



Australian Government

Department of Health  
Therapeutic Goods Administration

# Australian Public Assessment Report for ezetimibe and rosuvastatin (as calcium)

Proprietary Product Name: Ezalo Composite  
Pack / Rosuzet Composite Pack

Sponsor: Merck Sharp & Dohme Australia Pty  
Ltd

**March 2014**

## 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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# I. Introduction to product submission

## Submission details

<i>Type of submission:</i>	New combination of active ingredients
<i>Decision:</i>	Approved
<i>Date of decision:</i>	20 November 2013
<i>Active ingredients:</i>	Ezetimibe and rosuvastatin (as calcium)
<i>Product names:</i>	Ezalo Composite Pack / Rosuzet Composite Pack
<i>Sponsor's name and address:</i>	Merck Sharp & Dohme (Australia) Pty Limited Locked Bag 2234 North Ryde NSW 1670
<i>Dose form:</i>	Tablets
<i>Strengths:</i>	10 mg + 5 mg, 10 mg + 10 mg, 10 mg + 20 mg, 10 mg + 40 mg (ezetimibe + rosuvastatin, respectively)
<i>Pack sizes:</i>	20 tablets, 60 tablets
<i>Approved therapeutic use:</i>	<b>Primary Hypercholesterolaemia</b> Ezalo / Rosuzet Composite Pack 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: <ul style="list-style-type: none"><li>• not appropriately controlled with rosuvastatin or ezetimibe alone; or</li><li>• already treated with rosuvastatin and ezetimibe</li></ul> <b>Homozygous Familial Hypercholesterolaemia (HoFH)</b> Ezalo / Rosuzet Composite Pack is indicated for patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis).
<i>Route of administration:</i>	Oral
<i>Dosage:</i>	Rosuzet Composite Packs and Ezalo Composite Packs can be administered within the dosage range of 10/5 to 10/40 as a single daily dose. Specifically, the dosage regimen of Rosuzet Composite Pack and Ezalo Composite Pack is one Ezetrol and one MSD Rosuvastatin tablet to be taken at the same time, once daily, with or without food.
<i>ARTG numbers:</i>	203690, 203694, 203692, 203687, 203690, 203694, 203692, 203687

## Product background

This AusPAR describes a hybrid submission (clinical studies plus literature) by the sponsor, Merck Sharp & Dohme (Australia) Pty Limited (MSD), to register a composite pack containing two approved products:

- Ezetimibe (Ezetrol) 10 mg tablets (AUST R 91161) – sponsored and marketed by MSD;
- Rosuvastatin (as calcium) (Rosuvastatin SZ) 5/10/20/40 mg tablets (AUST R 183601, 183603, 183605, 183607) – sponsored by Sandoz (at the time of submission, MSD had applied to have the sponsorship of rosuvastatin transferred to MSD).

The submission consists of 2 new studies, 1 Periodic Safety Update Report (PSUR), and 52 literature papers (69 reports in total, including the manuscripts and abstracts, 17 of which were published in more than one journal or presented at more than one conference). The submission relies on the original studies submitted by the sponsor for the registration of ezetimibe as monotherapy and when co-administered with a statin plus this additional data in this submission. It is noted that the original ezetimibe submission did not include clinical studies with rosuvastatin.

The justification for the proposed composite pack was approved by the TGA (19 March 2012).

Two trade names are proposed: Rosuzet Composite Pack and Ezalo Composite Pack.

Ezetimibe (Ezetrol) is a compound that inhibits the intestinal absorption of cholesterol and plant related sterols. It was approved in 2003 in Australia, and is indicated for use as monotherapy or for co-administration with a statin. Rosuvastatin is a relatively newly approved statin in Australia, with a start date on the Australian Register of Therapeutic Goods (ARTG) of 26 April 2006 (Crestor). The rosuvastatin in the proposed combination is Rosuvastatin SZ. The ezetimibe Ezetrol ARTG start date was 23 June 2003.

The **approved** indication for ezetimibe is:

**Primary Hypercholesterolaemia:** *Ezetrol administered alone or with an HMG-CoA Reductase inhibitor (statin), is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia.*

**Homozygous Familial Hypercholesterolaemia (HoFH):** *Ezetrol, administered with a statin is indicated for patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis).*

**Homozygous sitosterolaemia (Phytosterolaemia):** *Ezetrol is indicated for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolaemia.*

The **approved** indication for the generic rosuvastatin (Rosuvastatin SZ), the statin in this application is:

*An adjunct to diet when the response to diet and exercise is inadequate for the treatment of hypercholesterolaemia (including familial hypercholesterolaemia).*

It has a second indication which is to:

*Prevent major cardiovascular events in men  $\geq 50$  years old and women  $\geq 60$  years old with no clinically evident cardiovascular disease but with at least two conventional risk factors for cardiovascular disease.*

Rosuvastatin SZ is indicated to:

*Reduce the risk of nonfatal MI, reduce the risk of nonfatal stroke, reduce the risk of coronary artery revascularisation procedures.*

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

The **proposed** indications are those recommended by the Advisory Committee on Prescription Medicines (ACPM) on 7 December 2012 and accepted by MSD for a similar ezetimibe and atorvastatin composite pack.

**Primary Hypercholesterolaemia:** *Rosuzet Composite Pack and Ezalo Composite Pack 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 Composite Pack and Ezalo Composite Pack is indicated for patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis).*

The prevention of major cardiovascular events is not requested as this is not in the current listing for ezetimibe, and treatment of sitosterolaemia is not requested as this is an indication for ezetimibe only.

## Regulatory status

A submission for a composite pack has not been lodged in the EU, USA or Canada and there are no such submissions planned. No other submissions have been made globally.

## Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

# II. Quality findings

## Drug substance and drug product

MSD has made this submission to register composite packs as wallets within a carton containing 10 mg ezetimibe tablets in blisters together with 5 mg, 10 mg, 20 mg and 40 mg rosuvastatin (as calcium) film coated tablets in blister packs containing 10 (starter packs) and 30 tablets with each active pharmaceutical ingredient (API) (that is, total 20 tablets for starter packs and 60 tablets commercial packs). The ezetimibe tablets are currently registered by MSD under the trade name Ezetrol (AUST R 91161) and the rosuvastatin tablets are currently registered by MSD under the trade name MSD Rosuvastatin (183601, 183603, 183605 and 183607).

No chemistry data have been provided for review. The sponsor is relying on data previously submitted in relation to the registered monotherapy products.

The proposed indications are for the treatment of:

### **Primary Hypercholesterolaemia**

*Rosuzet Composite Pack and Ezalo Composite Pack 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)**

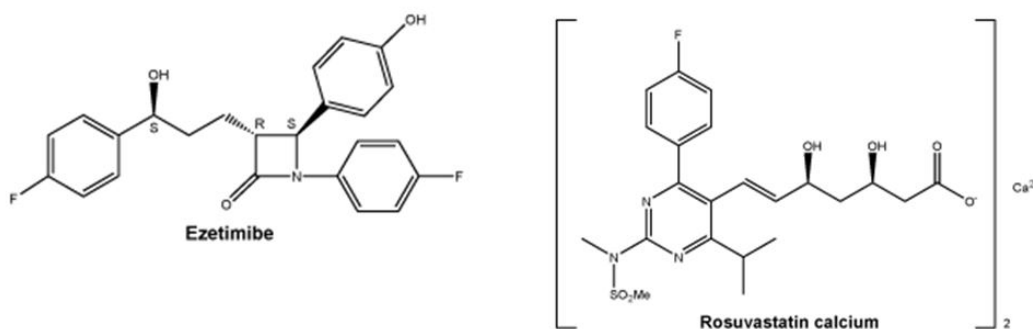
*Rosuzet Composite Pack and Ezalo Composite Pack is indicated for patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis).*

The ezetimibe drug substance used in 'Ezalo / Rosuzet Composite Pack 10mg + 5mg / 10mg + 10 mg / 10mg + 20 mg / 10 mg + 40 mg' is identical to that used in Ezetrol tablets.

The rosuvastatin as calcium drug substance used in 'Ezalo / Rosuzet Composite Pack 10mg + 5mg / 10mg + 10 mg / 10mg + 20 mg / 10 mg + 40 mg' is identical to that used in MSD Rosuvastatin tablets.

The structures of ezetimibe and rosuvastatin (as calcium) are shown in Figure 1.

**Figure 1: Structures of ezetimibe and rosuvastatin (as calcium [Ca]).**



There have been no changes with respect to quality of the APIs or finished products. The API and finished product specifications are the same as those for the already registered 'Ezetrol' and 'MSD Rosuvastatin' tablets.

The Ezetrol tablet is registered in one strength. The Ezetrol 10 mg tablet appearance is 'A white to off-white, capsule shaped tablet debossed with "414" on one side'.

The MSD Rosuvastatin tablets are registered in four strengths (5 mg, 10 mg, 20 mg and 40 mg).

The MSD Rosuvastatin 5 mg tablet appearance is 'Light brown, round, film coated tablets with "RSV 5" debossed on one side'. The MSD Rosuvastatin 10 mg tablet appearance is 'Brown, round, film coated tablets with "RSV 10" debossed on one side'. The MSD Rosuvastatin 20 mg tablet appearance is 'Brown, round, film coated tablets with "RSV 20" debossed on one side'. The MSD Rosuvastatin 40 mg tablet appearance is 'Brown, round, film coated tablets with "RSV 40" debossed on one side'.

The shelf life for the ezetimibe tablet component is 3 years when stored below 30°C in PVC/PCTFE (Aclar)/Al blisters. The shelf life for the rosuvastatin (as calcium) component is 2 years when stored below 25°C in Al/Al blisters. Given this, the shelf life for the proposed composite packs is 2 years when stored below 25°C in the above blisters within the composite pack wallet in a carton. Final mock ups labels have been provided. The wallet, blister and carton labels are acceptable from a chemistry perspective.

## Biopharmaceutics

The sponsor is relying on data previously submitted in relation to the registered ezetimibe monotherapy products (submission dated 17 April 2002) with respect to co-administration of ezetimibe with statins. Given this, the data have not been reviewed again.

- One 14 day pharmacokinetic/pharmacodynamic (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.
- Reference to 1 safety and efficacy clinical studies with 3 associated publications in relation to co-administration of ezetimibe with rosuvastatin.
- Reference to an additional 46 safety and efficacy data sets from 63 literature publications.

## 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

### Summary, conclusions and recommendation

- MSD is submitting a Category 1 Application to register a new composite pack for the treatment of hypercholesterolaemia. The composite pack consists of two approved products, Ezetrol (ezetimibe) 10 mg (AUST R 91161) and Rosuvastatin SZ (rosuvastatin as calcium) 5 mg (AUST R 18360 I) or 10 mg (AUST R 183603) or 20 mg (AUST R 183605) or 40 mg (AUST R183607).
- The nonclinical component of this submission primarily consisted of a justification for the absence of new nonclinical studies based on published guidelines.<sup>1</sup> In particular, the sponsor argued that the proposed ezetimibe and rosuvastatin composite pack fulfils the following criteria for which nonclinical studies are not required:
  - Ezetimibe and rosuvastatin individually are already 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 pharmacokinetic interactions have been identified.

This justification is acceptable from a nonclinical viewpoint.

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<sup>1</sup> European Medicines Agency, "Committee for medicinal products for human use (CHMP): Guideline on the nonclinical development of fixed combinations of medicinal products (EMA/CHMP/SWP/258498/2005)", 24 January 2008, Web, accessed 22 January 2014  
<[www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/10/WC500003976.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500003976.pdf)>.



- The sponsor also conducted an updated literature search on animal studies investigating ezetimibe co-administered with rosuvastatin. This resulted in the submission of a single published paper<sup>2</sup> investigating the influence of serum proprotein convertase subtilisin/kexin type 9 (PCSK9) protein levels on the LDL (low density lipoprotein) cholesterol (LDL-C) lowering of both rosuvastatin and/or ezetimibe in mice.
- Ezetimibe co-administered with rosuvastatin resulted in significantly greater reductions in serum non high density lipoprotein (HDL) compared to those seen for the individual components. This effect was also observed on apolipoprotein B (ApoB) levels. Serum non HDL, ApoB and triglyceride levels were further reduced with the addition of the Pcsk9 small interfering RNA (siRNA) with ezetimibe and rosuvastatin co-administration, with a near uniform reduction of all LDL cholesterol subfractions. Taken together, these data confirm the additive pharmacodynamic effects of ezetimibe and rosuvastatin in combination and also provide evidence that PCSK9 inhibitors, in combination with current therapies, have the potential to achieve greater reductions in both serum cholesterol and triglycerides.
- There are no objections to registration of the proposed composite pack of ezetimibe and rosuvastatin on nonclinical grounds.

## 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

This submission comprises 8 volumes of clinical data.

The submission comprises two new studies, 1 PSUR and 69 publications (including abstracts) that are all evaluated in this clinical evaluation report. The submission relies on the original studies submitted by MSD for the registration of ezetimibe as monotherapy and when co-administered with a statin plus this additional data in this submission. It is noted that the original ezetimibe submission did not include clinical studies with rosuvastatin. A CD called PART IV was also included; this included clinical study data from the ezetimibe submission (January 2002) that was reviewed and referred to but not re-evaluated.

Of the two new studies in this submission:

- One was a clinical Safety and Efficacy study with three associated publications
  - P139V1: A 6 week randomised, double blind, parallel arm study to evaluate the effects of ezetimibe 10 mg add on to rosuvastatin (5 mg or 10 mg) compared with doubling rosuvastatin dose (10 mg or 20 mg) in patients (n = 440) with hypercholesterolemia at moderately high and high risk for coronary heart disease (CHD).
- One was a PK/PD study with three associated publications
  - P03317: A 14 day study evaluating the effects of ezetimibe 10 mg and rosuvastatin 10 mg either alone or in combination in hypercholesterolaemic subjects.

The PSUR provided is that of ezetimibe, for 2011.

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<sup>2</sup> Ason B, et al. (2011) Improved efficacy for ezetimibe and rosuvastatin by attenuating the induction of PCSK9. *J Lipid Res.* 52: 679-687.

The literature based search was approved by the TGA on 30 May 2012 and included 69 references. As 21 of these included data that was published in more than one journal or abstracts submitted to more than one conference, there were thereby 48 literature studies, with either safety or efficacy data, for review:

- 11 Level II randomised controlled studies
- 3 Level III-1 controlled studies without randomization
- 6 Level III-2 studies with cohort or case controls
- 18 Level III-3 rime series studies
- 8 Level IV other observational studies including case series and case reports
- 2 Level I systematic reviews of statins (rosuvastatin was grouped with other statins)

## Pharmacokinetics

### Studies providing pharmacokinetic data

There was one new study with pharmacokinetic data, Study P03317 (Table 1). This was a 14 day study evaluating the effects of ezetimibe 10 mg and rosuvastatin 10 mg either alone or in combination in hypercholesterolaemic subjects. In summary, there was no clinically significant drug interactions reported between ezetimibe 10 mg and rosuvastatin 10 mg.

**Table 1. Submitted pharmacokinetic studies.**

PK topic	Subtopic	Study ID	Primary aim
<b>PK in healthy adults (with hypercholesterolemia)</b>	General PK - Single dose	P03317	To evaluate the PD effects and safety of the co-administration of ezetimibe and rosuvastatin in healthy hypercholesterolemia subjects
	- Multi-dose		
	Bioequivalence† - Single dose	P03317	
	- Multi-dose		
Food effect			
<b>PK in special populations</b>	Target population § - Single dose		
	- Multi-dose		
	Hepatic impairment		
	Renal impairment		
	Neonates/infants/children/adolescents		
	Elderly		
	@ {Other special pop'n}		
<b>Genetic/gender-related PK</b>	Males vs. females		
	@ {other genetic variable}		
<b>PK interactions</b>	@ [4]		
	@ {Drug B}		
	@ {Drug C}		
<b>Population PK analyses</b>	Healthy subjects		
	Target population		
	Other		

† Bioequivalence of different formulations.

