



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Ezetimibe + atorvastatin as calcium

Proprietary Product Name: Atozet Composite
Pack / Zeteze Composite Pack

Sponsor: Merck Sharp & Dohme

May 2013

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- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
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I. Introduction to product submission

Submission details

<i>Type of Submission:</i>	New fixed-dose combination in the form of a new composite pack
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	18 January 2013
<i>Active ingredients:</i>	Ezetimibe + atorvastatin as calcium
<i>Product Names:</i>	Atozet Composite Pack / Zeteze Composite Pack
<i>Sponsor's Name and Address:</i>	Merck Sharp & Dohme Locked Bag 2234 North Ryde NSW 1670
<i>Dose form:</i>	Tablet
<i>Strengths:</i>	10 mg ezetimibe and 10, 20, 40 and 80 mg atorvastatin
<i>Container:</i>	Blister pack
<i>Pack sizes:</i>	20's and 60's
<i>Approved Therapeutic use:</i>	Primary Hypercholesterolaemia <i>Atozet/Zeteze 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:</i> <ul style="list-style-type: none">• <i>not appropriately controlled with atorvastatin or ezetimibe alone; or</i>• <i>already treated with atorvastatin and ezetimibe</i> Homozygous Familial Hypercholesterolaemia (HoFH) <i>Atozet/Zeteze Composite Pack is indicated in patients with HoFH. Patients may also receive adjunctive treatments (e.g. LDL apheresis).</i>
<i>Route of administration:</i>	Oral (PO)
<i>Dosage:</i>	See Product Information (Attachment 1)
<i>ARTG Numbers:</i>	196150, 196151, 196152, 196153, 196154, 196155, 196156 and 196157

Product background

This AusPAR describes the application by Merck Sharp and Dohme (MSD) to register a new fixed-dose combination in the form of a new composite pack for the treatment of hypercholesterolaemia.

The composite pack will consist of two products already approved, Ezetrol (ezetimibe) 10 mg [AUST R 91161] and Atorvastatin SZ (atorvastatin as calcium) 10 mg [AUST R 156054], 20 mg [AUST R 156059], 40 mg [AUST R 156052] or 80 mg [AUST R 156053]. No new dosage forms or strengths are proposed.

As the proposed product contains two already registered products, tablets of each product are to remain in the currently approved blister packaging for each. No aspects of the quality information have been changed. Two trade names were originally proposed for the composite pack: Ezetrol Plus Atorva and Zetia Plus Atorva.

Ezetimibe inhibits the intestinal absorption of cholesterol. It is orally active and its molecular target is the sterol transporter, Niemann-Pick C1-Like (NPC1L1), which is responsible for the intestinal uptake of cholesterol and phytosterols. It is indicated in the treatment of primary hypercholesterolaemia, or HoFH and phytosterolaemia, as monotherapy or in conjunction with a statin.

Atorvastatin is a synthetic lipid-lowering agent indicated for the treatment of primary hypercholesterolaemia and in hypertensive patients with coronary heart disease (CHD) risk factors to reduce the risk of myocardial infarction or stroke. It is an inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. The innovator product, Lipitor, is sponsored by Pfizer Australia Pty Ltd and there are numerous generic versions, including Atorvastatin SZ (of Sandoz) which is now named MSD Atorvastatin and sponsored by MSD.

As noted by the sponsor, the two medicines, ezetimibe and atorvastatin, have complementary pharmacological actions. Whereas ezetimibe reduces cholesterol absorption in the small intestine, atorvastatin reduces hepatic synthesis of cholesterol. Ezetimibe also provides greater improvements in lipid profile when added to a statin compared to a statin alone. Clinical studies of the co-administration of ezetimibe and atorvastatin have demonstrated that, when taken together, these substances are more effective than either atorvastatin or ezetimibe alone. Thus, the sponsor argues that the composite pack therefore meets the justification criteria of “*an improvement in benefit/risk due to a level of efficacy above the one achievable by a single substance with an acceptable safety profile*”, as stipulated by the relevant TGA adopted European Union (EU) guideline on combination products¹.

The sponsor proposed the following indication for the new Composite Pack product in their application:

“Primary Hypercholesterolaemia

Ezetrol Plus Atorva is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia.

Homozygous Familial Hypercholesterolaemia (HoFH)

Ezetrol Plus Atorva is indicated in patients with HoFH. Patients may also receive adjunctive treatments (e.g. LDL apheresis).”

This proposed indication for Ezetrol Plus Atorva is not consistent with the approved indication for Vytorin®, a fixed-dose combination of ezetimibe + simvastatin which is already on the Australian Register for Therapeutic Goods (ARTG) and also sponsored by MSD. The approved indication for Vytorin® is as follows:

¹ CPMP/EWP/240/95 Rev. 1 Guideline on Clinical Development of Fixed Combination Medicinal Products, 1 Sep 2009, adopted by the TGA on 28 May 2010

“Primary Hypercholesterolaemia

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

Patients not appropriately controlled with a statin or ezetimibe alone; or

Patients already treated with a statin and ezetimibe

Homozygous Familial Hypercholesterolaemia (HoFH)

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

Both sets of wording, that is, that for the proposed new composite pack and that for the approved Vytorin are identical for the second part of each indication, namely for *Homozygous Familial Hypercholesterolaemia (HoFH)*. However, with regard to the first part of each indication relating to primary hypercholesterolaemia, the clear intention behind the approved wording for Vytorin is that it should be used second-line, that is, where patients are not appropriately controlled with a statin or ezetimibe alone or where they are already taking the combination of a statin and ezetimibe. The wording which is proposed for the corresponding first part of the Ezetrol Plus Atorva implies that the medicine may be used first-line. Reference to use in mixed hyperlipidaemia has also been removed in the proposed indication for Ezetrol Plus Atorva.

There are six TGA adopted European guidelines relevant to this submission, besides the general guidelines:

[CPMP/EWP/240/95 Rev. 1 \(pdf,81kb\)](#)

Guideline on Clinical Development of Fixed Combination Medicinal Products

Replaces: pp. 175 - 180 of Rules 1998 (3C) - 3CC10a

Published: TGA Internet site Effective: 28 May 2010

[pp. 127 - 132 of Rules 1998 \(3C\) - 3CC6a \(pdf,27kb\)](#)

Clinical Investigation of Medicinal Products for Long-Term Use

Replaces: pp. 163 - 165 of Rules 1989

Effective: 12 February 2002

See also: [pp. 121 - 125 of Rules 1998 \(3C\) - 3CC5a](#) (Adopted by TGA with conditions)

[EMA/CHMP/EWP/311890/2007 \(pdf,105kb\)](#)

Guideline on the Evaluation of Medicinal Products for Cardiovascular Disease Prevention

Published: TGA Internet site

Effective: 29 June 2009

[EMA/CHMP/EWP/297931/2008 \(pdf,32kb\)](#)

Concept Paper/Recommendation on the Need for Revision of (CHMP) Note for Guidance on the Investigation of Drug Interactions (CPMP/EWP/560/95)

Published TGA Internet site for information only, effective: 10 February 2009

[CPMP/EWP/560/95 \(pdf,79kb\)](#)

Note for Guidance on the Investigation of Drug Interactions

Published: TGA Internet site

Effective: 19 April 2001

[CPMP/EWP/3020/03 \(pdf,181kb\)](#)

Note for guidance on clinical investigation of medicinal products in the treatment of lipid disorders

Published: TGA Internet site

Effective: 20 May 2005

Regulatory status

Ezetimibe 10 mg tablet, under the trade name Ezetrol®, was approved to be co-administered with a statin, for the treatment of primary hypercholesterolaemia and homozygous familial hypercholesterolaemia on 18 June 2003 and has been marketed since October 2003 by MSD². It was considered by the Australian Drug Evaluation Committee (ADEC; now called Advisory Committee on Prescription Medicines (ACPM)) at its 227th and 228th meetings in April and June of 2003. There are no generic versions of Ezetrol on the ARTG.

With respect to the generic product atorvastatin, the innovator product, Lipitor, is sponsored by Pfizer Australia Pty Ltd. There are numerous generic versions of Lipitor, including Atorvastatin SZ (of Sandoz) which is now named MSD Atorvastatin and sponsored by MSD.³

A fixed dose combination (FDC) tablet containing ezetimibe and simvastatin (Vytorin)⁴ was approved in Australia in 2004 and another submission related to ezetimibe and atorvastatin has been evaluated recently by the TGA.

There have been no applications for marketing authorisation of the ezetimibe/atorvastatin composite packs by Merck Sharp and Dohme in the USA, Europe, the United Kingdom (UK), Switzerland, Canada or New Zealand.

Product Information

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

² The current approved indications of ezetimibe as the monotherapy Ezetrol® are as follows:

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.

³ The current approved indications of atorvastatin as the monotherapy Lipitor® are as follows:

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

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

LIPITOR is indicated in hypertensive patients with multiple risk factors for coronary heart disease (CHD) which may include diabetes, history of stroke or other cerebrovascular disease, peripheral vascular disease or existing asymptomatic CHD (see CLINICAL TRIALS, Prevention of Cardiovascular Disease) to reduce the risk of non-fatal myocardial infarction and non-fatal stroke.

These effects do not replace the need to independently control known causes of cardiovascular mortality and morbidity such as hypertension, diabetes and smoking.

⁴ The current approved indications of Vytorin® are as follows:

Primary Hypercholesterolaemia

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

Patients not appropriately controlled with a statin or ezetimibe alone

Patients already treated with a statin and ezetimibe

Homozygous Familial Hypercholesterolaemia (HoFH)

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

List of abbreviations used in this AusPAR

ALT	Alanine aminotransferase
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
API	Active pharmaceutical ingredient
Apo	Apolipoprotein
AST	Aspartate aminotransferase
ATP	Adult treatment panel
AUC	Area under the concentration-time curve
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CHD	Coronary Heart Disease
CI	Confidence interval
CK	Creatine phosphokinase
CRF	Case Report Form
C _{max}	Maximum concentration
CSR	Clinical study report
CV	Coefficient of variation
DDI	Drug drug interaction
ECG	Electrocardiogram
FDC	Fixed dose combination
FMI	Final marketing image
FSG	Fasting serum glucose
GI	Gastrointestinal
GMR	Geometric mean ratio
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolaemia
HoFH	Homozygous familial hypercholesterolaemia
HR	Heart rate
IV	Intravenous
IVRS	Interactive Voice Response System
LDL-C	Low-density lipoprotein cholesterol
LS mean	Least-squares mean
MS	Metabolic Syndrome
MSD	Merck Sharp & Dohme
NCEP	National Cholesterol Education Program

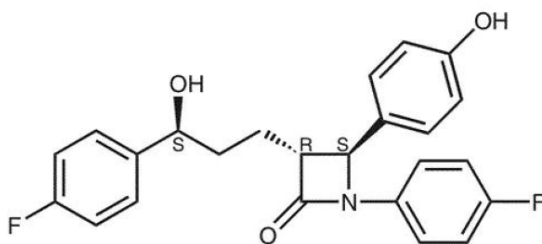
NDA	New drug application
NMSC	Non-melanoma skin cancer
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
QD	once daily
RBC	Red blood (cell) count
SD	Standard deviation
SEM	Standard error of the mean
SOC	System Organ Class
SPC	Summary of product characteristics
TC	Total cholesterol.
TG	Triglycerides
TSH	Thyroid Stimulating Hormone
ULN	Upper limit of normal
VLDL-C	Very low-density lipoprotein cholesterol.
WBC	White blood (cell) count

II. Quality findings

Drug substance (active ingredient)

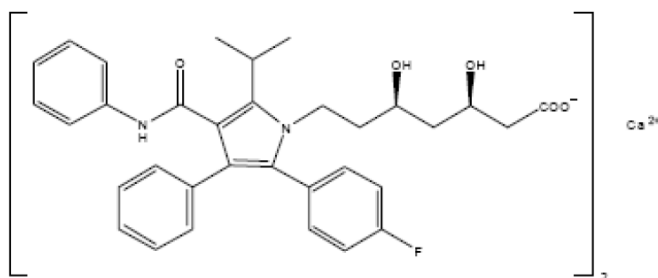
The chemical structure of ezetimibe (1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone is shown in Figure 1.

Figure 1. Chemical structure of ezetimibe



The empirical formula is C₂₄H₂₁F₂N₃O₃. Its molecular weight is 409.4.

The chemical structure of atorvastatin ([R-(R*, R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid) is shown in Figure 2 below.

Figure 2. Chemical structure of atorvastatin

The empirical formula of atorvastatin calcium is (C₃₃H₃₄FN₂O₅)₂Ca and its molecular weight is 1155.36.

As the proposed product contains two already registered products, the tablets of each product are to remain in the currently approved blister packaging for each. No aspects of the quality information have been changed.

Drug product

Ezetrol is a white to off-white, capsule-shaped tablet with “414” marked on one side.

Atorvastatin SZ 10 mg is a white to almost white, round biconvex film-coated tablet debossed with “HLA10” on one side. Atorvastatin SZ 20 mg and 40 mg are light yellow, round biconvex film-coated tablets, debossed with “HLA20” and with “HLA40”, respectively, on one side. Atorvastatin SZ 80 mg is a light yellow, oval biconvex film-coated tablet, debossed with HLA80 on one side.

III. Nonclinical findings

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

IV. Clinical findings

Introduction

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

Clinical rationale

The rationale for the composite pack provided by the sponsor is that *“having both products contained in one calendar pack would increase the awareness and emphasise the clinical importance of taking both medications concurrently and at the same time when both medications are co-prescribed. In addition, a composite pack would reduce the cost to patients, as patients will only pay for one PBS co-payment instead of two.”*

As a previously evaluated submission contained efficacy and safety studies with the free combination of ezetimibe and atorvastatin, the evaluator has used relevant data from that evaluation in this report.

