Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Saxagliptin (as hydrochloride)

Proprietary Product Name: Onglyza

Sponsor: Bristol-Myers Squibb Australia Pty Ltd

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 AusPARs

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

Contents

I. Introduction to product submission

Submission details

Type of Submission	Extension of indications
Decision:	Approved
Date of Decision:	19 September 2012
Active ingredient:	Saxagliptin (as hydrochloride)
Product Name:	Onglyza
Sponsor's Name and Address:	Bristol-Myers Squibb Australia Pty Ltd 4 Nexus Court Mulgrave Victoria, Australia, 3170
Dose form:	Film coated tablet
Strength:	5 mg
Container:	Blister pack
Pack size:	7, 28
Approved Therapeutic use:	Onglyza is indicated in patients with type 2 diabetes mellitus to improve glycaemic control as add-on therapy to premixed or basal insulin (with or without metformin) when premixed or basal insulin (with or without metformin) used with diet and exercise, do not provide adequate glycaemic control. Onglyza has not been studied in a regimen combining intermediate or long-acting insulin with mealtime bolus doses of short-acting insulin (basal:bolus regimens) and its efficacy in this context has not been established.[1]
Route of administration:	Oral
Dosage:	5 mg once daily
ARTG Number	157907

Product background

Saxagliptin is one of a class of oral antidiabetic agents from a class of drugs that inhibits selectively and reversibly the enzyme, dipeptidyl peptidase-4 (DPP-4) that is involved in glucose homeostasis. Saxagliptin inhibits dipeptidyl peptidase-IV (DPP-IV) and thereby delays the degradation of glucagon like peptide-4 (GLP-1) and glucose-independent insulinotropic polypeptide (GIP) that are released particularly in response to the ingestion of food.

[1] Note that this approved use differs from the amended indications proposed originally by the sponsor.

Onglyza is currently approved for the treatment of patients with type 2 diabetes mellitus (T2DM), as follows:

> *Add-on combination*
>
> *Onglyza is indicated in patients with type 2 diabetes mellitus, to improve glycaemic control, in combination with metformin, a sulfonylurea, or a thiazolidinedione, as an adjunct to diet and exercise, when the single agent alone does not provide adequate glycaemic control.*
>
> *Initial combination*
>
> *Onglyza is indicated for use as initial combination therapy with metformin, in patients with type 2 diabetes mellitus, to improve glycaemic control as an adjunct to diet and exercise, when dual saxagliptin and metformin therapy is appropriate. (i.e. high initial HbA1c levels and poor prospects for response to monotherapy).*

This AusPAR describes the application by Bristol Myers Squibb Australia Pty Ltd (the sponsor) to extend the indications for Onglyza to include add-on, combination use with insulin, as follows (proposed amendments to the current indications bolded):

> *Add-on combination*
>
> *Onglyza is indicated in patients with type 2 diabetes mellitus, to improve glycaemic control, in combination with metformin, a sulfonylurea, **~~or~~** a thiazolidinedione**, or insulin (with or without metformin)**, as an adjunct to diet and exercise, when the single agent alone does not provide adequate glycaemic control.*
>
> *Initial combination*
>
> *Onglyza is indicated for use as initial combination therapy with metformin, in patients with type 2 diabetes mellitus, to improve glycaemic control as an adjunct to diet and exercise, when dual saxagliptin and metformin therapy is appropriate. (i.e. high initial HbA1c levels and poor prospects for response to monotherapy).*

Regulatory status

The product received initial registration in the Australian Register of Therapeutic Goods (ARTG) on 18 March 2011. At the time of the current application, the use of saxagliptin as add-on therapy to insulin for the treatment of patients with T2DM was approved in Canada (May 2012) and the European Union (EU; November 2011).

Product Information

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

II. Quality findings

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

III. Nonclinical findings

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

IV. Clinical findings

A summary of the clinical findings is presented in this section. The full clinical findings can be found in Attachment 2.

Introduction

Background and rationale

This application seeks extension of use of the established oral anti-diabetic drug saxagliptin to patients with T2DM 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.

Scope of the clinical dossier

The submission contained two efficacy/safety studies, CV181057 and D1680C00007, of which the latter has been evaluated previously by TGA.[2]

Paediatric data

The submission did not include paediatric data.

Good clinical practice

The report of the new clinical Study (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).'*

Pharmacokinetics

No new data were provided.

Pharmacodynamics

No new data were provided.

Efficacy

Dosage selection for the pivotal study

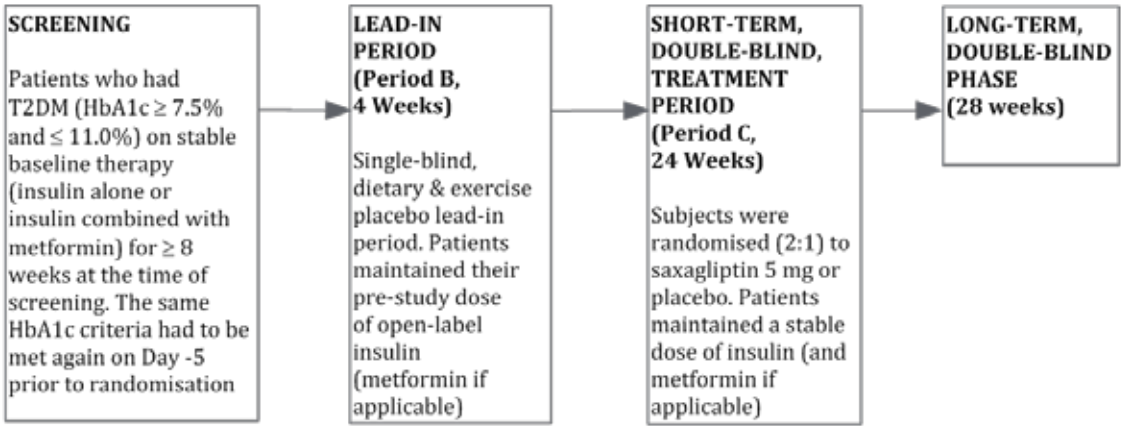
No change to the currently recommended dose (5 mg daily) was proposed.

Summary of studies

The pivotal Study CV181057 is a multi-centre, randomised, parallel-group, double-blind, placebo-controlled study. The design of the pivotal study is outlined below (Figure 1).

[2] Study D1680C00007 was submitted to the TGA to support a different application, involving the use of a new, reduced strength (2.5 mg) of saxagliptin for the treatment of T2DM in patients with renal impairment. This application was subsequently withdrawn; the AusPAR for this application is located at <http://www.tga.gov.au/pdf/auspar/auspar-saxagliptin-120625.pdf>

Figure 1. Study CV181057 - Overall study design



The report submitted with the present application covers only experience to the end of Period C (that is, 24 Weeks).

The pivotal Study CV181057 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. The evaluator considered 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 the percentage of glycosylated haemoglobin (HbA1c; 0.41%) was clearly statistically significant, and also indicated a clinically significant improvement in glycaemic control.

Additional details of efficacy endpoints and outcomes from the pivotal Study CV181057 are provided in the section on *Overall Conclusion and Risk/Benefit Analysis*, below.

