Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Saxagliptin (as hydrochloride)

Proprietary Product Name: Onglyza

Sponsor: Bristol-Myers Squibb Australia Pty Ltd

Date of CER: March 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 <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
ADA	American Diabetes Association
AE	Adverse event
ANCOVA	Analysis of covariance
AP	Alkaline phosphatase
BMI	Body mass index
CK	Creatine kinase
CRF	Case report form
DPP-4	Dipeptidyl peptidase 4
FPG	Fasting plasma glucose
GFR	Glomerular filtration rate
LOCF	Last observation carried forward
MTDDI	Mean total daily dose of insulin
MTT	Meal tolerance test
PI	Product information
PPG	Postprandial plasma glucose
T2DM	Type 2 diabetes mellitus
ULN	Upper limit of normal

UNITS

SI units were not used in all documentation. Where other units were used, the stated conversion was as shown below.

Plasma glucose 1 mg/dL = 0.0555 mmol/L

When actual values in alternative units were given in the text, these were often given at a different level of accuracy. For example (from Clinical Overview, referring to FPG values):

> "The difference in the adjusted mean change from baseline versus placebo was -12.94 mg/dL (-0.7 mmol/L) (95% CI [-22.27, -3.61 mg/dL; -1.2, -0.2 mmol/L])."

In cases like this, rather than adopt the inconsistency in numbers of significant figures, I have used the original US values, sometimes reducing the number of significant figures when this appeared to imply a spurious accuracy.

See also section on Clinical Questions below.

1. Clinical rationale

Extension of use of the established oral anti-diabetic drug saxagliptin to T2DM patients who are already being treated with insulin (and possibly metformin).

Insulin is frequently required for glycaemic control in patients with T2DM, and the application appears to be based on sound therapeutic principles.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The submission contained the following clinical information:

- Module 5
  - 2 efficacy/safety studies (CV181057 and D1680C00007, of which the latter has been evaluated previously by TGA).
- Module 2
  - Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

2.2. Paediatric data

The submission did not include paediatric data.

2.3. Good clinical practice

The report of the new clinical study (No. CV181057) in the submission includes certification that it was "conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonization and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)."

3. Pharmacokinetics

No relevant data.

4. Pharmacodynamics

No relevant data.

5. Dosage selection for the pivotal studies

No change in the currently approved dosage was proposed.

6. Clinical Efficacy

Use as add-on to insulin therapy (with or without metformin).

6.1. Pivotal efficacy study: CV181057

6.1.1. Study design, objectives, locations and dates

6.1.1.1. Design

Multi-centre, randomised, parallel-group, double-blind, placebo-controlled study.

The overall study design was provided is outlined below. The report submitted with the present application covers only experience to the end of Period C.

6.1.1.1.1. Single-blind, Dietary and Exercise Placebo Lead-in Period (4 Weeks)

This was a 4-week dietary and exercise placebo lead-in period. Eligible subjects remained on open-label insulin and metformin (if applicable) according to their current regimen and continued that regimen dose for the duration of the study. For standardisation purposes, subjects were instructed on a diet and an exercise program in accordance with the ADA or similar local guidelines to be followed for the study duration. Home glucose meters to monitor glucose control were given to subjects. Compliance was assessed during the lead-in period. Subjects were required to demonstrate good compliance with study medication during the lead-in period to be eligible for randomisation. During the lead-in period, subjects who had a fasting fingerstick glucose of ≥ 270 mg/dL for 3 consecutive days followed by a central laboratory fasting glucose of ≥ 270 mg/dL were to be discontinued from the study.

6.1.1.1.2. Short-term, Double-blind, Placebo Controlled, Treatment Phase (24 Weeks)

Subjects continued receiving their current open-label dose of insulin and metformin (if applicable) and, in addition, were randomised to 1 of 2 treatment arms (saxagliptin 5 mg or placebo). Subjects were followed for a total of 24 weeks on double-blind study medication. Routine review took place at 2, 4, 6, 8, 12, 16, 20 and 24 weeks.

6.1.1.1.3. The "Stable" Insulin Regimen.

All subjects were to remain on the "stable" insulin regimen wherever possible throughout the short-term treatment period. The stable insulin regimen aimed to continue insulin as it was being used by the subject at enrolment and lead-in, with no changes to insulin type and with as few changes in insulin dosage as possible. No short- or rapid-acting insulin was allowed at enrolment (except when part of a pre-mix), nor was it allowed at any time while subjects remained on the stable insulin regimen during the short-term treatment period. Subjects who experienced poor glycaemic control (as manifested either by rising glucose measurements or by persistent increases in insulin dose used) who met certain criteria were to be rescued, as described in the following sections. Subjects became eligible for rescue starting in Week 4. At the rescue visit, subjects were to complete a visit patterned after the Week 24 visit, with a meal tolerance test.

6.1.1.1.4. The "Flexible" Insulin Regimen

After they were rescued, subjects' insulin regimen was switched from the previous "stable" insulin regimen to a "flexible" insulin regimen. Under the "flexible" insulin regimen, the investigator could make any adjustments to the insulin regimen necessary (including increases in the dose of insulin and the addition of rapid- or short-acting insulin, if needed) to control the subject's hyperglycemias. Changes in insulin therapy were based on recommendations from the ADA guidelines or other relevant country-specific guidelines to achieve optimal glycaemic control. The study did not require any specific increases in insulin dose or change in type of insulin used.

After rescue, subjects were to remain in the short-term treatment period, and continue their planned series of study visits. It was only their type or dose of insulin regimen that changed.

Changes in metformin dose (if applicable) and addition of other anti-hyperglycaemic medications were still prohibited.

