Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Sitagliptin and Simvastatin

Proprietary Product Name: Juvicor / Xelezor / Tesozor

Sponsor: Merck Sharp & Dohme (Australia) Pty Ltd

June 2013

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

About AusPARs

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

Contents

I. Introduction to product submission

Submission details

Type of Submission:	New Fixed combination
Decision:	Approved
Date of Decision:	23 November 2012
Active ingredients:	Sitagliptin as phosphate monohydrate and Simvastatin
Product Names:	Juvicor®/Xelezor™/Tesozor
Sponsor's Name and Address:	Merck Sharp & Dohme (Australia) Pty Ltd, Level 4, 66 Waterloo Rd, North Ryde NSW 2113
Dose form:	Tablet, film coated
Strengths:	100 mg sitagliptin/10 mg simvastatin; 100 mg sitagliptin/20 mg simvastatin; 100 mg sitagliptin/40 mg simvastatin
Container:	Aluminium-aluminium blister packs
Pack sizes:	7's and 28's
Approved Therapeutic use:	*Adult patients with Type 2 diabetes mellitus in whom treatment with both sitagliptin and simvastatin is indicated according to the separate indications of these drugs.*[1]
Route(s) of administration:	Oral (PO)

[1] The indications for sitagliptin are:
• For the treatment of Type 2 diabetes mellitus in persons 18 years of age and older who have failed dietary measures and exercise as dual combination therapy with metformin, or with a sulfonylurea, or with a thiazolidinedione where the use of a thiazolidinedione is considered appropriate.
The indications for simvastatin are:
• Simvastatin is indicated as an adjunct to diet for treatment of hypercholesterolaemia.
Prior to initiating therapy with simvastatin, secondary causes of hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemias, obstructive liver disease, other drug therapy, alcoholism) should be identified and treated.
• Simvastatin is indicated in patients at high risk of coronary heart disease (CHD) (with or without hypercholesterolaemia) including patients with history of stroke or other cerebrovascular disease, peripheral vessel disease, or with existing CHD to reduce the risk of cardiovascular death, major cardiovascular events including stroke, and hospitalisation due to angina pectoris.
These effects do not replace the need to independently control known causes of cardiovascular mortality and morbidity such as hypertension, diabetes and smoking."

Dosage:	One tablet i.e. one of 100/10, 100/20, and 100/40 (mg sitagliptin/mg simvastatin) to be taken once daily as combination therapy with metformin, a sulfonylurea (clinical experience is with glimepiride as dual therapy), or a thiazolidinedione (clinical experience is with pioglitazone as dual therapy).
ARTG Numbers:	191482; 191478; 191481; 191476; 191474; 191477; 191475; 191479; and 191480

Product background

Patients with Type 2 diabetes (T2DM) have a risk for macrovascular complications, including coronary artery disease, stroke and peripheral arterial disease. In conjunction with lifestyle interventions, co-administration of an anti-hyperglycaemic (such as sitagliptin) and a lipid lowering agent (such as simvastatin) is expected to reduce the occurrence of complications that can result in significant morbidity and increase the risk of death in patients with Type 2 diabetes. Sitagliptin and simvastatin are commonly co-administered in the clinic.

This AusPAR describes the application by Merck Sharp & Dohme (Australia) Pty Ltd register a fixed dose combination tablet containing the antihyperglycaemic agent sitagliptin and the hypocholesterolaemic agent simvastatin, with the proposed tradenames Juvicor®/Xelezor™/Tesozor®. The proposed indications are the same as those for the individual components. Three presentations are proposed, with the maximum clinical doses (100 mg/day sitagliptin and 40 mg/day simvastatin) within the currently approved dose range for the individual components. The combination of these agents in one fixed combination tablet is proposed to improve compliance in the target patient group.

Monotherapy tablets containing 25 mg, 50 mg and 100 mg sitagliptin (as phosphate monohydrate) have been registered in Australia by Merck Sharp & Dohme (Australia) Pty Limited (MSD) for many years. Current proprietary names are "Januvia®" and "Xelevia®" for the treatment of diabetes mellitus Type 2 in persons 18 years of age and older. There is no generic product.

Monotherapy tablets containing 5, 10, 20, 40 and 80 mg of simvastatin have been registered by MSD for many years. Current proprietary names are "Zocor®", "Lipex®" and "Simvar" for use in patients with diabetes at high risk of coronary heart disease (CHD) with or without hypercholesterolaemia. There are now a number of generic products.

MSD has also registered various fixed-dose combination (FDC) tablets containing sitagliptin or simvastatin in combination with other drug substances in Australia. For example, Janumet® contains sitagliptin (as phosphate monohydrate) and metformin hydrochloride (50 mg/1000 mg, 50 mg/850 mg and 50 mg/500 mg) and Vytorin® contains ezetimibe and simvastatin (10/10, 10/20, 10/40 and 10/80 mg/mg).

The sitagliptin/simvastatin FDC tablet is indicated in patients for whom treatment with both sitagliptin and simvastatin is appropriate. The proposed indications include the indications for both sitagliptin and simvastatin and are listed below:

The indications for sitagliptin are:

For the treatment of diabetes mellitus Type 2 in persons 18 years of age and older who have failed dietary measures and exercise as dual combination therapy with metformin,

or with a sulfonylurea, or with a thiazolidinedione where the use of a thiazolidinedione is considered appropriate.

The indications for simvastatin are:

Simvastatin is indicated as an adjunct to diet for treatment of hypercholesterolaemia. Prior to initiating therapy with simvastatin, secondary causes of hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemias, obstructive liver disease, other drug therapy, alcoholism) should be identified and treated.

Simvastatin is indicated in patients at high risk of CHD (with or without hypercholesterolaemia) including patients with diabetes, history of stroke or other cerebrovascular disease, peripheral vessel disease, or with existing CHD to reduce the risk of cardiovascular death, major cardiovascular events including stroke, and hospitalisation due to angina pectoris.

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

As noted by the clinical evaluator, *"… the third registered indication for simvastatin, relating to the treatment of adolescents 10-17 years of age with familial heterozygous hypercholesterolaemia, has been omitted by the sponsor as it would be in conflict with the above stated indication for sitagliptin which restricts its use to persons 18 years of age and older*."

Regulatory status

This product has been approved in the USA (see Table 1 below) and is currently under review in New Zealand.

Table 1. Summary of Regulatory Status in the USA

Country	Filing date	Approval date	Approved indication
United States	08 Dec 2010	7 Oct 2011 *Please note: this is an approval, not a conditional approval as stated in the Delegate's Overview*	JUVISYNC™ (sitagliptin and simvastatin) is indicated in patients for whom treatment with both sitagliptin and simvastatin is appropriate. **Sitagliptin** Sitagliptin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. *[See Clinical Studies (14.1).]* **Simvastatin** 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 hypercholesterolemia. 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. In patients with coronary heart disease (CHD) or at high risk of CHD, simvastatin can be started simultaneously with diet.
			Reductions in Risk of CHD Mortality and Cardiovascular Events In patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, simvastatin is indicated to: • Reduce the risk of total mortality by reducing CHD deaths. • Reduce the risk of non-fatal myocardial infarction and stroke. • Reduce the need for coronary and non-coronary revascularization procedures. *Hyperlipidemia* Simvastatin is indicated to: • Reduce elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), and triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary hyperlipidemia (Fredrickson type IIa, heterozygous familial and nonfamilial) or mixed dyslipidemia (Fredrickson type IIb). • Reduce elevated TG in patients with hypertriglyceridemia (Fredrickson type lV hyperlipidemia). • Reduce elevated TG and VLDL-C in patients with primary dysbetalipoproteinemia (Fredrickson type lll hyperlipidemia). • Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

Product Information

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

List of abbreviations

Abbreviation	Meaning
AE	adverse event
CI	confidence interval
CMI	consumer medicine information
DPP	dipeptidyl peptidase 4
FDC	fixed dosage combination
GIP	gastric inhibitory peptide
GLP-1	glucagon like peptide-1
HMG CoA	hydroxy-methyl glutaryl coenzyme A
HbA1c	haemoglobin A1c
HPS	Heart Protection Study
LS	least squares
MSD	Merck Sharp and Dohme
PI	product information
PD	pharmacodynamics
PK	pharmacokinetics
SCS	summary of clinical safety
SOC	system organ class
T2DM	Type 2 diabetes mellitus

II. Quality findings

Drug substance (active ingredient)

Sitagliptin phosphate monohydrate is the monohydrate of the (1:1) phosphate salt of sitagliptin. See Product Information documents for structure and other details. It is

manufactured and controlled as for the registered MSD monotherapy products. It is soluble in water and control of particle size is not critical.

Drug product

Simvastatin is a white crystalline powder, practically insoluble in water. There are EP/BP and USP monographs for simvastatin. This material is controlled to meet the US Pharmacopeia (USP) requirements and the tests and acceptance limits for Butylated Hydroxyanisole (BHA) and other substances.

Acceptable stability data were provided for the storage and shipment of the intermediate. The sitagliptin layer for all presentations is the same, while the simvastatin layer is direct scale-up. The tablets contain no unusual excipients and the quality of the excipients is adequately controlled. The lactose used in the tablets is from an acceptable source.

The tablets are well controlled with satisfactory expiry limits and release limits that allow for the changes observed on storage.

Stability data was provided to support the proposed shelf lives of 24 months when stored below 30ºC in aluminium-aluminium blister packs. No other conditions are required.

The chemistry and quality control aspects of the draft PI were finalised to the satisfaction of the quality evaluator as part of *The sponsor response to Delegate's overview* as the company's proposal to consolidate all PI changes at this stage, in line with the streamlined submission process was accepted by the TGA. The carton and blister foil labels (with a distinct colour scheme for each strength) and the Provisional ARTG Records were finalised at the time of issuance of the final quality evaluation[2].

Biopharmaceutics

Clinical studies were performed with monotherapy tablets as registered in Australia and these tablets were comparable in bioequivalence (BE) studies with FDC tablets whose formulations are the same as those proposed for registration with the exception of the film coating.

Biostudies were provided comparing the pharmacokinetics (PK) of sitagliptin, simvastatin, and simvastatin acid after administration of the FDC 100 mg/80 mg tablet and 100 mg/10 mg and co-administration of corresponding doses of sitagliptin and simvastatin monotherapy products as individual tablets respectively (Studies 153 and 255). The effect of food on the pharmacokinetics of FDC tablets was also provided in Study 155.

Justifications were included for not providing other bioavailability data on all strengths and the difference in non-functional film coat. Appropriately validated test methods for the determination of simvastatin, simvastatin acid and sitagliptin were used in the studies.

Study 153

In a 2-part, 2-way crossover, this study compared the relative bioavailability of the 100 mg/80 mg tablet to the bioavailability from a dose consisting of a 100 mg sitagliptin tablet and an 80 mg simvastatin tablet in a probe fashion (Part I) and to demonstrate bioequivalence (Table 2).

[2] The Good Manufacturing Practice (GMP) Clearances for the overseas manufacturers were acceptable until at least 17 September 2012 at the time of issuance of the final quality evaluation. The sponsor was aware an update would be required prior to registration. Updated GMP Clearances have now been submitted.

The results (see below) indicate that the pharmacokinetic profiles of sitagliptin, simvastatin and simvastatin acid from the "100 mg/80 mg" fixed dose combination tablet are bioequivalent to those from the co-administration of separate 100 mg sitagliptin and 80 mg simvastatin monotherapy tablets.

Table 2. Study 153 Bioavailability

Pharmacokinetic Parameter	MK-0431D			Simvastatin + Sitagliptin			MK-0431D / (Simvastatin + Sitagliptin)	
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
Sitagliptin								
$AUC_{0-\infty}$ ‡ (nM*hr)	99	7877	(7607, 8156)	99	7982	(7709, 8265)	0.99	(0.98, 1.00)
AUC_{0-last} ‡ (nM*hr)	99	7791	(7523, 8068)	99	7890	(7620, 8171)	0.99	(0.98, 1.00)
C_{max} ‡ (nM)	99	913	(862, 966)	99	935	(884, 990)	0.98	(0.93, 1.02)
T_{max} ǀ (hr)	99	2.0	(0.5, 6.0)	99	2.0	(0.5, 6.0)	-	
Apparent $t_{1/2}$ § (hr)	99	11.5	3.2	99	11.9	3.2	-	
Simvastatin								
AUC_{0-last} ‡ (ng/mL*hr)	99	106.88	(95.98, 119.02)	99	108.10	(97.08, 120.38)	0.99	(0.93, 1.05)
C_{max} ‡ (ng/mL)	99	14.96	(13.32, 16.82)	99	15.20	(13.52, 17.08)	0.98	(0.92, 1.06)
T_{max} ǀ (hr)	99	1.5	(0.5, 12.0)	99	2.0	(0.5, 8.0)	-	
Simvastatin Acid								
AUC_{0-last} ‡ (ng/mL*hr)	99	51.05	(45.27, 57.57)	99	55.43	(49.15, 62.51)	0.92	(0.87, 0.98)
C_{max} ‡ (ng/mL)	99	4.07	(3.61, 4.58)	99	4.30	(3.82, 4.84)	0.95	(0.88, 1.02)
T_{max} ǀ (hr)	99	4.0	(2.5, 12.0)	99	4.0	(2.0, 12.0)	-	

‡ Back-transformed least-squares mean and confidence interval from linear mixed effects model performed on natural log-transformed values; GMR = Geometric least-squares mean ratio (MK-0431D / [Simvastatin + Sitagliptin])

ǀ Median (min, max) reported for T_{max}

§ Harmonic mean, jack-knife standard deviation reported for apparent $t_{1/2}$

GM = Geometric Least-Squares Mean, CI: Confidence Interval

Study 255

In a 2-way crossover, this study compared the relative bioavailability of the 100 mg/10 mg tablet to the bioavailability from a dose consisting of a 100 mg sitagliptin tablet and a 10 mg simvastatin tablet and demonstrated bioequivalence.

