Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Ezetimibe and Atorvastatin

Proprietary Product Names: Atozet, Zeteze

Sponsor: Merck Sharp & Dohme Australia Pty Ltd

August 2015

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About AusPARs

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

Contents

List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
ACPM	Advisory committee for prescription medicines
ADRs	Adverse drug reactions
AE	Adverse event/experience (used interchangeably)
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANCOVA	Analysis of covariance
APaT	All Patients as Treated
Apo	Apolipoprotein
API	active pharmaceutical ingredient
AST	Aspartate aminotransferase
Atorva	Atorvastatin
AUC	area under the plasma concentration time curve
BE	bioequivalence
CER	Clinical Evaluation Report
CHD	Coronary heart disease
CI	Confidence interval
CIOMS	The Council for International Organizations of Medical Sciences
CK	Creatine kinase or creatine phosphokinase
Cmax	Maximum concentration
CSR	Clinical study report
CTD	Common technical document
dL	deci litre
EMA	European Medicines Agency
EZ	Ezetimibe

Abbreviation	Meaning
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed dose combination
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GM	Geometric mean
GMR	Geometric mean ratio
HDL-C	High-density lipoprotein cholesterol
HeFH	heterozygous familial hypercholesterolaemia
HMG-CoA	Hydroxymethylglutaryl coenzyme A (3 hydroxy–3-methyl methylglutaryl coenzyme A)
HoFH	homozygous familial hypercholesterolaemia
hs-CRP	High-sensitivity C-reactive protein
ICH	International Conference on Harmonisation
LFT	Liver function test
LDL-C	Low-density lipoprotein cholesterol
LS	Least squares
MSD	Merck Sharp & Dohme
NCEP	National Cholesterol Education Program Adult Treatment Program III
PDCO	EMEA Paediatric Committee
Ph.Eur	European Pharmacopeia
PP	Per-Protocol
PVC	polyvinyl chloride
RMP	Risk management plan
Rosuva	Rosuvastatin
SAE	Serious adverse event

Abbreviation	Meaning
SD	Standard deviation
SDH	succinate dehydrogenase
SE	Standard error
SmPC	Summary of product characteristics
SOC	System Organ Class
TG	triglyceride
TGA	Therapeutic Goods Administration
T_{max}	The time after administration of a drug when the maximum plasma concentration is reached
Total-C	Total cholesterol
UK	United Kingdom
ULN	Upper limit of normal
USP-NF	United States Pharmacopeia and The National Formulary

I. Introduction to product submission

Submission details

Type of submission:	New combination of previously approved active ingredients
Decision:	Approved
Date of decision:	21 January 2015
Active ingredients:	Ezetimibe and Atorvastatin (as calcium)
Product names:	Atozet, Zeteze
Sponsor's name and address:	Merck Sharp & Dohme Australia Pty Ltd
Dose form:	Fixed dose combination tablet, multilayer
Strengths:	ezetimibe/atorvastatin 10 mg/10 mg, ezetimibe/atorvastatin 10 mg/20 mg, ezetimibe/atorvastatin 10 mg/40 mg, and ezetimibe/atorvastatin 10 mg/80 mg
Container:	Blister pack
Pack sizes:	10 or 30 tablets
Approved therapeutic use:	***Primary Hypercholesterolaemia*** *Atozet/Zeteze is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia where use of a combination product is appropriate in those patients:* · *not appropriately controlled with atorvastatin or ezetimibe alone; or* · *already treated with atorvastatin and ezetimibe.* ***Homozygous Familial Hypercholesterolaemia (HoFH)*** *Atozet/Zeteze is indicated in patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis).*
Route of administration:	Oral
Dosage:	The dose range is ezetimibe/atorvastatin (as calcium) from 10/10 mg to 10/80 mg once daily. The dosage is complex and should be individualised according to the target lipid levels [see approved Product Information for full *Dosage and Administration* (PI, attachment 1)].
ARTG number (s):	216956, 216957, 216958, 216959, 216960, 216961, 216962 and 216963

Introduction

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

> ***Primary Hypercholesterolaemia***
>
> *Atozet/Zeteze is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia where use of a combination product is appropriate in those patients:*
>
> - *not appropriately controlled with atorvastatin, rosuvastatin or ezetimibe alone; or*
> - *already treated with atorvastatin or rosuvastatin and ezetimibe.*
>
> ***Homozygous Familial Hypercholesterolaemia (HoFH)***
>
> *Atozet/Zeteze is indicated in patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis)*.

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. 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 hypercholersterolaemia on 18 June 2003.

Atorvastatin (as calcium) is a synthetic lipid lowering agent. It is an inhibitor of Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, the rate limiting enzyme that converts 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. The innovator product is Lipitor, and there are numerous generic versions, including atorvastatin. The dosage strengths available are 10, 20, 40 and 80 mg. The current approved indications of atorvastatin are as an adjunct to diet for the treatment of patients with hypercholesterolaemia.

Atozet,[1] ezetimibe and atorvastatin composite packs of two tablets[2] have been registered in Australia since February 2013.

The proposed FDC tablet in this submission is a new formulation of ezetimibe/atorvastatin FDC. The proposed formulation uses atorvastatin calcium trihydrate to address concerns about the known instability of atorvastatin calcium used in a previous FDC formulation.

In this submission the sponsor has applied to register these drugs in the same strengths as available in the composite packs with the same trade names for use in the treatment of hypercholesterolaemia.

Vytorin (ezetimibe/simvastatin) FDC has also been approved for this indication in Australia but instead of listing patients not appropriately controlled with simvastatin, it includes 'a statin' and also includes treatment of mixed hyperlipidaemia. The currently approved indications are as follows:

[1] The submission includes an application for two trade names Atozet and Zeteze. Throughout this document the product trade name Atozet will be used as the default trade name in place of both trade names. Both trade names are also used for the composite packs currently registered.
[2] Containing 10 mg ezetimibe tablet and 10 mg atorvastatin tablet; 10 mg ezetimibe tablet and 20 mg atorvastatin tablet; 10 mg ezetimibe tablet and40 mg atorvastatin tablet; 10 mg ezetimibe tablet and 80 mg atorvastatin tablet

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 (for example, LDL apheresis).*

Rosuzet (and Ezalo) (ezetimibe/rosuvastatin) composite pack and FDC have also been approved for this indication in Australia based on the Vytorin indication. The approved indications are as follows:

> ***Primary Hypercholesterolaemia***
>
> *Ezalo/ Rosuzet (composite pack) is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia where use of a combination product is appropriate in those patients:*
>
> · *not appropriately controlled with rosuvastatin or ezetimibe alone; or*
>
> · *already treated with rosuvastatin and ezetimibe.*
>
> ***Homozygous Familial Hypercholesterolaemia (HoFH)***
>
> *Ezalo/ Rosuzet (composite pack) is indicated for patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis).*

Guidance

The specific and general EU guidelines adopted by the TGA relevant to this submission include:

· CPMP/EWP/3020/03 Note for guidance on clinical investigation of medicinal products in the treatment of lipid disorders. Effective: 20 May 2005.

· EMEA/CHMP/EWP/350495/2009 Concept Paper on the Need to Update the Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Lipid Disorders (CPMP/EWP/3020/03) and the Note for Guidance on the Clinical Investigation on Medicinal Products in the Treatment of Hypertension (CPMP/EWP/238/95 REV. 2) to Discuss the Need for Outcome Studies Basis on Safety Data at the Time of MAA. Published TGA Internet site for information only, effective: 26 March 2010.

· EMEA/CHMP/EWP/311890/2007 Guideline on the Evaluation of Medicinal Products for Cardiovascular Disease Prevention. Effective: 29 June 2009.

· CPMP/EWP/240/95 Rev.1 Guideline on Clinical Development of Fixed Combination Medicinal Products Replaces: pp. 175 - 180 of Rules 1998 (3C) - 3CC10a. Effective: 28 May 2010.

· CPMP/QWP/EWP/1401/98 Rev 1 Guideline on the Investigation of Bioequivalence Replaces: pp. 231 - 244 of Rules 1998 (3C) (Adopted by TGA 12 February 2002) Replaces: CPMP/QWP/EWP/1401/98 (Adopted by TGA 10 April 2002) Effective: 16 June 2011. Adopted by TGA with the following notation:

'While this guidance suggests that the design and conduct of the study should follow EU regulations on Good Clinical Practice, sponsors should note that the EU Note for Guidance

on Good Clinical Practice (CPMP/ICH/135/95) has been adopted in Australia with TGA annotations.

The procedure for abridged applications claiming essential similarity to a reference product (that is, generics), which allows applications to be made to numerous Member States of the EU, based on bioequivalence with a reference product from one Member State, does not apply in Australia. An application for registration of a generic product in Australia should generally include a bioequivalence study versus a leading brand obtained in Australia.'

- pp. 127 - 132 of Rules 1998 (3C) - 3CC6a 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/191583/2005. Questions and Answers Document on the Clinical Development of Fixed Combinations of Drugs Belonging to Different Therapeutic Classes in the Field of Cardiovascular Treatment and Prevention. Effective: 17 December 2010 See also: CPMP/EWP/240/95 Rev. 1 Guideline on Clinical Development of Fixed Combination Medicinal Products.
- Appendix 15 of the Australian Regulatory Guideline for Prescription Medicines (ARGPM).

Regulatory status

The FDC products (this submission) received initial registration on the ARTG on 4 February 2015.

The composite packs for Atozet and Zeteze received registration on the ARTG on 11 February 2013.

At the time the TGA considered this application a similar application had been approved in USA May 2013, EU September 2014 (final approval at the national level was pending) and was under consideration in Korea and Taiwan.

Ezetimibe/atorvastatin calcium trihydrate has been approved for this indication in the USA (Liptruzet). The approved USA indications for Liptruzet are as follows:

Therapy with lipid altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolaemia. Drug therapy is indicated as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate.

Primary Hyperlipidemia

Liptruzet is indicated for the reduction of elevated total-C, LDL-C, Apolipoprotein (Apo) B, TG, and non-HDL-C, and to increase HDL-C in patients with primary (heterozygous familial and non-familial) hyperlipidemia or mixed hyperlipidemia.

Homozygous Familial Hypercholesterolaemia (HoFH)

Liptruzet is indicated for the reduction of elevated total-C and LDL-C in patients with homozygous familial hypercholesterolaemia, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

Limitations of Use

No incremental benefit of Liptruzet on cardiovascular morbidity and mortality over and above that demonstrated for atorvastatin has been established. Liptruzet has not been studied in Fredrickson type I, III, IV, and V dyslipidemias.

A submission has been lodged in Europe (September 2013) and is under evaluation. As of August 28, 2014 ezetimibe with atorvastatin (as either a composite pack or FDC tablet) is not registered in either Canada or New Zealand.

Product Information

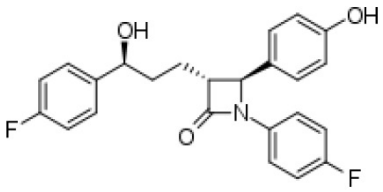
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

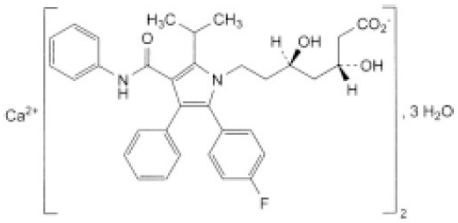
Drug substance (active ingredient)

Ezetimibe is a selective inhibitor of intestinal cholesterol and related phytosterol absorption and atorvastatin is a HMG-CoA reductase inhibitor. The structures of both compounds are shown in Figure 1.

Figure 1: Structures of ezetimibe and atorvastatin calcium trihydrate.



ezetimibe



atorvastatin calcium trihydrate

Ezetimibe drug substance is identical to that used in other ezetimibe products. There is no official monograph. The particle size is controlled. The manufacture, quality control, and stability of the active ingredient have been evaluated previously and are acceptable.

Atorvastatin calcium trihydrate is the subject of both European Pharmacopeia (Ph Eur) and United States Pharmacopeia and The National Formulary (USP-NF) monographs. Manufacture, quality control, and stability have been evaluated and are acceptable. There is public information suggesting that the proposed atorvastatin calcium trihydrate formulation will have more consistent particle behaviour and better chemical stability. The particle size is controlled. In keeping with modern practice, labelled doses (10, 20, 40 or 80 mg) are always the quantity of the active moiety atorvastatin, independent of the salt or hydrate form of the drug substance used in manufacture.

Drug product

The ezetimibe/atorvastatin FDC tablets are unscored, film coated, bilayer tablets intended to provide immediate release. Four tablet strengths are proposed: 10 mg ezetimibe/10 mg atorvastatin; 10 mg ezetimibe/20 mg atorvastatin; 10 mg ezetimibe/40 mg atorvastatin and 10 mg ezetimibe/80 mg atorvastatin. These are all capsule shaped, biconvex, white to off white tablets. Visual differentiation is poor for film-coated tablets; they are distinguished only by size and by tablet debossing on one side (10/10: '257', 10/20: '333', 10/40: '337', 10/80: '357'). The tablets are moderately large (circa 13 x 5, 14.5 x 5.8, 16 x 6, 19 x 8 mm).

There are no official finished product monographs for either ezetimibe or atorvastatin dosage forms. Assay limits are tighter than previously proposed and now comply with Therapeutic Goods Order 78 (92.5 to 107.5%).

Several atorvastatin degradants in the tablets have proposed expiry limits above the qualification threshold. These have been toxicologically qualified. Atorvastatin lactone, a metabolite, is limited to not more than 0.5%. The limits are considered acceptable.

Tablets are packed in nitrogen filled polyvinyl chloride (PVC)/ aluminium/polyamide/aluminium blisters. This is less protective than the complex pouched blisters proposed in the original submission which had an oxygen scavenger and desiccant. Stability data support the proposed shelf life of 24 months, stored below 30°C.

The chemistry, manufacturing and control aspects of the tablets are considered acceptable.

Biopharmaceutics

The submission included two bioequivalence studies and a food effect study.

The bioequivalence comparisons used single component Ezetrol (ezetimibe, MSD) and Liptor (atorvastatin, Pfizer) tablets sourced from the United Kingdom (UK) rather than from Australia. The sponsor confirmed that these are both identical to corresponding tablets marketed in Australia.

Study P391

Study P391 compared the bioequivalence of the proposed 10/10 mg FDC tablets versus co administered 10 mg strengths of separate ezetimibe and atorvastatin tablets. This was an open, two sequence, replicate crossover study in 70 healthy subjects with a 14 day washout. The tablets were bioequivalent with respect to ezetimibe and atorvastatin and the results are summarised in Table 1.

Table 1: Study P391 Bioequivalence study of ezetimibe and atorvastatin 10 mg/10 mg FDC tablet (proposed formulation) and co administration.

Based on Measured Plasma Total Ezetimibe Concentrations

A1 & B1: n = 68 / A2: n = 65 / B2: n = 66 Subject (Replicate Measures)

Parameter	Trt	N obs.	GM	95% CI for GM	Contrast	GMR (%)	90% CI for GMR (%)	Intra-Sbj CV(%) Trt A	Intra-Sbj CV(%) Trt B
AUC_t (h.ng/mL)	A	133	683.96	627.85 - 745.08	A vs. B	98.34	95.38 - 101.39	14	16
	B	134	695.48	637.05 - 759.28					
C_{max} (ng/mL)	A	133	74.19	67.97 - 80.97	A vs. B	96.33	91.46 - 101.46	25	23
	B	134	77.01	69.45 - 85.40					
AUC_{inf} (h.ng/mL)	A	126	744.59	677.91 - 817.83	A vs. B	97.99	94.33 - 101.80	17	20
	B	132	759.83	688.39 - 838.69					

Based on Measured Plasma Atorvastatin Concentrations

A1 & B1: n = 68 / A2: n = 65 / B2: n = 66 Subject (Replicate Measures)

Parameter	Trt	N obs.	GM	95% CI for GM	Contrast	GMR (%)	90% CI for GMR (%)	Intra-Sbj CV(%) Trt A	Intra-Sbj CV(%) Trt B
AUC_t (h.ng/mL)	A	133	16.400	14.837 - 18.128	A vs. B	100.46	97.34 - 103.69	12	15
	B	134	16.324	14.689 - 18.142					
C_{max} (ng/mL)	A	133	3.314	2.901 - 3.785	A vs. B	105.49	98.35 - 113.15	29	32
	B	134	3.141	2.743 - 3.598					
AUC_{inf} (h.ng/mL)	A	127	18.477	16.926 - 20.171	A vs. B	102.61	99.46 - 105.86	11	15
	B	127	18.007	16.335 - 19.850					

Study P392

Study P392 compared the bioequivalence of the proposed 10/80 mg FDC tablets versus co administered corresponding strengths of separate ezetimibe and atorvastatin tablets. This was an open, two sequence, replicate crossover study in 70 healthy subjects with a 14 day washout. The tablets were bioequivalent with respect to ezetimibe and atorvastatin (Table 2).

Table 2: Study P392. Bioequivalence study of ezetimibe and atorvastatin 10 mg/80 mg FDC tablet (proposed formulation) and co administration.

Analyte: Total Ezetimibe

Based on Measured Plasma Total Ezetimibe Concentrations

A1: n = 69 / B1: n = 68 / A2 & B2: n = 65 Subject (Replicate Measures)

Parameter	Trt	N obs.	GM	95% CI for GM	Contrast	GMR (%)	90% CI for GMR (%)	Intra-Sbj CV(%) Trt A	Intra-Sbj CV(%) Trt B
AUC_t (h.ng/mL)	A	134	615.84	566.09 - 669.96	A vs. B	99.63	96.68 - 102.68	15	15
	B	133	618.10	569.90 - 670.38					
C_{max} (ng/mL)	A	134	65.20	60.10 - 70.75	A vs. B	104.00	99.57 - 108.63	23	21
	B	133	62.70	58.02 - 67.74					
AUC_{inf} (h.ng/mL)	A	122	666.82	610.12 - 728.80	A vs. B	98.29	94.92 - 101.77	15	18
	B	128	678.45	619.99 - 742.42					

Analyte: Atorvastatin

Based on Measured Plasma Atorvastatin Concentrations

A1: n = 69 / B1: n = 68 / A2 & B2: n = 65 Subject (Replicate Measures)

Parameter	Trt	N obs.	GM	95% CI for GM	Contrast	GMR (%)	90% CI for GMR (%)	Intra-Sbj CV(%) Trt A	Intra-Sbj CV(%) Trt B
AUC_t (h.ng/mL)	A	134	151.131	134.261 - 170.122	A vs. B	107.06	103.33 - 110.93	18	17
	B	133	141.159	125.295 - 159.033					
C_{max} (ng/mL)	A	134	38.071	33.148 - 43.724	A vs. B	102.27	95.12 - 109.95	43	29
	B	133	37.226	32.735 - 42.334					
AUC_{inf} (h.ng/mL)	A	133	153.998	136.909 - 173.220	A vs. B	106.69	103.02 - 110.48	18	17
	B	132	144.348	128.359 - 162.328					

Study P415

Study P415 was a 2 period crossover study that compared the effect of food on the bioavailability of the 10 mg/80 FDC tablets in 24 healthy adult subjects. Doses were taken either after an overnight fast or with a high fat breakfast. Atorvastatin exposure ($AUC_{0-\infty}$) was slightly increased (approximately 4%) by food, with C_{max} decreased by approximately 7%, and the time after administration of a drug when the maximum plasma concentration is reached (T_{max}) is delayed by approximately 1.25 hours. Unconjugated ezetimibe AUC is unchanged by food, C_{max} is increased by approximately 3%, and T_{max} is delayed by approximately 0.75 hours. Total ezetimibe $AUC_{0\text{-last}}$ is increased approximately 2% by food, C_{max} is increased by approximately 15%, and T_{max} is delayed by approximately 0. 50 hours. These food effects are consistent with published data for the reference products.

Bioequivalence of other strengths

The submitted studies showed bioequivalence of the new 10/10 and 10/80 FDC formulations with the single component tablets, and with point estimates close to unity. These strengths are the extremes of the formulations which use a fixed ezetimibe layer and scaled atorvastatin layers. The sponsor argues that, given formulation similarities and dissolution comparisons, bioequivalence studies of the intermediate FDC 10/20 and 10/40 mg strengths are not required.

The dissolution comparisons are rather limited, only using a single batch of each strength. Comparisons at different pH are intrinsically limited by drug solubilities. The limited data are consistent with bioequivalence of the four proposed tablet strengths.

Very limited comparisons were also made with Ezetrol and Lipitor tablets, only for the 10/10 and 10/80 FDC tablets. These results show slightly faster dissolution of ezetimibe from Ezetrol in pH 6.8 buffer with surfactant (the only conditions tested giving sensible ezetimibe dissolution). Atorvastatin dissolution was rapid, comparable to Lipitor at pH 6.8 and pH 4.5, but the proposed tablets gave more rapid dissolution of atorvastatin in simulated gastric fluid (which is complicated by saturation in vitro).

More extensive in vitro data would be desirable but submitted results are consistent with similar drug release from all strengths.

Quality summary and conclusions

Registration is recommended with respect to chemistry, manufacturing and control aspects.

The proposed 10/10 and 10/80 FDC tablets are bioequivalent with the corresponding single component tablets. Limited in vitro data for the 10/20 and 10/40 FDC strengths are consistent with similar drug release from all of the proposed tablet strengths.

III. Nonclinical findings

Introduction

No significant new nonclinical data were submitted. This is acceptable as most of the nonclinical data supporting the combination use of ezetimibe and atorvastatin calcium (proposed formulation) were previously submitted to the TGA, while nonclinical data supporting the qualification of impurities/degradants specified at above the International Conference on Harmonisation (ICH) qualification threshold were previously evaluated in the withdrawn FDC submission for the previous formulation of atorvastatin calcium with ezetimibe.

Pharmacodynamics

A previous study in dogs given dietary ezetimibe/atorvastatin calcium (proposed formulation) in combination at 0.007/1 mg/kg/day for 14 days showed a 45% reduction in plasma cholesterol compared with 15% reduction with atorvastatin alone and a 25% reduction with ezetimibe alone. These results are consistent with the increased low density lipoprotein cholesterol (LDL-C) lowering ability of the FDC compared with atorvastatin alone observed in the clinical trial data.

