Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

Overview of CDR Clinical and Pharmacoeconomic Reports

CDR

September 2008

Sitagliptin
Januvia™ — Merck Frosst Canada Inc.
Indication — Type 2 Diabetes Mellitus

Supporting Informed Decisions

À l'appui des décisions éclairées

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Canadian Agency for Drugs and Technologies in Health

COMMON DRUG REVIEW

Overview of CDR Clinical and Pharmacoeconomic Reports

Sitagliptin

Januvia™ — Merck Frosst Canada Ltd.

Indication —Type 2 Diabetes Mellitus

September 2008

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LIST OF ABBREVIATIONS

AE	adverse event
CDR	Common Drug Review
CI	confidence interval
HbA1c	glycosylated hemoglobin
HDL-C	high-density lipoprotein cholesterol
LDL-C	low-density lipoprotein cholesterol
QALY	quality-adjusted life year
RCT	randomized controlled trial
RR	relative risk
UKPDS	United Kingdom Prospective Diabetes Study

REVIEW IN BRIEF

Sitagliptin (Januvia™) was submitted by the manufacturer to the Common Drug Review (CDR) for consideration for formulary listing by participating public drug plans. This summary is based on the best available clinical and pharmacoeconomic evidence identified and reviewed by the CDR, including information submitted by the manufacturer.

CEDAC Recommendation

The Canadian Expert Drug Advisory Committee (CEDAC) recommended that sitagliptin not be listed.

Reasons for the Recommendation

- While sitagliptin in combination with metformin reduced blood glucose and hemoglobin A1c (Hb A1c) compared to metformin alone in short term trials, randomized controlled trials (RCTs) have not examined the effect of sitagliptin on any clinically important diabetes-related vascular outcomes.
- Sitagliptin is not recommended in patients with moderate to severe renal insufficiency. The long term safety of sitagliptin is uncertain, and this is of critical importance given recent safety concerns with other oral hypoglycemic agents.
- The manufacturer submitted a confidential price for sitagliptin [redacted] which is more expensive than many alternative oral hypoglycemic agents (sulfonylurea agents, pioglitazone, acarbose, repaglinide). The manufacturer proposed that sitagliptin be listed on formularies with restriction to patients who have a contraindication to or are intolerant of a sulfonylurea agent. However, there is insufficient information on the effectiveness and cost-effectiveness of sitagliptin in these patients, and it is unclear what its place in therapy would be in comparison to less expensive alternative agents.

Drug

Sitagliptin is an inhibitor of dipeptidyl peptidase IV, the first of a new class of oral hypoglycemic agents, and is approved by Health Canada for use in combination with metformin in adult patients with type 2 diabetes mellitus to improve glycemic control when diet and exercise plus metformin do not provide adequate glycemic control.

Condition

Type 2 diabetes mellitus is a chronic metabolic disorder caused by insulin resistance: the body makes insulin but is unable to use it properly. There are many clinical manifestations that result from diabetes mellitus, including microvascular (retinopathy, neuropathy and nephropathy) and macrovascular (coronary artery disease, peripheral artery disease, and cerebrovascular disease) complications.

Clinical Review

- A systematic review was conducted of double-blind randomized placebo-controlled trials (RCTs) evaluating the combination of sitagliptin and metformin in adult patients with Type 2 diabetes , taking metformin, with inadequate glycemic control.
- Four trials comparing the combination of sitagliptin plus metformin with placebo plus metformin ranging in duration from 18 to 30 weeks met the inclusion criteria for the systematic review.
- One trial also included a treatment arm of rosiglitazone plus metformin but it was not designed to compare the effects of sitagliptin with rosiglitazone.

Results

- All trials reported that when compared with placebo, sitagliptin resulted in short-term statistically significant reductions in Hb A1c, with the mean difference between groups ranging from -0.51% to -1.0%.
- The proportion of patients achieving a target Hb A1c of <7% was also statistically significantly higher in patients treated with sitagliptin compared with placebo.
- No completed trials have examined clinically important outcomes of diabetes mellitus such as mortality, cardiovascular morbidity or microvascular outcomes.
- Results of extension trials with sitagliptin with follow-up from 54 to 104 weeks suggest

that glycemic control with sitagliptin may be attenuated with longer term use.

Adverse Events

- None of the trials reported statistically significant differences between sitagliptin and placebo in serious adverse events, severe hypoglycemic episodes, withdrawals due to adverse events, adverse events or weight gain or loss.
- Sitagliptin is not recommended for use in patients with moderate or severe renal insufficiency.
- A small placebo controlled trial of sitagliptin monotherapy in patients with renal insufficiency reported numerically higher rates of death, myocardial infarction and atrial fibrillation in patients treated with sitagliptin.

Pharmacoeconomic Review

The pharmacoeconomic analysis submitted by the manufacturer was assessed and critiqued.

Highlights

- The manufacturer submitted a confidential price for sitagliptin [redacted] which is similar to rosiglitazone ($2.02 to $2.88 for 4 mg to 8 mg daily) but more expensive than pioglitazone ($1.12 to $2.36 for 15 mg to 45 mg daily).
- Sitagliptin is higher in cost compared to repaglinide ($0.32 to $0.68 for 0.5 mg to 4 mg), nateglinide ($0.56 to $0.60 for 60 mg to 180 mg), and acarbose ($0.76 to $1.05 for 150 mg to 300 mg).
- The manufacturer submitted a cost utility analysis which considered the treatment of adults with Type 2 diabetes mellitus who have inadequate glycemic control on maximal tolerated doses of metformin as monotherapy and who are intolerant of, or have a contraindication to, a sulfonylurea agent.
- Sitagliptin plus metformin was reported to be associated with a cost per quality-adjusted life year (QALY) of $612 when compared to rosiglitazone plus metformin and $9,225 when compared to pioglitazone plus metformin. As there are no clinical trials designed to evaluate this patient population and with these comparators, the true cost-effectiveness of sitagliptin is uncertain.

What is the CDR?

The CDR conducts objective, rigorous reviews of the clinical and cost-effectiveness of drugs, and provides formulary listing recommendations to the publicly funded drug plans in Canada (except Québec).

OVERVIEW

Context

This document is an overview of two Common Drug Review (CDR) reports: the CDR Clinical Review Report (a systematic review of the clinical evidence) and the CDR Pharmacoeconomic Review Report (a critique of the pharmacoeconomic evaluation submitted by the manufacturer). These reports were prepared by the CDR to support the Canadian Expert Drug Advisory Committee (CEDAC) in making a formulary listing recommendation to participating publicly funded drug plans. The reviews are an assessment of the best available evidence that the CDR has identified and compiled, including that submitted by the manufacturer.

This Overview is based on the sitagliptin CDR Clinical Review Report, 79 pages in length with 81 references, and the sitagliptin CDR Pharmacoeconomic Review Report, 23 pages with 27 references. The manufacturer had the opportunity to provide feedback on each of the full reports and on this Overview Report. The CDR has considered the feedback in preparing the final versions of all of these reports. The manufacturer's confidential information as defined in the CDR Confidentiality Guidelines, may have been used in the preparation of these documents and thus considered by CEDAC in making its recommendation. The manufacturer has reviewed this document and has requested the deletion of confidential information.

