



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Ezetimibe and Rosuvastatin

Proprietary Product Names: Rosuzet, Ezalo

Sponsor: Merck Sharp & Dohme (Australia) Pty
Limited

January 2015

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 AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
ADR(s)	Adverse drug reaction(s)
AE(s)	Adverse event(s)
ALT	Alanine aminotransferase
ApoB	Apolipoprotein B
ARTG	Australian Register of Therapeutic Goods
$AUC_{0-\infty}/t$	Area under the concentration-time curve from time zero to infinity (extrapolated)/time of last measurement
CI	Confidence interval
CLcr	Creatinine clearance
Cmax	Maximum observed concentration
CMI	Consumer Medicine Information
CPMP	Committee for Propriety Medicinal Products
ECG	Electrocardiogram
EMA	European Medicines Agency
FH	Familial hypercholesterolaemia
HCP(s)	Health care provider(s)
HDL-C	High density lipoprotein cholesterol
HeFH	Heterozygous Familial Hypercholesterolaemia
HoFH	Homozygous Familial Hypercholesterolaemia
ICH	International Conference on Harmonisation of registration requirements for pharmaceuticals for human use
LDL/LDL-C	Low density lipoprotein cholesterol
LLD	Lipid-lowering drug
PBS	Pharmaceutical Benefits Scheme

Abbreviation	Meaning
PD	Pharmacodynamic/s
PI	Product information
PK	Pharmacokinetic/s
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SAE	Serious adverse event
Tmax	Time of observed Cmax

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New fixed dose combination
<i>Decision:</i>	Approved
<i>Date of decision:</i>	28 August 2014
<i>Active ingredients:</i>	Ezetimibe and rosuvastatin (as calcium)
<i>Product names:</i>	Ezalo, Rosuzet
<i>Sponsor's name and address:</i>	Merck Sharp & Dohme (Australia) Pty Limited Level 1, Building A 26 Talavera Road Macquarie Park NSW 2113
<i>Dose form:</i>	Fixed dose combination tablet
<i>Strengths:</i>	Ezetimibe/rosuvastatin: 10 mg/5 mg, 10 mg/10 mg, 10 mg/20 mg. and 10 mg/40 mg
<i>Container:</i>	Blister pack
<i>Pack sizes:</i>	9, 10 or 30 tablets
<i>Approved therapeutic use:</i>	Primary Hypercholesterolaemia <i>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:</i> <ul style="list-style-type: none">• <i>not appropriately controlled with rosuvastatin or ezetimibe alone; or</i>• <i>already treated with rosuvastatin and ezetimibe</i> Homozygous Familial Hypercholesterolaemia (HoFH) <i>Rosuzet/Ezalo is indicated for patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis).</i>
<i>Route of administration:</i>	Oral
<i>Dosage:</i>	The dose range is ezetimibe/rosuvastatin (as calcium) 10 mg/5 mg to 10 mg/40 mg once daily. The usual maximum dose is 10 mg/20 mg once per day [see approved Product Information for full <i>Dosage and Administration</i>]
<i>ARTG numbers:</i>	214121, 214114, 214119, 214116, 214120, 214115, 214117, and 214118

Product background

Ezetimibe is a selective inhibitor of intestinal cholesterol and related phytosterol absorption and was registered in Australia as 10 mg tablets in June 2003. Rosuvastatin (as calcium) is a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor and was registered as 5, 10, 20 and 40 mg tablets in April 2006.

The approved indications for ezetimibe monotherapy involve use in primary hypercholesterolaemia or homozygous familial hypercholesterolaemia (HoFH) or homozygous sitosterolaemia (phytosterolaemia) while the approved indications for rosuvastatin monotherapy involve prevention of cardiovascular events and use in patients with hypercholesterolaemia.

The ezetimibe and rosuvastatin tablets are separately registered by Merck Sharp & Dohme (Australia) Pty Limited under the trade names Ezetrol and MSD Rosuvastatin, respectively.

Composite packs containing ezetimibe and rosuvastatin tablets were registered to the sponsor in November 2013 (PM-2012-03419-1-3). These packs contain separate tablets of ezetimibe 10 mg and rosuvastatin 5, 10, 20 or 40 mg, respectively (trade names Ezalo Composite Pack, Rosuzet Composite Pack) and are approved for use in patients with primary hypercholesterolaemia and HoFH. The AusPARs for the composite pack registration applications are available at <<http://www.tga.gov.au/australian-public-assessment-reports-prescription-medicines-auspars>>.

This AusPAR describes the application by Merck Sharp & Dohme (Australia) Pty Limited (the sponsor) to register fixed dose combination tablets containing ezetimibe and rosuvastatin (as calcium) for the following indication:

Primary Hypercholesterolaemia

Ezalo/Rosuzet 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)

Ezalo/Rosuzet is indicated for patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis).

Regulatory status

The products received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 13 October 2014.

At the time the TGA considered this application, a submission for a fixed dose combination of ezetimibe and rosuvastatin had not been lodged in the EU, USA, Canada or New Zealand and there were no such submissions planned.

Product Information

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

II. Quality findings

Introduction

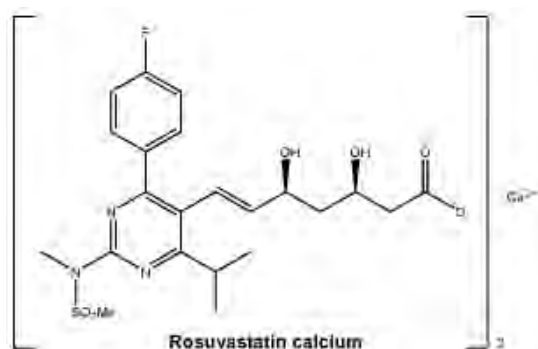
The sponsor has previously registered composite packs containing 10 mg ezetimibe tablets in blisters together with either 5 mg, 10 mg, 20 mg or 40 mg rosuvastatin (as calcium) film coated tablets under the trade name Ezalo/Rosuzet Composite Pack. The ezetimibe tablets are separately registered by the sponsor under the trade name Ezetrol and the rosuvastatin (as calcium) tablets are registered by the sponsor under the trade name MSD Rosuvastatin.

The structures of ezetimibe and rosuvastatin (as calcium) are presented below:

Figure 1: Structure of ezetimibe



Figure 2: Structure of rosuvastatin (as calcium)



Drug substance (active ingredient)

There have been no changes with respect to quality of the active pharmaceutical ingredients (APIs). The API specifications are the same as those for the already registered Ezetrol and MSD Rosuvastatin tablets.

Drug product

There have been no changes with respect to quality of the finished products.

The manufacturing process of the finished product is comprised of different manufacturing steps including preparation of ready to compress blends for ezetimibe and rosuvastatin calcium and compression of both the blends. Compressed tablets are packaged in the intended commercial packs.

The dissolution acceptance criterion for both ezetimibe and rosuvastatin in ezetimibe/rosuvastatin fixed dose combination tablets complies with Therapeutic Goods Order 78.

The limit for all degradation products of rosuvastatin calcium and ezetimibe, respectively, in the finished product is consistent with International Conference on Harmonisation of

registration requirements for pharmaceuticals for human use (ICH) identification and qualification thresholds.

The fixed dose combination tablets come in strengths of 10 mg/5 mg, 10 mg/10 mg, 10 mg/20 mg and 10 mg/40 mg and are described as white to off white, circular, uncoated, tablet with one side debossed with "C1", "C2", "C3" and "C4", respectively.

The shelf life for the fixed dose combination tablets is 12 months when stored below 30°C in polyamide/aluminium foil/polyvinylchloride/aluminium foil (PA/Al/PVC/Al) or PVC/polychlorotrifluoro ethylene (PCTFE) (Aclar)/Al blisters. Final mock-ups labels have been provided. The blister and carton labels are acceptable from a Module 3 (quality) perspective.

Biopharmaceutics

The sponsor has previously submitted data in relation to the registered ezetimibe monotherapy products with respect to co-administration of ezetimibe with statins. Given this, the data have not been reviewed again.

