Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Sitagliptin/Metformin

Proprietary Product Name: Janumet

Sponsor: MSD (Australia) Pty Limited

January 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.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <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:	Extension of Indications
Decision:	Approved
Date of Decision:	13 September 2012
Active ingredients:	Sitagliptin (as phosphate monohydrate)/Metformin Hydrochloride (HCl)
Product Name:	Janumet
Sponsor's Name and Address:	Merck, Sharp and Dohme (MSD) (Australia) Pty Limited
Dose form:	Film coated tablets
Strengths:	50 mg/500 mg sitagliptin/metformin 50 mg/850 mg sitagliptin/metformin 50 mg/1000 mg sitagliptin/metformin
Container:	Blister packs
Pack size:	Pack containing 56 tablets
Approved Therapeutic use:	*Janumet is indicated as initial therapy in patients with Type 2 diabetes mellitus to improve glycaemic control when diet and exercise do not provide adequate glycaemic control, when dual sitagliptin and metformin therapy is appropriate (i.e. high initial HbA1c levels and poor prospects of response to monotherapy).* *Janumet is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with Type 2 diabetes mellitus inadequately controlled on sitagliptin or metformin alone or in patients already being treated with the combination of sitagliptin and metformin.*
Route of administration:	Oral
Dosage:	Sitagliptin 100 mg daily and metformin 1000 mg to 2000 mg daily. Administered as two divided doses.
ARTG Numbers:	AUST R 149014, AUST R 149021 and AUST R 149023

Product background

Sitagliptin phosphate monohydrate is a dipeptidyl peptidase 4 (DPP-4) inhibitor. It acts by enhancing the levels of active incretin hormones, such as glucagon-like peptide-1 (GLP-1)

and glucose dependent insulinotropic polypeptide (GIP). These hormones form part of the endogenous glucose homeostatic mechanism.

Sitagliptin prevents the hydrolysis of incretin hormones by DPP-4, thereby increasing plasma concentrations of the active forms of GLP-1 and GIP. By enhancing these levels, sitagliptin increases insulin release and decreases glucagon levels in a glucose-dependant manner.

Metformin is a biguanide. It decreases hepatic glucose production, decreases the intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilisation.

Janumet is a fixed dose combination product containing both sitagliptin and metformin.

This AusPAR describes the application by Merck, Sharp and Dohme (MSD) (Australia) Pty Ltd to extend the indications of Janumet.

Proposed indications:

> *Janumet is indicated as initial therapy in patients with Type 2 diabetes mellitus to improve glycaemic control when diet and exercise do not provide adequate glycaemic control.*
>
> *Janumet is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with Type 2 diabetes mellitus inadequately controlled on sitagliptin or metformin alone or in patients already being treated with the combination of sitagliptin and metformin.*

Current indications:

> *As an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus inadequately controlled on metformin alone or in patients already being treated with the combination of sitagliptin and metformin.*

There are no new dosing instructions. The recommended dose of Janumet is based upon the patient's current dose of metformin. The draft product information document (PI) at submission included no specific dosing advice on initial combination therapy.

Regulatory status

The following table summarises the international regulatory status of Janumet (Table 1).

Table 1. International regulatory status.

COUNTRY	FILING DATE	APPROVAL DATE	INDICATION
United States	31 May 2006	30 Mar 2007	JANUMET is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both sitagliptin and metformin is appropriate. [See Clinical Studies (14).] Sitagliptin and Metformin Co-administration in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on Metformin Alone Sitagliptin Add-on Therapy vs. Glipizide Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on Metformin Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on the Combination of Metformin and Glimepiride Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on the Combination of Metformin and Insulin Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on the Combination of Metformin and Rosiglitazone
European Union		06 Jul 2008	Janumet is indicated as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of sitagliptin and metformin.
Canada		24 Sep 2009	JANUMET® (sitagliptin/metformin) is indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus inadequately controlled on metformin or in patients already being treated with the combination of sitagliptin and metformin.
Switzerland		9 Apr 2008	JANUMET is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus inadequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin. JANUMET is also indicated in combination with a sulfonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients with type 2 diabetes mellitus inadequately controlled with any two of the three agents: metformin, sitagliptin, or a sulfonylurea. If the blood glucose level is insufficiently controlled by diet and exercise and insulin - in combination with insulin.

Sitagliptin, the active ingredient in Janumet was first considered by the Australian Drug Evaluation Committee (ADEC) now called Advisory Committee on Prescription Medicines (ACPM) at its 254th Meeting on 4 – 5 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 that application.

The sponsor has also previously applied to the TGA for a first line indication for Janumet but it was rejected due to inadequate clinical experience to define efficacy and safety.

Specifically, this was due to "the long-term evidence is lacking to support the indications for Janumet's use in first line dual therapy".

Janumet was registered in April 2009 as an adjunct to diet and exercise in patients who are not adequately controlled on metformin or in patients already being treated with the combination of sitagliptin and metformin.

Product Information

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

List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
CI	confidence interval
CPK	creatinine phosphokinase
DAE	discontinuation due to adverse event
DPP-4	dipeptidyl-peptidase-4
ECG	electrocardiogram
FPG	fasting plasma glucose
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide 1
HbA1c	haemoglobin A1c (glycosylated haemoglobin)
HDL-C	high density lipoprotein cholesterol
HOMA-β	homeostasis model assessment – β-cell function
HOMA-IR	homeostasis model assessment – insulin resistance
hr	hour
LDL-C	low density lipoprotein cholesterol
LS	least squares
QUICKI	quantitative insulin sensitivity check index
SAE	serious adverse event
TG	triglyceride
TSH	thyroid stimulating hormone
TZD	thiazolidinedione
ULN	upper limit of normal

II. Quality findings

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

III. Nonclinical findings

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

IV. Clinical findings

Introduction

Clinical rationale

Janumet (sitagliptin/metformin) is currently registered as second line therapy. The sponsor has provided additional data in support of the current application to include use as initial therapy.

Although the USA Product Information document states Janumet can be used in patients where both sitagliptin and metformin are indicated, the New Zealand product document states that Janumet can be used in patients inadequately controlled on sitagliptin or metformin. The proposed Australian indications go further than either the USA or New Zealand.

Scope of the clinical submission

The submission contained the following clinical information:

- One pivotal extension study in support of efficacy and safety: Study P036X1

Good clinical practice

The studies presented in the submission were conducted according to Good Clinical Practice.

Pharmacokinetics

No new data were submitted.

Pharmacodynamics

No new data were submitted.

Efficacy

There was one pivotal extension study in support of efficacy and safety: Study P036X1.

Pivotal efficacy studies

Study P036X1

Study design, objectives, locations and dates

Study P036X1 was a 50 week extension to a multicentre randomised, double blind factorial study of the co-administration of sitagliptin and metformin in subjects with Type 2 diabetes mellitus who have inadequate glycaemic control. The study was conducted at 117 sites, 71 in the US and Puerto Rico, from May 2006 to February 2008.

Inclusion and exclusion criteria

The study included in the 54 week base study subjects with Type 2 diabetes mellitus, aged 18 to 78 years inclusive with inadequate glycemic control (glycosylated haemoglobin (HbA1c) ≥7.5% and ≤11%) on diet and exercise alone. Patients who completed the base study and who demonstrated adequate compliance (≥75%) with double-blind study medication were eligible to participate in the 50 week extension study. Patients who initiated rescue therapy during the base study were also eligible to participate in the extension study.

Study treatments

The treatment groups were:

1. Sitagliptin 100 mg once daily
2. Sitagliptin 50 mg twice daily/ metformin 500 mg twice daily
3. Sitagliptin 50 mg twice daily/ metformin 1000 mg twice daily
4. Metformin 500 mg twice daily
5. Metformin 1000 mg twice daily
6. Placebo for 24 weeks, then metformin

Rescue therapy was with open-label glyburide or glibenclamide.

Efficacy variables and outcomes

The primary efficacy outcome measure was the change from baseline in HbA1c.

The secondary efficacy outcome measures were:

- Change from baseline in FPG (fasting plasma glucose)
- Change from baseline in 2 hour post meal glucose

Other outcome measures were:

- Fasting proinsulin
- Fasting insulin
- Proinsulin/insulin ratio
- C-peptide
- HOMA-β (homeostasis model assessment - β-cell function)
- HOMA-IR (homeostasis model assessment - insulin resistance)
- QUICKI (quantitative insulin sensitivity check index)
- 2 hour post meal insulin
- 2 hour post meal C-peptide
- 2 hour incremental (above the fasting level) post meal glucose

- Incremental area under the plasma concentration time curve (AUC) glucose, insulin and C-peptide
- HbA1c goals (<6.5%, <7.0% and <7.5%)
- Body weight
- Waist circumference
- Lipid panel endpoints

The safety outcome measures were: Adverse events (AEs), laboratory values, vital signs and electrocardiogram (ECG) data.

Randomisation and blinding methods

Randomisation was in the ratio of 1:1:1:1:1:1 at the beginning of the study. There was no randomisation into the study extension.

Analysis populations

The analysis was performed on the all patients treated population.

Sample size

The sample size for the base study does not appear to have taken the extension study into account. However, estimates of the study population for the extension study were performed (50% to 70% of the base study) and the expected precision from this population (90 to 130 subjects per group) was determined.

Statistical methods

There were no formal hypothesis tests defined in the study protocol. Within group changes from baseline were analysed using analysis of covariance (ANCOVA) and some between group differences were also analysed.

Participant flow

A total of 685 subjects entered the study: 103 sitagliptin 100 mg q.d., 134 sitagliptin 50 mg/ metformin 500 mg b.i.d., 122 sitagliptin 50 mg/ metformin 1000 mg b.i.d.; 107 metformin 500 mg b.i.d., 121 metformin 1000 mg b.i.d., and 98 placebo/ metformin. There were 325 (47.4%) males, 360 (52.6%) females, and the age range was 20 to 78 years. A total of 517 subjects completed. Overall 86 (12.6%) subjects discontinued because of lack of efficacy but a higher proportion of subjects in the sitagliptin 100 mg q.d. group discontinued due to lack of efficacy: 26 (25.2%).