6.1.1.1.5. Assessment of Insulin Use During the Double-Blind Treatment Period

At each regularly scheduled visit during the double-blind period, the investigator reviewed the subject's diary of (1) fasting self-monitored blood glucose measurements (subjects were to record a minimum of 1 fasting self-monitored blood glucose measurement per day) and (2) actual total daily insulin used each day since the last visit. The mean total daily dose of insulin (MTDDI) was to be calculated by site staff at every visit using the values since the last regularly scheduled visit (minimum of 80% of days with a value). At every visit, the MTDDI was to be compared to the subject's baseline MTDDI (as measured during the lead-in period) to identify any changes in insulin use at that visit compared with insulin use at baseline.

6.1.1.1.6. Rescue

Rescue for high fasting plasma glucose during Short-Term Treatment Period

Some subjects may have been unable to remain on the same unchanging, stable dose of insulin because their fasting plasma glucose measurements were above certain limits. These subjects needed to be "rescued" and have their insulin doses increased. The conditions under which subjects were to be rescued are described in Table 1 below.

Table 1. Rescue for lack of glycaemic control

Visit During Double-Blind Treatment Period	FPG
Weeks 4 or 6	FPG > 240 mg/dL (13.3 mmol/L)
Week 8	FPG > 220 mg/dL (12.2 mmol/L)
Weeks 12, 16, or 20	FPG > 200 mg/dL (11.1 mmol/L)

Once criteria for rescue were fulfilled, the site was to bring the subject in for a "rescue visit". Information gathered at the rescue visit was entered on the CRF. Thereafter, the subject's insulin regimen was to be adjusted as needed to achieve ADA goals for glycaemic control.

Rescue for increased use of insulin during Short-Term Treatment Period

A second reason for rescue was if the subject had been using increased doses of insulin, despite encouragement and counsel from the investigator or site staff to maintain a stable dose of insulin. At the first visit in which a subject's MTDDI exceeded by 20% the subject's MTDDI at baseline, the investigator considered reasons for the increased insulin use and made every effort to have the subject return to his or her previous stable insulin regimen as used at baseline. If, for 2 consecutive visits, MTDDI still exceeded by > 20% the subject's MTDDI at baseline, the investigator was to order the subject to be rescued. Alternatively, in rare circumstances, the investigator could order the subject to be rescued at the first visit where the MTDDI exceeded by > 20% the subject's MTDDI at baseline, if the reason for the subject's increased insulin use was likely to continue beyond the next visit (eg injury, immobility, etc). Once criteria for rescue had been fulfilled, the site was to bring the subject in for a "rescue visit".

Changes in study conduct once the subject was rescued

After the rescue visit, the subject remained in the study as before, and continued to attend the same study visits as previously planned, and continue on study medication (and metformin if applicable). However, the insulin dosing regimen switched from the "stable" regimen to a "flexible" insulin regimen, which may have included short- or rapid-acting insulin). Changes in metformin dose (if applicable) and addition of other anti-hyperglycaemic medications were still prohibited. After rescue, data on the subject's glycaemic control (HbA1c and FPG) were no longer included in primary and secondary analyses of efficacy. For subjects rescued for increased FPG levels, the observations prior to rescue were to be carried forward (LOCF) in primary and secondary analyses of efficacy. For subjects rescued because of increased use of insulin, the last observation prior to rescue and prior to the subject's increase in insulin dose was carried forward. However, in all cases, the subject remained in analyses for safety.

6.1.1.1.7. Down titration of insulin

Insulin was not to be down titrated during any treatment period based on single episodes of hypoglycaemia or symptoms of hypoglycaemia unless clinically indicated. Down titration of insulin was at the discretion of the investigator in response to hypoglycaemia., but recommendations were issued to investigators. Once a subject's insulin dose had been down titrated, the subject was to continue in the study as before, with the lower insulin dosing reflected in the subject's daily diary. The subject's glucose measurements continued to be reviewed at each visit as before, and further changes to the insulin regimen (up or down) could be ordered by the investigator. In any case, the baseline (against which all changes in insulin dose were compared) remained the MTDDI, as measured during the lead-in period.

6.1.1.1.8. Other alterations of regimen

No adjustment of blinded study medication or metformin (if applicable) was allowed at any time during the study unless the subject was hospitalized as described below.

Metformin could not be added at any time to subjects who were not already on metformin at enrolment. Further, no other oral anti-hyperglycaemic agent was to be added to the subject's regimen at any time during the study.

Adjustment of baseline therapy during hospitalization

Increases or decreases in baseline therapy (doses of insulin, and of metformin if applicable) for ≤ 7 days were not to be considered grounds for rescue or for submission of a protocol deviation if they occurred in the context of a hospitalization, as long as the hospitalization was not for management of the subject's glycaemic control, and as long as the subject's doses of insulin and of metformin (if applicable) returned to their previous values once the subject was discharged from the hospital. Once the subject was discharged, criteria for rescue and for down-titration of insulin remained the same as before hospitalization.

6.1.1.2. Objectives

Primary

To compare the effects of saxagliptin versus placebo as add-on therapy to insulin (or to insulin combined with metformin) in improving glycaemic control (HbA1c) at 24 weeks (or rescue).

Secondary

To compare the effects of saxagliptin versus placebo as add-on therapy to insulin (or to insulin combined with metformin) for the following:

- The change from baseline to Week 24 (or rescue) in the PPG AUC from 0 to 180 minutes in response to a meal tolerance test.
- The change from baseline to Week 24 (or rescue) in the 120-minute PPG value in response to a meal tolerance test.
- The change in FPG from baseline to Week 24 (or rescue).
- The proportion of subjects achieving a therapeutic glycaemic response at Week 24 (or rescue), defined as HbA1c < 7%.
- The change in mean total daily insulin dose from baseline to Week 24.

6.1.1.3. Locations and Dates

Subjects were enrolled at 72 centres in 10 countries (9 Canada, 2 France, 6 Hungary, 7 India, 10 Mexico, 7 Poland, 8 Russia, 5 South Africa, 5 UK, and 13 USA).

Study Initiation Date: 13 November 2008.

Study Completion Date: 28 April 2010.

6.1.2. Inclusion and exclusion criteria

The study was done in the outpatient setting.