Study D1680C00007[3] 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 (it was noted that 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

[3] Study D1680C00007, submitted to the TGA to support an application for 2.5 mg saxagliptin in the treatment of T2DM in patients with renal impairment, had a short-term and long-term Phase. The former was a 12 week, multicentre, randomised, parallel group, double-blind, placebo-controlled study of saxagliptin 2.5 mg compared with placebo in the treatment of adult patients with T2DM and moderate, severe and end-stage renal impairment. The Long-term Phase consisted of an additional 40 week randomised, parallel group, double blind, placebo controlled observation period. This application was subsequently withdrawn; the AusPAR for this application is located at <http://www.tga.gov.au/pdf/auspar/auspar-saxagliptin-120625.pdf>

- 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.[4]

Evaluator's conclusions on clinical efficacy for the proposed indication.

This is an application in which only one pivotal study has been submitted in support of an extended efficacy claim. The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP; formerly the Committee for Proprietary Medicinal Products (CPMP)) *Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Diabetes Mellitus* (CPMP/EWP/1080/00, 30 May 2002) is of some relevance here, although 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. Nevertheless the '*prerequisites for one pivotal study applications*' (as described at section III.2 of the guideline on *Points to Consider on Application with 1. Meta-analysis; 2. One Pivotal study*; CPMP/EWP/2330/99, 31 May 2001) have generally been met.

On the question of consistency of findings for different endpoints: a statistically significant result was not obtained for change in fasting plasma glucose (FPG); however, the evaluator considers this endpoint of secondary relevance for this class of anti-diabetic agent, in view of its mechanism of action.

In a reasonably diverse population of patients with T2DM, adequate evidence for efficacy of Onglyza has been demonstrated in patients already receiving insulin (in fact, those "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 of the indication 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)*'.

Safety

Studies providing evaluable safety data

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

- General adverse events (AEs) were assessed by open-ended questioning at each review;
- AEs of particular interest: Efforts were made to validate reports of clinical hypoglycaemia 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.

The non-pivotal efficacy Study D1680C00007 included in the dossier provided safety data on use of the drug at different dosage, in a different patient population. For safety data

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

from Study D1680C00007, cross reference is made to the TGA evaluation report for the application to register Onglyza 2.5 mg in patients with T2DM and renal impairment.[5]

Tables 1 and 2 below present a summary of patient exposure to Onglyza. Only the data from Study CV181057 are included, 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 (under *Summary of studies*).

Table 1. 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 2. 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.

Evaluator's overall summary and conclusion on clinical safety

The safety data from Study CV181057 does not raise any concerns relating to the proposed usage. Data from the (non-pivotal) Study D1680C00007 also did not note any new safety concerns.

List of questions

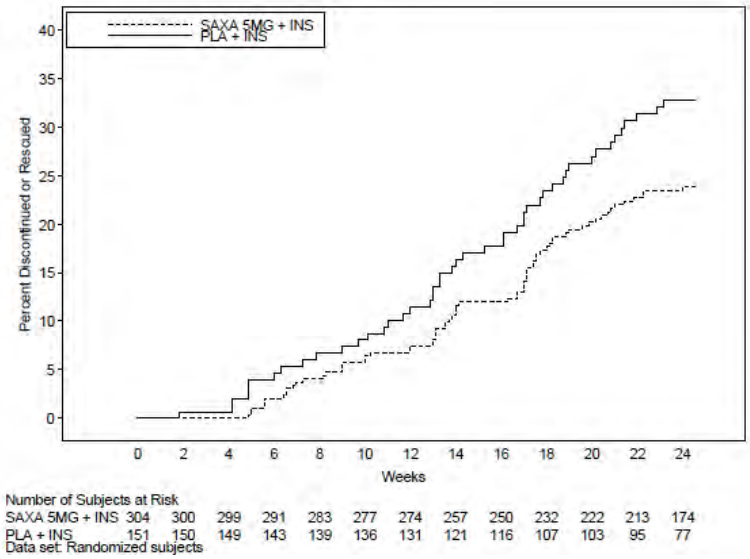
Efficacy

1. Please explain the odd assortment of implied accuracy in measurements presented in the summary document (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 Clinical Study Report (CSR)?

[5] The AusPAR for this application is available at <http://www.tga.gov.au/pdf/auspar/auspar-saxagliptin-120625.pdf>

2. The Kaplan-Meier plot, reproduced below at Figure 2, 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.

Figure 2. Time to study discontinuation for lack of glycaemic control or rescue for failing to achieve glycaemic targets



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.

4. The Protocol shows Day 1 as randomisation day. However, in the CSR, the table on *Adverse Events Leading to Discontinuation from Study During Lead-in and Short term Treatment Period* shows a subject as withdrawn on Day -1 yet randomised, and a table in another part of the CSR appears to include this subject in the number withdrawn during the short term treatment period because of AEs. Please explain the discrepancy.

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, based on information given elsewhere in the CSR. Please explain the discrepancy.

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

First Round Clinical Summary and Conclusions

Benefit risk assessment

First round assessment of benefits

The benefits of Onglyza in the proposed usage are:

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

First round assessment of risks

The study of use of Onglyza 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.

First round assessment of benefit-risk balance

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

Initial Recommendation

Approval is recommended.

Sponsor's response to the List of Questions

The TGA evaluation of the sponsor's responses to questions (see *List of Questions*, above) is presented in an Addendum to the CER (Attachment 2 to this AusPAR). A summary of the responses is provided under *Second Round Clinical Evaluation Report* and (in part) under *Overall Conclusion and Risk/Benefit Analysis*, below.

Second Round Clinical Evaluation Report

Evaluation of responses to TGA request for further information

Question 1:

The sponsor explained that all results were expressed as SI or US standard units and despatched to Bristol Myers Squibb (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 (in the dossier) is replaced with the correct tracking sheet. The laboratory values included in the dossier are stated to be accurate.

The evaluator considered this was an adequate explanation.

Question 2.

The requested Kaplan-Meier plots were provided (see below under *Overall Conclusion and Risk/Benefit Analysis*).

Question 3

The sponsor confirmed that the tabulations include data from patients for whom insulin rescue never occurred.

Question 4.

An explanation was provided for the apparent discrepancy concerning the fate of a subject. The evaluator noted this explanation.

Question 5.

The sponsor provided an acceptable explanation for the apparent discrepancy in the CSR with regard to the number of subjects experiencing serious AEs.

Question 6.

In relation to the six AEs of "Hypertensive crisis", 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

180/120 mmHg or more). Three had blood pressure of 145/90 mmHg and multiple medical morbidities.

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

Evaluator's overall conclusion

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

Second Round Benefit-Risk Assessment

Second round assessment of benefit

No change is proposed to the first round assessment.

Second round assessment of risks

No change is proposed to the first round assessment.

Second round assessment of benefit-risk balance

No change is proposed to the first round assessment.

Recommendation Regarding Authorisation

No change is proposed to the first round recommendation; that is, approval is recommended.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP), version number 9, document date 7 December 2011, which was reviewed by the TGA's Office of Product Review (OPR).

