



**Australian Government**

**Department of Health and Ageing**  
Therapeutic Goods Administration

# Australian Public Assessment Report for exenatide

Proprietary Product Name: Byetta

Sponsor: Eli Lilly Australia Pty Ltd<sup>1</sup>

**June 2013**

**TGA** Health Safety  
Regulation

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<sup>1</sup> Bristol-Myers Squibb Australia Pty Ltd is now the sponsor of this product in Australia.

## 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>>.

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- 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.

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# I. Introduction to product submission

## Submission details

<i>Type of Submission:</i>	Major Variation (Extension of indications)
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	7 September 2012
<i>Active ingredient:</i>	Exenatide
<i>Product Name:</i>	Byetta
<i>Sponsor's Name and Address:</i>	Eli Lilly Australia Pty Ltd <sup>2</sup> 112 Wharf Road West Ryde NSW 2114
<i>Dose form:</i>	0.25 mg/mL solution for injection in pre filled pen injector containing 60 doses
<i>Strengths:</i>	5 µg per 20 µl (1.2 mL in total) and 10 µg per 40 µl (2.4 mL in total)
<i>Approved Therapeutic use:</i>	Exenatide is indicated as adjunctive therapy to improve glycaemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea, or a combination of metformin and a basal insulin, but are not achieving adequate glycaemic control.
<i>Route of administration:</i>	Subcutaneous injection
<i>Dosage:</i>	5 µg Byetta per dose administered twice daily (bid) for at least one month in order to improve tolerability. The dose of Byetta can then be increased to 10 µg bid to further improve glycaemic control. Doses higher than 10 µg bid are not recommended.
<i>ARTG Numbers:</i>	123609 (5 µg exenatide per 20 µl) 123610 (10 µg exenatide per 40 µl)

## Product background

This AusPAR describes an application by the sponsor, Eli Lilly Australia Pty Ltd, to extend the approved use of exenatide (Byetta) in type 2 diabetes mellitus (T2DM) patients to use in combination with insulin, with or without metformin and/or a thiazolidinedione (TZD).

The current approved indication is:

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<sup>2</sup> Bristol-Myers Squibb Australia Pty Ltd, 4 Nexus Court, Mulgrave VIC 3170, is now the sponsor of this product in Australia.

*Exenatide is indicated as adjunctive therapy to improve glycaemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea but are not achieving adequate glycaemic control.*

The proposed additional indication is:

*Exenatide is indicated to improve glycaemic control in patients with type 2 diabetes mellitus in combination with a basal insulin, with or without metformin and/or a thiazolidinedione.*

When target glycaemic control cannot be achieved and maintained with oral anti hyperglycaemic medications (OAMs), insulin is often the next step in treatment intensification. If, after adding insulin, glucose control continues to fail, increasing the insulin dose or frequency is often the next step, although this is associated with additional weight gain and an increased risk of hypoglycaemia. Because basal analog insulin primarily improves fasting glucose and exenatide has a marked effect on postprandial glucose control, it was hypothesised that adding exenatide to insulin would improve overall glycaemic control, as measured by glycated haemoglobin (HbA1c).

## Regulatory status

Table 1 shows the international regulatory history of Byetta.