Introduction

Sitagliptin (Januvia) is a dipeptidyl peptidase IV inhibitor, the first of a new class of oral antihyperglycemic agents for patients with type 2 diabetes mellitus. Sitagliptin prevents the breakdown of glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide, which are incretin hormones that act on alpha and beta pancreatic cells to stimulate insulin release and suppress glucagon in a glucose-dependent manner.

Sitagliptin is approved by Health Canada for use in combination with metformin in adult patients with type 2 diabetes to improve glycemic control when diet and exercise plus metformin do not provide adequate glycemic control. Use in patients with congestive heart failure, hepatic insufficiency, and renal insufficiency is not recommended. The recommended dose is 100 mg once daily.

The goal of diabetes therapy is reduction of diabetes complications. Intensive therapy for type 2 diabetes has been shown to significantly reduce diabetic retinopathy, neuropathy, and nephropathy.[1] Several classes of pharmacotherapy are used as adjuncts to lifestyle modification for treatment of type 2 diabetes to achieve glycemic control: alpha-glucosidase inhibitors (acarbose), biguanides (metformin), sulphonylureas (glyburide, gliclizide, glimepiride), meglitinides (repaglinide), thiazolidinediones (pioglitazone, rosiglitazone), and insulin.

Clinical Review

Objective

To evaluate the effect of sitagliptin on patient outcomes compared with standard therapies and placebo when used in combination with metformin in adult patients with type 2 diabetes to improve glycemic control when diet and exercise plus metformin do not provide adequate glycemic control.

Methods

For information about the methodology employed in the full CDR Clinical Review of sitagliptin, refer to Appendix I.

Selection Criteria

Studies were chosen for inclusion in the review based on the criteria listed in Table 1.

Table 1: Selection Criteria

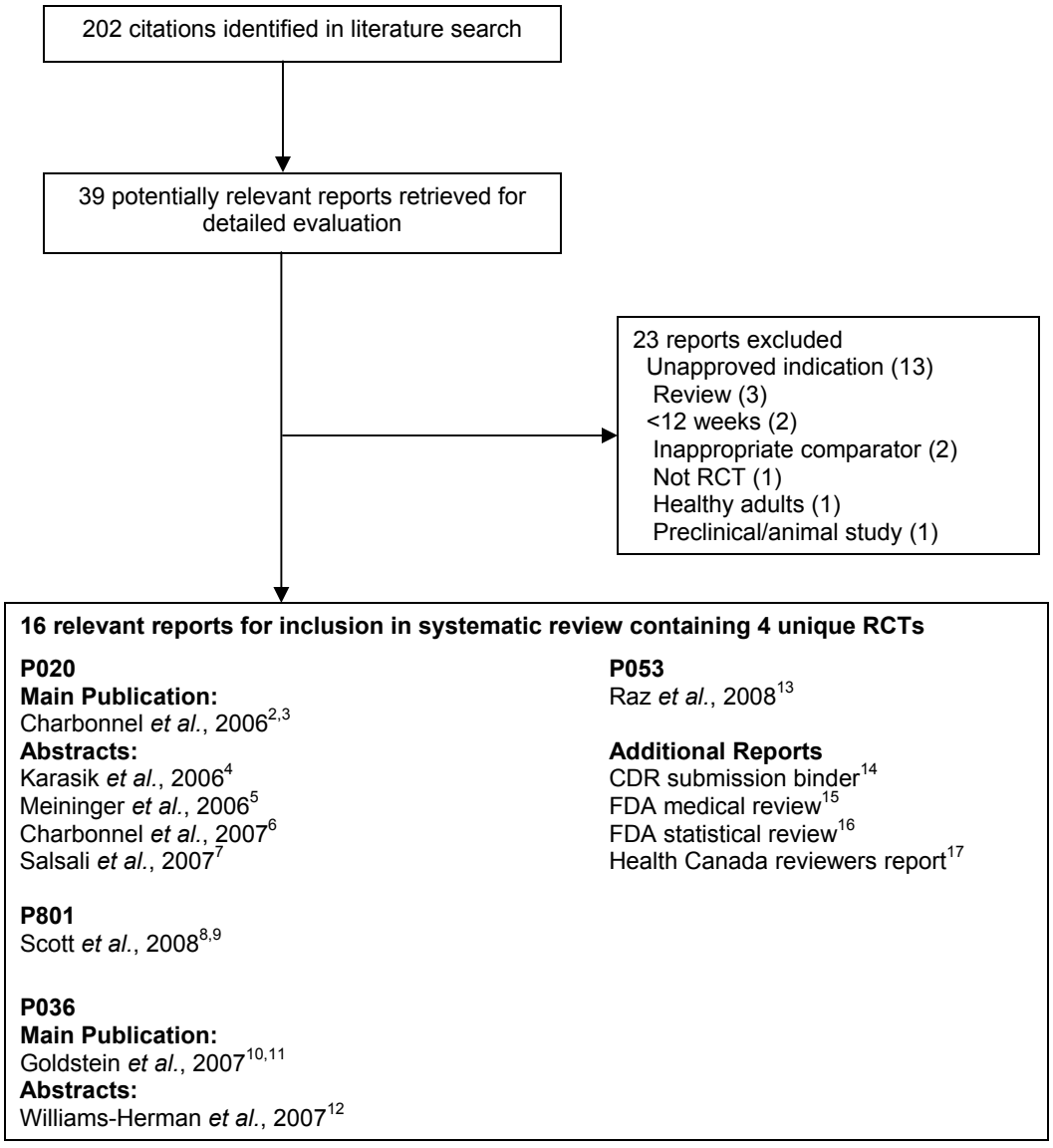
Clinical Trial Design	Patient Population	Interventions	Appropriate Comparators*	Outcomes (measured by validated methods)
Published and unpublished RCTs ≥12 weeks	Adults (≥18 years) with type 2 diabetes mellitus with inadequate glycemic control	Sitagliptin (100 mg daily or 50 mg twice daily) when used only in combination with metformin	- Placebo plus oral antihyperglycemic agents - Oral antihyperglycemic agents - Insulin - Lifestyle changes	• Mortality (all cause and diabetes-related) • Diabetes-related morbidity (including macrovascular: ischemic heart disease, myocardial infarction, stroke, peripheral vascular disease and microvascular: retinopathy, nephropathy, neuropathy) • SAEs and AEs • Hypoglycemia • Weight gain or loss • HbA1c (≥12 weeks) • Fasting plasma glucose • Post-prandial glucose • Changes in lipid profile (e.g., LDL-C, HDL-C) • Beta-cell function and survival • Patient tolerance to drug (WDAE, dose reductions) • Quality of life (any validated scale) • Health resource utilization (e.g., hospitalizations, physician visits)

AEs=adverse events; HbA1c=glycosylated hemoglobin; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; RCTs=randomized controlled trials; SAEs=serious adverse events; WDAE=withdrawal due to adverse event.
* Standard therapies available in Canada (may include drug or non-drug interventions).

