatin. The second patient had mild tenderness of the Achilles tendon while on rosuvastatin 20 mg and ezetimibe 10 mg. After ezetimibe was ceased and niacin and closevelam were added to rosuvastatin, the patient had Achilles tenderness and warmth and pain limited walking and exercise. The third patient was not on rosuvastatin or ezetimibe.

- **Lee 2013 (43)**

This article describes a case report of a 61 year old male with high density lipoprotein deficiency who had apolipoprotein A-I sequencing which revealed a novel mutation. He was on multiple concomitant medications including rosuvastatin 40 mg/day and ezetimibe 10 mg/day. Laboratory testing revealed normal values for a number of parameters including ALT, ALP, and bilirubin. AST was slightly increased.

- **Li 2012 (44)**

This article describes a case report. A 57 year old female with familial combined hyperlipidemia and a personal and family history suggestive of mitochondrial disease received concomitant treatment with 5 mg rosuvastatin once a week and 10 mg ezetimibe once daily. The patient had no adverse effects during six months of follow-up. The subject's younger sister, who also had familial combined hyperlipidemia and had been diagnosed with possible mitochondrial disease, received the same rosuvastatin and ezetimibe treatment regimen and had reported no muscle problems after four months of follow-up.

> **Comment**: There were no notable changes in the values, where reported, of ALT, AST and CK before and after four weeks of concomitant rosuvastatin and ezetimibe.

8.5.2. Treatment-related adverse events (adverse drug reactions)

8.5.2.1. Pivotal studies

8.5.2.1.1. Study P139V1

The following information is from the Australian PIs for Rosuzet composite pack and Ezalo composite pack (5, 6):

> "In a 6 week-active comparator study (P139V1), 440 subjects taking rosuvastatin (5 mg or 10 mg) were randomized to either rosuvastatin (10 mg or 20 mg) or ezetimibe 10 mg added to rosuvastatin (5 or 10 mg) therapy, equivalent to ROSUZET COMPOSITE PACK 10 mg + 5mg or 10mg + 10 mg. The co-administration was generally well tolerated (see table below).

Table 8: Drug related adverse events in any treatment group.

	Ezetimibe 10 mg + Rosuvastatin 5 or 10 mg (n = 221)	Rosuvastatin 10 mg or 20mg (n = 219)
Gastrointestinal disorders		
Abdominal distension	0.45%	0.0%
Abdominal pain	0.45%	0.0%
Constipation	0.90%	0.91%
Dry mouth	0.45%	0.0%
Nausea	0.45%	0.0%
General disorders and administration site conditions		
Asthenia	0.0%	0.46%
Fatigue	0.0%	0.46%
Musculoskeletal and connective tissue disorders		
Arthralgia	0.45%	0.0%
Myalgia	0.90%	0.46%
Skin and subcutaneous tissue disorders		
Allergic dermatitis	0.45%	0.0%
Eczema	0.45%	0.0%
Skin exfoliation	0.0%	0.46%

In this study, the incidence of clinically important elevations in serum transaminases (ALT ≥3 X ULN, consecutive) was 0.5% (n=1) for patients treated with ezetimibe + rosuvastatin and 0% for patients in the rosuvastatin only treatment group. No patients in either group had clinically significant elevations in AST. Clinically important elevations in creatine kinase (CK ≥10 X ULN) were seen in 0.5% (n=1) of patients in the rosuvastatin only treatment group and not seen in patients treated with ezetimibe + rosuvastatin."

8.5.2.2. Other studies

8.5.2.2.1. Study P03317

The following is an extract from the Clinical Evaluation Report for the Rosuzet/Ezalo Composite Pack (Submission PM2012-03419-1-3)(18):

"P03317 [The Frequency of treatment related treatment emergent AEs by body system is shown below (Table 9).]

Table 9: Frequency of treatment related treatment emergent AEs by body system

Number (%) of Subjects	Rosuva 10 mg + Eze 10 mg (n=12)	Rosuva 10 mg (n=12)	Eze 10 mg (n=8)	Placebo (n=8)
Subjects Reporting Any Adverse Event	8 (67)	5 (42)	4 (50)	1 (13)
Body As A Whole – General Disorders	5 (42)	0	2 (25)	1 (13)
Asthenia	1 (8)	0	1 (13)	0
Dizziness	0	0	1 (13)	0
Headache	3 (25)	0	1 (13)	1 (13)
Weakness	1 (8)	0	0	0
Centr And Periph Nerv Syst Disorders	0	0	1 (13)	0
Somnolence	0	0	1 (13)	0
Gastro-Intestinal System Disorders	5 (42)	3 (25)	2 (25)	1 (13)
Abdominal distension	1 (8)	0	0	0
Abdominal pain	2 (17)	1 (8)	1 (13)	0
Diarrhoea	1 (8)	0	0	0
Flatulence	2 (17)	2 (17)	0	0
Frequent bowel movement	0	1 (8)	0	0
Loose stool	0	1 (8)	0	0
Nausea	1 (8)	0	1 (13)	1 (13)
Musculo-Skeletal System Disorders	1 (8)	0	0	0
Myalgia	1 (8)	0	0	0
Psychiatric Disorders	0	1 (8)	0	0
Insomnia	0	1 (8)	0	0
Renal & Urinary System Disorders	0	0	1 (13)	0
Micturition frequency	0	0	1 (13)	0
Respiratory System Disorders	0	1 (8)	0	0
Rhinitis	0	1 (8)	0	0

Comment: Based on the above table, the numbers of subjects in each treatment groups experiencing a specific treatment-related TEAE were small. Due to the small numbers in each treatment group it would be difficult to pick up a safety signal with rosuvastatin + ezetimibe.

8.5.2.2.2. Study P417

Of the 16 total TEAEs, seven TEAEs were judged as possibly related to the test treatment (aspartate aminotransferase increased (n=3), alanine aminotransferase increased (n=3), vomiting (n=1)) and four to the reference treatment (aspartate aminotransferase increased (n=2), alanine aminotransferase increased (n=2)). One TEAE was possibly related to both treatments (aspartate aminotransferase increased). Four TEAEs were judged as unrelated to the treatment, two of which were TEAEs considered to be from both treatments (blood creatine phosphokinase increased (n=1), musculoskeletal pain (n=1)). Toothache (n=1) and pyrexia (n=1) following administration of the reference medicine, were also considered unrelated to the medicine.