Guidance

A pre-submission consultation took place on 19 September 2011. At this meeting the rationale for the composite pack was discussed, together with packaging and a request to waive the risk management plan.

Overall, the clinical development was conducted in line with the EU guidance document on products for the treatment of lipid disorders.⁵ The dossier was not, however, structured as a submission for a fixed dose combination even though the TGA adopted European Medicines Agency's (EMA's) guidelines state that "*the scientific principles applicable to fixed combination products will also be applied in the assessment of 'combination pack' medicinal products*".⁶

Scope of the clinical dossier

There was no clinical data and a justification for this was included in the sponsor's Clinical Overview. There was an additional section in the dossier labelled "Part IV". The sponsor stated the co-administration of the two products is based on the data package which was used to support the registration of ezetimibe (Ezetrol).

The submission contained the following clinical information:

- Part IV. This included clinical study data from the ezetimibe submission dated January 2002.

Subsequent to the TGA request for information from the sponsor (s31 questions) after the first round of evaluation, the sponsor submitted data from a previously-evaluated MSD dossier of ezetimibe and atorvastatin. The response included the following clinical information:

- 10 controlled clinical studies (P040, P079, P090, P112, P0692, P0693, P1030, P2154, P2173 and P2173R),
- 2 uncontrolled clinical studies (P1417 and P1418),
- a statistical analysis plan for the integrated summary of safety, and
- a summary of post-marketing data of ezetimibe with atorvastatin.

Paediatric data

The submission did not include paediatric data.

Good clinical practice (GCP)

The studies contained in the submissions for ezetimibe and for the combination of ezetimibe and atorvastatin were stated to have been conducted in accordance with GCP standards and relevant ethical and regulatory approval.

Pharmacokinetics

Studies providing pharmacokinetic data

No new pharmacokinetic data were submitted.

⁵Committee for medicinal products for human use (CHMP) (2004). Note for guidance on clinical investigation of medicinal products in the treatment of lipid disorders. CPMP/EWP/3020/03. London.

⁶Committee for medicinal products for human use (CHMP) (2009). Guideline on clinical development of fixed combination medicinal products. CPMP/EWP/240/95 Rev 1.

Summary of pharmacokinetics

As the products in the composite packs are the same as the registered products, no biopharmaceutic or pharmacokinetic data were submitted.

Evaluator's overall conclusions on pharmacokinetics

There was no clinically significant drug interaction reported between ezetimibe 10 mg and atorvastatin 10 mg.

It is noted that Lipitor (from the US) was the atorvastatin used in the clinical trials assessing the combination of ezetimibe and atorvastatin. No data has been provided to the evaluator on the bioequivalence of Atorvastatin SZ and the Lipitor (from US).

Pharmacodynamics**Studies providing pharmacodynamic data**

No new pharmacodynamic data were submitted.

Evaluator's overall conclusions on pharmacodynamics

There were seven studies assessing the PK and PD of ezetimibe with statin co-administration in the previous ezetimibe clinical evaluation report. These found that the combination was generally more effective in lowering lipids (low-density-lipoprotein cholesterol (LDL-C) and total cholesterol) than either agent alone and significantly more effective than placebo.

Efficacy**Dosage selection for the pivotal studies**

The proposed dosage is the same as the currently registered products (ezetimibe 10 mg and atorvastatin 10, 20, 40 and 80 mg) in the combinations of 10/10 mg, 10/20 mg, 10/40 mg and 10/80 mg.

Clinical efficacy

No new clinical efficacy studies were submitted in the original dossier. Data have been extracted from the evaluations of Ezetrol (ezetimibe) and from the clinical study reports in a previously-evaluated MSD dossier of ezetimibe and atorvastatin, the latter having been provided by the sponsor in response to the TGA request for information (s31 questions). The evaluator has summarised the relevant available data in two sections: Efficacy with statins and Efficacy with atorvastatin.

Evaluator's conclusions on clinical efficacy

The clinical efficacy data were derived from studies submitted as part of the original Ezetrol application. The evaluator also considered the evidence submitted as part of another submission, of ezetimibe and atorvastatin. Therefore, the efficacy and safety data from the submission are relevant to this submission. The clinical study data were subsequently provided in response to s31 questions.

All studies were in patients with primary hypercholesterolaemia apart from P1030 and its extension in HoFH. The evaluator had access to the clinical evaluation reports relating to these submissions as well as all clinical study data from the ezetimibe submission.

Data on ezetimibe efficacy with statins were primarily located in the original ezetimibe submission. Co-administration of ezetimibe with a statin was derived from four factorial studies (P0679, P0680, P0691 and P0692) which assessed lovastatin, simvastatin, pravastatin and atorvastatin, respectively. Data on ezetimibe therapy added to ongoing statin therapy comes from two placebo-controlled studies; P2173 and P040. Co-administration of ezetimibe with a statin compared to up-titration of the statin dose was assessed in two studies; P0700 (simvastatin) and P0693 (atorvastatin).

Data on the use of ezetimibe in combination with atorvastatin specifically come from five short term studies (6 to 14 weeks) in patients with primary hypercholesterolaemia (P079, P090, P112, P0692 and P0693). One study (P692) had a factorial design. The other four (P079, P090, P112 and P693) were add-on studies which compared the addition of ezetimibe to up-titration of the atorvastatin dose. All had 6 weeks treatment duration except P693 which had 14 weeks.

Study P693 was in patients with coronary heart disease (CHD) or multiple risk factors and compared ezetimibe + atorvastatin 10 mg to atorvastatin 20 mg with possible up-titration of atorvastatin in either group. In Study P079 in patients with moderate and high risk of CHD, treatment compared ezetimibe + atorvastatin 20 mg to atorvastatin 40 mg, while Study P090 in the same population compared ezetimibe + atorvastatin 40 mg to atorvastatin 80 mg. Study P112 was in the elderly and compared ezetimibe + atorvastatin 10 mg to atorvastatin 20 mg and 40 mg.

Long term data of ezetimibe with atorvastatin in primary hypercholesterolaemia came from two 52 week studies; one controlled (P2154 the extension of P692) which included 246 patients and one open label study and uncontrolled study (P1418 the extension of P693) which included 432 patients.

Data in the special population with HoFH came from the 50 patients (12 on atorvastatin 80 mg and 24 on ezetimibe + atorvastatin 40 mg or 80 mg) treated for 12 weeks in Study P1030. There was also a two year open label extension (P1417) which included 44 patients of whom 36 received ezetimibe + atorvastatin 40 mg or 80 mg.

Data on the population with mixed hyperlipidaemia were derived from a subgroup of 139 patients in P0692 who had hypercholesterolaemia with triglyceride (TG) levels ≥ 200 mg/dL. In this group, 66 received atorvastatin and 73 ezetimibe + atorvastatin for 12 weeks. Following questions in the previous evaluation further post-hoc analysis data from studies P079, P090 and P112 were provided including an additional 280 patients with TG ≥ 150 mg/dL.

The main clinical efficacy endpoint was mean percentage change from baseline in LDL-C. In general, LDL-C level was calculated using the Friedewald equation. Studies excluded patients with TG > 350 mg/dL. The proportion of patients attaining LDL-C targets was the main secondary efficacy variable (primary in P693). Safety was the primary objective in the long term studies with efficacy a secondary objective. Lipid assessment was centralised for all studies.

The four factorial studies (P0679, P0680, P0691, P0692) demonstrated an increased mean percentage LDL-C reduction with ezetimibe plus the statin compared to monotherapy (difference of approximately -14%). The effect was consistent across the four statins (lovastatin, simvastatin, pravastatin, and atorvastatin).

When ezetimibe was added to ongoing statin therapy (P2173 and P040) there was a significantly greater reduction in LDL-C levels than placebo (difference of -23.1% in P040 and -21.5% in P2173), with consistent results across CHD risk categories. When the

subgroup of patients taking atorvastatin was assessed, efficacy was comparable to the overall statin group (Table 1).

Table 1. Mean percent in changes in LDL-C from baseline at study endpoint modified Intention-to-Treat Approach P2173, P040, P079 and P090

	P2173		P040		P079		P090	
	Placebo + Atorva	EZ 10 mg + All Atorva	Placebo + All Atorva	EZ 10 mg + All Atorva	Atorva 40 mg	EZ 10 mg + Atorva 20 mg	Atorva 80 mg	EZ 10 mg + Atorva 40 mg
Baseline								
N	162	146	386	769	92	92	279	277
Mean (mg/dL)	133.75	104.81	130.7	129.2	118.1	120.3	89.7	88.6
SD	-	-	34.4	30.6	17.2	19.7	16.0	16.3
Percent Change From Baseline at Study Endpoint								
LS Mean	-4.01	-24.98	-4.2	-27.2	-10.9	-30.8	-11.0	-27.4
Difference From All Atorva								
LS Mean	-	-21.0**	-	-23.0***	-	-19.9***	-	-16.3***
(95% CI)	-	(-24.2, -17.8)	-	(-25.2, -20.8)	-	(-25.2, -14.5)	-	(-19.4, -13.2)
p-Value [†]	-	p<0.01	-	p<0.001	-	p<0.001	-	p<0.001
*p<0.05; **p<0.01; ***p<0.001. EZ = ezetimibe. All Atorva = atorvastatin (10, 20, 40, and 80 mg) pooled across doses. [†] p-Value for the primary comparison (EZ 10 mg + All Atorva versus All Atorva). - = Not Available								

The addition of ezetimibe to atorvastatin resulted in a significantly greater LDL-C reduction than up-titrating to the next atorvastatin dose (P079, P090, P112 and P693)(Tables 1-3). Target LDL-C level attainment was greater with ezetimibe compared to placebo added to atorvastatin and also greater when ezetimibe was added to atorvastatin compared to up-titrating the atorvastatin dose.

Table 2. Mean percent in changes in LDL-C from baseline at 6 and 12 weeks. Full Analysis Set Population. P112.

	Week 6		Week 12	
	Ezetimibe 10 mg + Atorvastatin 10 mg	Atorvastatin 20 mg + Placebo	Ezetimibe 10 mg + Atorvastatin 10 mg	Atorvastatin 20/40 mg + Placebo
Baseline				
N	515	515	516	509
Mean (mg/dL)	102.9	101.4	102.9	101.7
SD	27.8	20.5	27.8	20.6
Endpoint (Week 6 or 12)				
Mean (mg/dL)	75.2	88.7	79.1	83.1
SD	25.1	22.7	31.6	24.8
Percent Change From Baseline at Study Endpoint				
LS Mean	-26.7	-12.8	-22.5	-17.9
Between-Treatment Difference				
LS Mean	-13.8***	-	-4.6***	-
(95% CI)	(-16.0, -11.7)	-	(-7.4, -1.8)	-
*p<0.05; **p<0.01; ***p<0.001.				

Table 3. Mean percent in changes in LDL-C from baseline at four weeks. Modified Intention-to-Treat Approach. P693

	Atorva 20 mg	EZ 10 mg + Atorva 10 mg
Baseline		
N	316	305
LS Mean (mg/dL)	186.84	185.93
SE	2.62	2.66
Percent Change From Baseline at Study Endpoint (4 wks)		
LS Mean	-8.99	-23.84
Difference From All Atorva		
LS Mean	-	-14.85**
(95% CI)	-	(-16.87, -12.83)
*p<0.05; **p<0.01. EZ = ezetimibe. Atorva = atorvastatin.		

There was very limited long term efficacy data with ezetimibe and atorvastatin co-administration in the initial ezetimibe submission. The two long term studies in the previously-evaluated submission filled this gap. After 52 weeks of treatment in these two

studies, there was maintenance of LDL-C reduction and the proportion attaining LDL-C target levels that were achieved in the short term studies.

On cessation of ezetimibe (P2173R) lipid levels returned to baseline levels with no evidence of a rebound increase.

The effect on the reduction of other lipids (TG, total cholesterol (TC), apolipoprotein B (Apo B) and non-high density lipo-protein cholesterol (HDL-C)) was also more favourable with the combination treatment. There was less of an effect on increasing HDL-C.

Efficacy was seen in the small group of patients with HoFH and maintained for 2 years of treatment. Efficacy was also consistent across subgroups of age and gender. In post-hoc analyses, which included 419 patients with mixed hyperlipidaemia (TG \geq 150 mg/dL in P079, P090 and P112 and TG \geq 200 mg/dL in P0692), results indicated a consistent effect on lowering LDL-C in this subgroup. The magnitude of LDL-C reduction was in line with that seen in patients with baseline triglyceride levels <150 mg/dL.

Safety

Studies providing evaluable safety data

The most relevant source of safety data for the composite pack comes from the previously evaluated submission, the data for which was provided in the response to the s31 questions. The safety data from that clinical evaluation report have been reproduced here. In that submission there were 11 studies which provided evaluable safety data and they were grouped into three data pools for the safety analyses:

- Core Safety pool consisted of the seven controlled short term (6 to 14 weeks) studies P040, P079, P090, P112, P692, P693 and P2173. These studies included 4569 patients with 2041 and 2403 randomised to atorvastatin monotherapy and ezetimibe 10 mg + atorvastatin (all doses), respectively. There were also 60 and 65 patients who were randomised to placebo or ezetimibe monotherapy, respectively.
- Long Term (12 month) studies P2154 and P1418. These studies included 246 and 432 patients, respectively. These studies were analysed individually as P2154 was randomised (ezetimibe + atorvastatin versus atorvastatin) and blinded, while P1418 was open label (ezetimibe + atorvastatin).
- Special Population studies consisted of P1030 and P1417 in HoFH. There were 36 patients in P1030 (24 receiving ezetimibe + atorvastatin) and 35 (who received ezetimibe + atorvastatin) in the extension P1417.