Results

Findings from the Literature

Figure 1: QUOROM Flowchart Detailing Flow of Studies



Note: P020 had an extension phase from 24 to 54 weeks in which randomization was maintained but patients receiving placebo plus metformin were switched to glipizide plus metformin.[18] Because glipizide is not available in Canada, the abstract reporting results of the extension phase was excluded from the systematic review, and the results are reported in Appendix III.

Summary of Evidence

Included Studies and Trial Characteristics

Four double-blind randomized controlled trials (RCTs) that evaluated the efficacy and harms of sitagliptin plus metformin compared with placebo plus metformin in patients with type 2 diabetes with inadequate glycemic control were included in this systematic review.

- P020 (n=701) — 24-week trial to evaluate the superiority of sitagliptin (100 mg daily) compared with placebo in patients already receiving metformin alone (≥1,500 mg/day).[2] The active-controlled extension phase where subjects randomized to placebo were switched to glipizide (not available in Canada), is reported in Appendix III.[18]
- P801 (n=273) — 18-week trial to evaluate the superiority of sitagliptin (100 mg daily) compared with placebo in patients already receiving metformin monotherapy (≥1,500 mg/day). P801 also included a rosiglitazone arm, but the trial was not statistically powered for comparisons with this treatment arm.[8]
- P036 (n=1,091) — 24-week trial to evaluate the potential benefit of a fixed-dose of metformin and sitagliptin.[10] The trial included six arms (placebo; sitagliptin 100 mg once daily; metformin 500 mg twice daily; metformin 1,000 mg twice daily; sitagliptin 50 mg / metformin 500 mg twice daily; sitagliptin 50 mg / metformin 1,000 mg twice daily); however, results for placebo alone and sitagliptin 100 mg daily (monotherapy) are not reported here, in keeping with the review protocol. P036 also had an active-controlled extension phase to 54 weeks where patients receiving placebo were switched to metformin 1,000 mg twice daily.
- P053 (n=190) — 30-week trial to evaluate the superiority of sitagliptin (100 mg daily) compared with placebo as an add-on to metformin (≥1,500 mg/day) in patients with moderately severe type 2 diabetes as measured by a higher baseline HbA1c (HbA1c ≥8% and ≤11%).[13]

Studies were well-designed with appropriate randomization, blinding, and allocation concealment.

Summary of Results

See Tables 2 and 3 for a summary of trial outcomes.

Efficacy

Diabetes-related morbidity, mortality, quality of life, and health resource utilization were not measured as efficacy outcomes in any of the included trials.

- **HbA1c (≥12 weeks):** All four studies reported a statistically significant reduction in HbA1c from baseline with sitagliptin plus metformin compared with placebo plus metformin. In studies P020, P036, and P801, differences between sitagliptin plus metformin and placebo plus metformin ranged from -0.51 to -0.77%. In P053, the mean difference was slightly higher at -1.0%. Absolute reductions in HbA1c from baseline in the sitagliptin plus metformin arms in studies where metformin doses were titrated (≥1,500 mg/day), were -0.67% (P020), -0.73% (P801) and -1.0% (P053). When fixed doses of metformin were used (P036), absolute HbA1c reductions from baseline of -1.4% (sitagliptin 100 mg plus metformin 1,000 mg/day) and -1.8% (sitagliptin 100 mg plus metformin 2,000 mg/day) were observed at 54 weeks. The proportion of patients achieving target HbA1c <7.0% statistically

favoured sitagliptin plus metformin in all trials, ranging from 3% to 38% in the placebo plus metformin arms and from 14% to 66% in the sitagliptin plus metformin arms. Measurements of HbA1c at six-week intervals until the end of the study support a stable response between weeks 18 and 30 in studies P053 and P801.

- **Fasting plasma glucose:** All four studies reported statistically significant (p<0.001) between-treatment differences in reduction in fasting plasma glucose from baseline, ranging from -1.0 to -1.9 mmol/L and favouring sitagliptin plus metformin over placebo plus metformin.

- **Two-hour post-prandial glucose:** All four studies reported statistically significant (p<0.001) between-treatment differences in reduction of two-hour post-prandial glucose from baseline that favoured sitagliptin plus metformin over placebo plus metformin, ranging from -1.7 to -3.0 mmol/L.

- **Changes in lipid profile:** Changes in lipid profile are summarized in Table 3 and are of uncertain clinical importance.

- **Beta-cell function:** All four studies reported statistically significant (p≤0.05 to p<0.001) between-treatment increases from baseline in beta-cell function, favoring sitagliptin plus metformin over placebo plus metformin, as determined by the homeostasis model assessment.

Harms

- **Mortality:** No deaths were reported in the sitagliptin plus metformin group in any of the included trials. One death was reported in P053 in the placebo plus metformin group.

- **Serious adverse events:** No statistically significant differences were reported in the proportion of patients experiencing serious adverse events in the four studies of sitagliptin plus metformin versus placebo plus metformin. Serious adverse events ranged from 0% to 5% in patients receiving sitagliptin plus metformin and 1% to 5% in patients receiving placebo plus metformin.

- **Adverse events (AEs):** The difference in proportion of patients reporting total or clinical AEs was not statistically significant in the sitagliptin plus metformin arms (range 39% to 58%) versus the placebo plus metformin arms (range 30% to 62%). In P801 and P053, laboratory AEs were reported and were greater in the sitagliptin plus metformin arm than the placebo plus metformin arm. This difference was statistically significant in P053 [relative risk (RR)=3.7, 95% CI: 1.3 to 10.7] but could not be determined in P801 (7% versus 3% for sitagliptin plus metformin versus placebo plus metformin, respectively). Nasopharyngitis, urinary tract infection, arthralgia, back pain, and cough were observed more often in patients receiving sitagliptin plus metformin compared with placebo plus metformin in P020. Three of four trials reported slightly more gastrointestinal AEs among subjects receiving sitagliptin plus metformin, but no trends in specific gastrointestinal AEs were observed. A CDR pooled analysis of the four trials did not find any specific gastrointestinal AE to be higher in patients receiving sitagliptin plus metformin.

- **Hypoglycemia:** No severe hypoglycemic episodes were reported for sitagliptin plus metformin. One patient in P801 receiving placebo plus metformin had an episode of

hypoglycemia requiring medical assistance and one patient in P036 receiving metformin 1,000 mg twice daily had an episode requiring non-medical assistance.

- **Weight gain or loss:** There were no statistically significant differences in weight change between sitagliptin plus metformin and placebo plus metformin in all four trials.

- **Withdrawal due to adverse events:** The proportion of withdrawals due to adverse events ranged from 0.5% to 4% across study arms. There were no statistically significant differences in withdrawals due to adverse events in any of the four trials between sitagliptin plus metformin compared with placebo plus metformin.