**Table 1: Summary of international regulatory status of Byetta approvals.**

Country	Active Ingredient	Label Claim	Reg Status	Submission Date	Approval Date
Austria	Exenatide	Use with Insulin	Approved	8-Jun-11	19-Mar-12
Belgium	Exenatide	Use with Insulin	Approved	8-Jun-11	19-Mar-12
Bulgaria	Exenatide	Use with Insulin	Approved	8-Jun-11	19-Mar-12
Cyprus	Exenatide	Use with Insulin	Approved	8-Jun-11	19-Mar-12
Czech Republic	Exenatide	Use with Insulin	Approved	8-Jun-11	19-Mar-12
Denmark	Exenatide	Use with Insulin	Approved	8-Jun-11	19-Mar-12
Estonia	Exenatide	Use with Insulin	Approved	8-Jun-11	19-Mar-12
European Union	Exenatide	Use with Insulin	Approved	8-Jun-11	19-Mar-12
Finland	Exenatide	Use with Insulin	Approved	8-Jun-11	19-Mar-12
France	Exenatide	Use with Insulin	Approved	8-Jun-11	19-Mar-12
Germany	Exenatide	Use with Insulin	Approved	8-Jun-11	19-Mar-12
Greece	Exenatide	Use with Insulin	Approved	8-Jun-11	19-Mar-12
Hungary	Exenatide	Use with Insulin	Approved	8-Jun-11	19-Mar-12
Iceland	Exenatide	Use with Insulin	Approved	8-Jun-11	19-Mar-12
Ireland	Exenatide	Use with Insulin	Approved	8-Jun-11	19-Mar-12
Italy	Exenatide	Use with Insulin	Approved	8-Jun-11	19-Mar-12
Latvia	Exenatide	Use with Insulin	Approved	8-Jun-11	19-Mar-12
Lithuania	Exenatide	Use with Insulin	Approved	8-Jun-11	19-Mar-12
Luxembourg	Exenatide	Use with Insulin	Approved	8-Jun-11	19-Mar-12
Malta	Exenatide	Use with Insulin	Approved	8-Jun-11	19-Mar-12
Mexico	Exenatide	Use with Insulin	Approved	28-Jan-11	9-Mar-11
Netherlands	Exenatide	Use with Insulin	Approved	8-Jun-11	19-Mar-12
New Zealand	Exenatide	Use with Insulin	Approved	28-Sep-11	1-Mar-12
Norway	Exenatide	Use with Insulin	Approved	7-Jun-11	19-Mar-12
Poland	Exenatide	Use with Insulin	Approved	8-Jun-11	19-Mar-12
Portugal	Exenatide	Use with Insulin	Approved	8-Jun-11	19-Mar-12
Romania	Exenatide	Use with Insulin	Approved	8-Jun-11	19-Mar-12
Slovakia	Exenatide	Use with Insulin	Approved	8-Jun-11	19-Mar-12
Slovenia	Exenatide	Use with Insulin	Approved	8-Jun-11	19-Mar-12
Spain	Exenatide	Use with Insulin	Approved	8-Jun-11	19-Mar-12
Sweden	Exenatide	Use with Insulin	Approved	8-Jun-11	19-Mar-12
United Kingdom	Exenatide	Use with Insulin	Approved	8-Jun-11	19-Mar-12
United States	Exenatide	Use with Insulin	Approved	22-Dec-10	19-Oct-11

## **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. Further details of these clinical findings can be found in Attachment 2.*

### **Introduction**

The submission contained the following clinical information:

- 1 pivotal efficacy/safety study (Study GWCO).
- 1 other efficacy/safety study (Study IOPB).

The sponsor asserted that both studies submitted in the dossier had appropriate ethical approval and had been done in compliance with Good Clinical Practice (GCP).

### **Pharmacokinetics**

None submitted.

### **Pharmacodynamics**

None submitted.

### **Efficacy**

Study IOPB makes no contribution to evidence of efficacy. The rest of this section relates to Study GWCO.

Data on use with a TZD are inadequate because:

- the use of a TZD in Study GWCO is uncontrolled, so its role in any efficacy outcome cannot be discerned; and
- particularly in the absence of metformin, the number of relevant cases is insufficient.

Data on use with glargine in the absence of any OAM are inadequate because the number of relevant cases is insufficient. Thus, in my opinion the only conclusions that can justifiably be drawn from the study relate to the use of exenatide in patients who are already being treated with metformin and glargine.

The length of the one efficacy study submitted (30 weeks) is shorter than the minimum length envisaged in the relevant guideline for applications of this type. The relevant European Medicines Agency (EMA) guideline<sup>3</sup> advises that:

*"Whatever the situation (monotherapy, add on therapy or combination with insulin), continuation or extension of the studies to at least 12 months is desirable to assess the maintenance of efficacy and safety in the long term."*

The sponsor has drawn attention to a paper by Klonoff and colleagues<sup>4</sup> in support of durability of efficacy. The paper appears to describe open label extensions of some of the sponsor's studies of exenatide, but the clinical evaluator could not find in it any mention of patients treated with glargine. On the other hand, the clinical evaluator has some sympathy with the proposition that a drug which has been well studied in long term trials need not be subjected to durability studies pre approval for each new combination usage.