8.5.2.2.3. Study P425

Nine adverse events were reported or observed for seven subjects during the study, of which three were assessed as possibly related to the test treatment (high ALT, high AST; headache) and two possibly related to the reference treatment (diarrhoea, (n=2)).

Further details regarding the high AST and high ALT reported as possibly related to the test product are described in Section 8.6.

8.5.2.3. Literature

Please refer to Section 8.5.1.3 regarding adverse effects reported in the literature.

8.5.3. Deaths and other serious adverse events

8.5.3.1. Pivotal studies

8.5.3.1.1. Study P139V1

The following is an extract from the Clinical Evaluation Report for the Rosuzet/Ezalo Composite Pack (Submission PM2012-03419-1-3)(18):

> "No deaths
>
> SAEs - 1 on rosuvastatin 10mg (tendon rupture), 1 on rosuvastatin 20mg (sick sinus syndrome). Neither SAEs were considered to be drug related."

8.5.3.2. Other studies

8.5.3.2.1. Study P03317

The following is an extract from the Clinical Evaluation Report for the Rosuzet/Ezalo Composite Pack (Submission PM2012-03419-1-3)(18):

> "No SAEs, death or withdrawal due to AE during the study."

8.5.3.2.2. Study P417

There were no deaths or serious adverse events.

8.5.3.2.3. Study P425

There were no deaths or serious adverse events.

8.5.3.3. Literature

Please refer to Section 8.5.1.3 regarding adverse effects reported in the literature identified in the updated search.

Overall, based on the published literature identified from the original literature review to support the application to register the Rosuzet/Ezalo composite pack and the updated literature review for this submission, there were 70 deaths reported of which three were identified from the updated literature review.

> **Comment**: The causes of death, as listed in an Appendix of the submission, were varied but were primarily related to the cardiovascular system. For some of the patients who died, the drug and dose could not be determined or the duration of exposure and/or other medications was not stated. Forty eight of the patients who died were identified in one study (70). Only one subject who died was reported to have received ezetimibe and rosuvastatin concomitantly. The patient had hypercholesterolaemia and a history of CHD/ clinical evidence of atherosclerosis or a CHD risk equivalent and was receiving ezetimibe and rosuvastatin 40 mg. The cause of death was acute myocardial infarction, not considered to be related to the concomitant ezetimibe and rosuvastatin treatment (71). For the other subjects who died the drug and dose were either not determined or were not ezetimibe plus rosuvastatin.

8.5.4. Discontinuation due to adverse events

8.5.4.1. Pivotal studies

8.5.4.1.1. Study P139V1

The following information is from the Australian PIs for Rosuzet composite pack and Ezalo composite pack (5, 6):

"Twelve patients discontinued the study early, 6 due to adverse experiences. Treatment groups were similar in the proportion of patients with clinical adverse experiences, serious adverse experiences, drug-related adverse experiences or adverse experiences leading to discontinuation."

"The study discontinuation rate due to adverse experiences was 2.3% (n = 5) for the ezetimibe 10 mg + rosuvastatin 5 or 10 mg treatment arm and 0.5% (n = 1) for the rosuvastatin 10 mg or 20mg arm."

8.5.4.2. Other studies

8.5.4.2.1. Study P03317

The following is an extract from the Clinical Evaluation Report for the Rosuzet/Ezalo Composite Pack (Submission PM2012-03419-1-3)(18):

"No treatment withdrawals"

8.5.4.2.2. Study P417

Three subjects were withdrawn from the study due to adverse events. One subject with adverse events "aspartate aminotransferase increased" and "alanine aminotransferase increased" was withdrawn from the study due to high AST and high ALT values following administration of the test product (rosuvastatin calcium + ezetimibe 40/10 mg fixed dose combination tablet). Another subject was withdrawn from the study due to vomiting possibly related to the test treatment. The third subject was withdrawn due to toothache and fever following administration of the reference treatment (co-administration of Crestor 40 mg and Ezetrol 10 mg).

8.5.4.2.3. Study P425

The proportions of subjects who had at least one TEAE leading to withdrawal were comparable following administration of the test and reference products (test 1.7% (n=1); reference 1.8% (n=1)). Adverse events leading to withdrawal were high AST and high ALT following the test product (rosuvastatin calcium + ezetimibe 5/10 mg fixed dose combination tablet) and diarrhoea following administration of the reference product (co-administration of Crestor 5 mg and Ezetrol 10 mg).

8.5.4.3. Literature

Comment: Please see Section 8.5.1.3.

Discontinuations in the EXPLORER study (26-30) and GRAVITY study (31-33) are reported in the PIs for Rosuzet Composite Pack and Ezalo Composite Pack. In the EXPLORER study, 2.5% of patients in the combination therapy group and 1.3% in the monotherapy group discontinued as a result of any adverse event (5, 6). In the GRAVITY study, 81 of 833 patients did not complete the study and 31 withdrawals were due to adverse events (5, 6).

8.6. Laboratory tests

8.6.1. Study P139V1

Described in 8.5.1.1.

8.6.2. Study P03317

The following is an extract from the Clinical Evaluation Report for the Rosuzet/Ezalo Composite Pack (Submission PM2012-03419-1-3) (18):

"One patient in the combination rosuvastatin 10mg/ezetimibe 10mg group had an ALT concentration of 81 at study end. On closer examination it can be seen that the ALT

increased every week during the study, and resolved on ceasing the drug at the completion of the study,

There were no other clinically significant abnormalities detected in laboratory measurements although there were values outside the reference range. There were no abnormalities in in urinanalysis

No abnormalities in vital signs, physical examination and ECG findings were noted during the study (ECG done at screening only)"

8.6.3. Study P417

The proportions of subjects reported with the adverse events aspartate aminotransferase increased and alanine aminotransferase increased were slightly higher following the administration of the test medicine compared with the reference medicine but the absolute numbers were small (AST: test 5.0% (n=3); reference 3.5% (n=2); ALT: test 5.0% (n=3); reference 3.5% (n=2)).

A Subject had AST and ALT values more than three times the upper limit of normal at period 1 check out, 48 hours following the test treatment (AST 133.19 U/L) (normal range 9.00-37.00 U/L); ALT 153.05 U/L (normal range 9.00-43.00 U/L). The AST and ALT were still elevated at period II checkout following the reference treatment (AST 94.24 U/L; ALT 104.14 U/L). ALT and AST were within normal range at screening for this subject. This subject was withdrawn from the study.