Pharmacokinetics

In general, changes in either ezetimibe or atorvastatin plasma concentrations after combination dosing varied less than 2 fold. Other toxicokinetic measurements obtained with the ezetimibe/atorvastatin (proposed formulation) combination showed that exposures to total ezetimibe were increased further at very high doses of ezetimibe (1000 mg/kg/day) and high doses of atorvastatin (50 to 100 mg/kg/day) but plasma free ezetimibe and atorvastatin and its hydroxy metabolites concentrations were generally unaffected by co administration, except in pregnant rabbits.

Toxicology

Toxicity findings from previously submitted combination studies of atorvastatin calcium (proposed formulation) with ezetimibe generally represented enhancement of changes elicited by the statins alone or changes that may be expected with increased statin exposure. The liver was the clear target organ of toxicity.

Treatment related changes included increased serum enzymes (alanine aminotransferase (ALT) and, to a lesser extent, aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT) and/or succinate dehydrogenase (SDH)), hepatic lesions (cytoplasmic eosinophilia, hypertrophy and focal necrosis of hepatocytes, Kupffer cell hypertrophy or pigment accumulation, altered hepatic foci (rat only) and bile duct hyperplasia) and non glandular stomach acanthosis (rat only). Increased serum enzymes and hepatic changes were observed at all combination doses in rats and/or dogs with total statin exposures in rats and dogs approximately 2 to 3 times the expected clinical exposures (based on AUC) for atorvastatin (10 mg/day). Increased plasma enzymes but not bile duct hyperplasia, were attenuated by mevalonate co-treatment. No skeletal muscle toxicity was observed in rats dosed with atorvastatin in combination with ezetimibe.

The reproductive toxicity of an ezetimibe/atorvastatin (proposed formulation) combination (1000/5, 100/25 and 1000/50 mg/kg/day) was previously assessed in rabbits. The incidence of skeletal malformations or variations was increased in all treatment groups and included sternebral variations, fused caudal vertebrae and extra pair of thoracic ribs. The extra thoracic ribs finding appears to be related to ezetimibe dosing and has been seen with other ezetimibe/statin combinations. The reduced number of caudal vertebrae has also been observed in rabbits treated with ezetimibe/statin combinations but not statin or ezetimibe alone. For ezetimibe/atorvastatin the incidences were 1/1, 1/1 and 6/1 at 5, 25 and 50 mg/kg/day, respectively. This finding may not be relevant to humans.

The ezetimibe/atorvastatin combination should be classified as Australian Pregnancy Category D[3], in line with other statin containing medications.

Impurities

Four impurities (degradants) in the atorvastatin calcium drug product had shelf life specifications exceeding the ICH qualification threshold of 0.25%. All of these were suitably qualified in a 3 month per oral (PO) study in dogs, genotoxicity/clastogenicity assays and using in silico[4] methods (DEREK software).

Nonclinical summary and conclusions

Summary

- No significant new nonclinical data were submitted. This is acceptable as most of the nonclinical data supporting the combination use of ezetimibe and atorvastatin calcium (proposed formulation) were previously submitted to the TGA while nonclinical data supporting the qualification of impurities/degradants specified at above the ICH qualification threshold were previously evaluated by the TGA.

[3] Category D for the use of medicines in pregnancy is defined as: *Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details*.
[4] in silico means performed on a computer or via computer simulation.

- Pharmacodynamic studies in dogs showed increased LDL-C lowering ability of the FDC compared with atorvastatin or ezetimibe alone consistent with findings in the clinical trial data.
- Previously submitted toxicokinetic data with the ezetimibe/atorvastatin (proposed formulation) combination showed minimal pharmacokinetic interactions, except at very high combination doses of both drugs (ezetimibe 1000 mg/kg/day; atorvastatin 50 to 100 mg/kg/day).
- Toxicity findings from previously submitted combination studies of atorvastatin calcium (proposed formulation) with ezetimibe generally represented enhancement of changes elicited by the statins alone or changes that may be expected with increased statin exposure. The liver was the main target organ of toxicity.
- Several degradant impurities in the drug product were specified at limits exceeding the ICH qualification threshold. The general toxicity of these degradants was suitably qualified in a 3 month PO study in dogs. The genotoxicity/clastogenicity of these degradants was successfully qualified using a combination of mutagenicity assays (active pharmaceutical ingredient (API) spiked or neat impurity), clastogenicity assays and in silico methods using DEREK QSAR software.

Conclusions and recommendation

There are no nonclinical objections to the registration of Atozet/Zeteze.

No changes are recommended to nonclinical aspects of the draft Product Information.

IV. Clinical findings

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

> **Comments**: The only difference between the proposed indications for the Atozet and Zeteze FDC combination tablets and the approved indications for the currently registered Atozet and Zeteze composite packs relates to the addition of reference to previous treatment with rosuvastatin for primary hypercholesterolaemia.

Clinical rationale

The following rationale for the FDC of ezetimibe and atorvastatin was provided in the sponsor's covering letter:

- complementary mechanism of action for the two components and lack of interaction between them demonstrating that this is a rational combination
- an improvement in benefit/risk balance demonstrated by greater efficacy compared to the individual components with an acceptable safety profile
- the simplification of therapy by provision of a single dose unit of frequently co prescribed medications.

> **Comment:** The sponsor's rationale is considered to be satisfactory.

The proposed FDC tablet is a new formulation of the ezetimibe/atorvastatin FDC tablet previously submitted to the TGA for evaluation and subsequently withdrawn. In contrast to the previous FDC formulation, the new formulation is intended to address the TGA's concerns about the known instability of the previously proposed formulation of atorvastatin calcium and its susceptibility to oxidative degradation and hydrolysis.

Guidance

The sponsor agreed to the TGA's request to include two additional previously unevaluated supportive clinical efficacy and safety studies (P185 and P190), and to provide copies of 12 previously submitted and evaluated clinical efficacy and safety studies.

Contents of the clinical dossier

The clinical data were comprehensive and sufficient to support registration of the proposed FDC products. The relevant clinical data provided in the submission are outlined below:

- 1 new comparative bioavailability study comparing the FDC product in the fed and fasted states in healthy volunteers (P415).
- 2 new comparative bioavailability and bioequivalence studies in healthy volunteers comparing the FDC product (10/10 mg and 10/80 mg) with co administration of the two constituent medicines (P391, P392).
- 3 new reports of bioanalytical and analytical methods used in the human studies (1887, 1888, 1889).
- 1 previously submitted and evaluated multiple dose pharmacodynamic and pharmacokinetic interaction study between ezetimibe and atorvastatin in healthy volunteers (P460).
- 1 new pivotal Phase III clinical efficacy and safety study (P162).
- 2 new supportive Phase III clinical efficacy and safety studies (P185, P190).
- 10 previously submitted and evaluated controlled clinical efficacy and safety studies (P112, P090, P692, P079, P693, P040, P1030, P2173, P02173R and P02154).
- 2 previously submitted and evaluated uncontrolled clinical studies (P1417, P1418).
- 1 Merck Research Laboratories (MRL) Report: statistical analysis plan (amendment 002), integrated summary of safety, 2013 (P4651).
- 1 Suspect Adverse Reactions Report from the Council for International Organizations of Medical Sciences (CIOMS) - 10 October 2005 to 22 May 2013 (Ref: 5.3.6: 4647).
- Literature references.
- Sponsor’s Clinical Overview, with supplementary data including TGA’s clinical evaluation report (CER), Delegate's Overview, and ratified minutes of Advisory Committee on Prescription Medicines (ACPM) relating to the previous application to register the Atozet (and Zeteze) composite packs; sponsor’s Summary of Biopharmaceutic Studies with Associated Analytical Methods; Summary of Clinical Pharmacological Studies; Summary of Clinical Efficacy; Summary of Clinical Safety; as well as literature references; synopses of individual studies.

Table 12 under *Overall conclusion and risk/benefit assessment* (below), details which of the studies were submitted in the applications for the composite pack and the FDC of ezetimibe and atorvastatin.

The sponsor states that the efficacy and safety of the ezetimibe and atorvastatin composite pack has been established in the clinical development program previously evaluated by the TGA. The sponsor states that the clinical efficacy and data package supporting the current application consists of the same studies that supported registration of the composite pack plus one additional previously unevaluated study (P162). In addition to Study P162, the TGA requested the sponsor to provide two previously unevaluated clinical efficacy and safety studies with an FDC product in Module 5, but the studies were not referred to in the sponsor’s Clinical Overview, Summary of Clinical Efficacy or the

Summary of Clinical Safety. Other previously unevaluated clinical studies in the dossier included the comparative bioavailability (fasted/fed) study (P415), and two bioavailability/bioequivalence studies (P391/P392).

Paediatric data

The submission included no paediatric data. The sponsor states that it has been granted a product specific waiver from the EMA (Paediatric Committee (PDCO)) for the ezetimibe/atorvastatin FDC product on the grounds that 'this specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patient. The waiver applies to all subsets of the paediatric population from birth to less than 18 years of age, for both conditions.[5] In addition, the sponsor states that the Food and Drug Administration (FDA) waived the paediatric study requirement for the ezetimibe/atorvastatin FDC product (Lipruzet) *'because for ages 0 through 9 years necessary studies are impossible or highly impracticable; for paediatric patients aged 10 through 17 this product does not represent a meaningful therapeutic benefit over existing therapies for paediatric patients and is not likely to be used in a substantial number of paediatric patients*'.

Good clinical practice

All sponsored studies were conducted in accordance with the principles of good clinical practice (GCP).

Pharmacokinetics

Studies providing pharmacokinetic data

The clinical dossier included three new bioavailability/bioequivalence studies in healthy volunteers (P415, P391, P392), and these studies are outlined below in Table 3. The full evaluations of these three studies are provided in the CER (see Attachment 2). The only other study in the dossier providing pharmacokinetic (PK) data was the previously submitted and evaluated Study P460, which provided both PK and pharmacodynamic (PD) data in healthy volunteers. This study has been briefly reviewed in the Pharmacodynamics section of the CER (see Attachment 2). There were no new PK studies in patients with hypercholesterolaemia.

Table 3: Outline of three new bioavailability/bioequivalence studies in healthy volunteers; P391, P392, P415.

Study	Objectives	Design	N	Treatment	Parameters
P391	Comparative BA - EZ/AT FDC (10/10 mg), AT (10 mg), EZ (10 mg), single-dose, fasting, healthy volunteers.	Open-label, single-dose, 4-period, 2-sequence, 2-treatment, crossover, full replicate study.	70	FDC EZ/AT (10/10 mg); tablet; EZ 10 mg tablet + AT 10 mg tablet; single-dose, fasting.	AT, unconjugated EZ, total EZ: AUC_t, AUC_{inf}, C_{max}, T_{max}, Kel and $T_{½}$.

[5] Treatment of hypercholesterolaemia and treatment of mixed hyperlipidemia (EMEA/ PDCO/ 909929/2011).

Study	Objectives	Design	N	Treatment	Parameters
P392	Comparative BA - EZ/AT FDC (10/80 mg), EZ (10 mg), AT (80 mg), single-dose, fasting, healthy volunteers.	Open-label, single-dose, 4-period, 2-sequence, 2-treatment, crossover, full replicate study.	70	FDC EZ/AT (10/80 mg) tablet; EZ 10 mg tablet + AT 80 mg tablet; single-dose, fasting.	AT, unconjugated EZ, total EZ: AUC_t, AUC_∞, C_{max}, T_{max}, Kel and $T_{½}$.
P415	Comparative BA of EZ/AT FDC (10/80 mg) tablets in the fed and fasted states healthy volunteers.	Single-dose, randomised, 2-period, 2-sequence, 2-treatment, crossover, fed and fasted states.	24	EZ/AT FDC tablet (10/80 mg); single-dose, fasting and fed.	AT, unconjugated EZ, total EZ: AUC_t, AUC_∞, C_{max}, T_{max}, Kel and $T_{½}$.

AT; atorvastatin BA; bioavailability, EZ; ezetimibe, FDC; fixed dose combination

Evaluator's conclusions on pharmacokinetics

The submission included two new, previously unevaluated comparative bioavailability studies in 140 healthy volunteers (P391 (n = 70) and P392 (n = 70)) and one new, previously unevaluated food effect study in 24 healthy volunteers (P415). There were no new biopharmaceutical studies in patients with hyperlipidaemia.

The proposed FDC ezetimibe/atorvastatin 10/10 mg tablet was bioequivalent to co administered ezetimibe 10 mg plus atorvastatin 10 mg tablets, as regards both components of the combination, following single dose treatment in the fasting state in healthy volunteers (P391). The 90% confidence intervals (CIs) for the geometric mean ratios (GMRs) for unconjugated ezetimibe, total ezetimibe and atorvastatin were all within the standard bioequivalence interval of 80 to 125%. The FDC ezetimibe/atorvastatin 10/10 mg tablet was the formulation proposed for registration, the ezetimibe 10 mg tablet (Ezetrol) sourced from the UK was stated by the sponsor to be identical to the Australian registered product, and the atorvastatin 10 mg tablet (Lipitor) sourced from the UK was stated by the sponsor to be comparable to the corresponding Australian registered product based on information provided by the sponsor of Lipitor.

The proposed FDC ezetimibe/atorvastatin 10/80 mg tablet was bioequivalent to co administered ezetimibe 10 mg plus atorvastatin 80 mg tablets, as regards both components of the combination, following single dose treatment in the fasting state in healthy volunteers (P392). The 90% CIs for the GMRs for unconjugated ezetimibe, total ezetimibe, and atorvastatin were all within the standard bioequivalence interval of 80 to 125%. The FDC ezetimibe/atorvastatin 10/80 mg tablet was the formulation proposed for registration, the ezetimibe 10 mg tablet (Ezetrol) sourced from the UK was stated by the sponsor to be identical to the Australian registered product, and the atorvastatin 80 mg tablet (Lipitor) sourced from the UK was stated by the sponsor to be comparable to the corresponding Australian registered product based on information provided by the sponsor of Lipitor.

There were no bioavailability/bioequivalence studies with the FDC ezetimibe/atorvastatin tablets proposed for registration at the two intermediate strengths of 10/20 mg and

10/40 mg. However, the sponsor submitted a justification for not providing such studies based on similar manufacturing and pharmaceutical chemistry criteria for the four proposed strengths. The evaluation of these criteria is primarily a matter for the quality evaluator. No clinical justification for not providing such studies could be identified in the submission. However, based on the robustness of the two submitted bioavailability/ bioequivalence studies investigating the lowest (10/10 mg) and the highest (10/80 mg) strengths of the proposed FDC tablets, it is the opinion of this evaluator that clinically significant bio inequivalence of the two intermediate FDC tablets and their individual components is unlikely.

The bioavailability of the proposed FDC ezetimibe/atorvastatin 10/80 mg tablet in the fasting and fed state was investigated in a single dose study in 24 healthy volunteers (P451). In this study food had no significant effects on the bioavailability of atorvastatin or unconjugated ezetimibe based on the AUC_t and AUC_∞ values for the two analytes, with the 90% CI for the GMR (fed/fasted) for both parameters being with the standard bioequivalence interval (80 to 125%). However, the geometric mean (GM) C_{max} for atorvastatin was approximately 7% lower in the fed state and the 90% CI for the GMR (fed/fasted) was outside the standard bioequivalence interval of 80 to 125% (that is, GMR = 92.89% (90% CI: 72.9, 118.54)), the GM C_{max} for unconjugated ezetimibe was approximately 3% higher in the fed state and the 90% CI for GMR (fed/fasted) was outside the standard bioequivalence of 80 to 125% (that is, GMR = 103.3% (95% CI: 80.97, 131.77), and the GM C_{max} for total ezetimibe was approximately 15% higher in the fed state and the 90% CI for GMR (fed/fasted) was outside the standard bioequivalence of 80 to 125% (that is, GMR = 114.58% (95% CI: 99.12, 132.45).

The efficacy of the FDC tablet is likely to be primarily based on total systemic exposure (which was equivalent in the fed and fasted states for atorvastatin, unconjugated ezetimibe and total ezetimibe), while the safety of the tablet is likely to be based primarily on peak exposure (which was approximately 3% higher for unconjugated ezetimibe with an upper 90% CI of approximately 32%, approximately 15% higher for total ezetimibe with an upper 90% CI of approximately 33% in the fed state, and approximately 7% lower for atorvastatin with a lower 90% CI of approximately 27% in the fasted state). Based on the relatively small differences in C_{max} in the fed and fasted states for the three analytes, it is considered unlikely that there will be clinically significant differences in the safety of the proposed FDC tablets when administered in the fasted and fed states. Therefore, it is recommended that the proposed FDC tablets be administered without regard to food (as proposed by the sponsor).

Overall, it is considered that the submitted bioavailability/bioequivalence data indicate that the efficacy and safety of the proposed FDC tablets at the proposed doses are unlikely to differ significantly from the efficacy and safety of the registered composite packs at the corresponding doses. Therefore, it is considered that the submitted bioavailability/bioequivalence data allow the known efficacy and safety data of the registered composite packs to be safely extrapolated to the proposed FDC tablets.

Pharmacodynamics

Studies providing pharmacodynamic data

There were no new pharmacodynamic (PD) data submitted. However, the submission included one previously submitted and evaluated Phase I study (P460) in which the primary objectives were to investigate the safety, tolerance and pharmacodynamic effects of co administered ezetimibe 10 mg tablets and atorvastatin 10 mg tablets for 14 days in healthy subjects with hypercholesterolaemia (calculated LDL-C ≥ 130 mg/dL and

triglycerides (TG) ≤ 400 mg/dL at screening), and the secondary objectives were to evaluate the potential PK drug interaction of ezetimibe on atorvastatin.

The study was initially submitted to support the registration of ezetimibe. The clinical study report (CSR) states that the study was undertaken with ezetimibe to '*obtain PD, PK, and safety data with atorvastatin which will support ezetimibe/atorvastatin clinical efficacy and safety trials*'.

The study was randomised, investigator/evaluator blind, placebo controlled, multiple dose, and parallel dose in design. Subjects were randomised to placebo, ezetimibe (EZ) 10 mg, atorvastatin (Atorva) 10 mg, or co administered Atorva 10 mg + EZ 10 mg.

It is considered that the pharmacodynamic results of this small, short term (14 days) study should be interpreted as being exploratory rather than confirmatory. The study was also not designed to investigate bioequivalence of Atorva 10 mg + EZ 10 mg and Atorva 10 mg. More details of this study and the outcomes are provided in Attachment 2.

Pharmacodynamic results

The mean standard error (SE) percent changes from baseline to Day 14 on serum lipids in the four treatment groups are summarised below in Table 4.

Table 4: P460 - Mean (SE) Day 14 from baseline in serum lipids.

Treatment	LDL-C	Total-C	HDL-C	TG
Placebo (n=8)	- 6.9 (4.6)	- 6.1 (3.7)	- 12.8 (2.2)	22.6 (21.1)
EZ 10 mg (n=8)	- 22.7 (5.2) b	- 15.4 (4.6)	- 11.3 (2.6)	32.8 (15.6)
Atorva 10 mg (n=8)	- 40.0 (5.1) a	- 28.4 (4.6) a	- 0.5 (7.7)	0.5 (14.0)
Atorva 10 mg + EZ 10 mg (n=8)	- 55.7 (2.0) a, c, d	- 38.0 (2.4) a, d	- 1.1 (5.0)	- 8.6 (7.1)

a = p ≤ 0.01 versus placebo; b = p ≤ 0.03 versus placebo; c = p ≤ 0.02 versus atorvastatin 10 mg; d = p < 0.01 versus ezetimibe 10 mg; HDL-C = high-density lipoprotein cholesterol; Total-C = total cholesterol

Comment: Atorva 10 mg + EZ 10 mg resulted in a statistically significant greater mean percent reduction in LDL-C from baseline at Day 14 than placebo (p ≤ 0.01), Atorva 10 mg (p ≤ 0.02) and EZ 10 mg (p < 0.01), and a statistically significant greater mean percent reduction in total cholesterol (Total-C) at Day 14 than placebo (p ≤ 0.01) and EZ 10 mg (p < 0.01), but not for Atorva 10 mg. The mean percent reduction from baseline at Day 14 for the comparisons between Atorva 10 mg + EZ 10 mg and placebo, Atorva 10 mg and EZ 10 mg were not statistically significant (p > 0.05) for HDL-C and TG. No sample size calculations were undertaken and the small sample size suggests that the study was underpowered to detect statistically significant differences for all the undertaken pairwise comparisons. It is considered that the pharmacodynamic results of this small, short term (14 days) study should be interpreted as being exploratory rather than confirmatory.

Pharmacokinetic results - atorvastatin and orthohydroxy atorvastatin

The pharmacokinetic parameters (C_{max}, $AUC_{(0\text{-}24\ hr)}$ and T_{max}) for atorvastatin and orthohydroxy atorvastatin at Day 14 following co administered Atorva 10 mg + EZ 10 mg and Atorva 10 mg alone are summarised below in Table 5.

Table 5: P460 - Mean (CV%) for C_{max} and $AUC_{(0\text{-}24\ hr)}$ and median (range) for T_{max}.

Parameter		Atorva 10 mg + EZ 10 mg (n=8)		Atorva 10 mg (n=8)	
Atorvastatin					
Cmax	ng/mL	3.29	(CV = 67%)	2.70	(CV = 29%)
Tmax	hr	0.75	(range: 0.5, 3.0 hr)	0.50	(range: 0.5, 1.0 hr)
AUC(0-24 hr)	ng.hr/mL	22.1	CV = 58%)	21.3	(CV = 29%)
Orthohydroxy atorvastatin					
Cmax	ng/mL	1.62	(CV = 35%)	1.24	(CV = 10%)
Tmax	hr	3.00	(range: 1.0, 6.0 hr)	3.00	(range: 3.0, 8.0)
AUC(0-24 hr)	ng.hr/mL	18.8	(CV = 27%)	15.0	(CV = 7%)

The GMR ((A + E)/ (A)) for the atorvastatin C_{max} was 107% (90% CI: 72, 159), and for the atorvastatin $AUC_{(0\text{-}24\ hr)}$ was 95.6% (90% CI: 68, 134). The GMR ((A + E)/ (A)) for the orthohydroxy atorvastatin C_{max} was 125% (90% CI: 102, 154), and for the orthohydroxy atorvastatin $AUC_{(0\text{-}24\ hr)}$ was 122% (90% CI: 103, 144).