Table 3. Study 255 Bioavailability

Pharmacokinetic Parameter	MK-0431D			Simvastatin + Sitagliptin			MK-0431D / (Simvastatin + Sitagliptin)	
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
Sitagliptin								
$AUC_{0-\infty}$ ‡ (nM*hr)	94	8035	(7775, 8305)	97	7971	(7713, 8237)	1.01	(0.99, 1.02)
$AUC_{0\text{-last}}$ ‡ (nM*hr)	94	7945	(7686, 8212)	97	7874	(7618, 8137)	1.01	(0.99, 1.02)
C_{max} ‡ (nM)	95	896	(850, 946)	97	871	(826, 918)	1.03	(0.99, 1.07)
T_{max} ǀ (hr)	95	2.5	(0.5, 4.0)	97	2.5	(0.5, 6.0)	.	
Apparent Terminal $t_{1/2}$ § (hr)	94	11.3	3.1	97	11.5	3.2	.	
Simvastatin								
$AUC_{0\text{-last}}$ ‡ (ng/mL*hr)	95	8.55	(7.49, 9.77)	97	7.97	(6.98, 9.09)	1.07	(0.99, 1.16)
C_{max} ‡ (ng/mL)	95	2.24	(1.97, 2.55)	97	1.98	(1.75, 2.25)	1.13	(1.05, 1.21)
T_{max} ǀ (hr)	95	1.5	(0.5, 8.0)	97	1.5	(0.5, 12.0)	.	
Simvastatin Acid								
$AUC_{0\text{-last}}$ ‡ (ng/mL*hr)	95	7.07	(6.23, 8.01)	97	6.85	(6.04, 7.76)	1.03	(0.96, 1.11)
C_{max} ‡ (ng/mL)	95	0.77	(0.69, 0.87)	97	0.74	(0.66, 0.84)	1.04	(0.97, 1.12)
T_{max} ǀ (hr)	95	6.0	(2.5, 10.0)	97	6.0	(3.0, 12.0)	.	

‡ Back-transformed least-squares mean and confidence interval from linear mixed effects model performed on natural log-transformed values; GMR = Geometric least-squares mean ratio (MK-0431D / [simvastatin + sitagliptin])
ǀ Median (min, max) reported for T_{max}
§ Harmonic mean, jack-knife standard deviation reported for apparent terminal $t_{1/2}$
GM = Geometric Least-Squares Mean, CI: Confidence Interval

The results (see above) indicate that the pharmacokinetic profiles of sitagliptin, simvastatin and simvastatin acid from the "100 mg/10 mg" fixed dose combination tablet are bioequivalent to those from the co-administration of separate 100 mg sitagliptin and 10 mg simvastatin tablets.

Study 155

In a 2-way cross-over, this study compared the relative bioavailability of the sitagliptin/simvastatin 100 mg/80 mg FDC tablet under both fasted and fed (Treatments A and B, respectively) in healthy male and female subjects.

The results indicate that the administration of the sitagliptin/simvastatin 100 mg/80 mg FDC tablet after a standard high-fat meal does not affect the pharmacokinetics of sitagliptin nor meaningfully affect the $AUC_{0\text{-last}}$ of simvastatin and simvastatin acid, however it increases the C_{max} of both simvastatin and simvastatin acid by 20% and 116%, respectively, compared to administration in the fasted state. This was brought to attention of the Delegate.

Justification submitted for non-supply of bioequivalence data for the 100 mg/20 mg and 100 mg/40 mg tablets

No bioequivalence data have been provided for the proposed 100 mg/20 mg and 100 mg/40 mg sitagliptin/simvastatin FDC tablets comparing to their respective doses consisting of a 100 mg sitagliptin tablet and either 20 mg or 40 mg simvastatin tablets. A justification for this omission was provided. The chemistry and quality control aspects were acceptable to quality evaluator and the clinical aspects were acceptable to the Pharmaceutical Subcommittee (PSC).

Justification submitted for the non-functional film coat changes

The company proposed that commercial formulations will utilise the same materials (grades and quantities) as the batches used in the stability and BE studies, with the

exception of the film coating. The proposed commercial formulation contains the same base formula film coating, but with different levels of colourants (these have been adjusted in order to meet market colour preferences). A justification for this minor change in the quantity of colorant in the formulations was provided. The chemistry and quality control aspects were acceptable to quality evaluator as well as to the PSC.

Other bioavailability comments

No data on the absolute bioavailability of the tablets has been provided. However, given the results of the studies provided, it will be accepted that results for the proposed fixed-dose combination tablets are similar to those for the relevant monotherapy tablets.

No effects of simvastatin on the pharmacokinetics of sitagliptin were identified (Study P168). The effects of sitagliptin on the pharmacokinetics of simvastatin were investigated and it was not possible to conclude whether there is an interaction or not (Study P025)[3]. These studies were not evaluated by the quality evaluator.

Finally, the bioavailability information included in the draft PI documents are consistent with the results of the studies evaluated.

Advisory committee considerations

Details of this submission were presented at the 145th meeting of the PSC in May 2012. The PSC endorsed all questions raised by the quality evaluator and had no objections to approval of these products provided all issues were addressed to the satisfaction of the TGA. The PSC reiterated its objection to the use of multiple trade names for products containing the same drug substance.

The PSC recommended that the following Product Information should be amended:

- The "*Description*" section should be amended to include the pKa, solubility and partition coefficient as functions of pH.
- The following statement "Butylated hydroxyanisole is added as a preservative" under the "*Description*" section should be amended to read "Butylated hydroxyanisole is added as an antioxidant".
- The "*Excretion*" section includes information on the apparent terminal half-life for elimination of sitagliptin. This section should be amended to include comparable information for simvastatin.

The sponsor responded that they will consolidate all PI changes and submit as part of the sponsor response to Delegate's overview (see *Sponsor Response* below) in line with the streamlined submission process.

Quality summary and conclusions

Approval of the company's application is recommended with respect to chemistry and quality control.

With respect to bioavailability, data was provided (in this or earlier submissions):

- to demonstrate bioequivalence of sitagliptin, simvastatin and simvastatin acid when administered as the combination sitagliptin (as phosphate monohydrate) and

[3] Sponsor comment: "Both Studies P025 and P168 have been subject to clinical evaluation during the current submission. See pages 18-19 of this AusPAR for the clinical evaluator's conclusions on PK."

simvastatin tablets to sitagliptin, simvastatin and simvastatin acid when administered as a co-administration of sitagliptin and simvastatin monotherapy tablets.

- to show that food does not affect the pharmacokinetics of sitagliptin, nor meaningfully affect the $AUC_{0\text{-last}}$ of simvastatin and simvastatin acid. However it increases the C_{max} of both simvastatin and simvastatin acid by 20% and 116%, respectively, compared to administration in the fasted state.
- and that no effects of simvastatin on the PK of sitagliptin were identified. The effects of sitagliptin on the PK of simvastatin were investigated however it was not possible to conclude whether there is an interaction or not.

III. Nonclinical findings

Introduction

The nonclinical submission consisted of a 3-month toxicity study with the proposed combination in rats. Two reports on the toxicity of simvastatin were also submitted as reference material. The package of nonclinical studies was in accordance with recommendations in the TGA adopted EU guideline on the nonclinical development of fixed combinations of medicinal products.[4]

Pharmacology

There were no pharmacology data included with the nonclinical submission.

Pharmacokinetics

In human subjects, cytochrome P450 (CYP) isozyme CYP3A4 is the major enzyme involved in the oxidative metabolism of simvastatin. Sitagliptin undergoes limited metabolism and showed no clinically significant inhibition or induction of CYP450 enzymes. Based on these findings, metabolic drug interactions between sitagliptin and simvastatin are not predicted. Consistent with this, co-administration of simvastatin had no effect on the area under curve (AUC) of sitagliptin in rats or human subjects. Lower AUC values for simvastatin and its active metabolite, simvastatin acid, were seen in female rats receiving sitagliptin with 30 mg/kg/day PO simvastatin compared to simvastatin alone. This was not seen at a higher simvastatin dose (60 mg/kg/day per os (PO)), nor was it seen in male rats or in human subjects. Therefore, this effect in female rats is not expected to be clinically meaningful.

Toxicology

The repeat dose toxicity study of the sitagliptin/simvastatin combination in rats was of 3 months duration. Rats were considered an appropriate model for toxicity studies with sitagliptin and this species has been used previously to assess the toxicity of both sitagliptin and simvastatin. The study used the clinical route (PO) and the dose ratios of simvastatin/sitagliptin (1:3–1:6) were similar to that anticipated clinically (1:2.5–1:10). Exposures to simvastatin, simvastatin acid and sitagliptin were at least 2, 51 and 21 times the anticipated clinical exposure, respectively, indicating adequate doses were chosen.

[4]Guideline on the nonclinical development of fixed combinations of medicinal products (EMEA/CHMP/SWP/258498/2005) <http://www.tga.gov.au/pdf/euguide/swp25849805final.pdf>

Parallel single-agent control groups were used, although comprehensive post-mortem analyses were not conducted on the sitagliptin control group.

Toxicities with simvastatin in rats were consistent with those reported previously, with target organs being the liver (increased liver weights with increased incidence of centrilobular hypertrophy in females and increased levels of serum alanine aminotransferase (ALT)), non glandular stomach (acanthosis, hyperkeratosis and inflammation) and the thyroid (follicular cell hyperplasia).

No new toxicities were seen in animals treated with the simvastatin/sitagliptin combination. However, there appeared to be more marked hepatotoxicity in these groups *cf* those treated with sitagliptin or simvastatin alone. This was characterised by higher serum levels of ALT and heavier liver weights. At necropsy, bile duct hyperplasia was seen in 6/10 males treated with the high dose (HD) simvastatin/sitagliptin combination. This lesion was not observed in any animal from any other treatment group. As the livers in animals treated with the lower simvastatin dose were not examined extensively, a No observable effect level (NOEL) was not established.

Table 4. Relative exposures of simvastatin, simvastatin acid and sitagliptin in the repeat-dose toxicity study

Species (Strain); Study; [Treatment duration]	Dose (mg/kg/day)		AUC_{0-24h} (nM·h)					Exposure ratio[a]				
			Simvastatin		Simvastatin acid		Sitagliptin	Simvastatin		Simvastatin acid		Sita-gliptin
	Simvastatin	Sitagliptin	M	F	M	F	M/F	M	F	M	F	M/F
Rat (SD) TT #09-1083 [3 months]	30	0	237	851	2980	9020	–	2	7	51	154	–
	30	180	254	347	4740	4710	193 000	2	3	81	81	25
	60	0	609	1600	6230	15500	–	5	13	106	265	–
	60	180	686	1680	5590	13600	176 000	5	13	96	232	23
	0	180	–	–	–	–	163 000	–	–	–	–	21
Human[b] P153	40 mg	100 mg	127.5		58.5		7791	–		–		–

[a]calculated as animal:human AUC_{0-24h}; [b]maximum recommended clinical dose is 40/100 mg simvastatin/sitagliptin, plasma AUC_{last} values for this dose were extrapolated from the AUC_{last} data obtained after dosing with the 80/100 mg simvastatin/sitagliptin fixed dose tablets

Interactions with other anti-diabetic agents

Sitagliptin is not currently registered in Australia as monotherapy but it is registered as dual combination therapy with metformin, or with a sulfonylurea, or with a thiazolidinedione. The proposed indication for Juvicor simvastatin/sitagliptin fixed dose combination tablets appears to include concomitant use with metformin, a sulfonylurea or a thiazolidinedione. No data were provided in the nonclinical dossier to address the potential pharmacological, pharmacokinetic or toxicological interactions of these other antidiabetics with simvastatin. Evidence to support the use of these other antidiabetics with Juvicor should therefore rely entirely on clinical data submitted in the clinical dossier.

Nonclinical summary and conclusions

- No nonclinical studies were submitted to assess potential pharmacological interactions.
- Based on analyses of drug plasma levels in rats, no clinically meaningful pharmacokinetic drug interactions are predicted with the proposed combination.
- One repeat dose toxicity study of 3 months duration was submitted. No novel toxicities were seen in animals treated with the simvastatin/sitagliptin combination. However, the data indicate the potential for greater hepatotoxicity with a sitagliptin/simvastatin combination compared to sitagliptin or simvastatin alone.
- There are no objections on nonclinical grounds to the registration of Juvicor/Xelezor/Tesozor. The proposed indication for Juvicor includes concomitant use with metformin, a sulfonylurea or a thiazolidinedione. No data were provided to address potential pharmacological, pharmacokinetic or toxicological interactions of these other antidiabetics with simvastatin. Therefore, support for these combinations needs to rely solely on clinical data.
- Amendments to the draft Product Information were recommended but the details of these are beyond the scope of this AusPAR.