- One 14 day pharmacokinetics/pharmacodynamics (PK/PD) study (P03317, evaluating the effects of ezetimibe 10 mg and rosuvastatin 10 mg either alone or in combination in hypercholesterolaemic subjects) with 3 associated publications has been referred to in relation to co-administration of ezetimibe with rosuvastatin.
- Three safety and efficacy clinical studies with 3 associated publications have been referred to in relation to co-administration of ezetimibe with rosuvastatin.
- Forty six additional safety and efficacy data sets from 63 literature publications were referred to.

The sponsor has also conducted two bioequivalence studies demonstrates that the proposed tablets can be considered bioequivalent to the Australian innovator:

- A randomised, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of fixed dose combination of rosuvastatin calcium + ezetimibe 5 mg/10 mg tablets of Sun Pharmaceutical Industries Ltd., India and co-administration of Crestor (rosuvastatin calcium) 5 mg tablet of AstraZeneca with Ezetrol (ezetimibe) 10 mg tablets of Merck Sharp & Dohme, in 60 healthy human adult subjects, under fasting conditions.
- A randomised, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of fixed dose combination of rosuvastatin calcium + ezetimibe 40 mg/10 mg tablets of Sun Pharmaceutical Industries Ltd., India and co-administration of Crestor (rosuvastatin calcium) 40 mg tablet of AstraZeneca with Ezetrol (ezetimibe) 10 mg tablets of Merck Sharp & Dohme, in 60 healthy human adult subjects, under fasting conditions.

Advisory committee considerations

Not applicable.

Quality summary and conclusions

A number of issues were raised following the initial evaluation of this application, but all issues have since been satisfactorily resolved. There are now no objections to registration of these products.

III. Nonclinical findings

Introduction

The only new nonclinical data was a published paper by Verschuren et al. (2012¹) which was accompanied by a memorandum from the sponsor with a critical analysis of this paper (Qin et al., 2013²).

The sponsor has suitably justified the absence of further nonclinical studies in accordance with the following criteria noted in the European Medicines Agency (EMA) guidelines on fixed combination products³:

- Ezetimibe and rosuvastatin are already individually approved for the proposed indications;
- There is sufficient documented human experience of the individual and combined use of ezetimibe and rosuvastatin;
- The proposed combination is similar to that found in Vytorin, a combination of ezetimibe with simvastatin, a compound in the same class as rosuvastatin. This is a well established combination for which there is considerable clinical experience;
- No PK interactions have been identified.

The nonclinical development programmes supporting the registration of ezetimibe (Ezetrol) and rosuvastatin (Crestor 5 mg, 10 mg, 20 mg, and 40 mg tablets) as monotherapy have been previously evaluated by the TGA. Nonclinical data relating to the combination of ezetimibe with statins have previously been evaluated in the Ezetrol application and were augmented in a later submission (seeking registration of a composite pack of ezetimibe and rosuvastatin) where a literature search identified one new publication (Ason et al., 2011⁴).

No nonclinical objections were raised to the approval of ezetimibe as monotherapy or co-administration with a statin.

Updated nonclinical information/data

An updated literature search was performed by the sponsor on 22 April 2013 (search strategy approved by TGA on 31 May 2013). This search identified an additional publication, Verschuren et al. 2012, along with a Merck internal memorandum which critically analysed the gene profiling data used in that publication.

Nonclinical summary

- A new systems biology paper (Verschuren et al., 2012) investigated the differential expression of hepatic genes in ApoE*3Leiden transgenic mice fed an atherogenic, high cholesterol diet and treated with rosuvastatin or ezetimibe, either alone or in combination. The greater effectiveness of the combination treatment in reducing plasma lipids, serum amyloid A and aortic atherosclerotic lesion size was due to the

¹ Verschuren, L., Radonjic, M., Wielinga, P. Y., et al. Systems biology analysis unravels the complementary action of combined rosuvastatin and ezetimibe therapy. *Pharmacogenetics and Genomics* 2012;22:837-845.

² Chunhua Qin, C., Podtelezchnikov, A., Tanis, K. Profiling Data Review on the Verschuren Rosuvastatin/Ezetimibe Combination Study. Merck Research Laboratories, Internal Memorandum: 11 July 2013.

³ EMEA/CHMP/SWP/256498/2005, Section 4.2.1

⁴ Ason B., Tep S., Davis Jr HR. et al. Improved efficacy for ezetimibe and rosuvastatin by attenuating the induction of PCSK9. *J Lipid Res* 2011;52:679-687.

additivity of the complementary mechanisms of action of the individual drugs. Differential hepatic gene expression pathway analysis suggested that combination therapy exerted a significant effect on 16 mostly NF- κ B-linked signalling processes, 11 of which tended to be regulated in a similar direction with monotherapy. 'Canonical pathways' associated with these processes included molecular mechanisms of cancer, NF- κ B signalling, and growth factor signalling, with the authors' speculating that these results may have implications for the cancer findings in the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) Trial.

- There is no generally accepted canonical pathway for 'molecular mechanisms of cancer', despite intense research in this area. Moreover, a careful re-analysis of the Verschuren et al. gene profiling data (available in the public domain) by the sponsor using appropriate False Discovery Rate (FDR) statistical corrections for multiple tests showed that there was no evidence of activation of any cancer-associated growth factor receptor pathways, such as platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), stem cell factor (SCF), and insulin like growth factor-1 (IGF-1). Indeed, portions of the NF- κ B signalling pathway downstream of the growth factor receptors were actually down regulated. This down regulation would be mostly associated with inhibition of inflammation and inhibition of cancer development. Therefore, the profiling data does not appear to support the speculation by Verschuren et al. that the combination ezetimibe + rosuvastatin treatment poses an increased carcinogenicity risk.

Conclusions and recommendation

- The sponsor has suitably justified the absence of further nonclinical studies in accordance with the EMA guidelines on fixed-combination products.
- There is no novel pharmacokinetic or toxicity concern associated with the combination.
- The registration of Rosuzet/Ezalo is supported on nonclinical grounds.
- No changes are recommended to the sponsor's draft PI.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

The proposed indications for the ezetimibe and rosuvastatin (as calcium) fixed dose combination tablets 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).

Ezetrol can be administered with a statin for the treatment of primary hypercholesterolaemia and is indicated for patients with HoFH when administered with a statin. 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.

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 and Ezalo Composite Pack. 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.

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* (CHMP/EWP/240/95 Rev.1. 19 February 2009), 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.

Evaluator's comment: The primary benefit of the fixed dose combination tablet over the co-administration of the monotherapies 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* (CHMP/EWP/240/95 Rev.1.) 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.

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 (Guidance 15, *Biopharmaceutic studies*) of the Australian Regulatory Guidelines for Prescription Medicines (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 provide a comprehensive table of contents which includes the contents of Modules 1 and 2;
- the sponsor was requested to include an Risk Management Plan (RMP) in the submission.

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

Contents 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:

- Two bioequivalence studies: Study P417 and Study P425

- One clinical pharmacology study (Study P03317) that provided PK data and PD 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
- Literature references

Module 2:

- Clinical Overview and Clinical Summary

Evaluator's 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.

Paediatric data

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

Evaluator's comment: The draft PIs for the proposed 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.

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.

Evaluator's 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.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 1 shows the studies relating to each PK topic.

Table 1. Submitted pharmacokinetic studies

PK topic; Subtopic	Study ID	Primary objectives
PK in healthy adults; Bioequivalence† - Single dose	Study P417	<p>The two primary objectives were:</p> <p>to evaluate, under fasting conditions, the single dose PK profile (area under the concentration-time curve from time zero to time of last measurement (AUC_{0-t}) and maximum observed concentration (C_{max})) 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 mg/10 mg tablet) and reference formulations (co-administration of Crestor (rosuvastatin calcium) 40 mg with Ezetrol (ezetimibe) 10 mg as individual tablets);</p> <p>to evaluate, under fasting conditions, the single dose PK profile (AUC_{0-t} and C_{max}) of rosuvastatin after oral administration of a single dose of the test formulation (fixed dose combination of rosuvastatin calcium + ezetimibe 40 mg/10 mg tablet) and reference formulations (co-administration of Crestor (rosuvastatin calcium) 40 mg and Ezetrol (ezetimibe) 10 mg as individual tablets).</p>
	Study P425	<p>The two primary objectives were:</p> <p>to evaluate, under fasting conditions, the single dose PK profile (AUC_{0-t} and C_{max}) 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 mg/10 mg tablet) and reference formulations (co-administration of Crestor (rosuvastatin calcium) 5 mg with Ezetrol (ezetimibe) 10 mg as individual tablets)</p> <p>to evaluate, under fasting conditions, the single dose PK profile (AUC_{0-t} and C_{max}) of rosuvastatin after oral</p>

PK topic; Subtopic	Study ID	Primary objectives
		administration of a single dose of the test formulation (fixed dose combination of rosuvastatin calcium + ezetimibe 5 mg/10 mg tablet) and reference formulations (co-administration of Crestor (rosuvastatin calcium) 5 mg and Ezetrol (ezetimibe) 10 mg as individual tablets).