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

There were three publications arising from this dataset.

One literature reference, by Kosoglou and colleagues<sup>3</sup> was a summary of the main study P03317. The other two references (Kosoglou and colleagues<sup>4</sup> and a Schering-Plough study<sup>5</sup>) did not provide new data.

No other new pharmacokinetic data were submitted.

### **Evaluator's overall conclusions on pharmacokinetics**

The new pharmacokinetic study undertaken for this application provided pharmacokinetic data that shows that there are minor changes in the pharmacokinetics with co-administration however these are unlikely to be clinically significant.

It is noted that Crestor (from the Netherlands) was the rosuvastatin used in the clinical trials assessing the combination of ezetimibe and rosuvastatin evaluated in this application.

### **Pharmacodynamics**

#### **Studies providing pharmacodynamic data**

Study P03317 also provided pharmacodynamic data. In summary, this was a single centre, randomised, investigator/evaluator blind placebo controlled, multiple dose, parallel group study to assess the PD and PK effects of ezetimibe 10 mg and rosuvastatin 10 mg alone and in combination in otherwise healthy hypercholesterolemic subjects.

The pivotal Study P139V1 was a multicentre 6 week randomised, double blind, parallel arm study to evaluate the effects of ezetimibe 10 mg add on to rosuvastatin (5 mg or 10 mg) compared with doubling rosuvastatin dose (10 mg and 20 mg) in patients (n = 440) with hypercholesterolemia at moderately high and high risk for CHD, provided PD and safety data.

No other new pharmacodynamic data were submitted.

Table 2 shows the studies relating to each pharmacodynamic topic.

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<sup>3</sup> Kosoglou T, et al. (2004) Pharmacodynamic interaction between ezetimibe and rosuvastatin. *Current Medical Research and Opinion* 20: 1185-1189.

<sup>4</sup> Kosoglou T, et al. (2004) M.660 Pharmacodynamic interaction between ezetimibe and rosuvastatin. *Atherosclerosis Supplements* 5: 153.

<sup>5</sup> Schering-Plough/Merck. (2008) Assessment of potential interaction between ezetimibe and rosuvastatin in healthy subjects with high cholesterol (P00317) <[clinicaltrials.gov/show/NCT00651144](http://clinicaltrials.gov/show/NCT00651144)>.

**Table 2. Submitted pharmacodynamic studies.**

PD Topic	Subtopic	Study ID	Primary aim
<b>Primary Pharmacology</b>	Effect on LDL-C and other lipids	P03317	To evaluate the PD effects and safety of the co-administration of ezetimibe and rosuvastatin in healthy hypercholesterolemia subjects
	Effect on {@ PD parameter B}	P139V1	to evaluate the effects of ezetimibe 10mg add-on to rosuvastatin (5mg or 10mg) compared with doubling rosuvastatin dose (10mg or 20mg) in patients (n=440) with hypercholesterolemia at moderately-high and high-risk for CHD
<b>Secondary Pharmacology</b>	Effect on {@ PD parameter C}		
	Effect on {@ PD parameter D}		
<b>Gender other genetic and Age-Related Differences in PD Response</b>	Effect of gender		
	Effect of @ {genetic characteristic}		
	Effect of @ {genetic characteristic}		
	Effect of age		
<b>PD Interactions</b>	@ [4]		
	@ {Drug B}		
	@ {Drug C}		
<b>Population PD and PK-PD analyses</b>	Healthy subjects		
	Target population		

Neither of the pharmacodynamic studies had deficiencies that excluded their results from consideration. There were no other PD studies that were excluded from consideration due to study deficiencies.

### Evaluator's overall conclusions on pharmacodynamics

It should be noted that both of the new studies submitted in this application were very short term studies (2 weeks and 6 weeks), for drugs that are likely to be used for many years. Further, the primary outcome of the studies was pharmacodynamic endpoints, not clinical outcomes. However, there are now many studies and two meta analyses which clearly show the relationship between LDL cholesterol lowering and reductions in cardiovascular events. The studies show the incremental benefit on LDL cholesterol from using ezetimibe and rosuvastatin together.

### Efficacy

The evidence establishing efficacy for ezetimibe co-administered with rosuvastatin is based on the original approval of ezetimibe co-administered with statins, summarised in the Ezetrol PI (clinical trials section), the two new studies, and the 69 publications (including the abstracts) for review. It should be noted that the original Ezetrol/statin application did not include data for the statin discussed in this application, that is, rosuvastatin.

The evaluator has reviewed the Ezetrol CD submitted with this application that had the original ezetimibe studies presented to the TGA for registration. In addition, the 14 day PK/PD study of rosuvastatin and ezetimibe (Study P03317) has been evaluated. The clinical study report from the relatively pivotal study in this application (P0319V1; 6 week randomised, double blind, parallel arm study to evaluate the effects of ezetimibe 10 mg add on to rosuvastatin (5 mg or 10 mg) compared with doubling rosuvastatin dose (10 mg or 20 mg) in patients (n = 440) with hypercholesterolemia at moderately high and high risk for CHD) is evaluated. A further 46 additional datasets (63 publications) presented as a literature review were also evaluated and relevant aspects added where appropriate for this application. The PSUR for ezetimibe is discussed.

In this section of the clinical evaluation report, the evaluator has summarised the relevant new studies and literature data in two sections: efficacy of ezetimibe with statins generally and efficacy of ezetimibe with rosuvastatin specifically.

### **Literature review**

The methodology of the search strategy for the literature review in this application was approved by the TGA. Essentially the strategy aimed to examine any published studies containing data related to co-administration of ezetimibe and rosuvastatin, by searching EMBASE, PubMed, ClinicalTrials.gov, Cochrane library, Toxline and MSD's internal databases (CLIC). It is noted that a large number of references were from the same datasets, many were abstracts and acknowledgement of ethics approval is often not provided.

### **Evaluator's conclusions on clinical efficacy for hypercholesterolemia and HoFH**

Overall, clinical efficacy in terms of greater LDL-C reduction was seen in both hypercholesterolemia and HoFH with the combination therapy. In the pivotal study P139V1, the addition of ezetimibe 10 mg to rosuvastatin (5 or 10 mg) daily for 6 weeks reduced LDL cholesterol significantly more than doubling the baseline dose of rosuvastatin. Pooled across strata, the LS mean percent change from baseline in LDL cholesterol at study endpoint was -20.96% on rosuvastatin (5 or 10 mg) + ezetimibe 10 mg but only -5.71% on rosuvastatin alone (10 or 20 mg).

Specifically addition of ezetimibe 10 mg to rosuvastatin 5 mg daily for 6 weeks reduced LDL-C to a greater extent than doubling the baseline dose to rosuvastatin 10 mg. The treatment difference was -12.31% (95% CI [Confidence Interval] -18.95, -5.67). The clinical significance of 5% reduction is not stated.

Addition of ezetimibe 10 mg to rosuvastatin 10 mg daily for 6 weeks reduced the levels of LDL-C more than doubling the baseline dose to rosuvastatin 20 mg. The treatment difference was -17.46% (95% CI -23.92, -10.99).

Addition of ezetimibe to rosuvastatin (5 or 10 mg) (pooled across doses) daily for 6 weeks resulted in a significantly greater proportion of patients reaching their LDL-C goal compared with doubling the baseline dose of rosuvastatin (pooled) (59.4 versus 30.9, adjusted odds ratio = -4.5, p = <0.001).

Data from this short term study with data on only 2 of the fixed dose combination (FDC) doses proposed in this application is of much higher direct relevance to this application than the 69 references which were all reviewed. Specifically, the data from the literature review is, in general, in short term studies examining the effect of combination therapy on LDL-C lowering compared to monotherapy alone. In this regard, the data for statins ezetimibe generally is very clearly supportive of the added efficacy on LDL-C targets. What is not so clear from these studies is the magnitude of the effects specifically from the use of rosuvastatin, a more potent statin than many of the statins used in the combined studies.

Also, as the doses used in the studies were either not specified, or used a dose lower than that requested in this application (2.5 mg), the actual likely effect on LDL-C for each of the dosing combinations proposed in this application is not known with certainty.

The limitations of the data are thus three fold:

- the effect on clinical outcomes is not measured
- the long term efficacy was not measured
- the dose response of LDL-C for the different doses proposed in the FDC is not clear

Published guidelines<sup>6</sup> make reference to these issues. Specifically, the data has shown a reduction in LDL-C and other lipid targets for monotherapy as per the guidelines. However, the guidelines states that ‘in principle, combination strategies are not expected to be licensed as first line therapy on the basis on their effect on LDL-C and other lipid parameters, in particular triglyceride (TG) and HDL-C alone, unless the applicant is able to justify the benefit of such strategy in terms of morbidity and mortality.’

Most of the data in the review appeared to be in ‘high risk’ vascular patients or patients with hypercholesterolemia. Most of the data related to HoFH was in case reports; here there were patients still not meeting LDL-C targets with the combination (although many were, and in those who still did not meet targets, plasmapheresis appeared to be an effective additional therapy).

Importantly also, although the sponsor studies conform with Good Clinical Practice (GCP) guidelines, much of the literature is in abstract form and ethics approval is not stated.

The tolerability in short term studies appears to be similar to that seen with other statin ezetimibe studies, although long term data was not presented here.<sup>7</sup>

## Safety

### Studies providing evaluable safety data

Study P139V1 provided evaluable safety data: many studies in the literature review (which included many retrospective audits) also collected clinical and/or laboratory safety data.

### *Pivotal efficacy studies*

In the pivotal efficacy Study P139V1, the following safety data were collected:

- General adverse events (AEs) were assessed by physical examination, electrocardiograph (ECG), vital signs, AE assessment and blood tests: haematology, blood chemistry, urinalysis creatine kinase (CK), alanine aminotransferase (ALT), aspartate aminotransferase (AST). The All Patients as Treated population was used for safety in this study consisting of all randomised patients who received at least one dose of study treatment.
- The analysis of safety followed a 3 tiered approach
  - Tier 1: Including gastrointestinal related AEs, gallbladder related AEs, allergic reaction or rash AEs, hepatitis related AEs, elevations in ALT/AST  $\geq 3 \times$  Upper

<sup>6</sup> European Medicines Agency, “Committee for medicinal products for human use (CHMP): Notes for Guidance on Clinical Investigation of medicinal products in the treatment of lipid disorders (CPMP/EWP/3020/03)”, 29 July 2004, Web, accessed 23 January 2014  
<[www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003235.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003235.pdf)>.

<sup>7</sup> The sponsor responded to comments in this section. Details of this response are beyond the scope of this AusPAR.

Limit of Normal (ULN), elevations in CK  $\geq 10 \times$  ULN, elevations in creatine phosphokinase (CPK)  $\geq 10 \times$  ULN with muscle symptoms and elevations in CPK  $\geq 10 \times$  ULN with drug related muscle symptoms.

- Tier 2: one or more AEs, drugs related AEs, serious AEs (SAEs), discontinuations due to an AE
- Tier 3 was everything else
- AEs of particular interest, including laboratory measurements of ALT/AST and CPK were assessed by laboratory tests.

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

Overall, the addition of ezetimibe to rosuvastatin was generally well tolerated across the groups. The overall safety profile also appeared generally comparable between treatment groups. Specifically, pooled across Strata, there were no clinically relevant differences between rosuvastatin (5 and 10 mg) + ezetimibe 10 mg and rosuvastatin (10 or 20 mg) in the proportion of patients with clinical adverse experiences, SAEs, or drug related AEs leading to discontinuation.

There were no significant differences between rosuvastatin (5 or 10 mg) + ezetimibe 10 mg and rosuvastatin (10 or 20 mg) with respect to the percentage of patients with gastrointestinal (GI) related, allergic reactions or rash, and hepatitis related AEs, elevations in ALT or AST  $\geq 3 \times$  ULN or CK elevations  $\geq 10 \times$  ULN. As can be seen from the summary, 3 (3%) subjects in the rosuvastatin 5 mg + ezetimibe 10 mg and 2 (1.6%) subjects in the rosuvastatin 10 mg + ezetimibe 10 mg discontinued due to a drug related AE, compared with 0 in either of the two rosuvastatin groups alone. These are small numbers but the fact that they occurred in the ezetimibe combination groups and not the rosuvastatin alone should be highlighted.

### **Evaluator's overall conclusions on clinical safety**

There appear to be no new safety issues with the use of these two compounds together as opposed to the two components individually as monotherapy. It is difficult to make causality judgements without information regarding the fatal outcome due to pancreatitis in an elderly woman on rosuvastatin commencing ezetimibe. However, the practice of lowering LDL to meet 'targets' in an elderly woman deserves some discussion; specifically around a cut off age in the indication. The application states there is worldwide exposure to people up to the age of 89 years old.

It is noted that there were several reports in the ezetimibe PSUR of AEs which were not part of the Company Core Data Sheet (CCDS). These included:

- Muscular weakness
- Asthenia and malaise

Also in the PSUR, there were 5 possible drug interactions notified, 4 of which were on drugs known to interact with ezetimibe. 1 report describes a potential interaction with thyroxine which is not currently listed in the PI.

It should be noted that one of the elevated CPKs was in a patient on concomitant rosuvastatin.

In the pivotal Study P139V1, the summary of AEs showed that 3 (3%) in the rosuvastatin 5 mg + ezetimibe 10 mg and 2 (1.6%) in the rosuvastatin 10 mg/ezetimibe 10 mg discontinued due to a drug related AE, compared to zero in either of the two rosuvastatin groups alone even though these were used at double the dose. These are small numbers but the fact that they occurred in the ezetimibe combination groups and not the rosuvastatin alone should be highlighted. These also included a doubling of GI AEs in the combination arms compared to the double dose rosuvastatin.

In the literature study, use of the combination was very short; often 4-6 weeks and therefore safety data was either not reported, or unlikely to occur to the short term nature of the studies. In the study by Steg and colleagues,<sup>8</sup> statins as a group were not differentiated but it should be noted that CPK elevations 5 x ULN were seen in two patients after the addition of ezetimibe (0.1%). A patient (0.1%) developed ALT >3 x ULN after commencing ezetimibe.<sup>9</sup>

## Clinical summary and conclusions

### First round benefit-risk assessment

#### *First round assessment of benefits*

The benefits of Ezalo/Rosuzet in the proposed usage are:

- Lowers LDL-C than either drug alone;
- May reduce difficulties of people taking two drugs in two different packaging at once;
- Reduces the need to use high doses of potent statin, by providing an alternative LDL-C lowering agent;
- Lowers co-payment for people taking the two drugs separately, although this is not relevant in the context of this report and is beyond the remit of the TGA.

#### *First round assessment of risks*

The risks of Ezalo/Rosuzet in the proposed usage are:

- There is no clinical data to show that the use of both drugs reduced clinical endpoints compared to monotherapy, although it is known that lowering LDL-C in population studies (notably predominantly with statins) has shown LDL-C to be a surrogate marker of clinical outcomes;
- Increased side effects compared to using monotherapy or from doubling the dose of statin;
- May encourage use of two therapies when one in higher dose could suffice.

#### *First round assessment of benefit-risk balance*

The benefit-risk balance of Ezalo/Rosuzet is unfavourable given the proposed usage, but would become favourable if the changes recommended are adopted, specifically a tightened indication.

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<sup>8</sup> Steg PG, et al. (2008) A randomised trial of three counselling strategies for lifestyle changes in patients with hypercholesterolemia treated with ezetimibe on top of statin therapy (TWICE). *Archives of Cardiovascular Diseases* 101: 723-735.

<sup>9</sup> The sponsor responded to comments in this section. Details of this response are beyond the scope of this AusPAR.