Relatively few of the subjects entered into the extension were included in the all patients treated analysis: 50 (48.5%) in the sitagliptin 100 mg q.d. group; 96 (71.6%) in the sitagliptin 50 mg/ metformin 500 mg b.i.d., 105 (86.1%) in the sitagliptin 50 mg/ metformin 1000 mg b.i.d., 64 (59.8%) in the metformin 500 mg b.i.d., 87 (71.9%) in the metformin 1000 mg b.i.d. and 42 (42.9%) in the placebo/ metformin. The primary reason for this was lack of on-treatment data.

Baseline data

The treatment groups were similar in demographic characteristics apart from a lower proportion of females in the sitagliptin100 mg q.d. group and a higher proportion in the sitagliptin50 mg/ metformin 1000 mg b.i.d. group. Baseline HbA1c and FPG were lowest in the placebo/ metformin group and fasting insulin was highest. Other than this the baseline disease severity was similar for the treatment groups.

Results for the primary efficacy outcome

For the primary efficacy outcome variable (change in HbA1c from baseline) there was a greater effect size for the combination of sitagliptin and metformin than for sitagliptin

alone, or for the same dose of metformin alone (Table 2). The largest effect size was for sitagliptin 50 mg/ metformin 1000 mg b.i.d. (-1.66 [-1.81 to -1.50] %). The comparisons were statistically significant except for the comparison of sitagliptin 50 mg/ metformin 500 mg b.i.d. and sitagliptin 100 mg q.d. For all the treatment groups the effect diminished over time (over 104 weeks) (Figure 1).

Table 2. Analysis of Change from Baseline in HbA1c (%) at Week 104 All-Patients-Treated in the Extension Phase.

		Mean (SD)		Change from Baseline		
Treatment Group	N	Baseline	Week 104	Mean (SE)	LS Mean (SE)	95% CI for LS Mean
Sita 100 mg q.d.	50	8.50 (0.94)	7.35 (0.71)	-1.15 (0.14)	-1.15 (0.11)	(-1.37, -0.92)
Met 500 mg b.i.d.	64	8.57 (0.87)	7.46 (0.73)	-1.11 (0.12)	-1.06 (0.10)	(-1.26, -0.87)
Met 1000 mg b.i.d.	87	8.50 (0.84)	7.19 (0.92)	-1.31 (0.11)	-1.34 (0.09)	(-1.51, -1.17)
Sita 50 mg b.i.d. + Met 500 mg b.i.d.	96	8.65 (0.94)	7.16 (0.83)	-1.49 (0.11)	-1.39 (0.08)	(-1.55, -1.22)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d.	105	8.63 (0.96)	6.91 (0.87)	-1.73 (0.11)	-1.66 (0.08)	(-1.81, -1.50)
Placebo/Met 1000 mg b.i.d.	42	8.09 (0.69)	7.03 (0.78)	-1.07 (0.17)	-1.39 (0.12)	(-1.63, -1.15)

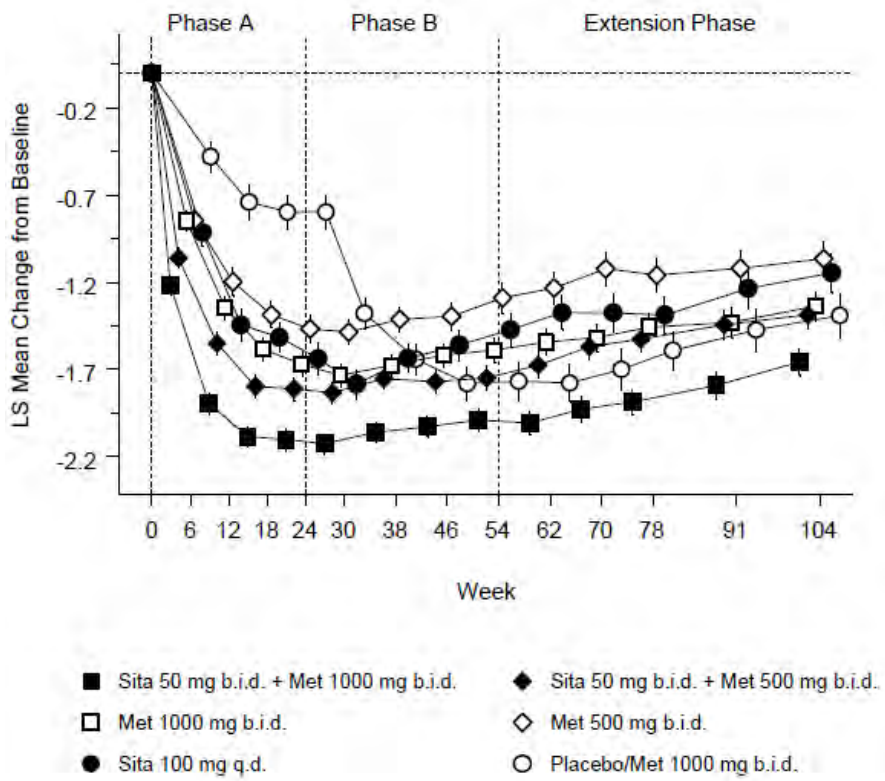
Comparing Co-administration with Individual Components	Difference in LS Means (95% CI)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 500 mg b.i.d.	-0.32 (-0.57, -0.07)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Sita 100 mg q.d.	-0.24 (-0.51, 0.03)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Met 1000 mg b.i.d.	-0.32 (-0.55, -0.09)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Sita 100 mg q.d.	-0.51 (-0.78, -0.24)

Other Comparisons	Difference in LS Means (95% CI)
Average of Differences[T]: Sita + Met vs. Met	-0.32 (-0.49, -0.15)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 1000 mg b.i.d.	-0.05 (-0.28, 0.19)
Root Mean Square Error of Change = 0.80	

[T]LS mean differences are averaged over the two metformin dose levels.

b.i.d. = twice daily; CI = Confidence Interval; LS = Least Squares; Met = Metformin; q.d. = once daily; SD = Standard Deviation; SE = Standard Error; Sita = Sitagliptin.

Figure 1. LS Mean Change from Baseline in HbA1c (%) Over Time (LS Mean ± SE) by Treatment Group All-Patients-Treated in the Extension Phase.



Results for other efficacy outcomes

For FPG, the greatest improvement was in the sitagliptin 50 mg/ metformin 1000 mg b.i.d. group (-57.3 [-63.7 to -50.8] mg/dL) (Table 3). The combination of sitagliptin and metformin had greater effect than either treatment alone. Although the sitagliptin 100 mg q.d. group had a significant improvement from baseline (LS mean change [95% CI] -26.8 [-36.2 to -17.4] mg/dL) this improvement was the least for all the treatment groups. For all the treatment groups the effect was maintained over the course of the study (Figure 2). Similarly, for 2 hour post meal glucose the greatest improvement was in the sitagliptin 50 mg/ metformin 1000 mg b.i.d. group (-110.0 [-120.9 to -99.1] mg/dL). The combination treatments had significantly greater effect than the individual treatments alone.

Table 3. Analysis of Change from Baseline in Fasting Plasma Glucose (mg/dL) at Week 104 All-Patients-Treated in the Extension Phase.

Treatment Group	N	Mean (SD)		Change from Baseline		
		Baseline	Week 104	Mean (SE)	LS Mean (SE)	95% CI for LS Mean
Sita 100 mg q.d.	50	178.0 (37.2)	156.0 (36.4)	-21.9 (5.9)	-26.8 (4.8)	(-36.2, -17.4)
Met 500 mg b.i.d.	63	178.1 (38.6)	141.3 (30.3)	-36.8 (5.1)	-41.4 (4.3)	(-49.8, -33.0)
Met 1000 mg b.i.d.	87	185.6 (45.4)	140.4 (40.0)	-45.2 (5.3)	-43.2 (3.6)	(-50.3, -36.2)
Sita 50 mg b.i.d. + Met 500 mg b.i.d.	96	187.7 (45.2)	137.0 (33.0)	-50.7 (5.5)	-47.5 (3.5)	(-54.3, -40.7)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d.	105	191.5 (51.9)	127.4 (32.7)	-64.1 (5.2)	-57.3 (3.3)	(-63.7, -50.8)
Placebo/Met 1000 mg b.i.d.	41	160.0 (31.0)	133.7 (34.1)	-26.3 (7.0)	-45.2 (5.3)	(-55.7, -34.8)

Comparing Co-administration with Individual Components	Difference in LS Means (95% CI)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 500 mg b.i.d.	-6.1 (-16.9, 4.6)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Sita 100 mg q.d.	-20.7 (-32.3, -9.2)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Met 1000 mg b.i.d.	-14.0 (-23.6, -4.4)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Sita 100 mg q.d.	-30.5 (-41.9, -19.0)