IV. Clinical findings

Introduction

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

Clinical rationale

The product is proposed as a therapeutic tool to help achieve improved clinical outcomes for patients with T2DM. Sitagliptin is documented to improve glycaemic control and is registered for therapeutic use in T2DM. Simvastatin is documented to reduce the atherogenic components of plasma cholesterol and in consequence to reduce the incidence of related cardiovascular events. Macrovascular disease is a major cause of morbidity in T2DM and it is documented that its clinical effects can be lessened by pharmacological control of both plasma glucose and cholesterol. Accordingly, therapeutic guidelines recommend lower targets for plasma cholesterol in patients with T2DM, as well as a higher threshold for the introduction of therapeutic agents such as statins. This is also reflected in the guidelines for subsidy of these drugs through the PBS.

As a result of the above factors, the sponsor identifies that there is a substantial population of Australian T2DM patients who are either already receiving or would justify the administration of the combination of sitagliptin and a statin. The sponsor argues that the availability of a combination of these two therapeutic classes would improve the convenience of, and compliance with, such combination treatment. Although not stated, it is also evident that such a combination product might imply a cost reduction for patients.

The choice of the specific substances comprising this fixed combination product is influenced by the sponsoring company's history of innovation in both therapeutic classes. Sitagliptin was the first member of the class of Dipeptidyl peptidase 4 (DPP4) inhibitors[5]

[5] Inhibitors of dipeptidyl peptidase 4, also DPP-4 inhibitors or gliptins, are a class of oral hypoglycemics that can be used to treat diabetes mellitus Type 2.

introduced for therapeutic use in the past decade. Much earlier, the company's products simvastatin and its immediate predecessor lovastatin were the first HMG-CoA reductase inhibitors introduced for clinical use, and the landmark 4S study[6] employing simvastatin was the first demonstration of improved cardiovascular outcomes with use of these drugs.

Scope of the clinical dossier

The submission contained the following clinical information:

- Seven clinical pharmacology studies, listed below, which specifically support the submission and provide data upon which this evaluation report is based.

Table 5. Clinical Pharmacology studies submitted

Study Type	Protocol Number
Biopharmaceutics Studies	
MK-0431D Tablet Probe Formulation Study	P154
MK-0431D Tablet Definitive Bioequivalence Study	P153
MK-0431D Tablet Food Effect Study	P155
MK-0431D Tablet Definitive Bioequivalence Study	P255
Pharmacokinetic Studies	
Simvastatin Interaction Study[1]	P025
Sitagliptin Interaction Study	P168
Digoxin Interaction Study	P169
[1] Component of original sitagliptin filing Dec-2005.	

Studies P025, P153, P155, P168, and P255 are regarded as pivotal.

- Additionally, there are included reports of 18 studies and 5 extensions thereof supporting various aspects of the efficacy/safety of sitagliptin. These, with the addition of Study P801, constitute the 19 studies referred to on pages 6 and 7 of the letter of application (not included in this AusPAR) as supporting the efficacy and safety of the product. They are regarded as supportive only as none involves the administration of the applicant's product and are derived from the original development program for sitagliptin. The majority have been previously evaluated by TGA, but 10 (P040, P047, P049, P051, P052, P053, P061, P064, P079; and P801 which is listed separately as reference 1996), along with 7 of the extension studies, have not. Summaries of all these studies (except P801) appeared in the form of a tabular listing.
- There were 208 documents containing analyses of various aspects of safety in relation to the concomitant use of simvastatin and sitagliptin and two literature references on safety aspects.

[6] The Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383-1389

Paediatric data

The submission did not include paediatric data. Paediatric use is excluded by the indications. Additionally, the sponsor points in their submission that simvastatin is not indicated for use in children, the combination is accordingly unlikely to be used in a substantial number of paediatric patients and therefore a waiver from the requirement for a paediatric development program is justified.

Good clinical practice

Apart from isolated episodes of non-compliance, none serious, documented in the study reports, the principles of good clinical practice appear to have been followed throughout the included trials.

Pharmacokinetics

Studies providing pharmacokinetic data

Summaries of the PK studies were included the Clinical Evaluation Report (CER). Table 6 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 6. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
PK in healthy adults	Bioequivalence† - Single dose	P154 P153 P255
	Food effect	P155
PK interactions	Sitagliptin on simvastatin PK	P025
	Simvastatin on sitagliptin PK	P168
	Sitagliptin + simvastatin on digoxin PK	P169

† Bioequivalence of different formulations.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Evaluator's overall conclusions on pharmacokinetics

The sponsor has provided good evidence that the proposed combination tablet is bioequivalent to its component substances simvastatin and sitagliptin coadministered as separate tablets, across the dose range proposed. The comparator preparations used in the studies supporting this conclusion are Australian registered products.

Evidence is produced that each of the component drugs is free of influence on the PK of the other.

Both simvastatin and sitagliptin have been previously documented to influence, by different mechanisms, the PK of digoxin so as to moderately increase its exposure. With co-administration, it is shown that these effects are additive. An appropriate comment is included in the proposed PI.

With regard to the possible food effect, if the conclusion is supported that increased simvastatin acid exposure occurs specifically with a high-fat meal, there might be a case for including a cautionary note about this finding in the PI; although perhaps the ultimate point is that patients being treated with simvastatin should not be having a high-fat meal in any case.

Pharmacodynamics

While no pharmacodynamic (PD) studies are included in the submission, the issue of the time course of the PD action of sitagliptin is felt to be of potential relevance in relation to the change from morning to evening administration of this component of the combination tablet, which is imposed by its dosing schedule.

Evaluator's overall conclusions on pharmacodynamics

As described above, substitution of MK-0431D for separate administration of its component substances simvastatin and sitagliptin involves a change in the timing of administration of sitagliptin from morning to evening. Section III.1.2 of the TGA adopted EU guideline on fixed combination products[7] states that under these circumstances "….. (the sponsor) should demonstrate that the change in timing of administration of one of the components of the combination does not affect the pharmacodynamic effect of any of the constituents of the combination. Therefore, in addition to the demonstration of a similar pharmacokinetic profile, a noninferiority pharmacodynamic study assessing the effect of the combination as compared with those components administered at their usual dose time is expected."

In the draft PI at 1.3.1, in a section reproduced verbatim from the Januvia PI, it is stated that "in phase 2 studies, sitagliptin 50 mg twice a provided no additional glycaemic efficacy compared to 100 mg once daily". This is the only information which can be found in the application related to variation in dosage schedule, apart from a brief statement on dosage timing, unsupported by data, in the sponsor's Summary of Clinical Efficacy. No data is provided regarding the impact, or lack of impact, of giving the daily dose in the evening. As noted in *Time course of pharmacodynamic effects* (of the CER), the possibility of a variation in glycaemic efficacy resulting from this change in dosage timing cannot be excluded.

The sponsor should either comply with the EU guideline recommendation regarding the performance of a PD study, or at a minimum justify non-performance of such a study with further data.

Efficacy

The sponsor's case for demonstrating efficacy of the Juvicor combination tablet is based on the following set of arguments, copied from the sponsor's Summary of Clinical Efficacy:

[7] EMEA guideline, 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 23 June 2005.
<http://www.tga.gov.au/pdf/euguide/chmp19158305en.pdf>

Bridging of the efficacy observed in the sitagliptin and simvastatin development programs to MK-0431D is supported by:

1. Demonstration of bioequivalence between the MK-0431D FDC tablets and the coadministration of corresponding doses of sitagliptin and simvastatin.
2. Demonstration of the absence of a clinically meaningful effect of sitagliptin on the pharmacokinetic properties of simvastatin.
3. Demonstration of the absence of a clinically meaningful effect of simvastatin on the pharmacokinetic properties of sitagliptin.
4. Data from individual sitagliptin studies showing generally neutral effects of sitagliptin on serum cholesterol levels.
5. Data from simvastatin and sitagliptin studies showing generally neutral effects of simvastatin/statins on glycaemic control in patients with T2DM.

Points 1 to 3 have already been covered above in the *Pharmacokinetics* section to the satisfaction of this evaluation.

Points 4 and 5 are addressed by the sponsor referring to and providing analyses of a total of 19 sitagliptin efficacy studies as listed in their letter of application and described under *Scope of the Clinical Dossier* above. Although some of these studies have been previously evaluated for TGA, the data on plasma cholesterol and other lipid levels has not received detailed attention in previous evaluation reports (2, 7), so brief descriptive summaries of all 19 were made by the clinical evaluator.

Dosage Selection for the pivotal studies

No Phase III studies involving the administration of the fixed dosage combination tablet are included in the submission. Evidence for efficacy and safety rests firstly on the pivotal biopharmaceutical and bioequivalence studies reviewed in earlier sections of this evaluation report, and secondly on interpretive summaries provided in the submission, based on data from the clinical development programs supporting registration of the parent products Januvia (sitagliptin) and Zocor (simvastatin) from which this fixed combination product is derived. The Phase III studies on which the summaries are based were reviewed.

Evaluator's conclusions on clinical efficacy

Given the adequate demonstration of bioequivalence of MK-0431D (Juvicor fixed combination tablet) with its component substances sitagliptin and simvastatin co-administered as separate tablets, and the demonstration that these two drugs were free of mutual PK interaction when coadministered, the task of The sponsor was to demonstrate that the therapeutic efficacy of the two components, for their respective indications, is maintained during co-administration. This has been adequately addressed by the strategy summarised under points 4 and 5 (see above)). It is therefore the conclusion of this evaluation that:

- the therapeutic efficacy of sitagliptin for glycaemic control in T2DM is unimpaired by its co-administration with simvastatin;
- the therapeutic efficacy of simvastatin for control of hypercholesterolaemia in T2DM patients is unimpaired by its co-administration with sitagliptin; and that
- with the proviso that efficacy of the sitagliptin component of the combination tablet might be influenced by pharmacodynamic factors relating to its being administered in the evening, efficacy of both of the above drugs is equivalent whether coadministered in the form of MK-0431D (Juvicor) or as the separate formulations Januvia and Zocor.

A further proviso is that the conclusion regarding the therapeutic efficacy of simvastatin remaining unimpaired during co-administration with sitagliptin rests on the pharmacokinetic data showing no interaction, and on there being no known plausible mechanism by which sitagliptin might interfere with simvastatin's biological action. A pharmacodynamic interaction study to firmly exclude that possibility has not been performed.

A further aspect of efficacy is that of compliance. Improved compliance can, in turn, improve efficacy both in individual patients and in an epidemiological sense. Compliance with this product, by comparison with separately taking its component substances, has not been directly studied but the sponsor provided an analysis of the compliance advantage gained by its combination lipid-lowering product Vytorin (simvastatin/ezetimibe). This averaged 12.2% over a range of comparator therapies requiring compliance with two separate lipid-lowering medications. Juvicor shares some characteristics with Vytorin, as a fixed dosage combination used in patients with a chronic metabolic disorder, usually asymptomatic, in whom long-term therapy is required. Extrapolation of these data to the clinical use of Juvicor therefore has some basis.

Safety

The only safety observations relating directly to administration of the combination tablet MK-0431D are those undertaken in the small population of healthy subjects who received mostly single doses of the product during the pharmacokinetic/bioequivalence studies described above in *Pharmacokinetics*. These data revealed no safety issues of concern regarding the product itself, as opposed to its interaction with digoxin, described in Study P169 but do not constitute an exposure population adequate or relevant for safety assessment.

For the reasons described in the efficacy evaluation in the section on *Safety*, safety assessment depends on analysis of data provided by the sponsor arising from the development programs for the parent products Januvia (sitagliptin) and Zocor (simvastatin). These data, derived from the studies, are presented in the sponsor's *Summary of Clinical Safety* using the approach of assessing safety and tolerability of the co-administration of sitagliptin and simvastatin in this pool of sitagliptin studies. It is assumed that the reciprocal of this approach has not been employed for the reason that sitagliptin was not available at the time simvastatin was under development. An additional approach used is to assess potential class effect of statins by examining the data of patients who were coadministered sitagliptin and a statin in a pool of sitagliptin studies.

The individual safety and adverse event profiles for sitagliptin and simvastatin are well documented and the only issues requiring consideration are whether any of the known safety concerns for either drug are amplified by co-administration with the other, and whether any additional adverse events have been identified exclusively in the co-administration setting.

As the sponsor of both component products at the innovator stage, the applicant has ready access to comprehensive data on which this safety assessment is based.

Altogether, the database for this safety assessment comprised 3665 patients, randomised to sitagliptin or placebo, and who were also co-administered at least one dose of any statin during the treatment period. Of these, 1582 had at least one dose of simvastatin specifically. Other oral hypoglycaemic agents were taken by 507 subjects, including 339 on metformin and 68 on a thiazolidinedione.

A summary of reported AE by system organ class (SOC) in patients belonging to the all statins populations, exposed or not exposed to sitagliptin 100 mg daily, were included.

Evaluator's overall conclusions on clinical safety

The sponsor has conducted a detailed analysis of the AE profile for the combined use of sitagliptin and simvastatin. This analysis was carried out on pooled data of controlled trials in which the possibility of AE is actively explored; the likelihood of under reporting of unusual events is therefore low. The overall result of the analysis shows no qualitative or quantitative pattern of AEs that cannot attributable to the known effects of the separate components of the product. Significant AE patterns include effects known to occur with statin use, including muscle disorders and related biochemical abnormalities, and liver function abnormalities. The incidence of these events was not increased in those taking sitagliptin as well as simvastatin or any statin: in summary, the side effect profile of the combination is basically that of the statin component with no evidence of any amplification due to co-administration of the two drugs.