The study population included male and female subjects with T2DM, aged between 18 and 78 years, who had inadequate glycaemic control and were on a stable dose of insulin. Full inclusion and exclusion criteria were provided.

6.1.3. Study treatments

Study treatment was saxagliptin 5 mg or placebo, once daily before breakfast. Saxagliptin tablets (batch 7J21765) were supplied by BMS Research and Development.

6.1.4. Efficacy variables and outcomes

The main efficacy variables were:

- Change in HbA1c.
- Change in AUC for PPG response to a MTT.
- Change in FPG.

The primary efficacy outcome was the change in HbA1c from baseline to Week 24. If no Week 24 measurement was available, then the last post-baseline measurement was used.

Other efficacy outcomes, assessed at Week 24, included:

- change from baseline in AUC from 0 to 180 minutes for postprandial glucose response to an MTT;
- change from baseline in the 120-minute postprandial glucose value during an MTT;

- change from baseline in FPG;
- proportion of subjects achieving a therapeutic glycaemic response (defined as HbA1c < 7%);
- change from baseline in mean total daily insulin dose based on information recorded on the subjects' daily diary.

6.1.5. Randomisation and blinding methods

At the screening visit, each subject was assigned a unique sequential subject number. Following completion of the lead-in period (Period B), subjects eligible for double-blind treatment (Period C) were randomly assigned to one of the two treatment arms in a 2:1 ratio (saxagliptin:placebo) using a blocked randomisation schedule. Randomisation was stratified by prior metformin use at enrolment, globally across the study.

In this study, no unblinding information was obtained or communicated with the sites.

6.1.6. Analysis populations

The Randomised Subjects Data Set consisted of all randomised subjects who took at least 1 dose of double-blind treatment.

The Evaluable Subjects Data Set, a subset of the above set, consisted of subjects who did not deviate from the terms of the protocol in ways which could have affected the primary endpoint in a relevant way. In the event, no analyses were done using this set because ≤ 10% of subjects in both treatment groups had relevant protocol deviations.

The Treated Subjects Data Set consisted of all subjects who received at least 1 dose of double-blind study drug during the short-term treatment period.

6.1.7. Sample size

Assuming a standard deviation of 1.0%, with total 390 subjects in a 2:1 ratio there is 90% power to detect a difference in HbA1c mean change of 0.35% between saxagliptin and placebo. Assuming a drop out rate of 10%, a total of 435 subjects (290 subjects in the saxagliptin treatment arm and 145 subjects in the placebo treatment arm) needed to be randomised.

6.1.8. Statistical methods

The primary efficacy analysis was performed using ANCOVA, with treatment group and metformin use at enrolment as fixed effects, and baseline value as a covariate in the model. It included subjects in the Randomised Data Set who had HbA1c assessments at baseline and post-baseline (excluding any post-rescue assessments − for efficacy analysis in "rescued subjects", see *Changes in study conduct once the subject was rescued* above). Within the framework of the ANCOVA model, point estimates and 95% confidence intervals for the mean changes between the saxagliptin treatment group and the placebo treatment group were calculated. Mean changes were adjusted for the covariates in the ANCOVA model. Each comparison of the saxagliptin treatment group versus the placebo treatment group was performed using a t-test at an α=0.05 level. The treatment by baseline interaction was tested and distributional assumptions were assessed.

Sequential testing (CSR): The statistical testing of the primary and secondary efficacy endpoints was planned to proceed in a sequential manner, to control the type I error rate within each treatment group at the 0.05 level. Thus, the significance or otherwise of the treatment comparisons for the primary efficacy endpoint would determine which, if any, statistical tests would be performed to compare treatments for the secondary efficacy endpoints.

6.1.9. Participant flow

See below

6.1.10. Major protocol violations/deviations

Criteria for relevant protocol deviations were determined before database lock and were defined as those that could possibly affect the primary endpoint of HbA1c. Only 4 subjects (2 in each group) met this definition.

6.1.11. Baseline data

Table 2. Demographic data

	Saxa N=304	Pbo N=151	Total N=455
Age: mean (sd)	57.2 (9.4)	57.3 (9.3)	57.2 (9.4)
Sex	120M, 184F	68M, 83F	188M, 267F
Weight (kg): mean (sd)	87.6 (19)	86.2 (17)	87.2 (18)
BMI	108 < 30, 196 ≥ 30	61 < 30, 90 ≥ 30	169 < 30, 286 ≥ 30

Table 3. Baseline data relating to disease state and treatment

	Saxa N=304	Pbo N=151	Total N=455
Duration of T2DM (years): mean (sd)	11.8 (6.9)	12.2 (7.4)	12.0 (7.1)
HbA1c (%): mean (sd)	8.7 (0.90)	8.6 (0.85)	8.7 (0.88)
FPG (mg/dL): mean (sd)	173 (54)	173 (56)	173 (55)
120-minute PPG (mg/dL): mean (sd)	252 (75)	253 (77)	252 (76)
MTDDI (units): mean (sd)	53.6 (23)	55.3 (25)	54.2 (24)
Number on metformin	209	105	314

6.1.12. Results for the primary efficacy outcome

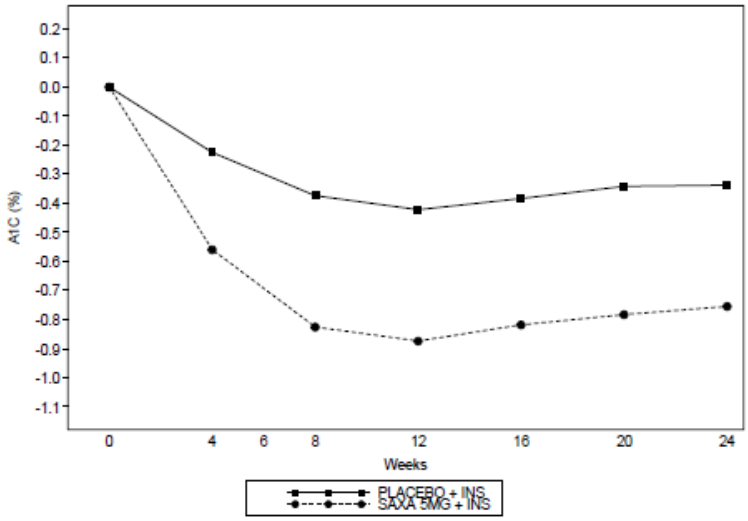
Table 4. Change in HbA1c, baseline to Week 24