In the efficacy studies, the following safety data were collected:

- General adverse events (AEs) were assessed by questioning at each study visit.
- AEs of particular interest included allergic reaction/rash AEs, gallbladder related AEs, gastrointestinal related AEs, liver effects (hepatitis, ALT and AST elevation, potential Hy's Law cases⁷), and creatinine phosphokinase (CK) and muscle-related symptoms.
- Laboratory tests, including blood chemistry (including aspartate aminotransferase (AST) /alanine aminotransferase (ALT) and CK), haematology and urinalysis were performed at baseline and study endpoint as well as at specified intervals. Thyroid function was assessed in P693, P1030 and P1417.
- Electrocardiograms (ECGs) were conducted in P692, P693, P2173, P1030 and P1418.

⁷ A potential Hy's Law case was defined as ALT or AST \geq 3x ULN with ALP \leq 2x ULN and total BR >2x ULN.

- Physical examination and vital signs.

Safety was based on analysis of all randomised patients who took at least one dose of study medication.

In addition to this main safety analysis, the safety data from the Ezetrol submission has been summarised (see Attachment 2 of this AusPAR).

Pivotal studies that assessed safety as a primary outcome

In the two long term extension studies (P2154 and P1418) safety was the primary objective. The data from these studies is discussed further in CER Attachment 2 of this AusPAR.

Patient exposure

In the core safety pool, the mean treatment duration was 82 days for placebo and ezetimibe monotherapy, 67 days for atorvastatin monotherapy and 63 days for ezetimibe + atorvastatin (all doses) (Table 4 below).

Table 4. Scope of the Core Safety Pool and Patient Population Treated with placebo, ezetimibe monotherapy, atorvastatin monotherapy and ezetimibe + atorvastatin.

	Placebo	EZ 10 mg Monotherapy	All Atorva Monotherapy	EZ 10mg + All Atorva
• Number of Studies	1	1	7	7
• Number of Patients	60	65	2041	2403
• Duration of Treatment:				
◊ Median Duration of Treatment (Weeks)	12	12	11	8
◊ Number of Patients:				
>3 weeks	59	64	1991	2345
>6 weeks	58	63	1560	1765
>12 weeks	22	22	623	621
Note: EZ 10 mg = Ezetimibe 10 mg; All Atorva = Atorvastatin (10, 20, 40 or 80 mg) pooled across all doses.				
Core safety pool studies (040, 079, 090, 112, 692, 693, and 2173)				

For the long term studies, the mean treatment duration in P2154 was 11 months in both groups.

In P1418, with the primary study P693 included, the mean exposure to ezetimibe and atorvastatin was 11.9 months in the 521 patients.

For patients with HoFH, the mean exposure in P1030 was 82 days and 87 days in the all atorvastatin and ezetimibe + atorvastatin groups, respectively. In P1417 combined with P1030, the mean exposure to the combination was 23.5 months in the 36 patients.

In the short term studies, 51% were male and 87% White. The mean age in the ezetimibe + atorvastatin group was 61.6 years, 69% had a pre-existing vascular disorder and 53% had a cardiac disorder. For P1030 in HoFH, the population treated with the combination had a mean age of 32.2 years, 58% were female and 92% White.

Postmarketing experience

A cumulative summary of postmarketing data relating the co-administration of ezetimibe with a statin and more specifically with atorvastatin was included in Module 5 of the previously evaluated submission. From October 2002 to December 2010 there were 5516

health care provider reports of ezetimibe with a statin with 22% serious and 78% non-serious. The most frequent adverse drug reactions (ADRs) were myalgia, raised CK, diarrhoea, nausea and increased ALT. Within this group, 2343 reports were of ezetimibe with atorvastatin with 25% of these serious. The System Organ Class (SOC) most frequently affected were Investigations (31%), Musculoskeletal and connective tissue disorders (29%), Gastrointestinal disorders (22%) and General disorders (21%). In the Investigation SOC, the most frequent serious ADRs were increased CK, increased ALT, increased AST, increased cholesterol, increased TG and abnormal liver function test. In the Musculoskeletal SOC, the most frequent serious ADRs were myalgia, rhabdomyolysis, muscle spasms, muscle weakness and extremity pain. The serious Gastrointestinal disorders were abdominal pain, nausea, pancreatitis, vomiting and upper abdominal pain with vomiting. Within the 265 myopathy-related ADRs, 39% were serious and there were 3 fatal events (though the sponsor believes it is possible one of these was a duplicate) There were only limited details available on these fatalities. There were 1020 events with hepatobiliary ADR terms, half were serious and 10 fatal. For these 10 deaths information detail was variable and four cases had hepatic ADRs included in the cause of death (one hepatic failure and cirrhosis, one vanishing bile duct syndrome with cirrhosis, one autoimmune hepatitis and cirrhosis and one breast cancer with liver metastases).

There were 29 reports of drug interactions in patients treated with ezetimibe and atorvastatin. Most (62%) related to ezetimibe and atorvastatin. Five reports related to drugs listed on the ezetimibe label (cyclosporine, coumadin anticoagulants, rosuvastatin, oral contraceptive). There were another 5 cases which involved fusidic acid, creatine, atenolol, varenicline and carbamazepine which are not on the product label.

Evaluator's overall conclusions on clinical safety

In the previous submission, safety data were collated from 11 clinical studies of which seven were short term (6 to 14 weeks) controlled trials which included 4569 patients with 2403 randomised to ezetimibe 10 mg + atorvastatin (all doses). The median duration of exposure in these studies was 8 weeks. There were two long term 12 month studies: one controlled with 246 patients and one open label uncontrolled with 432 patients. There was also one small short term study and a two year open label extension study in 36 patients with HoFH with mean exposure duration of 23.5 months.

In the short term pooled data, the atorvastatin monotherapy population was a similar size to the combination group (n=2041), while the ezetimibe monotherapy group was small (n=65). Consequently, the evaluator has made, in general, comparisons of AE rates between the combination and atorvastatin monotherapy.

In the short term studies, the exposure-adjusted adverse event rate was no higher in patients treated with the combination than in those receiving monotherapy or placebo. Overall the safety profile of the combination of ezetimibe with atorvastatin was in line with that seen with the individual components. The most frequent AEs in the ezetimibe + atorvastatin and atorvastatin group were nasopharyngitis (2.1% versus 1.9%), myalgia (2.5% versus 2.6%) and headache (2.5% versus 2.4%). In the controlled long term study, the most frequent AEs were myalgia (8.0% versus 8.9%), back pain (6.5% versus 2.2%), muscle spasms (6.0% versus 0%), arthralgia (6.0% versus 8.9%), extremity pain (6.0% versus 6.7%) and headache (6.0% versus 4.4%).

Gallbladder-related events were infrequent (0.1% versus 0.0%) and allergic reactions/rash occurred at similar rates to that of atorvastatin monotherapy (1.4% versus 1.5% short term and 5.0% versus 4.4% long term). Gastrointestinal disorders occurred at a similar rate to the atorvastatin monotherapy group in the short term studies with the most frequent being diarrhoea (1.8% in both groups) and nausea (1.1% versus 1.9%).

With long term treatment the rate increased (17.9%) but was less than with atorvastatin monotherapy (31.1%).

Effects on kidney function and haematology parameters were infrequent and similar between the combination and atorvastatin monotherapy. The combination therapy did not appear to have any clinically significant effect on vital signs or ECG results.

Hepatitis related events were infrequent (one case short term and one long term) in the ezetimibe + atorvastatin treated patients. In the short term studies, the rate of consecutive ALT/AST ≥ 3 times the upper limit of normal (ULN) was similar to atorvastatin (0.6% versus 0.5%). With longer term treatment there was an indication of a slightly higher rate of low level (2 to <3 x ULN) ALT/AST rise (6.5% versus 2.2%). It is noted that the safety evaluation of Ezetrol noted that there was a higher incidence of clinically important (≥ 3 x ULN) hepatic transaminase elevation with ezetimibe co-administration with a statin compared to statin monotherapy (increased ALT: 1.7% versus 0.6% and increased AST: 1.4% versus 0.4%).

In the short term studies, the rate of AEs of elevated CK (0.8% versus 0.6%), the rate of CK ≥ 10 x ULN (0% versus 0.1%) and the rates of lower levels of elevated CK were similar between the combination and atorvastatin monotherapy. In the three long term studies, there were two cases CK ≥ 10 x ULN which were not attributed to study treatment.

There were 4 deaths in the short term studies, with 2 in the ezetimibe + atorvastatin group, with one further death in a long term study. None was considered treatment-related. The exposure-adjusted serious AE (SAE) rate (per 100 patient years) in the short term studies (12.3) was mildly higher than atorvastatin (9.6). The most frequent SAEs were myocardial infarction and chest pain.

Study discontinuation due to AEs was low (2.6% versus 2.7%) in the short term studies and increased in the controlled long term study (9.0% versus 6.7%). The main reasons were Musculoskeletal and Gastrointestinal disorders. The discontinuation rate in the short term studies was lower than that reported in with ezetimibe and any statin in the Ezetrol submission (5.0%).

Safety was assessed in the elderly (≥ 65 years and ≥ 75 years) and by gender with no increased risk seen in older patients or for either gender. Numbers of non-Caucasians were too low to draw conclusions.

Withdrawal of ezetimibe treatment from co-administration with atorvastatin was assessed with no notable adverse effects.

Although the numbers were small, the AE profile appeared similar in the HoFH population.

Post-marketing data of 2343 reports with the combination of ezetimibe and atorvastatin found the most frequent ADRs were myalgia, raised CK, diarrhoea, nausea, increased ALT. There were 3 fatal myopathy-related and 10 fatal hepatobiliary related ADRs though details were lacking.

Overall, the safety data from the previously evaluated submission, which related to ezetimibe with atorvastatin, were consistent with those reported in the Ezetrol submission which related to ezetimibe with any statin.

First round benefit-risk assessment

First round assessment of benefits

The benefits of the combination of ezetimibe and atorvastatin in the proposed usage were:

- Efficacy in reducing LDL-C, and in terms of the proportion reaching National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) 8 LDL-C target levels, which was greater than either monotherapy. Efficacy was also demonstrated for reduction of TC, TG, non-HDL-C and Apo B.
- Efficacy with ezetimibe and atorvastatin 10, 20 and 40 mg was greater than monotherapy atorvastatin which had been titrated to the next respective dose.
- Efficacy was maintained for up to 1 year without evidence of tolerance or rebound on cessation of ezetimibe.
- Efficacy was seen in patients with primary hypercholesterolaemia and with HoFH.
- Safety data indicated no new safety signals with the combination compared to atorvastatin monotherapy. The treatment was generally well tolerated and the adverse event-related discontinuations were low.

First round assessment of risks

The risks of ezetimibe and atorvastatin in the proposed usage were:

- Gastrointestinal adverse effects including diarrhoea, nausea and abdominal pain.
- Muscular toxicity, either clinical or biochemical, that is well known to be associated with statins. This did not, however, appear greater than with atorvastatin monotherapy with the exception of the addition of adverse event of muscle spasms.
- Increased liver transaminases. The data indicated a similar risk to monotherapy atorvastatin in the short term with a possible small increase in risk in the longer term. It is noted that the ezetimibe evaluation found the risk to be greater for the combination than for statin monotherapy.
- Little clinical data on non-Caucasians.
- There were no data to indicate that adding ezetimibe to statin therapy will improve cardiovascular outcomes compared to a statin alone.

First round assessment of benefit-risk balance

The European Medicines Agency (EMA) guidelines on fixed dose combination products⁶ clearly states that the scientific principles for a FDC also apply to the assessment of the combination pack products. The dossier, as submitted, only referenced clinical data from the original ezetimibe submission (Ezetrol). It did not utilise or reference any of the data from the previously evaluated ezetimibe and atorvastatin submission. As a consequence, the sponsor failed to provide the most appropriate clinical data for evaluation of a composite pack.

The correspondence between the sponsor and the TGA indicated that the sponsor's rationale for using only the Ezetrol data was that, as ezetimibe is currently indicated for use with a statin, no additional clinical data were required for the composite pack submission. The evaluator does not agree with this. The principal reason for this is that the composite pack is, to all intents and purposes, a fixed dose combination product and therefore all data which throw light on how the two monotherapies interact when used in combination are relevant. This is supported by the sponsor's statement that the clinical rationale for the composite pack is that "having both products contained in one calendar pack would increase the awareness and emphasise the clinical importance of taking both medications concurrently and at the same time when both medications are co-prescribed". Thus, the clear intention behind the composite pack is that both products are to be always taken together for the one purpose. The evaluator, therefore, believes that the composite

⁶ <<http://www.scymed.com/en/smnxdj/edzr/edzr9610.htm>>

pack must satisfy all the requirements to be met by a fixed dose combination. This means that additional efficacy and safety data are necessary to support the combined use and that the data in the previously evaluated submission are relevant and appropriate and should have formed part of this dossier.

Furthermore, the data provided in the ezetimibe submission are inadequate for supporting approval of a composite pack of ezetimibe with atorvastatin due to the lack of long term efficacy and safety data with this combination. In fact, the sponsor's Clinical Overview summarised efficacy data on only 94 patients who were treated from 12 to <18 months with co-administered ezetimibe and any statin.