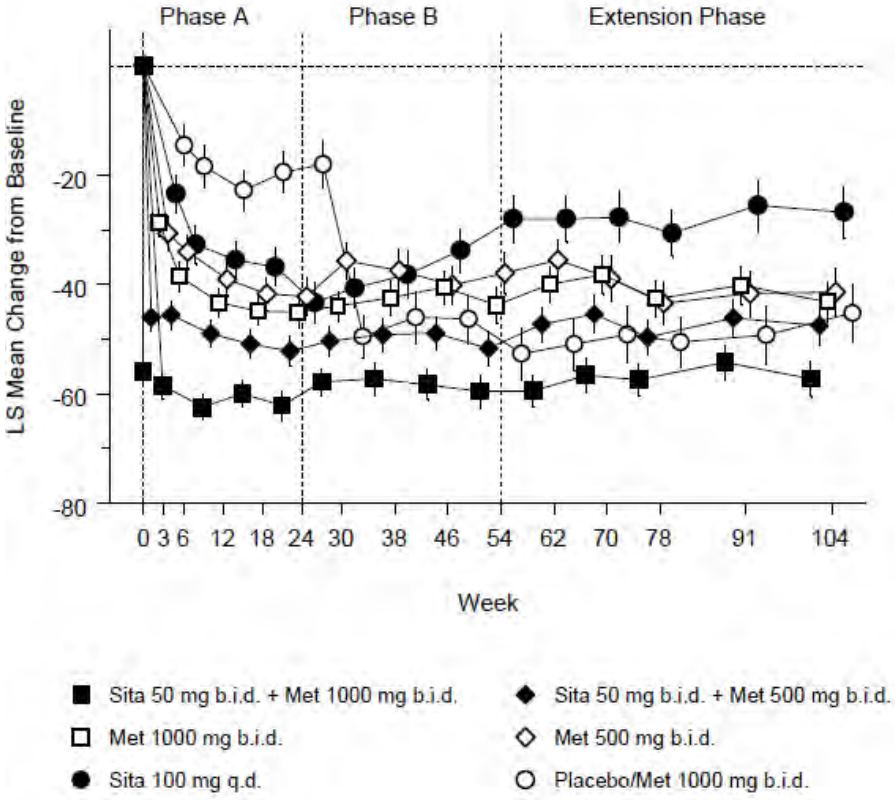
Other Comparisons	Difference in LS Means (95% CI)
Average of Differences[T]: Sita + Met vs. Met	-10.1 (-17.3, -2.9)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 1000 mg b.i.d.	-4.3 (-14.1, 5.5)

Root Mean Square Error of Change = 33.6

[T]LS mean differences are averaged over the two metformin dose levels.

b.i.d. = twice daily; CI = Confidence Interval; LS = Least Squares; Met = Metformin; q.d. = once daily; SD = Standard Deviation; SE = Standard Error; Sita = Sitagliptin.

Figure 2. LS Mean Change from Baseline in Fasting Plasma Glucose (mg/dL) Over Time (LS Mean ± SE) by Treatment Group All-Patients-Treated in the Extension Phase



In the sitagliptin 50 mg/ metformin 500 mg b.i.d. group there was no significant change from baseline in fasting serum insulin: least squares (LS) mean change (95% CI) 1.2 (-0.5 to 2.9) µIU/mL. In the sitagliptin 50 mg/ metformin 1000 mg b.i.d. group there was no significant change from baseline in fasting serum insulin: LS mean change (95% CI) 1.0 (-0.6 to 2.6) µIU/mL. In the sitagliptin 50 mg/ metformin 500 mg b.i.d. group there was a significant decrease from baseline in fasting serum proinsulin: LS mean change (95% CI) -12.7 (-16.9 to -8.4) pmol/L (Table 4). In the sitagliptin 50 mg/ metformin 1000 mg b.i.d. group there was a significant decrease from baseline in fasting serum proinsulin: LS mean change (95% CI) -13.9 (-17.8 to -10.0) pmol/L.

Table 4. Analysis of Change from Baseline in Fasting Serum Proinsulin (pmol/L) at Week 104 All-Patients-Treated in the Extension Phase

		Mean (SD)		Change from Baseline		
Treatment Group	N	Baseline	Week 104	Mean (SE)	LS Mean (SE)	95% CI for LS Mean
Sita 100 mg q.d.	24	23.9 (14.5)	17.2 (10.7)	-6.8 (2.1)	-12.6 (3.6)	(-19.7, -5.6)
Met 500 mg b.i.d.	29	31.3 (32.2)	23.0 (23.5)	-8.2 (3.3)	-10.6 (3.3)	(-17.1, -4.2)
Met 1000 mg b.i.d.	61	41.0 (38.7)	21.8 (25.6)	-19.3 (3.7)	-16.5 (2.2)	(-20.9, -12.1)
Sita 50 mg b.i.d. + Met 500 mg b.i.d.	65	35.3 (40.5)	22.8 (26.4)	-12.5 (3.0)	-12.7 (2.2)	(-16.9, -8.4)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d.	79	37.0 (32.2)	22.2 (26.1)	-14.9 (2.8)	-13.9 (2.0)	(-17.8, -10.0)
Placebo/Met 1000 mg b.i.d.	30	32.3 (21.9)	21.6 (23.2)	-10.7 (3.9)	-12.5 (3.2)	(-18.8, -6.2)

Comparing Co-administration with Individual Components	Difference in LS Means (95% CI)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 500 mg b.i.d.	-2.0 (-9.7, 5.6)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Sita 100 mg q.d.	-0.0 (-8.3, 8.2)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Met 1000 mg b.i.d.	2.6 (-3.2, 8.5)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Sita 100 mg q.d.	-1.2 (-9.3, 6.8)

Other Comparisons	Difference in LS Means (95% CI)
Average of Differences[†]: Sita + Met vs. Met	0.3 (-4.5, 5.1)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 1000 mg b.i.d.	3.9 (-2.3, 10.0)
Root Mean Square Error of Change = 17.4	

[†]LS mean differences are averaged over the two metformin dose levels.

b.i.d. = twice daily; CI = Confidence Interval; LS = Least Squares; Met = Metformin; q.d. = once daily; SD = Standard Deviation; SE = Standard Error; Sita = Sitagliptin.

There was no significant change from baseline, or difference between treatment groups, in fasting serum C-peptide. HOMA-β improved from baseline in all the treatment groups, with apparent additive effect for sitagliptin and metformin (Table 5).

Table 5. Analysis of Change from Baseline in HOMA-β at Week 104 All-Patients-Treated in the Extension Phase

Treatment Group	N	Mean (SD)		Change from Baseline		
		Baseline	Week 104	Mean (SE)	LS Mean (SE)	95% CI for LS Mean
Sita 100 mg q.d.	43	43.6 (38.5)	67.5 (72.6)	23.8 (7.6)	27.8 (9.2)	(9.8, 45.9)
Met 500 mg b.i.d.	55	44.4 (38.8)	72.4 (72.9)	27.9 (7.1)	30.7 (8.1)	(14.8, 46.6)
Met 1000 mg b.i.d.	78	47.5 (34.6)	71.6 (53.1)	24.1 (4.9)	23.5 (6.8)	(10.2, 36.8)
Sita 50 mg b.i.d. + Met 500 mg b.i.d.	85	45.1 (40.4)	86.9 (75.3)	41.7 (6.0)	43.6 (6.5)	(30.8, 56.4)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d.	98	46.0 (38.3)	98.3 (89.0)	52.3 (7.7)	51.3 (6.1)	(39.4, 63.1)
Placebo/Met 1000 mg b.i.d.	35	58.9 (32.5)	83.6 (72.3)	24.7 (13.2)	24.3 (10.2)	(4.3, 44.3)

Comparing Co-administration with Individual Components	Difference in LS Means (95% CI)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 500 mg b.i.d.	12.9 (-7.5, 33.2)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Sita 100 mg q.d.	15.7 (-6.3, 37.7)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Met 1000 mg b.i.d.	27.8 (9.9, 45.6)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Sita 100 mg q.d.	23.4 (1.7, 45.1)

Other Comparisons	Difference in LS Means (95% CI)
Average of Differences†: Sita + Met vs. Met	20.3 (6.8, 33.9)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 1000 mg b.i.d.	20.1 (1.6, 38.6)

Root Mean Square Error of Change = 59.8

†LS mean differences are averaged over the two metformin dose levels.

b.i.d. = twice daily; CI = Confidence Interval; LS = Least Squares; Met = Metformin; q.d. = once daily; SD = Standard Deviation; SE = Standard Error; Sita = Sitagliptin.

There was an improvement in HOMA-IR in the metformin treatment groups with no apparent additive effect for sitagliptin (Table 6). There was an apparent improvement in QUICKI with metformin with no additive effect for sitagliptin (Table 7). There was an increase in 2 hour post meal insulin in the metformin groups with no apparent additive effect for sitagliptin. There was no significant change in 2 hour post meal C-peptide in any of the treatment groups.

Table 6. Analysis of Change from Baseline in HOMA-IR at Week 104 All-Patients-Treated in the Extension Phase

Treatment Group	N	Mean (SD)		Change from Baseline		
		Baseline	Week 104	Mean (SE)	LS Mean (SE)	95% CI for LS Mean
Sita 100 mg q.d.	43	5.1 (4.3)	5.3 (4.5)	0.2 (0.7)	-0.4 (0.6)	(-1.5, 0.7)
Met 500 mg b.i.d.	55	5.8 (4.9)	4.6 (3.4)	-1.2 (0.4)	-1.5 (0.5)	(-2.4, -0.5)
Met 1000 mg b.i.d.	78	6.6 (4.9)	4.4 (3.0)	-2.2 (0.4)	-2.0 (0.4)	(-2.9, -1.2)
Sita 50 mg b.i.d. + Met 500 mg b.i.d.	85	6.3 (6.3)	5.1 (3.9)	-1.2 (0.5)	-1.2 (0.4)	(-1.9, -0.4)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d.	98	6.8 (6.4)	5.1 (5.3)	-1.7 (0.5)	-1.4 (0.4)	(-2.2, -0.7)
Placebo/Met 1000 mg b.i.d.	35	5.9 (3.0)	5.3 (6.6)	-0.6 (1.1)	-0.8 (0.6)	(-2.0, 0.4)

Comparing Co-administration with Individual Components	Difference in LS Means (95% CI)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 500 mg b.i.d.	0.3 (-0.9, 1.5)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Sita 100 mg q.d.	-0.8 (-2.1, 0.6)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Met 1000 mg b.i.d.	0.6 (-0.5, 1.7)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Sita 100 mg q.d.	-1.1 (-2.4, 0.3)

Other Comparisons	Difference in LS Means (95% CI)
Average of Differences†: Sita + Met vs. Met	0.4 (-0.4, 1.3)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 1000 mg b.i.d.	0.9 (-0.2, 2.0)

Root Mean Square Error of Change = 3.6

†LS mean differences are averaged over the two metformin dose levels.

b.i.d. = twice daily; CI = Confidence Interval; LS = Least Squares; Met = Metformin; q.d. = once daily; SD = Standard Deviation; SE = Standard Error; Sita = Sitagliptin.