HbA1c (%)	Saxa N=304	Pbo N=151
All patients with observations recorded		
n	300	149
Baseline: Mean (SE)	8.67 (0.052)	8.66 (0.070)
Week 24 LOCF: Mean (SE)	7.92 (0.061)	8.32 (0.089)
Mean change from baseline (SE)	-0.75 (0.053)	-0.34 (0.077)
Adjusted[1] mean change from baseline		
Mean (SE)	-0.73 (0.054)	-0.32 (0.074)
95% CI	(-0.83, -0.62)	(-0.46, -0.17)
Difference from control		
Mean (SE)	-0.41 (0.089)	
95% CI	(-0.59, -0.24)	
P-Value	< 0.0001	
Subgroup with metformin use		
n	206	103
Baseline: Mean (SE)	8.66 (0.063)	8.65 (0.088)
Week 24 LOCF: Mean (SE)	7.87 (0.075)	8.27 (0.107)
Adjusted mean change from baseline		
Mean (SE)	-0.79 (0.062)	-0.38 (0.087)
95% CI	(-0.91, -0.67)	(-0.55, -0.21)
Difference from control		
Mean (SE)	-0.41 (0.107)	
95% CI	(-0.62, -0.20)	
Subgroup without metformin use		

HbA1c (%)	Saxa N=304	Pbo N=151
n	94	46
Baseline: Mean (SE)	8.69 (0.092)	8.67 (0.113)
Week 24 LOCF: Mean (SE)	8.02 (0.107)	8.42 (0.161)
Adjusted mean change from baseline		
Mean (SE)	-0.67 (0.091)	-0.25 (0.130)
95% CI	(-0.84, -0.49)	(-0.51, 0.00)
Difference from control		
Mean (SE)	-0.41 (0.159)	
95% CI	(-0.72, -0.10)	

[1] See above.

Figure 1. Mean change from baseline (LOCF) over time during the 24-week treatment period



6.1.13. Results for other efficacy outcomes

Table 5. Change in AUC for PPG response to a MTT

AUC (mg.min/dL)	Saxa N=304	Pbo N=151
All patients with observations recorded		
n	258	122
Baseline: Mean (SE)	41852 (721)	42844 (1090)
Week 24 LOCF: Mean (SE)	37037 (706)	41291 (1178)
Mean change from baseline (SE)	-4815 (769)	-1554 (1143)
Adjusted mean change from baseline	•	•
Mean (SE)	-4548 (688)	-719 (982)
95% CI	(-5901, -3196)	(-2649, 1211)
Difference from control	•	•
Mean (SE)	-3830 (1166)	•
95% CI	(-6122, -1537)	•
P-Value	0.0011	•

Table 6. Change in FPG

FPG (mg/dL)	Saxa N=304	Pbo N=151
All patients with observations recorded		
n	300	149
Baseline: Mean (SE)	173 (3.1)	173 (4.6)
Week 24 LOCF: Mean (SE)	161 (2.9)	165 (4.2)
Mean change from baseline (SE)	-12.0 (3.5)	-7.90 (4.7)
Adjusted mean change from baseline	•	•
Mean (SE)	-10.1 (2.9)	-6.1 (4.0)
95% CI	(-15.7, -4.4)	(-13.9, 1.8)

Difference from control	•	•
Mean (SE)	-4.0 (4.7)	•
95% CI	(-13.3, 5.3)	•
P-Value	0.40	•

Figure 2. Percent of subjects achieving therapeutic glycaemic response (HbA1c <7%) at Week 24 (LOCF)

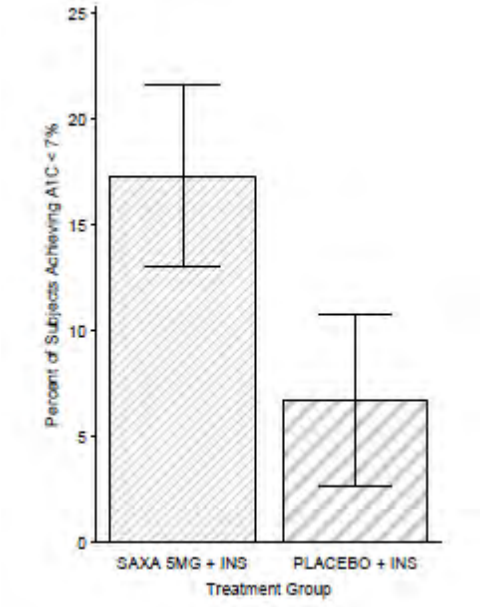
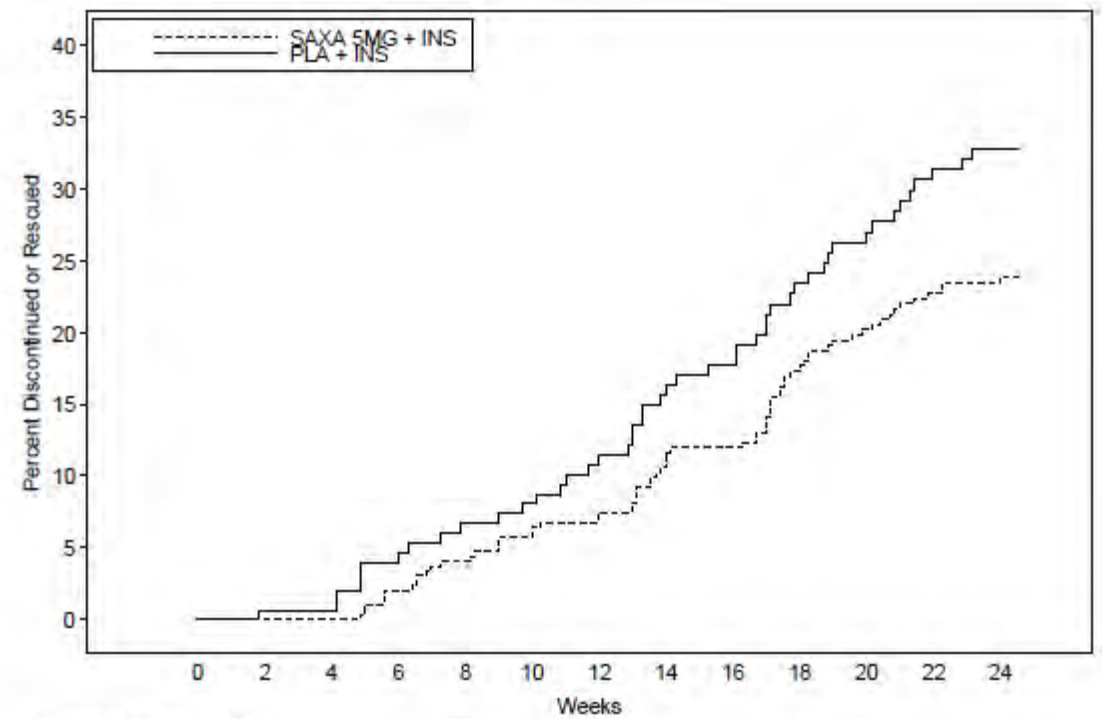