Safety Specification

Subject to the evaluation of the clinical aspects of the SS by the OMA, the summary of the Ongoing Safety Concerns as specified by the sponsor is as follows (Table 3):

Table 3. Ongoing Safety Concerns

Important Identified Risks	Hypersensitivity reactions Pancreatitis Infections Gastrointestinal-related AEs
Important Potential Risks	Skin Lesions (erosion, ulcer, necrosis) Lymphopenia Thrombocytopenia Hypoglycaemia Bone Fracture Severe cutaneous adverse reactions Opportunistic infections
Important Missing/limited information	Elderly population > 75 years old Paediatric safety Patients with Hepatic Impairment Cardiovascular disease including congestive heart failure. Immunocompromised subjects Pregnancy and breast-feeding Malignancy/neoplasm

Pursuant to the evaluation of the clinical aspects of the SS, the above summary of the ongoing safety concerns is considered acceptable.

Pharmacovigilance plan

Routine pharmacovigilance activities are proposed by the sponsor to monitor the ongoing safety concerns. Additional pharmacovigilance by means of clinical and epidemiological studies is also described to address some of the ongoing safety concerns.

The routine pharmacovigilance activities described by the sponsor are consistent with the activities outlined in *3.1.2 Routine pharmacovigilance practices. Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03).* The sponsor's rationale for routine pharmacovigilance only for some of the safety concerns, based on current clinical information, is considered to be appropriate.

The pharmaco-epidemiology study program, as part of the additional pharmacovigilance plan is acceptable.

Risk Minimisation Activities

Routine risk minimisation activities are proposed for all safety concerns. No additional risk minimisation activities are planned. This is acceptable.

Summary of Recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application:

- It is recommended that the implementation of RMP Version 9 (dated 7 December 2011), including information provided by the sponsor in response to the TGA request for information/documents and any future updates, be imposed as a condition of registration.

Pharmacovigilance plan:

- It is recommended that as a condition of registration the sponsor should provide reports of all ongoing studies to the TGA for review when completed.

Risk minimisation plan:

The evaluator recommended several revisions be made to the draft PI and Consumer Medicine Information (CMI) documents. Details of these are beyond the scope of this AusPAR.

VI. Overall conclusion and risk/benefit assessment

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

Quality

No new data were submitted.

Nonclinical

No new data were submitted, including combination studies with metformin and insulin or insulin alone. In the original submission for saxagliptin as a new chemical entity,[6] the evaluator did not object on nonclinical grounds to the registration of Onglyza as monotherapy for the proposed indication. Owing to an absence of nonclinical data regarding saxagliptin in combination with metformin, thiazolidinedione or a sulfonylurea, the safety of the proposed combinations would need to be addressed by clinical data.

Clinical

This application is for an extension of registered indications to include use of saxagliptin with insulin, with or without metformin; therefore the application is also an extension of indication to include triple therapy involving saxagliptin, insulin and metformin.

The proposed saxagliptin dose is 5 mg once daily, which is recommended currently. However, no specific advice is proposed to be given regarding the adding of saxagliptin to insulin with or without metformin, or vice versa.

Clinical data

The application comprised one pivotal and one supportive study. According to the sponsor's documentation, the pivotal study is Study CV181057.

Study D1680C00007 (CV181062) is also included in this application and is for supportive purposes only. This study has also been submitted to the TGA as a pivotal study for an application to register 2.5 mg saxagliptin for use in patients with T2DM and renal impairment. That application was under evaluation at the time this Overview was prepared.

[6] The AusPAR for this application is located at <http://www.tga.gov.au/pdf/auspar/auspar-onglyza.pdf>

For additional information on Study D1680C00007 (CV181062), cross reference was made to TGA evaluation reports for that application (see AusPAR at <http://www.tga.gov.au/pdf/auspar/auspar-saxagliptin-120625.pdf>).

The sponsor's letter of application states the following:

> "This application includes 24 Week results from the pivotal Phase IIIb study CV181057 (hereafter referred to as study 57), which assessed the efficacy and safety of saxagliptin 5 mg as an adjunct to insulin (or insulin plus metformin) in improving glycaemic control in adult subjects with T2DM. Study 57, a randomised, parallel, double-blind placebo-controlled multicentre trial compared the anti-hyperglycaemic activity of saxagliptin 5 mg added on as combination therapy with insulin or to insulin in combination with metformin in subjects with T2DM who had inadequate glycaemic control. Results for the short term (24 Week) treatment period are presented in this submission, while data for the long term treatment period is not currently available. In Study 57, saxagliptin added to insulin therapy resulted in a clinically relevant and statistically significant reduction in HbA1c compared with subjects treated with insulin alone. Mean HbA1c reduction from baseline, the primary efficacy endpoint, was statistically significantly greater ($p < 0.0001$) in the saxagliptin plus insulin treatment group compared with the placebo plus insulin group. Similar HbA1c reductions were achieved for subjects using saxagliptin plus insulin alone and saxagliptin plus insulin in combination with metformin.
>
> Additionally, results from Phase IIIb Study D1680C00007 (hereafter referred to as study 07), both short term (12 Week) and long term (52 Week) data are included which provide supportive efficacy and safety data in a special population, namely adult subjects with T2DM and renal impairment, the majority of whom were receiving background insulin therapy at baseline. While data from study 57 are being submitted for the first time, both short term and long term results from study 07 have previously been submitted to the TGA to support an application which is currently under evaluation."

Of note, the TGA evaluation report for Study D1680C00007 (CV181062) and its extension became available during the evaluation of the current application.

Guidelines

EU Guidelines of relevance to this application include:

- diabetes: *Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Diabetes Mellitus* (CPMP/EWP/1080/00, 30 May 2002) (available at <http://www.tga.gov.au/pdf/euguide/ewp108000en.pdf>);
- interactions: *Concept Paper/Recommendation on the Need for Revision of (CHMP) Note for Guidance on the Investigation of Drug Interactions (CPMP/EWP/560/95)*, (EMEA/CHMP/EWP/297931/2008, July 2008) (available at <http://www.tga.gov.au/pdf/euguide/ewp29793108en.pdf>); and
- geriatrics: *Clinical Investigation of Medicinal Products in Geriatrics* (CPMP/ICH/379/95, March 1994 (available at http://www.tga.gov.au/pdf/euguide/vol3cc9aen.pdf)

In regard to scientific principles, the Guideline *Points to Consider on Application with 1. Meta-analysis; 2. One Pivotal study*; CPMP/EWP/2330/99, 31 May 2001 (available at <http://www.tga.gov.au/pdf/euguide/ewp233099en.pdf>), relating to single studies (one pivotal study) to support efficacy, is of interest.

Efficacy

Pivotal efficacy Study CV181057

The study was conducted in inadequately controlled adult outpatients with T2DM. Patients enrolled were aged between 18 and 78 years and were required to be on a 'stable' dose of insulin (≥ 30 units to ≤ 150 units daily) with ≤ 20% variation in total daily dose for ≥ 8 weeks prior to screening with or without metformin. Patients received intermediate or long acting (basal) insulin or premixed insulin. Patients using short acting insulins were excluded unless the short acting insulin was administered as part of a premixed insulin product.