Table 7. Analysis of Change from Baseline in QUICKI at Week 104 All-Patients-Treated in the Extension Phase

Treatment Group	N	Mean (SD)		Change from Baseline		
		Baseline	Week 104	Mean (SE)	LS Mean (SE)	95% CI for LS Mean
Sita 100 mg q.d.	43	0.315 (0.029)	0.314 (0.033)	-0.001 (0.004)	0.003 (0.004)	(-0.005, 0.011)
Met 500 mg b.i.d.	55	0.311 (0.037)	0.321 (0.036)	0.009 (0.004)	0.011 (0.004)	(0.004, 0.018)
Met 1000 mg b.i.d.	78	0.303 (0.028)	0.320 (0.031)	0.017 (0.003)	0.015 (0.003)	(0.009, 0.021)
Sita 50 mg b.i.d. + Met 500 mg b.i.d.	85	0.312 (0.049)	0.314 (0.030)	0.003 (0.004)	0.004 (0.003)	(-0.001, 0.010)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d.	98	0.304 (0.031)	0.322 (0.037)	0.017 (0.003)	0.016 (0.003)	(0.011, 0.021)
Placebo/Met 1000 mg b.i.d.	35	0.303 (0.023)	0.319 (0.032)	0.015 (0.005)	0.014 (0.005)	(0.005, 0.023)

Comparing Co-administration with Individual Components	Difference in LS Means (95% CI)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 500 mg b.i.d.	-0.007 (-0.016, 0.002)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Sita 100 mg q.d.	0.001 (-0.008, 0.011)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Met 1000 mg b.i.d.	0.001 (-0.007, 0.009)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Sita 100 mg q.d.	0.013 (0.003, 0.023)

Other Comparisons	Difference in LS Means (95% CI)
Average of Differences[T]: Sita + Met vs. Met	-0.003 (-0.009, 0.003)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 1000 mg b.i.d.	-0.011 (-0.019, -0.002)
Root Mean Square Error of Change = 0.027	

[T]LS mean differences are averaged over the two metformin dose levels.
b.i.d. = twice daily; CI = Confidence Interval; LS = Least Squares; Met = Metformin; q.d. = once daily; SD = Standard Deviation; SE = Standard Error; Sita = Sitagliptin.

Glucose AUC decreased from baseline in the all of the treatment groups (Table 8). However the improvement was greater in the metformin groups and there was an additive effect for both sitagliptin and metformin. The changes in insulin AUC were not consistent between metformin doses and there was no significant effect for sitagliptin. There were no significant changes in C-peptide AUC. There was an additive effect for sitagliptin and metformin for the proportion of subjects achieving HbA1c <7% at Week 104 (Table 9). HDL-C increased in all the treatment groups with no apparent difference between the treatments. There were no other significant changes in plasma lipids. Body weight decreased in the metformin 1000 mg b.i.d. and sitagliptin 50 mg/metformin 1000 mg b.i.d. groups but no changes were attributable to sitagliptin. Waist circumference decreased from baseline only in the sitagliptin 50 mg/ metformin 1000 mg b.i.d. group: LS mean change (95% CI) -2.3 (-4.1 to -0.6) cm.

Table 8. Analysis of Change from Baseline in Glucose Total AUC (mg hr/dL) at Week 104 All-Patients-Treated in the Extension Phase

Treatment Group	N	Mean (SD)		Change from Baseline		
		Baseline	Week 104	Mean (SE)	LS Mean (SE)	95% CI for LS Mean
Sita 100 mg q.d.	39	469.7 (104.9)	389.5 (102.5)	-80.3 (18.0)	-105.7 (13.6)	(-132.4, -79.1)
Met 500 mg b.i.d.	50	503.1 (94.6)	382.2 (88.5)	-120.9 (16.6)	-120.0 (12.0)	(-143.5, -96.5)
Met 1000 mg b.i.d.	67	509.4 (120.6)	362.9 (82.6)	-146.5 (13.9)	-138.8 (10.3)	(-159.0, -118.6)
Sita 50 mg b.i.d. + Met 500 mg b.i.d.	78	509.8 (130.4)	342.8 (79.5)	-167.0 (16.3)	-160.3 (9.6)	(-179.1, -141.4)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d.	86	512.1 (127.4)	310.7 (89.4)	-201.4 (13.6)	-190.5 (9.1)	(-208.4, -172.6)
Placebo/Met 1000 mg b.i.d.	30	447.9 (82.4)	343.8 (89.8)	-104.1 (22.5)	-146.0 (15.5)	(-176.4, -115.5)

Comparing Co-administration with Individual Components	Difference in LS Means (95% CI)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 500 mg b.i.d.	-40.3 (-70.3, -10.3)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Sita 100 mg q.d.	-54.5 (-87.1, -21.9)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Met 1000 mg b.i.d.	-51.7 (-78.7, -24.7)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Sita 100 mg q.d.	-84.8 (-117.0, -52.5)

Other Comparisons	Difference in LS Means (95% CI)
Average of Differences†: Sita + Met vs. Met	-46.0 (-66.2, -25.8)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 1000 mg b.i.d.	-21.4 (-49.0, 6.1)
Root Mean Square Error of Change = 84.1	

†LS mean differences are averaged over the two metformin dose levels.
b.i.d. = twice daily; CI = Confidence Interval; LS = Least Squares; Met = Metformin; q.d. = once daily; SD = Standard Deviation; SE = Standard Error; Sita = Sitagliptin.

Table 9. Proportion of Patients with HbA1c Value < 7.0% at Week 104 All-Patients-Treated in the Extension Phase

Treatment Group	N	n (%)
Sita 100 mg q.d.	50	16 (32.0)
Met 500 mg b.i.d.	64	18 (28.1)
Met 1000 mg b.i.d.	87	39 (44.8)
Sita 50 mg b.i.d. + Met 500 mg b.i.d.	96	43 (44.8)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d.	105	63 (60.0)

Comparing Co-administration with Individual Components	Difference in Proportion (%) (95% CI†)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Met 500 mg b.i.d.	16.7 (1.3, 30.5)
Sita 50 mg b.i.d. + Met 500 mg b.i.d. vs. Sita 100 mg q.d.	12.8 (-4.0, 27.8)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Met 1000 mg b.i.d	15.2 (1.0, 28.5)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d. vs. Sita 100 mg q.d.	28.0 (11.2, 42.3)

† Confidence Interval computed using the Wilson score method.
b.i.d. = twice daily; CI = Confidence Interval; Met = Metformin; q.d. = once daily; Sita = Sitagliptin.

Evaluator's conclusions on clinical efficacy

In Study P036X1 relatively few of the subjects included in the extension phase were included in the analysis. Hence limited conclusions can be drawn from the data. However, sitagliptin in combination with metformin had additive efficacy. The effect was apparent over a 104 week follow-up period.

Safety

Studies providing evaluable safety data

There was one pivotal extension study in support of efficacy and safety: Study P036X1

Patient exposure

In Study P036X1, a total of 100 subjects were exposed to sitagliptin 50 mg twice daily in combination with metformin 500 mg twice daily, with 67 exposed for ≥270 days. A total of 107 subjects were exposed to sitagliptin 50 mg twice daily in combination with metformin 1000 mg twice daily, with 81 exposed for ≥270 days.

Adverse events

All adverse events (irrespective of relationship to study treatment)

In Study P036X1, treatment emergent AEs (TEAEs) were reported in 53 (53.0%) subjects in the sitagliptin 50 mg/ metformin 500 mg b.i.d. group, 59 (55.1%) in the sitagliptin 50 mg/ metformin 1000 mg b.i.d., 19 (36.5%) in the sitagliptin 100 mg q.d., 22 (33.8%) in the metformin 500 mg b.i.d., 48 (54.5%) in the metformin 1000 mg b.i.d. and 23 (54.8%) in the placebo/ metformin group. Infections were more common in the subjects treated with metformin, with or without sitagliptin.

Treatment-related adverse events (adverse drug reactions)

In Study P036X1, drug related AEs were reported in seven (7.0%) subjects in the sitagliptin 50 mg/ metformin 500 mg b.i.d. group, eight (7.5%) in the sitagliptin 50 mg/metformin 1000 mg b.i.d., two (3.8%) in the sitagliptin 100 mg q.d., five (7.7%) in the metformin 500 mg b.i.d., three (3.4%) in the metformin 1000 mg b.i.d. and two (4.8%) in the placebo/ metformin group.

Deaths and other serious adverse events (SAEs)

In Study P036X1, SAEs were reported in four (4.0%) subjects in the sitagliptin 50 mg/ metformin 500 mg b.i.d. group, four (3.7%) in the sitagliptin 50 mg / metformin 1000 mg b.i.d., one (1.9%) in the sitagliptin 100 mg q.d., one (1.5%) in the metformin 500 mg b.i.d., six (6.8%) in the metformin 1000 mg b.i.d. and two (4.8%) in the placebo/ metformin group. There was no apparent pattern to the SAEs. There was one death in the sitagliptin 50 mg / metformin 500 mg b.i.d. group (coronary artery disease) and one in the placebo/ metformin (unknown cause).

Discontinuation due to adverse events

In Study P036X1, discontinuation due to AE was not reported in the sitagliptin 50 mg/ metformin 500 mg b.i.d. group, the sitagliptin 50 mg / metformin 1000 mg b.i.d. or the metformin 1000 mg b.i.d.. There were two (3.1%) subjects in the metformin 500 mg b.i.d. group (palpitations and lung neoplasm) and one (2.4%) in the placebo/ metformin (cholelithiasis) that discontinued due to AE. Two subjects in the sitagliptin 100 mg q.d. group discontinued after initiation of glycaemic rescue.