Of note, a subject had an AST value of 108.33 U/L and ALT value of 132.77U/L at period 1 check out following administration of the reference treatment and after administration of the test treatment the AST and ALT remained high (AST value of 85.41 U/L and ALT value of 114.11 U/L).

It is reported that all final laboratory test results were within normal limits or were judged, by the study physician or investigator, to be not clinically significant.

Vital sign measurements were within the clinically acceptable range for all subjects during the study.

8.6.4. Study P425

A Subject had an AST of 34.15 U/L (normal range 9.00-37.00 U/L) and an ALT of 57.39 U/L (normal range 9.00-43.00 U/L) at screening. The patient's total bilirubin level at screening (1.52 mg/dL) was also above the upper limit of normal (0.20-1.20 mg/dL). At period I check out (3 days after administration of the test product (FDC)), AST was 106.5 U/L (almost 3 XULN) and ALT 151.74 U/L (ALT >3 x ULN). At period II check out, after administration of the reference product, AST had fallen to 58.86 U/L and ALT was 108.92 U/L.

A Subject had a fall in haemoglobin from 11.3 gm/dL at screening to 8.8 gm/dL at period II check out (normal range 12.0-18.0 gm/dL). Haematocrit also fell to below the lower limit of normal during the study (screening 36.9 %, period II check out 30.1% (normal range 35.00-55.00%).

For the other subjects, the results of laboratory investigations were reported to be within normal limits or judged to be clinically insignificant by the study physician or investigator. Vital sign measurements were within the clinically acceptable range for all subjects during the study.

Comment: Increases in ALT and/or AST are listed as common drug-related adverse experiences when Ezetrol is co-administered with a statin in the draft PIs. As the subject had a raised ALT and bilirubin at screening there may have been confounding factors influencing the ALT and AST results recorded following the fixed dose combination tablets and the co-administration of the mono-components. Similarly, [one of the]

subjects may have had medical conditions or concomitant medications that led to the falls in haemoglobin and haematocrit.

8.6.5. Literature

Of the new literature identified in the updated literature search, safety data, including the results of laboratory tests, where reported, are described in Section 8.5.1.3.

With regard to the literature search undertaken to support the registration of the ezetimibe and rosuvastatin composite pack, the following information is extracted from the Clinical Evaluation Report for the Rosuzet/Ezalo Composite Pack (Submission PM2012-03419-1-3)(18). The references from the extract [shown in square brackets in this report] are those cited in the Clinical Evaluation Report for the Rosuzet/Ezalo Composite Pack and the reference list for that report can be found in Section 15.2.

> "EXPLORER study [8], elevated transaminases up to 3 x ULN were reported but did not lead to discontinuation.
>
> Sharma 2008 [32] reported no abnormalities in ECG, clinical lab tests or vitals
>
> Yamagishi 2010 [28] reported no differences in biochemical data in combination (2.5mg/10mg) vs. rosuvastatin (5mg) alone
>
> Kouvelos 2013 [9] – reports of elevated CK and ALT in both groups (10mg/10mg) and rosuvastatin 10mg alone.
>
> Steg 2008 [44] did not differentiate the statins but CPK elevations 5 x ULN were seen in two patients after the addition of ezetimibe (0.1%). A patient (0.1%) developed ALT> 3 x ULN after commencing ezetimibe.
>
> Sawayama 2010 [10] 1 ezetimibe and 3 ezetimibe + rosuvastatin 2.5 had slight increase in ALT, 1 in each group had slight increase in ALT
>
> In the studies reported by Leibovitz 2006[15], Fras 2008 [20], Bennett 2007 [46], Gonzales 2007 [47], Igarashi 2010 [49], Ose 2005 [17], Stein 2005 [18] and 2007 [19], Pitsavos 2007 [51], no elevations in enzyme levels were reported.
>
> Sakurada 2008 [52]– one patient had elevated CPK but confounded by heavy labour before the study test. In a case report in HoFH from Martinez 2011 [69] the patients were treated with ezetimibe 10mg/rosuvastatin 20mg then ezetimibe 10mg/rosuvastatin 40mg – treatment was then suspended due to elevations in transaminases."

8.7. Post-marketing experience

The sponsor indicates that, from the PBS claims data for the period September 2007 to September 2011, there were approximately 21,000 patients in Australia on concomitant ezetimibe and rosuvastatin.

Safety data in relation to the concomitant use of ezetimibe and rosuvastatin, the mono-components of the proposed fixed dose combination tablet, are provided in Section 8. The sponsor has included the Periodic Safety Update Report (PSUR) Addendum Report for Ezetimibe, for the period 17 April 2012 to 16 April 2013, in this submission.

The international birth date for ezetimibe is 17 October 2002 (Germany). During this PSUR Addendum Report period, there were no regulatory or manufacturer actions that resulted in marketing authorisation withdrawal or suspension, failure to obtain marketing authorisation renewal, restriction on distribution, clinical trial suspension, dosage modification, change in target population or pharmaceutical changes for safety reasons.

Safety-related changes to the Company Core Data Sheet (CCDS) made during the PSUR Addendum Report period were in relation to paediatric use of ezetimibe. In particular, the age of use in such patients was changed from 10 years or older to six years or older and safety-related information from a clinical trial in patients aged 6 to 10 years was added to the CCDS.

The majority of serious, unlisted adverse events reported by health care providers (HCPs) were single cases. Of note, from the line listings, were the following serious unlisted events: febrile neutropaenia (n=1) neutropaenia (n=1), anaemia (n=1), hepatocellular injury (n=2), hepatic necrosis (n=1), mixed liver injury (n=1), drug-induced liver injury (n=1), hepatic failure (n=1), allergic alveolitis (n=1), pulmonary fibrosis (n=1), optic neuritis (n=1) and renal failure acute (n=3). For the hepatic events, causality was determined as related except for hepatic necrosis. For the reports of anaemia, febrile neutropaenia and neutropaenia causality was reported as unknown. Optic neuritis was reported as related. Of the three cases of renal failure acute, two were reported as causality unknown and one related. The cases of alveolitis allergic and pulmonary fibrosis were reported as related and the case of interstitial lung disease as not related.

Cumulatively, based on serious unlisted cases reported by HCPs, there have been 13 cases of drug-induced liver injury, 17 cases of hepatic failure and 2 cases of hepatitis fulminant.