Table 2: Summary of Trial Outcomes — HbA1c and Harms

Study Reference	Study Details	HbA1c, (%)		SAE (% subjects) RR, (95% CI)	AE (% subjects) RR, (95% CI)	Hypoglycemia (% subjects)	WDAE (% subjects) RR, (95% CI)
		Δ from Baseline Difference from PL+MF, (95%CI)	% Patients with HbA1c <7.0% RR, (95% CI)				
P020 Published (80-week extension phase in Appendix III, unpublished)	DBRCT 24-week superiority trial PL+MF: N=237 SITA+MF: N=464	**SITA+MF:** Δ= -0.65 (-0.77, -0.53) p<0.001	**PL+MF**: 18% **SITA+MF**: 47% RR=2.6 (1.9, 3.4) p<0.001	**PL+MF:** 3% **SITA+MF:** 3% RR=0.9 (0.4, 2.3) NSS	**PL+MF:** 54% **SITA+MF:** 56% RR=1.0 (0.9, 1.2) NSS	No episodes of severe hypoglycemia *	**PL+MF:** 4% **SIT+MF:** 4% RR=1.0 (0.4, 2.1) NSS
P801 Published	DBRCT 18 weeks PL+MF: N=92 SITA+MF: N=94 ROS+MF: N=87 **Designed to look at superiority of SITA+MF versus PL+MF**	**SITA+MF**: Δ= -0.5 (-0.7, -0.3) p<0.001 **ROS+MF:** Δ= -0.6 (-0.8, -0.4) p<0.001	**PL+MF**: 38% **SITA+MF**: 55% **ROS+MF**: 63% PL+MF versus SITA+MF p=0.006	**PL+MF**: 5% **SITA+MF**: 5% **ROS+MF**: 6% PL+MF versus SITA+MF RR=1.0 (0.3, 3.2) NSS	*Clinical AE* **PL+MF**: 30% **SITA+MF**: 39% **ROS+MF**: 44% PL+MF versus SITA+MF RR=1.3 (0.9, 2.0) NSS *Laboratory AE* **PL+MF**: 3% **SITA+MF**: 7% **ROS+MF**: 9% RR=not estimable	**PL+MF:** 1 patient with hypoglycemia requiring medical assistance or of marked severity	**PL+MF**: 1% **SITA+MF**: 3% **ROS+MF**: 2% PL+MF versus SITA+MF RR=2.9 (0.2, 27.7) NSS
P036 Published 30-week extension unpublished	DBRCT 24 weeks With 30-week extension MF1000: N=182 MF2000: N=182 SITA+MF1000: N=190 SITA+MF2000: N=182	**SITA+MF1000**: 24 weeks: Δ= -0.6(-0.81, -0.36) 54 weeks: Δ= -0.41(-0.64, -0.17) **SITA+MF2000:** 24 weeks: Δ= -0.8(-1.0, -0.55) 54 weeks: Δ= -0.47(-0.69, -0.24)	**24-week data** **MF1000:** 23% **SITA+MF1000**:43% RR=1.9 (1.4, 2.6) p<0.01 **MF2000**: 38% **SITA+MF2000:** 66% RR=1.7 (1.4, 2.1) p<0.01	**0 to 24 weeks and 24 to 54 weeks** **MF1000**: 2% and 2% **SITA+MF1000**: 3% and 1% NSS at 24 or 54 weeks **MF2000**: 1% and 0.7% **SITA+MF2000**: 0.5% and 3.8% NSS at 24 or 54 weeks	**0 to 24 weeks and 24 to 54 weeks** **MF1000**: 55% and 44% **SITA+MF1000**: 58% and 50% NSS at 24 or 54 weeks **MF2000**: 62% and 47% **SITA+MF2000**: 58% and 51% NSS at 24 or 54 weeks	**0 to 54 weeks** **MF1000:** 1 patient with hypoglycemia requiring non-medical assistance	**24-week data** **MF1000**: 2% **SITA+MF1000**: 2% RR=1.0 (0.2, 3.9) NSS **MF2000**: 3% **SITA+MF2000**: 0.5% RR=0.2 (0.02, 1.8) NSS
P053 Published	DBRCT 30 weeks Moderate-severe type 2 diabetes PL+MF: N=94 SITA+MF: N=96	**SITA+MF:** Δ= -1.0 (-1.4, -0.6) p<0.001	**PL+MF**: 3% **SITA+MF:** 14% p<0.001	**PL+MF**: 5% **SITA+MF:** 0% RR=0.1 (0, 1.6) NSS	*Clinical AE* **PL+MF**: 60% **SITA+MF:** 57% RR=1.0 (0.8, 1.2) NSS *Laboratory AE* **PL+MF**: 4% **SITA+MF:** 16% RR=3.7 (1.3, 10.7) p=0.02	No episodes of severe hypoglycemia	**PL+MF:** 3% **SITA+MF:** 2% RR=0.6 (0.1, 3.8) NSS

AE=adverse events; CI=confidence interval; DBRCT=double-blind randomized controlled trial; HbA1c=glycosylated hemoglobin; MF=metformin; NSS=not statistically significant at p>0.05; PL=placebo; ROS=rosiglitazone; RR=relative risk; SAE=serious adverse events; SITA=sitagliptin; WDAE=withdrawal due to adverse events.

Table 3: Summary of Trial Outcomes — Additional Efficacy Endpoints					
Study Reference	**Study Details**	**FPG (mmol/L) Baseline Δ, Difference from PL+MF**	**2h-PPG (mmol/L) Baseline Δ, Difference from PL+MF**	**Mean Weight Δ from Baseline (kg)**	**Mean % Lipid Δ from Baseline**
P020	DBRCT 24 weeks PL+MF: N=237 SITA+MF: N=464	**SITA+MF:** -1.4 95% CI (-1.7, -1.1) p<0.001	**SITA+MF**: -2.8 95% CI (-3.3, -2.2) p<0.001	NSS difference in mean baseline weight Δ between PL+MF and SITA+MF	*PL+MF versus SITA+MF** **HDL-C:** p<0.05 **TC:** p<0.05 **TG:** p<0.001 **Non-HDL-C**: p<0.01 **TG:HDL-C**: p<0.001 NSS difference in **LDL-C**
P801	DBRCT 18 weeks PL+MF: N=92 SITA+MF: N=94 ROS+MF: N=87 **Designed to look at superiority of SITA+MF versus PL+MF**	**SITA+MF**:-1.0 95% CI (-1.5, -0.4) p≤0.001 **ROS+MF**: -1.7 95% CI (-2.2, -1.1)	**SITA+MF**: -1.7 95% CI (-2.5, -0.8) p≤0.001 **ROS+MF**: -2.5 95% CI (-3.4, -1.7)	*Δ from baseline*: **PL+MF:** -0.8 kg 95% CI (-1.2, -0.4) **SITA+MF:** -0.4 kg 95% CI (-0.8, 0.0) **ROS+MF:** 1.5 kg 95% CI (1.0, 1.9) NSS difference in mean baseline weight Δ between PL+MF and SITA+MF	*PL+MF versus SITA+MF** **TC:** p≤0.05 **TG:** p≤0.05 **Non-HDL-C**: p≤0.05 **TC:HDL-C**: p≤0.05 NSS differences in **LDL-C** or **HDL-C**
P036	DBRCT 24 weeks M1000: N=182 M2000: N=182 SITA+M1000: N=190 SITA+M2000: N=182	**24-week data** **SITA+MF1000**: -1.1 p≤0.001 **SITA+MF2000:** -1.9 p≤0.001	**24-week data** **SITA+MF1000**: -2.2 p≤0.001 **SITA+MF2000:** -2.1 p≤0.001	**24-week data** Statistically significant reductions in body weight relative to baseline (p<0.05) were observed in all four arms. Weight loss was similar between SITA+MF and respective MF control arms.	Not reported
P053	DBRCT 30 weeks Moderate to severe type 2 diabetes PL+MET: N= 94 SITA+MET: N= 96	**SITA+MF:** -1.4 95% CI (-2.1, -0.7) p<0.001	**SITA+MF:** -3.0 95% CI (-4.2, -1.9) p<0.001 (Week 18 results)	*Δ from baseline*: Reductions of 0.5 kg were seen in both PL+MF and SITA+MF groups	NSS differences in **LDL-C, HDL-C, TC, TG, TG: cholesterol**