Adverse events of special interest

In Study P036X1, hypoglycaemic episodes were reported in two (2.0%) in the sitagliptin 50 mg/ metformin 500 mg b.i.d. group, five (4.7%) in the sitagliptin 50 mg/ metformin 1000 mg b.i.d. group, no subjects in the sitagliptin 100 mg q.d. group, one (1.5%) in the metformin 500 mg b.i.d. group, two (2.3%) in the metformin 1000 mg b.i.d. group and one (2.4%) in the placebo/ metformin group.

Laboratory tests

In Study P036X1, abnormal laboratory tests were reported as AEs in three (3.0%) subjects in the sitagliptin 50 mg/metformin 500 mg b.i.d. group, one (0.9%) subject in the sitagliptin 50 mg/ metformin 1000 mg b.i.d. group, one (1.9%) subject in the sitagliptin 100 mg q.d. group, four (6.2%) subjects in the metformin 500 mg b.i.d. group, two (2.3%) subjects in the metformin 1000 mg b.i.d. group but not in anyone in the placebo/ metformin. There was no apparent pattern in the laboratory AEs.

Evaluator's overall conclusions on clinical safety

There was a slightly higher rate of hypoglycaemic adverse events reported with the combination of sitagliptin and metformin 2000 mg/day than with either drug by itself. Other than this, the rates of AEs were as would be expected from the individual drugs.

List of questions

After an initial evaluation, a List of Questions to the sponsor was generated. The questions for the sponsor of this application were as follows:

Clinical questions

General

- In what way does the current Australian dossier differ to the data submitted in other countries to support initial combination therapy with sitagliptin/metformin?[1]

Can the sponsor provide documentation that initial combination therapy is approved in the USA and New Zealand?[2]

Clinical summary and conclusions

First round benefit risk assessment

First round assessment of benefits

In Study P036X1 relatively few of the subjects included in the extension phase were included in the analysis. Hence limited conclusions can be drawn from the data. However, sitagliptin in combination with metformin had additive efficacy. The effect was apparent over a 104 week follow-up period.

First round assessment of risks

There was a slightly higher rate of hypoglycaemic adverse events reported with the combination of sitagliptin and metformin 2000 mg/day than with either drug by itself. Other than this, the rates of AEs were as would be expected from the individual drugs.

First round assessment of benefit-risk balance

The benefit-risk balance of Janumet (sitagliptin/metformin), given the proposed usage, was considered to be favourable.

[1] Sponsor comment: "The sponsor responded to this question in the Section 31 *Response to Questions* (see page 20)."

[2] Sponsor comment: "The sponsor responded to this question in the Section 31 *Response to Questions* (see page 20)."

First round recommendation regarding authorisation

Janumet (sitagliptin/metformin) should be approved for the revised indication:

> *Janumet is indicated as initial therapy in patients with Type 2 diabetes mellitus to improve glycaemic control when diet and exercise do not provide adequate glycaemic control.*
>
> *Janumet is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with Type 2 diabetes mellitus inadequately controlled on sitagliptin or metformin alone or in patients already being treated with the combination of sitagliptin and metformin.*

Second round evaluation of clinical data submitted in response to questions

General

In answer to the question, the sponsor referred to a table in their submission. The original Module 1.10.3 (of the sponsor's submission) stated:

> *1.10.3 – Data Set Similarities*
>
> *This application, to support the use of Jamumet™ as first line therapy in patients with T2DM inadequately controlled on diet and exercise alone, is supported by clinical data from P036. The same study was used to support applications for the use of Janumet™ as initial combination therapy in other countries as well.*

The sponsor's response included a table showing that the 24 week Study P036 was provided in the original submission to Australia for the registration of Janumet, as well as to the European Union (EU), USA, New Zealand and Canada but the data up to 104 weeks for P036X1 were provided with this submission.

The second question asked if the sponsor could provide documentation that initial combination therapy is approved in the USA and New Zealand. Links were provided to the currently approved labels which show Indications as follows:

'The indication stated in the US Product Information document is:

> *Janumet is a dipeptidyl peptidase-4 (DPP-4) inhibitor and biguanide combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus when treatment with both sitagliptin and metformin is appropriate.*

The indication stated in the New Zealand Product Information document is:

> *Janumet is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with Type 2 diabetes mellitus inadequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin.*
>
> *Janumet is indicated as part of triple combination therapy with a sulfonylurea as an adjunct to diet and exercise in patients with Type 2 diabetes mellitus inadequately controlled with any two of the three agents: metformin, sitagliptin, or a sulfonylurea.*'

Evaluator comment

The US Prescribing Information at the linked site has a cross reference at the end of the first sentence of the Indication, '[See Clinical Studies (14)]', which refers the reader to section 14 of the US prescribing information. Compared to that proposed for the Australian PI, this section has some differences in presentation of P036 (17.1).

In the US PI presentation it is clear that not all 1091 subjects were receiving 'initial therapy' in the clinical sense of being drug-naive; n =550 were not on anti hyperglycaemic

agents at study entry, while n =541 who were on anti hyperglycaemic agents at study entry underwent 12 weeks of diet, exercise and a drug washout period of up to 12 weeks duration before those with inadequate glycaemic control underwent a 2 week single blind placebo run-in period. Also, the tabulation in the US PI has a line showing *'% patients receiving rescue medication'* which is omitted from the proposed Australian PI.

The US PI includes '*mean'* baseline and '*mean'* decreases, whereas '*mean'* is omitted from the descriptions in the proposed Australian PI.

There is an additional sentence in the US PI at the end of the description of P036:

> *'Initial combination therapy or maintenance of combination therapy should be individualized and are left to the discretion of the health care provider'.*

In combination with the actual wording of the US indication, this shows that the US indication is not explicitly for 'initial therapy' but 'when treatment with both sitagliptin and metformin is appropriate'.

The NZ Data Sheet does not state an Indication for 'initial therapy' but

> *'in patients with Type 2 diabetes mellitus inadequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin'.*

Thus, the statement of the First round clinical evaluator of this submission (page 8 of this AusPAR) is correct:

'The proposed Australian indications go further than either the US or New Zealand'.

Second round benefit risk assessment

Second round assessment of benefits

The answers to the clinical question do not contain new clinical data. Therefore, the First round assessment stands:

> 'In Study P036X1 relatively few of the subjects included in the extension phase were included in the analysis. Hence limited conclusions can be drawn from the data. However, sitagliptin in combination with metformin had additive efficacy. The effect was apparent over a 104 week follow-up period.'

The Second round evaluator notes that the numbers receiving 'initial therapy' with sitagliptin and metformin, in the sense of initial pharmacotherapy for Type 2 diabetes mellitus when diet and exercise do not provide adequate glycaemic control, are smaller than those quoted by the First round evaluator as entering the extension study; only 256 of 454 were not using antihyperglycaemic medications at screening and entered the extension phase without having initiated rescue therapy.

Second round assessment of risks

The answers to the clinical question do not contain new clinical data. Therefore, the First round assessment stands:

> 'There was a slightly higher rate of hypoglycaemic adverse events reported with the combination of sitagliptin and metformin than with either drug by itself. Other than this, the rates of AEs were as would be expected from the individual drugs.'

The potential for a higher rate of hypoglycaemic adverse events is relevant to consideration of an extension of indication of a fixed dose combination of drugs for 'initial therapy'. However the presentations include 500 mg, 850 mg and 1000 mg strengths for the metformin component, allowing for dose titration of metformin.

Second round assessment of benefit-risk balance

The extension Study P036X1 provides additional data for the efficacy and safety of the combination of sitagliptin and metformin over two years for a limited number of subjects.

The benefit-risk balance of Janumet (sitagliptin/metformin), for the proposed usage, an extension of the indication to specify 'initial therapy' for the fixed dose combination, is favourable provided the limitations of the data are made clear in the PI.

Second round recommendation regarding authorisation

If approval is received for sitagliptin ('Januvia') as 'initial' monotherapy, and 'in combination with metformin as initial therapy', then 'Janumet' (sitagliptin/metformin) may be approved for the revised Indication, provided the limited numbers of subjects with data up to 104 weeks, and the potential for increased rates of hypoglycaemia with the combination, are made clear in the PI. It is recommended that an amended Indication may be approved:

> *Janumet is indicated as initial therapy in patients with Type 2 diabetes mellitus to improve glycaemic control when diet and exercise do not provide adequate glycaemic control, when dual sitagliptin and metformin therapy is appropriate (i.e. high initial HbA1c levels and poor prospects of response to monotherapy).*
>
> *Janumet is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with Type 2 diabetes mellitus inadequately controlled on sitagliptin or metformin alone or in patients already being treated with the combination of sitagliptin and metformin.'*

V. Pharmacovigilance findings

Risk management plan

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

Safety specification

The sponsor provided a summary of Ongoing Safety Concerns which are shown at Table 10.