The evaluator did however, have access to the current evaluation of a previous submission related to ezetimibe and atorvastatin and in this dossier the sponsor included clinical efficacy and safety studies with the free combination of ezetimibe and atorvastatin, including two long term safety studies.

When assessing the available data from both Ezetrol and the previous submissions, one of the major deficiencies was the lack of clinical data linking the versions of atorvastatin. The studies in the previous dossier were conducted using the atorvastatin Lipitor available from the US. In the previous dossier, dissolution profiles and physicochemical/chemical evidence indicated that the Lipitor from the US and the Lipitor sourced from Australia were identical. The proposed composite pack includes Atorvastatin SZ (Sandoz). In order to bridge between the clinical trials with US Lipitor and Atorvastatin SZ, bioequivalence would need to be demonstrated. If other versions of atorvastatin were used in the ezetimibe submission studies, then similar bioequivalence data would also be needed.

The combination of ezetimibe and atorvastatin has demonstrated a level of efficacy which is above the one achievable by a single substance and this has been achieved with an acceptable safety profile which is comparable to atorvastatin monotherapy. Of clinical relevance, efficacy has been demonstrated while keeping the atorvastatin dose lower. This may potentially decrease safety risks associated with higher statin doses.

This improved benefit-risk balance, together with the complementary mechanisms of action of the two components, meets the EMA guideline criteria to justify the use of the combination⁶. The sponsor has estimated that 25,000 patients were being prescribed the combination in Australia in 2009 so there is a clinical place for the treatment. The sponsor's justification for the composite pack is that "*having both products contained in one calendar pack would increase the awareness and emphasise the clinical importance of taking both medications concurrently and at the same time when both medications are co-prescribed. In addition, a composite pack would reduce the cost to patients, as patients will only pay for one PBS⁹ co-payment instead of two.*" Lipid lowering therapy is an area which has poor long term compliance. The composite pack may offer convenience to patients and may stimulate awareness, however it is not certain that this will result in increased compliance and there has been no data submitted to support this possibility.

The proposed indication

Ezetrol Plus Atorva is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia

is too broad and suggests use as first line therapy. This combination therapy should be used as substitution for patients already treated with atorvastatin and ezetimibe or in patients not adequately controlled with atorvastatin or ezetimibe and in whom an additional agent is being considered. This change would put the product in line with Vytorin (ezetimibe + simvastatin) and also with that proposed for the previously evaluated submission. The evaluator proposes the following wording:

⁹ PBS=Pharmaceutical Benefits Scheme

Ezetrol Plus Atorva 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:

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

The data for the combination use are sufficient to maintain the indication in homozygous familial hypercholesterolaemia (HoFH) *Ezetrol Plus Atorva is indicated in patients with HoFH. Patients may also receive adjunctive treatments (e.g. LDL apheresis).*

The sponsor has proposed to have four strengths of ezetimibe/atorvastatin in composite packs: 10/10 mg, 10/20 mg, 10/40 mg and 10/80 mg. This is appropriate as, due to treatment needing to be titrated to lipid levels, all atorvastatin doses should be available.

The proposed trade name of 'Ezetrol plus Atorva' uses the word 'Plus' which could imply superiority of the product over other products. While there are clinical data indicating improved LDL-C reduction with the addition of ezetimibe to atorvastatin compared to monotherapy, there are fewer comparative data with other products. The evaluator recommends an alternate trade name be proposed.

The risks of liver toxicity have been adequately outlined in the PI with monitoring of liver function recommended before treatment initiation and periodically thereafter and dose reduction or withdrawal if transaminases increase. The risks of muscle toxicity are not adequately outlined in the draft PI as data have been cut and pasted from the two individual product PIs and not combined to make it relevant to a combination product. The monitoring of CK has been recommended based on clinical symptoms or in groups at risk of myopathy. The evaluator agrees with these recommendations. Due to the inherent risks, the evaluator believes that myopathy secondary to lipid lowering agents should be an added contraindication to treatment with this product.

In terms of other risks with ezetimibe and atorvastatin, the draft PI has adequately incorporated all the relevant sections of the approved monotherapy PIs, although fails to reference the combination therapy and in most instances refers to one or other monotherapy. Overall, the proposed PI has numerous inadequacies and needs to be rewritten. As the evaluator contends the appropriate data are from the specific ezetimibe and atorvastatin clinical studies, two main deficiencies in the draft PI are not using the efficacy and safety data from these studies in the *Clinical Trial* section and *Adverse Effects* sections.

There is currently no available evidence on cardiovascular outcomes with the combination of ezetimibe and a statin and so, while it may be anticipated that the improved lipid reduction with the addition of ezetimibe to atorvastatin will translate into improved cardiovascular outcomes, this remains speculative. A statement regarding this lack of data needs to be included in the PI.

In summary, the data in the dossier from the Ezetrol submission are insufficient to support the application for the composite pack. Nevertheless, if clinical data submitted for a previously-evaluated MSD dossier are used, then there are sufficient positive efficacy and safety data, including long term data, to support the combined use of ezetimibe and atorvastatin. A major deficiency still remains the lack of bioequivalence data to bridge between the proposed Atorvastatin SZ in the composite pack and the US Lipitor used in the clinical trials. Finally, the proposed PI is inadequate and needs substantial modifications and inclusions, the justification for the need of a composite pack or two currently registered products is not clinically compelling and the trade names needs to be altered. Given these issues, the evaluator finds the benefit-risk balance of Ezetrol plus Atorva given the proposed usage, is unfavourable.

First round recommendation regarding authorisation

The evaluator recommends rejection of authorisation of Ezetrol plus Atorva. The grounds for rejection are:

- inadequate provision of clinical efficacy and safety data in the dossier;
- a lack of bioequivalence data between atorvastatin SZ and atorvastatin used in the clinical trials;
- a product information which needs substantial modifications; and
- a non-compelling clinical justification for the product.

List of questions**Clinical pharmacokinetics**

The most appropriate clinical data on which to base efficacy and safety decisions for the combination product are the data in the previously evaluated submission. The proposed composite pack includes Atorvastatin SZ, while the relevant clinical trials of the free combination were conducted with Lipitor sourced in the US. If available, information needs to be provided to allow bridging of the data from the studies with US Lipitor to Atorvastatin SZ, otherwise comparable clinical effects cannot be assumed. A summary of which atorvastatin product has been used in the clinical trials in both the Ezetrol and the previously evaluated submissions and a discussion on the bioequivalence of these products to Atorvastatin SZ needs to be provided.

Are there any data on the pharmacokinetics of ezetimibe and atorvastatin in different races? This should be provided as well as be included in the PI.

Clinical efficacy

The sponsor has stated that the clinical rationale for the composite pack is that *“having both products contained in one calendar pack would increase the awareness and emphasise the clinical importance of taking both medications concurrently and at the same time when both medications are co-prescribed”*. Thus, the clear intention behind the composite pack is that both products are to be always taken together for the one purpose. The composite pack is then, to all intents and purposes, a fixed dose combination product and the evaluator believed that it must satisfy all the requirements to be met by a fixed dose combination. This is supported by EMA guidelines on fixed dose combination products⁶ which clearly state that the scientific principles for a FDC also apply to the assessment of the combination pack products.

Could the sponsor clearly and precisely articulate all its reasons for not including the previously evaluated and/or other relevant fixed dose combination efficacy data as part of the original submission.

Clinical safety

For the same reasons as outlined in the question above, could the sponsor clearly and precisely articulate all its reasons for not including the previously evaluated and/or other relevant fixed dose combination safety data as part of the original submission?

Clinical summary and conclusions

Second round evaluation of clinical data submitted in response to questions

Pharmacokinetics

1. Agency question

The most appropriate clinical data on which to base efficacy and safety decisions for the combination product are the data in the previously evaluated MSD dossier relating to ezetimibe and atorvastatin.

Sponsor's response

"Merck Sharp & Dohme (Australia) Pty Limited (MSD) does not concur with the evaluator's statement that the most appropriate data are that of the previously evaluated MSD submission. MSD would like to confirm the efficacy and safety data for the co-administration of ezetimibe and atorvastatin for the composite pack are based on the original approval of Ezetrol. MSD believes that these data provided sufficient evidence for efficacy and safety for the composite pack."

MSD also stated that it was their intention after approval to update the PI for the composite pack with additional data from the *previously evaluated MSD* submission. The sponsor believes that submission provides *"supporting rather than pivotal data for co-administration for ezetimibe and atorvastatin"*. These data were not included as part of the submission as *"co-administration of ezetimibe and atorvastatin is an approved indication."*

The sponsor included tabulation of the clinical studies from the original submission and the previously evaluated MSD dossier.

Evaluator's response

The sponsor has now submitted previously-evaluated data in relation to this application. It is again noted that sufficient long term efficacy and safety data for the combined use of ezetimibe and atorvastatin was located that dossier (Studies P2154 and P1418) and not the Ezetrol dossier.

2. Agency question

The proposed composite pack includes Atorvastatin SZ, while the relevant clinical trials in the previously evaluated MSD dossier were conducted with Lipitor sourced in the US. If available, information needs to be provided to allow bridging of the data from the studies with US Lipitor to Atorvastatin SZ, otherwise comparable clinical effects cannot be assumed. A summary of which atorvastatin product has been used in the clinical trials in both the Ezetrol and previously evaluated submissions and a discussion on the bioequivalence of these products to Atorvastatin SZ needs to be provided.

Sponsor's response

The evidence for bridging of Lipitor sourced in the US to the Atorvastatin SZ is based on two steps. Firstly, the comparison testing of the US Lipitor and Australian Lipitor that was included in the previously-evaluated submission. Comparability was demonstrated including on dissolution. Secondly, bioequivalence of Atorvastatin SZ to Australian Lipitor was demonstrated in the marketing application for Atorvastatin SZ.

Evaluator's response

These data are acceptable for demonstrating the two step bridging between the US Lipitor used in the previously evaluated ezetimibe and atorvastatin clinical trials and the proposed Atorvastatin SZ to be included in the composite pack.

3. Agency question

Are there any data on the pharmacokinetics of ezetimibe and atorvastatin in different races? This should be provided as well as be included in the PI.

Sponsor's response

As per the Ezetrol PI, there were no pharmacokinetic differences between Blacks and Caucasians based on the meta-analysis of the PK studies. The atorvastatin PI does not contain information on racial PK differences. For coadministration of ezetimibe and atorvastatin, the PK studies included only Caucasians and the efficacy studies had only small sample sizes in non-Caucasian subgroups. The core safety pool examined safety in Whites, Blacks and Asians and found no meaningful differences in adverse experiences between the race subgroups, though again subgroup numbers were small.

Evaluator's comments

There are minimal clinical data on non-Caucasians. This needs to be included in the PI.

Efficacy

4. Agency question

The sponsor has stated that the clinical rationale for the composite pack is that *"having both products contained in one calendar pack would increase the awareness and emphasise the clinical importance of taking both medications concurrently and at the same time when both medications are co-prescribed"*. Thus, the clear intention behind the composite pack is that both products are to be always taken together for the one purpose. The composite pack is then, to all intents and purposes, a fixed dose combination product and the evaluator believed that it must satisfy all the requirements to be met by a fixed dose combination. This is supported by EMA guidelines on fixed dose combination products⁶ which clearly state that the scientific principles for a FDC also apply to the assessment of the combination pack products. Could the sponsor clearly and precisely articulate all its reasons for not including the previous efficacy data as part of the original submission.

Sponsor's response

"As stated previously MSD believes that the data in the original EZETROL approval provide sufficient evidence for efficacy and safety. These are approved medicines at approved dosages in an approved regimen."

"These data are enhanced by the relevant clinical trials from previously-evaluated MSD submission now included here. The findings in these studies did not differ from the findings in the original Ezetrol submission and as proposed for the composite pack originally".

The Module 2 and 5 data from the previously-evaluated MSD submission were included with the response and the PI has been updated in the *Clinical Trial* and *Adverse Effects* sections.

Evaluator's response

In the round one evaluation, the data from the original Ezetrol submission were considered along with the data from the previously-evaluated MSD submission, the latter having been provided in response to the s31 questions. Together these provide sufficient clinical efficacy data on which to base a decision for the composite pack.

Safety

5. Agency question

For the same reasons as outlined in the question above, could the sponsor clearly and precisely articulate all its reasons for not including the previous safety data as part of the original submission.

Sponsor's response

"For the same reasons outlined in Section 12.2.3 above, safety data from the extra co-administration studies were not included as part of the original submission for this ezetimibe and atorvastatin composite pack. In addition, periodic safety update reports submitted for Ezetrol covering the period 17 April 2003 to 16 October 2006 immediately after registration and more recent PSURs¹⁰ submitted during the recent CKD evaluation did not reveal any major new safety signals for ezetimibe and atorvastatin co-administration.

Any significant safety data has been incorporated into the Ezetrol PI via safety-related notifications and these safety data are reflected in the proposed Composite Pack PI.

However, MSD concurs with the TGA that these extra supporting data would enhance the composite pack submission. MSD proposes to include the extra information regarding co-administration in the proposed Composite Pack PI."

Evaluator's response

In the round one evaluation, the data from the original Ezetrol submission were considered along with the data from the previously-evaluated MSD submission, the latter having been provided in response to the s31 questions. Together these provide sufficient clinical safety data on which to base a decision for the composite pack.

Second round benefit-risk assessment***Second round assessment of benefits***

After consideration of the responses to clinical questions, the benefits of ezetimibe and atorvastatin composite pack in the proposed usage are unchanged from those identified in the *First round assessment of benefits*.