The study was of multi-centre (n = 72 in 10 countries), randomised, parallel-group, double-blind, placebo-controlled design. Period B was a run-in phase. In period C, subjects continued receiving their current open-label dose of insulin and metformin (if applicable) and, in addition, were randomised to one of two treatment arms (saxagliptin 5 mg or placebo). The clinical evaluator stated that the study was reported only to the end of Period C; that is, 24 Weeks of "on study" data have been provided. During Period C, routine review took place at 2, 4, 6, 8, 12, 16, 20 and 24 weeks.

An outline of the design of the pivotal study is provided at Figure 1 of this AusPAR.

Insulin dosage: The CSR states: '*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 [basal insulin or a pre-mix], with no changes to insulin type and with as few changes in insulin dosage as possible.*' That is, bolus short acting insulin could not be added. Patients who experienced poor glycaemic control (as manifested either by rising glucose measurements or by persistent increases in insulin dose used) and who met certain criteria were to be rescued, starting in Week 4.

Rescue resulted in the 'flexible' insulin regimen, to include increases in the dose of insulin and the addition of rapid-acting or short acting insulin, if needed.

Downward titration of insulin was allowed on the grounds of hypoglycaemia in either the 'stable' or 'flexible' regimen groups.

Metformin dosage: Most patients were using metformin at baseline. Changes to the baseline dose of metformin were prohibited throughout the study. Neither metformin nor any other oral anti-hyperglycaemic agent was to be added to the subjects' regimens at any time during the study.

The primary efficacy aim was 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). 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.

Secondary aims were numerous. They were 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 postprandial plasma glucose (PPG) concentration-time area under the curve (AUC) from time 0 to 180 min in response to a meal tolerance test (MMT). [Endpoint - change from baseline in AUC from 0 to 180 min for PPG response to an MTT];
- The change from baseline to Week 24 (or rescue) in the 120 min PPG value in response to a MTT. [Endpoint - change from baseline in the 120 min PPG value during an MTT];

- The change in FPG from baseline to Week 24 (or rescue). [Endpoint - change from baseline in FPG];
- The proportion of subjects achieving a therapeutic glycaemic response at Week 24 (or rescue), defined as HbA1c < 7%. [Endpoint - proportion of subjects achieving a therapeutic glycaemic response (defined as HbA1c < 7%)];
- The change in mean total daily dose of insulin (MTDDI) from baseline to Week 24. [Endpoint - change from baseline in MTDDI based on information recorded on the subjects' daily diary].

The sample size was evidently determined for the primary endpoint. The CSR states:

> "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 dropout 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."

The study randomised 455 patients.

"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."

Outcomes, as reported by the evaluator:

Data on the primary outcomes are summarised in Table 4, below.

Table 4. Primary endpoint to week 24

HbA1c (%)	Saxagliptin N=304	Placebo 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		
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)	

Abbreviations: n - number; SE - standard error (of the mean); CI - confidence interval; LOCF - last observation carried forward.

Delegate comment: The subgroup analyses are of interest but they do not seem to be in the statistical plan as described above. The sponsor is requested to clarify this in their response to this Overview for presentation to the Advisory Committee on Prescription Medicines (ACPM; the pre-ACPM response). The quantum of benefit is small and would not be a large delta in a non-inferiority study.

Secondary Outcomes:

Secondary outcomes are summarised in Tables 5 and 6, below. It seems that statistical testing might have ceased when the first non-significant result was obtained:

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

AUC (mg.min/dL)	Saxagliptin N=304	Placebo 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)	Saxagliptin N=304	Placebo 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	

Other secondary outcomes are described in the CER (Attachment 2).

The efficacy findings of the supportive Study D1680C00007 (presented in the attached CER) were similar to the above in terms of the point estimate of improvement in HbA1c but at Week 12. The effect was larger and maintained at Weeks 28 and 52. The study recruited 164 patients but there were a significant number of dropouts.

Evaluator's conclusions regarding efficacy:

The clinical evaluator stated: '*The mean reduction in % HbA1c (0.41) was clearly statistically significant, and also indicated a clinically significant improvement in glycaemic control.*'

The evaluator does not accept the supportive study as useful for efficacy for the following reasons:

- 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. (it was noted that 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 clinical evaluator's recommendation concerning the proposed indication is noted:

"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 of the indication 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)*'".

Safety

Adverse effects:

Patient exposure to saxagliptin in this pivotal study is shown at Tables 1 and 2 of this AusPAR.

Adverse events of interest included hypoglycaemia. Confirmed hypoglycaemia with associated symptoms, regardless of rescue status: Onglyza group 16 (5.3%); placebo group 7 (4.6%). There was one death on study (presumptively myocardial infarction), and one case of acute coronary syndrome and one other acute myocardial infarction - all were in the saxagliptin group.

The clinical evaluator's conclusion is noted: '*The safety data from Study CV181057 does not raise any concerns relating to the proposed usage.*'

Evaluation of responses to the clinical evaluator's questions

The sponsor was requested to address several questions raised by the clinical evaluator. The full TGA evaluation of the sponsor's answers appears as an Addendum to the CER at Attachment 2 of this AusPAR. All questions were satisfactorily answered.

One of the questions requested the sponsor provide Kaplan-Meier plots, separately for those using and not using metformin, at baseline, showing time to study discontinuation for lack of glycaemic control or rescue for failing to achieve glycaemic targets. These were provided (Figures 3 and 4, below).

Figure 3. Time to study discontinuation for lack of glycaemic control or rescue for failing to achieve glycaemic targets during short term treatment period - subjects using metformin at baseline.

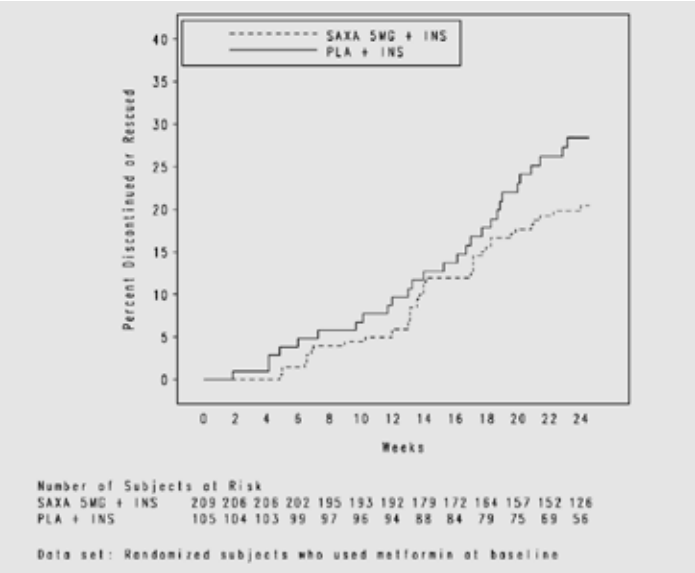
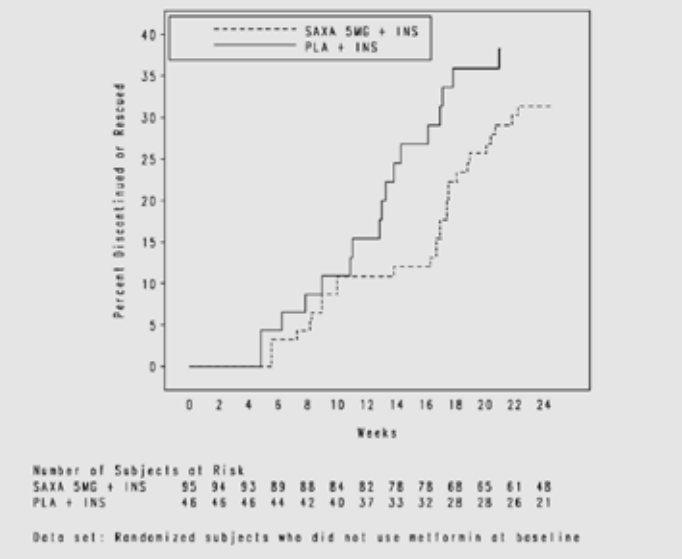


Figure 4. Time to study discontinuation for lack of glycaemic control or rescue for failing to achieve glycaemic targets during short term treatment period - subjects not using metformin at baseline.