† Bioequivalence of different formulations.

Two new PK 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 PK properties of the mono-components of the fixed dose combination tablets, ezetimibe and rosuvastatin are described in the respective Australian PI documents for Ezetrol and MSD Rosuvastatin. The PK 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 PI for the ezetimibe and rosuvastatin composite packs.

Evaluator's conclusions on pharmacokinetics

The PK 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 mg/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 (CIs) of the geometric mean ratios of the test and reference products for AUC_{0-t} and C_{max} 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 mg/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% CIs of the geometric mean ratios of the test and reference products for AUC_{0-t} for rosuvastatin, ezetimibe (unconjugated) and total ezetimibe were all within 80.00% to 125.00% as were the 90% CIs of the geometric mean ratios of the test and reference products for C_{max} for unconjugated ezetimibe and rosuvastatin.

Although the lower limit of the 90% CI of the geometric mean ratio of the test and reference product for C_{max} of total ezetimibe was below 80% (C_{max} 80.84 90% CI [74.90, 87.25]), this is unlikely to be of major concern from a clinical perspective as the 90% CI of the geometric mean ratio of the test and reference product for AUC_{0-t} of total ezetimibe, and the AUC_{0-t} and C_{max} of the parent compound, ezetimibe (unconjugated), were within the bioequivalence range.

Pharmacodynamics

Studies providing pharmacodynamic data

No new pharmacodynamic studies were included in the submission.

The clinical study report for Study P03317, a 14 day PD 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 and rosuvastatin composite pack (Submission PM-2012-03419-1-3). The primary objective of the study was to evaluate the PD effects and safety of the co-administration of ezetimibe and rosuvastatin.

Evaluator's comment: Three publications⁵ that were identified in the first literature search, to support the registration of the ezetimibe and rosuvastatin composite pack, relate to Study P03317.

Evaluator's conclusions on pharmacodynamics

No new PD studies were included in the submission. The PD effects of co-administered ezetimibe and rosuvastatin were established in the application for the registration of the ezetimibe and rosuvastatin composite packs (Submission PM-2012-03419-1-3).

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 packs (submission PM-2012-03419-1-3). 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.

Efficacy

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

⁵ **1:** Bays HE, Davidson MH, Massaad R, Flaim D, Lowe RS, Tershakovec AM and Jones-Burton C. Safety and efficacy of ezetimibe added on to rosuvastatin 5 or 10 mg versus up-titration of rosuvastatin in patients with hypercholesterolemia (the ACTE Study). *American Journal of Cardiology* 2011;108(4):523-530. **2:** Bays HE, Davidson M, Massaad R, Flaim D, Lowe R, Tershakovec A, Jones-Burton C. Efficacy and Safety of Ezetimibe Plus Rosuvastatin Versus Rosuvastatin Up-Titration in Hypercholesterolemic Patients at Risk for Atherosclerotic Coronary Heart Disease. *Journal of Clinical Lipidology* 2011;5(3):217-218. **3:** Merck. A Study of Ezetimibe Added On to Rosuvastatin Versus Up Titration of Rosuvastatin in Patients With Hypercholesterolemia (MK0653-139). Clinicaltrials.gov NCT00783263 (p1-28).

co-administered with statins, 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.

Evaluator's comment: The application for the ezetimibe and rosuvastatin composite pack (Submission PM-2012-03419-1-3) 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, or 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.

Evaluator's conclusions on efficacy

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 PM-2012-03419-1-3), 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, or 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) and intervention studies have shown that lowering LDL-C and TG, or raising high density lipoprotein cholesterol (HDL-C), has benefits on mortality and cardiovascular event rates. The guideline *Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Lipid Disorders* (CPMP/EWP/3020/03. 29 July 2004) 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 National Cholesterol Education Program (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.

Safety

Studies providing evaluable safety data

The following studies provided evaluable safety data:

- Efficacy Study P139V1 (previously evaluated);
- Pharmacodynamics Study P03317 (previously evaluated);
- Bioequivalence Study P417 and Study P425 (new);
- Literature (identified for this submission and previously identified for Submission PM-2012-03419-1-3);
- Ezetimibe studies in registration dossier (previously evaluated);
- PSUR Addendum Report for ezetimibe (new).

No new safety studies were included in the submission.

Evaluator's comment: The safety profiles of the mono-components of the proposed fixed dose combination tablet, ezetimibe and rosuvastatin, are described in the respective PI document for Ezetrol and MSD Rosuvastatin. 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.

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, the PIs for the Rosuzet Composite Pack, and the Ezalo Composite Pack, and the draft PIs for the proposed fixed dose combination tablets.

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.

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 2: 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%		

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.

Evaluator's 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 EMA guideline *Clinical Investigation of Medicinal Products for Long-term Use* (3CCC6a).

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.

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 (SAEs) 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 and Ezalo Composite Pack 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 for the fixed dose combination products.

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 PI documents for Ezetrol, MSD Rosuvastatin, Rosuzet Composite Pack and Ezalo Composite Pack.

Based on the 90% CI of the geometric mean ratios of the test and reference products for AUC_{0-t} and C_{max} for rosuvastatin in Study P417, the AUC_{0-t} of rosuvastatin could be as much as 5% higher and the C_{max} as much as 8% higher following administration of the 10 mg/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 PI for that product.

Postmarketing data

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, were provided. The sponsor has included the 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 AEs 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 pancytopenia, 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 pancytopenia, 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 AE 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.

Evaluator's 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 article⁶. 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 section in the Australian PI for Ezetrol (ezetimibe) 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 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

⁶ Nakamaru T, Hirano M and Kitta Y et al. A comparison of the efficacy of combined ezetimibe and statin therapy with doubling of statin dose in patients with remnant lipoproteinemia on previous statin therapy. *Journal of Cardiology* 2012; 60(1): 12-17.

effect. Most adverse drug reactions (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 previously indicated, in documentation for the application to register the ezetimibe + rosuvastatin composite packs (PM-2012-03419-1-3), that it proposed 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 (see also *Pharmacovigilance findings*, below).

Rhabdomyolysis and hypersensitivity reactions are included in the Australian PI for Ezetrol 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 was 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 (see *Clinical questions*, below).

The prevalence of amyotrophic lateral sclerosis is reported to be 3-5 per 100,000⁷. The aetiology of amyotrophic lateral sclerosis appears to be multifactorial and not clearly understood. 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 (CER) for the Rosuzet/Ezalo Composite Pack (Submission PM 2012-03419-1-3⁸). 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. 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 section in the PI for Ezetrol. The sponsor was 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 (see *Clinical questions*, below).

Evaluator's conclusions on 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 10 mg + 40 mg dose indicates that exposure to rosuvastatin could be higher with the fixed dose combination compared with the mono-therapies.

⁷ Naganska E and Matyia E. Amyotrophic lateral sclerosis - looking for pathogenesis and effective therapy. *Folia Neuropathol.* 2011;49(1):1-13.

⁸ The AusPARs and CER extract for the composite pack registration applications are available at <http://www.tga.gov.au/australian-public-assessment-reports-prescription-medicines-auspars>.

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 AEs.

It is recommended that the safety-related information in the PI for the fixed dose combination tablet is identical to that in PI 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.

First round benefit-risk assessment

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.

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 10 mg + 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 AEs, especially in patients with other risk factors that increase rosuvastatin exposure.

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.

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 recommended⁹ or providing justification as to why the recommended changes should not be made;
- the sponsor providing satisfactory answers to the clinical questions below.

Clinical questions

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 HCP 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.

Second round evaluation of clinical data submitted in response to questions

Evaluation of clinical data submitted in response to questions

Details of the sponsor’s response to clinical questions are found in the Extract from the CER (AusPAR Attachment 2) and in the Delegate’s Overview under *Overall conclusions and risk/benefit assessment*, below.