Second round assessment of risk

After consideration of the responses to clinical questions, the risks of ezetimibe and atorvastatin composite pack in the proposed usage are unchanged from those identified in *First round assessment of risks*.

Second round assessment of benefit-risk balance

The sponsor's responses to the questions raised after the first round of evaluation have satisfied a number of the submission's deficiencies. Data from the previously-evaluated MSD submission were provided. This allowed full evaluation of the combination of ezetimibe and atorvastatin in a variety of clinical situations. It also provided the necessary long term efficacy and safety data which were lacking in the Ezetrol dossier.

The sponsor has explained the bioequivalence linkage path between the atorvastatin products used in the clinical programs. This is via two steps from the US Lipitor to the Australian Lipitor and from the Australian Lipitor to Atorvastatin SZ (now referred to as MSD Atorvastatin). The evaluator believes this is satisfactory.

The sponsor has proposed new trade names as the use of the word "plus" in Ezetrol Plus Atorva was not felt acceptable. The two alternative trade names are "Atozet Composite Pack" and "Zeteze". Atozet Composite pack is a preferable name to Ezetrol Plus Atorva, however it is recommended Zeteze has the words "Composite Pack" as well. The pack dosage needs to be clear to ensure there is no confusion or prescribing errors.

The draft product information now includes updated clinical trial data which cover all relevant studies. The Adverse Effects section has also been revised and now refers to relevant pooled safety data from co-administration of ezetimibe and atorvastatin.

¹⁰ PSUR= Periodic Safety Update Report

The other major deficiency still outstanding is the proposed indication. The first round evaluation found the proposed indication too broad as it suggested use could be as a first line therapy. It is recommended that use be limited to substitution for patients already treated with atorvastatin and ezetimibe or to patients not adequately controlled with atorvastatin or ezetimibe and in whom an additional agent is being considered. The revised indication proposed by the evaluator was:

Primary Hypercholesterolaemia

TRADENAME 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:

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

Homozygous Familial Hypercholesterolaemia (HoFH)

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

This change was not adopted and there was no discussion provided by the sponsor as to why this was the case.

The submission provided considerable positive clinical efficacy data and acceptable safety data for co-administration of ezetimibe with atorvastatin, although the evaluator still maintains that having the products in one pack would provide minimal additional clinical benefit. It may, however, improve compliance. The sponsor has adequately addressed the other issues raised in the first round evaluation and, given this, the evaluator finds the benefit-risk balance of ezetimibe and atorvastatin in a composite pack for the treatment of primary hypercholesterolaemia is favourable. The PI still has outstanding issues to be addressed and the proposed indication needs to be altered to ensure the combination is not used as first line therapy.

Second round recommendation regarding authorisation

The evaluator recommends of approval of authorisation of the composite pack of ezetimibe 10 mg with atorvastatin (10 mg, 20 mg 40 mg or 80 mg) subject to:

- The sponsor satisfactorily addressing all the comments recommended for the draft PI and CMI.
- Alteration of the proposed indication.

The rationale for the differing recommendation from that made after the first round of evaluation in Section 10 is that the major outlined deficiencies have been addressed. These included the provision of clinical data from a previously-evaluated MSD submission and the provision of information which allowed bridging between the US Lipitor used in the clinical trials and Atorvastatin SZ (MSD Atorvastatin) in the composite pack.

V. Pharmacovigilance findings

A Risk Management Plan (RMP) waiver was granted by the Office of Product Review of the TGA at the time of pre-submission assessment.

VI. Overall conclusion and risk/benefit assessment

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

The sponsor's consistent position has been and is that the concomitant administration of ezetimibe and atorvastatin in patients with primary hypercholesterolaemia and homozygous familial hypercholesterolaemia (HoFH) has already been approved by the TGA following the evaluation of the initial Ezetrol submission for registration. The data on which the original approval for registration was based is described and referenced in the sponsor's submission.

Quality

As part of its s31 response, the sponsor provided evidence of comparable bioequivalence, dissolution profiles etc of the US Lipitor product, the Australian-registered Lipitor and Atorvastatin SZ. This was necessary as data involving the US Lipitor product had been included in the previously evaluated submission. The clinical evaluator considered the evidence acceptable as does the Delegate.

As the product contains two registered products with the tablets of each product remaining in their currently approved blister packaging, no aspects of the quality information have been changed other than the changes indicated below:

- Packing of registered blister slides into new carton artwork
- Additional manufacturers for this secondary packaging and release for supply.

Importantly, there have been no changes to manufacturing procedures, equipment, raw materials and finished product specifications.

Nonclinical

The submitted composite pack fulfils the requirements of the TGA adopted EU Guideline¹¹ and therefore no additional nonclinical data have been provided for this submission. The nonclinical evaluator was of the opinion that the sponsor had provided adequate justification for the absence of Module 4 (Nonclinical) data in the form of a Module 2.4 Nonclinical Overview. No Module 4 data were submitted and none were required. No Module 4 evaluation by the TGA was required.

Clinical

The clinical evaluator has recommended approval of the submission for the registration of the composite pack of ezetimibe 10 mg with atorvastatin (10 mg, 20 mg, 40 mg or 80 mg) subject to the sponsor satisfactorily addressing all the comments on the draft PI and CMI and alteration of the proposed indication.

Pharmacology

Pharmacokinetics

No new PK data were submitted. The clinical evaluator provided a summary of data taken from the relevant PI documents and from the clinical evaluation reports for ezetimibe and the previously evaluated ezetimibe and atorvastatin submission.

¹¹ EMEA/CHMP/SWP/256498/2005 Guideline on the nonclinical development of fixed combinations of medicinal products, 4.2.1 <<http://www.tga.gov.au/pdf/euguide/swp25849805final.pdf>>

Absorption: After oral administration, ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). After a single oral 10 mg dose of ezetimibe in fasting adults, mean ezetimibe C_{max} is attained within 4-12 hours. Ezetimibe-glucuronide mean C_{max} is attained within 1-2 hours. Atorvastatin is rapidly absorbed after oral administration, C_{max} occurring within 1-2 hours, the extent of absorption increasing in proportion to dose.

Influence of food: Concomitant administration of food was shown not to affect the oral bioavailability of ezetimibe 10 mg tablets. Food was shown to decrease the C_{max} and the area under the plasma concentration time curve (AUC) by 25% and 9%, respectively but the LDL-C reduction was not affected.

Distribution: The extent of binding to human plasma proteins of ezetimibe and ezetimibe-glucuronide is over 90% with the corresponding figure for atorvastatin being over 98%.

Metabolism: Ezetimibe is primarily metabolised in the small intestine and liver via glucuronide conjugation with subsequent biliary and renal excretion. In humans, ezetimibe is rapidly metabolised to ezetimibe-glucuronide with the latter accounting for 80-90% of the total drug in plasma. The half-life for both ezetimibe and ezetimibe-glucuronide is about 22 hours. Plasma concentration-time profiles exhibit multiple peaks, suggesting enterohepatic recycling. Both ezetimibe and its metabolite ezetimibe-glucuronide are pharmacologically active, with ezetimibe-glucuronide inhibiting cholesterol absorption to an extent at least as great as that for the unconjugated parent. Atorvastatin is extensively metabolised to ortho- and para-hydroxylated derivatives and various beta-oxidation products. Approximately 70% of circulatory inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Excretion: The proportions of an administered dose of ezetimibe found in faeces and urine were approximately 78% and 11%, respectively. Ezetimibe (unconjugated) was the major component in faeces while ezetimibe-glucuronide was the major component in urine. Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

Pharmacokinetics in subjects with impaired hepatic function: After a single dose of ezetimibe and compared with healthy subjects, the mean AUC values for total ezetimibe were increased approximately 1.7 fold, 3 to 4 fold and 5 to 6 fold in patients with mild, moderate or severe hepatic impairment, respectively. In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased.

Pharmacokinetics in subjects with impaired renal function: After a single 10 mg dose of ezetimibe in patients with severe renal disease, the mean AUC values for total ezetimibe, ezetimibe-glucuronide and ezetimibe unconjugated were increased by approximately 1.5 fold, compared with healthy subjects. Renal impairment has no influence on the plasma concentrations of or LDL-C reduction induced by atorvastatin.

Paediatric patients: Based on total ezetimibe, there are PK differences between adolescents and adults. For ezetimibe, there are no PK data in the paediatric population below the age of 10 years. For atorvastatin, PK data in the paediatric population are not available.

Geriatric patients: Plasma concentrations for total ezetimibe were about 2 fold higher subjects aged at least 65 years compared with those in younger subjects. Plasma concentrations of atorvastatin were found to be higher (by about 40% for C_{max} and by about 30% for AUC) in healthy subjects aged at least 65 years than in young adults.

There was no clinically significant drug-drug interaction reported between ezetimibe 10 mg and atorvastatin 10 mg.

Pharmacodynamics

No new PD data were submitted for evaluation. There were seven studies assessing the pharmacokinetics and pharmacodynamics of ezetimibe with statin co-administration in the ezetimibe clinical evaluation report. These found that the combination was generally more effective in lowering lipid levels (LDL-C and total cholesterol) than either agent was alone and significantly more effective than placebo.

Efficacy

No new clinical efficacy studies were submitted in the original dossier. Data were extracted by the clinical evaluator from the registration evaluation of Ezetrol (ezetimibe) and from the clinical study reports in the previously evaluated (ezetimibe and atorvastatin) submission, the latter having been provided by the sponsor in response to the s31 questions. The evaluator has summarised the relevant data in two sections: Efficacy with statins and Efficacy with atorvastatin.

In its response to a TGA request for information, the sponsor gave a very useful summary of the entire efficacy and safety data package available for evaluation which consisted of 10 controlled efficacy and safety studies and 2 uncontrolled efficacy and safety studies. Broadly, there were 2 parts to the dossier. There were the studies submitted in the original registration/marketing application for Ezetrol, these being the Studies P0692, P0693, P2173/2246 and P1030, all short-term and P1417 (extension of Study P1030), the latter being an interim study report out to 10.3 months. In the second part there were the new studies, included in the previously-evaluated MSD dossier and these were the Studies P2173R, P040, P079, P090, P112, all short-term and 2 long-term studies, P2154 (extension of Study P0692) and P1418 (extension of Study P0693).

All 12 studies can be classified by study type/design as follows:

- Initial therapy study, P0692, factorial design with 10 treatment groups, in original Ezetrol application and described in Ezetrol PI
- Ezetimibe as add-on to stable dose of statin, Studies P2173/2246 (primary hypercholesterolaemia) & P1030 (HoFH), both in the original Ezetrol application & described in the Ezetrol PI and Study P040, a new study
- Ezetimibe + atorvastatin versus atorvastatin titrated dose, Study P0693, part of the original Ezetrol submission & described in the Ezetrol PI and 3 new studies; P079, P090 and P112
- A reversibility Study P2173R (at the end of an 8 week treatment phase involving the combination of ezetimibe 10 mg and a statin given to patients with primary hypercholesterolaemia with CHD or CV risk factors, ezetimibe/placebo was withdrawn for 6 weeks); a new study
- Three long-term studies, P1417 (open-label safety in HoFH), part of original Ezetrol application and described in the Ezetrol PI and P2154 (placebo-controlled) and P1418 (open-label safety); the latter two are new studies.

In the original Ezetrol registration/marketing application there were a total of 703 patients with primary hypercholesterolaemia who were treated with the combination of ezetimibe + atorvastatin (in the 3 short-term studies P0692, P2173 and P0693) and 33 patients with HoFH on the combination of ezetimibe + either atorvastatin or simvastatin (in the short-term study P1030). Finally, 44 out of the 50 patients in P1030 enrolled in the extension study P1417 and of these 44, there were 36 treated with the combination of ezetimibe + atorvastatin. For the latter 36 patients there were data out to 10.4 months.

Additional to the data described in the preceding paragraph, there were, in the previously evaluated submission, data on 1678 patients with primary hypercholesterolaemia on the combination of ezetimibe + atorvastatin (in the 4 short-term studies P040, P079, P090 and P112), data out to 12 months for 201 patients with primary hypercholesterolaemia in the extension Study P2154 (extension of P0692), data out to 12 months for 403 patients with primary hypercholesterolaemia in the extension Study P1418 (extension of P0693) and finally data out to 24 months for 33 patients with HoFH in the extension Study P1417.

As noted by the clinical evaluator and as one can observe from the foregoing, as a result of the extra previously evaluated data there were now acceptable numbers of patients yielding long-term data on the effects of the combination of ezetimibe + atorvastatin.

Primary hypercholesterolaemia

Efficacy of ezetimibe with statins

The ezetimibe submission contained 4 multicentre, Phase III, randomised, placebo-controlled, 12 week factorial studies of ezetimibe co-administered with statins in 1861 patients with primary hypercholesterolaemia [Studies P0679, P0680, P0691 & P0692]. The four statins studied were lovastatin, simvastatin, pravastatin and atorvastatin. The mean % changes from baseline in the level of LDL-C were -39.0%, -49.9%, -37.7% and -54.5% for the co-administration of ezetimibe with pooled doses of lovastatin, simvastatin, pravastatin and atorvastatin, respectively. The difference of approx. -13.8% was consistent across the statins and was statistically significant ($p \leq 0.01$).