Subject to these concerns, the mean reduction in %HbA1c (0.71) was clearly statistically significant, and in my opinion also indicated a clinically significant improvement in glycaemic control in the population studied. That population was reasonably diverse, although representation by patients aged >75 included only two on exenatide.

Regarding secondary efficacy outcomes, the effects on weight, and on post prandial glucose, are of note.

## **Safety**

Overall, the observations on safety and tolerability of exenatide used in combination with insulin in Study GWCO were consistent with the currently approved PI.

## **Clinical summary and conclusions**

### **First round assessment of benefits**

The benefits of exenatide in the proposed usage are:

- improved mean HbA1c in patients who are already being treated with metformin and glargine; and
- possibly other benefits such as favourable effect on weight.

### **First round assessment of risks**

On the basis of the trial experience reported (a rather small trial of minimal duration), the risks of exenatide in the proposed usage appear similar to those of the usage which has already been approved.

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<sup>3</sup> European Medicines Agency, "Committee for Proprietary Medicinal Products (CPMP): Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Diabetes Mellitus (CPMP/EMP/1080/00)", 30 May 2002, Web, accessed 18 February 2013 <[www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003262.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003262.pdf)>.

<sup>4</sup> Klonoff DC, et al. (2008) Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. *Curr Med Res Opin.* 24: 275-286.

### **First round assessment of benefit-risk balance**

The benefit-risk balance of exenatide is unfavourable given the proposed usage, but would become favourable if the changes recommended below are adopted.

### **First round recommendation regarding authorisation**

The application should be approved only so far as to extend the indication to the following:

*Exenatide is indicated as adjunctive therapy to improve glycaemic control in patients with T2DM who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea, or a combination of metformin and a basal insulin, but are not achieving adequate glycaemic control.*

### **List of questions**

#### **Efficacy**

The sponsor should be asked to clarify the definition of Full Analysis Set in Study GWCO.

#### **Safety**

The sponsor should be asked:

- How is the absence of any routine collection of laboratory safety data after the screening visit consistent with the Protocol provisions (Safety Monitoring): "Lilly ... will review trends, laboratory analyses, and AEs at periodic intervals" (GWCO) and "Lilly will ... review trends, laboratory analytes, and AEs at periodic intervals" (IOPB)?
- How is the non availability of Visit 1 clinical chemistry data for Study IOPB consistent with the Protocol provision that the relevant assays would be done at a central laboratory, and with the declaration that the study was performed in compliance with the principles of GCP?

### **Second round assessment of benefits**

The assessment is unchanged from the first round assessment.

### **Second round assessment of risks**

The assessment is unchanged from the first round assessment.

### **Second round assessment of benefit-risk balance**

The assessment is unchanged from the first round assessment.

### **Second round recommendation regarding authorisation**

This recommendation is identical to the first round recommendation.



## V. Pharmacovigilance findings

### Risk management plan

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

### Safety specification

The sponsor provided a summary of Ongoing Safety Concerns which are shown below:

#### ***Identified important risks:***

- Pancreatitis
- Acute renal failure
- Rapid weight loss

#### ***Potential important risks***

- Risks associated with anti exenatide antibodies (focus on anaphylactic type reactions)
- Cardiac events
- Malignant neoplasm (focus on pancreatic cancer and thyroid neoplasms)

#### ***Important missing information:***

- Use in adolescent patients with type 2 diabetes
- Use in pregnancy
- Use in the very elderly ( $\geq 75$  years old)
- Use in the combination with other agents (TZDs and insulins)
- Use in patients with severe gastrointestinal disease (exenatide once weekly)
- Use in patients with various degrees of impaired renal function (exenatide once weekly)
- Use in patients with hepatic impairment (exenatide once weekly)

#### ***OPR reviewer's comment:***

The sponsor was asked to clarify why "use in the combination with other agents (TZDs and insulins)" is included as an area of missing information considering the indication sought in this submission is for use in combination with insulin. In response to the s31 request for information (dated 3 April 2012), the sponsor stated that this was added to the EU RMP as per the request of the EU Committee for Medicinal Products for Human Use (CHMP) although the sponsor did not believe that it should be included.