The electrocardiogram (ECG) event possibly related to increased exposure to digoxin in Study P169, and the overall results of that study showing increased exposure from the additive effects of simvastatin and sitagliptin, is in the opinion of this evaluator more significant than the study authors consider. A comment and related question are provided at *List of Questions Safety* below.

These conclusions on clinical safety need to be seen in the context that they represent an assessment of the risks associated with co-administration of sitagliptin and simvastatin, rather than the combination tablet as such. These two drugs are in common use in the target population of T2DM patients with high plasma cholesterol and in many cases the use of Juvicor will take the form of a substitution for existing therapy with both agents. However, it should be noted that as sitagliptin is not at this time authorised for first-line treatment in Australia, patients using Juvicor would by definition be using another antidiabetic agent. As noted above, there has been no specific analysis of safety for such multiple combinations and if the application is approved this should be a specific requirement for ongoing pharmacovigilance.

Clinical summary and conclusions

First round benefit-risk assessment

First round assessment of benefits

The benefits of Juvicor in the proposed usage are:

Improved glycaemic control of T2DM, as specified in the indications and supported by data for the parent product Januvia (sitagliptin); the benefit is no more and no less than that applying to sitagliptin for which the benefit profile is well established, including additional benefits in terms of parameters such as beta cell function which are suggested and supported by the data.

Reduction in low density lipoprotein (LDL) cholesterol levels as a result of the simvastatin component of the combination, and with long-term use a consequent reduction in cardiovascular events. Again, the benefit is no more and no less than that attributable to simvastatin given alone.

An additional benefit may be attributable to improvement in compliance. Obviously this benefit will only apply to that proportion of patients who take the medicine more regularly because of its combination nature.

First round assessment of risks

The risks of Juvicor in the proposed usage are those attributable to the adverse effect profile of the component drugs sitagliptin and simvastatin. These are products in common

use and with well established safety profiles which need not be detailed in this report. As outlined under *Safety*, there is no evidence of significant risks attributable to their co-administration or to their combination in a single formulation. Consistent with this, it is understood that TGA is not requiring a specific risk management plan for the combination product.

First round assessment of benefit-risk balance

The benefit-risk balance of Juvicor, given the proposed usage, appears favourable but cannot be properly assessed without answers to the questions on PK (meal effect) and PD (time of day effect) posed under *List of Questions* below, which may impact on the safety of the product.

First round recommendation regarding authorisation

The findings of this evaluation have raised a number of questions which preclude an immediate recommendation for authorisation. Pending resolution of these matters, the product may nevertheless be a suitable and worthwhile addition to the therapeutic armamentarium for the common comorbidities of Type 2 diabetes associated with dyslipidaemia.

If and when the application is approved, safety monitoring of the use of sitagliptin/simvastatin in combination with other oral hypoglycaemic agents should be a requirement for pharmacovigilance.

List of questions

1. **Pharmacokinetics**

   The sponsor should be asked to comment on the suggestion that the food (high-fat meal) effect on simvastatin PK demonstrated in Study P155, particularly the marked increase in exposure to the active hydroxyacid metabolite, might be clinically significant, particularly in the potential situation of co-administration of a CYP3A4 inhibitor, and whether they have further data which may clarify the situation. Note that this situation is potentially applicable to other formulations of simvastatin, not just the fixed combination tablet.

2. **Pharmacodynamics**

   The sponsor should be asked to justify the non-performance of a pharmacodynamic study in relation to dosage timing of sitagliptin.

3. **Efficacy**

   No questions raised except that the pharmacodynamics might influence efficacy.

4. **Safety**

   No questions except that implied by the suggested change in the PI statement regarding the effect of the combination therapy on digoxin PK.

5. **PI and CMI**

   No questions other than those raised above which may imply necessary changes to the PI and, in the case of the food effect, the Consumer Medicine Information (CMI).

Second round evaluation of clinical data submitted in response to questions

The questions put to the sponsor by TGA, arising from the first round report of this evaluation, are shown above. The sponsor's responses to these questions are summarised and discussed in the following sections of this second round report.

Second round benefit-risk assessment

Second round assessment of benefits

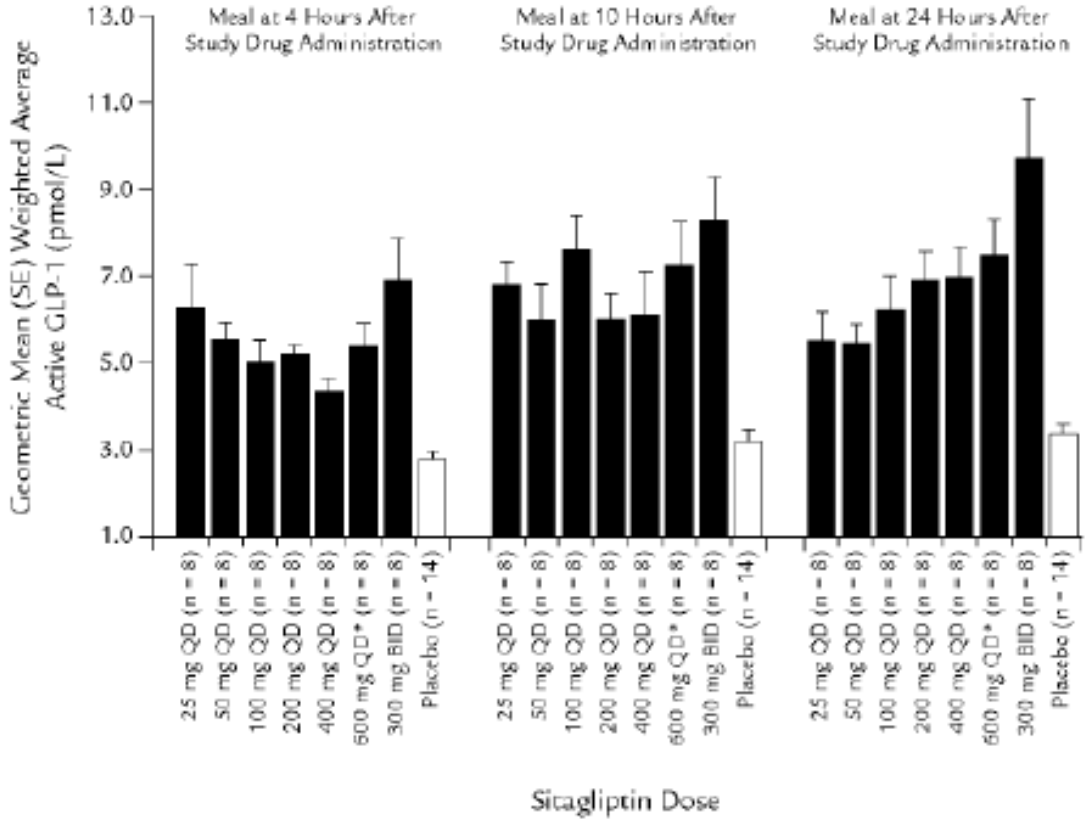
Questions 2 and 3 relate to the efficacy of the sitagliptin component of the combination tablet, the issue being whether the shift from morning to evening administration of sitagliptin, imposed by the obligation to give the product in the evening because of its simvastatin component, has any impact on its efficacy.

The sponsor's response to these questions (pp 29-33 of response letter; not included in this AusPAR) provides data from studies conducted in the development program for sitagliptin and can be summarised as follows:

PK of sitagliptin is suggested to be similar with morning and evening administration. A table is shown giving 12 h trough concentrations following evening dosing which are some 25% higher than those following morning dosing, with confidence intervals for the ratio not crossing unity, despite which it is suggested that these differences would not be "clinically meaningful". More importantly, evidence is quoted that 80% inhibition of DPP4 is maintained 24 h following the 100 mg dose at steady state.

The most relevant data appears in Figure 1 (included as Figure 2, page 31 of sponsor's response letter reproduced below):

Figure 1. Effect of food



The enhancement of GLP-1 response to feeding is the key PD response to DPP4 inhibition. Whether there is an improvement in glycaemia is in turn dependent on the remaining

level of beta cell function, but it is the GLP-1 response which should be used as a measure of PD action, particularly with regard to the present question of whether that action is preserved over the 24 hour period following drug administration. The above shows clearly that this response is similar at 10 h and 24 h following all dosing levels including the 100 mg dose for this product.

These data effectively answer the concerns expressed in the first round evaluation regarding a potential time of day effect with regard to dosing, and are accepted as adequate justification for not having carried out a specific pharmacodynamic study with evening administration.

Whether the efficacy of sitagliptin is preserved with evening as opposed to morning administration might also be affected by compliance. This is not strictly a second round issue, as the point was not raised in the first-round report, but it is felt necessary to make some comment about this. A brief review of the literature provides some support (second round references[8,9]) for what clinicians would intuitively suspect, which is that compliance with morning administration of medication is in general superior to that for evening administration. This, therefore, might be regarded as a factor having a negative influence on the benefit of the combination tablet with respect to its sitagliptin component. On the other hand, it has been argued by the sponsor that compliance might be improved by the use of the combination tablet, presumably due to factors of cost and convenience, as discussed above.

Second round assessment of risks

Question 1 has two components: firstly, it asks for a response to the point that the food effect on simvastatin PK evident in Study P155 did not receive adequate comment in the original submission; and secondly that the apparent increase in simvastatin metabolite PK might have safety implications.

In their response (pp 26-28 section 31 response; not included with this AusPAR), the sponsor agrees that there is an evident food effect but presents a number of arguments against this being clinically significant. Reference is made to a study which shows that simvastatin acid (measured in Study P155) comprises only 25% of active HMG CoA reductase inhibitors and it is argued that the increase in the remaining active inhibitors may have been more modest but this is speculative rather than based on any actual data.

With regard to the suggestion that the food effect might pose an additional risk in the setting of concomitant use with CYP3A4 inhibitors, the sponsor draws attention to safety provisions in the current PI for Zocor, the sponsor's simvastatin-only product which is the source of the simvastatin clinical data used for bridging purposes as outlined above. These consist of precautionary statements and dosage limitations in particular situations of concomitant use, and are particularly relevant as the sponsor has now submitted revised PI for the products incorporating changes which bring it into line with the existing approved PI for simvastatin (Zocor).

It was pointed out in the first-round report of this evaluation that this apparent food effect, along with its possible attendant safety risks, could be presumed to apply to other formulations of simvastatin, such as Zocor. The sponsor's response concurs with this and makes the case that any such safety issue might be reflected in adverse reactions, particularly muscle related side effects, reported in the safety studies and ongoing pharmacovigilance of Zocor. It is suggested that no such pattern of risk has been evident. Presuming that information available to TGA agrees with that assessment, this is seen as a

[8] Fujii J and Seki (1985). A.Compliance and compliance-improving strategies in hypertension: the Japanese experience. J Hypertens Suppl. 3(1):S19-22

[9] Hayes TL et al. (2009). A study of medication-taking and unobtrusive, intelligent reminding. J E Health 15(8):770-6.

valid argument. Because there is no evidence of PK interaction between the components of Juvicor, there should be no need to discriminate between Juvicor and other simvastatin formulations such as Zocor on safety grounds relating to simvastatin exposure.

Second round assessment of benefit-risk balance

The concerns expressed *First Round Assessment of Risks* regarding the possible impact of food effect on safety (risk), and a possible efficacy (benefit) issue relating to evening administration have been adequately addressed as noted above. In view of these considerations, the benefit-risk balance of the combination sitagliptin/simvastatin tablet (Juvicor) is seen as equivalent to that of the two medications administered as separate tablets, and therefore satisfactory in the context of the application.

The potential effect of evening by comparison with morning administration on compliance, as noted in *Studies Providing Pharmacokinetic Data* above, is a minor hypothetical concern with regard to the benefit of the product, but potentially counteracted by the sponsor's argument that compliance might be enhanced by the combination nature of the product.

Second round recommendation regarding authorisation

It is now the recommendation of this evaluation that the combination sitagliptin/simvastatin product Juvicor is suitable for authorisation for the indications stated in the application.

As recommended in First Round Recommendation Regarding Authorisation, safety monitoring of the use of sitagliptin/simvastatin in combination with other oral hypoglycaemic agents should be a requirement for pharmacovigilance.

V. Pharmacovigilance findings

The applicant was granted an exemption from undertaking a specific risk management plan by the Office of Product Review.

VI. Overall conclusion and risk/benefit assessment

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

Background

Januvia was first considered by the Australian Drug Evaluation Committee (ADEC; now called Advisory Committee on Prescription Medicines (ACPM) at its 254th Meeting on 4th – 5th October, 2007.

The proposed indications were:

> *Monotherapy: as an adjunct to diet and exercise to improve glycaemic control in patients with Type 2 diabetes mellitus.*
>
> *Dual Combination Therapy: in patients with Type 2 diabetes mellitus to improve glycaemic control in combination with metformin, a sulfonylurea, or a PPARγ agonist (e.g., thiazolidinediones) when diet and exercise, plus the single agent do not provide adequate glycaemic control.*
>
> *Triple Combination Therapy: in patients with Type 2 diabetes mellitus to improve glycaemic control in combination with both metformin and a sulfonylurea when diet and exercise, plus both agents do not provide adequate glycaemic control.*

Initial combination therapy with metformin was not a feature of the previous application.