Study P2173/2246 was evaluated as part of the ezetimibe submission. It was an 8 week randomised, double-blind, placebo-controlled multicentre study which assessed the effect of adding ezetimibe 10 mg to statin therapy in 769 patients with primary hypercholesterolaemia with coronary heart disease or cardiovascular risk factors who had not met target levels. Following the 8 week treatment phase, there was a 6 weeks cholesterol reversibility phase (P2173R). The proportions of subjects using the various statins were as follows: atorvastatin 31.3%, simvastatin 31.3% and pravastatin 14.3%. In the first 8 week treatment phase and in the all statins group, the LS mean % change from baseline in LDL-C was -25.1% in the ezetimibe + statin group compared with -3.7% in the placebo + statin group and the difference, -21.5%, was statistically significant ($p < 0.0001$). In the all statins analysis, the percentages of subjects attaining target LDL-C levels at Week 8 were 76% in the group on the combination of ezetimibe and a statin versus 27% in the group on placebo and a statin. Efficacy was demonstrated across the statin subgroups, including atorvastatin. The percentage reductions in LDL-C from baseline to Week 8 were -25% versus -4% and the percentages of patients attaining target LDL-C at Week 8 were 72% versus 27% in the ezetimibe + atorvastatin and placebo + atorvastatin sub-groups, respectively. One can observe that the results are very consistent across the all statins group and the atorvastatin sub-group. Following the extra 6 week reversibility phase, that is, at 6 weeks post ezetimibe cessation, the mean LDL-C levels were similar to the baseline levels (% LDL-C reduction from baseline: -1% in the ezetimibe + statin group versus -3% in the placebo + statin group).

Study P040 was a large Phase IV multicentre, double-blind, randomised, placebo-controlled, parallel-group study to evaluate the efficacy and safety of ezetimibe 10 mg per day when added to ongoing therapy with a statin compared to statin therapy alone in 3030 patients with hypercholesterolaemia who had not yet reached target LDL-C levels. The proportions of subjects using the various statins were as follows: atorvastatin 40%, simvastatin 29% and pravastatin 21-22%. For all statins, the LS mean % changes from baseline in LDL-C were -25.8% and -2.7% in the ezetimibe and placebo groups, respectively, giving a statistically significant ($p < 0.001$) difference of 23.1%. For all statins, the percentages of patients attaining target LDL-C levels at Week 6 were 75% in the group on the combination of ezetimibe and a statin versus 28% in the group on placebo and a

statin. Significantly greater reductions in LDL-C were also seen with the addition of ezetimibe than with placebo across each of the three statin sub-groups. For the atorvastatin sub-group, the LS mean % changes from baseline in LDL-C were -27% in the group on the combination of ezetimibe and atorvastatin versus -4% in the group on placebo + atorvastatin. Likewise for the atorvastatin sub-group, the percentages of patients achieving LDL-C target levels were 75% in the group on the combination of ezetimibe and atorvastatin versus 24% in the group on placebo and atorvastatin. One can observe that the results are very consistent across the all statins group and the atorvastatin sub-group.

Two multicentre, double-blind, randomised, 14 week studies evaluated the efficacy of ezetimibe co-administration with a statin compared to statin dose titration in patients not reaching LDL-C targets despite statin therapy. Study P0693 with atorvastatin is discussed below. In Study P0700 with simvastatin, after 4 weeks of treatment, the mean % reduction in LDL-C was -24.5% for those treated with ezetimibe 10 mg and simvastatin 20 mg compared to -11.1% for those treated with up-titrated simvastatin 40 mg ($p < 0.01$).

Efficacy of ezetimibe with atorvastatin

Study P0692 (briefly discussed above) was a Phase III, randomised, double-blind, placebo-controlled, parallel-group study in 628 subjects with primary hypercholesterolaemia. After a 4 week single-blind placebo run-in period, subjects were randomised to one of 10 treatment groups: ezetimibe 10 mg alone, atorvastatin 10, 20, 40 or 80 mg alone or ezetimibe 10 mg plus one of atorvastatin 10, 20, 40 or 80 mg or placebo, for 12 weeks. There were 628 patients randomised and 576 (92%) completed the study. For the primary analysis, data were pooled from the four atorvastatin monotherapy groups and from the four atorvastatin plus ezetimibe groups. The addition of ezetimibe to atorvastatin was more effective than atorvastatin alone ($p < 0.01$) or ezetimibe alone ($p < 0.01$) in reducing LDL-C levels. It was also found that the addition of ezetimibe 10 mg to atorvastatin 10 mg or 20 mg resulted in a significantly greater mean % reduction in LDL-C than the next higher dose of atorvastatin monotherapy (20 mg and 40 mg, respectively).

Study P02514 was a randomised, placebo-controlled, double-blind 12-month extension study of P0692. Patients who completed the latter were randomised in a 4:1 ratio to receive daily ezetimibe 10 mg or placebo on top of open-label atorvastatin 10 mg daily with up-titration of the latter if target levels were not attained. Of the 576 patients completing P0692, 246 (39%) entered the extension study, 45 in the atorvastatin + placebo group and 201 in the atorvastatin + ezetimibe group. The reduction in LDL-C was evident at 6 weeks and maintained over the year, with a greater response in the atorvastatin + ezetimibe group (-48.4% versus -38.6% at study end. Only small numbers had their atorvastatin dose titrated: 22% (10/45).

Study P0693 was a Phase III, randomised, double-blind, double-dummy, dose titration study of ezetimibe in addition to atorvastatin in 621 subjects with heterozygous familial hypercholesterolaemia (HeFH) or coronary heart disease or multiple cardiovascular risk factors and with primary hypercholesterolaemia inadequately controlled after 4 weeks on open-label atorvastatin 10 mg. Subjects were randomised 1:1 to receive 14 weeks of ezetimibe 10 mg or atorvastatin 10 mg. In addition, all subjects received background open-label atorvastatin 10 mg. If the target LDL-C levels were not met, atorvastatin dose was up-titrated at 4 weekly intervals to a maximum total of 80 mg in the atorvastatin monotherapy group and 40 mg in the atorvastatin + ezetimibe group. For the primary endpoint at Week 14, there were more subjects in the atorvastatin + ezetimibe group than the atorvastatin monotherapy group who met the target LDL-C level (22% versus 7%, respectively, $p < 0.01$). Target attainment for the subgroup with HeFH was also greater with atorvastatin + ezetimibe (17% versus 4%, respectively, $p < 0.01$).

Study P01418 was a 12 month, open-label extension Study of P0693. There were 432 subjects enrolled; 70% of the cohort randomised in P0693. LDL-C reduction was maintained for the 12 months of the study with a mean reduction of 28% at the study endpoint.

Study P079 was a Phase III, multicentre, randomised, double-blind, titration study to evaluate the efficacy and safety of ezetimibe added to atorvastatin 20 mg compared to up-titration of the atorvastatin dose to 40 mg in hypercholesterolaemic patients with a moderately high risk for coronary heart disease. There was a 6 week treatment period. This study found that these patients showed a greater reduction in LDL-C with the addition of ezetimibe 10 mg to atorvastatin 20 mg (-30.8%) compared to up-titration of atorvastatin to 40 mg (-10.9%).

Study P090, similar in design to the preceding one P079, was a Phase III, multicentre, randomised, double-blind, titration study to evaluate the efficacy and safety of ezetimibe added on to atorvastatin 40 mg compared to up-titration of the dose of atorvastatin to 80 mg in hypercholesterolaemic patients at high risk of coronary heart disease. As for P079, there was a 6 week treatment period. In these patients, the addition of ezetimibe 10 mg, compared to up-titration of the dose of atorvastatin to 80 mg, resulted in a greater reduction in LDL-C (-27.4% versus -11.0%) and a greater proportion of patients reaching target LDL-C (73.6% versus 31.5%).

Study P112 was a multicentre, randomised, double-blind, parallel arm, 12-week study to evaluate the efficacy and safety of ezetimibe 10 mg when added to atorvastatin 10 mg versus titration to atorvastatin 20 mg and 40 mg, in elderly patients (≥ 65 years) with hypercholesterolaemia at high risk of coronary heart disease. The study was similar in design to the two preceding ones; P079 and P090. The addition of ezetimibe 10 mg resulted in a significantly greater reduction in LDL-C after 6 weeks of treatment compared to up-titration to atorvastatin 20 mg (-26.7% versus -12.8%). The combination treatment also resulted in greater LDL-C reduction compared to a further 6 weeks of treatment at an up-titrated dose of atorvastatin 40 mg (-22.5% versus -17.9%).

Homozygous Familial Hypercholesterolaemia (HoFH)

Study P1030 was a 12 week, randomised, double-blind, parallel group, Phase III study in 50 subjects with HoFH with LDL-C not controlled on either atorvastatin 40 mg or simvastatin 40 mg. Subjects were randomised to either ezetimibe 10 mg + statin (40 mg or 80 mg of atorvastatin or simvastatin) or statin alone (atorvastatin or simvastatin 80 mg). Regular LDL apheresis or stable resin therapy continued during the study. Of the 50 subjects, 17 received statin alone and 33 received ezetimibe + statin (with 24 out of the 33 receiving ezetimibe + atorvastatin). The co-administration of ezetimibe + statin (40 mg or 80 mg) resulted in a significantly greater reduction of LDL-C compared to 80 mg of statin alone (-20.7% versus -6.7%). Ezetimibe + statin 80 mg also produced a significant difference in LDL-C reduction compared to statin 80 mg of -20.5%.

Study P1417 was a 24 month, open-label, multicentre extension study of P1030 with continued use of the same statin as in P1030. Treatment was with ezetimibe 10 mg combined with atorvastatin 40 mg or simvastatin 40 mg with possible up-titration of the statin dose to 80 mg after 4 weeks if the LDL-C was not at target levels. Of the 50 subjects randomised in P1030, 48 completed the study and 44 of these enrolled in the extension study with 36 treated with atorvastatin. The mean LDL-C reduction from baseline to study endpoint was -15.3% by calculated measurement with similar levels of reduction in both triglycerides and total cholesterol and an 8.6% increase in HDL-C.

Mixed hyperlipidaemia

The previously evaluated submission contained a post-hoc sub-group analysis from the factorial Study P0692. In this study there were 139 patients who received atorvastatin and

had baseline triglyceride levels ≥ 200 mg/dL. In this group, 66 received atorvastatin (doses pooled) and 73 received atorvastatin plus ezetimibe. The mean % reduction from baseline in LDL-C was -56.5% in the ezetimibe + all atorvastatin group compared to -45.5% in the all atorvastatin group. This result was similar to that achieved in the group of subjects with baseline triglyceride levels < 200 mg/dL.

From the previously evaluated submission, the sponsor provided sub-group analyses for subjects with baseline triglyceride levels ≥ 150 mg/dL or < 150 mg/dL in each of the 3 studies P079, P090 and P112. These three studies provided data on an additional 280 subjects with elevated triglyceride levels with results indicating a consistent effect on lowering LDL-C in this sub-group. The magnitude of the LDL-C reduction was in line with that seen in patients with baseline triglyceride levels < 150 mg/dL.

Safety

In the original Ezetrol submission there were pooled safety data from 1675 subjects who received ezetimibe 10 mg co-administered with a statin for a period of 8 to 12 weeks. The rate of SAEs was slightly higher with co-administration than with any statin alone (3.4% versus 2.2%) and there was a marginal increase in AEs leading to treatment discontinuation (5.0% versus 4.1%) and treatment-related AEs (21.2% versus 18.1%). The most frequent treatment-related AEs with co-administration of ezetimibe with a statin were myalgia, headache, fatigue, nausea, abdominal pain, diarrhoea and increased liver enzymes. Compared to statin monotherapy, the most notable risk was increased hepatic transaminases (increased ALT: 1.7% versus 0.6% and increased AST: 1.4% versus 0.4%). There was no evidence found for an increase in risk of clinical or biochemical muscle toxicity compared to statins alone. The sponsor reported that in the Ezetrol submission there were 295 subjects who received ezetimibe with a statin for at least 12 months. The clinical evaluator found that the long term safety data was in line with that reported in the short term trials and the rate of increased hepatic transaminases was 0.4% which was no higher than in the short term studies.

The final core safety data pool for this submission (n = 4569) consisted of subjects from 7 controlled short-term studies of 6-14 weeks' duration, namely P040, P079, P090, P112, P692, P693 and P2173. These subjects included:

- 2041 patients on atorvastatin monotherapy
- 2403 patients on ezetimibe 10 mg + atorvastatin (all doses)
- 60 patients on placebo, and
- 65 patients on ezetimibe monotherapy

There was long-term data out to 12 months from 2 studies, namely P2154 and P1418, involving 678 patients given atorvastatin or ezetimibe + atorvastatin (604 on the latter).

There was data on the special population with HoFH from 2 studies, namely P1030 and P1417, involving 59 patients on ezetimibe 10 mg + atorvastatin (including data on 33 patients out to 24 months).

In the short term studies, the exposure adjusted adverse event rate was no higher in patients treated with the combination than in those receiving monotherapy or placebo. Overall the safety profile of the combination of ezetimibe with atorvastatin was in line with that seen with the individual components. The most frequent AEs in the ezetimibe + atorvastatin and atorvastatin group were nasopharyngitis (2.1% versus 1.9%), myalgia (2.5% versus 2.6%) and headache (2.5% versus 2.4%). In the controlled long term study, the most frequent AEs were myalgia (8.0% versus 8.9%), back pain (6.5% versus 2.2%), muscle spasms (6.0% versus 0%), arthralgia (6.0% versus 8.9%), extremity pain (6.0% versus 6.7%) and headache (6.0% versus 4.4%).

Gallbladder related events were infrequent (0.1% versus 0.0%) and allergic reactions/rash occurred at similar rates to atorvastatin monotherapy (1.4% versus 1.5% short term and 5.0% versus 4.4% long term). Gastrointestinal disorders occurred at a similar rate to the atorvastatin monotherapy group in the short term studies with the most frequent being diarrhoea (1.8% in both groups) and nausea (1.1% versus 1.9%). With long term treatment the rate increased (17.9%) but was less than with atorvastatin monotherapy (31.1%).