## First round recommendation regarding authorisation

The requested indication is:

**Primary Hypercholesterolaemia:** *Rosuzet Composite Pack and Ezalo Composite Pack 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 Composite Pack and Ezalo Composite Pack is indicated for patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis).*

Based on the evidence in this report and safety and efficacy data from previous submissions, the evaluator believes there is reasonable support from both an efficacy basis (lowering LDL-C) and safety (known safety profile of both drugs) to support an application for a FDC. However, without clinical data from the LDL-C lowering perspective, any benefit to the population is uncertain. Further, the justification to reduce an extra script cost is non compelling given the lack of evidence showing any effect in a population that is already on a number of medications, and the effect of a prescription safety net for high users. It is also beyond the remit of the TGA.

The indication needs to be tighter with an explicit statement not to be used as a first line agent, and in people who are already stabilised on doses of the two drugs individually. Lastly, the doses studied in the two new studies were 10/5 ezetimibe/rosuvastatin and 10/10 ezetimibe/rosuvastatin versus 10 and 20 mg rosuvastatin, and 10 mg rosuvastatin versus 10 mg combination ezetimibe/rosuvastatin. The efficacy and safety evidence for the 40 mg is provided in some of the observational data in the literature review, but is single cases or non-randomised, small numbers and observational data only. Similarly, the data for the benefit of the FDC which includes rosuvastatin 2.5 mg is also weak, with small numbers only. Evidence for the benefit of 20 mg/10 mg FDC compared to 20 mg rosuvastatin alone was also sparse. Therefore, the evaluator believes that the 2.5 mg, the 20 and the 40 mg rosuvastatin dose in the FDC should not be included until further data is available.

Specifically, the evaluator is concerned that although it is likely, evidence of an actual clinical benefit from the LDL-C lowering, or of a benefit that outweighs risk (increased side effects) of taking combination therapy has not been clearly demonstrated. Although the additional LDL-C lowering benefit is clearly seen, the translation of a percentage change in LDL-C on clinical outcomes is assumed from data using predominantly statin populations. The size of that benefit from combination therapy on outcomes here is thus difficult to have certainty in. This could be mitigated by a statement in the PI to this effect.<sup>10</sup>

The only clinical data supplied in this submission that queries the strength of this assumption was the published study (Kouvelos et al.<sup>11</sup>) examining the risk of cardiovascular events in a group receiving rosuvastatin 10 mg versus rosuvastatin 10 mg/ezetimibe 10 mg. Here there was no difference between the two groups ( $p = 0.72$ ).

Thus, the recommendation of this evaluator would be to recommend approval of the FDC in the 5 and 10 mg rosuvastatin-ezetimibe FDC but for people who are already stabilised

<sup>10</sup> The sponsor responded to comments in this section. Details of this response are beyond the scope of this AusPAR.

<sup>11</sup> Kouvelos GN, et al. (2013) Effects of rosuvastatin with or without ezetimibe on clinical outcomes in patients undergoing elective vascular surgery: results of a pilot study. *J Cardiovasc Pharmacol Ther.* 18: 5-12.

on the two therapies. Without clinical endpoint data, the evidence does not support it being used first line. This is also consistent with published guidelines.<sup>12</sup>

### List of questions

None.

## V. Pharmacovigilance findings

### Risk management plan

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA's Office of Product Review (OPR).

### Safety specification

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

**Table 3. Ongoing safety concerns for Ezalo/Rozuset.**

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

### Comments

It is recommended to the Delegate to request the following:

- The sponsor adds hepatic failure as important identified risk to the summary of ongoing safety concerns to the RMP. Any risk mitigation and pharmacovigilance activities to address this risk, should also be included.
- The sponsor adds the higher incidence of hospitalisation for kidney injury associated with the use of high potency statins to the post marketing section in the PI.

This recommendation is based on a recently published study which describes increased frequency of hospitalisation of patients for acute kidney injury using high potency statins (this includes rosuvastatin at a dose of  $\geq 10\text{mg}$ ).<sup>13</sup> Diagnosis code for acute kidney injury was defined as any of the following diagnoses: ICD-9 584, 584.5, 584.6, 584.7, 584.8, or 584.9; ICD-10 N17, N17.0, N17.1, N17.2, N17.8, or N17.9.

It is recommended to the Delegate to request one or both of the following:

<sup>12</sup> European Medicines Agency, "Committee for medicinal products for human use (CHMP): Guideline on clinical development of fixed combination medicinal products (CHMP/EWP/240/95 Rev. 1)", 19 February 2009, Web, accessed 22 January 2014 <[www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003686.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003686.pdf)>.

<sup>13</sup> Dormuth CR, et al. (2013) Use of high potency statins and rates of admission for acute kidney injury: multicenter, retrospective observational analysis of administrative databases. *BMJ* 346: f880.

- The sponsor makes additions to the PI, informing health care professionals that co-administration of the two products causes an increase in rosuvastatin plasma concentration.
- Restrict the use of the highest rosuvastatin dose of 40 mg in combination with ezetimibe.

The sponsor provides data from the only conducted rosuvastatin/ezetimibe PD/PK study (Study P03317). This data shows an increase in rosuvastatin peak plasma drug concentration ( $C_{max}$ ) of 17% and area under the plasma concentration-time curve within first 24 h ( $AUC_{0-24h}$ ) of 19%. The sponsor recognises this increase in rosuvastatin levels (in the cover letter for this application) but concludes that this is not clinically significant. This study was conducted with a rosuvastatin dose of 10 mg and higher rosuvastatin doses were not used in this study. The RMP evaluator raises a concern that PD/PK profile is not established for rosuvastatin doses >10 mg. The increase in  $C_{max}$  and  $AUC_{0-24h}$  observed in the study may have the potential to be clinically significant, in particular, at a rosuvastatin dose of 40mg. This dose, as stated in the PI, should only be used after careful consideration of the risk/benefit for the patient and if close patient monitoring is planned. This dose causes a higher incidence of adverse events, including proteinuria and rhabdomyolysis. An increase in  $C_{max}$  of 17% and  $AUC_{0-24h}$  of 19%, due to co-administration with ezetimibe, may cause the plasma levels of rosuvastatin to be higher than with the highest approved single dose of rosuvastatin. Consequently, this may cause more SAEs. This is also of relevance for the Asian patient population where 20 mg of rosuvastatin is the highest recommended dose. Co-administration of ezetimibe with 20 mg of rosuvastatin may cause the plasma levels of rosuvastatin to be higher than with the 20 mg single dose of rosuvastatin.

### Pharmacovigilance plan

A summary of the pharmacovigilance plan is shown in Table 4.

**Table 4. Summary of pharmacovigilance plan.**

<b>Pharmacovigilance Plan</b>	<input checked="" type="checkbox"/> Acceptable	
	<input type="checkbox"/> Not acceptable	
	<input type="checkbox"/> Routine <input type="checkbox"/> Clinical Trial(s) <input type="checkbox"/> Meta-analysis <input type="checkbox"/> Retrospective analysis of completed trials <input type="checkbox"/> Pharmacoepidemiology/epidemiology study <input type="checkbox"/> Drug utilisation study <input type="checkbox"/> Patient registry	<input type="checkbox"/> Follow-up questionnaires <input type="checkbox"/> Case report forms <input type="checkbox"/> Adjudication committees <input type="checkbox"/> Physician surveys <input type="checkbox"/> Prescription event monitoring <input type="checkbox"/> Other (please specify): <input type="text"/>

### Risk minimisation activities

A summary of the risk minimisation activities are shown in Table 5.

**Table 5. Summary of risk minimisation activities.**

<b>Risk Minimisation activities</b>	<input checked="" type="checkbox"/> Acceptable	
	<input type="checkbox"/> Not acceptable	
	<input type="checkbox"/> Routine <input type="checkbox"/> Patient education <input type="checkbox"/> Healthcare professional education <input type="checkbox"/> Safety device design <input type="checkbox"/> Dear health professional letters	<input type="checkbox"/> Restricted access <input type="checkbox"/> Patient registry <input type="checkbox"/> Other (please specify): <input type="text"/>

**Summary of recommendations**

- The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of the ezetimibe + rosuvastatin RMP version 1.0, dated 6 December 2012 and any future updates is imposed as a condition of registration; and the submitted EU-RMP is applicable without modification in Australia unless so qualified. The draft PI and CMI documents should **not** be revised until the Delegate's Overview has been received.
- Safety considerations may be raised by the clinical and nonclinical evaluators through the consolidated section 31 request and/or the nonclinical and clinical evaluation reports, respectively. It is important to ensure that the information provided in response to these includes consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.

The font size of the adverse effect of Interstitial Lung Disease in the proposed PI should be changed. The font size for Interstitial Lung Disease in the AE section in the PI is smaller than all other writing in the PI. This should be adjusted to obtain consistency throughout the document.

It is recommended to the Delegate to request the following:

- The sponsor adds hepatic failure as important identified risk to the summary of ongoing safety concerns to the RMP. Any risk mitigation and pharmacovigilance activities to address this risk, should also be included.
- The sponsor adds the higher incidence of hospitalisation for kidney injury associated with the use of high potency statins to the post marketing section in the PI.

It is recommended to the Delegate to request one or both of the following:

- The sponsor makes additions to the PI, informing health care professionals that co-administration of the two products causes an increase in rosuvastatin plasma concentration.
- Restrict the use of the highest rosuvastatin dose of 40 mg in combination with ezetimibe.

The sponsor is asked to please clarify if the Ezalo Composite Pack contains Zetia and Rosuvastatin SZ. If this will be confirmed then amendments to the PI, CMI and the packaging are recommended to reflect that Ezalo is a combination of these two trade names.

## **Second round evaluation of the sponsor's response to the RMP evaluation**

Reconciliation of issues outlined in the RMP report is as follows.

### ***Recommendation in RMP evaluation report:***

The font size of the adverse effect of interstitial lung disease in the proposed PI should be changed. The font size for ILD in the AE section in the PI is smaller than all other writing in the PI. This should be adjusted to obtain consistency throughout the document.

### ***Sponsor's response (or summary of the response):***

This has been amended. The revised draft PI is included in Module 1.3.1 addendum.

### ***OPR evaluator's comment:***

This is considered acceptable.

### ***Recommendation in RMP evaluation report:***

It is recommended to the Delegate to request the sponsor adds hepatic failure as important identified risk to the summary of ongoing safety concerns to the RMP. Any risk mitigation and pharmacovigilance activities to address this risk, should also be included.

### ***Sponsor's response (or summary of the response):***

The sponsor agrees to add hepatic failure as an important identified risk to the summary of ongoing safety concerns in the RMP. The sponsor provides the assurance that this will be included in the next revision of the RMP, and the appropriate regulatory action will be taken to provide this to the TGA post registration in accordance with the conditions of registration for the product.

### ***OPR evaluator's comment:***

This is considered acceptable.

### ***Recommendation in RMP evaluation report:***

It is recommended to the Delegate to request the sponsor adds the higher incidence of hospitalisation for kidney injury associated with the use of high potency statins to the post marketing section in the PI. This recommendation is based on a recently published study which describes increased frequency of hospitalisation of patients for acute kidney injury using high potency statins (this includes rosuvastatin at a dose of  $\geq 10$  mg). Diagnosis code for acute kidney injury was defined as any of the following diagnoses: ICD-9 584, 584.5, 584.6, 584.7, 584.8, or 584.9; ICD-10 N17, N17.0, N17.1, N17.2, N17.8, or N17.9).<sup>14</sup>

### ***Sponsor's response (or summary of the response):***

The sponsor notes the recommendation to add the higher incidence of hospitalisation for kidney injury associated with the use of high potency statins to the post marketing section of the PI and will await the advice of the Delegate with regard to this recommendation.

### ***OPR evaluator's comment:***

The RMP evaluator would like to draw the Delegate's attention to this detail.

### ***Recommendation in RMP evaluation report:***

It is recommended to the Delegate to request one or both of the following:

- The sponsor makes additions to the PI, informing health care professionals that co-administration of the two products causes an increase in rosuvastatin plasma concentration.

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<sup>14</sup> Dormuth CR, et al. (2013) Use of high potency statins and rates of admission for acute kidney injury: multicenter, retrospective observational analysis of administrative databases. *BMJ* 346: f880.

- Restrict the use of the highest rosuvastatin dose of 40mg in combination with ezetimibe.

The sponsor provides data from the only conducted Rosuvastatin/Ezetimibe PD/PK study (P03317). This data shows an increase in rosuvastatin  $C_{max}$  of 17% and  $AUC_{0-24h}$  of 19%. The sponsor recognises this increase in rosuvastatin levels (in the cover letter for this application) but concludes that this is not clinically significant. This study was conducted with a rosuvastatin dose of 10 mg and higher rosuvastatin doses were not used in this study. The RMP evaluator raises a concern that PD/PK profile is not established for rosuvastatin doses >10mg. The increase in  $C_{max}$  and  $AUC_{0-24h}$  observed in the study may have the potential to be clinically significant, in particular, at a rosuvastatin dose of 40 mg. This dose, as stated in the PI, should only be used after careful consideration of the risk/benefit for the patient and if close patient monitoring is planned. This dose causes a higher incidence of adverse events, including proteinuria and rhabdomyolysis. An increase in  $C_{max}$  and  $AUC_{0-24h}$  of 19%, due to co-administration with ezetimibe, may cause the plasma levels of rosuvastatin to be higher than with the highest approved single dose of rosuvastatin. Consequently, this may cause more serious adverse events. This is also of relevance for the Asian patient population, where 20 mg of rosuvastatin is the highest recommended dose. Co-administration of ezetimibe with 20 mg of rosuvastatin may cause the plasma levels of rosuvastatin to be higher than with the 20 mg single dose of rosuvastatin.

***Sponsor's response (or summary of the response):***

The sponsor notes the recommended changes to the PI and will await the advice of the delegate with regard to these recommendations.

Please note that the following is already included under DOSAGE AND ADMINISTRATION in the draft PI:

*A dose adjustment can be made after 4 weeks of therapy where necessary. The usual maximum dose of rosuvastatin is 20 mg once per day.*

*A dose of 40 mg rosuvastatin once per day should only be considered in patients who are still at high cardiovascular risk after their response to a dose of 20 mg once per day is assessed. This may particularly apply to patients with familial hypercholesterolaemia. It is recommended that the 40 mg dose is used only in patients in whom regular follow-up is planned. A dose of 40 mg rosuvastatin must not be exceeded in any patient.*

*Specialist supervision should be considered when the dose is titrated to 40 mg.*

***OPR evaluator's comment:***

The RMP evaluator would like to draw the delegate's attention to this detail.

***Recommendation in RMP evaluation report:***

The sponsor is asked to please clarify if the Ezalo Composite Pack contains Zetia and Rosuvastatin SZ. If this will be confirmed then amendments to the PI, CMI and the Packaging are recommended to reflect that Ezalo is a combination of these two trade names.

From the information provided in the cover letter for this application, it is understood that Ezalo Composite Pack contains Zetia and Rosuvastatin SZ, and that Rosuzet Composite Pack contains Ezetrol and Rosuvastatin SZ. The sponsor is asked to please provide confirmation/clarification about this. If Ezalo Composite Pack contains Zetia and Rosuvastatin, then the statement in the Ezalo PI should read: Ezalo Composite Pack is a combination pack containing Zetia (ezetimibe) tablets 10mg and Rosuvastatin SZ (rosuvastatin) tablets 5, 10, 20, 40 mg. Moreover, the PI refers to Ezetrol instead to Zetia in various sections. This amendment also has to be made to the CMI and the packaging for Ezalo Composite Pack.

**Sponsor's response (or summary of the response):**

MSD confirms that the Ezalo Composite Pack contains Ezetrol and MSD Rosuvastatin.

References in the PI and CMI to Rosuvastatin-SZ have been changed to MSD Rosuvastatin following transfer of the registration and change in the name of these products, as discussed above.

References to Ezetrol remain unchanged.

**OPR evaluator's comment:**

This clarification that the Ezalo and the Rosuzet Composite pack both contain Ezetrol (ezetimibe) and MSD Rosuvastatin is noted.