Hypoglycaemia is not included as a safety specification in the RMP despite the fact that it is a known adverse effect associated with the use of insulin. Considering that this submission sought to extend the indication for use in combination with insulin, the sponsor was asked to clarify, especially since the PI has:

1. indicated that the clinical trial protocol to evaluate the efficacy and safety of combining exenatide and insulin was specifically designed to minimise the risk of hypoglycaemia by reducing the basal insulin dose (by 20%) in participants with HbA1c of  $\leq 8.0\%$ , and

- recommended that a reduction of basal insulin dose is considered when used with exenatide (in the *Dosage and Administration* section of the PI).

In response to the s31 request for information (dated 3 April 2012), the sponsor stated that the company did not consider hypoglycaemia to meet the RMP definition of an 'important identified risk' because it is not "*one judged to have implications for public health or one that impacts on the benefit-risk balance*" due to the mechanism of action of Byetta. The sponsor further elaborated:

*"The mechanisms of exenatide action include enhancement of glucose dependent insulin secretion, restoration of first phase insulin secretion, glucose dependent suppression of inappropriately elevated glucagon secretion, and slowing of the rate of gastric emptying... Exenatide does not inhibit the counter regulatory effects of glucagon under hypoglycemic conditions. Nonclinical and clinical studies also indicate that the effect of exenatide to slow gastric emptying, which in turn slows the rate of glucose entry into the circulation, is reversed during hypoglycaemia. These glucose dependent actions of exenatide lead to improvements in glucose control while minimising the risk of hypoglycemia... Hypoglycemia as a result of the combination of exenatide plus basal insulin is also included in product labelling, but not included in the RMP... there is no increase in incidence of hypoglycaemia when exenatide is used in combination with insulin glargine compared to insulin glargine alone."*

The above summary of the Ongoing Safety Concerns is considered acceptable, unless specific concerns are raised from the clinical evaluation by the Office of Medicines Authorisation (OMA).

### **Pharmacovigilance plan**

The following are proposed pharmacovigilance (PV) activities for each Ongoing Safety Concern (protocols for studies that have completed or initiated are not reviewed for this report).

#### ***Identified important risks***

##### ***1. Pancreatitis***

Routine PV activities:

- Routine monitoring and review of spontaneously reported events (to be updated in Periodic Safety Update Reports (PSURs)).

Additional PV activities:

- Expedited reporting of all post marketing cases.
- Monitor and review events of pancreatitis from the cardiovascular outcome study (Study H80-MC-GWDQ). See also 'cardiac events' section below:
- Targeted surveillance.
- Review of evolving aggregate data by an international expert advisory panel.
- Mechanistic study to evaluate potential change in gallbladder emptying as a surrogate measurement for increased tone of the sphincter of Oddi in healthy subjects treated with exenatide:
  - Initial study (Study H80-EW-GWCJ; summary report submitted Q2 2010 with PSUR 10) was terminated in November 2009 due to market withdrawal of caerulein, inducer of gallbladder emptying. New study (H80-US-GWDP) will be conducted in the US with an alternative agent, Kinevac, pending FDA's approval of the study protocol.

- This study was proposed as a result of the suggestion made by a panel of external (EU) experts to explore if pancreatitis can be caused by exenatide via an effect on the tone of sphincter of Oddi, resulting in the obstruction of pancreatic secretions into the duodenum and subsequent autodigestion of the pancreas by digestive enzymes (sponsor's response, dated 20 April 2011):
  - Gallbladder emptying is chosen as a non invasive surrogate marker for effect on sphincter of Oddi tone.
  - It is stated that the study outcomes are not expected to directly inform of safety or mitigate risk posed to T2DM patients treated with exenatide.