With regards to Safety questions 1, 2 and 3, the clinical evaluator concluded that the sponsor’s responses were acceptable. No change to the Australian PI for Ezetrol was warranted based on the information in the sponsor’s response on: the cumulative cases of Stevens Johnson Syndrome and leucocytoclastic vasculitis (response to question 1), cumulative cases of pancytopenia (response to question 2), or cumulative cases of “electrocardiogram QT prolonged” (response to question 3).

With regards to Safety question 4: The sponsor confirmed that hepatic failure has been added as a potential risk to the updated RMP (Version 1.3). The sponsor indicated 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 (OPR), the sponsor has included their rationale for including hepatic failure as a potential risk rather than an identified risk (see also *Pharmacovigilance findings*, below).

Evaluator’s 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.

⁹ Details of recommendations regarding revisions to PI and other product literature are beyond the scope of the AusPAR

Other issues pertinent to the submission***Rosuvastatin exposure in relation to the 10 mg/40 mg strength fixed dose combination tablet***

In the second round CER, the clinical evaluator reviewed the information in the Australian, European Union (EU), United States (US) and Canadian product information documents for Crestor (rosuvastatin (as calcium) monotherapy product) in relation to the interaction of rosuvastatin with other medicines. 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 include information relating to the co-administration of ezetimibe and rosuvastatin that is not in the Australian PI for Crestor.

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 C_{max} for rosuvastatin when rosuvastatin was co-administered with ezetimibe compared to the administration of rosuvastatin alone (AUC 119% [90% CI 87%-162%]; C_{max} 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 previously sought advice from the Advisory Committee on Prescription Medicines (ACPM). Specifically, the ACPM view was sought 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. The 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, was safe.

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:

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 10 mg +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 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. This contraindication is consistent with the Australian PI for Crestor and consistent statements are also proposed for the PI 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 (SmPC) for Crestor. It is indicated that changes to the EU SmPC 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. In the *Interactions with other medicinal products and other forms of interaction* section of the current EU SmPC 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.

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, reproduced as Table 3 below.

Table 3: 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. 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. 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 SmPC 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 organic anion transporter polypeptide 1B1 (OATP1B1) and breast cancer resistance protein (BCRP). It is recommended that alternative medicines are considered, and that consideration should be given, if necessary, to temporarily discontinuing Crestor. 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. 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 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 SmPC for Crestor indicates that a pharmacodynamic interaction, in terms of adverse effects, between Crestor and ezetimibe cannot be ruled out. The US prescribing information for Crestor 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 includes both this contraindication and recommendation. The Canadian product monograph also includes recommendations in the *Dosage and Administration* section similar to those in the *Posology and method of administration* section of the EU SmPC. From the information in the Canadian product monograph for Crestor 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 and the above-mentioned interpretation of the information in the EU SmPC for Crestor and Canadian product monograph for Crestor, it is recommended that advice is again sought from ACPM on this issue.

Second round benefit-risk assessment

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 the *First round assessment of benefits*, above.

Second round assessment of risks

After consideration of the responses to the 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 10 mg/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 AEs, 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. 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.

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.

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 recommended¹⁰ or providing justification as to why the recommended changes should not be made

¹⁰ Details of recommended revisions to the PI and CMI are beyond the scope of the AusPAR.

- 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 PI 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 Consumer Medicine Information (CMI) 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. 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 SmPC for Crestor and Canadian product monograph 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, it is information relevant to the safe use of rosuvastatin.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP): Australian-RMP for Ezetimibe + Rosuvastatin Composite Pack/Fixed Dose Combination Tablet, Version 1.2, dated 15 October 2013, data base lock 1 December 2012, which was reviewed by the TGA’s Office of Product Review (OPR).

The RMP is an updated version of the Ezetimibe + Rosuvastatin RMP, Version 1.0, dated 6 December 2012, which was evaluated by TGA for the submission to register Ezalo Composite Pack and Rosuzet Composite Pack.

There have been no changes to the safety specifications in the updated RMP Version 1.2 compared to the previous versions for the composite packs. The sponsor states in RMP Version 1.2 (and Version 1.1): *This is an update of the first RMP submission for ezetimibe + rosuvastatin to include a second formulation of this combination (fixed dose combination tablet). No new safety concerns have been identified since the previous version of the RMP.*

The RMP evaluated for this submission is essentially identical to the RMP evaluated in the previous submission for the composite packs¹¹ and therefore any issues raised in the evaluation report for the previous submission are applicable for the current submission.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 4.

Table 4: Summary of Ongoing Safety Concerns

Ongoing Safety Concerns	
Important Identified Risks	Rhabdomyolysis/Myopathy Abnormal liver function Hypersensitivity Drug interaction with: Warfarin; another coumarin anticoagulant, or flindione Cyclosporin Fibrates Protease Inhibitors Antacids
Important Potential Risks	Pancreatitis Cholecystitis/Cholelithiasis Interstitial Lung Disease
Important Missing Information	Exposure during pregnancy and lactation Use in children

Pharmacovigilance plan

Routine pharmacovigilance activities are proposed.

Risk minimisation activities

Routine risk minimisation activities are proposed.

Reconciliation of issues outlined in the RMP report

Table 5 summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

¹¹ The AusPARs for the composite pack registration applications are available at <http://www.tga.gov.au/australian-public-assessment-reports-prescription-medicines-auspars>.

Table 5: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
1. It is recommended that the sponsor includes "hepatic failure" as an identified risk in the table of ongoing safety concerns in an updated RMP as agreed by the sponsor during the evaluation for the previous submission.	Hepatic failure has now been added as a Potential risk to the table of ongoing safety concerns in the updated RMP as proposed by the sponsor and accepted by the Delegate during the evaluation of Rosuzet/Ezalo Composite Pack. The Delegate accepted the proposal to include Hepatic failure as a "Potential risk" rather than "Identified risk" based on the rationale provided by the sponsor	Pending the Delegate's acceptance of this justification, it is considered acceptable.
2. It is recommended that a statement be added to the <i>Precautions</i> section of the PI describing that a possible increase in rosuvastatin plasma exposure is due to co-administration of ezetimibe, or at least contains cross-reference to the <i>Pharmacokinetics</i> section of the PI.	The sponsor concurs. Cross-reference to the <i>Pharmacokinetics</i> section of the PI has been added under the <i>Precautions, Treatment with the 10/40 mg Dose</i> heading.	This is considered acceptable.
3. It is recommended that "Long-term safety of co-administration of Ezetimibe and Rosuvastatin at 10/40 mg" be added to the table of ongoing safety concerns to ensure separate reporting for this missing information in any future periodic safety update report (PSUR).	The sponsor proposes that "Long-term safety of co-administration of Ezetimibe and Rosuvastatin at 10/40 mg" not be added as missing information to the ongoing safety concerns in the Australian RMP based on the same rationale submitted to the TGA during the evaluation of Rosuzet/Ezalo Composite Pack, which was accepted by the Delegate.	Pending the Delegate's acceptance of this justification, it is considered acceptable. However, it is brought to the Delegate's attention that the clinical evaluator considers the addition of this ongoing safety concern appropriate (see clinical evaluator's comments below).
4. It is recommended that the sponsor provides this previously accepted PI for the Rosuzet	Relevant text from the Rosuzet Composite Pack PI approved 20 November 2013 has been incorporated into the revised Rosuzet fixed dose combination PI	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
Composite Pack (Rosuzet Composite Pack PI, version 1.6, 18 November 2013), with changes relevant for the current application included.	upon request of the clinical evaluator.	
5. It is recommended that the sponsor adds the "Increase in HbA1c and FSG" or "new onset diabetes" as potential risk to the table of ongoing safety concerns. Pharmacovigilance and risk-minimisation activities should be assigned as appropriate. Furthermore, it is recommended that the sponsor amends the safety specification section of the RMP to include provision of information/discussion about this potential risk.	The sponsor concurs. "Diabetes mellitus" has been added as a Potential risk to the table of ongoing safety concerns in the updated RMP.	This is considered acceptable.

Summary and recommendations

Outstanding issues

It is recommended that the Delegate check the validity of the statements made by the sponsor regarding points 1 and 3 in Table 5 above.