**Outstanding issues***Issues in relation to the RMP*

- The RMP evaluator recommended in the Round 1 RMP evaluation that the sponsor adds the higher incidence of hospitalisation for kidney injury associated with the use of high potency statins to the post marketing section in the PI.
- The RMP evaluator recommended in the Round 1 RMP evaluation report that the delegate could consider one or both of the following:
  - The sponsor makes additions to the PI, informing health care professionals that co-administration of the two products causes an increase in rosuvastatin plasma concentration.
  - Restrict the use of the highest rosuvastatin dose of 40 mg in combination with ezetimibe.<sup>15</sup>

*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***Office of Medicines Authorisation (OMA) Clinical Evaluation Report*

The clinical evaluator made the following statement regarding the safety specification of the RMP:

*The Safety Specification in the draft RMP (version 1.0) is satisfactory. Routine pharmacovigilance for the known AEs with ezetimibe are appropriate. There are no AEs seen in the clinical trials that were not documented in the RMP. Both components of the blister pack combination have been marketed for over 5 years. The RMP has assumed that pharmacovigilance issues are likely to be similar to the two agents taken either singularly (that is, in different populations) or in combination as single drugs. While this is a reasonable assumption, it should be noted (and is acknowledged in the RMP) that there is only one safety and efficacy study performed (Study P139V1). This is a small (440 subject), short term (6 week) randomised, double blind, parallel arm study to evaluate the effects of ezetimibe 10 mg add on to rosuvastatin (10-20 mg) in patients with hypercholesterolemia at moderately high and high risk for CHD.*

*Office of Scientific Evaluation (OSE) nonclinical evaluation report*

The nonclinical evaluator made the following statement regarding the nonclinical aspects of the RMP:

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<sup>15</sup> The sponsor responded to comments in this section. Details of this response are beyond the scope of this AusPAR.

*Results and conclusions drawn from the nonclinical program for Rosuzet detailed in the sponsor's draft RMP (Module 1.13, Section 1.1) are in general concordance with those of the nonclinical evaluator.*

#### **OPR evaluator's comments**

The evaluator has no objection to the above changes and recommends to the Delegate that the updated version is implemented.

#### **Suggested wording for conditions of registration**

##### **RMP**

Implement RMP for Ezetimibe + Rosuvastatin Composite Pack, version 1.0, dated 6 December 2012, data base lock 1 December 2012, and any future updates as a condition of registration.

##### **PSUR**

OMA to provide new wording when finalised.

## **VI. Overall conclusion and risk/benefit assessment**

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

### **Quality**

No chemistry data have been provided for review. The sponsor is relying on data previously submitted in relation to each of the registered monotherapy products.

There have been no changes with respect to the quality of the APIs or finished products. The specifications of both the latter are the same as those for the already registered 'Ezetrol' and 'MSD Rosuvastatin' (transfer of the Sandoz product 'Rosuvastatin SZ' to the sponsorship of MSD under the new tradename 'MSD Rosuvastatin'). The Ezetrol tablet is registered in one strength, 10 mg. The MSD Rosuvastatin tablets are registered in 4 strengths, 5 mg, 10 mg, 20 mg and 40 mg.

The composite pack consists of two currently registered products, in their currently approved blister packaging. One blister slide of each medicine is then packed into a wallet-style calendar pack. The shelf life of the ezetimibe tablet component is 3 years when stored below 30°C in its blisters while the shelf life of the rosuvastatin (as calcium) component is 2 years when stored below 25°C in its blisters. Given this, the shelf life of the proposed composite pack is 2 years when stored below 25°C in the blisters within the composite pack wallet in a carton. The wallet, blister and carton labels are acceptable from a Quality perspective.

There are no objections to registration of the composite pack from a Quality perspective.

### **Nonclinical**

There was no requirement for a nonclinical evaluation in a submission of this type. The nonclinical data for this submission primarily consisted of a justification for the absence of new nonclinical studies based on the published guidelines,<sup>16</sup> section 4.2.1. In particular,

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<sup>16</sup> European Medicines Agency, "Committee for medicinal products for human use (CHMP): Guideline on the nonclinical development of fixed combinations of medicinal products (EMA/CHMP/SWP/258498/2005)", 24



the sponsor argued that the proposed ezetimibe and rosuvastatin composite pack fulfils the following criteria for which nonclinical studies are not required:

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

The nonclinical evaluator was of the opinion that the justification was acceptable from a nonclinical viewpoint.

The sponsor also conducted an updated literature search on animal studies investigating ezetimibe co-administered with rosuvastatin. This resulted in the submission of a single published paper,<sup>17</sup> investigating the influence of serum PCSK9<sup>18</sup> protein levels on the LDL-C lowering of both rosuvastatin and/or ezetimibe in mice.

Ezetimibe co-administered with rosuvastatin resulted in significantly greater reductions in serum non HDL compared to those seen for the individual components. This effect was also observed on ApoB levels. Serum non HDL, ApoB, and triglyceride levels were further reduced with the addition of the Pcsk9 siRNA<sup>19</sup> with ezetimibe and rosuvastatin co-administration, with a near uniform reduction of all LDL cholesterol subfractions. Taken together, these data confirm the additive pharmacodynamic effects of ezetimibe and rosuvastatin in combination and also provide evidence that PCSK9 inhibitors, in combination with current therapies, have the potential to achieve greater reductions in both serum cholesterol and triglycerides.

The nonclinical evaluator concluded that there were no objections to registration of the proposed composite pack of ezetimibe and rosuvastatin on nonclinical grounds. In the nonclinical evaluation report, the evaluator made some recommendations concerning the PI, all of which are endorsed by the Delegate.

## Clinical

### Pharmacokinetics

There was one new study with PK data, Study P03317. This was a single centre, randomised, investigator/evaluator blind, placebo controlled, multiple dose, parallel group study in 40 subjects with hypercholesterolaemia but otherwise healthy. Subjects were randomised to one of the four following treatments, once daily for 14 days: ezetimibe 10 mg + rosuvastatin 10 mg (12 subjects); rosuvastatin 10 mg + placebo (12

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January 2008, Web, accessed 22 January 2014 Guideline on the non-clinical development of fixed combinations of medicinal products

<[www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/10/WC500003976.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500003976.pdf)>.

<sup>17</sup> Ason B, et al. (2011) Improved efficacy for ezetimibe and rosuvastatin by attenuating the induction of PCSK9. *J Lipid Res.* 52: 679-687.

<sup>18</sup> PCSK9 increases circulating LDL-C by binding to and inducing the internalization and subsequent degradation of the LDL receptor. Note: PCSK9, upper case, refers to the protein/enzyme, i.e. the product of gene expression whereas *Pcsk9*, italicised and part upper case and part lower case, refers to the underlying gene or gene-related material (such as mRNA or siRNA).

<sup>19</sup> Small interfering RNAs (siRNAs) were used to knock down the expression of proprotein convertase subtilising/kexin type 9 (*Pcsk9*).

subjects); ezetimibe 10 mg plus placebo (8 subjects); placebo + placebo (8 subjects). There was no cross over. Of the 40 subjects enrolled, 39 completed the study.

The relative bioavailability (90% CI) for the combination ezetimibe 10 mg + rosuvastatin 10 mg compared to rosuvastatin 10 mg + placebo was 117% (84%, 163%) based on the log transformed  $C_{max}$  and was 119% (87%, 162%) based on the log transformed AUC. While the point estimates were above 100%, both CIs spanned unity. The upper limits of each 90% CI indicate the possibility of 62-63% increases in the value of each rosuvastatin parameter in the presence of ezetimibe 10 mg. Such increases are not beyond the bounds of possibility. The point estimate is essentially a sample mean. Combinations of ezetimibe with a statin have the potential for wide uptake amongst patients with lipid abnormalities. Such a large population could be expected to be characterised by a huge range of inter individual differences with regard to the uptake, handling and disposition of drugs. Therefore, the numbers of people in whom there may be increases in  $C_{max}$  and in AUC above the level of the point estimate may in turn be large. While the bioavailability results are not so clinically significant for the lower dosage strengths of 5, 10 or 20 mg of rosuvastatin, there are possible if not highly probable ramifications when one considers the effect of ezetimibe 10 mg upon concomitant rosuvastatin 40 mg. The effect would in all likelihood involve higher exposures to rosuvastatin than would be experienced by exposure to rosuvastatin 40 mg monotherapy. Given that the rosuvastatin monotherapy PI expressly forbids dosages of rosuvastatin higher than 40 mg, this does present a potentially serious problem. The Delegate is of the opinion that it is a potentially serious problem. How is this problem to be managed? Should there be warnings about this issue in the PI? Is the issue sufficiently serious to warrant rejection of the dosage strength ezetimibe 10 mg + rosuvastatin 40 mg? Would it be possible to contra indicate the highest dosage strength ezetimibe 10 mg + rosuvastatin 40 mg for an identifiable subpopulation, for example, subjects with any degree of hepatic and/or renal impairment? Both the sponsor and the ACPM are requested to comment on this issue.

The effects mentioned in the preceding paragraph are likely to be exacerbated in the presence of either impaired hepatic function or impaired renal function. With regard to impaired hepatic function, the proposed PI states that no dosage adjustment is required in patients with mild hepatic insufficiency. Treatment is not recommended in patients with either moderate or severe hepatic dysfunction. Now, one knows from the PI for ezetimibe that after a single 10 mg dose of ezetimibe, AUC for total ezetimibe was increased ~1.7 fold in patients with mild hepatic impairment. This increased exposure to ezetimibe in the presence of mild hepatic impairment can be presumed to have a compounding effect on the already increased exposure to any concomitant rosuvastatin (by a factor of  $1.7 \times 1.19 = 2.02$ ). Thus, the Delegate is concerned about the levels of exposure to rosuvastatin when ezetimibe 10 mg is given in combination with rosuvastatin 40 mg in the presence of mild hepatic impairment. There can be no doubt that there would be higher exposures to rosuvastatin than would be experienced by exposure to rosuvastatin 40 mg monotherapy. In fact, based on the factor of 2.02, the exposure would be equivalent to  $2.02 \times 40 \text{ mg} = 80.8 \text{ mg}$ . There would also be concerns about a person with mild hepatic impairment being exposed to ezetimibe 10 mg + rosuvastatin 20 mg. The effective rosuvastatin exposure would just exceed that produced by rosuvastatin monotherapy 40 mg. The sponsor and the ACPM are asked to comment.

From the respective monotherapy PIs, it is known that subjects with severe renal impairment had a 3 fold increase in plasma concentration of rosuvastatin compared to healthy volunteers and that, after a single 10 mg dose of ezetimibe in patients with severe renal disease, the mean AUC for total ezetimibe was increased ~1.5 fold compared to healthy subjects. Based on point estimates, it is known that concomitant ezetimibe will increase the exposure to rosuvastatin by 19%, that is, by a factor of 1.19. Thus, it can be anticipated that in the presence of severe renal impairment, concomitant ezetimibe will increase the exposure to rosuvastatin by a factor of  $1.19 \times 1.5 \times 3 = 5.4$  fold. The current

advice in the rosuvastatin monotherapy PI is that for patients with severe renal impairment not on dialysis the dose of rosuvastatin should be started at 5 mg once daily and not exceed 10 mg once daily. This advice is clearly based on the 3 fold increase in AUC to rosuvastatin monotherapy in the presence of severe renal impairment, meaning that exposure to a 10 mg dose of rosuvastatin monotherapy in a person with severe renal impairment would give the same exposure as a 30 mg dose in a person with normal renal function. In this situation, exposure to possible rosuvastatin doses above the threshold of 10 mg, for example, 15 mg or 20 mg would yield exposures at levels higher than those experienced by subjects with normal renal function taking the maximum rosuvastatin dose of 40 mg. However, as the Delegate has already calculated, in the presence of both ezetimibe and severe renal impairment and taking into account the effect of that severe renal impairment on both ezetimibe and rosuvastatin, it can be anticipated that rosuvastatin exposure increases by a factor of 5.4. Thus, the proposed advice in the composite pack PI that, in the presence of severe renal impairment, the dosage of the rosuvastatin component could be increased to 10 mg, means that the person would be exposed to the same AUC as that to which a person with normal renal function would be exposed if that person with normal renal function had taken a dose of  $10 \text{ mg} \times 5.4 = 54 \text{ mg}$ . The latter is well above the maximum permitted dose of 40 mg. The Delegate is of the opinion that the proposed advice in the composite pack PI should state that, in the presence of severe renal impairment, the maximum dose of the composite pack should be ezetimibe 10 mg + rosuvastatin 5 mg. Both the sponsor and the ACPM are asked to comment.

With regard to mild to moderate renal impairment, the situation is not clear. The rosuvastatin monotherapy PI states that PK evaluation in subjects with varying degrees of renal impairment determined that mild to moderate renal disease had little influence on plasma concentrations of rosuvastatin. There is no information in the ezetimibe monotherapy PI about the effect on ezetimibe AUC of either mild or moderate renal impairment. The sponsor is requested, in its pre ACPM response, to provide the most precise details available about the effect of ezetimibe upon concomitant rosuvastatin exposure in the setting of mild or moderate renal impairment.

The relative bioavailability (90% CI) for the combination ezetimibe 10 mg + rosuvastatin 10 mg compared to ezetimibe 10 mg + placebo also involved somewhat heightened exposures to ezetimibe when given with concomitant rosuvastatin. Relative bioavailability (90% CI) based on log transformed  $C_{\max}$  was 104% (69%, 158%) for ezetimibe, 118% (81%, 172%) for conjugated ezetimibe, and 118% (89%, 143%) for total ezetimibe. Relative bioavailability (90% CI) based on log transformed AUC was 96.9% (70%, 133%) for ezetimibe, 114% (89%, 145%) for conjugated ezetimibe, and 113% (89%, 143%) for total ezetimibe. These results are not likely to be clinically significant.

## **Efficacy**

The original registration submission for ezetimibe monotherapy contained four multicentre, Phase III, randomised, placebo controlled, 12 week factorial studies of ezetimibe co-administered with statins in 1861 patients with primary hypercholesterolaemia. The four statins were lovastatin, simvastatin, pravastatin and atorvastatin. The changes from baseline in direct LDL-C were -39.0%, -49.9%, -37.7% and -54.5% (mean percentage) for the co-administration of ezetimibe with pooled doses of lovastatin, simvastatin, pravastatin and atorvastatin, respectively. These changes compared to -24.7%, -36.1%, -24.3% and -42.4% for the pooled statin monotherapy doses, respectively.

The pivotal study of the effect of concomitant rosuvastatin and ezetimibe was P139V1, a 6 week multicentre, randomised, double blind, parallel arm study to evaluate the effect of ezetimibe 10 mg added on to either rosuvastatin 5 mg or rosuvastatin 10 mg compared

with doubling the rosuvastatin dose (from either 5 mg to 10 mg or from 10 mg to 20 mg) in 440 patients with hypercholesterolaemia at moderately high to high risk for coronary heart disease. It should be noted that during the 4 or 5 week run in period (4 weeks for patients who were on rosuvastatin therapy prior to screening), patients received either open label rosuvastatin 5 mg or rosuvastatin 10 mg based on the patient's risk category, current statin therapy and current or historical (within the previous 12 weeks) LDL-C value. Thus, this study also examined the add on effect of ezetimibe 10 mg. Of the 440 patients randomised, 428 completed the study. Analysis of the primary efficacy variable showed that the addition of ezetimibe 10 mg to rosuvastatin, 5 or 10 mg, pooled across doses, daily for 6 weeks reduced LDL-C more than doubling the baseline dose rosuvastatin. The associated p-value was less than 0.001. Pooled across strata, the least squares mean percentage change from baseline in LDL-C at study endpoint was -20.96% on the combination of rosuvastatin (5 or 10 mg) + ezetimibe 10 mg compared with -5.71% on rosuvastatin alone but doubled in dose (10 or 20 mg). The least squares mean treatment difference was -15.25% with a 95% CI (-19.89%, -10.60%). There were also statistically significant treatment differences when each dose of rosuvastatin was examined separately. The results for the corresponding responder analysis, as evidenced by the proportion of patients reaching their LDL-C goal, were also statistically significant. The secondary efficacy results were by and large supportive.