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. This is satisfactory.

Clinical evaluator's recommendation

Overall, the clinical evaluator supported registration. One change to the product information document was suggested (to the indication): '*... it may be appropriate to rephrase the text of the indication 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)'*.

Risk management plan

Specific recommendations (see above under *Pharmacovigilance Findings*) were noted.

Risk-benefit analysis

Delegate considerations

No specific preclinical studies have been conducted on the toxicology of saxagliptin plus insulin plus metformin versus saxagliptin alone. Therefore there is only the clinical data package to 24 Weeks to support safety.

The proposed new indications are supported by one pivotal study for which there is an adopted Guideline *Points to Consider on Application with 1. Meta-analysis; 2. One Pivotal study*; CPMP/EWP/2330/99, 31 May 2001. The intent of the Guideline is clear - replication of studies is needed unless the results are statistically compelling and clinically relevant. It is arguable that the therapeutic effect has been demonstrated with reasonable consistency across a spectrum of patients with T2DM, but the efficacy of saxagliptin in monotherapy was poor and it is modest in the pivotal study here submitted. The supportive study is useful to contribute safety data in a special population.

The pivotal study was an add-on study in which saxagliptin was added to a fixed dose of basal insulin or an insulin pre-mix. Some patients were also taking metformin. All of them were inadequately controlled and the option was not to optimise the dose of insulin. That is, the test was not in terms of safety (sparing hypoglycaemia attributable to higher doses of insulin), but rather to test the efficacy advantage of adding saxagliptin. No information is available on the risks and benefits of adding insulin to patients who are escaping from control on a dual therapy regimen that includes saxagliptin and one other oral antidiabetic agent.

The study did not show sparing of hypoglycaemia with saxagliptin. The low prevalence of hypoglycaemia in the placebo arm of the study might suggest some conservatism in regard to dose titration with insulin. [The prevalence of confirmed hypoglycaemia with associated symptoms, regardless of rescue status was: Onglyza group 16 (5.3%); Placebo group 7 (4.6%).] The sponsor was invited to address this in the pre-ACPM response.

Clinical relevance

What was the model used in the pivotal study? It appears to be an add-on study for 24 weeks (with an ongoing extension that was not complete until June 2011 but is not yet submitted to the TGA) for patients who already need insulin. It does not explore adding insulin to saxagliptin or saxagliptin plus metformin.

In regard to the pivotal study, one issue is how significant was the improvement in glycaemic control. These patients were already failing to produce enough insulin and it would be logical for them to have been placed on a basal insulin regime before progressing to a basal:bolus regimen. The quantum of benefit is small and is comparable to use in monotherapy (an application for which was previously withdrawn).

It seems that, in the pivotal study of this submission, saxagliptin has been tested within this narrow window for 24 weeks and the extension phase of the study has not been submitted. That is, it is not known whether saxagliptin has a durable effect in these patients and, in particular, if saxagliptin might slow the time to requiring a basal:bolus regimen, and it cannot answer the question of whether there is value in adding saxagliptin to patients who already require a basal:bolus regimen.

The treatment sequence effects may be important but the draft PI is silent on this; that is, can one freely add and subtract any of the trio of drugs (insulin, saxagliptin, metformin) *ad libitum*?

The pivotal study seems to support adding saxagliptin to the regimen of patients who require insulin with or without metformin and who do not require a basal:bolus regimen. Should this requirement emerge, then there would be no evidence to support the

continued use of saxagliptin. This lack of evidence makes the proposed indication look like an ambit claim:

> *Onglyza is indicated in patients with type 2 diabetes mellitus, to improve glycaemic control, in combination with metformin, a sulfonylurea, **~~or~~** a thiazolidinedione **or insulin (with or without metformin)**, as an adjunct to diet and exercise, when the single agent alone does not provide adequate glycaemic control.*

The Delegate considered an approvable indication might be, as a separate sentence:

> *Onglyza is indicated in patients with type 2 diabetes mellitus, to improve glycaemic control, in combination with a **basal insulin (with or without metformin)**, as an adjunct to diet and exercise, when a **basal insulin (with or without metformin)** does not provide adequate glycaemic control. Saxagliptin has not been studied in basal:bolus insulin regimens and its efficacy in this context has not been established.*

The *Dosage and Administration* section of the PI would need much more specific advice to align it with the evidence that is available from the pivotal study.

If approval is granted, then the extension Phase of the study should be submitted as a condition of registration.

At this time, the Delegate held doubts about the adequacy of the data.

Proposed action

The Delegate proposed that the application by Bristol-Myers Squibb Australia Pty Ltd to register an extended indication for Onglyza film coated tablets containing 5 mg of saxagliptin (as saxagliptin hydrochloride) be rejected due to poor efficacy and a lack of data beyond 24 weeks. The sponsor would be encouraged to conduct further studies in patients that require basal:bolus insulin regimens and basal insulin only, as well as the extension to Study CV181057.

Advice requested from ACPM

The Delegate sought general advice on this application from the ACPM, and also requested the committee address the following:

1. The difference from control was about -0.4% for the HbA1c value in the pivotal study and it is noticed that improvement from baseline took place in the placebo group, despite the study's constraints. How clinically significant was the result of the primary outcome in the pivotal study?
2. Are the results from the pivotal study clinically important as well as statistically significant, as expected by the adopted Guideline on one pivotal study?

Response from Sponsor

Introduction

The sponsor acknowledges the position of the clinical evaluator regarding the sponsor's application to extend the indication for Onglyza (saxagliptin) 5 mg to include use in combination with insulin (with or without metformin) in patients with T2DM. The sponsor addressed the points raised by the Delegate in the request for ACPM advice.

The sponsor considers the findings from both Study CV181057 (hereafter referred to as Study 57) and Study D1680C00007 (hereafter referred to as Study 07) demonstrate a positive benefit:risk profile for saxagliptin when used in combination with insulin in adult patients with T2DM (with or without metformin). This is a population in whom treatment options are limited. Study 57 documented a statistically and clinically significant improvement in glycaemic control with saxagliptin at 24 weeks, with a safety profile for saxagliptin that was comparable to placebo. Findings at Week 52 from the long term (LT)

extension phase further established the durability of the efficacy and safety of saxagliptin in combination with insulin. The LT [52 Week] results from Study 57 have been submitted to TGA in support of another application[7] and are currently under evaluation.