As previously noted by the Committee "*The studies used intermediate endpoints such as HbA1c but no long term morbidity or mortality studies were submitted. Sitagliptin was significantly more efficacious in all studies than placebo in reducing HbA1c over 24-52 weeks in adult patients with Type 2 diabetes mellitus*."

The clinical evaluator recommended limited registration of sitagliptin as monotherapy and as dual combination therapy with metformin or with a PPARγ agonist. The evaluator considered that there was insufficient duration of experience to recommend the combination with sulphonylureas."

"*In the Delegate's view sitagliptin appears to offer some effects in early diabetes Type 2. The placebo controlled studies in monotherapy showed that sitagliptin is better than placebo over 24 weeks. The Phase III efficacy studies appear to have been well designed, with appropriate run-in periods and primary efficacy endpoints. However, failure to conduct a direct monotherapy comparison with metformin is a serious problem at least as far as assessing the place of sitagliptin in the Australian context. No information is available on the combination of sitagliptin with orlistat or acarbose, both of which might be used in early diabetes Type 2. In principle, sitagliptin might offer most benefit to patients with obesity and insulin resistance, making it likely to be used with metformin and in earlier stages of the disease when weight loss is still a possibility. The combination of sitagliptin with a thiazolidinedione would not ameliorate the adverse effects of the latter and the benefit of sitagliptin, lack of weight gain, would be lost. The current data set supports some role of sitagliptin in monotherapy but the durability of its effect is not known."*

"*The ADEC considered that although efficacy had been demonstrated there were insufficient safety data, especially long term, to recommend approval of sitagliptin for monotherapy. Clinical experience with sitagliptin in triple treatment with metformin and sulfonylureas was considered inadequate. However, data were adequate to recommend approval for sitagliptin as add-on therapy with metformin a sulfonylurea or with a thiazolidinedione*." Durability of efficacy was of some concern.

Resolution 9109

1. There should be no objection to approval of the submission from Merck Sharp & Dohme (Australia) Pty Ltd to register JANUVIA tablet containing the new chemical entity sitagliptin (as phosphate monohydrate) 25 mg, 50 mg and 100 mg for the indication:

   For the treatment of diabetes mellitus Type 2 in persons 18 years of age and older who have failed dietary measures and exercise:

   as dual combination therapy with metformin or with a sulfonylurea or with a thiazolidinedione where the use of a thiazolidinedione is considered appropriate.

2. Approval should be subject to the agreement to undertake a pharmacovigilance plan, acceptable to the TGA, especially addressing GIT tumours and late cancers; pancreatitis; GIT ischaemia; cardiovascular endpoint data; dental and skeletal effects; and the potential effects of any non-specificity of DPP4 antagonism.
3. Approval should be subject to finalisation of the Product Information to the satisfaction of the TGA.
   - The PI should include a statement that no data are yet available on sitagliptin's effects upon morbidity or mortality.
   - The PI should stress that use with sulfonylureas is associated with the risk of hypoglycaemia. The Dosage and Administration section of the PI should state which sulfonylurea has been studied in the clinical trial programme. The PI should

record the number of patients with hypoglycaemic events, not the number of events.

- The PI should address dental safety, monitoring for late cancers, and the cardiovascular endpoint data.
- The PI and CMI should clearly state that there are no long term morbidity and mortality outcome data and therefore the long-term risk:benefit ratio is unknown.
- The PI should include the toxicity tables from the clinical evaluation.
- The PI should express all efficacy results in SI units. It should report only the primary study endpoints unless the applicant can advance compelling reasons for presenting further intermediate endpoints.

4. The application by Merck Sharp & Dohme (Australia) Pty Ltd to register JANUVIA tablet containing the new chemical entity sitagliptin (as phosphate monohydrate) 25 mg, 50 mg and 100 mg for the indication:

   For the treatment of diabetes mellitus Type 2 in persons 18 years of age and older who have failed dietary measures and exercise:

   - a*s monotherapy adjunctive to diet and exercise to improve glycaemic control*
   - *as triple combination therapy with metformin and a sulfonylurea when both agents do not provide adequate glycaemic control*

should be rejected due to inadequate clinical experience to define efficacy and safety.

More recently, the Committee considered, at its 284th meeting in June 2012, a submission from Merck Sharp & Dohme Australia Pty Ltd to register an extended indication for Januvia film coated tablets containing sitagliptin (as phosphate monohydrate) 25 mg, 50 mg and 100 mg (the Products).

The proposed indication: (Replacement indications in bold):

*"**Monotherapy***

Januvia is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with Type 2 diabetes mellitus.

Individual Combination Therapy with metformin

Januvia is indicated in patients with Type 2 diabetes mellitus to improve glycaemic control in combination with metformin as initial therapy.

Add-on combination Therapy with Antihyperglycemic agents

For the treatment of diabetes mellitus Type 2 in persons 18 years of age and older who have failed dietary measures and exercise as dual combination therapy with metformin, or with a sulfonylurea, or with a thiazolidinedione where the use of a thiazolidinedione is considered appropriate."

The Delegate had proposed to register this indication:

"*Januvia is indicated for the treatment of diabetes mellitus Type 2 in persons 18 years of age and older who have failed dietary measures and exercise:*

- *as monotherapy, as an adjunct to diet and exercise to improve glycaemic control in patients with Type 2 diabetes mellitus, when metformin cannot be used.*
- *as dual combination therapy, with metformin, or with a sulfonylurea, or with a thiazolidinedione where the use of a thiazolidinedione is considered appropriate."*

In regard to efficacy, "*The ACPM considered the only new study submitted, P049, which was a non-inferiority multicentre, double blind randomised, controlled, parallel group comparison of sitagliptin 100 mg daily (N=455) to metformin (N=439), the dose of which was increased from 500 mg/day to 2000 mg/day over 3 weeks. A sample size of 400 subjects per group was estimated to deliver 97% power to determine a non-inferiority margin of 0.4%, assuming the true mean difference between treatments was <0.1%.*

The ACPM agreed that a 0.5% reduction in HbA1c has been associated with meaningful clinical benefit in Type 2 Diabetes Mellitus. The 0.4% reduction while less than desirable is not a trivial reduction and exceeds that seen with placebo in most of the studies submitted in support of this application. The ACPM advised that there is a discernable benefit from HbA1c reductions of this order in subjects with insulin dependent DM with baseline HbA1c of around 7%."

In regard to safety, "*The ACPM noted that elevated plasma lipids were observed in studies P021 and P023 and that this concerning signal should be specifically addressed in the RMP, together with the risk of:*

- *hypoglycaemia alone or with combination sulphonylurea therapy,*
- *AEs including vascular disease, pancreatitis, lactic acidosis and severe allergic reactions."*

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

Resolution 9668

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

Januvia is indicated for the treatment of diabetes mellitus Type 2 in persons 18 years of age and older who have failed dietary measures and exercise:

- *as monotherapy, as an adjunct to diet and exercise to improve glycaemic control in patients with Type 2 diabetes mellitus, when metformin cannot be used.*
- *as dual combination therapy, with metformin, or with a sulfonylurea, or with a thiazolidinedione where the use of a thiazolidinedione is considered appropriate.*

In making this recommendation, the ACPM noted and expressed disappointment in the study design due to the inadequacy in the design and selection of patients for the post 24 week duration of therapy.

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 to accurately reflect the limitations in the study design in terms of demonstrating the durability of the initial efficacy.
- A statement in the *Dosage and Administration* section of the PI and CMI to include reference to GFR and monitoring of the renal function and adverse effects.
- The ACPM advised that the Risk Management Plan be reviewed to ensure effective pharmacovigilance of the identified safety signals.''

Of note, the Committee retained concerns about the possible adverse effects of sitagliptin on blood lipids; there is also current interest in the literature about the increased risk of diabetes mellitus in persons to take HMG-CoA reductase inhibitors – see the FDA's

summary at http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm. This current matter of interest is of relevance to this application.

Tablets containing 5, 10, 20, 40 and 80 mg of simvastatin have been registered by Merck Sharp & Dohme (Australia) Pty Ltd for many years. There have been numerous applications in regard to extended indications and higher doses; these have been referred to the Committee. There are also numerous generic brands registered to other sponsors. The approved PI document includes specific reference to the benefits of simvastatin in patients who also have diabetes mellitus (The Heart Protection Study, the Scandinavian Simvastatin Survival Study).

Simvastatin is already registered in a fixed combination tablet: Vytorin® (Merck Sharp & Dohme (Australia) Pty Ltd) contains ezetimibe and simvastatin (10/10, 10/20, 10/40 and 10/80 mg/mg).

This current application, described in this AusPAR**,** comprised pharmaceutical chemistry, some nonclinical data and clinical data. In regard to the clinical data, the applicant said, when proposing the submission,

> "*Clinical:*
>
> *The sitagliptin and simvastatin tablets used in the bioequivalence studies comparing the single actives to the multilayer tablet are identical to the JANUVIA and ZOCOR tablets registered and marketed in Australia. The efficacy and safety of both sitagliptin (JANUVIA) and simvastatin (ZOCOR) have been established in separate clinical development programs, evaluated by the TGA.*
>
> *Submission is therefore based on:*
>
> 1. *Bioequivalence (BE) studies - P153, P154, P255, demonstrating BE of bilayer tablets to single actives.*
> 2. *Pharmacokinetic (PK) studies - P025 (previously evaluated in full by the TGA), P155, P168, P169, demonstrating no PK interactions between sitagliptin and simvastatin, and with food and digoxin.*
> 3. *De novo analyses of pooled data from 19 sitagliptin studies to support non-interaction and safety. This includes 2 studies previously evaluated by the TGA in full (P019, P035), 7 extensions to previously evaluated studies (P010, P014, P020, P021, P023, P024, P036), and 10 previously unevaluated studies (P040, P047, P049, P051, P052, P053, P061, P064, P079, P801). Full details of dataset similarities to previous submissions are outlined as a cover page to 2.7.6 and 5.2 (see attached).*
> 4. *Peer reviewed publication of pooled sitagliptin studies to support safety of sitagliptin.*
> 5. *Review of post-marketing data, including reports of drug-drug interactions, showing no new safe*ty concerns for concomitant sitagliptin and statin therapy."

Quality

The evaluator states that the bi-layered tablets comprise a sitagliptin layer that is for all presentations is the same, while the simvastatin layer is direct scale, for each strength, relative to the others. The tablets contain no unusual excipients and the quality of the excipients is adequately controlled. Stability data were provided to support the proposed shelf lives of 24 months when stored below 30ºC in aluminium-aluminium blister packs.

With regard to bioavailability, the submitted studies used formulations that are appropriate in terms of the currently registered single inactive ingredient tablets. The highest and lowest strength combination tablets (although with a difference in colour of

the film coat) were compared with the separate single active ingredient tablets, taken together. The evaluator was satisfied that validated test methods for the determination of simvastatin, simvastatin acid, and sitagliptin were used in the studies.

Study P153 examined the highest dose fixed combination tablet. It was of single centre, open label, randomised, 2-part, 2-way crossover design. One hundred subjects were enrolled in Part 2 of the study (the bioequivalence study). The enrolled volunteers were of mean age 35 years; weight: males 77.1 kg, females 62.2 kg; of these 98 completed Part 2 of the study.

Both the quality and clinical evaluators found the formulations to be bioequivalent.

Table 7. Part2. Pharmacokinetics Results

Pharmacokinetic Parameter	MK-0431D			Simvastatin + Sitagliptin			MK-0431D / (Simvastatin + Sitagliptin)	
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
Sitagliptin								
$AUC_{0-\infty}$ ‡ (nM*hr)	99	7877	(7607, 8156)	99	7982	(7709, 8265)	0.99	(0.98, 1.00)
$AUC_{0\text{-last}}$ ‡ (nM*hr)	99	7791	(7523, 8068)	99	7890	(7620, 8171)	0.99	(0.98, 1.00)
C_{max} ‡ (nM)	99	913	(862, 966)	99	935	(884, 990)	0.98	(0.93, 1.02)
T_{max} ǀ (hr)	99	2.0	(0.5, 6.0)	99	2.0	(0.5, 6.0)	-	
Apparent $t_{1/2}$ § (hr)	99	11.5	3.2	99	11.9	3.2	-	
Simvastatin								
$AUC_{0\text{-last}}$ ‡ (ng/mL*hr)	99	106.88	(95.98, 119.02)	99	108.10	(97.08, 120.38)	0.99	(0.93, 1.05)
C_{max} ‡ (ng/mL)	99	14.96	(13.32, 16.82)	99	15.20	(13.52, 17.08)	0.98	(0.92, 1.06)
T_{max} ǀ (hr)	99	1.5	(0.5, 12.0)	99	2.0	(0.5, 8.0)	-	
Simvastatin Acid								
$AUC_{0\text{-last}}$ ‡ (ng/mL*hr)	99	51.05	(45.27, 57.57)	99	55.43	(49.15, 62.51)	0.92	(0.87, 0.98)
C_{max} ‡ (ng/mL)	99	4.07	(3.61, 4.58)	99	4.30	(3.82, 4.84)	0.95	(0.88, 1.02)
T_{max} ǀ (hr)	99	4.0	(2.5, 12.0)	99	4.0	(2.0, 12.0)	-	

‡ Back-transformed least-squares mean and confidence interval from linear mixed effects model performed on natural log-transformed values; GMR = Geometric least-squares mean ratio (MK-0431D / [Simvastatin + Sitagliptin])

ǀ Median (min, max) reported for T_{max}

§ Harmonic mean, jack-knife standard deviation reported for apparent $t_{1/2}$

GM = Geometric Least-Squares Mean, CI: Confidence Interval

Study P255 was of similar design to Part 2 of Study P153 but it used a dose of 100 mg sitagliptin/10 mg simvastatin. The correct subject demographic data are:

Randomised:	100
Male (age range)	41 (19-54)
Female (age range)	59 (18-53)
Completed:	93
Discontinued:	7
Clinical adverse experience	0
Laboratory adverse experience	0
Other	7†

The BMI of the volunteers was <28kg/m^2.