> **Comment**: Plasma atorvastatin and orthohydroxy atorvastatin exposures were similar following co-administration of Atorva 10 mg + EZ 10 mg and those following administration of Atorva 10 mg alone. The 90% CIs for the relevant C_{max} and $AUC_{(0\text{-}24\ hr)}$ GMRs indicate that the two treatments were not BE as regards the two analytes (that is, 90% CIs not enclosed within the standard BE interval of 80 to 125%). However, this small study was not designed to investigate bioequivalence of Atorva 10 mg + EZ 10 mg and Atorva 10 mg.

Pharmacokinetic results - total ezetimibe, ezetimibe, and conjugated ezetimibe.

The pharmacokinetic parameters (C_{max}, $AUC_{(0\text{-}24\ hr)}$, T_{max}) for total ezetimibe, ezetimibe, and conjugated ezetimibe at Day 14 following co administered Atorva 10 mg + EZ 10 mg and Ezetimibe 10 mg alone are summarised below in Table 6.

Table 6: P460 - Mean (CV%) for C_{max} and $AUC_{(0\text{-}24\ hr)}$ and median (range) for T_{max}.

Parameter		Atorva 10 mg + EZ 10 mg (n=8)		Atorva 10 mg (n=8)	
Total ezetimibe					
Cmax	ng/mL	87.3	(CV = 50%)	73.0	(CV = 28%)
Tmax	hr	0.50	(range: 0.5, 3.0)	0.75	(range: 0.5, 2.0)
AUC(0-24 hr)	ng.hr/mL	707	(CV = 41%)	681	(CV = 25%)
Ezetimibe					
Cmax	ng/mL	6.07	(CV = 42%)	4.65	(CV = 38%)
Tmax	hr	4.50	(range: 0.0, 8.0)	6.00	(range: 4.0, 12)
AUC(0-24 hr)	ng.hr/mL	75.7	(CV = 45%)	62.2	(CV = 39%)
Conjugated ezetimibe					
Cmax	ng/mL	83.3	(CV = 52%)	70.0	(CV = 28%)
Tmax	hr	0.50	(range: 0.5, 3.0)	0.75	(range: 0.50, 2.0)
AUC(0-24 hr)	ng.hr/mL	632	(CV = 44%)	619	(CV = 26%)

Parameter		Atorva 10 mg + EZ 10 mg (n=8)		EZ 10 mg (n=8)	
Total ezetimibe					
Cmax	ng/mL	87.3	(CV = 50%)	73.0	(CV = 28%)
Tmax	hr	0.50	(range: 0.5, 3.0)	0.75	(range: 0.5, 2.0)
AUC(0-24 hr)	ng.hr/mL	707	(CV = 41%)	681	(CV = 25%)
Ezetimibe					
Cmax	ng/mL	6.07	(CV = 42%)	4.65	(CV = 38%)
Tmax	hr	4.50	(range: 0.0, 8.0)	6.00	(range: 4.0, 12)
AUC(0-24 hr)	ng.hr/mL	75.7	(CV = 45%)	62.2	(CV = 39%)
Conjugated ezetimibe					
Cmax	ng/mL	83.3	(CV = 52%)	70.0	(CV = 28%)
Tmax	hr	0.50	(range: 0.5, 3.0)	0.75	(range: 0.50, 2.0)
AUC(0-24 hr)	ng.hr/mL	632	(CV = 44%)	619	(CV = 26%)

Total ezetimibe: The GMR ((A + E)/ (A)) for the C_{max} was 112% (90% CI: 80, 157), and for the $AUC_{(0\text{-}24\ hr)}$ was 98.5% (90% CI: 72, 134).

Ezetimibe: The GMR ((A + E)/ (A)) for the C_{max} was 131% (90% CI: 98, 176), and for the $AUC_{(0\text{-}24\ hr)}$ was 121% (90% CI: 88, 166).

Conjugated ezetimibe: The GMR ((A + E)/ (A)) for the C_{max} was 110 (90% CI: 78, 157), and for the $AUC_{(0\text{-}24\ hr)}$ was 95.4% (90% CI: 68, 134).

> **Comment**: Plasma total ezetimibe, ezetimibe, and conjugated ezetimibe exposures were similar following co administration of Atorva 10 mg + EZ 10 mg and those following administration of Ezetimibe 10 mg alone. The 90% CIs for the relevant C_{max} and $AUC_{(0\text{-}24\ hr)}$ GMRs indicate that the two treatments were not bioequivalent as regards these three analytes (that is, 90% CIs not enclosed within the standard bioequivalence interval of 80 to 125%). However, this small study was not designed to investigate the bioequivalence of Atorva 10 mg + EZ 10 mg and Ezetimibe 10 mg.

Dosage selection for the pivotal studies

The ezetimibe and atorvastatin dosages selected for the FDC tablets were the same as the approved dosages for the composite packs.

Efficacy

Studies providing efficacy data

The submission included one previously unevaluated, pivotal Phase III study assessing the efficacy and safety of co administered ezetimibe tablets and atorvastatin as calcium (proposed formulation) tablets in patients with primary hypercholesterolaemia and high cardiovascular risk (P162). In this study, the atorvastatin as calcium (proposed formulation) used in the administered tablets was stated by the sponsor to be the same as that used in the FDC tablets proposed for registration. This study has been fully evaluated.

In addition to the pivotal study, the submission included two previously unevaluated supporting studies, provided by the sponsor in response to a request from the TGA, which assessed the efficacy and safety of two strengths of FDC ezetimibe/atorvastatin tablets in patients with primary hypercholesterolaemia at low, moderate or moderately high risk of cardiovascular disease: FDC 10/20 mg in Study P185 and FDC 10/40 mg in Study P190. In these two supportive studies, the previously submitted formulation of atorvastatin calcium was used with ezetimibe in the FDC. Both of these studies have been fully evaluated.

In addition to the one pivotal and two supportive studies, the submission included 12 previously submitted and evaluated clinical efficacy and safety studies supporting registration of the composite pack. The efficacy results from these studies have been briefly summarised.

There were no clinical efficacy and safety studies using the FDC tablets proposed for registration.

Pivotal study (Study P162).

The study was an 18 week randomized, double blinded, active controlled, multicentre Phase III study comprising of a 6 week screening/run in and a 12 week double blinded treatment period (2 phases, each of 6 weeks duration). Approximately 1,508 patients with hypercholesterolemia and high cardiovascular risk not adequately controlled with atorvastatin 10 mg at the end of a 5 week run in were randomized to 1 of 6 double blind treatment sequences. Full details of the design of this study can be found in Attachment 2. An outline of the Phases of this study is shown in Table 7.

Table 7. Study 162; Phase 1 and Phase 2 treatment sequences.

Treatment Sequence	Phase 1	Phase 2
1	ezetimibe 10 mg + atorvastatin 10 mg	-
2	ezetimibe 10 mg + atorvastatin 10 mg	ezetimibe 10 mg + atorvastatin 10 mg
3	atorvastatin 20 mg	ezetimibe 10 mg + atorvastatin 20 mg
4	atorvastatin 20 mg	atorvastatin 40 mg
5	rosuvastatin 10 mg	ezetimibe 10 mg + atorvastatin 20 mg

Treatment Sequence	Phase 1	Phase 2
6	rosuvastatin 10 mg	rosuvastatin 20 mg

Description of the study sequences in following parts of this document will be abbreviated. The transition from Phase 1 to Phase 2 will be indicated with an arrow. For example treatment sequence 5 will be described as Rosuva 10 mg ® EZ 10 mg + Atorva 20 mg.

Evaluator's conclusions on efficacy

The pivotal efficacy study (P162) was undertaken in patients with primary hypercholesterolaemia and high cardiovascular risk. The study demonstrated that the percent reduction in LDL-C from baseline after 6 weeks treatment (Phase 1[6]) in patients who had not been controlled on atorvastatin during a 5 week run in period was significantly greater after switching to co administration of ezetimibe 10 mg + atorvastatin 10 mg (n = 120) compared with doubling the dose of atorvastatin to 20 mg (n = 480) (difference = - 12.7% (95% CI: - 16.6, - 8.7); p < 0.001), and after switching to co administration of ezetimibe 10 mg + atorvastatin 10 mg (n = 120) compared with switching to rosuvastatin 10 mg (n = 939) (difference = - 9.1% (95% CI: - 12.9, - 5.4,); p < 0.001). The difference between treatments for both comparisons is considered to be clinically meaningful.

The pivotal efficacy study (P162) also showed that the percent reduction in LDL-C from baseline after 6 weeks treatment (Phase 2) in patients who had not been controlled on atorvastatin 10 mg during the 5 week run in period or atorvastatin 20 mg during the 6 week Phase 1 treatment period was significantly greater after switching to ezetimibe 10 mg + atorvastatin 20 mg (n = 124) compared with doubling the dose of atorvastatin to 40 mg (n = 123) (difference = - 10.5% (95% CI: - 15.9, - 5.1); p < 0.001). Similarly, the percent reduction in LDL-C from baseline after 6 weeks treatment (Phase 2) in patients who had not been controlled on atorvastatin 10 mg during the 5 week run in period or rosuvastatin 10 mg during the 6 week Phase 1 treatment period was significantly greater after switching to ezetimibe 10 mg + atorvastatin 20 mg (n = 231) compared with doubling the dose of rosuvastatin to 20 mg (n = 205) (difference = - 9.5% (95% CI: - 13,6 - 5.4); p < 0.001). The difference between treatments for both comparisons is considered to be clinically meaningful.

In addition, the pivotal efficacy study (P162) showed co administration of ezetimibe 10 mg + atorvastatin 10 mg achieved a significantly greater proportion of patients achieving target LDL-C levels < 2.59 mmol/L and < 1.81 at Week 6 (Phase 1) than both atorvastatin 20 mg and rosuvastatin 10 mg. Similarly, co administration of ezetimibe 10 mg + atorvastatin 20 mg achieved a significantly greater proportion of patients achieving target LDL-C levels < 2.59 mmol/L and < 1.81 at Week 6 (Phase 2) than both atorvastatin 40 mg and rosuvastatin 20 mg.

In the pivotal efficacy study (P162), the results for the secondary efficacy lipid/lipoprotein efficacy endpoints at the end of Phase 1 and Phase 2 supported the results for the primary efficacy endpoint for LDL-C at the corresponding time points. In general, the efficacy outcomes for the secondary lipid/lipoprotein endpoints were significantly better in patients in the co administered ezetimibe 10 mg + atorvastatin 10 mg group than in the atorvastatin 20 mg and rosuvastatin 10 mg groups (Phase 1), and in patients in the co

[6] Study P162 has two phases referred to in the Clinical Study Report (CSR) as Phase I and Phase II. For clarity the different phases of this study will be referred to as Phase 1 and Phase 2 to distinguish them from the Phase I and Phase II clinical trials.

administered ezetimibe 10 mg + atorvastatin 20 mg group than in the atorvastatin 40 mg and rosuvastatin 20 mg groups (Phase 2).

In contrast to the pivotal efficacy study (P162), the two supportive efficacy studies (P185 and P190) were undertaken in patients with primary hypercholesterolaemia with low, moderate, or moderately high cardiovascular risk, with high risk patients (coronary heart disease (CHD) or CHD risk equivalent) being excluded. Study P185 showed that FDC ezetimibe/atorvastatin 10/20 mg (n = 353) was equivalent to co administered ezetimibe 10 mg + atorvastatin 20 mg (n = 346), based on the percent change in LDL-C from baseline after 6 weeks treatment (difference = - 0.2% (97.5% expanded CI = - 1.7%, 1.3%)). Study P190 showed that FDC ezetimibe/atorvastatin 10/40 mg (n = 280) was equivalent to co administered ezetimibe 10 mg + atorvastatin 40 mg (n = 280) based on the percent change in LDL-C from baseline after 6 weeks treatment (difference = - 0.2% (97.5% expanded CI = - 1.8%, 1.4%)). In both studies, the 97.5% expanded CIs for the difference in means were well within the pre specified clinical equivalence limits of - 4% to +4%. In both studies, the secondary efficacy lipid/lipoprotein equivalence analyses supported the results for primary efficacy equivalence analyses relating to the LDL-C.

In the previously evaluated studies:

1. The factorial study (P00692) showed that co administered ezetimibe + atorvastatin (pooled across all doses) was more effective than atorvastatin alone (pooled across all doses) in reducing LDL-C from baseline through to 12 weeks
2. The add on studies (P02173/P2246, P040), demonstrated that co administered ezetimibe 10 mg + atorvastatin was more effective in reducing LDL-C than atorvastatin alone, and that patients not at target LDL-C levels were more likely to achieve target LDL-C levels after co administered ezetimibe 10 mg + atorvastatin compared with atorvastatin alone
3. The add on titration studies (P079, P090, P112, P00693) demonstrated that the addition of ezetimibe 10 mg to atorvastatin was more effective in reducing LDL-C than atorvastatin alone even when the atorvastatin monotherapy dose was titrated upwards
4. The long term studies of co administered ezetimibe + atorvastatin was effective in achieving and maintaining reductions in LDL-C levels over 12 months (P2154, P1418)
5. Co administered ezetimibe + atorvastatin was effective for the treatment of homozygous familial hypercholesterolaemia (p1030, P1417).

Safety

Studies providing safety data

The pivotal Phase III study (P162) included a comprehensive review of the safety of co administered ezetimibe and the formulation of atorvastatin as calcium being proposed for registration. The two supportive Phase III studies (P185, P190) included a comprehensive review of the safety of co administered ezetimibe + atorvastatin and FDC ezetimibe/atorvastatin tablets containing the previously withdrawn atorvastatin as calcium formulation. The safety data from these three studies have been evaluated and the results discussed in the CER (see Attachment 2).

The submission also included a sponsor's 'summary of clinical safety' providing data from 12 studies assessing the safety of co administration of ezetimibe + atorvastatin. These 12 studies included safety data from 11 previously submitted and evaluated studies (P00692, P00693, P01030, P01417, P01418, P02154, P02173/P2246, P040, P079, P090 and P112) and 1 newly submitted study (P162). The 'summary of clinical safety' did not include data

from the two new supportive studies (P185, P190). The substance of the 'summary of clinical safety' provided in the current submission remains unchanged that in the previously submitted and evaluated corresponding document relating to the application to register the composite packs. However, the updated integrated safety data in the summary of clinical safety for the core safety pool (CSP) containing data from eight studies of 6 to 14 weeks duration has been evaluated as this pool includes information from the newly submitted pivotal study (P162). However, the safety data in the summary document relating to the long term studies and studies in patients with HoFH have not been evaluated, as the data remain unchanged from that previously evaluated (composite pack application).

Patient exposure

The safety assessment in the pivotal study focused on the 12 week double blind treatment period (Phase 1 and Phase 2). Overall, 1539 (99.5%) of the 1,547 randomised patients took at least one dose of study medication and were included in the all patients as treated population (APaT) (the safety analysis population).

In Phase 1, the extent of exposure was comparable for the three treatment groups with an overall mean (standard deviation (SD)) exposure of 42.1 (6.5) days. In Phase 2, the extent of exposure was also comparable for the five treatment groups with an overall mean exposure of 41.7 (5.5) days.

Post marketing data

The submission included the CIOMS suspected adverse reaction reports relating to co administration of ezetimibe and atorvastatin received by the manufacturer from 10 October 2005 to 22 May 2013. There were no CIOMS reports relating to the FDC product, as this product did not receive marketing approval until after the analysis of CIOMS reports.

The summary of clinical safety included a review of the CIOMS suspected adverse reaction reports. The summary indicated that a total of 2,142 spontaneous individual case reports (ICSRs) involving ezetimibe as suspect therapy and atorvastatin as a concomitant or secondary suspect therapy had been received from health care providers from the date of market introduction of ezetimibe on 17 October 2002 through to 1 April 2013. A total of 2,142 ICSRs were identified for this time period and the CIOMS reports accompanied this submission. Of the 2,142 cases, 613 (29%) were serious and 1,529 (71%) were non serious. Age was reported in 1,634 (76%) of the 2,142 cases, including 983 (60%) cases between 18 and 64 years of age, 647 (40%) cases ≥ 65 years of age, and 4 cases aged < 18 years of age. Gender was noted in 1,990 (93%) of the reports, including 1,117 (56%) reports in males and 873 (44%) reports in females.

The system organ class (SOC) with ≥ 10% of adverse drug reactions (ADRs) in decreasing order of frequency were: 'investigations' (32%; 687 events); 'musculoskeletal and connective tissue disorders' (29%, 612 events); 'gastrointestinal disorders' (21%, 451 events); 'general disorders and administration site conditions (21%, 444 events); 'nervous system disorders' (13%, 288 events); and 'skin and subcutaneous tissue disorders' (10%, 222 events).

The most commonly occurring serious ADRs reported in ≥ 1% of the 2,142 cases in decreasing order of frequency: were myalgia (3.5%, n = 75); rhabdomyolysis (2.4%, n = 52); blood Creatine kinase or creatine phosphokinase (CK) increased (2.1%, n = 46); drug interactions (1.5%, n = 33); ALT increased (1.5%, n = 32); AST increased (1.5%, n = 32); asthenia (1.3%, n = 28); muscle spasms (1.3%, n = 27); fatigue (1.2%, n = 25); muscle weakness (1.1%, n = 24); and pain in extremity (1.1%, n = 24).

Fatal outcomes were reported to be associated with hepatobiliary related ADRs (13 deaths), and myopathy related ADRs (5 deaths).

The ADRs by SOC for spontaneous ICSRs reported by health care professionals are summarised in the CER, and most commonly reported SOCs are summarised in the CER (see Attachment 2).

> **Comment**: The post marketing ADRs from ICSRs provided by health care providers for co administered ezetimibe and atorvastatin are consistent with the known safety profile for co administration of these two drugs. In addition, the post marketing ADRs are similar to the AE experience observed in the clinical trial program for co administration of the two drugs. No new or unexpected ADRs were observed in the submitted post marketing safety data.

Summary of clinical safety

In this submission, the updated integrated safety profile based on all patients in the core safety pool (CSP) included additional 6 week double blind data from Study P162 (Phase 1) for 120 patients treated with atorvastatin 20 mg and 480 patients treated with ezetimibe 10 mg + atorvastatin 10 mg. The updated CSP now includes data from 8 studies (compared with 7 studies in the composite pack submission), all of which recruited similar patient populations, had a double blind design and a duration of 6 to 14 weeks of active treatment. These 8 studies are P00692, P00693, P02173, P040, P079, P090, P112 and P162 (Phase 1). The CSP included a total of 5,169 randomised patients, and the key comparison was between the atorvastatin monotherapy group (n = 2521) including pooled doses from 10 to 80 mg, and the co administered ezetimibe 10 mg + atorvastatin group (n = 2,523) including pooled atorvastatin doses from 10 to 80 mg. The mean duration of treatment was 62 days (range: 1, 162 days) in the Atorva group and 62 days (range: 1, 136) days in the EZ 10 mg + Atorva group. In addition to the 5,044 patients in the two key treatment groups, the CSP also included information on 60 patients treated with placebo and 65 patients treated with ezetimibe 10 mg.

The safety profiles for the atorvastatin monotherapy group and the co administered ezetimibe 10 mg groups in the updated CSP do not substantially differ from those in the previously submitted and evaluated CSP. Furthermore, the safety profiles of these two groups are consistent with the safety profiles of the corresponding groups in the pivotal study (P162) and the two supportive studies (P185, P190). No new safety signals have emerged from the updated safety analysis in the CSP. There were no new long term safety data in the submission and there were no new safety data from studies exclusively in patients with HoFH.

The post marketing safety data were consistent with the known safety profile of co administered ezetimibe 10 mg and atorvastatin 10 to 80 mg.

First round benefit-risk assessment

First round assessment of benefits

There were no clinical efficacy and safety studies in the submission using the proposed ezetimibe/atorvastatin FDC tablet formulation to treat patients with hypercholesterolaemia. Therefore, the assessment of the benefits of the proposed FDC tablets for the proposed indications is based on the data from the pivotal study (P162) relating to co administration of the two medicines in patients with primary hypercholesterolaemia with high cardiovascular risk, the data from the two supportive studies (P185, P190) relating to co administration of the two medicines and to administration of the two medicines in FDC tablets in patients with primary

hypercholesterolaemia with low, moderate, or moderately high cardiovascular risk (excluding patients with CHD or CHD risk equivalent), and from the previously submitted and evaluated efficacy data provided to support registration of the fixed dose composite packs.

Based on the submitted clinical efficacy data in patients with hypercholesterolaemia and the bioavailability data from studies P391 and 392 in healthy volunteers, it is considered that clinically meaningful differences between the benefits of the proposed ezetimibe/atorvastatin FDC tablets and the known benefits of co administration of the two medicines are unlikely.