*Completed activities:*

- Review by an Independent Adjudication Committee of gastroenterology experts of clinical trials and 300 spontaneously reported cases (summarised in PSUR 09).
- Completion of a United HealthCare (UHC) database study to evaluate patients treated with exenatide versus other anti diabetic drugs or patients without diabetes, with approximately 25,000 exenatide treated patients and greater numbers in the other cohorts. Patients who qualified for study cohorts between June 2005 and December 2007 were followed through March 2008. Final study report submitted in December 2009.
- Completion of additional pharmacoepidemiological study (IMS Health) to evaluate incidence of acute pancreatitis in patients using anti diabetic drugs including exenatide. Final report to be submitted in December 2009.
- Completion of a pooled analysis of previous pharmacoepidemiological studies (UHC3 and IMS) evaluating incidence of acute pancreatitis in T2DM patients treated with exenatide versus other anti diabetic drugs or in patients without diabetes. Pooled final data analysis submitted in May 2010. Pooled analysis done using data from two cohort studies involving 49,956 exenatide treated patients and about 700,000 in comparator group. Concluded that very little or no higher risk of acute pancreatitis associated with the use of exenatide.

*Specific to the exenatide once weekly formulation (Bydureon):*

- New once weekly clinical trial to include serum amylase and lipase measurements, with pancreas imaging in asymptomatic cases showing elevated enzyme levels by using a predefined algorithm:
  - the measurements of total amylase and pancreatic lipase are used as additional surrogate markers of severe and persistent gastrointestinal symptoms, although these markers are acknowledged to be nonspecific in asymptomatic patients (sponsor's response, dated 20 April 2011).
- (Newly added to this RMP) Modified Prescription Event Monitoring (PEM) study in the UK to identify possible acute pancreatitis cases in T2DM patients in primary care who are prescribed Bydureon:
  - Observational cohort study in primary care settings in the UK (patients identified through the National Health Service prescriptions).
  - Anticipated 5000 sample size to detect a two fold increase in acute pancreatitis with 80% power (background in non diabetics estimated at 0.2%), with follow up for 12 months.
  - Targeted questionnaires to general practitioners for information on patient population (including off label use and use during pregnancy).

- To describe cases and quantify incidence of acute pancreatitis and associated events that are indicative of pancreatitis, and to characterise any reported cases of pancreatic and thyroid cancers diagnosed after treatment initiation.

Initial questionnaire is to be sent out at least 12 months after initial Bydureon prescription and a follow up questionnaire to be sent to further evaluate outcomes of interest including acute pancreatitis and associated events or unknown causes of death.

## 2. *Acute renal failure*

Routine PV activities:

- Routine monitoring and review of spontaneously reported events (to be updated in PSURs).

Additional PV activities:

- Expedited reporting of all post marketing cases.
- Monitor and review of all serious renal events from the cardiovascular outcome study (Study H80-MC-GWDQ). See also 'cardiac events' section below:

Targeted surveillance on acute renal failure/insufficiency, including dehydration and hypovolaemia events.

## 3. *Rapid weight loss*

Routine PV activities:

- Routine monitoring and review of spontaneously reported events (to be updated in PSURs).

### **Potential important risks**

#### 1. *Risks associated with anti exenatide antibodies (focus on anaphylactic type reactions)*

Routine PV activities:

- Routine monitoring and review of spontaneously reported allergic/immunologic events (anaphylaxis or angioedema) (to be updated in PSURs).

Additional PV activities:

- Monitor and review of all serious immunologic events from the cardiovascular outcomes study (Study H80-MC-GWDQ):
  - Caveat: laboratory tests may be ordered by treating physicians, but routine collections of samples for antibodies will not be performed (sponsor's response, dated 20 April 2011).
- Targeted surveillance on allergic/immunologic events (anaphylaxis, angioedema and laryngeal oedema).
- Continuing three year study (Study H80-EW-GWBE) to collect anti exenatide antibody titres from approximately 500 subjects treated with exenatide and who reported serious, potentially immune related adverse events:
  - Patients have on average about 1.5 years of exposure.
  - Estimated final data submission in Q3 2011.

Protocol has not been evaluated previously as the study has already commenced at the time of review. The sponsor has confirmed that no new safety issues have been identified through this study so far and that a copy of the final study report will be made available to the TGA once completed (sponsor's response, dated 20 April 2011).

## 2. Cardiac events

### Routine PV activities:

- Routine monitoring and review of spontaneously reported serious cardiac events (to be updated in PSURs).