In the listing of follow-up cases there appear to have been three reports of pancytopaenia, two appear to relate to the one case. There do not appear to be details regarding the time between administration of the ezetimibe and the onset of the pancytopaenia, or information regarding concomitant medications and medical conditions which may have been confounding factors. There have been seven reports of pancytopenia from HCPs, cumulatively.

Twenty-three serious events of rhabdomyolysis were reported by HCPs. The event rhabdomyolysis was reported to be unlisted for one of these cases and a listed adverse event for 22 of the cases. There have been 57 cases cumulatively. No information is provided for these cases in relation to muscle symptoms, creatine phosphokinase levels and confounding factors.

From reports in the literature related to ezetimibe, it is noted that there have been 3 cases of amyotrophic lateral sclerosis cumulatively, for two of which the causality was determined to be related and one unknown. There have been 12 cases reported cumulatively from all report types (spontaneous, literature, study).

Cumulatively, there have been single HCP-reported cases of optic neuritis and allergic alveolitis, four cases of pulmonary fibrosis, 7 cases of interstitial lung disease, and 78 cases of renal failure acute.

There have been 7 reports of leucocytoclastic vasculitis and 7 cases of Stevens Johnson syndrome cumulatively but no reports of either in this PSUR Addendum Report period. There has been one HCP report of electrocardiogram QT prolonged cumulatively.

> **Comment**: There does not appear to be information in the PSUR Addendum Report regarding the use of ezetimibe with statins except in the section entitled "PSUR reference and articles for published case histories". Three cases were referred to in the same article (72). This article described a randomised study. The aim of the study was to examine, in patients with remnant lipoproteinemia on previous statin treatment, if ezetimibe added to ongoing statin therapy resulted in a greater improvement in lipid profiles and endothelial function than doubling the statin dose. Study subjects (n=63) were patients who had stable coronary artery disease, were on statin treatment and had high levels of remnant-like lipoprotein particle cholesterol. Subjects were randomised to ezetimibe 10 mg/day plus their prescribed statin and dose (n=32) or doubling of their ongoing statin dose (n=31). Rosuvastatin dose was doubled in nine subjects and ezetimibe was added to rosuvastatin for 7 subjects. During the study, three subjects in the statin + ezetimibe group and three subjects from the statin double dose group were

withdrawn due to adverse effects. For the three withdrawn subjects in the statin + ezetimibe group, it was not indicated which statin the subject was receiving.

The adverse effects in the Australian PI for Ezetrol (ezetimibe) (1) and CCDS are generally consistent. It is noted that the adverse effects reported in the CCDS are based on a larger number of subjects than the adverse effects in the PI. The Australian PI for Ezetrol (1) indicates that it is not recommended for use in children below the age of 10 years, which is more conservative than the CCDS, revised on 17 September 2012, which indicates that use in children aged less than 6 years is not recommended.

Based on the PSUR Addendum Report, no changes to the PI appear to be required at this point in time. With regard to the noted adverse effects, there was limited information in the line listing to assess the relationship between the adverse drug reactions reported and the administration of ezetimibe. Not all cases listed specify the dose of the product administered, the dates of treatment, or the event onset/time to onset. Concomitant medications and medical history are not listed but are required to assess a causal relationship between ezetimibe and the adverse effect. Most ADRs reported during the PSUR period were single cases except for liver ADRs, which were notable in their number and described a spectrum of liver injury. It is noted that the sponsor indicated, in the pre-ACPM response for PM-2012-03419-1-3, that it proposes to include hepatic failure as an important potential risk in the ezetimibe/rosuvastatin RMP (rather than an important identified risk as recommended by the TGA). The RMP version 1.2 does not include hepatic failure as a specific identified or potential risk in the summary of ongoing safety concerns.

Rhabdomyolysis and hypersensitivity reactions are included in the Australian PI for Ezetrol (1) as adverse reactions reported in post-marketing experience. Stevens Johnson Syndrome and leucocytoclastic vasculitis are not included as specific examples of hypersensitivity reactions. The sponsor is requested to provide details on the reported cases of Stevens Johnson Syndrome and leucocytoclastic vasculitis and comment on whether the cases are considered related to treatment with ezetimibe.

The prevalence of amyotrophic lateral sclerosis is reported to be 3-5 per 100,000 (73). The aetiology of amyotrophic lateral sclerosis appears to be multifactorial and not clearly understood (73). Although the exposure is not presented in the PSUR Addendum Report, it would be anticipated to be similar or greater to that reported in the Clinical Evaluation Report for the Rosuzet/Ezalo Composite Pack (Submission PM2012-03419-1-3)(18). During the six month period covered by the PSUR submitted with that application, April 2011 to October 2011, exposure was approximately 1,703, 146 patient-years of treatment (18). The number of reports of this condition from HCPs, cumulatively, is, therefore, small in comparison to the estimated cumulative exposure to ezetimibe.

Pancytopenia and QT prolongation are not included as an adverse effect in the PI for Ezetrol (1). The sponsor is requested to provide details on the cases of pancytopenia and QT prolongation reported cumulatively and comment on whether the cases are considered related to treatment with ezetimibe.

8.8. Safety issues with the potential for major regulatory impact

No new safety issues with the potential for major regulatory impact have been identified in this submission. The safety issues associated with the use of ezetimibe, rosuvastatin, and both ezetimibe and rosuvastatin concomitantly are described, respectively, in the Australian product information documents for Ezetrol, MSD Rosuvastatin, Rosuzet Composite pack and Ezalo composite pack (1, 3, 5, 6).

Based on the 90% confidence intervals of the geometric mean ratios of the test and reference products for AUC0-t and Cmax for rosuvastatin in Study P417, the AUC 0-t of rosuvastatin could be as much as 5% higher and the Cmax as much as 8% higher following administration of the 10mg/40 mg fixed dose combination compared with co-administration of the mono-components. This could potentially be an issue if the patient has other risk factors that increase exposure. The issue of increased rosuvastatin exposure was identified in relation to the composite pack and safety-related information was included in the product information for that product.

8.9. Evaluator's overall conclusions on clinical safety

The safety of the proposed fixed dose combination tablet is acceptable. The safety issues are anticipated to be the same as those for the ezetimibe and rosuvastatin composite pack. The dose strengths proposed for the fixed dose combination tablets are the same as the dose strengths for the composite packs, 10 mg ezetimibe plus 5 mg, 10 mg, 20 mg and 40 mg rosuvastatin. The ezetimibe and rosuvastatin composite pack has been approved by the TGA based on a subset of the information provided by the sponsor to support the current application. The adverse effects reported in the new safety data included in this submission are generally consistent with the known safety profiles for the co-administration of ezetimibe and rosuvastatin or the mono-components.