The benefits of treatment are discussed below:

- In the pivotal study (P162), percent reduction in LDL-C from baseline to Week 6 (Phase 1) was significantly greater in patients uncontrolled by prior treatment with atorvastatin 10 mg (5 week run in period) who had been switched to co administered ezetimibe 10 mg + atorvastatin 10 mg (n = 120) compared with patients whose atorvastatin dose had been doubled to 20 mg (n = 480): difference = - 12.7% (95% CI: - 16.6, - 8.7); $p < 0.001$.
- In the pivotal study (P162), percent reduction in LDL-C from baseline to Week 6 (Phase 1) was significantly greater in patients uncontrolled by prior treatment with atorvastatin 10 mg (5 week run in period) who had been switched to co administered ezetimibe 10 mg + atorvastatin 10 mg (n = 120) compared with patients who had been switched to rosuvastatin 10 mg (n = 939): difference = - 9.1% (95% CI: - 12.9, - 5.4); $p < 0.001$.
- In the pivotal study (P162), percent reduction in LDL-C from baseline to Week 6 (Phase 2) was significantly greater in patients uncontrolled by prior treatment with atorvastatin 10 mg (5 week run in) followed by atorvastatin 20 mg (6 week Phase 1) who had been switched to co administered ezetimibe 10 mg + atorvastatin 20 mg (n = 124) compared with patients whose atorvastatin dose had been doubled to 40 mg (n = 124): difference = - 10.5% (95% CI: - 15.9%, - 5.1); $p < 0.001$.
- In the pivotal study (P162), percent reduction in LDL-C from baseline to Week 6 (Phase 2) was significantly greater in patients uncontrolled by prior treatment with atorvastatin 10 mg (5 week run in) followed by rosuvastatin 10 mg (6 week Phase 1) who had been switched to co administered ezetimibe 10 mg + atorvastatin 20 mg (n = 231) compared with patients whose rosuvastatin dose had been doubled to 20 mg (n = 205): difference = - 9.5 (95% CI: - 13.6, - 5.5); $p < 0.001$.
- The pivotal study (P162) also showed that co administration of ezetimibe 10 mg + atorvastatin 10 mg achieved a significantly greater proportion of patients achieving target LDL-C levels of < 2.59 mmol/L and < 1.81 mmol/L at Week 6 (Phase 1) than both atorvastatin 20 mg and rosuvastatin 10 mg. Similarly, co administration of ezetimibe 10 mg + atorvastatin 20 mg achieved a significantly greater proportion of patients achieving target LDL-C levels of < 2.59 mmol/L and < 1.81 mmol/L at Week 6 (Phase 2) than both atorvastatin 40 mg and rosuvastatin 20 mg. In addition, the results in the pivotal study (P162) for percent changes from baseline in the secondary efficacy lipid/lipoprotein parameters at the end of Phase 1 and Phase 2 supported the results for the primary efficacy parameter analysis of percent change from baseline in LDL-C at these two time points.
- The two supportive equivalence studies showed that, based on percent change from baseline in LDL-C levels after 6 weeks treatment, FDC ezetimibe/atorvastatin 10/20 (n = 353) mg was equivalent to co administered ezetimibe 10 mg + atorvastatin 20 mg (n = 346) (Study P185), and FDC ezetimibe/atorvastatin 10/40 (n = 280) mg was equivalent to co administered ezetimibe 10 mg + atorvastatin 40 mg (n = 280) (Study

P190). In both studies, the difference in means (FDC minus co administered) for percent change in LDL-C from baseline after 6 weeks treatment was - 0.2%, and the 97.5% expanded CIs for the differences were well within the pre specified clinical equivalence limits of - 4% to + 4% (that is, - 1.7% to + 1.3% (Study P185) and - 1.9% to + 1.4% (Study P190)). In both supportive studies, the results for the secondary efficacy lipid/lipoprotein equivalence analyses supported the results for primary efficacy equivalence analyses (that is, percent reduction in LDL-C after 6 weeks treatment).

In the previously evaluated studies in patients with hypercholesterolaemia:

1. The factorial study (P00692) showed that in patients with primary hypercholesterolaemia co administered ezetimibe 10 mg + atorvastatin (pooled across doses 10 to 80 mg) was more effective than atorvastatin alone (pooled across doses 10 to 80 mg) in reducing LDL-C from baseline through to 12 weeks
2. The add on studies (P02173/P2246, P040) in patients with primary hypercholesterolaemia demonstrated that co administered ezetimibe 10 mg + atorvastatin (pooled across doses 5 to 80 mg) was more effective in reducing LDL-C than atorvastatin (pooled across doses 5 to 80 mg) alone, and that patients not at target LDL-C levels were more likely to achieve target LDL-C levels after co administered ezetimibe 10 mg + atorvastatin compared with atorvastatin alone
3. The add on titration studies in patients with hypercholesterolaemia (P079, P090, P112, P00693) demonstrated that the addition of ezetimibe 10 mg to atorvastatin was more effective in reducing LDL-C than atorvastatin alone even when the atorvastatin monotherapy dose was titrated upwards
4. The long term studies of co administered ezetimibe + atorvastatin was effective in achieving and maintaining reductions in LDL-C levels over 12 months in patients with primary hypercholesterolaemia (P2154, P1418)
5. Co administered ezetimibe + atorvastatin was effective for the treatment of homozygous familial hypercholesterolaemia (p1030, P1417).

First round assessment of risks

There were no clinical efficacy and safety studies in the submission using the proposed ezetimibe/atorvastatin FDC tablet formulations. Therefore, the assessment of the risks of the proposed FDC tablets is based on the data from the pivotal study (P162) relating to co administration of the two medicines in patients with primary hypercholesterolaemia and high cardiovascular risk, the data from the two supportive studies (P185, P190) relating to co administration of the two medicines and to administration of the two medicines in FDC tablets in patients with primary hypercholesterolaemia and low, moderate, or moderately high cardiovascular risk (excluding patients with CHD or CHD risk equivalent), from the updated safety data relating to co administration of the two medicines from the core safety pool (CSP) including 8 studies of 6 to 14 weeks duration, and from the previously submitted and evaluated safety data from the long term studies and the studies in patients with HoFH.

Based on the evaluation of the submitted clinical safety data in patients with hypercholesterolaemia and the bioavailability data from studies P391 and 392 in healthy volunteers, it is considered unlikely that there will be clinically meaningful differences in the risks of treatment with the proposed ezetimibe/atorvastatin FDC tablets compared with the known risks of treatment associated with co administration of the two medicines.

The risks of special interest observed in the pivotal study (P162), the two supportive studies (P185, P190) and the updated CSP are discussed below. There were no studies updating the risks of long term treatment or the risks of treatment in patients with HoFH.

However, there is no reason to believe that risks of treatment in patients with HoFH with the proposed FDC formulation will significantly differ from the known risks associated with co administration of the two medicines established for the composite packs.

Gastrointestinal disorders:

- The most frequently occurring risks of special interest were gastrointestinal disorders. The most commonly occurring specific gastrointestinal risks include diarrhoea, nausea, constipation and dyspepsia.
- In the pivotal study (P162, Phase 1), gastrointestinal related AEs were reported in 1.7% of patients in the EZ 10 mg + Atorva 10 mg group, 2.5% of patients in the Atorva 20 mg group and 2.0% of patients in the Rosuva 20 mg group. No specific gastrointestinal AEs were reported in ≥ 1.0% of patients in any of the four treatment groups.
- In the pivotal study (P162, Phase 2), gastrointestinal related AEs were reported in 1.6% of patients in both the Atorva 20 mg ® EZ 10 mg + Atorva 20 mg group and the Atorva 20 mg ® Atorva 40 mg group and in 0.9% of patients in the Rosuva 10 mg ® EZ 10 mg + Atorva 20 mg group and 1.0% of patients in the Rosuva 10 mg ® Rosuva 20 mg group. No specific gastrointestinal AEs were reported in ≥ 1.0% of patients in any of the four treatment groups. Doubling the doses of atorvastatin (co administered and monotherapy) or rosuvastatin from Phase 1 to Phase 2 did not increase the risks of gastrointestinal related AEs.
- In the supportive study (P185), gastrointestinal related AEs were reported in 4.4% of patients in the FDC 10/20 mg group and 3.6% of patients in the co administered 10 + 20 mg group. The only specific gastrointestinal AE reported in either treatment group in ≥ 1.0% of patients was dyspepsia (1.0% co administered versus 0.3% FDC).
- In the supportive study (P190), gastrointestinal related AEs were reported in 5.3% of patients in the FDC 10/40 mg group and 6.1% of patients in the co administered 10 + 40 mg group. Specific gastrointestinal AEs reported in either treatment group in ≥ 1.0% of patients (FDC versus co administered) were nausea (0.3% versus 1.9%), diarrhoea (1.0% versus 1.3%), vomiting (1.0% versus 0.3%), dyspepsia (0.3% versus 1.0%) and flatulence (1.0% versus 0%).
- In the CSP, the crude event rate for gastrointestinal disorders was 7.8% in the Atorva 10 to 80 mg group and 8.3% in the EZ 10 mg + Atorva 10 to 80 mg group, and the respective exposure adjusted exposure rates per 100 patient years were 38.28 and 40.14. The most commonly reported specific gastrointestinal AEs reported in ≥ 1.0% of patients in one or both treatment groups (Atorva 10 to 80 mg versus EZ 10 mg + Atorva 10 to 80 mg) were diarrhoea (1.5% versus 1.7%), nausea (1.6% versus 1.1%), constipation (1.1% versus 1.1%) and dyspepsia (1.0% versus 0.8%).

Allergic reaction/rash related adverse events:

- Risks of special interest related to allergic reactions/rash related AE were reported infrequently. The most commonly occurring specific risks of allergic reactions/rash related AEs include urticaria, rash, pruritis and hypersensitivity.
- In the pivotal study (P162, Phase 1), allergic reactions/rash related AEs were reported in no patients in the EZ 10 mg + Atorva 10 mg group, 0.4% in the Atorva 20 mg group and 0.9% in the Rosuva 10 mg group.
- In the pivotal study (P162, Phase 2), allergic reactions/rash related AEs were reported in no patients in the Atorva 20 mg ® EZ 10 mg + Atorva 20 mg group and 1 (0.8%) patient in the Atorva 20 mg ® Atorva 40 mg group (urticaria) and no patients in the

Rosuva 10 mg ® EZ 10 mg + Atorva 20 mg group and Rosuva 10 mg ® Rosuva 20 mg group.

- In the supportive study (P185), allergic reactions/rash related AEs were reported in 1.0% of patients in the both the FDC 10/20 mg group and the co administered 10+20 mg group. No specific events were reported in ≥ 1 patient in either treatment group. In the supportive study (P190), allergic reaction/rash related AEs were reported in 1.7% of patients in the FDC 10/40 group and 1.6% of patients in the co administered 10+40 mg group. Specific events reported in ≥ 2 patients in either treatment group were allergic rhinitis (n = 3) in the FDC 10/40 mg group and generalised pruritus (n=2) in the co administered 10 + 40 mg group.
- In the CSP, the crude event rate for allergic reaction/rash related AEs was 1.3% in both the Atorva 10 to 80 mg group and the EZ 10 mg + Atorva 10 to 80 mg group, and the respective exposure adjusted exposure rates per 100 patient years were 5.88 and 5.98. No allergic reaction/rash related AEs were reported in ≥ 1.0% of patients in either treatment group. Specific AEs reported in ≥ 0.2% of patients in one or both treatment groups (Atorva 10 to 80 mg versus EZ 10 mg + Atorva 10 to 80 mg) were urticaria (0.3% versus 0.2%), rash (0.2% versus 0.2%), pruritus (0.3% versus 0.2%) and hypersensitivity (0.1% versus 0.2%). Exposure adjusted event rates per 100 patient years for these specific events (Atorva 10 to 80 mg versus EZ 10 mg + Atorva 10 to 80 mg) were urticaria (1.28 versus 0.72), rash (1.09 versus 1.08), pruritis (1.46 versus 0.90) and hypersensitivity (0.55 versus 1.08).

Gall bladder related AEs:

- Gall bladder related AEs were reported infrequently, and the only specific events reported were cholelithiasis and cholecystitis.
- In the pivotal study (P162, Phase 1), gall bladder related AEs were reported in no patients in the EZ 10 mg + Atorva 10 mg, Atorva 20 mg or Rosuva 10 mg groups.
- In the pivotal study (P162, Phase 2), gall bladder related AEs were reported in no patients in the Atorva 20 mg ® EZ 10 mg + Atorva 20, Atorva 20 mg ® Atorva 40 mg, Rosuva 10 mg ® EZ 10 mg + Atorva 20 mg or Rosuva 10 mg ® Rosuva 20 mg groups.
- In the supportive study (P185), no gall bladder related AEs were reported in either the FDC 10/20 mg group or the co administered 10 + 20 mg group. In the supportive study (P190), gall bladder related AEs were reported in no patients in the FDC 10/40 mg group and 1 (0.3%) patient in the co administered 10 + 40 mg group (cholelithiasis).
- In the CSP, the crude event rate for gall bladder related AEs was < 0.1% (n = 1) in the Atorva 10 to 80 mg group (cholelithiasis) and 0.1% (n = 2) in the EZ 10 mg + Atorva 10 to 80 mg group (1 x cholecystitis, 1 x cholelithiasis).

Hepatitis related AEs:

- Hepatitis related AEs were reported infrequently and were limited to specific events of cholestasis, cholestatic hepatitis and hepatitis.
- In the pivotal study (P162, Phase 1), hepatitis related AEs were reported in no patients in the EZ 10 mg + Atorva 10 mg, Atorva 20 mg or Rosuva 10 mg groups.
- In the pivotal study (P162, Phase 2), hepatitis related AEs were reported in no patients in the Atorva 20 mg ® EZ 10 mg + Atorva 20, Atorva 20 mg ® Atorva 40 mg, Rosuva 10 mg ® EZ 10 mg + Atorva 20 mg or Rosuva 10 mg ® Rosuva 20 mg groups.
- In the supportive study (P185), no hepatitis related AEs were reported in either the FDC 10/20 mg group or the co administered 10+20 mg group. In the supportive study

(P190), no hepatitis related AEs were reported in either the FDC 10/40 mg group or the co administered 10 + 40 mg group.

- In the CSP, the crude event rate for hepatitis related AEs was 0.1% (n = 2) in the Atorva 10 to 80 mg group (2 x cholestasis), and < 0.1% (n = 1) in the EZ 10 mg + Atorva 10 to 80 mg group (1 x hepatitis).

Hy's law criteria for drug induced liver injury (DILI)

In the CSP, there were 2 (0.1%) patients in the EZ 10 mg + Atorva 10 to 80 mg group reported as meeting Hy's law criteria for DILI. There were no patients meeting Hy's law criteria for DILI in the pivotal study (P162) or either of the two supportive studies (P185, P190).

ALT and/or AST elevations

- In the pivotal study (P162, Phase 1), in the Rosuva 10 mg group, ALT and/or AST (consecutive) elevations ≥ 3 x upper limit of normal (ULN) were reported in 2 (0.2%) patients, ≥ 5 x ULN in 1 (0.1%) patient and ≥ 10 x ULN in 1 (0.1%) patient. No patients in the EZ 10 mg + Atorva 10 mg or Atorva 20 mg groups reported AST and/or AST elevations (consecutive) ≥ 3 x ULN, elevations ≥ 5 x ULN or elevations ≥ 10 x ULN.
- In the pivotal study (P162, Phase 2), ALT and/or AST (consecutive) elevations ≥ 3 x ULN were reported in 1 (0.8%) patient in Atorva 20 mg ® Atorva 40 mg group, 1 (0.4%) patient in the Rosuva 10 mg ® EZ 10 mg + Atorva 20 mg group and no patients in the Atorva 20 mg ® EZ 10 mg + Atorva 20 mg or Rosuva 10 mg ® Rosuva 20 mg groups. ALT and/or AST elevations ≥ 5 x ULN were reported in 1 (0.8%) patient in the Rosuva 10 mg ® EZ 10 mg + Atorva 20 mg group and no patients in the 3 other key treatment groups. ALT and/or AST elevations ≥ 10 x ULN were reported in 1 (0.4%) patient in the Rosuva 10 mg ® EZ 10 mg + Atorva 20 mg group and no patients in the 3 other key treatment groups.
- In the supportive study (P185), ALT (consecutive) elevations ≥ 3 x ULN were reported in 1 (0.3%) patient in both the FDC 10/20 mg group and the co administered 10+20 mg group, ALT elevations ≥ 5 x ULN were reported in no patients in the FDC 10/20 mg group and 1 (0.3%) patient in the co administered 10+20 mg group and ALT elevations ≥ 10 x ULN were reported in no patients in either treatment group. AST elevations (consecutive) ≥ 3 x were reported in 1 (0.3%) patient in both the FDC 10/20 mg group and the co administered 10+20 mg group, AST elevations ≥ 5 x ULN and ≥ 10 x ULN were reported in no patients in either treatment group.
- In the supportive study (P190), ALT elevations (consecutive) ≥ 3 x ULN were reported in 1 (0.3%) patient in the FDC 10/40 mg group and 2 (0.3%) patients in the co administered 10 + 40 mg group, ALT elevations ≥ 5 x ULN were reported in 1 (0.3%) patient in the FDC 10/40 mg group and no patients in the co administered 10 + 40 mg group, and ALT elevations ≥ 10 x ULN were not reported in either treatment group. There were no reports in either treatment group of AST elevations (consecutive) ≥ 3 x ULN, AST elevations ≥ 5 x ULN or AST elevations ≥ 10 x ULN.
- In the CSP, the data for ALT and/or AST elevations equal to or greater than specified levels for the Atorva 10 to 80 mg and EZ 10 mg + Atorva 10 to 80 mg groups are summarised below in Table 8.

Table 8: Number % of patients with post baseline values for ALT and AST greater than the upper limit of reference ranges – CSP.

ALT and/or AST	Atorva all (N=2467)	EZ 10 mg + Atorva all (N=2474)	Atorva all	EZ 10 mg + Atorva all
2 x ULN to < 3 x ULN	42 (1.7)	59 (2.4)	7.79	10.84
≥ 3 x ULN	17 (0.7)	22 (0.9)	3.13	4.01
≥ 3 x ULN, consecutive	11 (0.4)	14 (0.6)	2.02	2.54
≥ 5 x ULN	5 (0.2)	8 (0.3)	0.92	1.45
≥ 5 x ULN, consecutive	5 (0.2)	4 (0.2)	0.92	0.72
≥ 10 x ULN	0	2 (0.1)	0.0	0.36
≥ 10 x ULN, consecutive	0	1 (< 0.1)	0.0	0.18

Note: Consecutive includes those patients with (a) two consecutive measurements, (b) a single, last measurement, or (c) a measurement followed by a measurement that was taken more than 2 days after the last dose of study medication.

Creatine kinase (CK)elevations:

- CK elevations ≥ 10 x ULN, ≥ 10 x ULN with muscle symptoms and ≥ 10 x ULN with muscle symptoms considered drug related were reported infrequently.
- In the pivotal study (P162, Phase 1), CK elevations ≥ 10 x ULN, ≥ 10 x ULN with muscle symptoms and ≥ 10 x ULN with muscle symptoms considered drug related were reported in no patients in the EZ 10 mg + Atorva 10 mg, Atorva 20 mg or Rosuva 10 mg groups.
- In the pivotal study (P162, Phase 2), CK elevations ≥ 10 x ULN, ≥ 10 x ULN with muscle symptoms and ≥ 10 x ULN with muscle symptoms considered drug related were reported by no patients in the Atorva 20 mg ® EZ 10 mg + Atorva 20 mg, Atorva 20 mg ® Atorva 40 mg, Rosuva 10 mg ® EZ 10 mg + Atorva 20 mg, or Rosuva 10 mg ® Rosuva 20 mg groups.
- In the supportive study (P185), CK elevations ≥ 10 x ULN and ≥ 10 x ULN with muscle symptoms were each reported in 1 (0.3%) patient in the FDC 10/20 mg group and no patients in the co administered 10 + 20 mg group, and CK elevations ≥ 10 x ULN with muscle symptoms considered drug related were reported by no patients in either treatment group. In supportive study (P190), CK elevations ≥ 10 x ULN, ≥ 10 x ULN with muscle symptoms and ≥ 10 x ULN with muscle symptoms considered drug related were not reported in either the FDC 10/40 mg group or the co administered 10 + 40 mg group.

- In the CSP, CK elevations ≥ 10 x ULN were reported in 2 (0.1%) patients in the Atorva 10 to 80 mg group and no patients in the EZ 10 mg + Atorva 10 to 80 mg group, CK elevations ≥ 10 x ULN with muscle symptoms were reported in 1 (< 0.1%) patient in the Atorva 10 to 80 mg group and no patients in the EZ 10 mg + Atorva 10 to 80 mg group, and CK elevations ≥ 10 x ULN with muscle symptoms considered drug related were not reported in either treatment group.

First round assessment of benefit-risk balance

The benefit-risk balance of Atozet and Zeteze FDC (ezetimibe/atorvastatin as calcium) 10/10 mg, 10/20 mg, 10/40 mg and 10/80 mg tablets, given the proposed usage is favourable.

There were no clinical efficacy and safety studies in the submission using the FDC ezetimibe/atorvastatin formulation proposed for registration in patients with hypercholesterolaemia. However, based on the evaluation of the submitted clinical efficacy and safety data in patients with hypercholesterolaemia and the bioavailability data from Studies P391 and P392 in healthy volunteers, it can be reasonably inferred that the benefit-risk balance of the proposed FDC ezetimibe/atorvastatin formulation will be similar to the known favourable benefit-risk balance of co administration of the two medicines. The safety data provided in the submission for the ezetimibe/atorvastatin combination are consistent with the known risks associated with the two drugs and give rise to no new safety signals.

The proposed indications include patients with primary hypercholesterolaemia not adequately controlled on rosuvastatin alone or already being treated with rosuvastatin and ezetimibe. In the Pivotal study (P162), the percent reduction (M estimate) in the LDL-C level from baseline at the end of Phase 1 was statistically significantly greater in the EZ 10 mg + Atorva 10 mg group than in the Rosuva 10 mg group (- 22.2% versus - 13.0%, respectively; difference = - 9.1% (95% CI: - 12.9, - 5.4), $p < 0.001$). In addition, in the Pivotal study (P162), the percent reduction (M estimate) in the LDL-C level from baseline at the end of Phase 2 was statistically significantly greater in the Rosuva 10 mg ® EZ 10 mg + Atorva 20 mg group than in the Rosuva 10 mg ® Rosuva 20 mg group (- 17.1% versus - 7.5%, respectively; difference = - 9.5% (95% CI: - 13.6, - 5.5), $p < 0.001$). The pivotal study (P162) also demonstrated that the safety profile of co administered ezetimibe and atorvastatin did not markedly differ from that of rosuvastatin alone.