Figure 3. Time to study discontinuation for lack of glycaemic control or rescue for failing to achieve glycaemic targets



6.2. Other efficacy studies

6.2.1. Study D1680C00007

In the Clinical Overview, the sponsor argues:

> "The recommended daily dose for saxagliptin in patients with moderate and severe renal impairment and end-stage renal disease (ESRD) on hemodialysis is 2.5 mg, based on exposure to saxagliptin and BMS-510849, its main metabolite as demonstrated in a dedicated PK study (CV181019, not part of this application). In study 07, a majority of the patients were being treated with insulin at the time of randomisation and continued throughout the study. The dose adjustment of saxagliptin in this patient category is based on the fact that elimination of saxagliptin and its metabolite is dependent on renal function. The results in the subgroup receiving insulin demonstrated similar efficacy of saxagliptin 2.5 mg in this population as the 5 mg dose in patients with normal renal function in study 57. The findings in study 07 therefore support the use of saxagliptin in patients on insulin, and demonstrate clinically important improvement in glycaemic control in a patient category with limited choices of oral antidiabetic medications to further improve glycaemic control."

Study D1680C00007 was included in a previous submission (no. PM-2010-03800-3), which has been evaluated. I refer the reader to the CER dated 15 June 2011, of which the following is copied:

> *"Results for the primary efficacy parameter, change in HbA1c from baseline to week 12, are shown in Table [7] below (taken from the clinical study report, CSR)":*

Table 7. Change in HbA1c from baseline to week 12

Measure of HbA1c (%)	Saxa 2.5 mg (N=81)	Placebo (N=83)
Baseline mean (SE)	8.45 (0.135)	8.09 (0.119)
Week 12 mean (SE)	7.63 (0.132)	7.80 (0.137)
Mean change from baseline (SE)	-0.82 (0.114)	-0.29 (0.122)
Mean adjusted change from baseline (SE)	-0.86 (0.112)	-0.44 (0.109)
95% two-sided CI	(-1.08 to -0.64)	(-0.66 to -0.23)
Difference versus placebo[a]		
Mean (SE)[b]	-0.42 (0.151)	
95% two-sided CI	(-0.71 to -0.12)	
p-value	0.007	

[a] Difference in adjusted change from baseline for saxagliptin versus placebo.
[b] Estimate=(adjusted mean change for saxagliptin)–(adjusted mean change for placebo)

"A modest but statistically significant treatment effect of saxagliptin 2.5 mg, reducing HbA1c by 0.42%, is seen."

.....

"In the long-term follow-up (week 12-52) phase of study 07, the difference in HbA1c between active and placebo treatment groups was maintained. The difference in the adjusted mean change in HbA1c from baseline in the saxagliptin group compared with placebo was -0.73% (95% CI: -1.11 to -0.34) at Week 52 (p<0.001). There was a similar finding at 28 weeks."

6.3. Analyses performed across trials (pooled analyses and meta-analyses)

Not relevant.

6.4. Evaluator's conclusions on clinical efficacy

The pivotal study was necessarily complex, in that (hypothetically) inferior efficacy of placebo (compared with saxagliptin) could trigger increased insulin dosage, thus leading to compensation in terms of glycaemic control. To deal with this, the experimental design called for subjects to remain on the "stable" insulin regimen wherever possible throughout the short-term treatment period, and in the analysis, persistent increases in insulin dosage were treated as evidence of poor glycaemic control. I believe this to be a rational approach. The arrangements for adjustment of insulin dosage during the study appear consistent with reasonable clinical practice.

The mean reduction in % HbA1c (0.41) was clearly statistically significant, and in my opinion also indicated a clinically significant improvement in glycaemic control.

I accept that Study D1680C00007 provides some support in general terms for the efficacy of saxagliptin observed in Study CV181057. Note however that in Study D1680C00007

- The dosage was different (2.5 mg daily);
- All patients had renal impairment of at least moderate degree; and
- Not all subjects were on insulin. (The evaluator noted, in the *CER* dated 15 June 2011: "Insulin was the most prevalent existing diabetes therapy, being used by 86% of saxagliptin and 67% of placebo subjects in the safety analysis set".)

The therapeutic background

The therapy of T2DM is complex, and influenced by factors including the following:

- degree of success with modification of lifestyle factors;
- degree of obesity; and
- presence of end-organ damage.