### Additional PV activities:

#### *Specific to the exenatide once weekly formulation (BYDUREON):*

- Assess cardiovascular (CV) outcomes in a prospective long term study (Study H80-MC-GWDQ; EXSCEL; Clinical Study Protocol BCB109) in T2DM subjects who are randomised to standard of care diabetes regimens with or without Bydureon:
  - This is a Phase 3b/4 randomised, double blind, placebo controlled multinational clinical trial, that would include participants with T2DM, with (60%) or without (40%) a history of CV disease.
  - Study outcomes will include MACEs (Major Adverse Cardiovascular Events) such as non fatal myocardial infarction, non fatal stroke and cardiovascular related death.
  - Study to start in Q2 2010, with the last patient visit estimated in Q2 2017. However, it is stated that clinical study report is anticipated in Q4 2016, which is sooner than the estimated last patient visit in Q2 2017. The sponsor was requested to clarify this information. In response to the s31 request for information (dated 3 April 2012), the sponsor has stated that patient enrolment is currently progressing, with the last patient visit and final study report estimated in Q2 2017 and Q1 2018 respectively.
  - Approximately 9500 T2DM patients of  $\geq 18$  years old to be recruited over 3 years with a minimum follow up of 4 years (with visits at 1 week and 2 months after initial visit, and followed by six monthly visits until end of trial), randomised at 1:1 between Bydureon treatment and placebo, with continuing trial until adjudicated 1591 primary endpoints have been reached. Anticipated enrolled patients to consist of 1/3 from the Americas, 1/3 from Europe and 1/3 from Asia/Australasia (sponsor's response, dated 20 April 2011).

This study was initiated post approval of exenatide bid as part of FDA's recommendation in 2008 for the inclusion of CV risk evaluation for all new anti diabetic therapies to treat T2DM<sup>5</sup> (sponsor's response, dated 20 April 2011).

## 3. Malignant neoplasms (focus on pancreatic cancer and thyroid neoplasms)

### Routine PV activities:

- Routine monitoring and review of spontaneously reported events (to be updated in PSURs).

### Additional PV activities:

- Monitor and review of all pancreatic cancer and thyroid carcinoma events from the cardiovascular outcome study (Study H80-MC-GWDQ). See also previous 'cardiac events' section:

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<sup>5</sup> US Food and Drug Administration, "Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes", December 2008, Web, accessed 18 February 2013 <[www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf)>.

- Targeted surveillance for treatment emergent malignancies and neoplasms with focus on pancreatic cancer and thyroid neoplasms.
- Pharmacoepidemiological study titled “Incidence of Pancreatic Malignancy and Thyroid Neoplasm in Type 2 Diabetes Mellitus Patients who Initiate Exenatide Compared to Other Antihyperglycemic Drugs” (updated final protocol provided with s31 response dated 3 April 2012):
  - Primary objectives: to assess the absolute and relative incidences of newly diagnosed pancreatic cancer and thyroid cancer in T2DM patients who initiate exenatide versus other anti diabetic drugs.
  - Secondary objective: to estimate the absolute incidence of benign thyroid neoplasm, medullary thyroid cancer (MTC) and non MTC neoplasm in T2DM patients who initiate exenatide versus other anti-diabetic drugs.
  - Data sources: US based health insurance claims databases that will include medical and pharmacy claims – Life Sciences Research Database and Impact National Benchmark.
  - Study population: T2D patients with 9 months of continuous enrolment prior to index date (cohort entry), and who initiated treatment between 1 June 2005 and 31 July 2010 (with no prior exenatide or other anti diabetic drug dispensed within past 9 months).
  - Patients are to be followed up for 1 year after drug initiation, to date of first incident, loss to follow-up or end of study follow up period (reported as 31 December 2010 in Section 3.4 *Study Population* of the study protocol but as 31 December 2011 in Section 4.3 *Intent-to-treat Analysis* of the study protocol, provided in Appendix 4 of the RMP). Clarification was sought from the sponsor on the estimated end of study follow up. The sponsor has confirmed in the response to s31 request for information (dated 3 April 2012) that the correct estimated end of study follow up is 31 December 2010 and the final study report is anticipated in Q1 2013.
  - Each exenatide initiator will be matched with two other anti diabetic drug initiators. Incidents from claim cases with reported thyroid or pancreatic cancers 9 months prior to index date will be excluded.
  - Confirmation of available potential cases of study outcomes from medical records and independent adjudication by two different clinical experts.
  - It is stated that there were 61,834 exenatide treated patients with at least one Byetta prescription filled and preceded by at least 9 months of continuous health plan enrolment. The majority had up to 1 year of Byetta exposure time (51,834), with longer term exposures at 1-2 years (7,054), 2-3 years (2,130), 3-4 years (612), 4-5 years (199) and more than 5 years (6). Mean exenatide exposure time was 212.45 days.
  - Some of the major study limitations discussed: accuracy of medical data reported, relationship between insurance claims and actual medication utilisation, relatively short enrolment duration for follow up.