The supportive Study 07 was a Phase IIIb clinical study that investigated saxagliptin compared with placebo in adult patients with T2DM and renal impairment (moderate, severe, and end-stage) - the majority of whom (75.3%) were receiving background insulin therapy at baseline. In Study 07, therapy with saxagliptin in combination with insulin also resulted in a significant and clinically relevant reduction in HbA1c in individuals with renal insufficiency in both the short term (ST; 12 Weeks) and LT (additional 40 Weeks) phases of the study. In the CER for that application, the clinical evaluator wrote that '*despite the limitations of the data, it is therefore concluded that the efficacy of saxagliptin is maintained despite progressive impairment of renal function.*' The LT safety data from Study 07 provide additional evidence for the safety of saxagliptin in this particularly difficult-to-treat population, in whom treatment options are even more limited.

This response addresses issues raised by the Delegate in the following areas:

- Clinical significance of the results and relevance to diabetic patients
- Design of the clinical programme
- Durability of the efficacy and safety findings from Study 57
- Proposed indication

Clinical significance

Patients enrolled in Study 57 had an advanced stage of disease, as indicated by duration of illness (overall mean: 12.0 years) and use of high insulin doses (overall MTDDI: 54.2 units/day). In this population, reduction in HbA1c without substantial increase in insulin use is especially desirable. Study 57 achieved its primary objective and demonstrated that saxagliptin added to insulin produced a clinically relevant and a clearly statistically significant reduction in HbA1c. The overall adjusted mean change from baseline to Week 24 in the saxagliptin-treated group was -0.73%. The difference in adjusted mean changes from baseline between the 2 groups (saxagliptin minus placebo) was -0.41% (2-sided 95% confidence interval (CI), -0.59% to -0.24%; p<0.0001).

The recent EMA CHMP) *Guideline on Clinical Investigation of Medicinal Products in the Treatment or Prevention of Diabetes Mellitus* recognises '*that even apparently small reductions in HbA1c have been shown to be clinically relevant in terms of risk reduction of diabetic complications*' (see CPMP/EWP/1080/00 Rev. 1; adoption by CHMP, 14 May 2012[8]). In this context, the findings of Study 57 establish the clinical relevance of combination treatment with saxagliptin and insulin.

Treatment with saxagliptin was also associated with important glycaemic benefits beyond HbA1c, as described by the *National Evidence Based Guideline for Blood Glucose Control in Type 2 Diabetes* 2009.[9] This guideline stresses that postprandial hyperglycaemia is a powerful predictor of adverse outcomes. At Week 24 in Study 57, treatment with saxagliptin was associated with a clinically relevant and statistically significant reduction in postprandial glycaemic levels following the mixed meal tolerance test. The observed placebo-adjusted reduction in 120 min PPG of 1.28 mmol/L is a clinically important result.

[7] This refers to a new application that was in the early stages of evaluation by the TGA at the time the sponsor submitted the pre-ACPM response for the current application.

[8] TGA adopted guideline is the previous version: CPMP/EWP/1080/00, May 2002.

[9] Available from the NHMRC website a<http://www.nhmrc.gov.au> and the Diabetes Australia website: diabetesaustralia.com.au

The *Australian Diabetes Guideline*[10] recommends the following: '*The general HbA1c target in people with type 2 diabetes is ≤ 7%. Adjustment to diabetes treatment should be considered when HbA1c is above this level. (Grade A).*' In Study 57, a greater proportion of patients treated with saxagliptin compared with placebo reached the clinical goal of HbA1c < 7% at Week 24 (17.3% versus 6.7%). The proportion was higher in patients on background metformin (19.4% versus 7.8%). Achieving this essential therapeutic goal in a population with relatively high baseline HbA1c (8.66%) is clinically important and demonstrates the potential benefits of the combination use of saxagliptin and insulin.

The assessment of HbA1c in Study 57 occurred at the end of the ST treatment period (Week 24) or at the last assessment prior to receiving rescue treatment. An *ad hoc* analysis of MTDDI under the same conditions (that is, prior to rescue) showed that the placebo group had an adjusted mean increase of 1.74 units compared with an adjusted mean decrease of -0.08 units in the saxagliptin group (Table 7, below). In a similar analysis that included data after rescue, there was an adjusted mean increase from baseline in total daily insulin dose, which was higher in the placebo group (5.0 units) compared with the saxagliptin group (1.7 units). Thus, the reduction in HbA1c in saxagliptin-treated patients was not achieved through an increased use of insulin; on the contrary, the significant difference in the adjusted mean changes in HbA1c between the 2 treatment groups was achieved despite an increase in mean daily insulin dose in the placebo group.

Table 7. Mean total daily dose of insulin changes from baseline at Week 24 (LOCF) prior to rescue - Study 57

Measure: MTDDI	**Saxa 5 mg + Insulin**	**Pla + Insulin**
Unit: unit	**N = 304**	**N = 151**
Summary statistics		
n	299	151
Baseline Mean (SE)	53.37 (1.269)	55.26 (2.070)
Week 24 LOCF Mean (SE)	53.40 (1.235)	57.08 (2.203)
Mean change from baseline (SE)	0.03 (0.325)	1.81 (0.569)
Adjusted Mean Change from Baseline		
Mean (SE)	-0.08 (0.371)	1.74 (0.512)
95% two sided CI	[-0.81, 0.65]	[0.74, 2.75]
Difference in Adjusted Change from Baseline vs Placebo + Insulin		
Mean (SE)[a]	-1.82 (0.609)	
95% 2-sided CI	[-3.02, 0.63]	

Dataset: Randomised patients; ANCOVA model: post - pre = pre + treatment + metformin
a Estimate = Adjusted mean change for Saxa + Insulin - Adjusted mean change for Pla + Insulin
ANCOVA Analysis of covariance; CI Confidence interval; LOCF Last observation carried forward; MTDDI Mean total daily dose of insulin; Pla Placebo; Saxa Saxagliptin; SE Standard error

The addition of saxagliptin to insulin was safe and well tolerated. The incidence of AEs, of serious AEs, and of AEs leading to discontinuation was similar in the saxagliptin plus insulin group compared with the placebo plus insulin group. The overall incidence of reported hypoglycaemia, an AE of particular interest in this population, was 18.4% for saxagliptin-treated patients, and 19.9% for placebo-treated patients. The incidence of

[10] ibid

confirmed hypoglycaemic events with associated symptoms was 5.3% compared with 3.3% in the saxagliptin and placebo groups, respectively.

The *Australian National Evidence Based Guideline for Blood Glucose Control in Type 2 Diabetes* states that '*improving blood glucose control is frequently associated with weight gain*.' The guideline further clarifies that '*the magnitude of weight gain is related to the therapy used to improve glycaemic control.*' In this regard, it is important to note that the improvement in glycaemic control with the use of saxagliptin in Study 57 was achieved without a significant increase in body weight compared with the placebo group.