Apart from general agreement that (following attention to lifestyle factors) metformin is an appropriate first-line drug treatment in the obese patient without renal impairment, the optimal sequence for introducing other medications (sulfonylureas, thiazolidinediones, acarbose, insulin, DPP-4 inhibitors) has not been established (NHMRC 2009).

6.4.1. Conclusions from the efficacy evidence

This is an application in which only one pivotal study has been submitted in the application in support of an extended efficacy claim. The guideline EMEA (2002) is of some relevance here, although I believe the points it makes are of diminishing importance as more experience is gained with a drug, and as the drug's indications are extended beyond those initially registered. In any case, the guideline's "prerequisites for one clinical study applications" have generally been met. On the question of consistency of findings for different endpoints: a statistically significant result was not obtained for change in FPG (see above); however, I consider this endpoint of secondary relevance for this class of anti-diabetic, in view of its mechanism of action.

In a reasonably diverse population of T2DM patients, adequate evidence for efficacy of Onglyza has been demonstrated in patients already receiving insulin (in fact, "On a stable dose of insulin"), with or without metformin, but not other prescription anti-diabetic medication.

The evidence does not cover the addition of insulin to a regimen which already includes Onglyza. On a strict reading of the amended indications now proposed, perhaps this is clear; however, it may be appropriate to rephrase the text to eliminate any ambiguity. Rephrasing is also necessary to correct the confusing use of the words "the single agent alone" when referring to "insulin (with or without metformin)".

7. Clinical safety

7.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

Pivotal efficacy studies

In the pivotal efficacy study (CV181057), the following safety data were collected:

- General AEs were assessed by open-ended questioning at each review (see above).
- AEs of particular interest: Efforts were made to validate reports of clinical hypos by asking patients to obtain a fingerstick glucose at the time of any suggestive symptoms.
- Laboratory tests, including standard haematology and clinical chemistry, were performed at each review. Patients were issued with blood glucose meters for self-monitoring. Urine was tested at the 12 and 24 week visits.

Pivotal studies that assessed safety as a primary outcome

Not applicable.

Dose-response and non-pivotal efficacy studies

The non-pivotal efficacy study D1680C00007 included in the dossier (see above) provided safety data on use of the drug at different dosage, in a different patient population.

Other studies evaluable for safety only

Not applicable.

7.2. Pivotal studies that assessed safety as a primary outcome

None submitted.

7.3. Patient exposure

I have included in Table 8 below only the data from Study CV181057, on the basis that inclusion of data from the other study submitted in this dossier (Study D1680C00007) would mislead, in view of the major differences outlined above.

Table 8. Exposure to Onglyza and comparator in clinical studies.

Study type/ Indication	Controlled studies		Uncontrolled studies	Total Onglyza
	Onglyza	Placebo	Onglyza	
Clinical pharmacology	0	0	0	0
Pivotal[1]	304	151	0	304
Other	0	0	0	0
TOTAL	304	151	0	304

[1] Double-blind period only.

Table 9. Exposure to Onglyza in clinical studies according to dose and duration.

Study type/ Indication	Dose 5 mg/day			
	≥ 82 Days	≥ 166 days	≥ 365 days	Any duration
• Placebo-controlled[1]	293	259	0	304
• Active-controlled	0	0	0	0
• Uncontrolled	0	0	0	0
TOTAL	293	259	0	304

[1] Double-blind period only.

7.4. Adverse events

For the reasons given above, I have not included here data from Study D1680C00007. The safety data from that study are presented in the CER dated 15 June 2011.

7.4.1. All adverse events (irrespective of relationship to study treatment)

7.4.1.1. Pivotal study CV181057

Tabulations of AEs by SOC, excluding hypoglycaemic events, regardless of insulin rescue status were provided.

7.4.2. Treatment-related adverse events (adverse drug reactions)

7.4.2.1. Pivotal study CV181057

AEs classified as at least possibly† related to treatment, by SOC, excluding hypoglycaemic events, excluding events after insulin rescue, were provided.

† On a scale of investigator judgement Certain, Probable, Possible, Unlikely, Unrelated; or missing relatedness to the study drug on their CRF.

Confirmed hypoglycaemia with associated symptoms, regardless of rescue status:

- Onglyza group 16 (5.3%)
- Placebo group 7 (4.6%)

7.4.3. Deaths and other serious adverse events

7.4.3.1. Pivotal study CV181057

Tabulations of AEs by SOC, including hypoglycaemic events were provided.

One subject **([Information redacted])** died during the study: a 58 year old male in the Onglyza treatment group, whose last dose of study medication was on Day 111. He was found unconscious on Day 125, and died the same day. Cause of death was reported as myocardial infarction, and judged by the investigator to be unrelated to study medication. Two other subjects **([Information redacted]**), both in the Onglyza treatment group, experienced cardiovascular SAEs: acute coronary syndrome and acute myocardial infarction, respectively. Relatedness to study drug was judged "not related" and "not likely", respectively.

7.4.4. Discontinuation due to adverse events

7.4.4.1. Pivotal study CV181057

Double-blind period only; regardless of rescue.

- Onglyza group: 5 (2 ↓GFR; 1 hypoglycaemia; 1 breast cancer; 1 dyspepsia and diarrhoea)†
- Placebo group: 3 (1 abdominal pain upper; 1 ↑CK; 1 ↑creatinine)

†See below.

7.4.5. Laboratory tests

7.4.5.1. Liver function

7.4.5.1.1. Pivotal study CV181057

Overall, there were no consistent changes from baseline in ALT, AST, AP, and total bilirubin values. There were no subjects with marked abnormalities of AP (> 3 x baseline and > 3 x ULN) or elevated AST (> 3 x ULN). AP levels elevated > 1.5 x ULN were noted for 9 subjects in the Onglyza group and 3 subjects in the placebo group. Markedly abnormal elevated ALT (> 3 x ULN) was reported for 2 subjects in the Onglyza group and 1 subject in the placebo group. One subject in the Onglyza group had markedly abnormal total bilirubin (> 2 mg/dL or > 1.5 x ULN). However, no subject had ALT >3 x ULN and total bilirubin > 1.5 x ULN, or ALT >3 x ULN and total bilirubin > 2 mg/dL.