*Completed activities:*

- Completed a signal detection exercise utilising Aperio in a UHC claims database, with study summary submitted in December 2009. Patients who initiated medications between 1 June 2005 and 30 June 2008 were followed through to 30 June 2009. Additional analyses using a different methodology are being conducted.

- Completed an additional database study to assess the incidence of pancreatic cancer and thyroid neoplasms in patients with T2DM. A retrospective cohort study using claims from US managed care database from 1 January 2004 to 31 December 2008, involving a total of 1,120,255 patients with T2DM with no cancer diagnoses in previous year compared to 2,240,510 patients with no prior claim for diabetes or cancer in previous year:
  - Concluded that there is an increased risk of de novo pancreatic cancer in patients with T2DM compared to non diabetics, with a hazard ratio of 1.66 (incidence of 0.64/1000 person years in T2DM versus 0.39/1000 person years in non diabetics), and no evidence of association of T2DM and thyroid cancer.
  - Final study report submitted in Q2 2010 with PSUR 10.

*Specific to the exenatide once weekly formulation (BYDUREON):*

- New once weekly clinical trial (BCB108) to include calcitonin level screening and monitoring:
  - Calcitonin is used as a surrogate marker of thyroid c-cell hyperplasia and medullary carcinoma (sponsor's response, dated 20 April 2011).
- (Newly added to this RMP) Pharmacoepidemiological study using one or more European (may include UK) databases to identify possible cases of thyroid neoplasms (benign and malignant) and pancreatic cancer in T2DM patients with who initiate Bydureon:
  - Protocol title: Incidence of Thyroid Neoplasm and Pancreas Cancer in Patients with Type 2 Diabetes Mellitus Who Initiate Bydureon Compared to other Antidiabetic Drugs in Europe.
  - Primary study objectives: to estimate absolute and relative incidences of new onset thyroid cancer and pancreatic cancer in T2DM patients ( $\geq 18$  years old) who initiated Bydureon compared to other anti diabetic drugs.
  - Secondary study objective:
    - to characterise the incidence of malignant thyroid cancer subtypes in T2DM patients who initiated Bydureon compared to other anti-diabetic drugs.
    - to estimate the comparative incidences of thyroid and pancreatic cancers over exposure time.
    - to estimate incidence of benign thyroid neoplasms in T2DM patients who initiated Bydureon compared to other anti diabetic drugs
    - to determine incidence of events of interest prior to exenatide or comparator drug exposure.
  - Patients are to be followed up to date of first incident, death, loss to follow-up or end of study, after a minimum of 1 year enrolment. Incidents of thyroid or pancreatic cancers will be included for analysis after one year of drug initiation.
  - Stated that the reported incidence for pancreatic cancer is estimated at 11 per 100,000 patients and for thyroid cancer is 10.2 per 100,000 patients in the US (while incidence per 100,000 populations for thyroid cancer in Europe ranges from 0.9-2.9 for males and 2.3-7.1 for females).
  - Estimated sample size of 55,000 Bydureon treated subjects for a 3 fold detection rate of thyroid cancer (assuming background incidence of 5/100,000 patients) over that of expected rate in comparison cohort, based on 80% power, two sided alpha of 0.05 and 1:4 BYDUREON to comparator ratio.