No pivotal studies that assessed the safety of an ezetimibe and rosuvastatin fixed dose combination tablet as a primary outcome are included in the application. The bioequivalence study for the 10mg/40 mg dose indicates that exposure to rosuvastatin could be higher with the fixed dose combination compared with the mono-therapies. Although the possible increase in exposure is anticipated to be small, as the maximum recommended dose of rosuvastatin is 40 mg, an increase in exposure with this proposed dose strength may increase the risk of adverse events.

It is recommended that the safety-related information in the product information for the fixed dose combination tablet is identical to that in the product information for the composite pack. The PIs for Rosuzet composite pack and Ezalo composite pack include specific precautionary statements in relation to liver enzymes, skeletal muscle, and treatment using ezetimibe 10 mg in combination with the highest dose of rosuvastatin, 40 mg. The safety issues with the potential for major regulatory impact to which these precautionary statements pertain are also safety issues for the fixed dose combination tablet.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of ezetimibe and rosuvastatin fixed dose combination tablet in the proposed usage are:

- It is more convenient for the patient to take one tablet rather than separate tablets for ezetimibe and rosuvastatin, which may improve patient compliance with lipid-lowering treatment.
- The proposed fixed dose combination tablet provides an additional dose form for the administration of ezetimibe and rosuvastatin.

9.2. First round assessment of risks

The risks of ezetimibe and rosuvastatin fixed dose combination tablet in the proposed usage are:

- If an adverse effect occurs with the fixed dose combination tablet that necessitates the cessation of treatment, the patient is required to discontinue ezetimibe and rosuvastatin simultaneously, regardless of whether only one component is the suspected cause of the adverse effect.
- Long-term efficacy and safety data in relation to the co-administration of ezetimibe and rosuvastatin in the proposed usage are limited.
- The bioequivalence study for the 10mg/40 mg dose indicates that exposure to rosuvastatin could be higher with the fixed dose combination compared with co-administration of the mono-components. Although the possible increase in exposure is anticipated to be small, as the maximum recommended dose of rosuvastatin is 40 mg, an increase in exposure with this proposed dose strength may increase the risk of adverse events, especially in patients with other risk factors that increase rosuvastatin exposure.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of the ezetimibe and rosuvastatin fixed dose combination tablet, given the proposed usage, is favourable.

10. First round recommendation regarding authorisation

It is recommended that the proposed ezetimibe and rosuvastatin fixed dose combination tablet, in the strengths 10 mg/5 mg, 10 mg/10 mg, 10 mg/20 mg and 10 mg/40 mg, is approved subject to the following:

- the sponsor amending the draft PIs as recommended[2] or providing justification as to why the recommended changes should not be made
- the sponsor providing satisfactory answers to the questions below.

11. Clinical questions

11.1. Pharmacokinetics

No questions.

11.2. Pharmacodynamics

No questions.

11.3. Efficacy

No questions.

[2] The section discussing PI and other product literature is not included in this extract from the CER.

11.4. Safety

1. Please provide details on the cases of Stevens Johnson Syndrome and leucocytoclastic vasculitis reported cumulatively by healthcare providers in the PSUR Addendum Report for Ezetimibe (17 April 2012 to 16 April 2013) and provide comment on whether they are considered related to treatment with ezetimibe.
2. Please provide details on the seven cases of pancytopenia reported by healthcare providers cumulatively in the PSUR Addendum Report for Ezetimibe (17 April 2012 to 16 April 2013) and provide comment on whether they are considered related to treatment with ezetimibe.
3. Please provide details on the single healthcare provider case report of "electrocardiogram QT prolonged" in the PSUR Addendum Report for Ezetimibe (17 April 2012 to 16 April 2013) and provide comment on whether they are considered related to treatment with ezetimibe.
4. Please clarify if hepatic failure, as a specific term, will be added to the RMP as an ongoing safety concern.

12. Second round evaluation of clinical data submitted in response to questions

12.1. Evaluation of clinical data submitted in response to questions

12.1.1. Safety question 1

Sponsor's response: The sponsor indicates that a new cumulative search of their Adverse Reporting and Review System (MARRS) Database up to 16 April 2013 was undertaken for reports of ezetimibe use and Stevens Johnson Syndrome and leucocytoclastic vasculitis. Reports of seven cases of Stevens Johnson Syndrome and seven cases of leucocytoclastic vasculitis were identified from the search, all of which were spontaneous post-marketing reports from healthcare providers.

Of the seven reports of Stevens Johnson Syndrome cumulatively, the sponsor reports that there was insufficient information to make a causality assessment for one of the cases, and the remaining six cases were confounded by concomitant medications that may be associated with Stevens Johnson Syndrome. The sponsor indicates that these cases were also on additional concomitant therapies. The sponsor highlights that a case who was receiving concomitant azithromycin had a negative dechallenge to ezetimibe, which supported the reporter's opinion that the case's symptoms were not related to ezetimibe. In another case, it was considered unlikely that the Stevens Johnson Syndrome was from the ezetimibe due to the appearance of symptoms within 12 hours of the first ezetimibe dose and celecoxib was identified as a secondary suspect drug. A causal relationship between ezetimibe and Stevens Johnson Syndrome was reported unlikely for a third case who had a Drug-induced Lymphocyte Stimulation Test that was negative for ezetimibe but positive for another drug.

Of the seven reports of leucocytoclastic vasculitis cumulatively, the sponsor reports that there was insufficient information in the reports for five of the cases to make an assessment of causality. The other two cases were confounded by medications that can be associated with leucocytoclastic vasculitis.

> **Comment**: The sponsor's response is acceptable. No change to the Australian PI for Ezetrol is warranted based on the information in the sponsor's response regarding the cumulative cases of Stevens Johnson Syndrome and leucocytoclastic vasculitis.

12.1.2. Safety question 2

Sponsor's response: The sponsor reports that a cumulative search of the MARRS database up to 16 April 2013 for ezetimibe and pancytopenia identified seven reports of pancytopenia, all of which were spontaneous post-marketing reports from healthcare providers. The sponsor indicates that for five of the seven cases, there was insufficient information to make a causality assessment and the remaining two cases were confounded. The sponsor highlights that one of the cases had a number of other medical conditions and was receiving concomitant medications that may be associated with pancytopenia, aplastic anaemia or myelosuppression and the other case had temporary asymptomatic mild pancytopenia and was reported to be confounded by alcohol ingestion.