Australian patients with T2DM on insulin have few options beyond increasing their daily dose of insulin or introducing additional insulin injections to achieve glycaemic targets. The overall mean duration of T2DM was 12 years in Study 57. At this stage of disease, most available oral anti-diabetic treatments have been utilised and any incremental HbA1c decrease would be clinically important in achieving glycaemic control. Saxagliptin accomplished this in Study 57, with a safety profile that was comparable to placebo.

Study design / Clinical programme

Clinical programme and regulatory guidance: The EMA 2012 diabetes guideline (see CPMP/EWP/1080/00 Rev. 1, May 2012) states the following:

> "For appropriate evaluation of both safety and efficacy of the test compound in combination with insulin, the test agent should be added in patients with type 2 diabetes inadequately controlled on a reasonable dose of insulin as single therapy or in combination with another glucose-lowering agent, typically metformin or both, if stratified. Treatment groups should be balanced with respect to insulin regimens (for example, basal only versus basal-bolus regimen). In order to support a general claim 'combination therapy with insulin', the study population should represent a wide range of BMI [body mass index] and include a substantial percentage of patients with long diabetes duration (for example, ≥ 10 year) and elderly patients to adequately reflect the whole target population."

In particular, the EMA suggests this approach and not an approach of adding insulin to the test agent:

> "Even though a study in which insulin is initiated in patients not reaching glycaemic control with the test agent (alone or in combination with another glucose-lowering agent, most likely metformin) would reflect the most common clinical scenario, it is not expected to provide relevant data on the effect of the test drug in this setting. However, relevant safety information on the combined use of the test agent and insulin may be gained from such a study and may be reflected in the Product Information."

Study 57 followed the recommendations set forward by the EMA 2012 diabetes guideline.

Metformin subgroup analysis: Data on the treatment effect by metformin use for the primary efficacy endpoint (adjusted mean change in HbA1c from baseline to Week 24) were presented in the CSR. The difference in adjusted mean changes in HbA1c between the two treatment groups (saxagliptin minus placebo) was the same (-0.41%) in patients treated with metformin at baseline and in patients not being treated with metformin at baseline. In the Statistical Analysis Plan for the short term (ST) period data, metformin use was pre-specified as one of the subgroup variables on which HbA1c would be assessed.

Insulin regimen: The Delegate stated that Study 57 did not examine the effect of adding saxagliptin to a basal-bolus insulin regimen. In Study 57, most patients were using premixed insulin at baseline (see Table 8). The premixed formulation could include short- or rapid-acting (bolus) insulin as one component in addition to intermediate- or long-acting (basal) insulin. Thus, treatment with premixed insulin in Study 57 is representative of a basal-bolus regimen.

It is important to note that regardless of the type of insulin utilised by the patients in Study 57, administration of saxagliptin was associated with a greater HbA1c reduction compared with placebo. Table 8 presents results for the change from baseline to Week 24 (LOCF) in HbA1c for the combination of insulin regimen and metformin use.

The model used for this subgroup analysis was consistent with the model presented in the CSR for the subgroup analysis of treatment effect by metformin use. This analysis classified insulin use into regimens that used premixed insulin and regimens that did not use premixed insulin. There were 13 patients who took both premixed and long/intermediate-acting insulins; these patients were classified as using premixed insulin for this analysis. Results showed that for each combination of insulin regimen and metformin-use subgroup, there was a numerically larger decrease from baseline to Week 24 in HbA1c among saxagliptin-treated patients compared with the placebo group. Differences between treatments in the adjusted mean change in HbA1c (saxagliptin minus placebo) ranged from -0.25% to -0.70%.

Although some caution should be used when interpreting these results due to small sample sizes within treatment groups for several of the insulin regimen and metformin-use subgroups, and some numerical differences from subgroup to subgroup are expected, there was no evidence to indicate a differential treatment effect among the 4 subgroups (interaction p value = 0.57).

Table 8. HbA1c Changes from Baseline at Week 24 (LOCF) - Evaluation in subgroups based on metformin use and insulin regimen - Study 57

Subgroup Statistics	Saxa 5 mg + Insulin N = 304	Pla + Insulin N = 151
P-value = 0.5692[a]		
Long/Intermediate-Acting Insulin and Metformin use		
n (%)	86 (28.3)	48 (31.8)
Baseline Mean (SE)	8.79 (0.101)	8.59 (0.139)
Week 24 Mean (SE)	7.90 (0.115)	8.24 (0.188)
Adjusted Mean Change from Baseline	-0.85 (0.096)	-0.38 (0.128)
95% CI of Adjusted Mean Change from Baseline	[-1.03, -0.66]	[-0.63, -0.12]
Difference from Pla + Insulin (SE)[b]	-0.47 (0.160)	NA
95% CI of Difference from Pla + Insulin	[-0.78, -0.16]	NA
Premixed Insulin and Metformin Use		
n (%)	120 (39.5)	55 (36.4)
Baseline Mean (SE)	8.57 (0.080)	8.70 (0.122)
Week 24 Mean (SE)	7.85 (0.098)	8.31 (0.119)
Adjusted Mean Change from Baseline	-0.76 (0.081)	-0.38 (0.119)
95% CI of Adjusted Mean Change from Baseline	[-0.91, -0.60]	[-0.62, -0.15]
Difference from Pla + Insulin (SE)[b]	-0.37 (0.144)	NA
95% CI of Difference from Pla + Insulin	[-0.66, -0.09]	NA
Long/Intermediate-Acting Insulin and No Metformin Use		
n (%)	28 (9.2)	19 (12.6)
Baseline Mean (SE)	8.75 (0.185)	8.66 (0.163)
Week 24 Mean (SE)	7.90 (0.205)	8.54 (0.288)
Adjusted Mean Change from Baseline	-0.83 (0.167)	-0.13 (0.203)
95% CI of Adjusted Mean Change from Baseline	[-1.16, -0.50]	[-0.53, 0.27]
Difference from Pla + Insulin (SE)[b]	-0.70 (0.263)	NA
95% CI of Difference from Pla + Insulin	[-1.22, -0.18]	NA
Premixed Insulin and No Metformin Use		
n (%)	66 (21.7)	27 (17.9)
Baseline Mean (SE)	8.66 (0.106)	8.68 (0.158)
Week 24 Mean (SE)	8.07 (0.125)	8.33 (0.188)
Adjusted Mean Change from Baseline	-0.60 (0.109)	-0.34 (0.170)
95% CI of Adjusted Mean Change from Baseline	[-0.81, -0.38]	[-0.68, -0.01]
Difference from Pla + Insulin (SE)[b]	-0.25 (0.202)	NA
95% CI of Difference from Pla + Insulin	[-0.65, 0.14]	NA

Data set: Randomised patients; ANCOVA model: post-pre = pre (metformin and insulin regimen group) treatment treatment × (metformin and insulin regimen group)

[a] P-value for the treatment by metformin use and insulin regimen group at baseline interaction

[b] Difference from control in adjusted mean change from baseline

ANCOVA Analysis of covariance; CI Confidence interval; LOCF Last observation carried forward; NA Not applicable; Pla Placebo; Saxa Saxagliptin; SE Standard error

Durability (long term results)