2h-PPG=two-hour post-prandial glucose; CI=confidence interval; DBRCT=double-blind randomized controlled trial; FPG=fasting plasma glucose; HDL-C=high-density lipoprotein cholesterol; HOMA-β=homeostasis model assessment – beta-cell function; LDL-C=low-density lipoprotein cholesterol; MF=metformin; NSS=Not statistically significant at p<0.05; PL=placebo; ROS=rosiglitazone; SITA=sitagliptin; TC=total cholesterol; TG=triglycerides.

* All statistically significant differences favored sitagliptin plus metformin treatment arms versus placebo plus metformin arms.

Discussion

Limitations

Although the RCTs were conducted in accordance with current regulatory guidance for phase III clinical trials,[19] there are numerous limitations in the clinical trials such as the use of surrogate outcomes, the short duration of trials, and the lack of non-inferiority comparisons between sitagliptin plus metformin and active comparators available in Canada. Furthermore, variability in the use of metformin in these trials (e.g., doses, titrations, and stabilization periods) may be confounding the ability to truly assess the additional effect provided by sitagliptin when added to metformin.

Efficacy

- Discrepant findings raise questions about the role of HbA1c as a valid surrogate outcome to predict macrovascular complications (e.g., cardiovascular disease) and diabetes-related mortality in type 2 diabetes (Appendix II). There is stronger evidence for HbA1c's ability to predict microvascular complications, but uncertainty still exists.
- What constitutes a clinically significant reduction in HbA1c has been debated among clinicians. All trials reported that, when compared with placebo, sitagliptin resulted in short-term statistically significant reductions in HbA1c, with the mean difference between groups ranging from -0.51% to -1.0%. The large absolute reductions observed in P036 [-1.4% (for metformin 1000 mg/day plus sitagliptin) and -1.8% (for metformin 2000 mg/day plus sitagliptin) at 54 weeks] may be due to a population that is still responsive to metformin (e.g., metformin dose was not stabilized before randomization). Therefore, results of P036 may not be generalizable to the Health Canada approved indication for patients with inadequate glycemic control on metformin alone.
- Evaluation of fixed doses of metformin and sitagliptin in P036 demonstrated that, in patients responsive to metformin, the dose of metformin that is used in combination with sitagliptin influences the HbA1c lowering effect of the sitagliptin plus metformin combination, with higher metformin doses providing a greater reduction in HbA1c. These data, along with the complementary mechanisms of sitagliptin and metformin, provide support for the additive efficacy of sitagliptin and metformin.
- Baseline HbA1c is an important consideration when evaluating the effect of diabetes therapies on lowering HbA1c. Patients with a higher baseline HbA1c are more likely to show a decrease in HbA1c when exposed to any new treatment.[20] This effect is supported by Study P053, where subgroup analyses reported the greatest reduction in HbA1c in patients with baseline HbA1c >10% and the smallest reduction in patients with baseline HbA1c <9%.
- While P801 was not designed to directly compare sitagliptin with rosiglitazone, rosiglitazone plus metformin appeared to be similar to sitagliptin plus metformin in lowering HbA1c.
- Decreases in baseline fasting plasma glucose and two-hour post-prandial glucose were reported in all studies, although mean values at 18 to 30 weeks did not reach the glycemic targets outlined in the Canadian diabetes clinical practice guidelines.
- The impact of sitagliptin plus metformin on lipid profiles is of uncertain clinical importance, and effects are confounded by reporting of relative changes, the absence of information on baseline dyslipidemia, baseline use of lipid-lowering therapies, and changes to lipid-lowering therapy during the trials.
- Although, sitagliptin plus metformin is purported to enhance beta-cell function and survival, surrogate outcomes with uncertain validity were measured in these RCTs.
- In all studies, missing data were handled using the last observation carried forward method and data obtained after initiation of rescue therapy were treated as missing. Therefore,

carrying forward data from patients who discontinued early may have reduced the estimate of HbA1c-lowering efficacy in a treatment group.

Harms

- Use of sitagliptin in patients with moderate or severe renal impairment is not recommended.
- A small placebo controlled trial of sitagliptin monotherapy in patients with moderate or severe renal insufficiency reported numerically higher rates of death, myocardial infarction and atrial fibrillation in patients treated with sitagliptin. (Study P028).
- Slight increases in gastrointestinal AEs, immune-related AEs, and arthralgia associated with sitagliptin have been observed either in the included clinical trials or pooled analyses conducted by the manufacturer. Greater clinical experience with sitagliptin plus metformin is necessary to clearly assess potential harms associated with this new class of drugs.

Other Considerations

- The manufacturer requested listing of sitagliptin for the treatment of type 2 diabetes mellitus in patients not achieving adequate glycemic control (HbA1c >7% and/or two-hour post-prandial glucose ≥10 mmol/L or fasting plasma glucose ≥7 mmol/L) and intolerant or contraindicated to a sulfonylurea and are on maximal tolerated doses of metformin. Trial P801 was conducted in patients not achieving adequate response with metformin, and the addition of sitagliptin showed a statistically significant improvement in HbA1c [-0.5, 95% CI (-0.70 to -0.32)] compared with metformin alone. The clinical significance of this improvement is not clear.
- Results of extension trials with sitagliptin with follow-up from 54 to 104 weeks suggest that glycemic control with sitagliptin may be attenuated with longer term use. Data up to 104 weeks, which was reviewed, indicate that the sitagliptin plus metformin HbA1c-lowering effect peaked at 30 weeks. The deterioration from 30 to 104 weeks paralleled that observed with glipizide plus metformin. Further long-term data are required to assess the durability of the treatment effect of sitagliptin plus metformin.