The results reflect bioequivalence as shown in Table 8 below.

Table 8. Bioequivalence data

Pharmacokinetic Parameter	MK-0431D			Simvastatin + Sitagliptin			MK-0431D / (Simvastatin + Sitagliptin)	
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
Sitagliptin								
$AUC_{0-\infty}$ ‡ (nM*hr)	94	8035	(7775, 8305)	97	7971	(7713, 8237)	1.01	(0.99, 1.02)
AUC_{0-last} ‡ (nM*hr)	94	7945	(7686, 8212)	97	7874	(7618, 8137)	1.01	(0.99, 1.02)
C_{max} ‡ (nM)	95	896	(850, 946)	97	871	(826, 918)	1.03	(0.99, 1.07)
T_{max} ǀ (hr)	95	2.5	(0.5, 4.0)	97	2.5	(0.5, 6.0)	.	
Apparent Terminal $t_{1/2}$ § (hr)	94	11.3	3.1	97	11.5	3.2	.	
Simvastatin								
AUC_{0-last} ‡ (ng/mL*hr)	95	8.55	(7.49, 9.77)	97	7.97	(6.98, 9.09)	1.07	(0.99, 1.16)
C_{max} ‡ (ng/mL)	95	2.24	(1.97, 2.55)	97	1.98	(1.75, 2.25)	1.13	(1.05, 1.21)
T_{max} ǀ (hr)	95	1.5	(0.5, 8.0)	97	1.5	(0.5, 12.0)	.	
Simvastatin Acid								
AUC_{0-last} ‡ (ng/mL*hr)	95	7.07	(6.23, 8.01)	97	6.85	(6.04, 7.76)	1.03	(0.96, 1.11)
C_{max} ‡ (ng/mL)	95	0.77	(0.69, 0.87)	97	0.74	(0.66, 0.84)	1.04	(0.97, 1.12)
T_{max} ǀ (hr)	95	6.0	(2.5, 10.0)	97	6.0	(3.0, 12.0)	.	

‡ Back-transformed least-squares mean and confidence interval from linear mixed effects model performed on natural log-transformed values; GMR = Geometric least-squares mean ratio (MK-0431D / [simvastatin + sitagliptin])
ǀ Median (min, max) reported for T_{max}
§ Harmonic mean, jack-knife standard deviation reported for apparent terminal $t_{1/2}$
GM = Geometric Least-Squares Mean, CI: Confidence Interval

It is noted that the values obtained for simvastatin are not dose linear versus the previous study.

Study P155 was a 2-way cross-over, food study that compared the relative bioavailability of the sitagliptin/simvastatin 100 mg/80 mg FDC tablet under both fasted and fed (Treatments A and B, respectively) in healthy male and female subjects. Thirty-two subjects were enrolled (14 female); average age 32.3 years, body mass index (BMI) 26.2 (female) 25.8 (male). All enrolled subjects completed the study. A food effect (after a high-fat meal) was only found for the peak plasma concentration (C_{max}) of simvastatin and simvastatin acid, "[food] increases the C_{max} of both simvastatin and simvastatin acid by 20% and 116%, respectively, compared to administration in the fasted state." Of note, simvastatin acid is the principal active metabolite of simvastatin.

Table 9. Results from Study P155

Pharmacokinetic Parameter	MK-0431D Fed			MK-0431D Fasted			MK-0431D Fed/Fasted	
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
Sitagliptin								
$AUC_{0-\infty}$ † (nM•hr)	32	7266	(6907, 7643)	32	7263	(6904, 7640)	1.00	(0.98, 1.02)
AUC_{0-last} † (nM•hr)	32	7163	(6808, 7536)	32	7165	(6810, 7539)	1.00	(0.98, 1.02)
C_{max} † (nM)	32	764	(689, 846)	32	809	(731, 897)	0.94	(0.87, 1.03)
T_{max} ‡ (hr)	32	2.3	(0.5, 6.0)	32	2.0	(0.5, 5.0)		
Apparent terminal $t_{1/2}$ ǁ (hr)	32	12.9	2.7	32	12.6	2.8		
Simvastatin								
AUC_{0-last} † (ng/mL•hr)	32	67.39	(55.76, 81.45)	32	88.76	(73.44, 107.27)	0.76	(0.64, 0.90)
C_{max} † (ng/mL)	32	16.89	(13.61, 20.97)	32	14.08	(11.35, 17.48)	1.20	(0.97, 1.48)
T_{max} ‡ (hr)	32	2.0	(0.5, 6.0)	32	1.5	(0.5, 5.0)		
Simvastatin Acid								
AUC_{0-last} † (ng/mL•hr)	32	67.67	(54.36, 84.23)	32	49.27	(39.58, 61.33)	1.37	(1.16, 1.63)
C_{max} † (ng/mL)	32	9.33	(7.44, 11.70)	32	4.31	(3.44, 5.41)	2.16	(1.84, 2.55)
T_{max} ‡ (hr)	32	5.0	(2.3, 8.0)	32	4.0	(2.0, 12.0)		

† Back-transformed least-squares mean and CI from mixed effect model performed on natural log-transformed values; GMR = Geometric least-squares mean ratio (MK-0431D Fed/MK-0431D Fasted)
‡ Median (min, max) reported for T_{max}
ǁ Harmonic mean, jack-knife standard deviation reported for terminal apparent $t_{1/2}$
GM = Geometric Least-Squares Mean; CI = Confidence Interval

In regard to the difference in the quantity of colorants in the film layer of the tablets, a justification was provided. The chemistry and quality control aspects were acceptable to the evaluator as well as to the PSC.

Not all amendments to the draft PI document had been implemented by the time of finalisation of the evaluator's advice.

This submission was considered at the 145th meeting of the Pharmaceutical Subcommittee of ACPM in May, 2012. The PSC reiterated its objection to the use of multiple trade names for products containing the same drug substance.

The evaluator supports registration on chemistry and quality control grounds.

Nonclinical

The evaluator notes that the maximal clinical doses (100 mg/day sitagliptin and 40 mg/day simvastatin) are within the currently approved dose range for the individual components.

No new data were submitted to assess potential pharmacological interactions between simvastatin and sitagliptin. There were no toxicological studies on the proposed combination in combined use with other commonly used oral antidiabetic drugs.

Metabolic interactions are not expected between simvastatin and sitagliptin.

One repeat dose toxicity study, in rats, of 3 months duration was submitted on the combination that is proposed: it used the oral route; the dose ratios of simvastatin/sitagliptin (1:3–1:6) were similar to that expected clinically (1:2.5–1:10); and, exposures to simvastatin, simvastatin acid and sitagliptin were at least 2, 51 and 21 times the anticipated clinical exposure, that is, there is an adequate exposure margin in the study versus the proposed clinical dose. There were no treatment-related mortalities. The evaluator remarked, "*No new toxicities were seen in animals treated with the simvastatin/sitagliptin combination. However, there appeared to be more marked hepatotoxicity in these groups compared to those treated with sitagliptin or simvastatin alone*." "*However, these animals tended to have higher serum ALT levels and higher liver weights compared to animals in the simvastatin or sitagliptin only groups. At necropsy, bile duct hyperplasia was seen in 6/10 males treated with the HD simvastatin/sitagliptin combination. This lesion was not observed in any animal from any other treatment group*."

Some amendments to the proposed product information document were proposed.

Registration is not opposed on nonclinical grounds.

> *Comment*: The single new study warrants consideration in terms of its implications for detecting safety signals in humans. The study's results might suggest a higher risk of hepatotoxicity attributable to the combination than to monotherapy with either active. Specific post-marketing surveillance should be considered.

Clinical

The report is a composite of the initial and second round (reflecting answers to questions) reports.

The evaluator notes that the fixed combination product might offer some convenience to patients who require both drugs. The applicant also suggested improved compliance, without specific data.

In regard to the proposed dosing schedule, the evaluator observed,

> *"An immediately obvious conflict for this product is that of dosage timing. It is recommended in the draft PI that Juvicor be taken as a single dose in the evening; it is a combination of one drug (simvastatin) which is for good reasons … given in the evening, and another (sitagliptin) which is for less obvious reasons given in the morning. The approved PI for sitagliptin (Januvia) recommends once daily administration without being specific about timing of dosage, but usual clinical practice is to give it in the morning and certainly the bulk of the clinical data supporting its use … employed morning administration, except for a few studies with treatment arms in which the drug was given twice daily. All of the studies supporting the present application were conducted with morning administration of both component substances.*
>
> *This variance between the supporting data and the dosage timing proposed for Juvicor, with reference to its sitagliptin component, is not addressed or justified in the letter of application or, so far as could be ascertained by this evaluator, anywhere in the submission*."

Marketing approval was granted in the USA in October 2011; as a FDA Post-Marketing Requirement, a further study is to be done to assess the effects of the combination product compared to sitagliptin alone in Type 2 diabetes mellitus patients on metformin. No postmarketing data were included in the dossier in regard to the fixed combination product.

Bioavailability

The evaluator accepted that a separate bioavailability study is not needed for each of the strengths:

> *"Given the satisfactory outcome of the two included studies, the fact that only one dose level of sitagliptin is involved, and the previously established linearity of dose response for simvastatin …, this approach is considered valid. It should be noted that the 100 mg sitagliptin/80 mg simvastatin strength is not proposed for marketing."*

The evaluator suggested that the food effect as shown in Study P155 might be significant. *"If, for example, this increased exposure occurred in the setting of coincident consumption of grapefruit juice or co-administration of other CYP3A4 inhibiting substances, it is very likely that the level of risk of muscle events including rhabdomyolysis would be increased."*

Pharmacokinetics

Several new studies were submitted. None used the combination tablet (see Table 6 above).

Although the studies did not detect a pharmacokinetic interaction, the evaluator was concerned about their limited sensitivity, "*The bounds for 90% CI of (0.50, 2.00) prespecified in these drug/drug interaction studies so as to exclude what is described as a clinically meaningful effect might be seen as somewhat generous, allowing as they do for up to a twofold increase or a halving in exposure to drug A in the event that its PK is affected by drug B.*"

An interaction was seen in Study P169, "*The data from study P169 likewise showed a significant increase in the digoxin exposure following a single oral dose of digoxin 0.5 mg coadministered with 80 mg simvastatin (Zocor) and 100 mg sitagliptin (Januvia) tablets at steady state. GMR (co-administration/digoxin alone) with 90% CI was 1.26 (1.13, 1.41) for AUC and 1.41 (1.20, 1.66) for Cmax. These increases of 26% for AUC and 41% for Cmax approximately represent addition of the individual drug effects described [in the PI of each drug]*."

Pharmacodynamics

No new studies were submitted. A matter of interest is whether the switch from morning to evening dosing of sitagliptin might have clinical implications, "…*if [simvastatin] is taken before bed, and the level of DPP4 inhibition diminishes over the latter part of the 24 hour period, glycaemic efficacy following the evening (usually main) meal the following day might be decreased.*" "The essential issue is whether there is significant within-period of variation in the level of DPP4 inhibition following once daily dosage with sitagliptin. Information available to this evaluation on this point is limited." *In brief, the previously submitted data do not exclude the possibility of some impact arising from a change to the time of administration.*

Efficacy

As noted by the evaluator, no Phase III studies involving the administration of the fixed dosage combination tablet were included in the submission. The application included analyses of 19 sitagliptin efficacy studies to address these two matters:

Data from individual sitagliptin studies showing generally neutral effects of sitagliptin on serum cholesterol levels.

Data from simvastatin and sitagliptin studies showing generally neutral effects of simvastatin/statins on glycaemic control in patients with diabetes mellitus Type 2.

The studies (of which 19 were Phase III studies) were contributory of efficacy and safety data in regard to sitagliptin alone or in various combinations in the treatment of diabetes mellitus Type 2. Of them, the evaluator remarks, "*The summaries presented in the previous section confirm that glycaemic efficacy of sitagliptin has been demonstrated in a variety of therapeutic settings including those which comprise the therapeutic indications proposed in the application for the [fixed dose combination], and that the 19 Phase III studies submitted constitute a valid source of glycaemic (HbA1c) efficacy data for The sponsor's analysis of glycaemic efficacy by statin use/non-use as described in point [2] above…*"

Comment: The studies were not intended to test the matter of Point 2.

The evaluator refers to the tables on pages 47-50 of the report to support a conclusion that no significant effects were seen on plasma cholesterol. Plasma triglycerides were variably affected. The evaluator cites the study by study comparisons on pages 22-23 of the report to support a conclusion that, "*There is no overall trend towards impairment of glycaemic response by statin or simvastatin use*."