> **Comment**: The sponsor's response is acceptable. No change to the Australian PI for Ezetrol is warranted based on the information in the sponsor's response regarding the cumulative cases of pancytopenia.

12.1.3. Safety question 3

Sponsor's response: The sponsor reports that a cumulative search of the MARRS Database up to 16 April 2013 for reports of ezetimibe and "electrocardiogram QT prolonged" yielded two case reports from healthcare providers. The sponsor highlights that one of these cases, identified in a US Food and Drug Administration Adverse Event Reporting System line listing, was a patient with coronary artery disease and atrial fibrillation who was receiving concomitant dofetilide, reported to be the primary suspect drug, and escitalopram, a secondary suspect along with ezetimibe. The sponsor indicates that there was insufficient information in relation to the other case to make a causality assessment.

> **Comment**: The sponsor's response is acceptable. No change to the Australian PI for Ezetrol is warranted based on the information in the sponsor's response regarding the cumulative cases of "electrocardiogram QT prolonged".

12.1.4. Safety question 4

Sponsor's response: The sponsor confirms that hepatic failure has been added as a potential risk to the updated RMP (version 1.3). The sponsor indicates that the addition of hepatic failure as a potential risk was accepted by the Delegate during the evaluation of the submission for the Rosuzet/Ezalo composite pack (Submission PM-2012-03149-1-3). In their response to a question raised by the TGA Office of Product Review, the sponsor has included their rationale for including hepatic failure as a potential risk rather than an identified risk, which was also provided in their Pre-ACPM response for Submission PM-2012-03149-1-3.

> **Comment**: The sponsor's response is acceptable. The rationale for including hepatic failure as a potential risk rather than an identified risk in the RMP is noted.

12.2. Other issues pertinent to the submission

12.2.1. Rosuvastatin exposure in relation to the 10/40 mg strength fixed dose combination tablet

Since the Round 1 evaluation (above), the information in the Australian, European Union (EU), United States (of America) (US) and Canadian product information documents for Crestor in relation to the interaction of rosuvastatin with other medicines has been reviewed by the evaluator. The information in these product information documents resulted in the evaluator further considering the issue of rosuvastatin exposure and the co-administration of 10 mg ezetimibe and 40 mg rosuvastatin. The EU, US and Canadian product information documents for Crestor (77-79) include information relating to the co-administration of ezetimibe and rosuvastatin that is not in the Australian PI for Crestor (4).

The issue of patients potentially having a rosuvastatin exposure higher than that expected for the maximum recommended dose of 40 mg rosuvastatin, due to interacting medicines or other risk factors, was considered in the evaluation of the application to register the Rosuzet/Ezalo composite pack (Submission PM-2012-03419-1-3). In Study P03317, submitted for evaluation in Submission PM-2012-03419-1-3, there was an increase in the mean AUC and the mean Cmax for rosuvastatin when rosuvastatin was co-administered with ezetimibe compared to the administration of rosuvastatin alone (AUC 119% [90%CI 87%-162%]; Cmax 117% [90%CI 84%-163%]). It is assumed by the evaluator that the increase in rosuvastatin AUC when rosuvastatin 40 mg is co-administered with ezetimibe 10 mg is the same as that reported when rosuvastatin 10 mg was co-administered with ezetimibe 10 mg in Study P03317.

In relation to the evidence that ezetimibe co-administered with rosuvastatin increases rosuvastatin plasma levels, as well as concerns regarding the quality and extent of long term safety data particularly for the 10 mg ezetimibe + 40 mg rosuvastatin strength of the composite pack, the Delegate sought advice from ACPM as to whether there were sufficient concerns to recommend rejection of the ezetimibe 10 mg + rosuvastatin 40 mg strength of the composite pack, or whether other risk minimisation strategies such as appropriate contraindications and/or strengthened precautions in the PI, as well as amendments to the RMP, were possible alternative strategies. Based on the ratified minutes of Meeting 294 of ACPM, ACPM was of the view that the increased rosuvastatin levels when rosuvastatin was co-administered with ezetimibe were no different from other drug interactions and should be managed accordingly. ACPM recommended that the PI and RMP should be strengthened, especially for the highest dose. The post-marketing data were considered sufficient to suggest that the highest dose strength, 10 mg ezetimibe + 40 mg rosuvastatin, is safe.

It is noted that the 10 mg ezetimibe + 40 mg rosuvastatin strength of the Rosuzet/Ezalo composite pack is registered on the ARTG and the following safety-related statements are included in the PI for the Ezalo composite pack (6):

> *CLINICAL TRIALS*
>
> *Long term studies*
>
> *There is limited clinical data on the long term effects of ezetimibe and rosuvastatin co-administration, especially at the 10 mg + 40 mg dose.*
>
> *PRECAUTIONS*
>
> *Treatment with the 10mg +40 mg Dose*
>
> *There is limited long term safety data of EZALO COMPOSITE PACK. Due to risk factors such as hepatic or renal impairment that may increase rosuvastatin exposure and the potential for increased adverse effects at the highest dose (10 mg + 40 mg) (e.g. muscle effects, renal impairment and elevated liver enzymes), monitoring of patients on the highest dose of EZALO COMPOSITE PACK is recommended.*

The PI for the Rosuzet composite pack (5) includes consistent statements.

The above-mentioned precaution highlights the potential for risk factors to increase rosuvastatin exposure and recommends monitoring for patients on the highest dose of the Rosuzet/Ezalo composite pack. However, it is noted that, due to the rosuvastatin component, Rosuzet/Ezalo composite pack 10 mg +40 mg is contraindicated in patients with pre-disposing factors for myopathy/rhabdomyolysis, including situations where an increase in rosuvastatin plasma levels may occur (5,6). This contraindication is consistent with the Australian PI for Crestor (4) and consistent statements are also proposed for the product information for the Rosuzet/Ezalo fixed dose combination tablet. Logically this contraindication would appear to preclude the co-administration of ezetimibe 10 mg with rosuvastatin 40 mg as there may be an increase in rosuvastatin AUC when rosuvastatin is co-administered with ezetimibe based on the results of Study P03317.