Summary

- In four DB RCTs, the additional value that sitagliptin provides when added to metformin ranged from a baseline HbA1c reduction of -0.51% to -1.0%, measured as between-treatment comparisons of sitagliptin plus metformin and placebo plus metformin. The largest absolute baseline HbA1c reductions were observed in P053 (-1.0%), which included patients with moderate to severe type 2 diabetes and in P036 (-1.4% and -1.9%), in which the population was still responsive to metformin.
- RCTs were well-designed with appropriate randomization, blinding, and allocation concealment. The strength of evidence for sitagliptin plus metformin is limited by the use of surrogate outcomes, the short duration of trials, and the variability of metformin dosing to evaluate the combination of sitagliptin plus metformin.
- Long-term data are needed to adequately resolve a number of issues including the durability of sitagliptin plus metformin efficacy and the effect of sitagliptin plus metformin on beta-cell function and survival. As well, the effects of sitagliptin plus metformin on reducing macrovascular outcomes and mortality were not assessed in these trials and cannot be predicted with certainty using the surrogate outcome of HbA1c.

Pharmacoeconomic Review

Context

The CDR assesses and critiques the economic evaluation, submitted by the manufacturer, with respect to its quality and validity, including the appropriateness of the methods, assumptions and inputs, and results. The CDR may provide additional information on the cost-effectiveness of the submitted drug, where relevant, from other sources or by using the economic model to consider other scenarios.

Objective of the Manufacturer's Submitted Economic Evaluation

The objective of the evaluation was to investigate the incremental cost per quality-adjusted life year gained by incorporating sitagliptin in a progressive treatment algorithm versus incorporation of either rosiglitazone or pioglitazone for patients using maximal doses of metformin who are unable to tolerate or have a contraindication to sulfonylureas.

Summary of the Manufacturer's Pharmacoeconomic Submission

A cost-effectiveness analysis was submitted that evaluated the costs and clinical benefits of sitagliptin compared with rosiglitazone and pioglitazone, when taken in combination with metformin. A discrete event simulation model was developed based on the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model.[21] The manufacturer's model predicts patient risks of diabetes related complications and AEs based on patient characteristics, risk factors, and current treatments for control of HbA1c levels. Patient characteristics were obtained by the manufacturer from a retrospective chart review of patients in various European countries. Patients were then assigned to specific treatment regimens and resultant HbA1c levels were predicted based on clinical trial data. Based on patient attributes and control of HbA1c, risk factors for diabetes-related complications and AEs were determined based on the UKPDS equations. Total costs were derived based on the cost of treatment, management of diabetes, and the treatment of diabetes-related complications. Decreases in patients' utilities were applied depending on the diabetes-related complications and AEs (e.g., hypoglycemia, weight gain) incurred. Costs and clinical benefits were discounted at a rate of 5% per annum over the patient lifetime time horizon (maximum 99 years).

Cost Comparison

CDR produced Tables 4 and 5 to provide a comparison of the cost of treatment of the submitted drug with comparator treatments deemed appropriate by clinical experts. The manufacturer submitted a confidential price for sitagliptin [redacted] which is similar to rosiglitazone but more expensive than pioglitazone. Comparators may reflect recommended or actual practice. Comparators are not restricted to drugs, but may include devices or procedures where appropriate. Costs are manufacturer list prices, unless otherwise specified.

Table 4: Cost comparison of Sitagliptin versus Metformin, Thiazolidinediones, and Sulfonylureas

Drug/ Comparator	Strength	Dosage Form	Price ($)	Average Daily Use	Average Daily Drug Cost ($)
Sitagliptin (Januvia)	**100 mg**	**tablet**	[redacted]*	**100 mg daily**	[redacted]
Biguanides					
Metformin (most generics)	500 mg	tablet	0.0965	500 mg to 2,500 mg daily (divided 2 or 3 times daily)	0.10 to 0.48
Metformin (Glucophage)	500 mg	tablet	0.2128†		0.21 to 1.06
Thiazolidinediones (TZDs)					
Pioglitazone (generics)	15 mg 30 mg 45 mg	tablet	1.1225 1.5726 2.3646	15 mg to 45 mg daily	1.12 to 2.36
Pioglitazone (Actos)†	15 mg 30 mg 45 mg	tablet	2.2451 3.1453 4.7293		2.25 to 4.73
Rosiglitazone (Avandia)	2 mg 4 mg 8 mg	tablet	1.2853 2.0169 2.8842	4 mg to 8 mg daily	2.02 to 2.88
Insulin Secretagogues, Sulfonylureas					
Chlorpropamide generics	100 mg 250 mg	tablet	0.0782‡ 0.0454‡	100 mg to 500 mg daily	0.08 to 0.09
Gliclazide (generics)	80 mg	tablet	0.1863	40 mg to 320 mg daily (in divided doses if ≥160 mg daily)	0.09 to 0.75
Gliclazide (Diamicron)	80 mg	tablet	0.3725†		0.19 to 1.49
Gliclazide long acting (Diamicron MR)	30 mg	ER tablet	0.3725	30 mg to 120 mg daily	0.37 to 1.49
Glimepiride (Amaryl)	1 mg 2 mg 4 mg	tablet	0.8085** 0.8896** 0.9702**	1 mg to 4 mg daily	0.81 to 0.97
Glimepiride (generics)††	1 mg 2 mg 4 mg	tablet	0.4851** to 0.5390**		0.49 to 0.54
Glyburide (Diabeta)†	2.5 mg 5.0 mg	tablet	0.1163 0.2084	2.5 mg to 20 mg daily (in divided doses >10 mg daily)	0.12 to 0.83
Glyburide (most generics)	2.5 mg 5.0 mg	tablet	0.0393 0.0683		0.04 to 0.27
Tolbutamide (generics)	500 mg	tablet	0.0908**	500 mg 2 to 3 times daily	0.18 to 0.54

ER=extended release.
All prices from the Ontario Drug Benefit Formulary (February 2008) except where noted.
*Manufacturer's (Merck Frosst Canada Ltd.) submission binder (confidential price).
†Ontario pays generic price.
‡Saskatchewan Drug Benefit Formulary (February 2008).
**Manitoba Drug Benefit Formulary (January 2008).
†† Glimepiride generics have flat pricing for 1, 2, or 4 mg tablets, but each generic manufacturer has its own flat price.

Table 5: Cost Comparison of Sitagliptin versus Other Oral Antidiabetic Agents					
Drug/ Comparator	**Strength**	**Dosage Form**	**Price ($)**	**Average Daily Use**	**Average Daily Drug Cost ($)**
Sitagliptin (Januvia)	**100 mg**	**tablet**	[redacted]*	**100 mg daily**	[redacted]
Insulin secretagogues, meglitinides					
Nateglinide (Starlix)	60 mg 120 mg 180 mg	tablet	0.5636† 0.5636† 0.6035†	60 mg to 180 mg daily	0.56 to 0.60
Repaglinide (Gluconorm)	0.5 mg 1.0 mg 2.0 mg	tablet	0.3170† 0.3298† 0.3391†	0.5 mg to 4 mg daily	0.32 to 0.66
Alpha-glucosidase inhibitors					
Acarbose (Glucobay, formerly Prandase)	50 mg 100 mg	tablet	0.2518 0.3487	50 mg to 100 mg 3 times daily	0.76 to 1.05
Intestinal lipase inhibitor					
Orlistat (Xenical)	120 mg	capsule	1.5095‡	120 mg 3 times daily	4.53
Combination Products					
Rosiglitazone / Glimepiride (Avandaryl)	4 mg / 1 mg 4 mg / 2 mg 4 mg / 4 mg	tablet	2.9916**	1 tablet daily	2.99
Rosiglitazone / Metformin (Avandamet)	1 mg / 500 mg 2 mg / 500 mg 4 mg / 500 mg 2 mg / 1,000 mg 4 mg / 1,000 mg	tablet	0.6773† 1.2248† 1.6820† 1.3377† 1.8287†	4 mg / 1,000 mg to 8 mg / 2,000 mg daily	2.45 to 3.67

*Manufacturer's (Merck Frosst Canada Ltd.) submission binder (confidential price).
All prices from the Ontario Drug Benefit Formulary (February 2008) except where noted.
†Saskatchewan Drug Benefit Formulary (February 2008).
‡PPS Buyer's Guide (January 2008).
**Non-Insured Health Benefits (Health Canada, 2008).