Regarding point 3 in Table 5 above: It was brought to the Delegate's attention that the clinical evaluator considers the addition of the ongoing safety concern of "Safety of co-administration of Ezetimibe and Rosuvastatin at 10/40 mg" appropriate (see *Comments on the safety specification of the RMP, Clinical evaluation report* below).

The issues raised by the clinical evaluator have to be addressed by the sponsor to the satisfaction of the RMP evaluation section.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

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

A revised Ezetimibe + Rosuvastatin Composite Pack/Fixed Dose Combination Tablet Australian RMP, Version Number 1.3, was provided in response to the TGA request for further information. The Safety Specification of the revised RMP was reviewed by the clinical evaluator.

In the TGA request for further information, the OPR recommended that the sponsor add to the RMP “hepatic failure” as an identified risk, “long-term safety of the co-administration of ezetimibe and rosuvastatin at 10/40 mg” as missing information, and “increase in HbA1c and FSG” or “new onset diabetes” as a potential risk.

In the RMP Version Number 1.3, the sponsor has added “diabetes mellitus” and “hepatic failure” as new potential risks.

The sponsor indicates that the Delegate for the composite pack submission PM-2012-03419-1-3 previously accepted their rationale for adding “hepatic failure” as a potential risk, rather than an identified risk, and their rationale for not adding to the RMP as missing information “long-term safety of the co-administration of ezetimibe and rosuvastatin at 10/40 mg”.

It is noted that in RMP Version Number 1.3, in the column to the left of the identified risk “abnormal liver function”, the terms “alanine aminotransferase increased”, “aspartate aminotransferase increased” and “hepatitis” are listed. In Version Number 1.2 of the RMP “hepatic failure” was also included in this list but has been removed from Version Number 1.3.

Due to the rosuvastatin component, it is indicated in the draft PIs that Rosuzet/Ezalo 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. As co-administration of ezetimibe and rosuvastatin may increase rosuvastatin AUC, this would appear to preclude the use of the 10 mg/40 mg strength ezetimibe and rosuvastatin fixed dose combination tablet.

If the 10 mg/40 mg strength of the fixed dose combination tablet is approved, it is recommended that the interaction between ezetimibe and rosuvastatin is added to the RMP as a potential risk. It is noted that, in the response to the OPR Question 3 (see Table 5 above), the sponsor indicates that the *Precautions* section of the Australian PI has been updated to note “Due to the potential increase in rosuvastatin exposure when combined with ezetimibe, monitoring of patients on the highest dose of Rosuzet/Ezalo is recommended”. This statement supports the inclusion of the interaction between ezetimibe and rosuvastatin as a potential risk for the proposed 10 mg/40 mg strength of the fixed dose combination tablet if it is approved. It is noted that this specific statement does not appear to be in the draft PIs for Rosuzet and Ezalo. It is recommended that this statement is added to the PIs if the 10 mg/40 mg strength of the fixed dose combination tablet is approved.

No other important identified risks, potential risks and missing information, that could impact on the risk-benefit balance of the product or have implications for public health, have been identified in the second round evaluation.

Key changes to the updated RMP

In the response to the TGA request for information the sponsor provided an updated RMP (Version 1.3). Key changes from the version evaluated at Round 1 are summarised below:

Table 6: Key changes to the RMP Version 1.3 compared with Version 1.2

RMP updates	
Safety specification	Hepatic failure has been added as potential risk Diabetes mellitus has been added as potential risk
Pharmacovigilance activities	Routine pharmacovigilance Routine pharmacovigilance
Risk minimisation activities	Routine risk-minimisation Routine risk-minimisation

The OPR evaluator has no objection to the above changes. However changes as recommended by the clinical evaluator (above) should be addressed in an updated version of the RMP.

Suggested conditions of registration

- Implement Australian RMP for Ezetimibe + Rosuvastatin Composite Pack/Fixed Dose Combination Tablet, updated from RMP Version 1.3, data lock point 1-Dec-2012 to include the amendments requested by the clinical evaluator.

Any commitments made by the sponsor in their response to the TGA request for information regarding RMP issues have to be implemented as agreed with the TGA.

VI. Overall conclusion and risk/benefit assessment

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

Introduction

The approved indications for Ezetrol (ezetimibe) monotherapy involve use in primary hypercholesterolaemia or homozygous familial hypercholesterolaemia (HoFH) or homozygous sitosterolaemia (phytosterolaemia) while the approved indications for MSD Rosuvastatin monotherapy are the same as those for Crestor, the innovator rosuvastatin product, and involve prevention of cardiovascular events and use in patients with hypercholesterolaemia.

The proposed indications for the fixed dose combination are the same as those already approved for the Rosuzet and Ezalo Composite Packs, that is:

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).

Quality

The shelf-life of the fixed dose combination tablets is 12 months when stored below 30°C in their blister packs.

The sponsor had previously submitted data in relation to the registered ezetimibe monotherapy co-administered with various statins in a previous submission. For this submission these data were not reviewed. However, for this submission, the sponsor did conduct two bioequivalence studies which, in the view of the pharmaceutical chemistry evaluator, demonstrated that the proposed fixed dose combination tablets can be considered bioequivalent to the Australian innovator monotherapy products, that is, to Ezetrol and to Crestor. The clinical evaluator has also reviewed these two studies.

Nonclinical

In the view of the nonclinical evaluator the sponsor has suitably justified the absence of further nonclinical studies in accordance with the EMA guidelines on fixed dose combination products.

There is no novel pharmacokinetic or toxicity concern associated with the combination.

The registration of Ezalo/Rosuzet is supported on nonclinical grounds.

No changes were recommended by the nonclinical evaluator to the sponsor's draft PI for Ezalo/Rosuzet.

Clinical

Pharmacology

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, administration of the test product, ezetimibe +rosuvastatin calcium 10 mg/5 mg fixed dose combination tablet, was compared with co-administration of the reference products Ezetrol (ezetimibe) 10 mg tablet and Crestor (rosuvastatin calcium) 5 mg tablet. The 90% CIs of the geometric mean ratios of the test and reference products for AUC_{0-t} and C_{max} for rosuvastatin, ezetimibe (unconjugated) and total ezetimibe were all within the pre-defined range of bioequivalence (80.00% to 125.00%).

In Study P417, administration of the test product, ezetimibe + rosuvastatin calcium 10 mg/40 mg fixed dose combination tablet, was compared with co-administration of the reference products Ezetrol (ezetimibe) 10 mg tablet and Crestor (rosuvastatin calcium) 40 mg tablet. The 90% CIs of the geometric mean ratios of the test and reference products for AUC_{0-t} for rosuvastatin, ezetimibe (unconjugated) and total ezetimibe were all within 80.00% to 125.00% as were those for C_{max} for unconjugated ezetimibe and rosuvastatin. Although the lower limit of the corresponding 90% CI for C_{max} for total ezetimibe was below 80% (C_{max} 80.84 90% CI [74.90, 87.25]), this is unlikely to be of clinical significance.

Efficacy

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. This evidence is acceptable.

Safety

As noted by the clinical evaluator, 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, ezetimibe 10 mg plus rosuvastatin 5, 10, 20 or 40 mg. 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 for the mono-components.

According to Table 2, above, there have been a total of 145 patients exposed to the highest dosage strength combination, namely ezetimibe 10 mg + rosuvastatin 40 mg for between 12 and 24 weeks. There are no clinical trial patients who have been exposed to this dosage strength for any longer periods. The sponsor was requested to confirm that this is the case.

In its pre-ACPM response the sponsor was requested to provide the most up-to-date assessment of all post-marketing data available to the sponsor, data which can elucidate the AE profile of the highest dosage strength combination, namely ezetimibe 10 mg + rosuvastatin 40 mg.