Following completion of the 24 week ST treatment period of Study 57, patients were eligible to enter a controlled double-blind LT treatment period. Patients continued to take the same blinded study medication that they were assigned during the ST treatment period (saxagliptin 5 mg or placebo added on to insulin with or without metformin). During the LT treatment extension, changes in both the dose and type of insulin were allowed. Of the patients who continued into the LT treatment period, 268 (88.2% of randomised) patients and 134 (88.7% of randomised) patients were taking saxagliptin 5 mg plus insulin and placebo plus insulin (with or without metformin), respectively. Results from the LT extension period demonstrated that reductions from baseline HbA1c observed in the saxagliptin group compared with the placebo group were sustained to Week 52; the difference in the HbA1c change for saxagliptin (n = 244 observed) compared with placebo (n = 124 observed) was -0.4% at Week 52. Results were similar for patients using metformin and not using metformin at baseline. Increases from baseline in mean total daily dose of insulin occurred in both treatment groups through Week 52, with a numerically smaller increase in the saxagliptin group (5 units saxagliptin versus 6 units placebo). As indicated above, the 52 week data have been submitted in support of another

submission and are currently under evaluation; however, please note that the results are summarised in the Canadian Product Monograph for Onglyza (*Clinical Trials* section). Saxagliptin once daily added to insulin was generally safe and well tolerated and no new safety findings were noted in the ST plus LT treatment period compared with the ST treatment period.

Supportive safety data for the current submission are provided by the 52 Week LT results from Study 07. The cumulative safety results from the ST plus LT (52 Week) treatment period for both Study 57 and Study 07 demonstrated: (1) there were no new safety findings when saxagliptin was used in combination with insulin compared with the previously established safety profile of saxagliptin, which was extensively characterised in the original saxagliptin submission, and (2) no new safety findings were noted in the cumulative ST plus LT treatment periods for either study compared with the ST treatment periods.

Proposed indication

The sponsor acknowledges that the alternate indication proposed by the Delegate is adequately supported by the data provided as part of the submission. However, the sponsor considers that the initially proposed indication - consistent with the discussion of the results of Study 57 above - is appropriate with the following minor modification (bolded) to clarify the wording as identified by the clinical evaluator:

> *Onglyza is indicated in patients with type 2 diabetes mellitus, to improve glycaemic control, in combination with metformin, a sulfonylurea, a thiazolidinedione or insulin (with or without metformin), as an adjunct to diet and exercise, when the* ~~***single agent alone***~~ ***existing treatment regimen*** *does not provide adequate glycaemic control.*

Conclusion

The Sponsor considers the positive benefit:risk profile for saxagliptin in combination with insulin (with or without metformin) has been appropriately demonstrated for patients with T2DM. Therapy with the combination provides a clinically important and statistically significant improvement in glycaemic control in patients receiving different insulin regimens.

Australian patients with T2DM who have progressed to the stage of needing insulin treatment have few treatment options beyond increasing their daily dose of insulin or introducing additional injections of insulin, since most available oral anti-diabetic treatments have already been utilised. Therefore, the reduction in HbA1c afforded by saxagliptin is important in helping patients achieve glycaemic targets. The addition of a single daily dose of saxagliptin has demonstrated clinically relevant improvements in glycaemic control in combination with insulin - with a safety profile consistent with that observed in the core Phase III programme - thereby establishing saxagliptin as a valuable agent for combination treatment for patients with T2DM requiring insulin.

Advisory Committee Considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of safety and efficacy agreed with the delegate that this product had insufficient evidence of efficacy to enable an assessment of the overall benefit-risk profile for the proposed indication.

In making this recommendation the ACPM expressed concern that the submitted data for only 24 weeks demonstrate only marginal efficacy for the proposed population and did not support a reliable assessment of the long term durability of efficacy in a condition that required treatment over extended periods.

In addition, the ACPM recommended that longer term studies be submitted for evaluation.

Post-ACPM discussions

Following receipt of the ACPM considerations, the sponsor conceded that the pivotal study did not support the initially proposed indication but asserted that some benefit had been shown as add-on therapy to insulin. In response to the ACPM concerns, the sponsor agreed to the narrower indication which the Delegate had considered approvable (see above under *Delegate Considerations*). The sponsor now proposed the extension to the indications comprise the following, as a separate sentence:

> *Onglyza is indicated in patients with type 2 diabetes mellitus to improve glycaemic control as add-on therapy to premixed or basal insulin (with or without metformin) when premixed or basal insulin (with or without metformin) used with diet and exercise, do not provide adequate glycaemic control. Onglyza has not been studied in a regimen combining intermediate or long-acting insulin with mealtime bolus doses of short acting insulin (basal:bolus regimens) and its efficacy in this context has not been established.*

Additionally, consistent with the revised proposed indication (above), the sponsor agreed to amend the *Dosage and Administration* information to specifically describe use with insulin; and other areas of the proposed PI were amended to describe the pivotal Study in more objective terms.[11]

The Delegate considered it was therefore the case that the Phase III Study had been proposed in this later iteration to support a more realistic indication and restricted dosing advice. In view of the sponsor's agreement, the Delegate proposed to approve the revised indications and revised PI amendments.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Onglyza tablets, containing 5 mg saxagliptin (as hydrochloride) for the following indication:

> *Onglyza is indicated in patients with type 2 diabetes mellitus to improve glycaemic control as add-on therapy to premixed or basal insulin (with or without metformin) when premixed or basal insulin (with or without metformin) used with diet and exercise, do not provide adequate glycaemic control. Onglyza has not been studied in a regimen combining intermediate or long-acting insulin with mealtime bolus doses of short-acting insulin (basal:bolus regimens) and its efficacy in this context has not been established.*

The full Indications are now:

> *Add-on combination*
>
> *Onglyza is indicated in patients with type 2 diabetes mellitus, to improve glycaemic control, in combination with metformin, a sulfonylurea, or a thiazolidinedione, as an adjunct to diet and exercise, when the single agent alone does not provide adequate glycaemic control.*
>
> *Onglyza is indicated in patients with type 2 diabetes mellitus to improve glycaemic control as add-on therapy to premixed or basal insulin (with or without metformin) when premixed or basal insulin (with or without metformin) used with diet and exercise, do not provide adequate glycaemic control. Onglyza has not been studied in a regimen combining intermediate or long-acting insulin with mealtime bolus doses of short-acting insulin (basal:bolus regimens) and its efficacy in this context has not been established.*

[11] Details of PI amendments are beyond the scope of this AusPAR.

Initial combination

Onglyza is indicated for use as initial combination therapy with metformin in patients with type 2 diabetes mellitus, to improve glycaemic control as an adjunct to diet and exercise, when dual saxagliptin and metformin therapy is appropriate. {i.e. high initial HbAlc levels and poor prospects for response to monotherapy).

Specific conditions of registration applying to these goods

The implementation in Australia of the Onglyza saxagliptin (as hydrochloride) RMP, Version 9.0 dated 7 December 2011), included with this submission, and any subsequent revisions with any accompanying caveats and requests for pharmacovigilance activities as agreed with the TGA and its OPR. All ongoing pharmaco-epidemiology studies, as part of the additional pharmacovigilance plan must be provided to the TGA for review when completed.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the current Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

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