***Literature review – comparison of monotherapy (either rosuvastatin or ezetimibe) to combination therapy (rosuvastatin + ezetimibe)***

Evidence here came from four studies including the pivotal study, P139V1, discussed in the previous paragraph. Overall across the four studies, combination therapy reduced LDL-C more than either monotherapy and (when data was available) a higher proportion of patients in the combination group reached LDL-C targets than in either monotherapy group. The most important of the three studies besides Study P139V1 was the EXPLORER study<sup>20</sup> which investigated the efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe 10 mg for 6 weeks in 469 patients at high risk of coronary heart disease. The Delegate would agree with the sponsor that this was a well designed study published in a prestigious, peer reviewed journal and one which is referenced extensively in the medical literature. It provided robust evidence with respect to the effects on a surrogate marker, namely LDL-C. Unfortunately, it was only a 6 week study with thus the opportunity lost to assess long term efficacy and safety data in a large number of patients in a well controlled setting.

***Literature review – addition of ezetimibe to rosuvastatin***

There were seven studies identified by the clinical evaluator as offering evaluable evidence of the add-on effect of ezetimibe to rosuvastatin. Overall, the percentage reduction in LDL-C when ezetimibe 10 mg was added to rosuvastatin varied between 10.6% and 70%. The total number of people subject to the add on therapy, by the Delegate's calculation, was 430 (60 + 20 + 21 + 36 + 73 + 107 + 113). The Delegate asks that the sponsor please confirm this is the case.

***Literature review – addition of ezetimibe to rosuvastatin compared to doubling or titration upwards of the dose of rosuvastatin***

Again, the pivotal study P139V1 was captured in this group. Apart from P139V1, there were two studies of value.<sup>21</sup> In general, addition of ezetimibe to rosuvastatin reduced LDL-

<sup>20</sup> Ballantyne CM, et al. (2007) Efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe in patients at high risk of cardiovascular disease (results from the EXPLORER study). *Am J Cardiol.* 99: 673-680.

<sup>21</sup> Okada K, et al. (2011) Clinical usefulness of additional treatment with ezetimibe in patients with coronary artery disease on statin therapy - From the viewpoint of cholesterol metabolism. *Circ J.* 75: 2496-2504;

C numerically more than increasing the dose of rosuvastatin. By the Delegate's calculation, the numbers of patients exposed to the addition of ezetimibe to rosuvastatin in this setting in these two studies were 67 (50 + 17). The sponsor should confirm that this is the case.

### ***Literature review – addition of ezetimibe to rosuvastatin compared to addition of ezetimibe to other statins***

There were 12 publications of which the most important were the paper by Sharma and colleagues<sup>22</sup> and the paper reporting the GRAVITY study. In GRAVITY, there were four groups, each of which took a statin alone for 6 weeks (rosuvastatin 10 mg, rosuvastatin 20 mg, simvastatin 40 mg, and simvastatin 80 mg) followed by another 6 weeks at which point ezetimibe was added to the statin. The percentage changes in LDL-C from baseline were -59.72%, -63.48%, -55.22% and -57.43% across the four groups, respectively. This study also showed that a higher proportion of patients treated with the ezetimibe + rosuvastatin combination 10 mg + 10 mg achieved LDL-C goal < 70 mg/dL (1.8 mmol/L) compared with those treated with the ezetimibe + simvastatin combination 10 mg + 40 mg (67.1% versus 55.3%, respectively). A similar responder difference was observed when comparing the ezetimibe + rosuvastatin combination 10 mg + 20 mg with the ezetimibe + simvastatin combination 10 mg + 80 mg (77.0% versus 67.7%, respectively).

### ***Summary of efficacy***

Clinical efficacy in terms of greater LDL-C reduction was seen in both hypercholesterolaemia and HoFH with the combination therapy. The most useful evidence came from the pivotal study, P139V1 with useful evidence also from the EXPLORER and GRAVITY studies in particular. According to section 2.2 of the relevant EU guideline,<sup>23</sup> for a new lipid modifying agent a relative reduction in LDL-C is acceptable in patients with primary hypercholesterolaemia as a valid surrogate endpoint, provided that no claims are made regarding morbidity and mortality. This same guideline also makes a clear statement about drugs intended to be used in combination with other lipid modifying agents. In section 5.3.2.2, it states:

*In principle, combination strategies are not expected to be licensed as first line therapy on the basis of their effect on LDL-C and other lipid parameters, in particular TG and HDL-C alone, unless the applicant is able to justify the benefit of such strategy in terms of morbidity and mortality.*

The indication originally sought by the sponsor in the letter of application was essentially unfettered, except for the reference to adjunctive treatments such as diet and allows first line use. However, subsequent to the approval of ezetimibe + atorvastatin composite pack, the sponsor has agreed to a consistent second line indication. In the response to the clinical evaluation report, the sponsor has also agreed to include a statement in the PI that the product should not be used as a first line agent. Such a statement should appear under *Dosage and Administration*.

With regard to the add on component of the indication, the clinical evaluator expressed concern that the relevant studies enrolled only small numbers of subjects. By the Delegate's reckoning, the number of subjects experiencing add on therapy equalled at least 497 (430 + 67 from above) in those studies which provided evaluable, reasonably robust evidence. This figure does not include the numbers from the GRAVITY study. In its pre

Yamagishi T. (2010) Efficacy and safety of ezetimibe added onto rosuvastatin (2.5 mg) compared with uptitration of rosuvastatin (5 mg) in hyperlipidemic patients. *Jpn Pharmacol Ther.* 38: 305-311.

<sup>22</sup> Sharma AD, et al. (2008) Comparative evaluation of the efficacy, tolerability and safety of rosuvastatin + ezetimibe and atorvastatin + ezetimibe in Indian patients with dyslipidaemia. *Arteriothrombosis* e97.

<sup>23</sup> European Medicines Agency, "Committee for medicinal products for human use (CHMP): Notes for Guidance on Clinical Investigation of medicinal products in the treatment of lipid disorders (CPMP/EWP/3020/03)", 29 July 2004, Web, accessed 23 January 2014 <[www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003235.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003235.pdf)>.

ACPM response, the sponsor is asked to provide a detailed reckoning and breakdown of the numbers of subjects actually exposed to add on therapy in the dossier, for each of the indications, hypercholesterolaemia and HoFH, separately. At this stage, the Delegate is satisfied that there is sufficient evidence of reasonable quality to permit the add on component of the indication.

## **Safety**

### ***Pivotal study P139V1***

The extent of exposure was comparable among treatment groups. Overall adverse experiences were reported by 64 patients (14.5%).

Data contained in the clinical evaluation report displays the differences in adverse event incidences (with CIs) between the two pooled treatment groups, that is, rosuvastatin 5 or 10 mg + ezetimibe 10 mg versus rosuvastatin 10 or 20 mg. Treatment groups were similar in the proportions of patients with clinical adverse experiences, serious adverse experiences, drug related adverse experiences, or adverse experiences leading to discontinuation.

No patients died during the study. Five (5) patients experienced myalgia during the study: 2 on rosuvastatin 5 mg + ezetimibe 10 mg, 1 on rosuvastatin 10 mg, and 2 on rosuvastatin 20 mg. Among 5 patients who discontinued due to drug related adverse experiences, only 1 patient (on rosuvastatin 5 mg + ezetimibe 10 mg) experienced myalgia.

Differences between treatment groups in the incidence of clinical AEs by system organ class (with 95% CIs and where incidence > 4 patients in one or more treatment groups) were compared. The most marked differences (to the disadvantage of the combination versus the monotherapy) were in the rates of gastrointestinal disorders (4.1% versus 1.4%, respectively) and of skin and subcutaneous disorders (1.8% versus 0.5%, respectively). These differing rates should be reported in the PI.

Clinical trial adverse experiences determined by the investigator to be related to study drug were compared. Overall, there were 10 patients (4.5%) and 6 patients (2.7%) who reported drug related adverse experiences in the rosuvastatin (5 or 10 mg) + ezetimibe 10 mg group and the rosuvastatin (10 or 20 mg) group, respectively. There were no marked differences between the two treatment groups in the rates of specific drug-related adverse experiences.

No patient deaths were reported during the conduct of the study.

A total of 2 patients with serious AEs were reported: 1 AE recorded in 1 patient from the rosuvastatin 10 mg group, and 1 AE in 1 patient from the rosuvastatin 20 mg group. Neither serious AE was considered by the investigator to be drug related nor led to discontinuation.

Overall, 6 patients (1.4%) discontinued study therapy due to a clinical AE: 5 patients (2.3%) in the rosuvastatin 5 or 10 mg + ezetimibe 10 mg group (arthralgia 1, constipation 1, myalgia 1, and dermatitis 2 [allergic 1 and eczema 1]) and 1 patient (0.5%) in the rosuvastatin 10 or 20 mg group (dizziness 1). These differing rates should be reported in the PI.

Overall, laboratory AEs were reported in 7 patients (1.6%).

### ***Events of special interest***

#### ***Effects on the liver***

One patient (0.5%) in the rosuvastatin 5 or 10 mg + ezetimibe 10 mg group experienced single and/or consecutive elevations in ALT  $\geq 3 \times$  ULN. No patient in the rosuvastatin 10 or 20 mg group experienced such elevations. There were no elevations of AST  $\geq 3 \times$  ULN.

There were no patients whose liver function tests met Hy's Law criteria. Only one patient (0.5%) in the rosuvastatin 10 or 20 mg group experienced an elevation of CK  $\geq 10 \times$  ULN and this elevation was not associated with muscle symptoms.

In addition, there were no marked differences between the treatment groups in the proportions of patients with elevations in ALT and AST from  $2 \times$  ULN to  $< 3 \times$  ULN and in CK. However, there were obvious differences between both treatment groups in the proportions of patients with elevations in ALT and AST from  $1 \times$  ULN to  $< 2 \times$  ULN. There was only 1 patient with an elevation in creatine kinase of between  $5$  and  $10 \times$  ULN.

#### *Other effects*

A total of 4 patients had an AE involving an allergic reaction or rash: 3 from the rosuvastatin 10 mg + ezetimibe 10 mg group had dermatitis allergic, eczema and rash, respectively, while 1 patient from the rosuvastatin 20 mg group experienced skin exfoliation.

There were 12 patients (2.7%) with gastrointestinal AEs: 9 (4.1%) in the rosuvastatin 5 or 10 mg + ezetimibe 10 mg group and 3 (1.4%) in the rosuvastatin 10 or 20 mg group. There was no clinically relevant pattern observable for the gastrointestinal AEs. No gallbladder related AEs were reported during the study. Two (2) patients from the rosuvastatin 10 or 20 mg group experienced increased bilirubin and increased GGT, respectively. No patients from the rosuvastatin 5 or 10 mg + ezetimibe 10 mg group experienced a hepatitis-related AE.

#### *Other studies*

There were no new safety signals from the 14 day clinical pharmacology study, P03317 or any from the studies from the literature review.

#### *PSUR data for ezetimibe alone*

The PSUR for the period April 2011 to October 2011 was part of the dossier. The clinical evaluator has noted that hepatic failure, musculoskeletal and connective tissue disorders and neoplasms were the majority of the individual case study reports (ICSRs) but that there was no new safety issues apparent. Given that hepatic failure is not recorded as a possible AE in the Ezetrol PI, the Delegate requests that the sponsor provide a detailed summary of the cases of hepatic failure reported in this PSUR, in the most recently available PSUR. In addition, the sponsor is requested to give a detailed appraisal of the cumulative summary of cases of hepatic failure in the entire global safety database for Ezetrol, including details of those determined to be ezetimibe related. Finally, the sponsor should justify why hepatic failure should not be reported in the Ezetrol PI and also in the various PIs for composite packs of which ezetimibe is a component.

A quarter of the ICSRs for this period were musculoskeletal, consisting of myalgia (59), muscle spasm (13), rhabdomyolysis (11), muscular weakness (10) and arthralgia (6). Muscular weakness is not labelled in the CCDS. The Delegate requests that muscular weakness is reported in the relevant part of the *Adverse Effects* section of the PI.

Under GI disorders (18% of all reports), the most frequent adverse drug reactions were diarrhoea (923), abdominal pain upper/lower (14), nausea (10) and constipation (7). All are noted in the CCDS.

General disorders (14% of all reports) included malaise (11), fatigue (8), asthenia (6) and drug interactions (5). Fatigue is listed in the CCDS while asthenia and malaise are not. The delegate requests that both asthenia and malaise are reported in the PI.

Skin and subcutaneous disorders included rash (9), pruritus (5), alopecia (5), hyperhidrosis (4) and urticaria. These were all non serious apart from one report of urticaria. Urticaria is listed.

The Delegate notes with great concern the report of the death of an elderly woman due to pancreatitis. It would appear that this woman had been on rosuvastatin and had been recently commenced on ezetimibe prior to her death from pancreatitis. The Delegate shares the concern of the clinical evaluator that such an elderly patient may have been commenced on ezetimibe for the purpose of meeting lipid level targets. The sponsor is requested to provide to the ACPM a detailed summary of this case including the sponsor's opinion as to the likelihood that ezetimibe contributed to this woman's death. It is noted that pancreatitis is already listed as a possible adverse effect in both the PIs of ezetimibe and rosuvastatin. Later in this overview under the heading 'Other safety issues', the Delegate will be asking the sponsor for more information about all possible adverse effects which are already shared between the two drugs and exactly how much is known about the likelihood of increased rates of these particular adverse effects when the drug combination is taken.

Review of the serious adverse drug reactions raised no new safety concerns.

There were 5 possible drug interactions notified, 4 of which were with drugs known to interact with ezetimibe. There was one report which described a potential interaction with thyroxine. The sponsor is requested to provide full details of this interaction in its pre ACPM response and justify why this should not be reported in the relevant PIs.

### ***Long term safety data***

A major concern of the Delegate is whether there is sufficient long term safety data, particularly at the highest dosage strength, that is, ezetimibe 10 mg + rosuvastatin 40 mg.

Of the 2262 patients from all studies with clearly distinguishable co-administration of ezetimibe and rosuvastatin, only 186 received the combination for 52 weeks or more. Most of the 186 were made up of 126 patients who took ezetimibe 10 mg + rosuvastatin 10 mg. For the remaining 60 subjects, the dosage strengths were not specified. Of some possible reassurance is that 8 subjects took the highest dosage strength combination ezetimibe 10 mg + rosuvastatin 40 mg for 24-26 weeks and 145 for 12 to 20 weeks (Table 7).

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

Duration weeks	Eze + Rosuva 2.5	Eze + Rosuva 5	Eze + Rosuva 10	Eze + Rosuva 20	Eze + Rosuva 40	Eze + Rosuva dose not specified	Total Eze + Rosuva	Percentage
2			12				12	0.5
4	1					38	39	1.7
6		99	373	204	255	268	1199	53.0
8 to 10			21			203	224	9.9
12 to 20	132	54			145	218	549	24.3
24 to 26	17				8	28	53	2.3
52 or more			126			60	186	8.2
	150	153	532	204	408	815	2262	
Percentage	6.6	6.8	23.5	9.0	18.0	36.0		

Table 8 shows the extent of exposure from other studies in the dossier in which numbers of patients exposed to the combination of ezetimibe and rosuvastatin were estimated. One can observe that it is estimated that there were 14 patients who were on the highest combination dosage strength of ezetimibe 10 mg + rosuvastatin 40 mg for 52 weeks or more. The sponsor is requested to provide to the ACPM exact details of how this estimate was arrived at.