In the second round of the clinical evaluation, the sponsor was asked to comment on a number of safety issues. These are summarised below:

1. The sponsor was asked to provide details on the cases of Stevens Johnson Syndrome and leucocytoclastic vasculitis reported by healthcare providers in the PSUR Addendum Report for ezetimibe (17 April 2012 to 16 April 2013). Of the seven reports of leucocytoclastic vasculitis cumulatively, the sponsor reported 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. The sponsor's response was judged to be acceptable by the clinical evaluator and the Delegate agrees.
2. The sponsor was asked to provide details on the cases of pancytopenia reported by healthcare providers in the PSUR Addendum Report for ezetimibe (17 April 2012 to 16 April 2013). The sponsor indicated that for five of the seven cases, there was insufficient information to make a causality assessment and the remaining two cases were confounded. Again the Delegate agrees with the clinical evaluator that the sponsor's response is acceptable.
3. The sponsor was asked to provide details on the reports of "electrocardiogram QT prolonged" in the PSUR Addendum Report for ezetimibe (17 April 2012 to 16 April 2013). There were two such cases, one of which 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 while for the other case, the sponsor responded that there was insufficient information to make a causality assessment. Again the Delegate agrees with the clinical evaluator that the sponsor's response is acceptable.
4. The sponsor was asked to clarify whether hepatic failure, as a specific term, would be added to the RMP as an ongoing safety concern. The sponsor confirmed that hepatic failure had been added as a potential risk to the updated RMP (Version 1.3). The sponsor indicated 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). This is acceptable to the Delegate of this submission.

Under '*Other issues pertinent to the submission*', above, the clinical evaluator discussed an issue which was of concern to the Delegate in the submission for the composite pack of ezetimibe and rosuvastatin (PM-2012-03419-1-3) and which remains of concern to the Delegate in this submission for the fixed dose combination tablet. This issue concerns the potential for a patient to have a rosuvastatin exposure after taking the fixed dose combination of ezetimibe 10 mg and rosuvastatin 40 mg higher than that after taking rosuvastatin 40 mg monotherapy.

In Study P03317, submitted for evaluation in Submission PM-2012-03419-1-3 (for the ezetimibe plus rosuvastatin composite packs), there was an increase in the mean AUC and the mean C_{max} for rosuvastatin when rosuvastatin was co-administered with ezetimibe compared to the administration of rosuvastatin alone [AUC 119% [90% CI 87%-162%]; C_{max} 117% [90% CI 84%-163%]]. Thus there is a 19% increase in the mean AUC which would represent an approximate 1.2 fold increase in that parameter. Since the associated 90% CI includes unity, the result is not statistically significant. However, as the Delegate has previously argued in the registration process for the composite pack, there will be some people who take the simple combination of ezetimibe 10 mg and rosuvastatin 40 mg, that is, in the absence of other relevant factors and whose rosuvastatin levels will be higher than if they had been exposed to the rosuvastatin 40 mg alone. In other words, the simple act of taking this combination in the absence of other relevant factors would constitute a situation "where an increase in rosuvastatin plasma levels may occur". The latter clinical situation is written into the currently approved Crestor (rosuvastatin) monotherapy PI and the currently approved PIs for the composite packs of ezetimibe and rosuvastatin as a contraindication to the taking of Crestor 40 mg or of the combination of ezetimibe 10 mg + rosuvastatin 40 mg. If there are other relevant clinical factors in play, the rosuvastatin plasma levels will be even higher than those arising simply by virtue of the combination. This issue is taken up again at the end of this section on safety, below.

The Delegate for the application to register ezetimibe + rosuvastatin composite packs had sought the advice of ACPM on this issue. The advice of the committee was 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 also recommended that the PI and RMP should be strengthened, especially for the highest dose.

In the approved PIs for the Ezalo and Rosuzet Composite Packs, there are several statements about the highest dosage strength. With the exception of a few minor amendments, largely the addition of cross-references and the change from reporting dosage strengths in monotherapy terms to fixed dose combination terms, the same statements are being carried across to the proposed PIs for the fixed dose combination tablets. The ACPM will be asked whether it considers that these statements are adequate or whether they need to be strengthened or added to in any way.

Changes to the EU SmPC 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. In the *Interactions with other medicinal products and other forms of interaction* section of the current EU SmPC for Crestor, 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. In the updated EU SmPC there is a table which includes interactions resulting in specific fold increases and percentage decreases in rosuvastatin AUC as well as interactions resulting in no change in rosuvastatin AUC. From this table it would appear that the dose adjustment recommendations pertain only to those interactions that result in approximately 2 fold or higher increases in rosuvastatin AUC although this is not clearly stated. The updated EU SmPC does not specify a dose reduction for rosuvastatin when it is co-administered with ezetimibe. Both the US and Canadian product information documents indicate that the

19% increase in rosuvastatin AUC resulting from the co-administration of ezetimibe and rosuvastatin is not considered clinically significant.

The clinical evaluator and also the RMP evaluator have identified a potential inconsistency in the *Contraindications* section of the presently approved Ezalo and Rosuzet Composite Pack PIs and the proposed PIs for the corresponding fixed dose combination tablets. This particular contraindication has been referred to above in this Overview. In the second part of the *Contraindications* there is a list of pre-disposing factors for myopathy/rhabdomyolysis which would contraindicate the combination of ezetimibe 10 mg + rosuvastatin 40 mg because of the presence of the rosuvastatin component at a dose level of 40 mg. One of these pre-disposing factors is listed as “situations where an increase in rosuvastatin plasma levels may occur”. The full list of contraindicating pre-disposing factors is in fact directly carried over from the Crestor (rosuvastatin) monotherapy PI. Firstly, it is noted that the contraindication clearly states that it only has to be a situation where an increase in rosuvastatin plasma levels may occur (Delegate’s underlining). Secondly, there may be other relevant factors which would compound such increases. Finally, under the sub-heading ‘*Renal Insufficiency*’ in the section *Dosage and Administration* section in both the approved PIs for the composite packs and in the proposed PIs for the fixed dose combination tablets, the sponsor acknowledges that there may be increased exposure to rosuvastatin in patients receiving this combination.

Clinical evaluator’s recommendation

The clinical evaluator 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 amendments to the PI and CMI.

The evaluator 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. 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 SmPC for Crestor and Canadian product monograph 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, it is information relevant to the safe use of rosuvastatin.

Risk management plan

The RMP evaluator has noted that, in the draft PIs, Rosuzet/Ezalo 10 mg/40 mg would be contraindicated in patients with pre-disposing factors for myopathy/rhabdomyolysis including situations where an increase in rosuvastatin plasma levels may occur¹². As further noted by the RMP evaluator, co-administration of ezetimibe and rosuvastatin may

¹² A fact also noted by the clinical evaluator and one which arises from the direct carry-over of the contraindications related to pre-disposing factors for myopathy/rhabdomyolysis from firstly the Crestor PI and secondly from the recently approved PIs for the ezetimibe + rosuvastatin composite pack PIs.

increase rosuvastatin AUC and so this would appear to preclude the use of the 10 mg/40 mg strength ezetimibe and rosuvastatin fixed dose combination tablet, that is, under any circumstances.

The RMP evaluator has recommended that, if the 10 mg/40 mg strength of the fixed dose combination tablet is approved, then the interaction between ezetimibe and rosuvastatin should be added to the RMP as a potential risk. In particular, the evaluator has recommended that the statement, "*Long-term safety of co-administration of ezetimibe and rosuvastatin at 10/40 mg*" be added to the table of ongoing safety concerns to ensure separate reporting for this missing information in any future PSUR. In turn the sponsor has proposed that this statement not be added as missing information to the ongoing safety concerns in the Australian RMP based on the same rationale submitted to the TGA during the post-ACPM negotiation period for the Rosuzet/Ezalo Composite Pack (PM-2012-03419-1-3), a rationale accepted at the time by the Delegate.

During the evaluation period for the composite packs, the sponsor submitted tabular data showing the number of PBS subsidised prescriptions written annually for rosuvastatin monotherapy and for rosuvastatin plus ezetimibe combination therapy. While the number of co-prescriptions for ezetimibe 10 mg + rosuvastatin 40 mg has been steadily rising, the data does not inform as to how many people are actually taking the combination, how long they remain taking the combination, how many may discontinue taking the combination (for whatever reason) and most importantly how many suffer AEs which may be attributable to the combination. No information can be gleaned as to the nature of any AEs suffered while someone is on the combination. If greater numbers of people are being exposed to this combination, then it is of fundamental importance that as much information as possible be gathered and as efficiently and accurately as possible, information which can elucidate the actual rate of AEs suffered by people taking the combination. The Delegate is strongly of the view that the recommended statement be added as missing information to the ongoing safety concerns in the Australian RMP. The ACPM was specifically requested to comment on this issue by the Delegate.