Based on the greater efficacy of co administration of ezetimibe and atorvastatin compared with rosuvastatin alone and the similar safety profiles of the two treatments, it can be reasonably inferred that the benefit risk profiles of the proposed FDC ezetimibe/atorvastatin as calcium tablets 10/10 mg, 10/20 mg, and 10/40 mg tablet will be superior to rosuvastatin monotherapy 10 mg, 20 mg, and 40 mg respectively. Therefore, it is considered that patients not adequately controlled on rosuvastatin alone can be safely switched to ezetimibe/atorvastatin FDC tablets with an expectation of superior benefits and no significant change in the risks.

However, for patients already treated with co administered rosuvastatin and ezetimibe, switching to the proposed ezetimibe/atorvastatin FDC tablet is more problematic. There were no pivotal efficacy and safety data comparing ezetimibe plus atorvastatin with ezetimibe plus rosuvastatin. Consequently, the benefit-risk balance for switching from rosuvastatin plus ezetimibe to atorvastatin plus ezetimibe cannot be satisfactorily determined. Furthermore, there were no data on the most appropriate dose of atorvastatin to be used in the ezetimibe/atorvastatin FDC tablet when switching from co administered rosuvastatin and ezetimibe. This is of particular importance as rosuvastatin at doses of 10 mg, 20 mg, and 40 mg reduces LDL-C levels to a significantly greater extent than atorvastatin at the corresponding doses.

First round recommendation regarding authorisation

It is recommended that Atozet fixed dose combination (ezetimibe/atorvastatin as calcium) 10/10 mg, 10/20 mg, 10/40 mg and 10/80 mg tablets be approved for:

> *Primary Hypercholesterolaemia*
>
> *Atozet/Zeteze is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia where use of a combination product is appropriate in those patients:*
>
> - *not appropriately controlled with atorvastatin, rosuvastatin or ezetimibe alone; or*
> - *already treated with atorvastatin and ezetimibe.*
>
> *Homozygous Familial Hypercholesterolaemia*
>
> *Atozet/Zeteze is indicated in patients with HoFH. Patients may also receive adjunctive treatments (e.g. LDL apheresis).*

It is recommended that Atozet FDC (ezetimibe/atorvastatin as calcium) 10/10 mg, 10/20 mg, 10/40 mg and 10/80 mg tablets be rejected for the treatment of patients with primary hypercholesterolaemia already treated with rosuvastatin and ezetimibe.

This indication should be rejected as there are no pivotal studies in the submission assessing the benefit-risk balance of switching from co administered ezetimibe and rosuvastatin to co administered ezetimibe and atorvastatin. In addition, the are no data in the submission relating to the most appropriate dose of atorvastatin to be used in the ezetimibe/atorvastatin FDC tablet when switching from co administered rosuvastatin and ezetimibe. This is of particular importance as rosuvastatin at doses of 10 mg, 20 mg, and 40 mg reduces LDL-C levels to a significantly greater extent than atorvastatin at the corresponding doses.

Clinical questions

Efficacy

1. Supportive Studies P185 and P190: In either of the two studies, did the percent change from baseline in LDL-C or other lipid/lipoprotein variables analysed by the analysis of covariance (ANCOVA) violate the assumption of normality? If so, please justify using the ANCOVA model in these circumstances rather than a robust regression analysis using M estimates with multiple imputation of missing values.
2. In Studies P185 and P190, analysis of the primary efficacy endpoint of percent change from baseline in LDL-C (mmol/L) was based on an ANCOVA repeated measures model in the per-protocol (PP) population with covariate terms for treatment, baseline LDL-C, period and sequence. In the analyses, statistically significant covariate effects were seen for baseline LDL-C ($p < 0.001$) in both studies and period ($p = 0.011$) in Study P185. Please comment on clinical significance of the statistically significant covariate effects observed in the primary analyses in both studies.

Safety

1. Please provide the definitions for consecutive ALT and/or AST elevations ≥ 5 x ULN and ≥ 10 x ULN used in the summary of safety for Tier 1 events occurring in the relevant patient populations (for example, CSP). The definitions of the identifying superscripts for these elevations provided in the explanatory notes immediately

under all relevant tables for Tier 1 events in the clinical summary appear to be incorrect as they relate to consecutive ≥ 3 x ULN elevations.

Second round evaluation of clinical data submitted in response to questions

Sponsor's response to clinical questions

Details of the sponsor's response and the evaluator comments on these responses are detailed in Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

No new clinical information was submitted in response to the clinical questions. Accordingly, the benefits of the proposed ezetimibe/atorvastatin FDC tablet formulations to treat patients with hypercholesterolaemia are unchanged from those identified in the first round assessment of benefits.

Second round assessment of risks

No new clinical information was submitted in response to the clinical questions. Accordingly, the risks of the proposed ezetimibe/atorvastatin FDC tablet formulations to treat patients with hypercholesterolaemia are unchanged from those identified in first round assessment of risks.

Second round assessment of benefit-risk balance

The benefit-risk balance of Atozet fixed dose combination (ezetimibe/atorvastatin as calcium) 10/10 mg, 10/20 mg, 10/40 mg and 10/80 mg tablets, given the proposed usage is favourable.

Second round recommendation regarding authorisation

It is recommended that Atozet fixed dose combination (ezetimibe/atorvastatin as calcium) 10/10 mg, 10/20 mg, 10/40 mg and 10/80 mg tablets be approved for:

Primary Hypercholesterolaemia

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

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

Homozygous Familial Hypercholesterolaemia

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

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP) Core RMP Version 1.0 (dated 26 September 2013); and an Australian Specific Annex (ASA) dated 30 October 2013.

Subsequently the sponsor then submitted the EU-RMP Version 1.0 (dated 11 September 2013) with justification for differences from the Core RMP in their correspondence dated 11 December 2013. It is in this context that these documents have been reviewed in this report.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 9.

Table 9. Summary of Ongoing Safety Concerns.

Ongoing Safety Concerns	
Important Identified Risks	Rhabdomyolosis/myopathy Abnormal Liver Function Hypersensitivity
Important Potential Risks	Cholecystitis/cholelithiasis Pancreatitis Interstitial lung disease Increased Haemoglobin A1c and fasting serum glucose Haemorrhagic stroke
Important Missing Information	Exposure during pregnancy and lactation Use in children less than 18 years of age Use in patients with moderate or severe hepatic impairment

Pharmacovigilance plan

Routine pharmacovigilance activities are proposed.

Risk minimisation activities

Routine risk minimisation activities are proposed.

Reconciliation of issues outlined in the RMP report

Table 10 summarises the Post Market Surveillance Branch (PSMB's) first round evaluation of the RMP, the sponsor's responses to issues raised by the PSMB and the PSMB's evaluation of the sponsor's responses.

Table 10. Reconciliation of issues outlined in the RMP report.

Recommendation in RMP evaluation report	Sponsor's response	PSMB evaluator's comment
It is acknowledged that the sponsor has attempted to provide a comparison of the draft Australian PI to the draft EU SmPC[7] in the Australian Safety Annex (ASA). However, in this context the initial submission of the Core RMP instead of the EU-RMP would appear to have added an unnecessary layer of complexity to the evaluation. The subsequent submission of the EU-RMP necessitated the need to identify and justify any differences between this document and the Core RMP. It is the TGA's view that the concurrent submission of more than one RMP document does not lend itself to expeditious evaluation.	The sponsor states: 'MSD acknowledges the complexity and, hence, difficulty this action raised. It is MSD's intent to present the sponsor's Core position on safety in a product's RMP. However, where a country or territory disagrees with the sponsor's position and requires additional risks and/or different interpretations of a risk, as occurred with the ezetimibe/atorvastatin RMP, the need arises to meet those requests in that country or territory. Similar to a CCDS[8], which does allow for occasional country-specific labelling differences, the Core RMP reflects MSD's interpretation of the overall safety profile for one of its products. As the TGA assessor did not request changes to the list of risks in our Core RMP, there appears to be agreement with the sponsor's risk selections. However, MSD will comply with the TGA's preference and provide Australia with the EU RMP for future submissions.'	This is acceptable.
Since the ASA references the EU-RMP, the former should be revised to include justification for the differences in the summary of the Ongoing Safety Concerns observed between these documents.	The sponsor states: 'The ASA has been revised to include justification for the differences between the summary of Ongoing Safety Concerns in the EU-RMP and the ASA. A	This is acceptable.

[7] EU SmPC; European Union summary of product characteristics.
[8] CCDS is a company core data sheet.

Recommendation in RMP evaluation report	Sponsor's response	PSMB evaluator's comment
	summary of the differences has been included in the Australian Specific Risk Minimisation Plan'.	
At this time there are no objections to the pharmacovigilance activities proposed by the sponsor. Nevertheless Table 1– 'Summary of the AUS RMP' of the ASA should be amended to indicate routine pharmacovigilance is proposed to monitor the important identified risk: 'Abnormal liver function'.	The sponsor has made this amendment.	This is acceptable.
At this time the specified ongoing safety concerns would not appear to warrant additional risk minimisation activities, therefore the sponsor's conclusion that routine risk minimisation activities for all the specified ongoing safety concerns are sufficient is acceptable.	The sponsor acknowledges and accepts this recommendation.	n/a
At this time the sponsor's handling of the potential for medication errors using routine pharmacovigilance and risk minimisation activities is acceptable.	The sponsor acknowledges and accepts this recommendation.	n/a
At this time the sponsor's proposed application of routine risk minimisation activities would appear to be in general reasonable and therefore acceptable. Nevertheless as previously mentioned the sponsor should not just identify, but also provide reasons for any differences between the EU-RMP and the local implementation of risk management activities in the ASA, for example: any differences between the risk minimisation activities undertaken as reflected in the	The sponsor states: 'The ASA has been amended to include reasons for differences between the content of the EU SmPC and the proposed Australian PI.' These amendments are reflected in Table 2 – 'Summary of differences relating to ongoing safety concerns between the Proposed PI and the EU SPC' of the ASA.	In the main where these differences occur the sponsor now states: 'AU PI reflects the approved prescribing information for ezetimibe and atorvastatin in Australia.' This is not considered to be an explanation for such differences particularly where it appears the EU SmPC is more restrictive than the proposed Australian PI, but

Recommendation in RMP evaluation report	Sponsor's response	PSMB evaluator's comment
content of the EU SmPC and the proposed Australian PI.		rather a statement of fact. Consequently this remains an outstanding recommendation that should be adequately addressed before this application is approved.

Summary of recommendations

Outstanding issues

In regard to Table 2 – 'Summary of Differences relating to ongoing safety concerns between the Proposed PI and the EU SPC' of the ASA, the sponsor was asked to not just identify, but also provide reasons for any differences between the EU-RMP and the local implementation of risk management activities in the ASA, for example: any differences between the risk minimisation activities undertaken as reflected in the content of the EU SmPC and the proposed Australian PI. The sponsor now states: 'The ASA has been amended to include reasons for differences between the content of the EU SmPC and the proposed Australian PI.' However, in the main where these differences occur the sponsor now states: 'AU PI reflects the approved prescribing information for ezetimibe and atorvastatin in Australia.' This is not considered to be an explanation for such differences particularly where it appears the EU SmPC is more restrictive than the proposed Australian PI, but rather a statement of fact. Consequently this remains an outstanding recommendation that should be adequately addressed before this application is approved.

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

ACSOM advice was not sought for this submission. Key changes to the updated RMP

In their response to the TGA request for information the sponsor provided an updated ASA (dated 13 June 2014). Key changes from the version evaluated at Round 1 are summarised in Table 11 below:

Table 11. Key changes to the RMP

RMP Updates
Addition of a tabular 'The Summary of Ongoing Safety Concerns on which the Australian Specific Risk Minimisation Plan is based differs from the EU Summary of Ongoing Safety Concerns' in Section 3.1: 'Australian specific risk minimisation plan'.

Suggested conditions of registration

Implement The European Risk Management Plan (Version 1.0, dated 11 September 2013), with an ASA (dated 13 June 2014) to be revised as agreed by the TGA.

VI. Overall conclusion and risk/benefit assessment

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

Product background

The intention of the current application is to replace the composite pack of Atozet; ezetimibe and atorvastatin calcium with the FDC pack. The currently approved indications for the composite pack were based on those for Vytorin (ezetimibe/simvastatin) (see Introduction to the Submission) and are consistent with the indication proposed for this FDC, with the exception that the FDC indication also proposes the inclusion of patients with primary hypercholesterolaemia not appropriately controlled with rosuvastatin.

The composite pack application did not contain new PK, PD or clinical data. The clinical evaluator of the composite pack summarised data from the PIs of the individual products and from CERs for ezetimibe (Ezetrol) and the original (withdrawn) ezetimibe/atorvastatin FDC tablet (see next paragraph below). The studies submitted in the original registration/marketing application for Ezetrol were: 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. These data were considered sufficient from a safety and efficacy perspective to register the Atozet composite pack and Zeteze composite pack.

The studies included in this application were: 5 short term studies (P2173R, P040, P079, P090, P112) and 2 long term studies (P2154 (extension of P0692) and P1418 (extension of Study P0693.Ezetimibe/atorvastatin calcium trihydrate has been approved for this indication in the USA (Liptruzet) with slightly different wording (see *Regulatory status* above). When Liptruzet was first approved (May 2013) it contained the previous FDC formulation of atorvastatin. The FDC formulation proposed in this submission was recently approved for Liptruzet (May 2014).

All but one of the clinical efficacy and safety studies (P162) has previously been evaluated by the TGA in relation to at least one of the original Ezetrol, the Atozet composite pack, or previous Atozet FDC submissions (see Table 12). In addition, 2 new supportive Phase III clinical efficacy and safety studies (P185, P190) were included at the request of the Delegate during a pre submission consultation. These studies compared the efficacy and safety of the previous formulation of the Atozet 10/20 mg and 10/40 mg FDC tablets with co administration of the corresponding strength individual tablets (ezetimibe and Lipitor) in patients with primary hypercholesterolaemia.

Table 12: Comparison of the Clinical Data Packages for the composite pack and FDC of ezetimibe and atorvastatin (based on tabular listing of all clinical studies and CSRs)

Study No and Name	Composite Pack Application	Previous FDC Application	Current FDC Application
BA and Comparative BA and bioequivalence study reports			
P145: A study to evaluate the definitive bioequivalence of MK-0653C[9] with marketed	ü	ü	X

Study No and Name	Composite Pack Application	Previous FDC Application	Current FDC Application
products			
P146: An open label, randomised, 2 period crossover study to compare the effects of food on MK-0653C[9] in healthy adult subjects	ü	ü	X
MK-9396/ P001: An open label, randomised, single dose, 3 period, balanced crossover study to compare the pharmacokinetic profiles of 3 formulations of atorvastatin in healthy young adult subjects	ü	ü	X
P183: A study to evaluate the definitive bioequivalence of MK-0653C with U.S. marketed products	ü	ü	X
P391: A single dose, full replicate comparative bioavailability study of two formulations of ezetimibe/atorvastatin Calcium 10 mg/10 mg FDC Tablets versus Ezetrol administered with Lipitor under fasting conditions	X	X	ü
P392: A single dose, full replicate comparative bioavailability study of two formulations of ezetimibe/atorvastatin Calcium 10 mg/80 mg FDC tablets versus. Ezetrol administered with Lipitor under fasting conditions	X	X	ü
P415: A Study of the Comparative Fed and Fasted Bioavailability of MK-0653C[9] 10/80 mg in Healthy Subjects	X	X	ü
P1887: Bio-analytical report: a study of the comparative fed	X	X	ü

Study No and Name	Composite Pack Application	Previous FDC Application	Current FDC Application
and fasted. bioavailability of MK-0653C[9] 10/80 mg in healthy subjects (MK-0653C PN415-00), 2013.			
P1888: Bio-analytical report: A single dose, full replicate, comparative bioavailability study of two formulations of ezetimibe/atorvastatin calcium 10 mg – 10 mg FDC tablets versus ezetrol administered with Lipitor under fasting conditions (Protocol 391-00), 20-Jul-2012	X	X	ü
P1889: Bio-analytical report: A single dose, full replicate, comparative bioavailability study of two formulations of ezetimibe/atorvastatin calcium 10 mg – 80 mg FDC tablets versus ezetrol administered with Lipitor under fasting conditions (Protocol 392-00), 20-Jul-2012.	X	X	ü
Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials			
P460 - Schering-Plough clinical study report, single site study: SCH 58235: assessment of a multiple dose drug interaction between SCH 58235 (ezetimibe) and atorvastatin in healthy volunteers (Protocol No. P00460), 12-Jul-2001	X	X	ü
Efficacy and Safety Studies			
P112: 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 to 40 mg in elderly patients with hypercholesterolemia at high	ü	ü	ü

[9] MK-0653C is FDC ezetimibe/atorvastatin calcium (proposed form)

Study No and Name	Composite Pack Application	Previous FDC Application	Current FDC Application
risk for CHD			
P090 – Titration study to evaluate and compare the efficacy and safety of ezetimibe added on to atorvastatin 40 mg versus up titration to atorvastatin 80 mg in hypercholesterolemia patients at high risk for CHD not adequately controlled on atorvastatin 40 mg	ü	ü	ü
P079 – titration study to evaluate and compare the efficacy and safety of ezetimibe added on to atorvastatin 20 mg versus up titration to atorvastatin 40 mg in hypercholesterolemia patients at moderately high risk for CHD	ü	ü	ü
P040 – 6-week study to evaluate the efficacy and safety of ezetimibe 10 mg/day when added to ongoing therapy with a statin versus statin therapy alone, in patients with hypercholesterolemia who have not reached national cholesterol education program adult treatment panel III target LDL-cholesterol level.	ü	ü	ü
P2173 - A multicentre, double blind, randomised, placebo controlled study to evaluate the lipid-altering efficacy, safety, and tolerability of SCH 58235 (ezetimibe) when added to ongoing therapy with an HMG-CoA reductase inhibitor (statin) in patients with primary hypercholesterolemia, known CHD, or multiple cardiovascular risk factors	ü	ü	ü
P2173R – Reversibility phase of P2173/2246: A double blind, placebo controlled study to	ü	ü	ü

Study No and Name	Composite Pack Application	Previous FDC Application	Current FDC Application
evaluate the lipid altering efficacy, safety, and tolerability of ezetimibe 10 mg when added to ongoing therapy with statin in patients with primary hypercholesterolemia, known CHD or multiple cardiovascular risk factors			
P2154 – Long term, safety and tolerability study of ezetimibe or placebo in addition to atorvastatin in subjects with primary hypercholesterolaemia (extension of P692)	ü	ü	ü
P1417 – Long term, open label, safety and tolerability study of ezetimibe in addition to atorvastatin or Simvastatin in the therapy of homozygous familial hypercholesterolaemia (extension of P1030)	ü	ü	ü
P1418 – Long term, open label, safety and tolerability study of ezetimibe in addition to atorvastatin in subject with CHD or multiple risk factors and with primary hypercholesterolaemia not controlled by a starting dose (10 mg) of atorvastatin (extension of P693)	ü	ü	ü
P162 – A randomised, double blind, active controlled, multicentre study of patients with primary hypercholesterolaemia and high cardiovascular risk who are not adequately controlled with atorvastatin 10 mg: A comparison of the efficacy and safety of switching to co administration ezetimibe and atorvastatin versus doubling the dose of atorvastatin or switching to Rosuvastatin	X	X	ü

Study No and Name	Composite Pack Application	Previous FDC Application	Current FDC Application
(Parts 1 - 4)			
P692 / P692a- A Phase III double-blind efficacy and safety study of ezetimibe (SCH 58235) 10 mg in addition to atorvastatin compared to placebo in subjects with primary hypercholesterolemia (Protocol P00692) - Part 1 and Part 2 (see also P2154 – extension study)	ü	ü	ü
P693/ P693a/ P693b - A double blind, double dummy safety and efficacy study of ezetimibe in addition to atorvastatin in subjects with hypercholesterolemia not controlled by starting dose atorvastatin (Part 1 , Part 2 and Part 3)	ü	ü	ü
P1030 /P1030a - A Phase III efficacy and safety study of SCH 58235 (10 mg) in addition to atorvastatin or Simvastatin in the treatment of homozygous familial hypercholesterolemia - Part 1 and Part 2	ü	ü	ü
P185 - MRL CSR: A randomised, double blind, active controlled, multicentre, crossover study to evaluate the efficacy and safety of ezetimibe/atorvastatin 10 mg/20 mg FDC Tablet compared to co administration of marketed ezetimibe 10 mg and atorvastatin 20 mg in patients with primary hypercholesterolemia - Part 1 and Part 2	X	X	ü
P190 - MRL CSR: A randomised, double blind, active controlled, multicentre, crossover study to evaluate the efficacy and safety of ezetimibe/atorvastatin 10 mg/40 mg FDC tablet	X	X	ü

Study No and Name	Composite Pack Application	Previous FDC Application	Current FDC Application
compared to co administration of marketed ezetimibe 10 mg and atorvastatin 40 mg in patients with primary hypercholesterolemia			

Quality

The quality evaluator has recommended approval for the FDC of ezetimibe/atorvastatin 10/10, 10/20, 10/40 and 10/80 mg tablets. The proposed tablets are unscored, film-coated, bilayer tablets intended to provide immediate release. The tablets are moderately large with the smallest being 12.74 mm by 5.10 mm and the largest being 19.05 mm by 7.94 mm for the 10/80 mg strength. The evaluator comments that '*there is public information suggesting that the proposed formulation of atorvastatin in the FDC will have more consistent particle behaviour and better chemical stability*' (than the previous atorvastatin formulation).

Two bioequivalence studies and a food effect study were submitted (P392, P392, P415). The 10/10 mg and 10/80 mg FDC tablets (proposed formulation)were demonstrated to be bioequivalent to the corresponding co administered strengths of separate ezetimibe (Australian registered product) and atorvastatin (UK Lipitor, but identical to the Australian registered product). Bioequivalence studies of the intermediate 10/20 and 10/40 mg strengths were not conducted, and the sponsor stated that they were not required '*given formulation similarities and dissolution comparisons*'. The evaluator stated that '*Limited in vitro data for the 10/20 and 10/40 strengths are consistent with similar drug release from all of the proposed tablet strengths'* and concluded that the *'limited data are consistent with bioequivalence of the four proposed tablet strengths'*.