**Table 8: Summary of extent of exposure from other studies with co-administration of ezetimibe and rosuvastatin in which numbers of patients were estimated.**

Duration weeks	Eze + Rosuva 2.5	Eze + Rosuva 5	Eze + Rosuva 10	Eze + Rosuva 20	Eze + Rosuva 40	Eze + Rosuva dose not specified
6						(2)
8 to 10			(120)			
12 to 20			(4)			(195)
24 to 26						
52 or more	(59)				(14)	

With regard to the relevant published guideline,<sup>24</sup> the Delegate would like to point out that this guideline has not been revised since February 1987. In section 3 of this guideline with regard to products envisaged for long term use, such as the combination of ezetimibe + rosuvastatin, it is stated that

*The total clinical experience must generally include data on a large and representative group of patients (e.g. 100) exposed to the substance for at least 12 months, irrespective of indications.*

It must be remembered that this guideline is simply that, a guideline. With regard to fixed combinations, in section 4 it is stated that

*In principle the present note for guidance applies to new fixed combinations as well as to entirely new compounds. However, requirements in the individual case will depend upon the nature of the compounds and the originality of the fixed combination and its proposed use.*

While there is ample long term evidence of the safety of each of the separate components, it is still only known with certainty that 126 patients have been documented as taking the combination of ezetimibe + rosuvastatin at a known dose for 52 weeks or more and that dose was at the lower end of the dosage range, ezetimibe 10 mg + rosuvastatin 10 mg. It is not known with any certainty what dosage strength the other 60 patients took. The figure of 14 having taken ezetimibe 10 mg + rosuvastatin 40 mg for 52 weeks or more from the second of the tables above cannot be regarded as robust.

Furthermore, with regard to the large and representative group of patients of at least 100 spoken about in the note for guidance, the guidance goes on to state that

*These patients should be fully monitored for clinical, biochemical and haematological adverse reactions.*

The clear implication of this statement is that this full monitoring should be over the entire period of at least 12 months. What is more, the guideline then goes on to state that

*This fully monitored group will, as a rule, only comprise part of the total clinical experience relating to long-term use.*

It is extremely doubtful that the any of the 186 patients cited would have been subject to full monitoring for clinical, biochemical and haematological adverse reactions over the entire period of 52 weeks or more. It is also extremely difficult to gain an accurate idea of the extent of the total clinical experience relating to long term use of ezetimibe and rosuvastatin in combination. The sponsor is requested to give a summary of the evidence concerning the long term combined use of ezetimibe and rosuvastatin and any adverse reporting associated with that combined use from the sponsor's cumulative global safety and PSUR database for ezetimibe.

<sup>24</sup> Clinical investigation of medicinal products for long-term use

### ***Other safety issues***

As foreshadowed earlier in the discussion of the death of the elderly woman from pancreatitis, the Delegate requests that the sponsor construct a summary list of all adverse effects which are common to both ezetimibe and rosuvastatin, for example pancreatitis. For each adverse effect on the list, the sponsor is requested to provide commentary on whether the frequency/incidence of the particular adverse effect is likely to be subject to a more than additive effect, that is, is likely to be greater than the result of adding the individual frequencies/incidences. The sponsor is also requested to investigate its entire global safety database to see what evidence is available to support any hypotheses/conjectures which are made. The sponsor is also requested to comment on what implications this issue may have for the RMP.

### **Risk management plan**

There were a number of issues raised in the RMP evaluation.

First, the RMP evaluator recommended the sponsor add hepatic failure as an important identified risk to the summary of ongoing safety concerns in the RMP and that any risk mitigation and pharmacovigilance activities to address this risk should be included. Initially, the sponsor agreed to this course of action. However, in its response to the Milestone 5 reports (formally called notification of errors/omissions), the sponsor has reconsidered its previous position on hepatic failure as an important identified risk. The sponsor has stated there is no clear evidence indicating an increased risk of hepatic failure with either monotherapy or combination and has now concluded that hepatic failure only meets the definition of an important potential risk. Both liver function test abnormalities and hepatitis are listed as possible adverse effects of each of the monotherapies and hepatic failure is identified as a possible adverse effect, with unknown frequency, in the rosuvastatin PI. In the assessment of the PSUR data for ezetimibe alone, the clinical evaluator noted that hepatic failure, musculoskeletal and connective tissue disorders and neoplasms were the majority of the individual case study reports. The Delegate has already requested that the sponsor provide a detailed summary of the numbers of cases of hepatic failure recorded in its cumulative global safety database for ezetimibe. From this database, the sponsor is requested to provide as accurate an estimate as possible of all cases of hepatic failure associated with the use of the combination of ezetimibe + rosuvastatin. In its pre ACPM response, the sponsor is requested to provide a detailed justification for its change of position on the issue of the classification of hepatic failure in the RMP. The ACPM is invited to comment on this issue.

Second, the RMP evaluator requested that the sponsor add, to the post marketing section of the PI, the higher incidence of hospitalisation for kidney injury associated with the use of high potency statins. This recommendation is based on recently published studies describing an increased frequency of hospitalisation for acute kidney injury of patients using high potency statins. The publications referenced by the RMP evaluator and which were the basis for the recommendation of the RMP evaluator, were still being assessed by the TGA's Signal Investigation Unit at the time the RMP evaluation report was being written. The assessment by the Signal Investigation Unit has now been completed and a summary of that assessment and the recommendation arising from the assessment are given in the following paragraphs.

The sources of the safety concern were published articles<sup>25</sup> finding increased risk of acute kidney injury with high potency compared to low potency statins.

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<sup>25</sup> Dormuth CR, et al. (2013) Use of high potency statins and rates of admission for acute kidney injury. *BMJ* 346: f880; Chung Y-H, et al. (2013) Statins of high versus low cholesterol-lowering efficacy and the development of severe renal failure. *Pharmacoepidemiol Drug Saf.* 22: 583-592.

The study by Dormuth and colleagues<sup>26</sup> was a nested case control in over 2 million patients using databases from Canada, the UK, and the US. Patients were aged 40 or over newly treated with a statin. High potency statin use was defined as at least 10 mg rosuvastatin, 20 mg atorvastatin, or 40 mg simvastatin daily. Outcome was hospitalisation for any acute kidney injury. The analysis used high dimensional propensity score methods including covariates such as diagnoses, drug use, hospital admissions, body mass index (BMI), and smoking status. Information on covariates was not available equally across all databases studied. Patients using high potency statins were 34% more likely (rate ratio 1.34, 95% CI 1.25-1.43) to be hospitalised with acute kidney injury within the first 120 days of starting treatment than patients using low potency statins. Restating the result as a number needed to harm, 1700 patients without chronic kidney disease would need to be treated for 120 days with a high potency statin instead of a low potency statin to cause one additional hospitalisation for acute kidney injury.

The study by Chung and colleagues<sup>27</sup> was a retrospective cohort study in over 60,000 patients aged 20 or over using an administrative database in Taiwan. Patients were anyone newly treated with a statin. High potency statin use was defined as any use of atorvastatin or rosuvastatin. Outcome was severe renal failure requiring either dialysis or transplantation. The analysis used a proportional hazard regression model with adjustment for propensity scores. The adjusted hazard ratio for severe renal failure with high potency statins compared to low potency statins was 1.12 (95% CI 1.02-1.26).

As noted by the assessor in the Signal Investigation Unit, there appears to be no universally accepted definition of high versus low potency for statins. The study by Chung and colleagues<sup>28</sup> ranked statin potency based on average LDL reduction at a dose of 40 mg daily, whereas the study by Dormuth and colleagues<sup>29</sup> used data on LDL reduction at different doses for each statin.

Neither the Australian PI for Crestor (rosuvastatin) nor Lipitor (atorvastatin) refers to this issue. The UK Summary of Product Characteristics (SPC) for Crestor states that:

*The reporting rate for serious renal events in post marketing use is higher at the 40 mg dose. An assessment of renal function should be considered during routine follow up of patients treated with a dose of 40 mg.*

The Signal Investigation Unit concluded that a full review was not required and the reasons for this decision were as follows. Statin prescribing is guided by target lipid levels. The benefit of statins in reducing the incidence of cardiovascular events and stroke is considered to be proportional to the reduction in cholesterol levels.<sup>30</sup> Hence, high potency statins are used in those people at greater risk, and are expected to confer greater benefit. Conversely, higher potency statins are also already known to be associated with a greater risk of AEs, such as rhabdomyolysis. Despite the sophisticated analysis techniques used in these two studies, it cannot be completely excluded that the patients receiving higher potency statins were not already at higher risk for renal adverse events because of pre existing risk factors which led to the prescribing choice. Thus, a possible conclusion from these studies is that patients who receive higher potency statins tend to be those at high

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<sup>26</sup> Dormuth CR, et al. (2013) Use of high potency statins and rates of admission for acute kidney injury. *BMJ* 346: f880.

<sup>27</sup> Chung Y-H, et al. (2013) Statins of high versus low cholesterol-lowering efficacy and the development of severe renal failure. *Pharmacoepidemiol Drug Saf.* 22: 583-592.

<sup>28</sup> Chung Y-H, et al. (2013) Statins of high versus low cholesterol-lowering efficacy and the development of severe renal failure. *Pharmacoepidemiol Drug Saf.* 22: 583-592.

<sup>29</sup> Dormuth CR, et al. (2013) Use of high potency statins and rates of admission for acute kidney injury. *BMJ* 346: f880.

<sup>30</sup> Law MR, et al. (2003) Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* 326: 1423.

risk for both cardiovascular and renal disease, and while the statins may reduce cardiovascular risk, they have less effect on renal risk.

This issue was discussed at the regular pharmacovigilance teleconference between OPR, US Food and Drug Administration (FDA), Health Canada, Medsafe, and Singapore's Health Sciences Authority (HAS) on 16 July 2013. All agencies indicated that they were reviewing or had reviewed the issue. Concerns expressed with the published studies included the possibility of channelling of high risk (for kidney injury) patients to higher potency statins; the lack of information about diabetes control; and the possibility of misclassification of patients at study entry. No agency was considering further regulatory action at this stage.

Given the identified limitations of the published studies, no further action was recommended by the Signal Investigation Unit of the TGA.

The third major recommendation of the RMP evaluator was that the sponsor be requested to do one or both of the following: to make additions to the PI informing health care professionals that co-administration of the two drugs causes an increase in rosuvastatin plasma concentration and to restrict the use of the highest rosuvastatin dose of 40 mg in combination with ezetimibe. The sponsor responded that it would await the recommendations of the Delegate. The Delegate has already independently highlighted his concerns about the increased bioavailability of rosuvastatin when concomitantly administered with ezetimibe, particularly in the setting of hepatic and/or renal impairment. Further, the Delegate has expressed concerns about the lack of an acceptably robust level of long term safety data. These two issues – increased levels of rosuvastatin when co-administered with ezetimibe and safety concerns – are inextricably linked as one may reasonably expect higher rates of AEs with higher plasma levels.

In line with the recommendation of the RMP evaluator, the delegate will be recommending as a condition of registration that the sponsor implement the RMP for the ezetimibe + rosuvastatin composite pack, version 1.0, dated 6 December 2012, data base lock 1 December 2012 and any future updates as may be agreed to by the OPR of the TGA.

## **Risk-benefit analysis**

### **Delegate considerations**

The clinical pharmacology ezetimibe-rosuvastatin interaction study has shown an increase of 17% in  $C_{max}$  and of 19% in AUC (based on point estimates) of rosuvastatin when co-administered with rosuvastatin. Indeed, the upper limits of the 90% CIs associated with these point estimates showed the possibility of increases in both parameters of at least 60%. Such effects are highly likely to be significantly compounded in the settings of hepatic and/or renal impairment. Clearly these effects are of extreme importance when one is dealing with the highest dosage strength of the combination, namely ezetimibe 10 mg + rosuvastatin 40 mg. The rosuvastatin monotherapy PI expressly forbids doses of rosuvastatin above 40 mg and furthermore urges great caution when one is contemplating increasing a person's rosuvastatin dose from 20 to 40 mg. These effects are also of importance for prescribing rosuvastatin to Asian patients for whom the maximum recommended dose is 20 mg. The potential for adverse consequences of these effects have also been highlighted by the RMP evaluator.

Evidence of efficacy all comes from short term studies using surrogate markers, namely lipid levels but is sufficient for the indication sought, including the add on component of the indication. There must be an unequivocal, unambiguous statement at the beginning of the clinical trials section that **all** of the evidence for the efficacy of the combination of ezetimibe and rosuvastatin comes from short term studies with surrogate endpoints and

that there have been no long term studies with clinical outcome endpoints for the combination.

While there appear to be no new safety signals from the short term studies in the dossier, the Delegate is far from satisfied about the amount and quality of evidence of the safety of the combination in the long term, particularly at the highest dosage strength, that is, ezetimibe 10 mg + rosuvastatin 40 mg. This lack of evidence at that highest dosage strength is seriously compounded by the concerns of the Delegate and of the RMP evaluator with regard to increased exposure to rosuvastatin in the presence of ezetimibe. Anyone taking ezetimibe 10 mg + rosuvastatin 40 mg would be necessarily exposed to levels of rosuvastatin greater than those resulting from exposure to the absolute maximum recommended dose of rosuvastatin monotherapy, that is, 40 mg. As noted by the Delegate, it is extremely doubtful that any of the 186 patients cited as having been exposed to long term treatment with the combination would have been subject to full monitoring for clinical, biochemical and haematological adverse reactions over the entire period of 52 weeks or more of their exposure. It is not clear whether any of those 186 subjects were exposed to the maximum dosage strength, ezetimibe 10 mg + rosuvastatin 40 mg or even to the higher of the intermediate doses, namely ezetimibe 10 mg + rosuvastatin 20 mg. It is also extremely difficult to gain an accurate idea of the extent of the total clinical experience relating to long term use of ezetimibe and rosuvastatin in combination.

At this stage, the Delegate is not convinced that the highest proposed dosage strength of the composite pack, that is, ezetimibe 10 mg + rosuvastatin 40 mg ought to be registered. The Delegate's reasons for this position have been outlined above, particularly in the preceding paragraph. However, the Delegate is willing to hear further argument from the sponsor. What is abundantly clear is that before this highest dosage strength can be safely registered, there must be very major and very clearly articulated amendments and additions to the clinical pharmacology, clinical trials, precautions, adverse effects and dosage and administration sections of the PI. The Delegate has foreshadowed such amendments which would be many in number. The Delegate very much wishes to hear the opinion of the ACPM on this critical issue. Does the fact that anyone taking ezetimibe 10 mg + rosuvastatin 40 mg would be necessarily exposed to levels of rosuvastatin greater than those resulting from exposure to the absolute maximum recommended dose of rosuvastatin monotherapy, that is, 40 mg, mean that ezetimibe 10 mg + rosuvastatin 40 mg cannot be safely registered under any circumstances? In other words, would there be no other risk management or risk amelioration strategy available?

The Delegate recommends the approval of the lower three dosage strengths, namely ezetimibe 10 mg + rosuvastatin 5 mg, ezetimibe 10 mg + rosuvastatin 10 mg and ezetimibe 10 mg + rosuvastatin 20 mg. Should these three be the only dosage strengths registered, the PI would still require considerable amendment, along the lines already foreshadowed.

In the next section, the Delegate has collected all the questions asked of the sponsor so far.

#### ***Questions, requests for further information***

- The sponsor is requested to provide a detailed comment on the increased plasma levels of rosuvastatin when co-administered with ezetimibe and the implications that this has for the highest proposed dosage strength, ezetimibe 10 mg + rosuvastatin 40 mg.
- The sponsor is requested to provide a detailed comment on the increased plasma levels of rosuvastatin when co-administered with ezetimibe in the setting of mild hepatic impairment.