Table 10. Summary of the Ongoing Safety Concerns as specified by the sponsor

Identified Risks	• Lactic acidosis • Hypersensitivity reactions :Anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, skin exfoliation and Stevens-Johnson syndrome • Hypoglycaemia with concomitant sulphonylurea • Hypoglycaemia with concomitant insulin • Gastrointestinal disorders: Nausea, vomiting, constipation, diarrhoea, abdominal pain, flatulence, abdominal pain upper, and related terms (dyspepsia and gastritis) • Musculoskeletal disorders: osteoarthritis, pain in extremity, and related terms(e.g. arthralgia, myalgia, myopathy)
Potential Risks	• Infections: upper respiratory tract, nasopharyngitis and related terms (bronchitis, bronchitis acute, pharyngitis, sinusitis and rhinitis) • Neurotoxicity: tremor, ataxia and balance disorders • Suicidal ideation, suicide and depression • Skin reactions: pruritis and contact dermatitis • Drug-drug interactions in renal-insufficiency patients • Pancreatitis • Impaired renal function, including acute renal failure (sometimes requiring dialysis)
Missing Information	• Patient below 18 years of age • Exposure during pregnancy and lactation • Adverse events in Renal Insufficiency patients • Cardiovascular adverse events in patients on sitagliptin/metformin FDC or on a combination of sitagliptin/metformin FDA and PPARγ agonist • Theoretic carcinogenic potential

OPR reviewer comment

Pursuant to the evaluation of the clinical aspects of the safety specifications, the above summary of the Ongoing Safety Concerns should be modified to incorporate the concern of the clinical evaluator regarding hypoglycaemic events. It is recommended that the Important Identified Risk could include Hypoglycaemia with Janumet alone (or words to that effect). Routine pharmacovigilance activities and inclusion in the PI, with modification of the Consumer Medicines Information (CMI) in the manner described in the clinical evaluation as routine Risk Minimisation activities would be acceptable.

Pharmacovigilance plan

The sponsor proposed routine pharmacovigilance activities[3] for all Ongoing Safety Concerns except those described in Table 11 below.

Table 11. Proposed additional pharmacovigilance activities

Potential Risks **Pancreatitis**	Routine Pharmacovigilance Monitoring of pancreatitis events in P082 (ongoing)
Missing Information **Patient below 18 years of age**	Routine Pharmacovigilance Clinical research trials in Paediatric Patients: Planned trials: P170, P289
Exposure during pregnancy and lactation	Enhanced Pharmacovigilance
Cardiovascular adverse events in patients on sitagliptin/metformin FDC or on a combination of sitagliptin/metformin FDA and PPARγ agonist	Routine Pharmacovigilance Monitoring of cardiovascular events in P082 (ongoing)
Theoretic carcinogenic potential	Routine Pharmacovigilance Monitoring of cardiovascular events in P082 (ongoing)

The sponsor has provided the following milestones for the study protocols in the pharmacovigilance plan (Table 12):

Table 12. Milestones for study protocols

Study	Protocol Version	Protocol status	Planned Date for submission of interim data	Planned Date for submission of final data
P082	P082-01	Ongoing		Third quarter 2015
P170	P170-00	Planned		First quarter 2018 (targeted)
P289	P289-00	Planned		To be determined

The sponsor has provided the study protocols for Studies P082 and P170. The sponsor has provided an outline for Study P289.

[3] Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

The sponsor has advised that the Drug Utilisation Study identified in RMP Version 3.0 does not qualify as an additional pharmacovigilance activity and is not mentioned in Version 4.0, however it does appear as an ongoing activity in Table 2.6 of the RMP Version 4.0 entitled 'Summary of Outstanding Actions, Including Milestones'.

In Annex 3 of RMP Version 4.0 the sponsor provides a table of synopses of completed and ongoing clinical trials. In this table P082, P121, P229, P403 are listed as ongoing, however the pharmacovigilance plan only identifies P082 and P170 as the additional pharmacovigilance activities. The sponsor has provided justification for the difference between the two pharmacovigilance plans. Some studies did not include specific safety objectives designed to address the Important identified/Potential risks or Important missing information from the RMP and are therefore removed. The sponsor indicated that additional safety information obtained from all these studies will be conveyed to the TGA via Periodic Safety Update Reports (PSURs).

OPR reviewer's comments in regard to the pharmacovigilance plan (PP) and the appropriateness of milestones

The sponsor has provided a satisfactory explanation of the proposed pharmacovigilance plan in Version 4.0 of the RMP.

The study protocols for P170 and P082 have been provided. It is acceptable for the sponsor to include these as additional pharmacovigilance activities. The sponsor states that Study P289 is yet to have a finalised study protocol. The sponsor is requested to provide a synopsis of this study to the TGA upon finalisation, for review. [4]

Furthermore, it is acceptable for the sponsor to include additional safety information derived from studies outside the pharmacovigilance plan with the PSURs.

See Safety Specification section above for evaluator comments regarding routine pharmacovigilance activities for the additional safety concern 'Hypoglycaemia with Janumet alone'.

Risk minimisation activities

The sponsor proposed routine risk minimisation activities for all safety concerns[5]. The sponsor indicates that the language of the PI is adequate to address all safety concerns. The sponsor also identifies that the CMI is adequate patient education. The sponsor also clearly identifies in Annex 8 (of the RMP) that no educational program is proposed for this change of indication.

OPR reviewer comment:

The sponsor has not provided an updated proposed Australian PI and CMI to accompany the RMP Version 4.0. Therefore the documents provided with the original submission documents are considered the risk minimisation activities referred to in RMP Version 4.0.

The risk outlined by the sponsor in the table "Summary table for Important Safety Concerns" differ from the table "Summary of the risk Management Plan".

The language in the labelling is mentioned by the sponsor as risk minimisation in both tables but the safety concerns addressed by the labelling differ between the two tables. It is assumed by the evaluator that the more detailed Summary table for Important Safety Concerns" should be referred to when identifying the sponsor's planned risk minimisation activities.

[4] Sponsor comment: "The sponsor provided the TGA with the synopsis for Study P289 post-approval."

[5] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

With respect to the other safety concerns the language in the proposed PI ((MK043-T-092010S-D11022(first line) v1 Tracer No: 0431-AUS-2011-02730 (*110321*) is not consistent with the claims in the RMP table "Summary table for Important Safety Concerns" in that there is:

1. No mention of suicidal ideation, suicide or depression as reported events
2. No mention of neurotoxicity
3. Although dosing in renal failure is mentioned drug-drug interaction in patients with renal insufficiency is not.

In regard to the proposed routine risk minimisation activities, it was recommended to the Delegate that the draft PI and CMI documents be revised but this is beyond the scope of this AusPAR.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of RMP Version 4.0 is imposed as a condition of registration when so qualified:

The sponsor must clarify to the satisfaction of OPR the intended contents of Annex 6 of the RMP Version 4.0 as the statement 'At *this time there are newly available study reports'* is not considered adequate. [6]

Summary of the Ongoing Safety Concerns should be modified to incorporate the concern of the clinical evaluator regarding hypoglycaemic events from clinical trials. It is recommended that the Important Identified Risk should include Hypoglycaemia with Janumet alone (or words to that effect). Routine pharmacovigilance activities and inclusion in the PI, with modification of the CMI in the manner described in the CER as Risk minimisation activities would be acceptable.[7]

Pharmacovigilance plan

The sponsor states that Study P289 is yet to have a finalised study protocol. The sponsor is requested to provide a synopsis of this study to the TGA upon finalisation, for review. [8]

Risk minimisation

The PI should be amended to include mention of all important and potential risks as is stated in the risk minimisation plan. The language in the labelling is the only proposed risk minimisation activity and should be consistent with the sponsor's outlined plan.

The RMP evaluator supports the request from the clinical evaluator to include hypoglycaemia with Janumet alone to be included in the PI.

PI and CMI

Recommendations were also made with respect to the PI and CMI but these are beyond the scope of this AusPAR.

[6] Sponsor comment: "The sponsor clarified this statement during the *Reply to Completed Evaluation Reports*."

[7] Sponsor comment: " The sponsor provided a scientific rationale as to why this modification was not necessary during the *Reply to Completed Evaluation Reports* (see page 31)"

[8] Sponsor comment: "The sponsor provided the TGA with the synopsis for Study P289 post-approval"

Other recommendations

It is recommended that the Delegate give consideration to clarification in the Indication that this product does not have the evidentiary support for paediatric use at this time, to reduce the risk of inadvertent off-label use in this group.[9]

VI. Overall conclusion and risk/benefit assessment

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

This application comprised clinical data only.

As stated by the applicant in the *Clinical Summary* document,

> "Results from one pivotal study support the current application: MK-0431 P036 was a Phase III factorial study spanning 104 weeks (a 54-week base study [Phase A and Phase B] followed by a 50-week extension) in patients with T2DM and inadequate glycemic control (HbA1c 7.5 – 11%) on diet and exercise that was designed to assess the glycemic efficacy and safety of sitagliptin 100 mg daily coadministered with metformin (500 mg twice a day (b.i.d.) or 1000 mg b.i.d.) compared with placebo for the first 24 weeks (switched to metformin at Week 24 and titrated to 1000 mg b.i.d.) and either agent alone. Additional patients meeting all non-glycemic eligibility criteria, but who had an HbA1c >11% or a fasting glucose value >280 mg/dL (15.6 mmol/L) after the run-in period, were assigned to an open-label cohort treated with sitagliptin 50mg b.i.d. co-administered with metformin 1000 mg b.i.d. for 24 weeks. The results of this study demonstrate that co-administration of sitagliptin and metformin is efficacious and well-tolerated when used as initial combination therapy for the treatment of patients with T2DM.
>
> As presented in the initial Janumet registration dossier, the demonstration of bioequivalence between the FDC and corresponding doses of the individual sitagliptin and metformin tablets allowed for bridging of the data obtained with co-administration of sitagliptin and metformin to the combination tablet. In addition, the efficacy and safety profiles of sitagliptin 50 mg b.i.d. have been demonstrated to be similar to those of sitagliptin 100 mg q.d. . Thus, the data from MK-0431 P036, a study utilizing the co-administration of sitagliptin and metformin, extrapolate directly to the FDC tablet."

Study P036 was previously evaluated but now includes extension phase data to an additional 80 weeks, that is, a total of 104 weeks.

Quality

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

Nonclinical

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

Clinical

No new pharmacokinetic or pharmacodynamic studies were submitted. Long term morbidity or mortality studies have not been submitted.

[9] Sponsor comment: "This was included in the PI submitted by the sponsor pre-ACPM."

It is unclear that post marketing data were included in the dossier.