Results (as submitted by the manufacturer)

The manufacturer concluded that sitagliptin has an incremental cost per quality-adjusted life year of $612 versus rosiglitazone and $9,225 versus pioglitazone, when considering the average dose based on an examination of claims data (Table 6).

Table 6: Manufacturer's Base-Case Results

	Comparator	Incremental		Incremental Cost per QALY
		Cost	QALY	
Sitagliptin versus	**Rosiglitazone**			
	4 mg	$174	0.053	$3,298
	8 mg	-$362	0.037	Sitagliptin dominant*
	Weighted by share of claims 4 mg: 73.2% 8 mg: 26.8%	$30	0.049	$612[†]
	Pioglitazone (generic)			
	15 mg	$687	0.050	$13,862
	30 mg	$441	0.050	$8,903
	45 mg	$9	0.025	$364
	Weighted by share of claims 15 mg: 23.9% 30 mg: 55.4% 45 mg: 20.7%	$410	0.045	$9,225

QALY= quality-adjusted life year

Source: Manufacturer's (Merck Frosst Canada Ltd.) submission binder.
*Sitagliptin is associated with greater benefits at a lower incremental cost.
[†]Manufacturer's submission states that sitagliptin dominates rosiglitazone, but in actuality the incremental cost per QALY is $612 based on CDR calculation and manufacturer's confirmation.

Pharmacoeconomic Analysis Discussion Points

In reviewing the manufacturer's submission, the reviewers noted the following:

- Limitations in comparing RCT evidence for sitagliptin and comparators: No head-to-head RCTs, powered to detect differences between sitagliptin and comparators, were found that met the inclusion criteria for the CDR Clinical Review. In the *Manufacturer's Pharmacoeconomic Submission*, Trial P801 was used as the basis of clinical efficacy and AEs for the comparison of sitagliptin and rosiglitazone (8 mg), used in combination with metformin. Trial P801 included a treatment arm where patients received rosiglitazone; however, the study was not statistically powered for comparisons with the sitagliptin treatment arm. Further, based on a published clinical trial by Goldberg *et al.*,[22] the manufacturer assumes that rosiglitazone (8 mg) and pioglitazone (45 mg) are associated with similar reductions in HbA1c; thus applying the results from the rosiglitazone-controlled arm from P801 to efficacy estimates for pioglitazone (45 mg). To derive efficacy estimates for rosiglitazone 4 mg, a published clinical trial by Fonseca *et al.*[23] was used to calculate a dose-response factor to adjust the efficacy estimates for rosiglitazone 8 mg. Finally, results from several published clinical trials[22,24-26] were used to support the assumption of similar reductions in HbA1c for rosiglitazone (4 mg) and pioglitazone (30 mg). It is unclear whether this approach accurately captures the comparative efficacy of sitagliptin and the comparators.
- Lack of evidence for the patient population for which reimbursement is being sought: The manufacturer is seeking reimbursement for sitagliptin (plus metformin) for patients who are

intolerant to, or contraindicated for, treatment with a sulfonylurea (plus metformin). The manufacturer has suggested that the precedent for this subpopulation of patients with type 2 diabetes is found in the listing criteria for newer oral anti-diabetic agents as established by the public drug plans participating in the CDR, where listing criteria for glitazones and meglitinides typically stipulate a restricted use where patients must first be considered inappropriate candidates for sulfonylureas due to primary treatment failure, intolerance, or contraindication. The manufacturer did not provide information from their patient chart review regarding this specific patient population. In addition, the manufacturer did not provide any evidence from clinical trials involving this patient population. It is unclear whether the results (clinical effects and tolerability) from the available clinical trials can be applied to this specific patient population. The CDR Clinical Review did review evidence from trial P024[27] that compared sitagliptin with glipizide (a sulfonylurea that is not available in Canada) and reported that there was a slightly higher incidence of AEs in the sitagliptin plus metformin versus the glipizide plus metformin groups (summarized in Appendix III), however, this study was not conducted in the population identified by the manufacturer for reimbursement. When considering the approved indication of sitagliptin, sulfonylureas are appropriate comparators, which are lower in cost ($0.04 to $1.49 daily) compared with sitagliptin ([redacted] daily).

- Exclusion of relevant comparators: The manufacturer did not consider other alternatives that are less expensive than sitagliptin and that are used for treatment of type 2 diabetes in patients who are not adequately-controlled with metformin monotherapy: meglitinides (repaglinide and nateglinide) and alpha-glucosidase inhibitors (acarbose). Failing to consider these lower cost alternatives may bias the analysis in favour of sitagliptin.
- Limitations regarding the use of a surrogate outcome (changes in HbA1c): The manufacturer's model is based on the UKPDS Outcomes Model[21] which links HbA1c levels to patient-oriented outcomes such as morbidity, mortality, and their associated utilities. The CDR Clinical Review has noted limitations with HbA1c as a surrogate outcome. In addition, the Cochrane Reviews of pioglitazone (2006)[28] and rosiglitazone (2007)[29] found that these agents result in similar reductions of HbA1c compared to other oral antidiabetic drugs, yet concluded that published studies of at least 24 weeks of rosiglitazone or pioglitazone treatment in people with type 2 diabetes did not provide convincing evidence that patient-oriented outcomes like mortality, morbidity, adverse effects, costs and health-related quality of life are positively influenced by these agents. This raises further uncertainty regarding the validity of the surrogate outcome (changes in HbA1c).

Summary of the Clinical and Pharmacoeconomic Reviews

- In four DB RCTs, the additional value that sitagliptin provides when added to metformin ranged from a baseline HbA1c reduction of -0.51% to -1.0%, measured as between-treatment comparisons of sitagliptin plus metformin and placebo plus metformin. The largest absolute baseline HbA1c reductions were observed in P053 (-1.0%), which included patients with moderate-severe type 2 diabetes and in P036 [-1.4% (for metformin 1000 mg plus sitagliptin) and -1.8% (for metformin 2000 mg plus sitagliptin)] in which the population was still responsive to metformin.
- RCTs were well-designed with appropriate randomization, blinding, and allocation concealment. The strength of evidence for sitagliptin plus metformin is limited by the use of surrogate outcomes, the short duration of trials, and the variability of metformin dosing to evaluate the combination of sitagliptin plus metformin.