Bioequivalence studies of the intermediate 10/20 and 10/40 mg strengths were not conducted, and the sponsor argued that this was in line with the EU guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr)[10] The clinical evaluator considered '*that comparative bioavailability studies for the proposed FDC intermediate strength tablets of 10/20 mg and 10/40 mg are not required*'. This is considered acceptable by the Delegate.

A high fat breakfast slightly increased (approximately 4%) atorvastatin $AUC_{0-\infty}$, decreased C_{max} by approximately 7%, and delayed T_{max} by approximately 1.25 hours. Food had no effect on the AUC of unconjugated ezetimibe, increased C_{max} by approximately 3%, and delayed T_{max} by approximately 0.75 hours. Food increased the total ezetimibe AUC_{0-last} by approximately 2%, increased C_{max} by approximately 15%, and delayed T_{max} by approximately 0.50 hours. These effects are consistent with published data for the reference products.

Nonclinical

No significant new nonclinical data were submitted. Nonclinical data supporting the combination use of ezetimibe and atorvastatin calcium trihydrate (proposed formulation) were previously evaluated. These data showed minimal PK interactions, except at very

[10] CPMP/QWP/EWP/1401/98 Rev 1 Guideline on the Investigation of Bioequivalence:

high combination doses of both drugs (ezetimibe 1000 mg/kg/day; atorvastatin 50 to 100 mg/kg/day) and toxicity findings generally represented enhancement of changes elicited by the statins alone or changes that may be expected with increased statin exposure. The liver was the main target organ of toxicity.

In a previously evaluated pharmacodynamic study in dogs an increased LDL-C lowering ability of the FDC compared to atorvastatin or ezetimibe alone was demonstrated, consistent with findings in the clinical trial data.

The nonclinical evaluator concluded that there were no non-clinical objections to the registration of Atozet ezetimibe/atorvastatin (as calcium trihydrate) FDC pack.

Clinical

The clinical evaluator has recommended approval for ezetimibe/atorvastatin as calcium trihydrate for the proposed indications.

Pharmacology

The three bioequivalence studies noted the following findings:

Studies P391/P392

Studies P391/P392: Ezetimibe/atorvastatin calcium 10 mg/10 mg FDC tablets (proposed formulation) were bioequivalent to co administered Ezetrol (ezetimibe) 10 mg tablets plus Lipitor (atorvastatin) 10 mg tablets after a single dose in healthy volunteers under fasting conditions. The 90% CIs for unconjugated and total ezetimibe, and atorvastatin GMR values for $AUC_{(t)}$, $AUC_{(inf)}$ and C_{max} are within the standard bioequivalence interval of 80.00 to 125.00%. Similar results were noted for ezetimibe/atorvastatin calcium 10 mg/80 mg FDC tablets (proposed formulation) which were bioequivalent to co administered ezetimibe 10 mg tablets plus Lipitor 80 mg tablets. From a clinical perspective the evaluator considered that comparative bioavailability studies for the proposed FDC intermediate strength tablets of ezetimibe/atorvastatin 10/20 mg and 10/40 mg are not required '*given the robustness of the comparative bioavailability data for the 10/10 mg strength and the 10/80 mg strength'*.

Study P415

Study P415: Ezetimibe/atorvastatin calcium 10 mg/80 mg FDC tablets were bioequivalent to co administered ezetimibe 10 mg tablets plus atorvastatin 80 mg tablets in the fed and fasted state in healthy volunteers. The 90% CIs for unconjugated and total ezetimibe, and atorvastatin GMR values for $AUC_{(t)}$, and $AUC_{(inf)}$ are within the standard bioequivalence interval of 80.00 to 125.00%. While the 90% CIs for unconjugated and total ezetimibe, and atorvastatin GMR values for C_{max} were outside these levels, because the absolute difference in GMR values were relatively small (3.3 to 15%), the evaluator considered the differences unlikely to be clinically significant.

Study P460

Study P460: This Phase I, PK/PD study was previously evaluated in the submission to support the registration of ezetimibe. The primary objectives were to investigate the safety, tolerance and pharmacodynamic effects of co administered ezetimibe 10 mg tablets and atorvastatin (Atorva) 10 mg tablets for 14 days in healthy subjects with hypercholesterolaemia, and the secondary objectives were to evaluate the potential PK drug interaction of ezetimibe on atorvastatin. The co administration of atorvastatin and ezetimibe reduced LDL-C to a greater extent than either drug alone or placebo. Plasma atorvastatin, orthohydroxy atorvastatin, total ezetimibe, ezetimibe, and conjugated

ezetimibe exposures were similar following co administration of Atorva 10 mg + ezetimibe 10 mg and those following administration of Atorva or ezetimibe 10 mg alone.

Efficacy

New Studies

Study P162

Study P162 was a Phase III, multinational, multicentre, randomised, double blind, active controlled, two phase efficacy and safety study of co administered ezetimibe 10 mg and Atorva 10 mg versus Atorva 20 mg or rosuvastatin (Rosuva) 10 mg in approximately 1,508 patients with primary hypercholesterolaemia at high cardiovascular risk and not adequately controlled with Atorva 10 mg alone during the run in period of the study. The LDL-C criteria for inclusion in the study were levels ≥ 2.59 mmol/L and ≤ 4.14 mmol/L. The study was conducted over 18 weeks: a 6 week screening/run in and a 12 week DB treatment period (2 phases, each of 6 weeks duration). To be eligible for screening, patients were either naïve to, or currently on a statin, ezetimibe, or statin + ezetimibe combination with LDL-C lowering efficacy equivalent to or less than Atorva 10mg, and with an LDL-C screening value within the protocol specified range. At the end of Phase 1, patients whose LDL-C remained inadequately controlled (as per inclusion criteria), continued into Phase 2 as per the Table 7 above.

The primary efficacy endpoint of percent change from baseline (M Estimate) in LDL-C at the end of Phase 1 (after 6 weeks treatment) in the Full Analysis Set (FAS) was:

- - 9.5% in the Atorva 20 mg monotherapy treatment group
- - 13.0% in the Rosuva 10 mg monotherapy treatment group
- - 22.2% in the ezetimibe 10 mg + Atorva 10 mg co administration treatment group (difference - 9.1%, 95% CI - 12.9, - 5.4%; p < 0.001 versus. Rosuva 10 mg; difference - 12.7%, 95% CI - 16.6, - 8.7%; p < 0.001 versus. Atorva 20 mg).

Results were generally consistent in the subgroup analyses (gender, age (< 65 versus ≥ 65 years), race (White versus Non-White), and diabetic status (diabetic, metabolic syndrome without diabetes, neither).

The secondary efficacy endpoint, of percent change from baseline (M Estimate) in LDL-C at the end of Phase 2 (6 weeks after treatment was switched) in the FAS was:

- - 17.4% in the Atorva 20 mg ⟶ ezetimibe 10 mg + Atorva 20 mg treatment group
- - 6.9% in the Atorva 20 mg ⟶ Atorva 40 mg treatment group
- - 17.1% in the Rosuva 10 mg ⟶ ezetimibe 10 mg + Atorva 20 mg treatment group
- - 7.5% in the Rosuva 10 mg ⟶ Rosuva 20 mg treatment group
- - 10.5% in the Atorva 20 mg ⟶ ezetimibe 10 mg + Atorva 20 mg treatment group versus. the Atorva 20 mg ⟶ Atorva 40 mg treatment group (95% CI - 15.9, - 5.1%; p < 0.001)
- - 9.5% in the Rosuva 10 mg ⟶ ezetimibe 10 mg + Atorva 20 mg treatment group versus the Rosuva 10 mg ⟶ Rosuva 20 mg treatment group (95% CI - 13.6, - 5.5%; p < 0.001).

Results for the majority of the other secondary efficacy endpoints (the percentage of patients who reached target LDL-C levels of < 2.59 mmol/L and < 1.81 mmol/L at endpoint; and percent change from baseline to endpoint in TC, TG, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, LDL-C/HDL-C ratio, TC/HDL-C ratio, non-HDL-C/HDL-C ratio, Apo B, Apo A-I, Apo B/Apo A-I ratio and high sensitivity C-reactive

protein (hs-CRP) were supportive. The majority of lipid/lipoprotein parameters were statistically significantly superior in the co administered ezetimibe 10 mg + Atorva 10 mg group compared with either the Atorva 20 mg group or the Rosuva 10 mg group in Phase 1, and in the group switching from Rosuva 10 mg to ezetimibe 10 mg + Atorva 20 mg compared with the group who doubled their dose of Rosuva (from 10 mg to 20 mg) in Phase 2. More than half the lipid/lipoprotein parameters were statistically significantly superior in the group that added ezetimibe 10 mg to their previous dose of Atorva (20 mg) compared with the group that doubled their dose of Atorva (from 20 mg to 40 mg). In Phase 1, a significantly higher percentage of patients on ezetimibe 10 mg + Atorva 10 mg reached an LDL-C < 2.59 mmol/L compared with Atorva 20 mg or Rosuva 10 mg (56.3% versus 37.4% versus 43.6%). A similar result was seen for the percentage of patients reaching LDL-C < 1.81 mmol/L (19.3% versus 3.0% versus 6.6%). In Phase 2, patients switched from statin monotherapy to statin plus ezetimibe were significantly more likely to reach both target LDL-C levels than those whose dose of statin was doubled.

Studies P185 and P190

These two supportive studies were of identical design, apart from the strength of the ezetimibe/Atorva FDC product (previous formulation) being assessed (10/20 mg in Study P185 and 10/40 mg in Study P190). Both studies were Phase II, multicentre USA, randomised, double blind, active controlled, two period crossover efficacy and safety studies of co administered ezetimibe and Atorva (10 + 20 mg or 10 + 40 mg, respectively) versus the FDC of ezetimibe/Atorva (10/20 mg or 10/ 40 mg, respectively) in approximately 676 patients (376 in P185, 300 in P190) with primary hypercholesterolaemia at low, moderate, or moderately high cardiovascular risk and naïve to lipid lowering agents or currently taking allowable statin or ezetimibe-statin combination therapy from which they could be washed off and switched to study medication. The studies were conducted over 25 weeks: a 5 week washout, a 2 week single blind placebo run in period, and two 6 week treatment periods separated by a 6 week single blind placebo washout period.

The primary efficacy endpoint of percent change from baseline (LS Mean) in LDL-C after 6 weeks treatment in the PP population was:

Study P185:

- - 54.0% in the ezetimibe/Atorva 10/20 mg FDC treatment group.
- - 53.8% in the ezetimibe + Atorva 10 + 20 mg co administration treatment group (difference - 0.2%, 97.5% expanded CI - 1.7, 1.4).

Study P190:

- - 58.9% in the ezetimibe/Atorva 10/40 mg FDC treatment group.
- - 58.7% in the ezetimibe + Atorva 10 + 40 mg co administration treatment group (difference - 0.2%, 97.5% expanded CI - 1.8, 1.4).

Analyses in the FAS were consistent with the primary analyses and were generally consistent in subgroup analyses where a meaningful number of patients were included.

Results for the secondary efficacy variables (percent changes from baseline in: TC; TG; HDL-C; non-HDL-C; and Apo B after 6 weeks of treatment) were generally consistent with the primary efficacy variable results (difference in LS Means ranged from - 0.3 to +1.5%).

Previously evaluated studies

The summaries for these studies were extracted/modified from Delegate's request for ACPM Advice for the ezetimibe/atorvastatin composite pack application and confirmed from summaries in current CER (see Attachment 2).

Primary hypercholesterolaemia

Study P0692:

Study P0692 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, Atorva 10, 20, 40 or 80 mg alone or ezetimibe 10 mg plus one of Atorva 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 Atorva monotherapy groups and from the four Atorva plus ezetimibe groups. The addition of ezetimibe to Atorva (pooled across all doses) was more effective than Atorva alone (pooled across all doses, $p < 0.01$) or ezetimibe alone ($p < 0.01$) in reducing LDL-C levels. The addition of ezetimibe to each of the individual doses of Atorva was also more effective than the corresponding dose of Atorva monotherapy in reducing LDL-C (incremental mean % change ranged from approximately - 8.3% to - 15%, $p < 0.01$ for each comparison). It was also found that the addition of ezetimibe 10 mg to Atorva 10 mg or 20 mg resulted in a significantly greater mean percent reduction in LDL-C than the next higher dose of Atorva monotherapy (20 mg and 40 mg, respectively).

Study P2173/2246

Study P2173/2246 was an 8 week randomised, double blind, placebo controlled multicentre study which assessed the effect of adding ezetimibe 10 mg to existing statin therapy (dose not specified, but maintained throughout the study) in 769 patients with primary hypercholesterolaemia with CHD 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). Efficacy was demonstrated across the statin subgroups, including Atorva. The percentage reductions in LDL-C from baseline to endpoint were - 25% versus - 4% and the percentages of patients attaining target LDL-C at Week 8 were 72% versus 27% in the ezetimibe + Atorva and placebo + Atorva sub groups respectively. Following the extra 6 week reversibility phase, that is, at 6 weeks post ezetimibe cessation, the mean LDL-C levels had returned to the baseline levels (% LDL-C reduction from baseline: - 1% in the ezetimibe + statin group versus - 3% in the placebo + statin group) and were generally similar for each individual statin.

Study P040

Study P040was 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 (dose maintained throughout the study) in 3,030 patients with hypercholesterolaemia who had not yet reached target LDL-C levels. For the pooled Atorva sub group (n = 1,115), after 6 weeks treatment patients had a greater reduction in LDL-C on the combination of ezetimibe + Atorva compared with patients on placebo + Atorva (- 27% versus - 4%). Likewise, the percentages of patients achieving LDL-C target levels were higher in the group on the combination of ezetimibe + Atorva compared with the group on placebo + Atorva (75% versus 24%). These results were consistent across the all statins group and the Atorva sub group. Results were not presented for individual Atorva doses but the pooled Atorva group included patients on 10 mg (approximately 32%), 20 mg (approximately 30%), 40 mg (23%), and 80 mg (approximately 15%).

Study P079

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

titration of Atorva to 40 mg (- 10.9%) and a higher percentage reached the target LDL-C level (83.7% versus. 48.9%, respectively).

Study P090

Study P090 was a Phase III, multicentre, randomised, double blind, titration study to evaluate the efficacy and safety of ezetimibe added on to Atorva 40 mg compared to up titration of the dose of Atorva to 80 mg in hypercholesterolaemic patients at high risk of CHD. After a 6 week treatment period, the addition of ezetimibe 10 mg, compared to up titration of the dose of Atorva 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

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 Atorva 10 mg versus up titration to Atorva 20 mg and 40 mg, in elderly patients (≥ 65 years) with hypercholesterolaemia at high risk of CHD. 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 Atorva 20 mg (- 26.7% versus - 12.8%). The combination treatment also resulted in greater LDL-C reduction compared to a further 6 weeks treatment at an up titrated dose of Atorva 40 mg (- 22.5% versus - 17.9%). The combination treatment also resulted in a higher percentage of patients reaching their target LDL-C at both 6 (47.4% versus 17.9%) and 12 weeks (43.6% versus 32.2%).

Study P0693

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

Study P02514

Study P02514 was a randomised, placebo controlled, double blind 12 month extension study of P0692. Patients who completed P0692 were randomised in a 4:1 ratio to receive daily ezetimibe 10 mg or placebo on top of open label Atorva 10 mg daily with up titration of the latter (to a maximum of 80 mg) if target levels were not attained. Of the 576 patients completing P0692, 246 (39%) entered the extension study, 45 in the Atorva + placebo group and 201 in the Atorva + ezetimibe group. The reduction in LDL-C was higher in the Atorva + ezetimibe group (- 48.4% versus. - 38.6% at study end) and was essentially maintained from Week 6 through to Month 12/Endpoint in both treatment groups. Fewer patients in the Atorva + ezetimibe group required dose titration (9% (19/201)) compared with the Atorva + placebo group (22% (10/45)).

Study P01418

Study P01418 was a 12 month, open label extension study of P0693. Of the 576 patients completing P0693, 432 (75%) entered the extension study. LDL-C reduction was maintained for the 12 months of the study with a mean reduction of 28% and 24% of patients achieving the target LDL-C goal (≤ 2.59 mmol/L) at the study endpoint.

Homozygous Familial Hypercholesterolaemia (HoFH)

Study P1030

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 Atorva 40 mg or simvastatin 40 mg. Subjects were randomised to ezetimibe 10 mg + statin (40 mg or 80 mg of Atorva or simvastatin) or statin alone (Atorva 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 + Atorva). 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

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 Atorva 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 Atorva. The mean LDL-C reduction from baseline to study endpoint was - 15.3% by calculated measurement. Similar levels of reduction were observed in both triglycerides and total cholesterol, while HDL-C increased by 8.6%.

Mixed hyperlipidaemia

Study P0692

Study P0692: a post hoc sub group analysis was performed in the 139 patients who received atorvastatin and had baseline triglyceride levels ≥ 200 mg/dL. In this group, 66 received Atorva (doses pooled) and 73 received Atorva plus ezetimibe. The mean % reduction from baseline in LDL-C was - 56.5% in the ezetimibe + all Atorva group compared to - 45.5% in the all Atorva group. This result was similar to that achieved in the group of subjects with baseline triglyceride levels < 200 mg/dL.

Studies P079, P090 and P112

P079, P090 and P112: sub-group analyses were performed for subjects with baseline triglyceride levels ≥ 150 mg/dL or < 150 mg/dL. 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 1,675 subjects who received ezetimibe 10 mg co administered with any statin for a period of 8 to 12 weeks. The rate of serious adverse events (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 didn't appear to be 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.

In the Atozet composite pack submission there were pooled safety data from 4,569 subjects from 7 controlled short term studies of 6 to 14 weeks duration (P040, P079, P090, P112, P692, P693 and P2173). These subjects included: 2,041 patients on atorvastatin monotherapy, 2,403 patients on ezetimibe 10 mg + atorvastatin (all doses), 60 patients on placebo, and 65 patients on ezetimibe monotherapy. In addition, there was 12 month data from 2 studies (P2154 and P1418) involving 678 patients on either, atorvastatin, or ezetimibe + atorvastatin (604 on the latter); and data on patients with HoFH from 2 studies (P1030 and P1417) involving 59 patients on ezetimibe 10 mg + Atorva (including data on 33 patients out to 24 months). In the short term studies the exposure adjusted AE rate was similar in patients treated with the combination and in those receiving monotherapy or placebo. Overall the safety profile of the combination of ezetimibe with Atorva was in line with that seen with the individual components. The most frequent AEs in the ezetimibe + Atorva and Atorva monotherapy group were nasopharyngitis, myalgia and headache. In the long term studies 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%). 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 x 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%). There were 4 deaths in the short term studies with 2 in the ezetimibe + Atorva group, with one further death in a long term study. None were considered treatment related. The exposure adjusted SAE rate (per 100 patient years) in the short term studies (12.3) was slightly higher than atorvastatin (9.6). The most frequent SAEs were myocardial infarction and chest pain. No increased risk was seen in older patients (≥ 65 years and ≥ 75 years) or for either gender. Although the numbers were small the AE profile appeared similar in the HoFH population.

The final core safety pool (CSP) for this submission (n = 5,169) consisted of subjects from 8 studies of 6 to 14 weeks duration including safety data from 7 previously submitted and evaluated studies (P00692, P00693, P02173/P2246, P040, P079, P090 and P112) and 1 newly submitted study (P162, Phase 1 only). These subjects included: 2,521 patients on Atorva monotherapy (all doses), 2,523 patients on co administered ezetimibe 10 mg + Atorva (all doses), 60 patients on placebo, and 65 patients on ezetimibe monotherapy. The safety profiles for the Atorva monotherapy group and the co administered ezetimibe 10 mg + Atorva (all doses) groups in the updated CSP are comparable to those in the previously submitted and evaluated CSP. In addition, the safety profiles of these two groups are consistent with the safety profiles of the corresponding groups in the pivotal study (P162) and the two supportive studies (P185 and P190) (see points below). No new safety signals have emerged from the updated safety analysis in the CSP. In particular, there were no AE reports of either rhabdomyolysis or myopathy, although 1 patient on ezetimibe + Atorva 10 + 40 mg met the criteria for myopathy (reported as SAE of increased CPK), and 1 patient on Atorva 20 mg had a CPK ≥ 10 x ULN with associated muscle pain that was attributed to exercise by the investigator. In the long term studies (P2154, P1418, P1030 and P1417), there were no AE reports of either rhabdomyolysis or myopathy. In the CSP, there were 2 (0.1%) patients in the ezetimibe 10 mg + Atorva 10 to 80 mg group reported as meeting Hy's law criteria for drug induced liver injury (DILI). There were no patients meeting Hy's law criteria for DILI in the pivotal study (P162) or either of the two supportive studies (P185 and P190). There were no new long-term safety data in the submission and there were no new safety data from studies exclusively in patients with HoFH.

Safety with ezetimibe + atorva 10 + 80 mg

In Study P692, 40 of the 248 subject on Atorva monotherapy and 35 of the 255 patients on co administered ezetimibe + Atorva were on the 80 mg atorvastatin dose. A similar percentage of subjects on the highest Atorva dose experienced any treatment related AE compared with the pooled treatment groups (24% versus 17% (monotherapy) and 17% versus 23% (co administration)). For individual AEs the frequency was similar across the treatment groups with the possible exception of increases in ALT (< 2 x ULN) which ranged from 20% (Atorva 10 mg) and 31% (ezetimibe + Atorva 10 + 10 mg) up to 31% (Atorva 80 mg) and 42% (ezetimibe + Atorva 10 + 80 mg). Similar differences occurred with AST < 2 x ULN (27% (Atorva 10 mg) and 42% (ezetimibe + Atorva 10 + 10 mg) up to 37% (Atorva 80 mg) and 50% (ezetimibe + Atorva 10 + 80 mg). For ALT/AST < 3 x ULN, ≥ 3 x ULN and consecutive ≥ 3 x ULN, the numbers were too small to determine a clear dose relationship across individual treatment groups.