There was one pivotal extension study in support of efficacy and safety: Study P036X1, an extension of the previously evaluated Study P036.

Efficacy

Study P036

This study was submitted as part of the supporting data in connection with the original application to register Janumet; it began as a Phase III, multicentre, randomised double blind study of sitagliptin in patients with Type 2 diabetes mellitus who had inadequate glycaemic control on diet and exercise (HbA1c ≥7.5% and ≤11%; either not on antidiabetic drugs at study entry or after a run-in/wash-off period). The primary objective was to ascertain the safety and efficacy of the combination therapy versus the individual components. The initial phase was of 24 weeks duration. The treatments in the initial phase allocated amongst the following groups: sitagliptin 50 mg b.i.d. with metformin 500 mg b.i.d.; sitagliptin 50 mg b.d. with metformin 1000 mg b.i.d.; metformin 500mg b.i.d., metformin 1000 mg b.i.d., sitagliptin 100 mg daily or placebo.

It was initially reported at *24* weeks (end of Phase A) with these results for HbA1c (Table 13).

Table 13. HbA1c results

Treatment group	N	Mean (SD)		Change from Baseline			
		Baseline	24 weeks	Mean (SE)	LS Mean (SE)	95% CI for LS Mean	LS mean diff (95%CI) from placebo
STG 100 mg daily	175	8.87 (0.99)	8.18 (1.45)	-0.69 (0.10)	-0.66 (0.08)	(-0.83,-0.50)	-0.83 (-1.06,-0.60)
MET 500 mg bid	178	8.90 (1.00)	8.04 (1.36)	-0.85 (0.09)	-0.82 (0.08)	(-0.98, 0.66)	-0.99 (-1.22,0.75)
MET 1000 mg bid	177	8.68 (0.91)	7.58 (1.27)	-1.09 (0.08)	-1.13 (0.08)	(-1.29,0.97)	-1.30 (-1.53,-1.06)
SGL 50 mg bid + MET 500 mg bid	183	8.79 (1.00)	7.37 (1.20)	-1.42 (0.09)	-1.40 (0.08)	(-1.56,1.24)	-1.57 (-1.80,-1.34)
SGL 50 mg bid + MET 1000 mg bid	178	8.76 (0.95)	6.87 (1.09)	-1.89 (0.08)	-1.90 (0.08)	(-2.06,-1.74)	-2.07 (2.30,-1.84)
Placebo	165	8.68 (1.00)	8.21 (1.81)	0.20 (0.09)	0.17 (0.09)	(-0.00, 0.33)	-

The study was extended thereafter to 54 weeks. In this first extension phase, those on placebo were switched to metformin.

Study P036X1, submitted in this data set, was a 50 week extension phase to the 54 week time point of the above. Compliant patients from Phase A were enrolled in the first extension phase (Phase B), including those given rescue treatment (glibenclamide). Patients who were given placebo were then switched to metformin after Week 24 of 54. A

total of 685 subjects entered the study: 103 sitagliptin 100 mg q.d., 134 sitagliptin 50 mg/ metformin 500 mg b.i.d., 122 sitagliptin 50 mg/metformin 1000 mg b.i.d.; 107 metformin 500 mg b.i.d., 121 metformin 1000 mg b.i.d., and 98 placebo/metformin. Sample size calculations were not done. There was no randomisation or re-randomisation into the study extension. There were no formal hypothesis tests defined in the study protocol.

As noted in the clinical evaluation report, efficacy appeared to be better for sitagliptin 50 mg/ metformin 1000 mg b.i.d. and for metformin 1000mg b.i.d. alone than sitagliptin 100 mg q.d. alone. Efficacy in general waned over time (over 104 weeks; see Figure 1).

Efficacy conclusions

"In Study P036X1 relatively few of the subjects included in the extension phase were included in the analysis. Hence limited conclusions can be drawn from the data. However, sitagliptin in combination with metformin had additive efficacy. The effect was apparent over a 104 week follow-up period."

Safety

Hypoglycaemic episodes were reported in two (2.0%) in the sitagliptin 50 mg/metformin 500 mg b.i.d. group, five (4.7%) in the sitagliptin 50 mg/metformin 1000 mg b.i.d., no subjects in the sitagliptin 100 mg q.d., one (1.5%) in the metformin 500 mg b.i.d., two (2.3%) in the metformin 1000 mg b.i.d. and one (2.4%) in the placebo/ metformin.

The evaluator concluded that, "There was a slightly higher rate of hypoglycaemic adverse events reported with the combination of sitagliptin and metformin than with either drug by itself. Other than this, the rates of AEs were as would be expected from the individual drugs".

First round risk: benefit conclusion

Some efficacy was shown. The conclusions are the same as those made concerning efficacy and safety. The risk: benefit balance was favourable. The inclusion of the data on the extension study in the text of the product information document (PI) was suggested.

Second round evaluation

A few questions were asked of the applicant (data set differences in foreign submissions; documentation that initial combination therapy is approved in the US and New Zealand), resulting in a secondary evaluation of these replies.

In regard to the first question, the 24 week study P036 was provided in the original submission to Australia for the registration of Janumet, as well as to the EU, USA, New Zealand and Canada but the data up to 104 weeks for P036X1 were provided with this submission.

In regard to the second question, the New Zealand indication apparently does not refer to first line combination therapy although the applicant asserted this:

> *"Janumet is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with Type 2 diabetes mellitus inadequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin.*
>
> *Janumet is indicated as part of triple combination therapy with a sulfonylurea as an adjunct to diet and exercise in patients with Type 2 diabetes mellitus inadequately controlled with any two of the three agents: metformin, sitagliptin, or a sulfonylurea."*

… and the USA indication is more general in neither specifying nor excluding first line combination therapy:

> *"Janumet is a dipeptidyl peptidase-4 (DPP-4) inhibitor and biguanide combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus when treatment with both sitagliptin and metformin is appropriate."*

The evaluator describes the US PI as more informative than the current Australian document. It was noted that 256 of 454 enrolled patients were not using antihyperglycaemic medications at screening and entered the extension phase without having initiated rescue therapy.

The evaluator finds that, "The benefit-risk balance of Janumet (sitagliptin/metformin), for the proposed usage, an extension of the indication to specify 'initial therapy' for the fixed dose combination, is favourable provided the limitations of the data are made clear in the PI."

The suggested indication is:

> *Janumet is indicated as initial therapy in patients with Type 2 diabetes mellitus to improve glycaemic control when diet and exercise do not provide adequate glycaemic control, when dual sitagliptin and metformin therapy is appropriate (i.e. high initial HbA1c levels and poor prospects of response to monotherapy).*
>
> *Janumet is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with Type 2 diabetes mellitus inadequately controlled on sitagliptin or metformin alone or in patients already being treated with the combination of sitagliptin and metformin.'*

Various significant and relevant changes to the text of the product information document (PI) were suggested (that is, the limited numbers of subjects with data up to 104 weeks and the potential for increased rates of hypoglycaemia with the combination, are to be made clear).

Risk management plan

The evaluator of the risk management plan notes that the applicant intends to pursue routine pharmacovigilance activities and proposes international clinical trials for all Identified and Potential risks and Missing information. The sponsor proposes routine risk minimisation in the form of the text of the PI and patient education via the CMI.

The evaluator asks that the, "'Summary of the Ongoing Safety Concerns' in the RMP should be modified to incorporate the concern of the clinical evaluator regarding hypoglycaemic events from clinical trials. It is recommended that the Important Identified Risk should include Hypoglycaemia with Janumet alone (or words to that effect)". Some changes to the PI were also proposed.[10]

Unresolved issues relate to the increased risk of hypoglycaemia that arises from combination therapy in first-line use. There is also a suggestion of a disclaimer about use in the paediatric population.[11]

[10] Sponsor comment: "The sponsor provided a scientific rationale as to why this modification was not necessary during the *Reply to Completed Evaluation Reports* (see page 31)."

[11] Sponsor comment: "The sponsor responded to the issue of hypoglycaemia as part of the *Reply to Completed Evaluation Reports* (see page 31). The disclaimer regarding use in children was included in the PI submitted by the sponsor pre-ACPM."

Applicant's Reply to Completed Evaluation Reports:

The applicant's reply was included in full in the agenda papers to the ACPM. A summary follows:

1. Clinical evaluation report

The applicant explained,

> *"In MK-0431 P036, any event with symptoms consistent with hypoglycaemia could be considered to be an adverse event of hypoglycaemia; a confirmatory blood or plasma glucose measurement was not required for this definition." "…there were no episodes of adverse events of hypoglycaemia that were of marked severity (i.e., depressed level of consciousness, loss of consciousness, or seizure), that required assistance from others to treat, or that resulted in discontinuation of study medication in the sitagliptin/metformin co-administration groups."*
>
> *"As already stated, the Sponsor has included the risk of hypoglycaemia with the use of Janumet concomitantly with insulin secretagogues, like sulfonylureas or insulin, in the RMP. This risk is also described in the Company Core Data Sheet with recommendations to lower the dose of these agents to reduce the risk of hypoglycaemia."*

A relatively minor error of fact was also corrected.

Risk management plan

Risk management plan evaluation report

In regard to the "Summary of the Ongoing Safety Concerns" the evaluator of the risk Management Plan suggested that it should be modified to incorporate hypoglycaemic events. The applicant states in reply:

> "The hypoglycaemia results from this study are consistent with the cumulative, global clinical trial experience, and do not support an increased risk of hypoglycaemia with use of combination therapy with sitagliptin and metformin, relative to monotherapy with either agent. Consequently, this concept does not meet the definition of an 'important identified risk,' which requires that there be clinical data providing 'adequate evidence of an association with the medicinal product'…"

The applicant does not agree to amend the "Summary of the Risk Management Plan" to align with the "Summary of the Ongoing Safety Concerns" and explains the rationale for the differences.

Potential risks need not be included in the PI, the applicant responded.