- Long-term data are needed to adequately resolve a number of issues including the durability of sitagliptin plus metformin efficacy and the effect of sitagliptin plus metformin on beta-cell function and survival. As well, the effects of sitagliptin plus metformin on reducing macrovascular outcomes and mortality were not assessed in these trials and cannot be predicted with certainty using the surrogate outcome of HbA1c.
- The daily drug cost of sitagliptin ([redacted] for 100 mg) is higher than generic pioglitazone ($1.12 to $2.36 for15 to 45 mg), repaglinide ($0.32 to $0.68 for 0.5 to 4.0 mg), nateglinide ($0.56 to $0.60 for 60 to 180 mg), and acarbose ($0.76 to $1.05 for 150 to 300 mg).

CEDAC Final Recommendation — Issued June 18, 2008

Following careful consideration and deliberation of the information contained within the CDR Clinical and Pharmacoeconomic Review Reports, CEDAC recommended that sitagliptin not be listed.

APPENDIX I: Methodology for the Full CDR Clinical Review

Methods

Reviewer Information

- Systematic Review of Clinical Trials and Executive Summary were prepared by two CDR clinical reviewers in consultation with an external clinical expert specializing in endocrinology.
- Supplemental Issues were prepared by three CDR clinical reviewers.
- Background Information on the Condition was prepared by an external clinical expert specializing in endocrinology.

Systematic Review Methods

Review Protocol

- The review protocol was developed jointly by the two CDR clinical reviewers and the external clinical expert in consultation with the internal and external pharmacoeconomic reviewers. Members of the Canadian Expert Drug Advisory Committee (CEDAC) also provided input and comments.

Literature Search Methods

- The literature search was performed by an internal CDR information specialist using a peer-reviewed search strategy.
- Published literature was identified by searching the following bibliographic databases: BIOSIS Previews, EMBASE and MEDLINE through Ovid, and The Cochrane Library (2008, Issue 1) through Wiley InterScience.
- Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. The initial search was completed on January 23, 2008. Regular alerts have been established to update the search until CEDAC's May 21, 2008 meeting.
- Grey literature was obtained by searching the web sites of regulatory, health technology assessment, and related technology assessment agencies, as well as clinical trial registries. Google and other Internet search engines were used to search for a variety of web-based information including conference abstracts.
- In addition, the manufacturer of the drug was contacted for additional trial data.

Selection of Studies

- Each CDR clinical reviewer independently selected studies for inclusion according to the predetermined selection criteria. All articles considered potentially relevant by at least one reviewer were acquired from library sources. Reviewers independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Selection Criteria

- Studies were chosen for inclusion in the review based on the criteria listed in Table 2, located in the body of this report.

Quality Assessment

- Study bias was critically assessed independently by the two CDR clinical reviewers.

Data Analysis Methods

- CDR reviewers calculated relative risks, number needed to treat, mean differences, 95% CIs, and p-values where possible and where appropriate.

Methods for Supplemental Issues

In addition to the systematic review, a number of supplemental issues were extensively considered and reported within a 24-page supplemental issue section.

Supplemental issues included the following:

- Mechanism of action
- Additional harms information
- Comparing sitaglitpin versus glipizide (P024, P020x)
- Sitagliptin monotherapy studies (P021, P023, P028)
- Sitagliptin plus pioglitazone combination (P019)
- Sitagliptin in triple combination: sitagliptin plus glimepiride plus metformin (P035)
- HbA1c and the UKPDS: validity of outcomes
- Beta cell function: validity of outcomes

Note: Supplemental issues contained in the full CDR review may or may not be included in this overview. Where they are included, supplemental issues may represent in full or may be summaries of those contained in the full CDR review.

APPENDIX II: HbA1c and the UKPDS: Validity of Outcome Measures

Objective

HbA1c is often used as a surrogate marker for outcomes such as diabetes complications (microvascular and macrovascular) and diabetes-related mortality in RCTs. The United Kingdom Prospective Diabetes Study (UKPDS) is the largest and longest trial to date in patients with type 2 diabetes and is a valuable source of information on the relationship between glycemic control and patient-related diabetes outcomes in type 2 diabetes. Therefore, it may be able to clarify the validity of HbA1c as a surrogate outcome. The objective of this supplemental issue is to summarize the main findings from the UKPDS with respect to the effect of intensive glycemic control on patient-related outcomes including mortality, macrovascular events, and microvascular events (UKPDS 33) and to clarify any specific macrovascular advantage to the use of metformin in the overweight cohort of patients receiving intensive therapy with metformin (UKPDS 34).[30]

Summary

The UKPDS 33[1] showed that intensive blood-glucose control by either sulphonylureas or insulin decreases the risk of retinal complications, yet not macrovascular disease or mortality, in patients with type 2 diabetes, with an increase in the risk of hypoglycemia. UKPDS 34[30] showed that in overweight patients with type 2 diabetes, metformin may have additional beneficial effects on cardiovascular outcomes beyond glycemic control; however, the possible benefits of metformin on cardiovascular outcomes was not confirmed in the subsequent combined analysis. Observational analyses in UKPDS 35[31] provide support for a relationship between HbA1c and macrovascular and microvascular outcomes.

Given the limitations of the UKPDS, there is only weak RCT evidence that intensive glucose control, as measured by HbA1c, reduces the risk of microvascular outcomes such as retinopathy and nephropathy in type 2 diabetes. The UKPDS did not demonstrate a significant reduction in the clinically important outcomes of blindness or renal failure for type 2 diabetes. Similarly, a statistically significant reduction in cardiovascular endpoints or death has not been demonstrated in the UKPDS, with the exception of overweight individuals with type 2 diabetes treated with metformin. Inconsistencies in the UKPDS results highlight the possibility that drug- or class-specific effects may have an important impact on clinically relevant outcomes that is independent of HbA1c.

APPENDIX III: COMPARING SITAGLIPTIN WITH GLIPIZIDE (P024 AND P020X)

Objective

Study P024[27] and the extension phase of P020[18] (P020X) did not meet selection criteria for inclusion in the systematic review because the comparator, glipizide, is a sulfonylurea that is not available in Canada. The objective of this supplemental issue is to evaluate how sitagliptin plus metformin compares with a drug representing the class of sulfonylureas.

Summary

In P024, sitagliptin plus metformin was non-inferior to glipizide plus metformin, based on the pre-specified upper limit of the two-sided 95% CI between-treatment mean HbA1c difference criterion of 0.3% but there was a higher rate of discontinuation in the sitagliptin plus metformin versus the glipizide plus metformin group due to lack of efficacy. The 80-week data from P020X provides evidence that the durability of sitagliptin plus metformin is similar to that of glipizide plus metformin.

In P024 patients in the sitagliptin plus metformin group experienced a numerically higher incidence of fatigue, dizziness, nasopharyngitis, sinusitis, urinary tract infection, osteoarthritis, and pain in the extremity compared with the glipizide plus metformin group. In both P024 and P020X, sitagliptin plus metformin was associated with fewer episodes of hypoglycemia and a reduction in weight compared to glipizide plus metformin.

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