The RMP evaluator expressed concern that the statement, "*Due to the potential increase in rosuvastatin exposure when combined with ezetimibe, monitoring of patients on the highest dose of Rosuzet/Ezalo is recommended*", did not appear to have been included in the draft PIs for the Rosuzet/Ezalo fixed dose combination tablets. The Delegate agrees that this precaution has not been made explicit in the PI. The statement which is proposed to appear first under the heading *Precautions* is the following:

Treatment with the 10 mg +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."

This statement does not explicitly refer to the possibility of increased exposure to rosuvastatin by virtue of rosuvastatin's combination with ezetimibe and, like the RMP evaluator, the Delegate is of the view that there should be such a reference.

The Delegate strongly supports the recommendation of the RMP evaluator that the statement, "*Long-term safety of co-administration of ezetimibe and rosuvastatin at 10/40 mg*" be added to the table of ongoing safety concerns in the Australian RMP to ensure separate reporting for this missing information in any future PSUR.

Risk-benefit analysis

Delegate's considerations

The clinical evaluator is of the view that the overall benefit-risk balance for the ezetimibe/rosuvastatin 10 mg/5 mg, 10 mg/10 mg and 10 mg/20 mg fixed dose combination tablets, in the context of the proposed usage, is favourable. The Delegate agrees with this recommendation.

However, the clinical evaluator has recommended that the benefit-risk balance for the ezetimibe/rosuvastatin 10 mg/40 mg fixed dose combination tablets, in the context of the proposed usage, is unfavourable. There are no issues of bioequivalence with the respective monotherapies and no question that the fixed dose combination is not efficacious.

There is one unresolved issue which has safety implications and that is the potential for increased exposure to rosuvastatin above the level to which one would be exposed if one took rosuvastatin 40 mg monotherapy. Previous advice from the ACPM has been the issue should be managed in the same way that one should manage any other drug-drug interaction. However, the Delegate would argue that the situation is not so simple. While the approximate 1.2 fold increase in mean rosuvastatin AUC associated with the highest fixed dose combination is not statistically significant and may, of itself, be not clinically significant, the proposed product is a fixed dose combination tablet in which the potential for such increased exposures is an inherent, in-built characteristic of the product. The latter has created its own potentially elevated baseline and that is before any other relevant risk factors are taken into consideration.

In addition, as both the clinical evaluator and the RMP evaluator have pointed out, there is an inconsistency in the contraindications in the currently approved PI for the Ezalo/Rosuzet Composite Packs and in the draft PIs for the Ezalo/Rosuzet fixed dose combination tablets. The relevant contraindication concerns "situations where an increase in rosuvastatin plasma levels may occur". Under the subheading 'Renal Insufficiency' in the section *Dosage and Administration* in both the approved PIs for the composite packs and in the proposed PIs for the fixed dose combination tablets, the sponsor acknowledges that there may be increased exposure to rosuvastatin in patients receiving this combination. As has already been pointed above, the logical effect of this contraindication is seemingly to preclude the use of the highest dose strength combination. Furthermore, any amendment of this contraindication would have to be undertaken in such a way as not to be in conflict with the Crestor PI which is the ultimate source of this particular contraindication.

Overall, the Delegate is of the view that the ezetimibe/rosuvastatin 10 mg/40 mg fixed dose combination tablet is approvable provided that adequately strengthened precautions and warnings are inserted in the PI. The Delegate requested the sponsor consider this issue in its response to this Overview and provide appropriate PI amendments. The Delegate also proposed to request ACPM advice on this issue.

As already noted, the Delegate strongly supports the recommendation of the RMP evaluator that the statement, "Long-term safety of co-administration of ezetimibe and rosuvastatin at 10/40 mg" be added to the table of ongoing safety concerns in the Australian RMP to ensure separate reporting for this missing information in any future PSUR. As well, the Delegate endorsed the RMP evaluator's request that there be an explicit warning in the PI for monitoring of patients on the highest fixed dose combination due to the potential for increase in rosuvastatin exposure when rosuvastatin is combined with ezetimibe.

Proposed action

The Delegate had no reason to say, at this time, that the application for Rosuzet and Ezalo fixed dose combination tablets should not be approved for registration.

Specific conditions of registration proposed

The sponsor would be required to implement the Australian RMP for the ezetimibe + rosuvastatin composite pack and for the ezetimibe/rosuvastatin fixed dose combination tablet, updated to the satisfaction of the TGA from the RMP Version 1.3, data lock point 1-Dec-2012.

Request for ACPM advice

The Delegate proposed to seek general advice on this application from the ACPM and to request the committee provide advice on the following specific issues:

1. The ramifications of the currently worded contraindication which rules out the use of the fixed dose combination of ezetimibe/rosuvastatin 10/40 mg in “situations where an increase in rosuvastatin plasma levels may occur” (Delegate’s underlining).
2. Whether there should be an explicit warning in the PI that due to the potential increase in rosuvastatin exposure when combined with ezetimibe, monitoring of patients on the highest dose of Rosuzet/Ezalo is recommended.
3. Whether there are any other precautions and/or warnings specifically concerning the ezetimibe/rosuvastatin 10 mg/40 mg dosage strength which should be included in the proposed PI.
4. Whether the statement, “Long-term safety of co-administration of ezetimibe and rosuvastatin at 10/40 mg” should be added to the table of ongoing safety concerns in the Australian RMP to ensure separate reporting for this missing information in any future PSUR.
5. The overall safety profile of the ezetimibe/rosuvastatin 10 mg/40 mg fixed dose combination.

Response from sponsor

The sponsor concurs with the Delegate’s view that all doses, including the 10 mg/40 mg dose of ezetimibe/rosuvastatin fixed dose combination tablets, are approvable. The proposed indications for this fixed dose combination are identical to those already registered for ezetimibe + rosuvastatin composite pack 10 + 5 mg, 10 + 10 mg, 10 + 20 mg, 10 + 40 mg:

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 for patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis).

The Delegate has requested that the precautions and warnings in the PI be strengthened, and this matter is addressed below.

Although the co-administration of ezetimibe with rosuvastatin may increase rosuvastatin exposures by approximately 20% (Crestor US PI, Study P03317), the sponsor maintains that this increase is modest, largely within patient variability, is not clinically relevant and does not require dose adjustments or additional guidance for physicians for the following reasons. As set forth in rosuvastatin prescribing information, the rosuvastatin dose is individualised according to the goals of therapy and patient response, taking into account lipid levels, tolerability and the risk for adverse reactions. In this regard, rosuvastatin when administered as monotherapy is titrated from a starting dose, typically 10 mg, with administration of 40 mg only recommended for those patients not achieving LDL-C target following 20 mg administration. The Rosuzet/Ezalo product is expected to be prescribed in a similar manner. The safety of rosuvastatin (40 mg) with ezetimibe has been established in a clinical trial (EXPLORER, N=469) and supports the absence of any clinically meaningful pharmacokinetic differences in rosuvastatin exposure. Nevertheless, the sponsor has proposed further safety changes to the Rosuzet/Ezalo PI which are consistent with the Australian Crestor PI, US PI, Canadian Product Monograph, and EU SmPC as discussed below.

In addition to the lack of clinical relevance of the approximately 20% increase in the point estimate of the plasma concentration of rosuvastatin determined in P03317, a review of the Crestor prescribing information for special populations and drug interactions confirms that the reported mean change of approximately 20% is not clinically significant and does not require a dosing adjustment or further guidance. To this end, a mean change in AUC and C_{max} of up to approximately 2 fold has been accepted by the innovator of rosuvastatin as not requiring a dose adjustment (for example, Itraconazole, Eltrombopag, Darunavir and Dronedarone), as described in the Crestor labelling [Australian PI, US PI and Canadian PM]. This is consistent with the following comments the Delegate has made in the Delegate's overview:

- From this table (of drug interactions in the EU SmPC) it would appear that the dose adjustment recommendations pertain only to those interactions that result in approximately 2 fold or higher increases in rosuvastatin AUC. The updated EU SmPC does not specify a dose reduction for rosuvastatin when it is co-administered with ezetimibe
- Both the US and Canadian product information documents indicate that the 19% increase in rosuvastatin AUC resulting from the co-administration of ezetimibe and rosuvastatin is not considered clinically significant

Therefore, co-administration of rosuvastatin with ezetimibe resulting in approximately 20% increases does not require dose adjustment or other guidance, which is consistent with the prescribing information.