7.4.5.2. Kidney function

7.4.5.2.1. Pivotal study CV181057

There were no consistent changes from baseline in either treatment group for serum creatinine values, and little to no mean change in sodium, potassium, and chloride mean values from baseline. No marked changes in serum creatinine.

7.4.6. Other clinical chemistry

7.4.6.1. Pivotal study CV181057

Plasma glucose: See above.

CK: Four (1.3%) subjects in the Onglyza group and 1 (0.7%) subject in the placebo group had CK > 5 x ULN. In most cases these elevations represented a single high value and CK levels had returned to within normal limits (or were much lower) by the last recorded value.

7.4.7. Haematology

7.4.7.1. Pivotal study CV181057

Because of known effects of saxagliptin, lymphocytes and platelets were the subject of particular attention.

Mean absolute lymphocyte counts and mean platelet counts were generally stable across both treatment groups during the short-term treatment period. No marked† abnormalities were reported for decreased platelets. Lymphopenia was noted for 3 subjects in the Onglyza group and 1 subject in the placebo group.

† Predefined degrees of abnormal test results, generally moderately severe.

7.4.8. Electrocardiograph

7.4.8.1. Pivotal study CV181057

Shifts from baseline to Week 24 of the double-blind period are summarised below:

Table 10. ECG: Shifts from baseline to Week 24.

Treatment group	Tracing Week 24	Baseline tracing - number (%) of subjects					
		Normal		Abnormal		Total	
Onglyza N=304	Normal	112	(87.5)	21	(29.2)	133	(66.5)
	Abnormal	16	(12.5)	51	(70.8)	67	(33.5)
	Total	128	(100.0)	72	(100.0)	200	(100.0)
Placebo N=151	Normal	50	(96.2)	11	(31.4)	61	(70.1)
	Abnormal	2	(3.8)	24	(68.6)	26	(29.9)
	Total	52	(100.0)	35	(100.0)	87	(100.0)
Total N=455	Normal	162	(90.0)	32	(29.9)	194	(67.6)
	Abnormal	18	(10.0)	75	(70.1)	93	(32.4)
	Total	180	(100.0)	107	(100.0)	287	(100.0)

A varying spectrum of ECG abnormalities was noted across treatment groups.

7.5. Post-marketing experience

No data submitted.

7.6. Other safety issues

7.6.1. Safety in special populations

Subject to my remarks above, the experience from Study D1680C00007 (see CER dated 15 June 2011) provides some reassurance regarding safety in patients with moderate, severe and end-stage renal impairment.

7.7. Evaluator's overall conclusions on clinical safety

The safety data from Study CV181057 does not raise any concerns relating to the proposed usage. The CER covering Study D1680C00007 also did not note any new safety concerns.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

The benefits of Onglyza in the proposed usage are:

- Improved glycaemic control in T2DM patients who have been on treatment with insulin; and
- Increased flexibility in designing a treatment regimen.

8.2. First round assessment of risks

The study of use in combination with insulin has not identified any specific risk of the combination, although it could not be expected to reveal uncommon AEs. Presumably, the addition of Onglyza to any regimen carries at least an additional risk reflecting the AEs listed in the currently approved PI.

8.3. First round assessment of benefit-risk balance

The benefit-risk balance of Onglyza, given the proposed usage, is favourable.

9. First round recommendation regarding authorisation

Approval is recommended.

10. Clinical questions

10.1. Efficacy

The sponsor might be asked to explain the odd assortment of implied accuracy in measurements presented in Module 2, which cites an instance of the value 12.94 mg/dL (4 significant figures) being given as equivalent to the value 0.7 mmol/L (1 significant figure). Was the same approach used in converting observations originally recorded in SI units (in European sites) to US units for the purposes of the CSR?

A Kaplan-Meier plot (see Figure 4, below) shows time to study discontinuation for lack of glycaemic control or rescue for failing to achieve glycaemic targets. It may be of interest to see separate plots for those using, and not using, metformin at baseline.

10.2. Safety

In the CSR for Study CV181057, data are frequently tabulated for the period "prior to rescue". The sponsor should be asked to confirm that such tabulations include data from patients for whom insulin rescue never occurred.

The Protocol shows Day 1 as randomisation day. However, a Table in the CSR Adverse Events Leading to Discontinuation from Study During Lead-in and Short-term Treatment Period shows subject no. [**Information redacted**] as withdrawn on Day -1 yet randomised, and another Table in the CSR appears to include this subject in the number withdrawn during the short term treatment period because of AE. The sponsor might be asked to explain the discrepancy.

The CSR asserts "No SAE was reported for more than 1 subject during the short-term treatment period ...", but it appears that this was not so (see above). The sponsor might be asked to explain the discrepancy.

The sponsor might be asked to comment on the 6 AEs of "Hypertensive crisis" recorded in the Onglyza treatment group.

11. Second round evaluation of clinical data submitted in response to questions

See Addendum

12. Second round benefit-risk assessment

12.1. Second round assessment of benefits

No change is proposed to the round 1 Assessment.

12.2. Second round assessment of risks

No change is proposed to the round 1 Assessment.

12.3. Second round assessment of benefit-risk balance

No change is proposed to the round 1 Assessment.

13. Second round recommendation regarding authorisation

As for first round Recommendation.

14. References

Studies presented in the dossier:

Study no.	Title	Location in dossier
CV181057	A Multicenter, Randomized, Double-Blind, Phase 3 Trial to Evaluate the Efficacy and Safety of Saxagliptin Added to Insulin Monotherapy or to Insulin in Combination with Metformin in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control on Insulin Alone or on Insulin in Combination with Metformin. Note. The report covered the first 24 weeks of a planned 52 week study.	Module 5, vol 1

Other references

European Agency for Evaluation of Medical Products (EMEA). 2001. *Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study.* 31 May 2001.