Effects on kidney function and haematology parameters were infrequent and similar between the combination and atorvastatin monotherapy. The combination therapy did not appear to have any clinically significant effect on vital signs or ECG results.

Hepatitis related events were infrequent (one case short term and one long term) in the ezetimibe + atorvastatin treated patients. In the short term studies, the rate of consecutive ALT/AST ≥ 3 times ULN was similar to atorvastatin (0.6% versus 0.5%). With longer term treatment there was an indication of a slightly higher rate of low level (2 to <3 times ULN) ALT/AST rise (6.5% versus 2.2%). It is noted that the safety evaluation of Ezetrol noted that there was a higher incidence of clinically important (≥ 3 times ULN) hepatic transaminase elevation with ezetimibe co-administration with a statin compared to statin monotherapy (increased ALT: 1.7% versus 0.6% and increased AST: 1.4% versus 0.4%).

In the short term studies, the rate of AEs of elevated CK (0.8% versus 0.6%), the rate of CK ≥ 10 times ULN (0% versus 0.1%) and the rates of lower levels of elevated CK were similar between the combination and atorvastatin monotherapy. In the three long term studies, there were two cases CK ≥ 10 times ULN which were not attributed to study treatment.

There were 4 deaths in the short term studies; 2 in the ezetimibe + atorvastatin group and one further death in a long term study. None was considered treatment related. The exposure adjusted SAE rate (per 100 patient years) in the short term studies (12.3) was mildly higher than atorvastatin (9.6). The most frequent SAEs were myocardial infarction and chest pain.

Study discontinuation due to AEs was low (2.6% versus 2.7%) in the short term studies and increased in the controlled long term study (9.0% versus 6.7%). The main reasons were Musculoskeletal and Gastrointestinal disorders. The discontinuation rate in the short term studies was lower than that reported in with ezetimibe and any statin in the Ezetrol submission (5.0%).

Safety was assessed in the elderly (≥ 65 years and ≥ 75 years) and by gender with no increased risk seen in older patients or for either gender. Numbers of non-Caucasians were too low to draw conclusions.

Withdrawal of ezetimibe treatment from co-administration with atorvastatin was assessed with no notable adverse effects.

Although the numbers were small, the AE profile appeared similar in the HoFH population.

Postmarketing data of 2342 reports with the combination of ezetimibe and atorvastatin found the most frequent ADRs were myalgia, raised CK, diarrhoea, nausea, increased ALT. There were 3 fatal myopathy-related and 10 fatal hepatobiliary related ADRs though details were lacking.

Overall, the safety data from the previously evaluated submission, which related to ezetimibe with atorvastatin, were consistent with those reported in the Ezetrol submission which related to ezetimibe with any statin.

Risk management plan

A Risk Management Plan (RMP) waiver was granted by the Office of Product Review of the TGA at the time of pre-submission assessment.

Risk-benefit analysis

Delegate considerations

Risk/benefit discussion

Efficacy

Efficacy, measured as positive effects on a number of lipid-related parameters, was demonstrated for the combination of ezetimibe + atorvastatin. For each of these parameters, the size of the effect was consistently greater for the combination than for either monotherapy component. From the previously evaluated submission there was good evidence of maintenance of efficacy for up to 12 months. Efficacy was demonstrated in patients with primary hypercholesterolaemia and in those with HoFH although, given the nature of the latter, the numbers of subjects with HoFH who were studied, were quite small.

Safety and RMP

From the safety data there was no new safety signals observable with the combination compared to atorvastatin monotherapy. The Delegate agreed with the clinical evaluator that treatment with the combination was generally well tolerated and that the rate of discontinuations related to adverse events was low.

Indications

The Delegate agreed with the clinical evaluator that the proposed part of the indication relating to primary hypercholesterolaemia, viz. *'Ezetrol Plus Atorva is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia'*, is too broad and includes possible use as first-line therapy. The Delegate further agreed with the clinical evaluator that the combination therapy should be used either in patients already treated with separate ezetimibe and atorvastatin, that is, as substitution therapy or in patients not adequately controlled on either ezetimibe or atorvastatin alone and for whom addition of the alternative, that is, atorvastatin or ezetimibe, respectively, is being considered. Such a change would bring the indications into line with those of Vytorin (ezetimibe + simvastatin). The Delegate endorses the clinical evaluator's proposed wording which is as follows:

'Ezetrol Plus Atorva 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:

Patients not appropriately controlled with atorvastatin or ezetimibe alone; or

Patients already treated with atorvastatin and ezetimibe.'

Does the ACPM agree with the above amendment of the part of the indication relating to primary hypercholesterolaemia?

The Delegate agreed with the clinical evaluator that there are sufficient data to support the indication in homozygous familial hypercholesterolaemia (HoFH), as follows;

'Ezetrol Plus Atorva is indicated in patients with HoFH. Patients may also receive adjunctive treatments (e.g. LDL apheresis).'

Thus the wording of the entire indications recommended by the Delegate is as follows:

'Ezetrol Plus Atorva 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:

Patients not appropriately controlled with atorvastatin or ezetimibe alone; or

Patients already treated with atorvastatin and ezetimibe.

Ezetrol Plus Atorva is indicated in patients with HoFH. Patients may also receive adjunctive treatments (e.g. LDL apheresis).'

Trade names

The Delegate agreed with the clinical evaluator that the proposed tradenames Ezetrol Plus Atorva and Zetia Plus Atorva may, by the use of the word 'Plus', imply superiority of the product over other lipid lowering products. As noted by the clinical evaluator, while there are clinical data indicating improved LDL-C reduction etc with the addition of ezetimibe to atorvastatin compared to either monotherapy, there are limited comparative data with other proprietary products. It would appear that the sponsor has proposed the alternative trade names 'Atozet Composite Pack' and 'Zeteze'. For consistency, the Delegate would recommend that the latter be re-named 'Zeteze Composite Pack'. In line with the convention of including dosage strengths in the tradenames of all fixed-dose combination products, the Delegate would recommend strongly that the proposed tradenames include relevant information on dosage strengths. For example, this would mean re-naming *Atozet Composite Pack* as *Atozet Composite Pack 10 mg + 10 mg*, *Atozet Composite Pack 10 mg + 20 mg* etc. The ACPM was asked to comment on this recommendation of the Delegate.

The Delegate proposed to approve this submission by Merck Sharp & Dohme (Australia) Pty Limited to register Ezetrol Plus Atorva/Zetia Plus Atorva (to be re-named as previously indicated), composite packs of ezetimibe 10 mg and of atorvastatin 10 mg or atorvastatin 20 mg or atorvastatin 40 mg or atorvastatin 80 mg, based on the quality, safety and efficacy of the product having been satisfactorily established for the indication below, for the reasons stated above in the Risk/Benefit Discussion and subject to provision of a PI and Consumer Medicine Information (CMI) documents acceptable to the TGA.

'Ezetrol Plus Atorva 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:

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

Ezetrol Plus Atorva is indicated in patients with HoFH. Patients may also receive adjunctive treatments (e.g. LDL apheresis).'

The sponsor should address the following issues in the Pre-ACPM response:

The sponsor was requested to provide as one of the appendices to the pre-ACPM response a table which displays the studies which were included in the original registration/marketing application for Ezetrol and a second table which displays the extra studies included in the updated response to the TGA, that is, in the previously evaluated submission. For each study there should be sufficient information about design, numbers enrolled and randomised, treatment arms, primary and major secondary endpoints with results and also information about most common or important adverse events. The appendix could immediately follow the sponsor's pre-ACPM response.

Submitted for ACPM advice with the following questions for the Committee

1. Does the ACPM agree that the indication as proposed by the sponsor is too broad and that it should be amended to one which is consistent with that of a similar fixed-dose combination product, namely Vytorin (ezetimibe + simvastatin)? The indication recommended by both the clinical evaluator and the Delegate can be found above in this AusPAR.
2. Since the product contains two active ingredients, does the ACPM agree that the trade name should also contain indications of the individual dosage strengths, as is the case with all fixed-dose combination products? Thus for example should the proposed trade name Atozet Composite Pack be amended to Atozet Composite Pack 10 mg + 10 mg, Atozet Composite Pack 10 mg + 20 mg, etc.

Response from sponsor

Merck Sharp & Dohme (MSD) concurred with the clinical evaluator's assessment that "*the benefit-risk balance of ezetimibe and atorvastatin in a composite pack for the treatment of primary hypercholesterolaemia is favourable*" and with the Delegate's proposed action to approve the registration of the Atozet/Zeteze composite pack containing ezetimibe 10 mg tablets and atorvastatin 10, 20, 40 or 80 mg tablets; indicated for the treatment of patients with primary and Homozygous Familial hypercholesterolaemia.

Proposed indication

MSD does not concur with the Delegate's conclusion that the proposed indication is too broad and that the combination should only be used in patients already being treated with separate ezetimibe and atorvastatin or in patients not adequately controlled on either monotherapy.

Evidence has been presented in the form of the placebo-controlled, ezetimibe and atorvastatin factorial study (P0692) that demonstrates the efficacy and safety of ezetimibe initiated concurrently with atorvastatin. Co-administered ezetimibe and atorvastatin was significantly more effective at reducing Low Density Lipoprotein Cholesterol (LDL-C) than at least the next highest dose of atorvastatin monotherapy over the 12 week treatment period. In addition, the co-administered dose of ezetimibe and the lowest dose of atorvastatin (10/10 mg) was shown to be as effective, and the next two higher co-administered doses (10/20 and 10/40 mg) more effective, at LDL-C reduction as the highest dose of atorvastatin monotherapy (80 mg). Thus superior LDL-C reduction can be achieved using a lower dose of atorvastatin when it is initiated concurrently with ezetimibe. The benefits of co-administration of ezetimibe and atorvastatin are discussed in further detail below but these details support the positive benefit/risk profile for initiating with this Dual Therapy.

MSD believes that initial therapy with a combination has a clinical place in the treatment of hyperlipidaemia and that physicians should have the option of initiating ezetimibe and atorvastatin concurrently in patients where they believe it may be warranted. This may include patients with multiple risk factors for coronary heart disease (CHD). In patients with multiple risk factors, classified as high risk patients (> 15% absolute risk of CVD events over 5 years), a rapid and significant reduction in lipid levels will be of benefit in reducing their overall risk of developing cardiovascular events. The use of an effective combination, which increases overall efficacy with no increase in safety concerns, is therefore warranted in these high risk patients. In addition, the use of a lower dose of statin to achieve a significant reduction in LDL-C would be an advantage in patients who are likely to be intolerant of higher statin doses, as this would enable these patients to reach treatment targets without the need to titrate to the maximum approved dose of atorvastatin.

MSD requests ACPM's consideration of these factors in reaching a conclusion on the approved indication for Atozet/Zeteze Composite Pack. MSD however, appreciates that similar therapy such as VYTORIN is not approved for use as first-line therapy and if ACPM concurs with the Delegate's recommendation MSD is prepared to accept that the approved indication should be consistent with that of Vytorin.

Clinical benefits of the Atozet/Zeteze composite pack

a) More Patients Reach Target with Co-administration of ezetimibe and atorvastatin.

Epidemiological studies have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C. In observational studies, there is a roughly log-linear relationship between CHD mortality and blood cholesterol. The data indicate that proportionally lower cholesterol is associated with lower CHD mortality across the total plasma cholesterol range above 155 mg/dL (corresponding to LDL-C about 85 mg/dL, or 2.2 mmol/L). This indicates that for patients with LDL-C of greater than 2.2 mmol/L, a reduction in LDL-C will reduce their risk of CHD mortality. The National Cardiovascular Disease Prevention Alliance Guidelines for the Management of Absolute Cardiovascular Risk¹² recommend an LDL-C target of <2 mmol/L for patients at all CVD risk levels.

Thus, one of the goals in the management of cardiovascular risk and prevention of coronary heart disease is the reduction of LDL Cholesterol. Meta-analyses of lipid-lowering trials have shown that the reduction in CHD risk is proportional to the absolute change in LDL-C, that is, greater reductions of LDL-C lead to greater cardiovascular risk reductions. Despite the LDL-C lowering efficacy of statins, a significant proportion of the statin-treated hypercholesterolaemic population fails to reach recommended therapeutic goals for LDL-C concentrations. This is attributed to both the extent of cholesterol lowering required in some individuals as well as the use of inadequate doses of statins due to a variety of reasons. Studies in patients at high risk of cardiovascular disease, including some with entry baseline LDL-C less than 100 mg/dL (2.59 mmol/L), have demonstrated that targeting even lower LDL-C such as <70 mg/dL (1.8 mmol/L) has incremental clinical benefit.

The combination of ezetimibe and a statin reduces lipid levels by two complementary mechanisms of action. Ezetimibe inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. The resultant reduction in cholesterol stores leads to an increase in clearance of cholesterol from the blood. Statins, such as atorvastatin, inhibit HMG-CoA reductase and hence cholesterol synthesis in the liver and increase the number of hepatic LDL receptors to enhance uptake and catabolism of LDL. The reduction in total-C, LDL-C, Apo B, TG and non-HDL-C observed with combination therapy has been demonstrated to be greater than that observed with either treatment alone.