Proposed changes to the product information

The Delegate has requested that the sponsor provide appropriate amendments to the contraindication "situations where an increase in rosuvastatin plasma levels may occur" which are not in conflict with the Crestor PI and include strengthened precautions and warnings around the 10/40 mg dose.

The PI has been revised as per the Delegate's request. Details are beyond the scope of the AusPAR.

Safety of the ezetimibe/rosuvastatin 10/40 mg fixed dose combination

The Delegate has requested that the sponsor confirm the total number of patients exposed to ezetimibe 10 mg + rosuvastatin 40 mg for between 12 and 24 weeks.

From the clinical data provided with the present application, a total of 400 patients have been exposed to the highest dosage strength (10 mg/40 mg) combination (EXPLORER,

Stein 2005¹³, Stein 2007¹⁴, Ose 2005¹⁵ and Leibovitz 2006¹⁶). Of these, 145 were exposed for 12 to 24 weeks and 255 were exposed for 6 weeks. All studies showed the 10/40 mg combination to be well-tolerated with no treatment-related SAEs or AEs of concern beyond those seen in rosuvastatin 40 mg monotherapy, with the exception of alanine transaminase (ALT) elevations occurring more frequently in the 6 week EXPLORER study (n=235, 2.5% versus 0.4%), which is already documented in the proposed PI: *“the incidence of increased ALT at the 10 mg + 40 mg dose was 2.5% (n=6) for ezetimibe + rosuvastatin and 0.4% (n=1) for rosuvastatin alone.”*

The Delegate has also requested a summary and most up-to-date assessment of the post-marketing data available to describe the adverse profile of ezetimibe 10 mg + rosuvastatin 40 mg.

Ezetimibe (Ezetrol) has been marketed worldwide by the sponsor since 2002 and the sponsor has been collecting post-marketing AE reports in the Merck Adverse Event Reporting and Review System (MARRS) database since this time. However, because the sponsor has not marketed any products containing rosuvastatin to date, such extensive post-marketing data is not currently available for rosuvastatin and a comprehensive description of the adverse profile of ezetimibe 10 mg + rosuvastatin 40 mg cannot be provided. Nevertheless, a search of the MARRS database between 1 August 2013 and 15 June 2014 has not revealed any AE reports for this combination. The sponsor will continue to monitor the use of the ezetimibe and rosuvastatin combination and provide separate reporting for the long-term safety of the 10 mg/40 mg dose post-market (refer *Risk Management Plan* below).

Based on the greater efficacy of the 10 mg/40 mg dose, the present safety findings demonstrate a positive benefit-risk balance for the 10 mg/40 mg dose, especially in patients at high risk of chronic heart disease (CHD) and those with uncontrolled LDL-C levels despite treatment with the highest dose of rosuvastatin monotherapy.

Risk management plan

The Delegate is of the view that *“Long-term safety of co-administration of ezetimibe and rosuvastatin at 10/40 mg”* should be added as missing information to the ongoing safety concerns in the Australian RMP.

The sponsor concurs with the Delegate and proposes to add *“Long-term safety of co-administration of ezetimibe and rosuvastatin at 10/40 mg”* to the table of ongoing safety concerns such that this missing information will be reported separately in future PSURs.

Conclusion

The above evidence demonstrates that the potential for a slight increase in rosuvastatin plasma levels shown in one study is not clinically significant and would not preclude the use of the 10 mg/40 mg dose in patients at high risk of CHD and those with uncontrolled LDL-C levels despite treatment with rosuvastatin 40 mg. The sponsor believes that the additional information proposed in the PI and post-marketing surveillance of the safety of the 10 mg/40 mg dose would support safe use of the Rosuzet/Ezalo combination across all proposed dose strengths.

¹³ Stein, E., et al., Ezetimibe added to rosuvastatin for severely hypercholesterolemic patients: effects on low-density lipoprotein cholesterol and C-reactive protein, in 54th Annual Scientific Session of the American College of Cardiology 2005, *J American College of Cardiology*: 2005; p. 392A

¹⁴ Stein, E.A., et al., Further reduction of low-density lipoprotein cholesterol and C-reactive protein with the addition of ezetimibe to maximum-dose rosuvastatin in patients with severe hypercholesterolemia. *J Clinical Lipidology* 2007;1(4):280-286.

¹⁵ Ose, L., et al., W16-P-064 Ezetimibe added to rosuvastatin for severely hypercholesterolemic patients: Effects on lipid measures and C-reactive protein. *Atherosclerosis Supplements* 2005;6(1):117.

¹⁶ Leibovitz, E., et al., Th-P16:276 Efficacy and safety of rosuvastatin-ezetimibe combination for the treatment of severe hypercholesterolemia. *Atherosclerosis Supplements* 2006;7(3): 554.

Advisory committee considerations

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

The ACPM resolved to recommend to the TGA delegate of the Minister and Secretary that:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Rosuzet/Ezalo bilayer tablets, containing ezetimibe and rosuvastatin (as calcium) as a new combination of active ingredients in the doses of 10 mg/5 mg ezetimibe + rosuvastatin, 10 mg/10 mg ezetimibe + rosuvastatin, 10 mg/20 mg ezetimibe + rosuvastatin and 10 mg/40 mg ezetimibe + rosuvastatin to have an overall positive benefit-risk profile for the indications as follows;

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).

In making this consideration, the ACPM advised that the proposed changes to the PI and the RMP are sufficient for safe use of the proposed product.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

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

The ACPM agreed with the delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI).

Specific advice

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

1. The ramifications of the currently worded contraindication which rules out the use of the fixed dose combination of ezetimibe/rosuvastatin 10/40 mg in "situations where an increase in rosuvastatin plasma levels may occur" (Delegate's underlining).

The ACPM considered that the sponsor's proposed statements in the *Interactions with other drugs* section in the PI regarding the 19% increase in rosuvastatin AUC when co-administered with ezetimibe ... *the small increase was not considered clinically significant (see Precautions)* satisfactorily addressed the contradiction of the current PIs and would allow use of the highest dose of the combination product in circumstances where an increase in rosuvastatin levels might be expected.

2. Whether there should be an explicit warning in the PI that due to the potential increase in rosuvastatin exposure when combined with ezetimibe, monitoring of patients on the highest dose of Rosuzet/Ezalo is recommended.

The ACPM agreed with the Delegate that the PI should include a recommendation for monitoring of patients on the highest dose of Rosuzet/Ezalo. The ACPM considered that the proposed statement in the sponsor's pre-ACPM response was acceptable.

3. Whether there are any other precautions and/or warnings specifically concerning the ezetimibe/rosuvastatin 10 mg/40 mg dosage strength which should be included in the proposed PI.

Other than those identified by the Delegate, the ACPM did not consider that there were any other precautions and/or warnings that required in the PI.

4. Whether the statement, "Long-term safety of co-administration of ezetimibe and rosuvastatin at 10/40 mg" should be added to the table of ongoing safety concerns in the Australian RMP to ensure separate reporting for this missing information in any future PSUR.

The ACPM agreed that this statement should be added to the table of ongoing safety concerns in the Australian RMP. The ACPM noted that the sponsor in its pre-ACPM response agreed to report the missing information separately in future PSURs.

5. The overall safety profile of the ezetimibe/rosuvastatin 10 mg/40 mg fixed dose combination.

The ACPM considered that provided the changes were made to the PI and the RMP then the overall safety profile of the ezetimibe/rosuvastatin 10 mg/40 mg fixed dose combination was acceptable.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Rosuzet and Ezalo fixed dose combination tablets containing ezetimibe/rosuvastatin (as calcium) 10 mg/5 mg, 10 mg /10 mg, 10 mg/20 mg, and 10 mg/40 mg, indicated for:

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 for patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis).

Specific conditions of registration applying to these goods

- The Ezetimibe+ Rosuvastatin Composite Pack/Fixed Dose Combination Tablet Australian Risk Management Plan (RMP), Version 1.4 (undated, Data Lock Point 1 December 2012), included with submission PM-2013-02434-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The Product Information approved for Rosuzet at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at

<<https://www.tga.gov.au/product-information-pi>>. The PI for Ezalo is identical except for the product name.

Attachment 2. Extract from the Clinical Evaluation

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