- The sponsor is requested to provide a detailed comment on the increased plasma levels of rosuvastatin when co-administered with ezetimibe in the setting of severe renal impairment.
- The sponsor is requested to provide a detailed comment on the increased plasma levels of rosuvastatin when co-administered with ezetimibe in the setting of mild to moderate renal impairment.
- The sponsor is requested to confirm the total number of subjects exposed to the add-on therapy in the seven studies identified in the literature review as studies evaluating the addition of ezetimibe to rosuvastatin.
- The sponsor is requested to confirm the total number of subjects exposed to the add on therapy in the studies identified in the literature review as studies evaluating the addition of ezetimibe to rosuvastatin compared to doubling or titration upwards of the dose of rosuvastatin.
- In its pre ACPM response, the sponsor is asked to provide a detailed reckoning and breakdown of the numbers of subjects actually exposed to add on therapy in the dossier, for each of the indications, hypercholesterolaemia and HoFH, separately.
- Given that hepatic failure is not recorded as a possible AE in the Ezetrol PI, the delegate requests that the sponsor provide a detailed summary of the cases of hepatic failure reported in this PSUR, in the most recently available PSUR. As well the sponsor is requested to give a detailed appraisal of the cumulative summary of cases of hepatic failure in the entire global safety database for Ezetrol, including details of those determined to be ezetimibe related. Finally, the sponsor should justify why hepatic failure should not be reported in the Ezetrol PI and also in the various PIs for composite packs of which ezetimibe is a component.
- The Delegate notes with great concern the report of the death of an elderly woman due to pancreatitis. It would appear that this woman had been on rosuvastatin and had been recently commenced on ezetimibe prior to her death from pancreatitis. The Delegate shares the concern of the clinical evaluator that such an elderly patient may have been commenced on ezetimibe for the purpose of meeting lipid level targets. The sponsor is requested to provide to the ACPM a detailed summary of this case including the sponsor's opinion as to the likelihood that ezetimibe contributed to this woman's death. It is noted that pancreatitis is already listed as a possible adverse effect in both the PIs of ezetimibe and rosuvastatin.
- The sponsor is requested to provide full details of the single report of the interaction between ezetimibe and thyroxine.
- The sponsor is requested to provide full details of how the estimate of 14 as the number of patients on the highest combination strength of ezetimibe 10 mg + rosuvastatin 40 mg for 52 weeks or more.
- The sponsor is requested to give a summary of the evidence concerning the long-term combined use of ezetimibe and rosuvastatin and any adverse reporting associated with that combined use from the sponsor's cumulative global safety and PSUR database for ezetimibe.
- As foreshadowed earlier in the discussion of the death of the elderly woman from pancreatitis, the Delegate requests that the sponsor construct a summary list of all adverse effects which are common to both ezetimibe and rosuvastatin, for example, pancreatitis. For each adverse effect on the list, the sponsor is requested to provide commentary on whether the frequency/incidence of the particular adverse effect is likely to be subject to a more than additive effect, that is, is likely to be greater than the result of adding the individual frequencies/incidences. The sponsor is also requested

to investigate its entire global safety database to see what evidence is available to support any hypotheses/conjectures which are made. The sponsor is also requested to comment on what implications this issue may have for the RMP.

- The Delegate has already requested that the sponsor provide a detailed summary of the numbers of cases of hepatic failure recorded in its cumulative global safety database for ezetimibe. From this database, the sponsor is requested to provide as accurate an estimate as possible of all cases of hepatic failure associated with the use of the combination of ezetimibe + rosuvastatin. In its pre ACPM response, the sponsor is requested to provide a detailed justification for its change of position on the issue of the classification of hepatic failure in the RMP.<sup>31</sup>

### Summary of issues

In line with published guidelines on the clinical investigation of medicinal products in the treatment of lipid disorders,<sup>32</sup> the sponsor has agreed to include a statement in the PI that the composite pack should not be used as a first line agent. The sponsor has not provided any details as yet of the nature or the position of that proposed statement. The wording of the indications as originally proposed in the sponsor's letter of application did permit first line usage since those indications were framed in exactly the same way as the corresponding parts of the indications for the monotherapies. However, since the approval of the composite pack Atozet (ezetimibe + atorvastatin), the sponsor has agreed that the proposed wording of the indications for the composite pack of ezetimibe and rosuvastatin should reflect second line usage. Thus the indications proposed for the composite pack of this submission will be consistent with the already approved indications for the fixed dose combination tablet Vytorin (ezetimibe + simvastatin) and the composite pack Atozet (ezetimibe + atorvastatin). The Delegate will request the sponsor to provide detailed information about its proposed statement that the composite pack of ezetimibe + rosuvastatin should not be used as first line therapy, in particular the nature and location of that statement.

The clinical evaluator has only recommended approval of the composite pack for people already stabilised on the two therapies, that is, as substitution therapy only. In its response to the clinical evaluation report, the sponsor has presented arguments in support of an "add on" indication, in particular pointing to the data in the dossier which demonstrates the additional LDL-C lowering effect of adding ezetimibe to ongoing rosuvastatin therapy.

Perhaps the most important issue concerns the registration of the highest composite dosage strength, namely ezetimibe 10 mg + rosuvastatin 40 mg. There is evidence that ezetimibe co-administered with rosuvastatin causes increased plasma levels of the latter. The rosuvastatin monotherapy PI urges strong caution when increasing the dose of rosuvastatin from 20 to 40 mg, advising specialist supervision as well as other measures. The usual maximum rosuvastatin dosage is 20 mg and the monotherapy PI expressly forbids exceeding a dose of 40 mg. Further increased levels of rosuvastatin can be reliably expected to occur in the setting of hepatic and/or renal impairment of any degree. Even slight increases become important when one is considering the position of the highest dosage strength combination ezetimibe 10 mg + rosuvastatin 40 mg. The Delegate also has serious concerns about the quality and extent of any long term safety data, particularly in relation to this highest dosage strength combination. At this stage the Delegate is minded

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<sup>31</sup> The sponsor responded to comments in this section. Details of this response are beyond the scope of this AusPAR.

<sup>32</sup> European Medicines Agency, "Committee for medicinal products for human use (CHMP): Notes for Guidance on Clinical Investigation of medicinal products in the treatment of lipid disorders (CPMP/EWP/3020/03)", 29 July 2004, Web, accessed 23 January 2014 <[www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003235.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003235.pdf)>.

to recommend rejection of the highest dosage strength combination unless appropriately worded contraindications and/or precautions can be developed to reduce the risk of unacceptable levels of adverse consequences attached to the use of that highest dosage strength combination.

### **Advice sought**

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

- The nature and location of the sponsor's proposed statement that the composite pack of ezetimibe + rosuvastatin should not be used as first line therapy.
- The quality and extent of the evidence in the dossier supporting the "add on" component of the indication.
- Whether there are sufficient concerns to recommend rejection of the highest dosage strength combination of ezetimibe 10 mg + rosuvastatin 40 mg or whether other risk minimisation strategies such as appropriate contraindications and/or strengthened precautions in the PI as well as amendments to the RMP are possible alternative strategies.
- Whether the sponsor, in its pre ACPM response, has satisfactorily answered all of the Delegate's questions/requests.

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

### **Pre ACPM assessment**

The Delegate has no reason to say, at this time, that the application for Rosuzet Composite Pack and Ezalo Composite Pack for the particular dosage strengths 10 mg + 5 mg, 10 mg + 10 mg & 10 mg + 20 mg (ezetimibe + rosuvastatin, respectively) should not be approved for registration.

### **Response from sponsor**

MSD concurs with the Delegate's recommendation to approve the registration of the Rosuzet Composite Pack and Ezalo Composite Pack (ezetimibe + rosuvastatin) for the dose strengths of 10mg + 5mg, 10mg + 10 mg and 10mg + 20mg.

The Delegate raised concern related to the potential safety of the highest dose strength (10mg + 40mg) of Rosuzet Composite Pack and Ezalo Composite Pack based on the Delegate's interpretation of the results of the Pharmacodynamic and Pharmacokinetic Interaction Study (Study P03317) as outlined in the Delegate's Overview. MSD maintains that although the co-administration of ezetimibe with rosuvastatin may increase rosuvastatin exposure by ~20%, this increase is modest, not clinically relevant and does not require dose adjustments. This study had been reviewed by other regulatory authorities including the FDA and European Medicines Agency (EMA). The FDA and EMA agreed that no clinically significant pharmacokinetic interactions were seen when ezetimibe was co-administered with rosuvastatin and thus no dosage adjustment was required. This conclusion is reflected in the Product Information for Ezetrol/Zetia (ezetimibe) in the US and Europe. Similarly, the PI for Crestor in the US also reflects the same conclusion. MSD has addressed the questions raised by the Delegate and responded below to the specific issues where the Delegate has sought advice from the ACPM. MSD believes that the data presented in this Marketing Application supports the registration of all presentations, including the highest dose strength of Rosuzet Composite Pack and Ezalo Composite Pack, which has been shown to have significant clinical benefit in the treatment



of high risk patients who did not reach target LDL-C despite treatment with 40 mg rosuvastatin monotherapy.

**Issue 1: The nature and location of the sponsor's proposed statement that the composite pack of ezetimibe + rosuvastatin should not be used as first line therapy**

MSD's response:

As requested by the Delegate, MSD proposes to include the following statement at the beginning of the *Dosage and Administration* section:

*This combination product is not indicated for first line use.*

**Issue 2: The quality and extent of evidence in the dossier supporting the "add on" component of the indication**

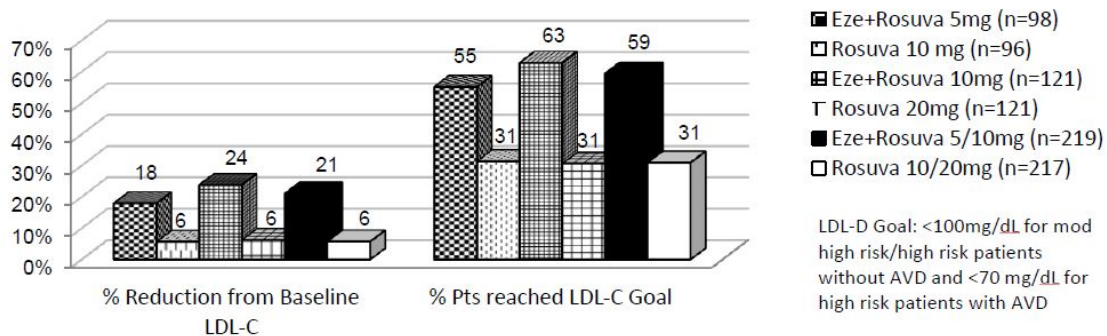
MSD's response:

MSD concurs with the Delegate's conclusion that there is sufficient evidence of reasonable quality to permit the "add on" component of the indication. As requested by the Delegate, a detailed reckoning and breakdown of the numbers of subjects actually exposed to "add on" therapy in the Marketing Application for each indication is presented. A total of 1692 subjects with hypercholesterolaemia and 4 subjects with HoFH were exposed to ezetimibe and rosuvastatin therapy, to support the "add on" indication. The very limited number of patients with HoFH being treated with the combination of ezetimibe and rosuvastatin is due to the rarity of this condition compared with other forms of hyperlipidaemia. Combinations of ezetimibe with other statins are indicated to treat these patients. Therefore, the Rosuzet Composite Pack and Ezalo Composite Pack should also be approved to treat these patients.

Three pivotal studies (P139V1; EXPLORER; GRAVITY) and 11 supporting studies, as outlined in MSD's response to the Additional Question from the Delegate support the "add on" indication.

Study P139V1 was a 6 week multicentre, randomised, double blind, parallel arm study to evaluate the effect of ezetimibe 10 mg added on to either rosuvastatin 5 mg or 10 mg compared with doubling the rosuvastatin dose in 440 patients with hypercholesterolaemia at moderately high to high risk for CHD. Of the 440 patients randomised, 428 completed the study. Results from this study showed that the addition of ezetimibe 10 mg to rosuvastatin 5 mg or 10 mg produced greater reduction in LDL-C (21% versus 6%) and more patients reached LDL-C target (59% versus 31%) than doubling the rosuvastatin dose (Figure 2).

**Figure 2: Study P139V1: The effect of ezetimibe 10 mg added on to either rosuvastatin 5 mg or 10 mg compared with doubling the rosuvastatin dose.**



EXPLORER<sup>33</sup> was a randomised, 6 week, open label, parallel group, multicentre study to evaluate the effect of ezetimibe 10 mg added to 40 mg rosuvastatin in 469 patients with hypercholesterolaemia and a history of CHD or clinical evidence of atherosclerosis or CHD risk equivalent. The Delegate agreed with the sponsor that this was a well designed study published in a prestigious, peer reviewed journal and one which is referenced extensively in the medical literature. Results from this study showed that the addition of ezetimibe 10 mg to rosuvastatin 40 mg (n = 231) resulted in a greater reduction in LDL-C levels (70% versus 57%) and greater proportion of patients reaching target LDL-C (94% versus 79%) than rosuvastatin 40 mg alone (n = 226).

GRAVITY<sup>34</sup> was a randomised, 12 week, open label study to evaluate the efficacy and safety of rosuvastatin 10 mg and 20 mg plus ezetimibe 10 mg against simvastatin 40 mg and 80mg plus ezetimibe 10 mg in 814 patients with hypercholesterolaemia and CHD or CHD risk equivalent, atherosclerosis or a 10 year CHD risk of >20%. Patients received monotherapy with rosuvastatin or simvastatin for 6 weeks and ezetimibe 10 mg was added for a further 6 weeks. At the end of the study, significantly more patients achieved LDL-C goals of below 100 mg/dL (p < 0.05) and below 70 mg/dL (p < 0.001) with rosuvastatin 20 mg + ezetimibe 10 mg (95.6% for <100 mg/dL and 77% for <70 mg/dL) than with simvastatin 40 mg + ezetimibe 10 mg (87.4% and 55.3%, respectively) or simvastatin 80 mg + ezetimibe 10 mg (88.6% and 67.7%, respectively). Ezetimibe added to rosuvastatin provides a valuable treatment option for patients with high risk cardiovascular disease who cannot reach their LDL-C target with monotherapy and would benefit from reaching the more stringent lipid target of <70 mg/dL.

In addition to these pivotal studies, the results from the 11 supporting studies showed a further reduction in LDL-C and a greater percentage of patients reaching their LDL-C target were consistently achieved following the addition of ezetimibe to existing rosuvastatin treatment at all rosuvastatin doses.

***Issue 3: Whether there are sufficient concerns to recommend rejection of the highest dosage strength combination of ezetimibe 10 mg + rosuvastatin 40 mg or whether other risk minimisation strategies such as appropriate contraindications and/or strengthened precautions in the PI as well as amendments to the RMP are possible alternative strategies***

*MSD's response:*

Efficacy and safety of ROSUZET/EZALO Composite Pack 10 mg + 40 mg

There were four main studies in the literature that evaluated the efficacy and safety of ezetimibe and rosuvastatin at the highest proposed dose (10 mg + 40 mg) in 400 patients (Table 9) with severe hypercholesterolaemia either uncontrolled on rosuvastatin 40mg monotherapy<sup>35</sup> or at high risk of coronary heart disease (EXPLORER).

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<sup>33</sup> Ballantyne CM, et al. (2007) Efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe in patients at high risk of cardiovascular disease (results from the EXPLORER study). *Am J Cardiol*. 99: 673-680.

<sup>34</sup> Ballantyne CM, et al. (2010) Randomized comparison of rosuvastatin plus ezetimibe versus simvastatin plus ezetimibe: results of the GRAVITY study. *J Am Coll Cardiol*. 55: A49.E463.

<sup>35</sup> Stein EA, et al. (2007) 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 Clin Lipidol*. 1: 280-286; Ose L, et al. (2005) W16-P-064 Ezetimibe added to rosuvastatin for severely hypercholesterolemic patients: Effects on lipid measures and C-reactive protein. *Atherosclerosis Supplements* 6: 117; Leibovitz E, et al. (2006) Th-P16:276 Efficacy and safety of rosuvastatin-ezetimibe combination for the treatment of severe hypercholesterolemia. *Atherosclerosis Supplements* 7: 554.