In the factorial study (P0692), a significantly greater reduction in LDL-C was observed between ezetimibe administered with each dose of atorvastatin (10, 20 and 40 mg) and the next higher dose of atorvastatin monotherapy. In addition, the lowest co-administration dosage of ezetimibe/atorvastatin 10/10 mg provided a mean reduction in LDL-C of approx. 53%, a result similar to the LDL-C reduction for a maximal 80 mg dose of atorvastatin alone (approx. 54%). Thus, the additional reduction of LDL-C provided by the addition of ezetimibe 10 mg to atorvastatin 10 mg represents approximately the equivalent of 3 doublings (or titration steps) of the dose of atorvastatin to the highest approved dose of 80 mg.

¹² National Vascular Disease Prevention Alliance. Guidelines for the management of absolute cardiovascular disease risk. 2012

These results are also reflected in the add-on titration studies submitted in support of this application. The addition of ezetimibe to an established dose of atorvastatin in patients who had not achieved their pre-defined LDL-C goal was compared to doubling (up-titrating) the atorvastatin dose. Ezetimibe co-administered with atorvastatin was shown to be superior to at least the next highest atorvastatin monotherapy dose. These results are summarised in Table 5.

Table 5. Mean % change in LDL-C from baseline in add-on titration studies.

Study (N) Duration Treatments	% change in LDL-C – ezetimibe + atorvastatin		% change in LDL-C – atorvastatin monotherapy		Difference (p)
P079 (196) 6 weeks EZE + atorva 20 mg vs. atorva 40 mg	-30.8		-10.9		-19.9 (<0.001)
P090 (579) 6 weeks EZE + atorva 40 mg vs. atorva 80 mg	-27.4		-11.0		-16.3 (<0.001)
P112 (1053) 12 weeks EZE + atorva 10 mg vs. atorva 20 mg (could be further up-titrated to 40 mg if goal not reached)	6 weeks EZE + Atorva 10 mg	-26.7	6 weeks Atorva 20 mg	-12.8	-13.8 (<0.001)
	12 weeks EZE + Atorva 10 mg	-22.5	12 weeks Atorva 20/40 mg	-17.9	-4.6 (0.001)
P0693 14 weeks EZE + Atorva 10 mg vs. atorvastatin 20 mg (atorva dose could be up-titrated after 4 weeks in both arms)	4 weeks EZE + atorva 10 mg	-23.84	4 weeks Atorva 20 mg	-8.99	-14.85 (95% CI -16.87, -12.83)

In addition, the co-administration of ezetimibe with a statin, including atorvastatin, resulted in more patients attaining specified LDL-C targets during clinical studies. Table 6, below, summarizes the proportion of subjects attaining LDL-C target where this was a study outcome. Notably, a larger proportion of co-administration subjects in studies P090 and P112 (74%, 44%) attained the target LDL-C of < 70 mg/dL (that is, 1.8 mmol/L) compared with those taking atorvastatin monotherapy at a higher titrated dose (32% for both studies).

Table 6. Proportion of subjects attaining LDL-C targets in Ezetrol and clinical studies from previously-evaluated submission.

Study	N	LDL-C Goal (Treatment duration)	% Atorva subjects achieving LDL-C target	% EZE/Atorva subjects achieving LDL-C target
P2173* EZE/statin vs. placebo/statin	769	<100 mg/dL (<2.59 mmol/L) (8 weeks)	19	72
P0693 EZE/atorva 10 mg vs. atorva 20 mg	621	<100 mg/dL (<2.59 mmol/L) (14 weeks)	7	22
P040 EZE/atorva (5-80 mg; mean 30 mg)	1155	NCEP ATP III Target [#]	28	75
P090 EZE/atorva 40 mg vs. atorva 80 mg	579	<70 mg/dL (< 1.8 mmol/L) (6 weeks)	32	74
P112 EZE/atorva 10 mg vs. atorva 20/40 mg	1053	< 70 mg/dL (< 1.8 mmol/L) (12 weeks)	32	44
P079 EZE/atorva 40 mg vs. atorva 40 mg	196	<100 mg/dL (<2.59 mmol/L) (6 weeks)	49	84

* (% not at target at baseline)

[#]With CHD or equiv. <100 mg/dL (<2.59 mmol/L); Without CHD or equiv. and with 2+ CHD risk factors <130 mg/dL (3.4 mmol/L); Without CHD or equiv. and < 2 CHD risk factors <160 mg/dL (4.1 mmol/L)

Thus, the addition of ezetimibe to atorvastatin is more effective than titrating to the next higher statin dose at reducing LDL-C to the target recommended for the effective prevention of cardiovascular disease regardless of the patient's other risk factors and the overall CVD risk.

Combining the two mechanisms of action of ezetimibe and atorvastatin results in a therapy that provides:

1. more effective reduction of LDL-C than statin monotherapy,
2. greater reductions in LDL-C compared to at least the next highest dose of atorvastatin and
3. improvement in other key lipid parameters that are significantly better than with atorvastatin alone.

In addition, the combination enables more patients to reach treatment goals than atorvastatin alone. The combination increases physicians' ability to achieve target LDL-C levels and therefore more effectively manage CHD risk, and there are clear indications that this can often be achieved using a lower dose of atorvastatin in combination than to achieve the same goals with statin monotherapy. The safety profile of the combination observed in clinical trials was very similar to that of the corresponding dose of atorvastatin alone at all dosages. Therefore, the addition of ezetimibe to atorvastatin improves achievement of treatment goals and does not result in any increase in the safety concerns associated with statin use.

b) The composite pack and medication adherence

Further to efficacy and safety there are other factors that may impact the effectiveness of lipid reduction therapy with ezetimibe and atorvastatin. The full benefit of the combination will only be achieved if patients take both tablets every day and any initiatives that may assist patients in taking the medicines correctly and persisting with lipid lowering therapy are advantageous. The Atozet/Zeteze Composite Pack may help in addressing some of the barriers to adherence that prevents patients from obtaining the full benefit of their therapy.

Reminder packaging

An important factor in adhering to a treatment regimen is remembering to take the medication, and a large proportion of non-adherence is related to omissions of doses or delays in the timing of doses. It has been observed that simple dosing (one pill, once daily) helps to maximize adherence and that written instructions are better than oral advice for reminding patients to take medication.^{13, 14} The design of the calendar pack may assist with addressing these issues. The calendar pack (a wallet containing 10 ezetimibe tablets and 10 atorvastatin tablets) includes clear instructions that the two medicines must be taken together and at the same time. The individual tablets are labelled by day to be taken (Day 1, Day 2 and so on) providing a clear indication that each medicine must be taken each day. The fact that both medicines are supplied in a single wallet acts as a memory aid to patients to take both tablets, as it will be apparent if the dose of one medication has not been taken for a specific day. This design improves the convenience and reduces the complication of the regimen.

Patient education and encouragement

Adherence to treatment may be impacted by a lack of engagement between doctors and patients leading to a lack of understanding by the patient of the benefits of their medicine

¹³ Osterberg L & Blaschke T 2005. Adherence to medication. *New England Journal of Medicine* 353: 487-497.

¹⁴ Jin J, Sklar G, Min Sen Oh V, Chuen Li S. Factors affecting therapeutic compliance: A review from the patient's perspective. *Ther Clin Risk Manag.* 2008 February; 4(1): 269-286

and the goals of treatment.^{13,15} Patients are more likely to adhere to treatment if they understand that the condition being treated could pose serious consequences to their health, and that the proposed therapy will be effective, in addition to understanding how to take their medication most effectively to achieve treatment goals.^{14,15} The effect of lowering lipid levels is unlikely to be apparent to the patient making it very difficult for them to appreciate the necessity to take their medication. Good communication between physicians and patients has been suggested as one measure that improves the likelihood of adherence.^{13,14}

MSD plans to distribute starter packs to prescribers which will consist of one 10-day calendar pack, identical to the calendar packs supplied in the trade pack. Whilst still in the doctor's surgery, the patient has an opportunity to see the dose pack which they will later be supplied on prescription, and can gain an understanding of how to take the medicines and discuss any concerns or issues with the prescriber at that time. In addition, the prescriber then has the opportunity to engage the patient in a conversation about the importance of taking both medicines to achieve the desired therapeutic outcome, further reinforcing the message about why they are taking the medicines and potentially improving their ability to manage their disease through better understanding.

Cost

In an international survey examining issues of safety, health care and access to care, Australian participants indicated that one in five skipped doses or did not fill prescriptions owing to cost.⁵ A number of studies found that patients who had low income were more likely to be non-compliant to treatment. *'If the patient feels that the cost of therapy is a financial burden, the compliance with therapy will definitely be threatened'*.¹⁴ For some patients, even the concessional co-payment may represent an unwelcome burden on the household budget. This is unacceptable from an equity perspective, particularly since those cardiovascular risk factors. By requiring a single co-payment for two medications, this may reduce the chance that patients will under medicate by missing doses or not getting prescriptions refilled owing to cost considerations.

c) Current prescribing practice

The use of the combination of ezetimibe with a statin is consistent with the approved indication for Ezetrol (ezetimibe 10 mg tablets) and is well accepted in Australian clinical practice. Pharmaceutical Benefits Scheme (PBS) data indicates that in 2009 almost 50, 000 patients were being co-prescribed ezetimibe and a statin, and approximately 25, 000 of these were prescribed atorvastatin. As evidenced by this data there is an established clinical need for the combination.

Trade name

In response to the clinical evaluator's comments on the proposed trade names, the Delegate has been consulted and an agreement was reached on the following:

Atozet Composite Pack 10 mg + 10 mg

Atozet Composite Pack 10 mg + 20 mg

Atozet Composite Pack 10 mg + 40 mg

Atozet Composite Pack 10 mg + 80 mg

Zeteze Composite Pack 10 mg + 10 mg

Zeteze Composite Pack 10 mg + 20 mg

Zeteze Composite Pack 10 mg + 40 mg

¹⁵ Australian Institute of Health and Welfare: Senes S and Penm E. Medicines for cardiovascular health: are they used appropriately? Cardiovascular diseases series no. 27. Cat. No. 36. Canberra: AIHW

Zeteze Composite Pack 10 mg + 80 mg

Updated labelling has been provided to the Pharmaceutical Chemistry section at the TGA and the Product Information and Consumer Medicine Information have been updated to reflect the amended trade names.

Table of clinical studies

As requested by the Delegate, a table which displays the studies which were included in the original registration/marketing application for Ezetrol and a second table which displays extra studies included in the updated response to the TGA, that is, the previously evaluated submission were provided as an appendix to this sponsor response.

Product Information

MSD acknowledges the changes to the PI recommended by the clinical evaluator and the Delegate. These recommendations have been addressed in the PI.

Conclusion

The provision of two commonly co-prescribed medicines in a composite pack has many of the advantages of a fixed dose combination (one tablet/one dose). Addition of ezetimibe has been demonstrated to improve lipid lowering compared to titrating the dose of statin. There is currently one fixed combination of ezetimibe and a statin available in Australia; however PBS figures show prescribers have preferences for various statins. The availability of Atozet/Zeteze Composite Pack as an alternative therapeutic choice will enable prescribers the flexibility to choose an alternate statin for co-administration with ezetimibe, with the convenience of both medications being supplied in the same pack with one patient co-payment.

Advisory committee considerations

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

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered these products to have an overall positive benefit–risk profile for the indication;

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

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

Atozet Composite Pack and Zeteze Composite Pack are indicated in patients with homozygous familial hypercholesterolaemia (HoFH). Patients may also receive adjunctive treatments (e.g. LDL apheresis).

In making this recommendation, the ACPM agreed with the Delegate that the wording of the approved indication for these composite products must ensure approved use as second line treatment only. The ACPM agreed with the Delegate that the efficacy of combined products was clinically significant and greater than the individual products alone.

The slight increase in adverse events reporting was noted, although the ACPM further advised that there are additional safety concerns attributed to fixed dose combination and composite pack products and therefore each combination must independently satisfy the requirements for clinical evidence. The ACPM advised that for this indication it is not acceptable to defer only to evidence used in support of the separately registered products.

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- Assurance that the PI and CMI for the composite products fully align with those of the individual products.

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.

The ACPM noted the change in trade names from Ezetrol plus Atorva and Zetia plus Atorva to the current trade names that reflect the composite nature of the products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Atozet Composite Pack 10 mg + 10 mg ezetimibe 10 mg tablets and atorvastatin (as calcium) 10 mg tablets composite pack; Atozet Composite Pack 10 mg + 20 mg ezetimibe 10 mg tablets and atorvastatin (as calcium) 20 mg tablets composite pack; Atozet Composite Pack 10 mg + 40 mg ezetimibe 10 mg tablets and atorvastatin (as calcium) 40 mg tablets composite pack; Atozet Composite Pack 10 mg + 80 mg ezetimibe 10 mg tablets and atorvastatin (as calcium) 80 mg tablets composite pack; Zeteze Composite Pack 10 mg + 10 mg ezetimibe 10 mg tablets and atorvastatin (as calcium) 10 mg tablets composite pack; Zeteze Composite Pack 10 mg + 20 mg ezetimibe 10 mg tablets and atorvastatin (as calcium) 20 mg tablets composite pack; Zeteze Composite Pack 10 mg + 40 mg ezetimibe 10 mg tablets and atorvastatin (as calcium) 40 mg tablets composite pack; Zeteze Composite Pack 10 mg + 80 mg ezetimibe 10 mg tablets and atorvastatin (as calcium) 80 mg tablets composite pack for oral administration, indicated for:

Primary Hypercholesterolaemia

Atozet/Zeteze 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 atorvastatin or ezetimibe alone; or*
- *already treated with atorvastatin and ezetimibe*

Homozygous Familial Hypercholesterolaemia (HoFH)

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

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the current 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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Reference/Publication #