Comment: this sort of comparison is not particularly robust. The numbers of statin users are rather low, perhaps surprisingly but the confidence intervals reflect this.

The Heart Protection Study (which is mentioned in the PI of simvastatin) is cited as a large study from a random sample of 1087 participants, who were selected to undergo HbA1c measurement at baseline and after an average 4.6 years of follow-up, any difference between simvastatin 40 mg daily and placebo.

The evaluator concluded that the application supported the applicant's conclusions about efficacy.

Adverse effects

The only specific safety data that are of direct relevance to the submission derive from the bioavailability study.

Data on exposure to both drugs can be extracted from the applicant's clinical trial data base.

Postmarketing data might contribute useful information on multidrug combinations.

First round risk: benefit conclusion

The therapeutic benefits of the combination are attributable to the separate actives' benefits. There are no additive effects.

There is no evidence of significant risks attributable to the actives' co-administration or to their combination in a single formulation.

> *Comment:* The last statement is literally true, depending for its veracity on three bioequivalence studies.

A number of questions were asked of the applicant before registration could be recommended (see *List of Questions* above). These are addressed in the second round evaluation (see above).

Second round evaluation

Question: Pharmacodynamics - Please justify the non-performance of a pharmacodynamic study in relation to dosage timing of sitagliptin; the question on pharmacodynamics might influence efficacy.

Answer: The applicant's reply included evidence that the pharmacokinetics of sitagliptin are similar with morning and evening dosing. Evidence was quoted that 80% inhibition of DPP4 is maintained 24 h following the 100 mg dose at steady state. See Figure 3 on page 34 of the report [noting the small number of individuals involved].

Question: Please comment on the suggestion that the food (high-fat meal) effect on simvastatin pharmacokinetics demonstrated in Study P155, particularly the marked increase in exposure to the active hydroxyacid metabolite (see discussion above) might be clinically significant, particularly in the potential situation of co-administration of a CYP3A4 inhibitor.

Answer: The matter has been addressed by changes to the PI, "*With regard to the suggestion that the food effect might pose an additional risk in the setting of concomitant use with CYP3A4 inhibitors, The sponsor draws attention to safety provisions in the current PI for Zocor, The sponsor's simvastatin-only product which is the source of the simvastatin clinical data used for bridging purposes as outlined above in section 7, page 17 of this report . These consist of precautionary statements and dosage limitations in particular situations of concomitant use, and are particularly relevant as The sponsor has now submitted revised PI for the applicant products incorporating changes which bring it into line with the existing approved PI for simvastatin (Zocor)*."

Other aspects of the answer from the applicant amount to arguing from an absence of evidence.

Other comments by the evaluator: the issue of the effects upon compliance of morning versus evening dosing is unresolved.

Risk management plan

The applicant was granted an exemption from undertaking a specific risk management plan by the Office of Product Review.

Risk-benefit analysis

Delegate considerations

Applicant's reply to completed evaluation reports

The applicant's reply was included in full, in the agenda papers, to the ACPM.

Clinical evaluation report

The postmarketing commitment is to provide routine pharmacovigilance, that is, including the provision of periodic safety update reports.

Some minor errors of fact in the evaluation report were alluded to.

Comments:

The introductory sentence of the proposed indications appears to be an extension of indications to other uses. It does not say, for example, "*Juvicor (sitagliptin and simvastatin) is indicated in adult patients with diabetes mellitus Type 2 in whom treatment with both sitagliptin and simvastatin is indicated according to the separate indications of these drugs*" and then state these separate indications. This is disappointing after numerous pre-submission iterations with the applicant.

As is almost invariably true in regard to applications to register novel fixed combinations, the applicant here argues in favour of improved compliance with no specific evidence to support such a claim.

It is difficult to say that sitagliptin and simvastatin do not antagonise each other based on this submission. They do not exert complementary effects on each other.

The potential therapeutic benefits of the fixed combination product have not been shown in this submission and neither have some negative consequences been entirely excluded. A specific study on lipids and glycaemic control in patients who were treated on the separate actives and then switched to the fixed combination could have addressed compliance, effects of efficacy of each component upon the other when taken together.

A suggested indication is:

"*Juvicor (sitagliptin and simvastatin) is indicated in adult patients with diabetes mellitus Type 2 in whom treatment with both sitagliptin and simvastatin is indicated according to the separate indications of these drugs.*

Sitagliptin:

For the treatment of diabetes mellitus Type 2 in persons 18 years of age and older who have failed dietary measures and exercise as dual combination therapy with metformin, or with a sulphonylurea, or with a thiazolidinedione where the use of a thiazolidinedione is considered appropriate.

Simvastatin:

Simvastatin is indicated as an adjunct to diet for treatment of hypercholesterolaemia.

Simvastatin is indicated in patients at high risk of CHD (with or without hypercholesterolaemia) including patients with diabetes, history of stroke or other cerebrovascular disease, peripheral vessel disease, or with existing CHD to reduce the risk of cardiovascular death, major cardiovascular events including stroke, and hospitalisation due to angina pectoris."

However, it is arguable that the second part of the indication of simvastatin requires further adjustment (removal of redundancy) to reflect that is already being used in diabetic patients.

"*Simvastatin is indicated in patients at high risk of CHD (with or without hypercholesterolaemia) including patients with ~~diabetes~~, history of stroke or other cerebrovascular disease, peripheral vessel disease, or with existing CHD to reduce the risk of cardiovascular death, major cardiovascular events including stroke, and hospitalisation due to angina pectoris.*"

If acceptable for registration the trade names must include the ratio of the actives, thus Juvicor 100/10, Xelezor 100/20 and Tesozor 100/40.

Questions addressed to the committee

Without wishing to limit or constrain the Committee's discussion or general discussion or general advice, the following specific questions are asked.

1. Have the questions that were raised by the clinical evaluator been adequately answered? For example, is it clear that evening dosing of sitagliptin is no worse than morning dosing?
2. Is the PI an adequate means to deal with the effect of a fatty meal on the pharmacokinetics of sitagliptin?
3. Should the applicant have submitted a specific efficacy and safety study for the proposed indication?
4. Does the Committee agree that the indications are adequately expressed to reflect the available data?

Proposed actions

The application by Merck Sharp & Dohme (Australia) Pty Ltd to register new fixed combination oral tablets Juvicor 100/10, Juvicor 100/20, and Juvicor 100/40 containing100 mg sitagliptin base equivalent in film coated, unscored tablets and simvastatin 10 mg or 20 mg or 40 mg should be approved. The registered indication should be:

"Juvicor (sitagliptin and simvastatin) is indicated in adult patients with diabetes mellitus Type 2 in whom treatment with both sitagliptin and simvastatin is indicated according to the separate indications of these drugs.

Sitagliptin:

For the treatment of diabetes mellitus Type 2 in persons 18 years of age and older who have failed dietary measures and exercise as dual combination therapy with metformin, or with a sulphonylurea, or with a thiazolidinedione where the use of a thiazolidinedione is considered appropriate.

Simvastatin:

Simvastatin is indicated as an adjunct to diet for treatment of hypercholesterolaemia

Simvastatin is indicated in patients at high risk of CHD (with or without hypercholesterolaemia) including patients with ~~diabetes~~, history of stroke or other cerebrovascular disease, peripheral vessel disease, or with existing CHD to reduce the risk of cardiovascular death, major cardiovascular events including stroke, and hospitalisation due to angina pectoris."

The planned postmarketing study, requested by FDA, should be submitted as a condition of registration.

The application was submitted to the ACPM for advice.

Response from sponsor

Merck Sharp & Dohme Australia Pty Limited (MSD) concurs with the evaluators' recommendations and the Delegate's proposed action to approve the registration of new fixed dose combination tablets:

Juvicor® 100/10, Juvicor® 100/20, and Juvicor® 100/40 containing 100 mg sitagliptin and simvastatin 10 mg or 20 mg or 40 mg in tablets; indicated in patients for whom treatment with both sitagliptin and simvastatin is appropriate.

Juvicor®, the new fixed dose combination, aligns with multiple goals for the management of patients with Type 2 diabetes mellitus and is proposed as a therapeutic tool to help achieve improved clinical outcomes for patients with Type 2 diabetes mellitus. Sitagliptin is documented to improve glycaemic control and is registered for therapeutic use in Type 2 diabetes mellitus since 2008.

Simvastatin is documented to reduce the atherogenic components of plasma cholesterol and in consequence to reduce the incidence of related cardiovascular events and registered since 1990.

Macrovascular disease is a major cause of morbidity in Type 2 diabetes mellitus and it is documented that the risks associated with this disease can be lessened by pharmacological control of both plasma glucose and cholesterol. Improvement of cardiovascular risk factors, such as diabetic dyslipidaemia, with the use of statins has been demonstrated to reduce the risk for cardiovascular events, including mortality, in patients with Type 2 diabetes mellitus. Accordingly, therapeutic guidelines recommend lower targets for plasma cholesterol in patients with Type 2 diabetes mellitus, as well as a higher threshold of the introduction of therapeutic agents such as statins. This is also reflected in the guidelines for subsidy of these drugs through the Pharmaceutical Benefit Scheme (PBS), and to-date PBS data showed that a substantial diabetes population in Australia are already receiving the combination of sitagliptin and a statin since 2008. In asymptomatic chronic diseases, such as Type 2 diabetes mellitus and hyperlipidaemia, patient adherence to medication may be low. Juvicor® provides a simplified treatment regimen for patients who have been prescribed multiple medications by reducing their tablet burden thus improving the convenience, compliance and reducing cost to patients (with one PBS co-pay).

The Delegate, requested advice from the ACPM regarding four specific questions as outlined (see above *Questions Addressed to the Committee*). MSD's response to these questions is presented below:

Issue 1: Have the questions that were raised by the clinical evaluator been adequately answered? For example, is it clear that evening dosing of sitagliptin is no worse than morning dosing?

MSD's response

The justification provided by MSD has been accepted by the clinical evaluator. The evaluator stated that *"These data effectively answer the concerns expressed in the first round evaluation regarding a potential time of day effect with regard to dosing, and are accepted as adequate justification for not having carried out a specific pharmacodynamics study with evening administration"*.

MSD concurs with the clinical evaluator, that "The most relevant data appears in Figure 1 (Figure 2, page 31 of their letter; not included in this AusPAR) and is reproduced below:" [see Figure 1 in this AusPAR]. *The enhancement of GLP-1 response to feeding is the key PD response to DPP4 inhibition. Whether there is an improvement in glycaemia is in turn dependent on the remaining level of beta cell function, but it is the GLP-1 response which should be used as a measure of PD action, particularly with regard to the present question of whether that action is preserved over the 24 hour period following drug administration. The*

above shows clearly that this response is similar at 10 h and 24 h following all dosing levels including the 100 mg dose for this product".

The Delegate noted the number of individuals involved in the pharmacodynamics study. For pharmacodynamics studies, 8 subjects in each treatment group and 14 in placebo group are considered appropriate. What is more important is that all subjects participated in all assessment time point to ensure that the results are robust and meaningful.

In summary, the data presented showed that the pharmacodynamics effect of sitagliptin is maintained 24 h following dosing. Sitagliptin 100 mg once daily to be taken in the morning or in the evening is not expected to result in different efficacy.

Furthermore, although Januvia (sitagliptin) 100 mg is recommended in the Product Information to be taken once daily in the morning, Janumet (sitagliptin/metformin) 50/500; 50/850; 50/1000 fixed dose combination tablet is recommended in the Product Information to be taken twice daily, one in the morning and one in the evening. Sitagliptin 100 mg administered once daily has been shown to be clinically equivalent to sitagliptin 50 mg administered twice daily.

Furthermore, the clinical evaluator, in their second round assessment of benefit-risk balance commented that "*the potential effect of evening by comparison with morning administration on compliance, as noted in section 4.1, is a minor hypothetical concern with regard to the benefit of the product, but potentially counteracted by the sponsor's argument that compliance might be enhanced by the combination nature of the product.*". The Delegate noted that "*the issue of the effects upon compliance of morning versus evening dosing is unresolved.*"

There is insufficient evidence based on current literature to suggest morning dosing is associated with improved compliance compared to evening dosing, with medication adherence influenced by multiple biopsychosocial factors including age and medication type. Nevertheless, there is consistent evidence in published literature both in randomised controlled trials and meta-analysis to suggest that fixed combination products result in improved compliance in patients with chronic conditions including diabetes (details were provided to the TGA). This is consistent with MSD's data on Vytorin (simvastatin/ezetimibe) fixed dose combination which demonstrated a 12.2 % compliance improvement gained by Vytorin over comparator therapies requiring two separate lipid-lowering medications. As Juvicor shares some characteristics with Vytorin, as a fixed dose combination used in patients with a chronic metabolic disorder, usually asymptomatic, in whom long-term therapy is required, the evaluator accepted the extrapolation of the compliance benefit of Vytorin to the clinical use of Juvicor.

Issue 2: Is the PI an adequate means to deal with the effect of a fatty meal on the Pharmacokinetics of sitagliptin?