**Table 9: Studies from the literature evaluating the safety and efficacy of the ezetimibe 10 mg and rosuvastatin 40 mg combination.**

STUDY	Number Subjects Eze+ Rosuva	DIAGNOSIS	DESIGN & DURATION	LDL-C REDUCTION		COMMON AEs / AEs OF INTEREST (Eze+Rosuva vs. Rosuva)
EXPLORER	235	Hypercholesterolemia with CHD history/ Atherosclerosis/ 10-year CHD risk score of 20%	6 weeks dietary lead-in (lipid-lowering drugs discontinued); then 6 weeks Rosuva 40mg or Eze + Rosuva 40mg (randomised)	Rosuva 40 (n=230)	-57%	Myalgia (2.9% vs. 3.0%) ALT increased (2.5% vs. 0.4%) Angina pectoris (0.4% vs. 2.6%) Nausea (2.5% vs. 2.2%) Proteinuria (0.4% vs. 4.5%) ALT >3xULN (1.3% vs. 0.0%) CK >5xULN (0.8% vs. 0.9%) Cr >50-100% increase (0.4% vs. 1.3%)
				Eze + Rosuva 40 (n=235) [p<0.001]	-70%	
STEIN-2007	109	Severely Hypercholesterolaemic, Uncontrolled LDL-C after receiving Rosuva 40mg in a larger trial	Add Eze for 12 weeks	Eze + Rosuva 40 vs. Baseline	-65%	The Eze+Rosuva combination was well tolerated.  No treatment-related serious adverse events were reported.  No cases of myopathy, no elevations in CK >10 xULN, and no elevations in serum transaminases >3xULN were observed.
				Eze + Rosuva 40 vs. Rosuva 40	-29%	
				Change from baseline due to Eze	-15%	
OSE-2005	36	Severely hypercholesterolaemic (familial), Uncontrolled LDL-C after receiving Rosuva 40mg for at least 3.5 years	<ul style="list-style-type: none"> <li>Dietary lead-in (lipid-lowering drugs discontinued)</li> <li>Start Rosuva 40mg</li> <li>Add Eze for 12 weeks</li> </ul>	Eze + Rosuva 40 vs. Dietary [p<0.001]	-67%	Rosuva and Eze+Rosuva were well tolerated.  There were no hepatic enzyme or creatine kinase elevations.
				Eze + Rosuva 40 vs. Rosuva 40 [p<0.001]	-14%	
LEIBOVITZ-2006	20	Severely hypercholesterolaemic, Uncontrolled LDL-C after receiving Rosuva 40mg in an open label phase III trial	Add Eze for 6 weeks	Eze + Rosuva 40 vs. Baseline	-44%	All patients tolerated Eze+Rosuva combination well.  CK and liver enzyme levels did not change throughout the study period.
				Eze + Rosuva 40 vs. Rosuva 40	-21%	
<b>TOTAL</b>	<b>400</b>					

The largest of these studies was EXPLORER, a randomised, 6 week, open label, controlled trial in patients with hypercholesterolaemia and a history of CHD or clinical evidence of atherosclerosis or CHD risk equivalent. A total of 235 patients received ezetimibe 10mg + rosuvastatin 40 mg and 230 received rosuvastatin 40 mg after a 6 week dietary lead in period. Although ALT elevations occurred more frequently in the combination therapy group, the incidence of other AEs of concern (myalgia, angina pectoris, proteinuria, CK and creatinine elevations) was generally lower or comparable to the rosuvastatin monotherapy group. Furthermore, the LDL-C lowering effect (70% versus 57%, respectively) and proportion of patients reaching LCL-C target (94% versus 79%, respectively) were substantially greater in the combination group compared to the monotherapy group.

Stein and colleagues<sup>36</sup> evaluated the addition of ezetimibe to rosuvastatin 40 mg for 12 weeks in 109 patients uncontrolled on rosuvastatin monotherapy. The combination of ezetimibe + rosuvastatin 40 mg was well tolerated and no treatment related serious adverse events were reported. In addition, no cases of myopathy, CK elevations above 10x ULN, or serum transaminase elevations above 3x ULN were observed and the combination reduced LDL-C by a further 29% from rosuvastatin monotherapy baseline.

<sup>36</sup> Stein EA, et al. (2007) 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 Clin Lipidol.* 1: 280-286.

Ose and colleagues<sup>37</sup> also evaluated the addition of ezetimibe to rosuvastatin 40 mg for 12 weeks in patients uncontrolled on rosuvastatin monotherapy (n = 36). A wash out period of unknown duration was introduced prior to re-initiation of rosuvastatin 40 mg and ezetimibe add on. The combination was well tolerated and there were no hepatic enzyme or CK elevations. Ezetimibe + rosuvastatin 40 mg reduced LDL-C by a further 14% from rosuvastatin monotherapy baseline.

Leibovitz and colleagues<sup>38</sup> evaluated the addition of ezetimibe to rosuvastatin 40 mg for 6 weeks in patients uncontrolled on rosuvastatin monotherapy (n = 20). All patients tolerated the combination well and no changes were observed in CK and liver enzyme levels throughout the study period. Ezetimibe + rosuvastatin 40 mg reduced LDL-C by a further 21% from rosuvastatin monotherapy baseline.

It can be seen from these studies that there is a clear clinical benefit and need for the highest proposed dose of ezetimibe and rosuvastatin (10 mg + 40 mg), especially in patients at high risk of CHD and those with uncontrolled LDL-C levels despite treatment with the highest dose of rosuvastatin monotherapy. From the studies which evaluated the “add on” of ezetimibe in patients having prior experience with rosuvastatin 40 mg monotherapy,<sup>39</sup> an incremental reduction in LDL-C was observed without indication of intolerance or increased adverse effects. This suggests that the benefit of administering the 10 mg + 40 mg dose outweighs the risk provided that ezetimibe is initiated after maximal titration of rosuvastatin as per the guidelines for the management of absolute cardiovascular disease risk published by the National Stroke Foundation.

Potential for interaction between ezetimibe and rosuvastatin during co-administration

The pharmacodynamic interaction (effect of LDL-C lowering) between rosuvastatin and ezetimibe was investigated in Study P03317 and the combination produced a greater reduction in LDL-C compared with monotherapy. This study also determined that the co-administration of rosuvastatin and ezetimibe resulted in a mean increase of approximately 20% in exposure to rosuvastatin that the Delegate considered may be significant. The pharmacokinetic conclusion of the study authors was that this increase in exposure would not be clinically significant and this view was shared by the clinical evaluator. The Crestor (rosuvastatin) PI describes the interaction studies conducted with rosuvastatin and a similar extent of exposure (~30% increase) with an agent such as itraconazole was not considered to be clinically relevant or to require dose adjustment. Where rosuvastatin exposure was altered by fold values, a change in dosing has been recommended. As noted in the previous section, those studies conducted with the highest dose combination (10 mg + 40 mg) including the EXPLORER study found that this combination was well tolerated and the adverse events were similar between combination therapy and monotherapy. There is no theoretical basis for an interaction between ezetimibe and rosuvastatin. As such the dosing instructions with the combination product for patients with hepatic or renal impairment remain consistent with the instructions for the monotherapy or the more restrictive directions where not aligned.

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<sup>37</sup> Ose L, et al. (2005) W16-P-064 Ezetimibe added to rosuvastatin for severely hypercholesterolemic patients: Effects on lipid measures and C-reactive protein. *Atherosclerosis Supplements* 6: 117.

<sup>38</sup> Leibovitz E, et al. (2006) Th-P16:276 Efficacy and safety of rosuvastatin-ezetimibe combination for the treatment of severe hypercholesterolemia. *Atherosclerosis Supplements* 7: 554.

<sup>39</sup> Stein EA, et al. (2007) 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 Clin Lipidol*. 1: 280-286; Ose L, et al. (2005) W16-P-064 Ezetimibe added to rosuvastatin for severely hypercholesterolemic patients: Effects on lipid measures and C-reactive protein. *Atherosclerosis Supplements* 6: 117; Leibovitz E, et al. (2006) Th-P16:276 Efficacy and safety of rosuvastatin-ezetimibe combination for the treatment of severe hypercholesterolemia. *Atherosclerosis Supplements* 7: 554.

## RMP

While limited long term safety studies with the highest dose combination of ezetimibe and rosuvastatin (40 mg) are presented in this Marketing Application, a significant number of patients worldwide have been and are currently being treated with ezetimibe and rosuvastatin 40 mg and there are no safety alerts from the post marketing surveillance data. The usage data on ezetimibe and rosuvastatin in Australia from 2007 to 2012 are presented in Table 10.

**Table 10: The Annual Number of PBS Prescriptions Written Annually for Rosuvastatin Monotherapy and Rosuvastatin plus Ezetimibe Combination Therapy.**

	2007	2008	2009	2010	2011	2012
Rosuvastatin 5mg	25,938	51,763	79,938	107,355	137,275	172,883
Ezetimibe+Rosuvastatin 5mg	1,972	3,147	4,171	4,588	5,612	6,674
Rosuvastatin 10mg	98,292	169,395	248,954	307,390	358,584	401,739
Ezetimibe+Rosuvastatin 10mg	2,237	3,110	4,626	5,764	5,574	7,660
Rosuvastatin 20mg	30,792	66,059	105,421	136,744	165,413	190,327
Ezetimibe+Rosuvastatin 20mg	1,555	2,768	3,868	4,854	6,295	7,433
Rosuvastatin 40mg	10,049	22,904	38,718	52,331	65,111	76,791
Ezetimibe+Rosuvastatin 40mg	2,389	4,247	6,978	8,760	11,376	14,183

Routine post marketing surveillance will continue to monitor for emergent adverse events. The proposed RMP adequately monitors and minimises the risk of rhabdomyolysis/myopathy and abnormal liver function (Important Identified Risks), the serious and dose dependent AEs of most concern in patients with hepatic and renal impairment. The RMP and PI texts will be updated as required to ensure the combination product is used in a safe and appropriate manner.

Proposed changes to the PI

The PI has been updated as requested by the Delegate to include the following statement:

*All of the evidence for the efficacy of the combination of ezetimibe and rosuvastatin comes from short term studies with surrogate endpoints. There have been no long term studies with clinical outcome endpoints for this combination. The studies described include sponsor-initiated clinical trials and other placebo or comparator controlled clinical trials.*

This is included at the beginning of the Clinical Trials section to advise on the lack of evidence to support the long term treatment with this combination.

The contraindications, precautions and dosage and administration are consistent with the monotherapy components and where conflicting advice is noted the more restrictive advice has been adopted. A description of the pharmacokinetic data derived from Study P03317 has also been included as requested by the Delegate. The adverse effects section now contains adverse events from the combination study (P139V1) conducted by the sponsor as well as from the ezetimibe and rosuvastatin monotherapy Product Information texts.

### **Conclusion**

The clinical data presented in the Marketing Application supports the registration of Rosuzet Composite Pack and Ezalo Composite Pack for the following indications:

#### **Primary Hypercholesterolaemia**

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

The studies presented in the Marketing Application showed that there is a clear clinical benefit and need for the highest proposed dose of ezetimibe and rosuvastatin (10 mg + 40 mg), especially in patients with high risk cardiovascular disease who cannot reach their LDL-C target with monotherapy and would benefit from reaching the more stringent lipid target of <70 mg/dL.

The co-administration of rosuvastatin and ezetimibe resulted in a mean increase of ~20% in exposure to rosuvastatin which is not clinically significant and no dose adjustment is required. This view is shared by the FDA and EMA. As noted in the previous section, those studies conducted with the highest dose combination (10 mg + 40 mg) including the EXPLORER study found that this combination was well tolerated and the adverse events were similar between combination and monotherapy. This suggests that the benefit of administering the 10 mg + 40 mg dose outweighs the risk provided that ezetimibe is initiated after maximal tolerated titration of rosuvastatin as per the guidelines for the management of absolute cardiovascular disease risk.

We trust that the Committee will concur and support that all dose strengths of Rosuzet Composite Pack and Ezalo Composite Pack should be registered.

**Advisory committee considerations**

The submission seeks to register a new combination of active ingredients for currently registered products.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered Ezalo Composite Pack/Rosuzet Composite Pack Ezetrol tablet + MSD Rosuvastatin film coated tablets containing 10 mg + 5 mg, 10 mg + 10 mg, 10 mg + 20 mg and 10 mg + 40 mg of ezetimibe / rosuvastatin (as calcium) to have an overall positive benefit-risk profile for the indication;

**Primary Hypercholesterolaemia**

*Rosuzet Composite Pack/Ezalo Composite Pack 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 Composite Pack/Ezalo Composite Pack is indicated in patients with HoFH. Patients may also receive adjunctive treatments (e.g. LDL apheresis).*

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

- The nature and location of the sponsor's proposed statement that the composite pack of ezetimibe + rosuvastatin should not be used as first-line therapy

The statement is at start of *Dosage & Administration* section and is consistent with approved Atozet (composite pack containing ezetimibe and atorvastatin) PI.

- The quality and extent of the evidence in the dossier supporting the "add on" component of the indication

Efficacy supported in literature submission; however, mortality data and long term safety data at high doses is lacking.

- Whether there are sufficient concerns to recommend rejection of the highest dosage strength combination of ezetimibe 10 mg + rosuvastatin 40 mg or whether other risk minimisation strategies such as appropriate contraindications and/or strengthened precautions in the PI as well as amendments to the RMP are possible alternative strategies

Post marketing data is sufficient to suggest the highest dose 10/40 mg is safe.

The ACPM was of the view that the increased rosuvastatin levels when co-administered with ezetimibe were no different from other drug interactions and should be managed accordingly. The PI and RMP should be strengthened, especially for the highest dose.

- Whether the sponsor, in its pre ACPM response, has satisfactorily answered all of the Delegate's questions/requests.

The ACPM was of the view that the pre ACPM response was, by precedent, adequate.

#### ***Proposed conditions of registration***

The ACPM agreed with the delegate on the proposed conditions of registration and specifically advised on the inclusion of the following:

- Subject to satisfactory negotiation of the RMP most recently approved by the TGA,
- Negotiation of PI and CMI to the satisfaction of the TGA.

#### ***Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments:***

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI.

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

#### **Outcome**

Based on a review of quality, safety and efficacy, TGA approved the registration of:

- Rosuzet Composite Pack 10 mg + 40 mg ezetimibe 10 mg tablets and rosuvastatin (as calcium) 40 mg tablets composite pack
- Ezalo Composite Pack 10 mg + 40 mg ezetimibe 10 mg tablets and rosuvastatin (as calcium) 40 mg tablets composite pack
- Ezalo Composite Pack 10 mg + 10 mg ezetimibe 10 mg tablets and rosuvastatin (as calcium) 10 mg tablets composite pack
- Rosuzet Composite Pack 10 mg + 5 mg ezetimibe 10 mg tablets and rosuvastatin (as calcium) 5 mg tablets composite pack
- Ezalo Composite Pack 10 mg + 20 mg ezetimibe 10 mg tablets and rosuvastatin (as calcium) 20 mg tablets composite pack
- Rosuzet Composite Pack 10 mg + 20 mg ezetimibe 10 mg tablets and rosuvastatin (as calcium) 20 mg tablets composite pack
- Ezalo Composite Pack 10 mg + 5 mg ezetimibe 10 mg tablets and rosuvastatin (as calcium) 5 mg tablets composite pack

- Rosuzet Composite Pack 10 mg + 10 mg ezetimibe 10 mg tablets and rosuvastatin (as calcium) 10 mg tablets composite pack

indicated for:

***Primary Hypercholesterolaemia***

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

**Specific conditions of registration applying to these therapeutic goods**

- The Ezalo/Rosuzet Composite Pack RMP, version 1.0, dated 6 December 2012, database lock 1 December 2012, and the responses to the outstanding RMP matters in the sponsor's Pre-ACPM Response of 16 September 2013 and email dated 5 November 2013, included with this submission, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

## **Attachment 1. Product Information**

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

## **Attachment 2. Extract from the Clinical Evaluation Report**



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