Such an interpretation of this contraindication appears to be supported by information in the current EU Summary of Product Characteristics for Crestor (77). It is indicated that changes to the EU Summary of Product Characteristics for Crestor, made on 1 May 2013, included clarification of the effect of co-administered medicinal products on rosuvastatin, explanations on the interactions requiring rosuvastatin dose adjustments, and the addition of information on concomitant therapy (80). In the *"Interactions with other medicinal products and other forms of interaction"* section of the current EU Summary of Product Characteristics for Crestor (77), it is recommended that the dose of Crestor should be adjusted when it is necessary to co-administer Crestor with other medicinal products known to increase rosuvastatin exposure. It is also recommended that the maximum daily dose of Crestor should be adjusted so that the expected exposure (AUC) to rosuvastatin would not likely exceed that of a 40 mg daily dose of Crestor taken without interacting medicinal products (77).

The effects of co-administered medicinal products, including ezetimibe, on rosuvastatin exposure (AUC) from published clinical trials are presented in a table in the Crestor SmPC (77), reproduced as Table 10 below.

Table 10: Effect of co-administered medicinal products on rosuvastatin exposure (AUC; in order of decreasing magnitude) from published clinical trials

Interacting drug dose regimen	Rosuvastatin dose regimen	Change in rosuvastatin AUC*
Ciclosporin 75 mg BID to 200 mg BID, 6 months	10 mg OD, 10 days	7.1-fold ↑
Atazanavir 300 mg/ritonavir 100 mg OD, 8 days	10 mg, single dose	3.1-fold ↑
Lopinavir 400 mg/ritonavir 100 mg BID, 17 days	20 mg OD, 7 days	2.1-fold ↑
Clopidogrel 300 mg loading, followed by 75 mg at 24 hours	20 mg, single dose	2-fold ↑
Gemfibrozil 600 mg BID, 7 days	80 mg, single dose	1.9-fold ↑
Eltrombopag 75 mg OD, 10 days	10 mg, single dose	1.6-fold ↑
Darunavir 600 mg/ritonavir 100 mg BID, 7 days	10 mg OD, 7 days	1.5-fold ↑
Tipranavir 500 mg/ritonavir 200 mg BID, 11 days	10 mg, single dose	1.4-fold ↑
Dronedarone 400 mg BID	Not available	1.4-fold ↑
Itraconazole 200 mg OD, 5 days	10 mg, single dose	**1.4-fold ↑
Ezetimibe 10 mg OD, 14 days	10 mg, OD, 14 days	**1.2-fold ↑
Fosamprenavir 700 mg/ritonavir 100 mg BID, 8 days	10 mg, single dose	↔
Aleglitazar 0.3 mg, 7 days	40 mg, 7 days	↔
Silymarin 140 mg TID, 5 days	10 mg, single dose	↔
Fenofibrate 67 mg TID, 7 days	10 mg, 7 days	↔
Rifampin 450 mg OD, 7 days	20 mg, single dose	↔
Ketoconazole 200 mg BID, 7 days	80 mg, single dose	↔
Fluconazole 200 mg OD, 11 days	80 mg, single dose	↔
Erythromycin 500 mg QID, 7 days	80 mg, single dose	28% ↓
Baicalin 50 mg TID, 14 days	20 mg, single dose	47% ↓

*Data given as x-fold change represent a simple ratio between co-administration and rosuvastatin alone. Data given as % change represent % difference relative to rosuvastatin alone.
Increase is indicated as "↑", no change as "↔", decrease as "↓".
**Several interaction studies have been performed at different Crestor dosages, the table shows the most significant ratio
OD = once daily; BID = twice daily; TID = three times daily; QID = four times daily

The table includes interactions resulting in specific fold increases and percentage decreases in rosuvastatin AUC as well as interactions resulting in no change in rosuvastatin AUC (77). It is recommended that treatment with Crestor is initiated with a 5 mg once daily dose if the

expected increase in AUC is approximately 2-fold or higher and that the adjusted maximum rosuvastatin doses when Crestor is co-administered with gemfibrozil (1.9-fold increase) and atazanavir/ritonavir (3.1-fold increase), respectively, are given as examples (77). For the other interacting medicinal products which result in a specified fold increase in rosuvastatin AUC, a recommended dose adjustment is not specified for rosuvastatin. It is not clear if the dose adjustment recommendations pertain only to those interactions that result in 2-fold and higher increases in rosuvastatin AUC or if the recommendations relate to all the interactions that are reported in the interactions table as resulting in a specified fold increase. However, it is interpreted by the evaluator that the dose adjustment recommendations pertain to all interactions resulting in a specified fold increase, which includes the co-administration of rosuvastatin with ezetimibe resulting in a 1.2 fold increase in rosuvastatin AUC. Therefore, this recommendation would also appear to preclude the co-administration of ezetimibe 10 mg with rosuvastatin 40 mg as it may result in a rosuvastatin AUC that exceeds that of a 40 mg daily dose of rosuvastatin taken without interacting medicinal products, based on the results of Study P03317.

The *"Posology and method of administration"* section of the EU Summary of Product Characteristics (77) does not specify a dose reduction for rosuvastatin when it is co-administered with ezetimibe. However, it includes recommendations that relate to concomitant administration of rosuvastatin with medicines that may increase the plasma rosuvastatin concentration due to interactions with transporter proteins such as OATP1B1 and BCRP (77). It is recommended that alternative medicines are considered, and that consideration should be given, if necessary, to temporarily discontinuing Crestor (77). If the co-administration is unavoidable, it is recommended that the benefit and risk of the concurrent treatment and dosing adjustments of Crestor should be carefully considered (77). It is not clear to the evaluator if ezetimibe is an inhibitor of any of the transporter proteins for which rosuvastatin is a substrate and, therefore, whether this recommendation is pertinent to the co-administration of rosuvastatin and ezetimibe. It is noted that the combination of tipranavir and ritonavir co-administered with rosuvastatin is given as an example. The increase in rosuvastatin AUC when rosuvastatin is co-administered with tipranavir and ritonavir is 1.4-fold. Therefore, even if this dosage recommendation does not relate specifically to co-administration of rosuvastatin and ezetimibe, it indicates that a less than 2-fold increase in rosuvastatin AUC requires consideration by the prescriber, regardless of the dose being administered.