CPMP/EWP/2330/99.

European Agency for the Evaluation of Medical Products (EMEA). 2002. *Note for guidance on clinical investigation of medicinal products in the treatment of diabetes mellitus*. 30 May 2002.

Document CPMP/EWP/1080/00.

National Health and Medical Research Council (NHMRC). 2009. *National Evidence Based Guideline for Blood Glucose Control in Type 2 Diabetes*. 14 July 2009

15. Addendum

15.1. Evaluation of responses to TGA request for further information.

15.1.1. Efficacy

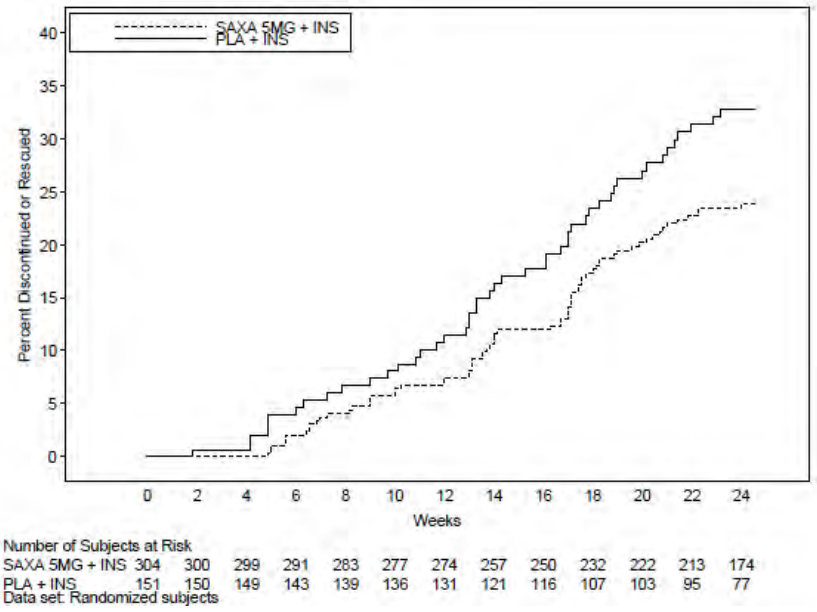
1. *Please explain the odd assortment of implied accuracy in measurements presented in Module 2. For example, Module 2 cites an instance of the value 12.94 mg/dL (4 significant figures) being given as equivalent to the value 0.7 mmol/L (1 significant figure). Was the same approach used in converting observations originally recorded in SI units (in European sites) to US units for the purposes of the CSR?*

The sponsor explains this by stating that all results were expressed as SI or US standard units and despatched to BMS . BMS converts the data to US units. Conversion factors used in these laboratory results are based on published references. For the Australian dossier, values were converted to SI units from values used in the original analysis.

A wrong tracking sheet submitted is replaced with the correct tracking sheet. The laboratory values included in the dossier are stated to be accurate.

Evaluator's comments: An adequate explanation has been submitted by the sponsor.

Figure 4. Kaplan-Meier plot of time to study discontinuation for lack of glycaemic control or rescue for failing to achieve glycaemic targets



2. *As shown above, the Kaplan-Meier plot shows time to study discontinuation for lack of glycaemic control or rescue for failing to achieve glycaemic targets, in the pivotal study CV181057.*

   Please provide separate plots for those using, and not using, metformin at baseline.

They have been provided. The sponsor states that the Kaplan Meier curves are consistent with overall results. The numbers discontinuing due to lack of glycaemic control or rescue were greater for placebo treated than saxagliptin treatment patients.

Evaluator's comment: This is satisfactory.

15.1.2. Safety

3. *In the CSR for Study CV181057, data are frequently tabulated for the period "prior to rescue". Please confirm that such tabulations include data from patients for whom insulin rescue never occurred*.

This is confirmed by the sponsor.

4. *The Protocol shows Day 1 as randomisation day. However, a Table in the CSR shows subject* [**Information redacted**] *as withdrawn on Day -1 yet randomised, and another Table in the CSR appears to include this subject in the number withdrawn during the short term treatment period because of AE. Please explain the discrepancy*.

Response: "During Study CV181057, subject [**Information redacted**] had an AE (decrease in estimated creatinine clearance) that occurred prior to randomisation and first dose, on Day -1, which eventually led to discontinuation on Day 13. This subject contributed information during the ST treatment period and also discontinued during the short-term treatment period on Day 13, see ST CSR CV181057, Appendix 2.4. Although the adverse event occurred prior to randomization, we have reflected that this subject discontinued during the ST treatment period, and ultimately discontinuation occurred due to an adverse event.

For adverse event analyses, adverse event listings capture all events starting from lead-in, even though only treatment-emergent events are included in tabulations of adverse events. The CSR for Study CV181057, mentions this subject in addition to the other subjects who had AEs leading to discontinuation."

Evaluator comment: noted.

5. *The CSR asserts "No SAE was reported for more than 1 subject during the short-term treatment period ...", but it appears that this was not so (see above). Please explain the discrepancy.*

It is explained that the table included subjects "prior to rescue" as stated in the table title.

Evaluator comment: Acceptable.

6. Please provide full details of and comment on the 6 AEs of "Hypertensive crisis" recorded in the Onglyza treatment group.

Details of the subjects' medical history, concomitant medications and blood pressure were provided. All were reported from one site in Russia. None were in the category of a hypertensive emergency (defined as 180/120mmHg or more). Three had BP of 145 /90 and multiple medical morbidities.

Evaluator comment: The explanation is noted. There are several confounding factors that make assessment difficult.

Overall conclusion: These responses do not affect the recommendation of the evaluator. Thus the original recommendation of the evaluator is valid.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au