Study P162

In Phase 1 there were 120 subjects exposed to ezetimibe 10 mg + Atorva 10 mg, 480 patients exposed to Atorva 20 mg and 939 patients exposed to Rosuva 10 mg with an overall mean exposure of 42.1 days which was comparable across the treatment groups (42 to 43 days). In total, 712 patients continued into Phase 2: 124 patients with an inadequate response to Atorva 20 mg were switched to ezetimibe 10 mg + Atorva 20 mg and 124 had their Atorva dose doubled to 40 mg; 231 patients with an inadequate response to Rosuva 10 mg were switched to ezetimibe 10 mg + Atorva 20 mg and 205 had their Rosuva dose doubled to 20 mg; 28 patients who had been initially randomised to ezetimibe 10 mg + Atorva 10 mg continued on this regimen in Phase 2 in order to maintain the double blinded study design. The mean duration of exposure in all patients was 41.7 days which was comparable across the treatment groups (41 to 42 days).

In Phase 1, AEs were numerically higher in the Rosuva 10 mg group (n = 13.6%) than in the Atorva 20 mg (11.9%) and ezetimibe 10 mg + Atorva 10 mg (7.5%) groups, but there were no clinically significant differences in the AE profiles. Drug related AEs were numerically higher in the Atorva 20 mg group (3.1%) than in the Rosuva 10 mg (2.9%) and ezetimibe 10 mg + Atorva 10 mg (0.8%) groups. The most frequently reported drug related AEs by SOC were related to 'GI disorders', 'investigations', and 'musculoskeletal and connective tissue disorders'. Again there were no clinically significant differences in the AE profiles and no individual AE was observed in ≥ 1.0% of patients in any of the treatment groups.

In Phase 2, AEs were numerically higher in the Rosuva 10 mg → ezetimibe 10 mg + Atorva 20 mg group (15.6%), compared with the Atorva 20 mg → Atorva 40 mg (10.5%), the Atorva 20 mg → ezetimibe 10 mg + Atorva 20 mg (8.9%) and the Rosuva 10 mg → Rosuva 20 mg groups (8.8%). Only the difference between the Rosuva 10 mg → ezetimibe 10 mg + Atorva 20 mg and Rosuva 10 mg → Rosuva 20 mg groups was statistically significant (difference = 6.8% (95% CI: 0.6, 3.0)), which appeared to be driven by a higher proportion of 'musculoskeletal and connective tissue disorders' in the co administered group compared with the monotherapy group (3.5% versus 0.5%). No specific AEs were reported in ≥ 4 patients or in ≥ 2% of patients in any treatment group. The observed differences in the incidence of AEs occurring in ≥ 1% of patients in at least one of the treatment groups were small and not considered clinically meaningful. Drug related AEs were numerically higher in the Rosuva 10 mg → ezetimibe 10 mg + Atorva 20 mg group (3.5%), compared with the Atorva 20 mg → Atorva 40 mg (2.4%), the Atorva 20 mg → ezetimibe 10 mg + Atorva 20 mg (1.6%) and the Rosuva 10 mg → Rosuva 20 mg groups (1.0%). None of the pairwise comparisons were statistically significant. The most frequently reported drug related AEs by SOC were related to 'investigations'. No drug related AEs grouped by SOC occurred in ≥ 1.0% of patients in any of the treatment groups.

Specific AEs of interest for ezetimibe and statins:

Gastrointestinal related AEs

In Phase1 these were comparable across the 3 treatment groups: Atorva 20 mg (2.5%), Rosuva 10 mg (2.0%) and ezetimibe 10 mg + Atorva 10 mg (1.7%). In Phase 2, they were higher in the Atorva 20 mg → ezetimibe 10 mg + Atorva 20 mg and Atorva 20 mg → Atorva 40 mg groups (1.6% each), compared with the Rosuva 10 mg → Rosuva 20 mg group (1.0%), and Rosuva 10 mg → ezetimibe 10 mg + Atorva 20 mg (0.9%) groups.

Allergic reaction/rash related AEs

In Phase 1 they occurred more frequently in patients on Rosuva 10 mg (0.9%), than in patients on Atorva 20 mg (0.4%) or ezetimibe 10 mg + Atorva (0.0%). In Phase 2 they only occurred in 1 patient on Atorva 20 mg → Atorva 40 mg (0.8%).

Pre specified ALT and/or AST elevations

In Phase 1 they were only reported in patients on Rosuva 10 mg (0.2% ≥ 3 x ULN (consecutive events), and 0.1% each for ≥ 5 x ULN and ≥ 10 x ULN). In Phase 2 they were only reported in patients on Atorva 20 mg → Atorva 40 mg (0.8%) for a ≥ 3 x ULN (consecutive) event, and Rosuva 10 mg → ezetimibe 10 mg + Atorva 20 mg group (0.4%) for each of ≥ 3 x ULN (consecutive), ≥ 5 x ULN, and ≥ 10 x ULN events.

No pre specified CK elevations (with or without muscle symptoms), hepatitis related AEs or gall bladder related AEs and no cases meeting Hy's Law criteria for drug induced liver injury were reported in any of the treatment groups in Phase 1 or 2.

In Phase 1, 2 deaths (1 x bile duct carcinoma, 1 x myocardial infarction) occurred in the Rosuva 10 mg group. In Phase 2, 1 death occurred (alcohol poisoning) in the Rosuva 10 mg → ezetimibe 10 mg + Atorva 20 mg group. All of the deaths were considered to be unrelated to the study drug.

In Phase 1, SAEs (including deaths) occurred infrequently and were reported in 0.8% of patients in the three treatment groups combined. There were no SAEs in the ezetimibe 10 mg + Atorva 20 mg group (0%), while SAEs occurred marginally more frequently in patients in the Rosuva 10 mg group (1.1%) than in the Atorva (0.6%). There were no statistically significant differences in the SAEs between the ezetimibe 10 mg + Atorva 10 mg and Atorva 20 mg groups or the ezetimibe 10 mg + Atorva 10 mg and Rosuva 20 mg groups. No specific SAEs occurred in more than 1 patient in any of the treatment groups. No drug related SAEs occurred in any of the treatment groups. Overall, no specific patterns of SAEs were observed in any of the treatment groups.

In Phase 2, SAEs (including death) occurred in 1.4% (n = 10) of the 712 APaT population. Numerically more SAEs were reported in the Rosuva 10 mg → ezetimibe 10 mg + Atorva 20 mg group (2.2%), and the Atorva 20 mg → Atorva 40 mg and Atorva 20 mg → ezetimibe 10 mg + Atorva 20 mg groups (1.6% in each group), compared with the Rosuva 10 mg → Rosuva 20 mg group (0.5%). No patterns of SAEs were observed in the treatment groups, and the differences among the groups are not considered to be clinically meaningful.

Discontinuations due to AEs occurred in 1.4% and 0.6% of patients in Phase 1 and 2, respectively. There were no statistically significant differences in the discontinuations due to drug related AE rates between any of the treatment groups in Phase 1 or 2.

Study P185

This study included 383 patients treated with FDC ezetimibe/Atorva 10/20 mg and 388 patients treated with co administered ezetimibe 10 mg + Atorva 20 mg. The overall mean duration of treatment was 41.8 days and 41.7 days in the FDC and co administration groups, respectively. Overall and drug related AEs occurred in a similar proportion of patients in the FDC and co administration groups. The most common drug related AEs

were: muscle spasms (0.5% versus 1.0%), fatigue (0.8% versus 0.5%), constipation (0.8% versus 0.3%), dyspepsia (0.3% versus 0.8%), abdominal discomfort (0% versus 0.5%), and arthralgia (0.5% versus 0%). Six SAEs were reported, 2 in the FDC group (myocardial infarction and hypokalaemia) and 4 in the co administration group (ventricular extrasystoles, 'stress cardiomyopathy', ischaemic colitis, and basal cell carcinoma). None of the SAEs were considered by the investigators to be related to drug treatment. There were no deaths reported during the course of the study. AEs leading to drug discontinuation were considered to be drug related in 5 patients in the FDC group (1 each for flatulence, hyperbilirubinaemia, pain in extremity, migraine and paraesthesia), and 8 patients in the co administration group (2 each for muscle spasms and myalgia, and 1 each for abdominal discomfort, gastrointestinal pain, muscular weakness, and pain in extremity). The most commonly occurring AEs of special interest were gastrointestinal related events (4.4% versus 3.6%), and allergic reaction/rash related AEs (1% versus 1%). There were no patients in either treatment group with hepatitis or gall bladder related AEs or meeting Hy's Law criteria for drug induced liver injury. Predefined increases in AST/ALT levels ≥ 3 x ULN were observed in 0.3% patients in the FDC and co administration groups, ≥ 5 x ULN in 0.3% patients in the co administration group, and ≥ 10 x ULN in no patients. One patient in each treatment group reported CK levels ≥ 10 x ULN, while CK levels ≥ 10 x ULN with muscle symptoms (not considered to be drug related) were reported in 1 (0.3%) patient in the FDC group.

Study P190

Study P190 included 303 patients treated with FDC ezetimibe/Atorva 10/40 mg and 313 patients treated with co administered ezetimibe 10 mg + Atorva 40 mg. The overall mean duration of treatment was 41.6 days and 40.7 days in the FDC and co administration groups, respectively. AEs occurred in a similar proportion of patients in the FDC and co administration groups, but drug related AEs were numerically higher in the FDC group (8.3% versus 5.1%). The most common drug related AEs were: gamma-GT increased (1.0% versus 0.6%), blood creatinine increased (0.3% versus 1.0%), arthralgia (1.0%, versus 0%), dyspepsia (0% versus 1.0%), ALT increased (0% versus 1.0%), AST increased (0% versus 0.6%), and diarrhoea (0.7% versus 0%). Five SAEs were reported, 3 in the FDC group (cholecystitis and sepsis, unstable angina, and squamous cell carcinoma) and 2 in the co administration group (myocardial infarction and coronary artery disease). None of the SAEs were considered by the investigators to be related to drug treatment. There were no deaths reported during the course of the study. AEs leading to drug discontinuation were considered to be drug related in 3 patients in the FDC group (1 each for abdominal pain, myalgia and loss of libido) and 5 patients in the co administration group (1 each for fatigue, ALT increased, blood CK increased, myalgia and dizziness). The most commonly occurring AEs of special interest were gastrointestinal related events (5.3% versus. 6.1%), allergic reaction/rash related AEs (1.7% versus. 1.6%), and gall bladder related AEs (0.0% versus. 0.3%). There were no patients in either treatment group with hepatitis related AEs or meeting Hy's Law criteria for drug induced liver injury. Predefined increases in ALT levels ≥ 3 x ULN were observed in 0.3% patients in the FDC and 0.6% in the co administration group, ≥ 5 x ULN in 0.5% patients in the FDC group, and ≥ 10 x ULN in no patients. No increase in CK levels was reported in either treatment group.

The post-marketing safety data were consistent with the known safety profile of co administered ezetimibe 10 mg and Atorva 10 to 80 mg.

Clinical evaluator's recommendation

The clinical evaluator has recommended approval for ezetimibe/atorvastatin as calcium trihydrate for the proposed indications.

Risk management plan

The PSMB has accepted the EU Risk Management Plan for Atozet /Zeteze (ezetimibe and atorvastatin as calcium FDC Tablet), version 1.0, dated 11 September 2013, with the Australian Specific Annex (ASA), dated 13 June 2014.

The following were outstanding matters that should be followed up with PSMB prior to finalisation of this submission and responded to in the Pre-ACPM Response:

The sponsor is asked to provide reasons for any differences between the EU-RMP and the local implementation of risk management activities in the ASA, for example: any differences between the risk minimisation activities undertaken as reflected in the content of the EU SmPC and the proposed Australian PI.

Risk-benefit analysis

Delegate's considerations

Efficacy

The new pivotal study confirmed the efficacy findings of the previously evaluated clinical data for the combination of ezetimibe + atorvastatin in the treatment of patients with primary hypercholesterolaemia. The reduction in LDL-C and other lipid related parameters was consistently greater for the combination than for either monotherapy component. This was also demonstrated for those patients who were switched from rosuvastatin (10 mg) to combination ezetimibe + atorvastatin compared with doubling the dose of rosuvastatin (20 mg). The supportive studies demonstrated that the FDC tablet was equivalent in efficacy to co administered ezetimibe and atorvastatin. Previously evaluated data from the Atozet composite pack submission and earlier FDC submission demonstrated that efficacy was maintained for up to 12 months. In a limited number of patients with HoFH, efficacy of the combination of ezetimibe + atorvastatin was also demonstrated. The Delegate agrees with the clinical evaluator that '*clinically meaningful differences between the benefits of the proposed ezetimibe/atorvastatin FDC tablets and the known benefits of co-administration of the two medicines are unlikely*'.

Safety and RMP

The safety of the combination of ezetimibe and atorvastatin is well characterised, and the additional data supplied with this submission, including the updated CSP, did not identify any new safety signals. However the data indicated more AEs (approximately double) for patients switching from rosuvastatin 10 mg to Atozet 10/20 mg than if patients doubled their rosuvastatin dose, with the difference being statistically significant. This appeared to be mainly driven by an increase in musculoskeletal and connective tissue AEs which were numerically higher in the Rosuva 10 mg → ezetimibe 10 mg + Atorva 20 mg group than in the Rosuva 10 mg → Rosuva 20 mg group (3.5% versus 0.5%); no specific AE was experienced by more than 2 patients, and only 3 AEs (1 each of arthralgia, muscle spasms and musculoskeletal pain, all in the Rosuva 10 mg → ezetimibe 10 mg + Atorva 20 mg group) were considered drug related.

Overall, the duration and amount of safety data for the combination of ezetimibe and Atorva was sufficient to establish that it is well tolerated and is consistent with the current known safety profile of both the individual component drugs and their use in combination as the currently registered composite pack (see below regarding rosuvastatin). The Delegate agrees with the clinical evaluator that '*it is considered unlikely that there will be clinically meaningful differences in the risks of treatment with the proposed ezetimibe/atorvastatin FDC tablets compared with the known risks of treatment associated with co-administration of the two medicines*'.

Tablet size

The tablet dimensions are moderately large with the 10/80 mg strength being 19.05 mm by 7.94 mm. Such large tablets which are not scored could represent a swallowing difficulty for patients, especially elderly patients. The clinical data package did not include efficacy and safety studies with the FDC tablets proposed for registration but rather used co administered ezetimibe and atorvastatin tablets. It is therefore unclear on whether this represents a problem or safety concern for patients given the lack of use of the actual tablets for registration. There were however bioequivalence studies using the FDC but it is unclear if these tablets had the same dimensions as proposed for registration. The sponsor is asked to provide further information on this matter.

Indication

After first round evaluation, the clinical evaluator recommended the indication be modified to exclude the treatment of patients with primary hypercholesterolaemia already treated with rosuvastatin and ezetimibe as no data had been submitted to support the most appropriate dose of atorvastatin to be used in the ezetimibe/atorvastatin FDC tablet when switching from co administered rosuvastatin and ezetimibe. The sponsor acknowledged the lack of data and agreed to removal of rosuvastatin from the indication in relation to those patients switching from co administered ezetimibe + rosuvastatin tablets to the atorvastatin/ezetimibe FDC. The Delegate supports this amendment to the indication. This is also consistent with the indication for the current Atozet composite pack registered in Australia. The US approved indications for ezetimibe/atorvastatin (Liptruzet) are broader than (but consistent with) those proposed in Australia.

The previously evaluated clinical data was considered sufficient to support the current indications for the Atozet composite pack and is therefore considered by the Delegate sufficient to support the proposed indications for the Atozet FDC pack in patients with primary hypercholesterolaemia not appropriately controlled with atorvastatin or ezetimibe alone; or already treated with atorvastatin and ezetimibe; and for patients with HoFH. However only one study (P162) was submitted in support of the proposed indication relating to patients with primary hypercholesterolaemia not appropriately controlled with rosuvastatin alone. In this study the co administration of ezetimibe 10 mg + Atorva 10 mg was more effective than Rosuva 10 mg in reducing LDL-C (- 9.1%, $p < 0.001$); and switching treatment from Rosuva 10 mg to ezetimibe 10 mg + Atorva 20 mg was more effective than doubling the dose of Rosuva to 20 mg (- 9.5%, $p < 0.001$). However, no data was presented regarding the efficacy of switching from the 5 mg, 20 mg or 40 mg doses of rosuvastatin to any combination of ezetimibe + atorvastatin. It is not known if there would be additional efficacy by switching from, for example, rosuvastatin 20 mg or 40 mg, to a combination of ezetimibe + atorvastatin. The data are therefore limited to support the inclusion of rosuvastatin at this time although the clinical evaluator thought that one may be able to infer the risk/benefit profile. From a safety perspective, the data also indicated that there were less AEs for patients doubling their rosuvastatin dose from 10 mg to 20 mg than there were if they switched to ezetimibe + atorvastatin 10 + 20 mg (statistically significant difference = 6.8% (95% CI: 0.6, 3.0)), which appeared to be driven by a higher proportion of 'musculoskeletal and connective tissue disorders' in the co administered group compared with the monotherapy group (3.5% versus 0.5%). Given the limited efficacy and safety data and the increase in AEs for patients switching from rosuvastatin to the combination, then the Delegate recommends that rosuvastatin is not included in the indication at this time. ACPM's advice is sought on this matter.

The Delegate therefore proposes amending the wording of the indication to be consistent with the current wording for the Atozet composite pack, namely:

Primary hypercholesterolaemia

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

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

Homozygous Familial Hypercholesterolaemia (HoFH)

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

Data deficiencies

While the 10/10 and 10/80 mg FDC tablets (proposed formulation) were demonstrated to be bioequivalent to the corresponding co administered strengths of separate ezetimibe and atorvastatin, there is no bioequivalence data for the intermediate 10/20 and 10/40 mg strengths of the FDC of ezetimibe and atorvastatin. The quality evaluator considered that the limited in vitro data are consistent with similar drug release from all of the proposed tablet strengths, thereby suggesting that bioequivalence studies of the intermediate strengths are not required. The clinical evaluator also considered that bioequivalence studies of the intermediate strengths are not required from a clinical perspective.

Only one study (P162) was submitted in support of the proposed indication relating to patients with primary hypercholesterolaemia not appropriately controlled with rosuvastatin alone. In this study the co administration of ezetimibe 10 mg + Atorva 10 mg was more effective than Rosuva 10 mg in reducing LDL-C; and switching treatment from Rosuva 10 mg to ezetimibe 10 mg + Atorva 20 mg was more effective than doubling the dose of Rosuva to 20 mg. However, no data was presented regarding the efficacy or safety of switching from the 5 mg, 20 mg or 40 mg doses of Rosuva. ACPM's advice is sought on this matter.

There are no clinical outcome data regarding a reduction in morbidity or mortality outcomes for the combination over and above that demonstrated for atorvastatin.

Proposed action

The Delegate had no reason to say, at this time, that the application for Atozet Fixed Dose Combination should not be approved for registration with the exception of the inclusion of rosuvastatin. The proposed revised indication is below:

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

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

Homozygous Familial Hypercholesterolaemia (HoFH)

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

Specific conditions of registration proposed

The sponsor will be required to implement in Australia the EU Risk Management Plan for Atozet /Zeteze (ezetimibe & atorvastatin as calcium), version 1.0, dated 11 September 2013), with an ASA (dated 13 June 2014), and the RMP agreements from the Pre-ACPM

Response of (date), included with submission PM-2013-03231-1-3, and any subsequent revisions, as agreed with the TGA.

Questions for the sponsor

The sponsor is requested to address the following issues in the Pre-ACPM Response:

1. Would the sponsor please confirm the formulation(s) of atorvastatin (calcium) (proposed versus previous) in each of the trials?
2. Would the sponsor please confirm whether the atorvastatin, ezetimibe and rosuvastatin products used in the clinical trials are the same as the Australian registered products, or summarise how the products used in the clinical trials relate to the Australian registered atorvastatin, ezetimibe and rosuvastatin. Has bioequivalence been demonstrated between the formulations of ezetimibe and atorvastatin used in the clinical trials to Atozet proposed for registration?
3. It is understood that the proposed Atozet tablets for registration have been shown, at the 10/10 and 10/80 strengths, to be bioequivalent with the currently registered 10 mg Ezetrol and 10 mg and 80 mg Lipitor (UK Lipitor which has been stated to be the same as the Australian registered Lipitor). Would the sponsor confirm whether it has been demonstrated that Atozet is also bioequivalent with MSD atorvastatin?
4. What evidence is there to support the proposed indication that Atozet FDC is efficacious and safe for patients with hypercholesterolaemia not appropriately controlled with rosuvastatin alone at the 5 mg, 20 mg and 40 mg doses?
5. The tablets are moderately large which may cause difficulties in swallowing. Please summarise, from the clinical trial database, any reports of difficulty swallowing these tablets or any further information or justification to support the proposed safety of the tablets from this perspective.
6. The sponsor is requested to confirm that the strengths of the tablets will form part of the product name for this range of tablets, for example, Atozet 10 mg/10 mg, and will be consistent with the Best practice guideline on prescription medicine labelling on the TGA website.

Request for ACPM advice

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

1. Whether the limited in vitro data for the intermediate 10/20 and 10/40 mg strengths of the FDC of ezetimibe and atorvastatin calcium trihydrate are sufficient, given that the 10/10 and 10/80 mg FDC tablets were demonstrated to be bioequivalent to the corresponding co administered strengths of separate ezetimibe and atorvastatin?
2. Whether there is sufficient data to support the use of Atozet in patients not appropriately controlled with rosuvastatin?

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

Response from sponsor

Response from sponsor to specific additional questions from the delegate

Question 1

Would the sponsor please confirm the formulation(s) of atorvastatin (proposed vs previous) in each of the trials?

Sponsor's response:

The atorvastatin formulations for the relevant studies are provided in Table 13 below.