MSD response:

In the food effect Study P155, the pharmacokinetic (PK) characteristics of the sitagliptin component of the combination tablet remained unaltered whether the medication was given fasting or following the ingestion of a high-fat meal (~845 Kcal, 59% fat). MSD assumes that the Delegate refers to simvastatin, as raised by the clinical evaluator as part of the consolidated S31 request. The MSD's response was deemed acceptable by the clinical evaluator. In particular, the evaluator noted that "*The concerns expressed in section 9.3 of the first-round report regarding the possible impact of food effect on safety (risk), and a possible efficacy (benefit) issue relating to evening administration have been adequately addressed as noted above*."

In its response, MSD agrees with TGA evaluator's comment that the data from Study P155 present some evidence that the administration of the combination tablet with a high-fat meal results in increased exposure to simvastatin acid, particularly for C_{max}. However,

based on the following points, the increased in C_{max} for simvastatin acid is considered not clinically meaningful:

a. Upon oral administration, simvastatin (inactive) is rapidly metabolised to a mixture of metabolites, including simvastatin acid and four additional other structurally related active metabolites (Zocor PI). These active metabolites are pharmacologically active HMG-CoA reductase inhibitors. An inhibitory assay that measures the total HMG-CoA reductase inhibitor activity in plasma therefore better predicts both efficacy and safety compared to measuring simvastatin acid level alone, particularly as Simvastatin acid only contributes to approximately 25% of the active HMG-CoA reductase inhibitors. Though active HMG-CoA reductase inhibitors were not measured in Juvicor food interaction study P155, it is likely that the increase in active HMG-CoA reductase inhibitors is more modest compared to the increase in simvastatin acid (37% increase in mean AUC), because other active metabolites will be derived not only from the absorbed simvastatin acid but also from simvastatin lactone, which has a lower bioavailability with food (24% reduction in mean AUC).

b. The effect of food (an American Heart Association low-fat meal ~438 Kcal, 29% fat) on the pharmacokinetics/pharmacodynamic of simvastatin 60-mg has been previously assessed by measuring both total and active plasma HMG-CoA reductase inhibitor concentrations. No effect of the low-fat meal was observed on simvastatin exposures relative to the fasted state, as reflected in the GMR (95% CI) (fed/fasted) of the AUC for total, and active HMG-CoA reductase inhibitors; 1.03 (0.86, 1.23) and 1.03 (0.76, 1.38), respectively. Results from this study are included in the Product Information for ZOCOR stating that *"Relative to the fasting state, the plasma profile of inhibitors was not affected when simvastatin was administered immediately before a test meal".* Consequently, ZOCOR is recommended to be taken in the evening with no specific instruction in term of fasting or fed.

c. It is estimated that up to 40% of patients are non-compliant with the American Heart Association Therapeutic Lifestyle Changes diet and take Zocor with a high fat meal based on epidemiology studies. Zocor is widely prescribed and has been used in dyslipidaemia patients globally since 1988. The real world experience of Zocor suggests Zocor, taken with or without meal (including a high fat meal), is well tolerated at the recommended dose range. Based on the clinical experience with Zocor it is unlikely that a potential acute effect of a high-fat meal on exposures to a corresponding magnitude will be clinically meaningful. No dose adjustment of Juvicor is recommended when taken with a high-fat meal. The clinical evaluator commented that *"because there is no evidence of PK interaction between the components of Juvicor, there should be no need to discriminate between Juvicor and other simvastatin formulation such as Zocor on safety grounds relating to simvastatin exposure*".

The food effect should also not pose an additional risk in the setting of concomitant use with CYP3A4 inhibitors. Product Information for Zocor states:

a. Strong CYP3A4 inhibitors: simvastatin is contra-indicated

b. Moderate CYP3A4 inhibitor: simvastatin is limited to 10 mg. In the presence of moderate CYP3A4 inhibitors such as verapamil and diltiazem, the increase in active inhibitors is within 2 fold for both AUC and Cmax. In case where simvastatin is also administered with a high-fat meal, the total increase in active inhibitors exposure would still be within approximately 4 fold, assuming comparable food effect on active inhibitors and simvastatin acid. Since 40 mg

simvastatin is well-tolerated, 10 mg simvastatin is still appropriate for dosing with moderate CYP3A4 inhibitors, with and without a high fat meal.

c. Mild CYP3A4 inhibitor: simvastatin is limited to 20 mg. Based on data from amlodipine, weak CYP3A4 inhibitors are expected to have minimal effect on the exposure of active inhibitors. If simvastatin was to be administered with a high fat meal, the overall increase in active inhibitors with weak CYP3A4 inhibitors is approximately 2 fold. This is again consistent with the current PI for Zocor, which states that simvastatin doses 20 mg or lower can be given together with weak CYP3A4 inhibitors.

The revised PI for Juvicor provided in Appendix C1 to this response (not in this AusPAR) incorporates all recent safety changes submitted to the TGA for sitagliptin and simvastatin. These safety changes include addition of information relating to CYP3A4 interactions. Taken together, in the potential situation of co-administration of a CYP3A4 inhibitor, the effect of a high-fat meal on simvastatin pharmacokinetics will not impact the current recommendations in the proposed PI and is not likely to have a clinically significant impact.

Issue 3: Should the applicant have submitted a specific efficacy and safety study for the proposed indication?

MSD response:

No Phase III studies involving the administration of Juvicor were included in this submission, as the efficacy and safety of sitagliptin and simvastatin has been well established, to warrant registration of these medicines in Australia. This application included analyses of simvastatin and sitagliptin studies to demonstrate that sitagliptin has no adverse effect on serum cholesterol levels and simvastatin also has no adverse effect on glycaemic control in patients with Type 2 diabetes mellitus.

Data on plasma lipid profiles in the sitagliptin phase III studies showed that the changes from baseline in total, LDL and HDL cholesterol vary by 1-2% between the sitagliptin and placebo groups. These analyses support that sitagliptin has neutral effects on serum cholesterol levels.

The neutral effect of simvastatin on glycaemic control in patients with Type 2 diabetes mellitus was confirmed in Heart Protection Study (HPS) and pooled analyses of 19 sitagliptin clinical trials.

a. In the Heart Protection Study (HPS), the change in glycaemic control (A1C) over the followup period was assessed in patients with Type 2 diabetes mellitus. Out of the randomised 20,536 patients, 5,963 patients had Type 2 diabetes mellitus at baseline. Patients were randomly allocated to receive 40 mg simvastatin or matching placebo. Among all randomised patients with Type 2 diabetes mellitus at baseline, a random sample of 1,087 participants was selected to undergo A1C measurement in blood collected both at the initial screening visit and after an average of 4.6 years of follow-up. There was no significant difference between the treatments groups in the change in A1C observed during follow-up (0.15% simvastatin, 0.12% placebo). In addition, at the final follow-up visit no meaningful differences between the simvastatin group and the placebo group were observed in the number (%) of patients who had initiated or stopped antihyperglycaemic agents. This suggests that simvastatin 40 mg daily does not have a clinically meaningful effect on glycaemic control in patients with Type 2 diabetes mellitus. In summary, the analyses of the change in glycaemic control in patients with Type 2 diabetes mellitus who entered a randomised, double-blind, placebo-controlled study with simvastatin did not demonstrate clinically meaningful effects of simvastatin on A1C.

b. In order to evaluate the effects of simvastatin and statins on the glycaemic efficacy of sitagliptin, subgroup analyses of change from baseline in A1C were conducted for each of the 19 individual sitagliptin studies that were included in the Integrated Summary of Safety (ISS) for Juvicor (sponsor's *Summary of Clinical Safety*). The efficacy analyses were performed at the primary time point for each study, and were performed on the following subgroups:

   i. Simvastatin Users;

   ii. Statin Users and

   iii. Non-statin Users.

The results of these analyses demonstrated generally similar between group differences in the change from baseline in A1C with sitagliptin, when compared with placebo or an active comparator, in the subgroups of patients on simvastatin, patients on a statin, and patients not treated with a statin. The numbers of patients included in the subgroups of Simvastatin Users or Statin Users were low for some studies. As a result, the 95% CIs around the between-group differences in the change from baseline in A1C were wide. For all studies, the 95% CIs around between-group differences overlapped for the individual subgroups. The data do not suggest a general effect of simvastatin (or a statin) on the glycaemic efficacy of sitagliptin.

c. Review of the change from baseline HbA1c in patients who initiated simvastatin/statin during the treatment period in the sitagliptin clinical development program did not suggest a clinically significant effect on the initiation of simvastatin or another statin on glycaemic control. MSD concurs with the clinical evaluator's comment that the combination of the above approaches provide adequate justification that the glycaemic efficiency of sitagliptin in Type 2 diabetes mellitus is not impaired by its co-administration with simvastatin.

   In addition, as part of an FDA Post-Marketing Requirement (included in the FDA Approval that was issued on Oct 07 2011) for the fixed dose combination of sitagliptin and simvastatin, MSD will be conducting a randomised, double-blind, active-controlled clinical trial to study the effect of sitagliptin and simvastatin fixed-dose combination versus sitagliptin on glycaemic control in Type 2 diabetic patients on background metformin therapy (PMR 1826-1). The results of this study will be submitted to the TGA upon completion.

Issue 4: Does the Committee agree that the indications are adequately expressed to reflect the available data?

MSD accepts the recommendation by the Delegate to revise the wording of the indication statement to improve clarity. The proposed Product Information (PI) has been amended accordingly.

Nonclinical study results

The Delegate also noted "*the single new study warrants consideration in terms of its implications for detecting safety signals in humans. The study's results might suggest a higher risk of hepatotoxicity attributable to the combination than to monotherapy with either active. Specific post-marketing surveillance should be considered*."

The results in the new study (TT #09-1083) show that these differences were limited in nature and were a known effect of simvastatin in rats seen in previous studies. Therefore treatment of rats with sitagliptin at 180 mg/kg/day in combination with simvastatin at 60 mg/kg/day was considered not to substantially influence simvastatin-associated changes. A section of the sponsor's *Summary of Clinical Safety* is devoted to analyses of liver function tests performed as part of the pooled safety analysis. The results of these analyses

do not suggest that, among patients taking simvastatin, there is a higher risk of hepatotoxicity in patients taking sitagliptin compared with patients not taking sitagliptin.

As with all MSD products, the company currently monitors the safety data received for sitagliptin and simvastatin. The sponsor will assemble and analyse all data received during post marketing use of combination sitagliptin/simvastatin, and discuss any adverse events in the Periodic Safety Update Reports that will be submitted to the TGA, in compliance with the specific conditions of registration.

Conclusion

In summary, MSD has demonstrated that the benefits of the concomitant administration of sitagliptin and simvastatin outweigh its risks. In addition, as Type 2 diabetes mellitus patients are at high risk for macrovascular complications, sitagliptin and simvastatin are already commonly co-prescribed, and Juvicor Fixed Dose Combination offers the benefit of convenience and may increase compliance.

Advisory committee considerations

The 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, considered these products to have an overall positive benefit – risk profile, for the indication:

> *(abridged): Juvicor (sitagliptin and simvastatin) is indicated in patients for whom treatment with both sitagliptin (for Type 2 diabetes mellitus) and simvastatin (for hypercholesterolaemia) is appropriate. (See indications for separate products)*

In making this recommendation the ACPM expressed general concern about FDCs and the need for prescribers and consumers to be particularly vigilant in the titration of dosing and inadvertent duplication of administration.

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- a statement in the *Dosage and Administration* section of the PI and relevant sections of the CMI to ensure the reference to impact of dosing with a fatty meal.
- a statement in the *Precautions* section to ensure the product is not used in patients with renal insufficiency.

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

- The requirement that the CMI and PI for the individual products must match those of the fixed dose combination products to support safe use of these products, and that these documents reflect the multiple trade names available.

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 Juvicor sitagliptin 100 mg (as phosphate monohydrate) and simvastatin 10 mg/ 20 mg/ 40 mg tablet blister pack; Tesozor sitagliptin 100 mg (as phosphate monohydrate) and simvastatin 10 mg/ 20 mg/ 40 mg; Xelezor sitagliptin 100 mg (as phosphate monohydrate) and simvastatin 10 mg/ 20 mg/ 40 mg tablet blister pack indicated in:

> *Adult patients with Type 2 diabetes mellitus in whom treatment with both sitagliptin and simvastatin is indicated according to the separate indications of these drugs.*
>
> *The indications for sitagliptin are:*
>
> *For the treatment of Type 2 diabetes mellitus in persons 18 years of age and older who have failed dietary measures and exercise as dual combination therapy with metformin, or with a sulfonylurea, or with a thiazolidinedione where the use of a thiazolidinedione is considered appropriate.*
>
> *The indications for simvastatin are:*
>
> *Simvastatin is indicated as an adjunct to diet for treatment of hyper cholesterolaemia.*
>
> *Prior to initiating therapy with simvastatin, secondary causes of hyper cholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemias, obstructive liver disease, other drug therapy, alcoholism) should be identified and treated.*
>
> *Simvastatin is indicated in patients at high risk of CHD (with or without hypercholesterolaemia) including patients with history of stroke or other cerebrovascular disease, peripheral vessel disease, or with existing CHD to reduce the risk of cardiovascular death, major cardiovascular events including stroke, and hospitalisation due to angina pectoris. These effects do not replace the need to independently control known causes of cardiovascular mortality and morbidity such as hypertension diabetes and smoking."*

Attachment 1. Product Information

The Product Information approved for Juvicor (the PIs for Xelezor and Tesozor are identical except for the trade name) at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

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