Both the US and Canadian product information documents (78, 79) indicate that the 19% increase in rosuvastatin AUC resulting from the co-administration of ezetimibe and rosuvastatin is not considered clinically significant. In comparison, the current EU Summary of Product Characteristics for Crestor (77) indicates that a pharmacodynamic interaction, in terms of adverse effects, between Crestor and ezetimibe cannot be ruled out. The US prescribing information for Crestor (78) does not contraindicate use of the 40 mg dose in situations where an increase in rosuvastatin plasma levels may occur or include the recommendation that the maximum daily dose of Crestor should be adjusted so that the expected exposure (AUC) to rosuvastatin would not likely exceed that of a 40 mg daily dose of Crestor taken without interacting medicinal products. However, the Canadian product monograph for Crestor (79) includes both this contraindication and recommendation. The Canadian product monograph (80) also includes recommendations in the DOSAGE AND ADMINISTRATION section similar to those in the "Posology and method of administration" section of the EU Summary of Product Characteristics (77). From the information in the Canadian product monograph for Crestor (79), it could be interpreted that even though the 19% increase in rosuvastatin AUC is not considered clinically significant, the 40 mg dose should not be given with ezetimibe as the maximum recommended rosuvastatin exposure may be exceeded.

As the 1.2 fold increase in rosuvastatin AUC is based on a point estimate from subjects enrolled in one study, in an individual patient the effect of ezetimibe on rosuvastatin AUC may be higher or lower than the reported point estimate increase. In addition, the patient may have other risk

factors that augment or counterbalance any increase in rosuvastatin AUC that may result from the co-administration of ezetimibe and rosuvastatin. It is anticipated that a patient requiring the co-administration of ezetimibe 10 mg and rosuvastatin 40 mg would be receiving specialist supervision and the risks and benefits of such co-administration would be considered. However, in view of the contraindication to the use of 40 mg rosuvastatin in situations where an increase in rosuvastatin plasma levels may occur that is specified in the Australian PI for Crestor (4) and the above-mentioned interpretation of the information in the EU Summary of Product Characteristics for Crestor (77) and Canadian product monograph for Crestor (79), it is recommended that advice is again sought from ACPM on this issue.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the responses to the TGA clinical questions, the benefits of ezetimibe and rosuvastatin fixed dose combination tablet in the proposed usage are unchanged from those identified in Section 9.1.

13.2. Second round assessment of risks

After consideration of the responses to the TGA clinical questions, and review of the information in the Australian, EU, US and Canadian product information for Crestor regarding interaction with other medicinal products, the risks of ezetimibe and rosuvastatin fixed dose combination tablet in the proposed usage are as follows:

- If an adverse effect occurs with the fixed dose combination tablet that necessitates the cessation of treatment, the patient is required to discontinue ezetimibe and rosuvastatin simultaneously, regardless of whether only one component is the suspected cause of the adverse effect.
- Long-term efficacy and safety data in relation to the co-administration of ezetimibe and rosuvastatin in the proposed usage are limited.
- The bioequivalence study for the 10mg/40 mg strength ezetimibe and rosuvastatin fixed dose combination tablet indicates that exposure to rosuvastatin could be higher with the fixed dose combination compared with co-administration of the mono-components. Although the possible increase in exposure is anticipated to be small, as the maximum recommended dose of rosuvastatin is 40 mg, an increase in exposure with this proposed dose strength may increase the risk of adverse events, especially in patients with other risk factors that increase rosuvastatin exposure.
- Situations where an increase in rosuvastatin plasma levels may occur is a contraindication to the use of Crestor 40 mg (4). Administration of the 10 mg/40 mg strength ezetimibe and rosuvastatin fixed dose combination tablet may result in increased rosuvastatin AUC and, therefore, would be contraindicated.

13.3. Second round assessment of benefit-risk balance

The overall benefit-risk balance for the 10 mg/5 mg, 10 mg/10 mg and 10 mg/ 20 mg strength ezetimibe and rosuvastatin fixed dose combination tablets, respectively, given the proposed usage, is favourable.

The benefit-risk balance for the 10 mg/40 mg strength ezetimibe and rosuvastatin fixed dose combination tablet, given the proposed usage, is unfavourable.

14. Second round recommendation regarding authorisation

It is recommended that the proposed ezetimibe and rosuvastatin fixed dose combination tablet, in the strengths 10 mg/5 mg, 10 mg/10 mg, and 10 mg/20 mg, is approved subject to the following:

- the sponsor amending the draft PIs as recommended[3] or providing justification as to why the recommended changes should not be made
- the sponsor clarifying why the recommendations in relation to the co-administration of the Rosuzet/Ezalo composite pack with fibrates in the PRECAUTIONS section, under "Skeletal muscle" and "Fibrates", respectively, in the PIs for the Rosuzet composite pack and Ezalo composite pack are not consistent
- the sponsor providing further clarification as to why it proposes to include, under the sub-heading "Fibrates" in the PRECAUTIONS section of the PI, the statement "Therefore, co-administration of EZALO and fibrates (other than fenofibrate) is not recommended (see INTERACTIONS WITH OTHER MEDICINES).", rather than a statement consistent with the more conservative statement in the product information for the composite pack
- the sponsor providing the evidence to support the proposed recommendation "Therefore, co-administration of EZALO and fibrates (other than fenofibrate) is not recommended (see INTERACTIONS WITH OTHER MEDICINES).", under the sub-heading "Fibrates" in the PRECAUTIONS section of the PI
- the sponsor amending the draft CMIs as recommended or providing justification as to why the recommended changes should not be made.
- It is recommended that the proposed ezetimibe and rosuvastatin fixed dose combination tablet 10 mg/40 mg strength is not approved for the following reasons:
- Situations where an increase in rosuvastatin plasma levels may occur is a contraindication to the use of Crestor 40 mg (4). Administration of the 10 mg/40 mg strength ezetimibe and rosuvastatin fixed dose combination tablet in the proposed usage may result in increased rosuvastatin AUC and, therefore, would be contraindicated.
- The current EU Summary of Product Characteristics for Crestor (77) and Canadian product monograph (79) indicate that the maximum daily dose of Crestor should be adjusted so that the expected exposure (AUC) to rosuvastatin would not likely exceed that of a 40 mg daily dose of Crestor taken without interacting medicinal products. This safety-related information appears to preclude the co-administration of ezetimibe 10 mg with rosuvastatin 40 mg as it may result in rosuvastatin AUC that exceeds that of a 40 mg daily dose of rosuvastatin taken without interacting medicinal products based on the results of Study P03317. Although this information is not in the Australian PI for Crestor (4), it is information relevant to the safe use of rosuvastatin.

[3] The sections detailing recommendations regarding the PI and CMI are not included in the extract from the CER.

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