Table 13. Clinical trial formulations used in the clinical studies.

Study number and name	Formulation of atorvastatin (proposed or previous)
BA and Comparative BE Study Reports	
P145: A Study to Evaluate the Definitive Bioequivalence of MK-0653C with Marketed Products	Previous (MK0653C) Comparator: Proposed
P146: An Open-Label, Randomised, 2-Period Crossover Study to Compare the Effects of Food on MK-0653C in Healthy Adult Subjects	Previous (MK0653C) Comparator: Proposed
MK-9396/P001: An Open-Label, Randomised, Single- Dose, 3-Period, Balanced Crossover Study to Compare the Pharmacokinetic Profiles of 3 Formulations of Atorvastatin in Healthy Young Adult Subjects	Treatment A: Previous Treatment B: Previous Treatment C: Proposed
P183: A Study to Evaluate the Definitive Bioequivalence of MK-0653C with U.S. Marketed Products	Previous(MK0653C) Comparator: Proposed
P391: A Single-Dose, Full Replicate Comparative Bioavailability Study of Two Formulations of Ezetimibe/Atorvastatin Calcium 10 mg/10 mg FDC Tablets vs. Ezetrol administered with Lipitor under Fasting Conditions.	Proposed
P392: A Single-Dose,. Full Replicate Comparative Bioavailability Study of Two Formulations of Ezetimibe/Atorvastatin Calcium 10 mg/80 mg FDC Tablets vs. Ezetrol administered with Lipitor under Fasting Conditions	Proposed
P415: A Study of the Comparative Fed and Fasted Bioavailability of MK-0653 10/80 mg in Healthy Subjects	Proposed
Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials	
P460 – Schering-Plough Clinical Study Report, Single-Site Study: SCG58235: Assessment of a Multiple-Dose Drug Interaction Between SCH58235 and Atorvastatin in Healthy Volunteers (Protocol No. P00460), 12 Jul 2001	Proposed

Study number and name	Formulation of atorvastatin (proposed or previous)
Efficacy and Safety Studies	
P112: 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 to 40 mg in Elderly Patients With Hypercholesterolemia at High Risk for CHD	Proposed
P090: Titration Study to Evaluate and Compare the Efficacy and Safety of Ezetimibe Added On to Atorvastatin 40 mg Versus Up Titration to Atorvastatin 80 mg in Hypercholesterolemic Patients at High Risk for CHD Not Adequately Controlled on Atorvastatin 40 mg	Proposed
P079: Titration Study to Evaluate and Compare the Efficacy and Safety of Ezetimibe Added on to Atorvastatin 20 mg Versus Up Titration to Atorvastatin 40 mg in Hypercholesterolemic Patients at Moderately High Risk for Coronary Heart Disease	Proposed
P040: 6-Week Study to Evaluate the Efficacy and Safety of Ezetimibe 10 mg/day When Added to Ongoing Therapy With a Statin Versus Statin Therapy Alone, in Patients With Hypercholesterolemia Who Have Not Reached National Cholesterol Education Program Adult Treatment Panel III Target LDL-Cholesterol Level	Proposed
P2173 - A Multicenter, Double-blind, Randomised, Placebo-controlled Study to Evaluate the Lipid-Altering Efficacy, Safety and Tolerability of SCH 58235 When Added To Ongoing Therapy With an HMG-CoA Reductase Inhibitor (Statin) in Patients with Primary Hypercholesterolemia, Known Coronary Heart Disease or Multiple Cardiovascular Risk Factors	Proposed
P2173R - Reversibility Phase of P2173/2246: A Doubleblind, Placebo-controlled Study to Evaluate the Lipid-Altering Efficacy, Safety and Tolerability of Ezetimibe 10 mg When Added To Ongoing Therapy With Statin in Patients with Primary Hypercholesterolemia, Known CHD or Multiple Cardiovascular Risk Factors	Proposed
P2154: Long-term, safety and tolerability study of ezetimibe or placebo in addition to atorvastatin in subjects with primary hypercholesterolemia (Extension of P692)	Proposed
P1417 - Long-Term, Open-Label, Safety and Tolerability Study of Ezetimibe in Addition to Atorvastatin or Simvastatin in the Therapy of Homozygous Familial	Proposed

Study number and name	Formulation of atorvastatin (proposed or previous)
Hypercholesterolemia (Extension of P1030)	
P1418 - Long term, open–label, safety and tolerability study of ezetimibe in addition to atorvastatin in subjects with CHD or multiple risk factors and with Primary hypercholesterolemia not controlled by a starting dose (10 mg) of atorvastatin (Extension of P693)	Proposed
P162 – A Randomised, Double-Blind, Active-Controlled, Multicentre Study of Patients with Primary Hypercholesterolaemia and High Cardiovascular Risk Who Are Not Adequately Controlled with Atorvastatin 10 mg: A Comparison of the Efficacy and Safety of Switching to Co-Administration Ezetimibe and Atorvastatin versus Doubling the Dose of Atorvastatin or Switching to Rosuvastatin (Parts 1 to 4)	Proposed
P692/692a - A Phase 3, double-blind efficacy and safety study of ezetimibe (SCH 58235) 10 mg in addition to atorvastatin compared to placebo in subjects with primary hypercholesterolemia (Protocol P00692) – Part 1 and Part 2 (see also P2154 – extension study)	Proposed
P693/693a/693b - A double-blind, double-dummy safety and efficacy study of ezetimibe in addition to atorvastatin in subjects with hypercholesterolemia not controlled by starting dose atorvastatin (Part 1, Part 2 and Part 3)	Proposed
P1030/1030a - A Phase III efficacy and safety study of SCH 58235 (10 mg) in addition to atorvastatin or simvastatin in the Treatment of homozygous familial hypercholesterolemia – Part 1 and Part 2	Proposed
P185 – MRL Clinical Study Report: A Randomised, Double-Blind, Active-Controlled, Multicentre, Crossover Study to Evaluate the Efficacy and Safety of Ezetimibe/Atorvastatin 10 mg/20 mg Fixed-Dose Combination Tablet Compared to Co-administration of Marketed Ezetimibe 10 mg and Atorvastatin 20 mg in Patients with Primary Hypercholesterolaemia – Part 1 and Part 2	MK0653C: Previous Marketed Lipitor: Proposed
P190 – MRL Clinical Study Report: A Randomised, Double-Blind, Active-Controlled, Multicenter, Crossover	MK0653C: Previous Marketed Lipitor: Proposed

Study number and name	Formulation of atorvastatin (proposed or previous)
Study to Evaluate the Efficacy and Safety of Ezetimibe/Atorvastatin 10 mg/40 mg Fixed-Dose Combination Tablet Compared to Co-administration of Marketed Ezetimibe 10 mg and Atorvastatin 40 mg in Patients with Primary Hypercholesterolaemia	

Question 2:

Would the sponsor please confirm whether the atorvastatin, ezetimibe and rosuvastatin products used in the clinical trials are the same as the Australian registered products, or summarise how the products used in the clinical trials relate to the Australian registered atorvastatin, ezetimibe and rosuvastatin. Has bioequivalence been demonstrated between the formulations of ezetimibe and atorvastatin used in the clinical trials to Atozet proposed for registration?

Sponsor's response:

The atorvastatin and rosuvastatin products studied in the clinical trials were generally the commercially available formulations of rosuvastatin and atorvastatin sourced by the innovator (Astra Zeneca and Pfizer, respectively).

Ezetimibe: Concerning ezetimibe, there is only one formulation of ezetimibe marketed globally, which is or is equivalent to the formulation studied.

Rosuvastatin: In general, the rosuvastatin studied was the innovator (UK-sourced Astra Zeneca) product, which is qualitatively equivalent to the commercially available Crestor available in Australia.

Atorvastatin: The form of atorvastatin in the proposed Atozet FDC is the same form of atorvastatin as the innovator (Pfizer), which is the form of atorvastatin commercially available in Australia. In clinical trials P40 and P2173 subjects continued on their own prescribed (locally available) atorvastatin.

In the biopharmaceutics Studies P391 and P392, the 10/10 mg and 10/80 mg FDC tablets (proposed formulation) of Atozet were demonstrated to be bioequivalent to the corresponding co administered strengths of individual ezetimibe and atorvastatin tablets sourced from the UK. The atorvastatin purchased in the UK is identical to the atorvastatin sold in Australia as confirmed in a declaration letter from Pfizer.

Question 3:

It is understood that the proposed Atozet tablets for registration have been shown, at the 10/10 and 10/80 mg strengths, to be bioequivalent with the currently registered 10 mg Ezetrol and 10 mg and 80 mg Lipitor (UK Lipitor which has been stated to be the same as the Australian registered Liptor). Would the sponsor confirm whether it has been demonstrated that Atozet is also bioequivalent with MSD atorvastatin?

Sponsor's response:

There has not been a direct demonstration that Atozet is bioequivalent with MSD atorvastatin. However an indirect comparison can be made.

The sponsor provided TGA with information and data that demonstrated bioequivalence between atorvastatin (as supplied for the composite pack) and Lipitor. The clinical

evaluator concluded that these data were acceptable for demonstrating bridging between the US reference product used in the clinical studies and atorvastatin.

Data in this application has demonstrated bioequivalence between UK Lipitor and the Atozet FDC and MSD has provided a declaration confirming that UK Lipitor is equivalent to Australia Lipitor. Therefore, since both atorvastatin MSD and the Atozet FDC have been shown to be equivalent to the Australian marketed Lipitor, it may be concluded that these two are also equivalent to each other.

Question 4

What evidence is there to support the proposed indication that Atozet FDC is efficacious and safe for patients with hypercholesterolaemia not appropriately controlled with rosuvastatin alone at the 5 mg, 20 mg and 40 mg doses?

Sponsor's response

MSD acknowledges the Delegate's conclusion that the data are limited to support the inclusion of rosuvastatin in the indication for Atozet at this time. MSD does not currently have any additional evidence to demonstrate the safety and efficacy of switching to Atozet FDC in patients not appropriately controlled on rosuvastatin 5, 20 or 40 mg alone. MSD therefore accepts the Delegate's proposal to amend the wording of the indication to be consistent with the current wording for the Atozet composite pack.

Question 5

The tablets are moderately large which may cause difficulties in swallowing. Please summarise, from the clinical trial database, any reports of difficulty swallowing these tablets or any further information or justification to support the proposed safety of the tablets from this perspective.

Sponsor's response:

A review of all bioequivalence studies in which subjects were treated with Atozet tablets revealed no reports or adverse events related to swallowing difficulties.

The size of the Atozet tablets is consistent with other prescription and over the counter products available in Australia.

A study of oesophageal transit times of different tablet shapes and sizes with a specific quantity of water was conducted. Based on the data from this study, the proposed Atozet carton label, PI and CMI contain the dosing instruction '*Swallow the tablet whole with a full glass of water*'. As a result, patients are unlikely to have trouble swallowing the tablet if these instructions are followed. Moreover, all strengths of Atozet tablets are oval shaped and film coated, which should assist with the tablet's transition through the oesophagus.

Question 6

The sponsor is requested to confirm that the strengths of the tablets will form part of the product name for this range of tablets, for example, Atozet 10 mg/10 mg, and will be consistent with the Best practice guideline on prescription medicine labelling on the TGA website.

Sponsor's response:

The sponsor confirms that the strengths of the tablets will form part of the product name, that is, Atozet 10 mg/10 mg, Atozet 10 mg/20 mg, Atozet 10 mg/40 mg, Atozet 10 mg/80 mg, consistent with the best practice guideline on prescription medicine labelling. The appearance of the product names have been revised on the carton artwork to more clearly reflect this naming convention.

Response from sponsor to request for ACPM advice from the delegate

The sponsor concurs with the Delegate's recommendation to approve this application to register a new fixed combination (FDC) tablet of ezetimibe/atorvastatin calcium trihydrate for the following indications:

> ***Primary Hypercholesterolaemia***
>
> *Atozet/Zeteze is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia where use of a combination product is appropriate in those patients:*
>
> · *Not appropriately controlled with atorvastatin or ezetimibe alone; or*
>
> · *Already treated with atorvastatin and ezetimibe*
>
> ***Homozygous Familial Hypercholesterolaemia***
>
> *Atozet/Zeteze is indicated in patients with HoFH. Patients may also receive adjunctive treatments (e.g. LDL apheresis).*

This FDC tablet includes the same combination as the already approved Atozet (or Zeteze) composite pack. These two medicines (ezetimibe and atorvastatin) are frequently prescribed together for the management of hypercholesterolaemia. The inclusion of these two medicines in a single FDC tablet provides a further simplification of the approach to the management of hypercholesterolaemia which will be positively received by prescribers and patients.

The Delegate has identified two issues and has sought the advice of the ACPM on these matters. The sponsor's response to these matters is set out below.

Question 1

Issue background

There are no bioequivalence data for the intermediate 10/20 and 10/40 mg strengths of the FDC of ezetimibe and atorvastatin calcium trihydrate. The quality evaluator considered that the limited in vitro data are consistent with similar drug release from all of the proposed tablet strengths, thereby suggesting that bioequivalence studies of the intermediate strengths are not required. The clinical evaluator considered that from a clinical perspective that comparative bioavailability studies for the proposed FDC intermediate strength tablets of ezetimibe/atorvastatin 10/20 mg and 10/40 mg are not required.

Whether the limited in vitro data for the intermediate10/20 and 10/40 mg strengths of the FDC of ezetimibe and atorvastatin calcium trihydrate are sufficient, given that the 10/10 and 10/80 mg FDC tablets were demonstrated to be bioequivalent to the corresponding co administered strengths of separate ezetimibe and atorvastatin?

Sponsor's response:

As provided by the sponsor, a biowaiver was requested for the intermediate (10/20 mg and 10/40 mg) FDC strengths Given that bioequivalence was demonstrated between the FDC tablets and the corresponding co administered individual ezetimibe and atorvastatin tablets at the lowest and highest dose strengths (bracketing approach), a biowaiver was deemed to be scientifically appropriate in support of the intermediate strengths of 10 mg/20 mg and 10 mg/40 mg including on the basis of dissolution similarity across the FDC tablet strengths The sponsor confirms that the biowaiver was conducted in accordance with the relevant EU guideline.[11]

[11] European Medicines Agency 'Guideline on the Investigation of Bioequivalence' (CPMP/EWP/QWP/1401/98 Rev.1/Corr)

This position was affirmed by the clinical evaluator in that '*based on the robustness of the two submitted bioavailability/bioequivalence studies investigating the lowest (10/10 mg) and the highest (10/80 mg) strengths of the proposed FDC tablets, it is the opinion of this evaluator that clinically significant bio-inequivalence of the two intermediate FDC tablets and their individual components is unlikely*'.

Question 2

Issue background

The proposed indication for the Atozet FDC includes patients not appropriately controlled with rosuvastatin. However only one trial was conducted in patients switched from rosuvastatin to co administration of ezetimibe + Atorva, and this was only in patients not adequately controlled on rosuvastatin 10 mg. In the Crestor PI, patients with hypercholesterolaemia have a recommended starting dose of 5 mg or 10 mg with a dose adjustment to 20 mg after 4 weeks of therapy if required. An increase in the dose to 40 mg should only be considered in patients who are still at high cardiovascular risk on the 20 mg dose.

Advice Sought: Whether there is sufficient data to support the use of Atozet in patients not appropriately controlled with rosuvastatin?

Sponsor's response:

As discussed in the response to the Delegate's Question 4 (above), the sponsor accepts the Delegate's proposal to delete references to rosuvastatin from the indication for Atozet FDC. The sponsor acknowledges that the data submitted previously in support of the application of the Atozet composite pack, and the additional data included with this application, is supportive of the use of the FDC in patients whose hypercholesterolaemia is not adequately controlled with ezetimibe or atorvastatin alone, or as a single tablet alternative to patients who are already taking both ezetimibe and atorvastatin as separate tablets.

Other matters

Risk management plan

The following were outstanding matters that should be followed up with PMSB prior to finalisation of this submission and responded to in the pre-ACPM Response: The sponsor is asked to provide reasons for any differences between the EU-RMP and the local implementation of risk management activities in the ASA, for example: any differences between the risk minimisation activities undertaken as reflected in the content of the EU SmPC and the proposed Australian PI.

Sponsor's response:

The sponsor has revised the Australian Specific Annex (ASA) to the RMP to provide reasons for differences between the EU-RMP and the local implementation of risk management activities. The revised ASA is included with this response. It should be noted that the application to register this product in the EU has only very recently received a positive recommendation and final approval has not yet been received. Further changes to the RMP and/or Australian Specific Annex may be required following finalisation of the EU labelling.

Data deficiencies

While the 10/10 and 10/80 mg FDC tablets (proposed formulation) were demonstrated to be bioequivalent to the corresponding co administered strengths of separate ezetimibe and atorvastatin, there is no bioequivalence data for the intermediate 10/20 and 10/40 mg strengths of the FDC of ezetimibe and atorvastatin. The quality evaluator considered that the limited in vitro data are consistent with similar drug release from all

of the proposed tablet strengths, thereby suggesting that bioequivalence studies of the intermediate strengths are not required. The clinical evaluator also considered that bioequivalence studies of the intermediate strengths are not required from a clinical perspective.

Sponsor's response:

Reference is made to the sponsor's response to issue (Question 1) above.

Issue regarding

Only one study (P162) was submitted in support of the proposed indication relating to patients with primary hypercholesterolaemia not appropriately controlled on rosuvastatin alone. ACPM's advice is sought on this matter.

Sponsor's response:

As discussed above, the sponsor is no longer pursuing the indication for patients not appropriately controlled with rosuvastatin alone.

Issue regarding:

There are no clinical outcome data regarding a reduction in morbidity or mortality outcomes for the combination over and above that demonstrated for atorvastatin.

Sponsor's response:

The sponsor acknowledges the lack of clinical outcome data regarding the reduction in morbidity or mortality outcomes for the combination.

In response to this comment, the sponsor notes that the EU Guideline on clinical investigation of medicinal products in the treatment of lipid disorders (adopted in Australia) supports the link between LDL-C levels and cardiovascular morbidity or mortality, The guideline contends that '*a large body of epidemiological evidence now exists demonstrating a strong positive correlation and causal relationship between serum LDL and the risk of CHD*'.

Despite the support for this epidemiological link, the sponsor is not proposing to make any additional claims in the PI with regard to cardiovascular morbidity and mortality for the combination. The EU guideline allows that the relative reduction in LDL-C levels is acceptable as a primary efficacy endpoint in patients with primary hypercholesterolaemia, providing that claims in the label are restricted to a lipid lowering effect. It also mentions that until clinical trial data showing a benefit on morbidity and mortality are available, it should be specifically mentioned in the SmPC (or the PI in the case of Australia) that beneficial effects on morbidity and mortality have not been evaluated. Since the proposed PI does not make claims with regard to cardiovascular morbidity or mortality, and the PI includes a statement regarding the fact that benefits or morbidity and mortality for the combination have not been established, the clinical data in support of this fixed combination meets these criteria of the EU Guideline.

Advisory Committee Considerations

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

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Atozet/Zeteze tablets containing

10 mg ezetimibe/10 mg atorvastatin calcium trihydrate (Atozet 10/10)

10 mg ezetimibe/20 mg atorvastatin calcium trihydrate (Atozet 10/20)

10 mg ezetimibe/40 mg atorvastatin calcium trihydrate (Atozet 10/40)

10 mg ezetimibe/80 mg atorvastatin calcium trihydrate (Atozet 10/80)

to have an overall positive benefit–risk profile for the Delegate's amended indication;

Primary Hypercholesterolaemia

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

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

Homozygous Familial Hypercholesterolaemia (HoFH)

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

Proposed conditions of registration

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

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

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

- A statement in the Clinical Trials section of the PI and relevant sections of the CMI to ensure the limitations of the data, in terms of lack of evidence to support a benefit on morbidity or mortality of combined therapy such as is contained in the US PI.
- There is a need to address the title on Table 5 in PI to reflect the nature of the treatment, that is 'co administered' not 'Azotet/ Zeteze'.
- A statement in the CMI regarding periodic checking of liver function (LFTs) consistent with the PI.
- A stronger statement in the CMI to more accurately reflect use in pregnancy.

Specific advice

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

1. Whether the limited in vitro data for the intermediate 10/20 and 10/40 mg strengths of the FDC of ezetimibe and atorvastatin calcium trihydrate are sufficient, given that the 10/10 and 10/80 mg FDC tablets were demonstrated to be bioequivalent to the corresponding co administered strengths of separate ezetimibe and atorvastatin?

The ACPM agreed with the evaluator and the Delegate that it was reasonable to extrapolate bioequivalence for the intermediate 10/20 and 10/40 mg strengths of the FDC from the data. However, the PI should clearly state that bioequivalence studies were only carried out for the 10/10 and 10/80 formulation. Bioequivalence was extrapolated for the two mid-range doses (10/20 and 10/40).

2. Whether there is sufficient data to support the use of Atozet in patients not appropriately controlled with rosuvastatin?

The ACPM noted that the sponsor had agreed to removal of rosuvastatin from the indication.

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

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Atozet (and Zeteze) fixed dose combination tablets containing ezetimibe/atorvastatin (as calcium) 10mg/10mg, 10mg/20mg, 10mg/40mg, and 10mg/80mg indicated for:

> ***Primary Hypercholesterolaemia***
>
> *Atozet/Zeteze is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia where use of a combination product is appropriate in those patients:*
>
> *•not appropriately controlled with atorvastatin or ezetimibe alone; or*
>
> *•already treated with atorvastatin and ezetimibe.*
>
> ***Homozygous Familial Hypercholesterolaemia (HoFH)***
>
> *Atozet/Zeteze is indicated in patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis).*

Specific conditions of registration applying to these goods

The Atozet/Zeteze (ezetimibe and atorvastatin as calcium) EU Risk Management Plan (RMP), version 1.0, dated 11 September 2013, with an Australian Specific Annex (dated 12 September 2014, included with submission PM-2013-03231-I-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

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

Attachment 2. Extract from the Clinical Evaluation Report

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