Risk-benefit analysis

Delegate considerations

The original Delegate's concerns about the lack of long term efficacy and safety data have been addressed in this submission as extension data from one study.

The original 24 week phase of Study P036 did not directly support first line combination therapy apart from suggestion that sitagliptin 50 mg b.i.d. + metformin 1000 mg b.i.d. showed a greater therapeutic response than metformin 1000 mg b.i.d. Study P036 did not appear to be stratified by baseline HbA1c levels. This stratification would have enabled a sub-analysis to support an advantage for initial combination therapy in those with higher baseline HbA1c levels. However, one would expect that advantage to be true on the basis of biological plausibility just as the use of the combination might risk hypoglycaemia in those with HbA1c levels that are closer to target levels.

The extension phases of the study support continued efficacy and safety in responders but with a tendency to loss of efficacy over time, that is, durability remains of concern and the evaluators' recommendations for a clear representation of this in the PI is supported.

The clinical evaluator's suggested indication is an attempt to balance likely risk and benefit and it represents a generous interpretation of the data.

The draft PI did not provide for instructions on patient selection and dose titration in the proposed setting of intial combination therapy. As far as the Delegate can see, Study P036 gives no guidance for the first of these principles and the dose escalation schedule in Phase A of the study would inform the second. Clearly, specific dose titration data will be needed in patients who qualify for first line combination therapy and this must advise slow escalation of the metformin component on the basis of tolerability and the absence of hypoglycaemia. Other changes to the PI as suggested by the evaluators are also reasonable. It will be necessary for the applicant to annotate the version that is attached to the pre ACPM response with the rational basis for declining these changes.[12]

It is notable that the current indication, "Janumet is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with Type 2 diabetes mellitus inadequately controlled on metformin alone or in patients already being treated with the combination of sitagliptin and metformin" does not preclude use with other agents.

Proposed actions

The application by Merck Sharp & Dohme (Australia) Pty Ltd to register an extended indication for Janumet 50 mg/500 mg, Janumet 50 mg/850 mg and Janumet 50 mg/ 1000 mg tablets containing 50 mg sitagliptin base equivalent and metformin 500 mg, 850 mg or 1000 mg respectively in film coated, unscored tablets should be approved. The registered indication should be:

> *Janumet is indicated as initial therapy in patients with Type 2 diabetes mellitus to improve glycaemic control when diet and exercise do not provide adequate glycaemic control, when dual sitagliptin and metformin therapy is appropriate (i.e. high initial HbA1c levels and poor prospects of response to monotherapy).*
>
> *Janumet is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with Type 2 diabetes mellitus inadequately controlled on sitagliptin or metformin alone or in patients already being treated with the combination of sitagliptin and metformin.'*

Submitted by the Delegate for ACPM advice.

Response from sponsor

Merck Sharp & Dohme (MSD) agreed with the Delegate's proposed action to approve the extension of the indication for Janumet (sitagliptin phosphate/metformin HCl) to include initial therapy in patients with Type 2 diabetes.

MSD also agreed with the Delegate's proposed addition of a qualifying statement to the initial therapy indication. The proposed indications for Janumet are as follows, with text proposed by the Delegate in **bold**:

> *Janumet is indicated as initial therapy in patients with type 2 diabetes mellitus to improve glycaemic control when diet and exercise do not provide adequate glycaemic control, when dual sitagliptin and metformin therapy is appropriate (**i.e. high initial HbA1c levels and poor prospects of response to monotherapy**).*

[12] Sponsor comment: "A revised PI incorporating these changes was submitted by the sponsor pre-ACPM."

Janumet is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus inadequately controlled on sitagliptin or metformin alone or in patients already being treated with the combination of sitagliptin and metformin.

Durability of effect

MSD acknowledged the Delegate's comments regarding the decrease in efficacy over time during the extension of Study P036X1. Progressive deterioration of beta-cell function is observed with increasing duration of disease in patients with Type 2 diabetes mellitus; this continued worsening of beta-cell function is believed to underlie the waning of clinical responses observed with most of the current treatment options for type 2 diabetes mellitus, including metformin, sulfonylureas, thiazolidinediones and DPP-IV inhibitors as demonstrated in randomised, controlled, clinical trials. It also explains why many patients eventually require insulin therapy for glucose control.

MK-0431 P036X1 had a secondary objective to assess the durability of effect; this was evaluated by assessing.

1. the 'durability' of the A1C-lowering effect of therapy by computing a 'coefficient of durability' (COD), and
2. the proportion of patients who achieved (at Week 24) and maintained (at Week 104) a desired A1C goal (for example,<7.0%).

The COD was calculated as follows in the CSR for MK-0431 P036X1: The HbA1C at Week 24 was considered as the nadir HbA1C; the LS means for HbA1C at each subsequent time point were then treated as individual values in a simple linear regression. The COD is the slope of the regression line fit to the LS means. A COD of 0.013 for example, implies that the A1C increases (on average) 0.013% per week after reaching its nadir at Week 24. Higher (that is, more positive) values for the COD suggest a less durable response. The COD was similar for all treatment groups, and there was overlap of the 95% confidence intervals for all groups (see below), suggesting that the HbA1C-lowering observed with initial co-administration of sitagliptin and metformin is at least as durable as that observed with metformin over this period of time.

Table 14.

Coefficient of Durability (COD)
Determined Using HbA_{1c} LS Means from Week 24 to Week 104
All-Patients-Treated in the Extension Phase

Treatment Group	COD (% per Week)	SE	95% CI
Sita 100 mg q.d.	0.007	0.001	(0.004, 0.010)
Met 500 mg b.i.d.	0.006	0.001	(0.003, 0.008)
Met 1000 mg b.i.d.	0.005	0.001	(0.003, 0.006)
Sita 50 mg b.i.d. + Met 500 mg b.i.d.	0.006	0.001	(0.004, 0.008)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d.	0.005	0.001	(0.004, 0.007)
LS=Least Squares; SE=Standard Error; CI=Confidence Interval.			

Of the 144 patients in the initial combination therapy groups who had achieved an HbA1C of <7.0% at Week 24, 100 (69%) maintained an HbA1C of <7.0% at Week 104 (see below).

Table 15.

Proportion of Patients with HbA_{1c} Value < 7.0% at Week 24 and Week 104 All-Patients-Treated in the Extension Phase

Treatment Group	N	n (%)
Sita 100 mg q.d.	30	15 (50.0)
Met 500 mg b.i.d.	29	11 (37.9)
Met 1000 mg b.i.d.	55	35 (63.6)
Sita 50 mg b.i.d. + Met 500 mg b.i.d.	60	40 (66.7)
Sita 50 mg b.i.d. + Met 1000 mg b.i.d.	84	60 (71.4)
N = Number of patients who met goal of HbA_{1c} Value < 7.0% at Week 24. n = Number of patients who also met the goal of HbA_{1c} Value < 7.0% at Week 104.		

Taken together, these data (on the COD and the proportion of patients who achieved and maintained HbA1C at goal) indicate a relatively high durability of effect for the combination of sitagliptin and metformin used for initial therapy of patients with Type 2 diabetes mellitus.

Other Product Information (PI) changes

The Delegate requested that specific dose titration recommendations for patients are included in the PI. The Delegate also recommended that instructions on patient selection are included in the PI. The sponsor agreed with both these requests, and included them in the PI submitted pre-ACPM.

Conclusion

In conclusion, the sponsor agreed with the Delegate's proposed action to recommend the approval of Janumet (sitagliptin phosphate/metformin HCl) for the indication:

> *Janumet is indicated as initial therapy in patients with type 2 diabetes mellitus to improve glycaemic control when diet and exercise do not provide adequate glycaemic control, when dual sitagliptin and metformin therapy is appropriate (i.e. high initial HbA1c levels and poor prospects of response to monotherapy).*
>
> *Janumet is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus inadequately controlled on sitagliptin or metformin alone or in patients already being treated with the combination of sitagliptin and metformin.*

Advisory Committee Considerations

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

The ACPM taking into account the submitted evidence of efficacy, safety and quality considered these products to have an overall negative benefit–risk profile for the proposed extended indication to these combination products.

In making this recommendation the ACPM:

- Expressed significant concern about the inadequacy of the clinical trial design, specifically:
  - The studies did not pre-stratify the patient population for high HbA1c levels and as the cardiovascular benefits were not measureable there was an overall lack of

specificity and clarity in the clinical trial to clearly define the population that would benefit from the initial combination therapy.

  - The evidence to support sustained long term efficacy of glycaemic and HbA1c control and subsequent cardiovascular morbidity benefit is only determined through long term study. The studies were not conducted beyond the 24 week phase and projections beyond this timeframe were not acceptable.

- The ACPM further advised that the proposed indication must be considered in the context of clinical practice and the evidence is not adequate to support this combination as initial drug therapy.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Janumet (sitagliptin/metformin) 50 mg/500 mg, 50 mg/850 mg and 50 mg/1000 mg tablet blister packs for oral administration, indicated for:

> *Janumet is indicated as initial therapy in patients with Type 2 diabetes mellitus to improve glycaemic control when diet and exercise do not provide adequate glycaemic control, when dual sitagliptin and metformin therapy is appropriate (i.e. high initial HbA1c levels and poor prospects of response to monotherapy).*
>
> *Janumet is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with Type 2 diabetes mellitus inadequately controlled on sitagliptin or metformin alone or in patients already being treated with the combination of sitagliptin and metformin.*

Specific conditions applying to these therapeutic goods:

1. The implementation in Australia of the Janumet sitagliptin (as phosphate monohydrate)/metformin hydrochloride RMP version 4.0, and any subsequent revisions with any accompanying caveats and requests for pharmacovigilance activities as agreed with the TGA and its Office of product Review. The sponsor must undertake to give specific consideration of all reported occurrences of hypoglycaemia in the Periodic Safety Update Reports.

Attachment 1. Product Information

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

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Reference/Publication #