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**Important missing information****1. Adolescents**

Additional PV activities:

- Study H80-MC-GWBQ to assess safety and efficacy on exenatide twice daily in adolescents with T2DM:
  - This is a 28 week, placebo controlled, randomised, 3 arm clinical trial.
  - Study was initiated in June 2008 with a target of 195 participants; however, as of 2 July 2010, only 79 participants have been screened and 42 participants were randomised.
  - An update on study enrolment rate provided with the response to s31 request for information (dated 3 April 2012); as of 20 March 2012, 75 participants were randomised with 41 having completed the study.
  - Participant age group is 10-17 years old inclusive, with the number of participants at 17 years old limited to no more than 10% of each treatment arm (response to s31 request for information dated 3 April 2012).
  - Treatment randomisation at ratio 2:2:1:1 (5 µg exenatide: 10 µg exenatide: placebo at volume of 5 µg exenatide: placebo at volume of 10 µg exenatide).
  - Last patient visit is expected in October 2012.
  - Study protocol previously provided (sponsor's response, dated 20 April 2011).

*Specific to the exenatide once weekly formulation (Bydureon):*

- Double blind, placebo controlled study to assess safety and efficacy of BYDUREON as monotherapy and adjunct therapy to other anti diabetic drugs in children and adolescents with T2DM:
  - Study BCB114 protocol previously provided (protocol restricted to 10-17 years old; sponsor's response, dated 20 April 2011, Attachment 8):
  - Phase 3, 14 week, randomised, placebo controlled study, followed by 52 week extension open label period with all participants receiving Bydureon;
  - Primary objectives: efficacy (glycemic control as measured by HbA1c) and safety;
  - Secondary objectives: to include measurements of fasting plasma glucose concentration, body weight and Tanner pubertal stage, blood pressure and lipids, beta cell function (HOMA-B) and insulin sensitivity (HOMA-S);
  - Age of participants confirmed to be from 10 to <18 years old (response to s31 request for information dated 3 April 2012);
  - Approximately 100 subjects assigned at a ratio of 2 Bydureon: 1 placebo;
  - Approximately 20 participants will be followed further for another 10-12 weeks after discontinuation of exenatide treatment to assess postprandial beta cell function (assessed by C-peptide secretion), postprandial glucose and glucagon response during a mixed meal test.

Study start date anticipated in mid 2011 and will be conducted in multiple countries including US and Europe.



## 2. *Pregnant women*

### Additional PV activities:

- Pregnancy registry (BCA401) to determine if exenatide poses a risk to pregnant women or developing foetuses:
  - Registry was initiated in December 2007, with only 3 patients enrolled to date. Target recruitment is 200 exenatide treated and 200 non exenatide treated T2DM patients.
  - Clinical study report is expected in Q3 2012.
  - Study protocol submitted previously (sponsor's response, dated 20 April 2011):
    - Sample size of 200 is expected to yield approximately 105 live births assuming a 15% loss of follow up and 65% live birth rate. Live births of 105 is expected to provide 80% power to detect a relative risk of 2.57, based on the expected 9% birth defect generally observed in T2DM population;
    - Study to include infant assessments at 4 months and 12 months after birth;
    - Study to be conducted in the US only, with enrolment period of 3-5 years.

Study may be discontinued from low enrolment rate.

## 3. *Very elderly ( $\geq 75$ years of age)*

### Routine PV activities:

- Routine monitoring and review of spontaneously reported adverse events in very elderly patients (to be updated in PSURs).

## 4. *Use in combination with other agents (TZDs and insulins)*

### Routine PV activities:

- Routine monitoring and review of spontaneously reported adverse events associated with anti diabetic drug combinations (that is, TZDs and insulins) that are not yet globally approved (to be updated in PSURs).

## 5. *Severe gastrointestinal disease (exenatide once weekly)*

### Routine PV activities:

- None proposed as exenatide is not recommended for use in patients with severe gastrointestinal disease. It is stated in the RMP that PSURs 1-9 did not reveal any new safety information.

## 6. *Various degrees of impaired renal function (exenatide once weekly)*

### Routine PV activities:

- Routine monitoring and review of spontaneously reported adverse events in patients with mild to moderate renal impairment or potential off label use in patients with severe renal impairment (to be updated in PSURs).

## 7. *Hepatic impairment (exenatide once weekly)*

### Routine PV activities:

- Routine monitoring and review of spontaneously reported adverse events in patients with hepatic impairment (to be updated in PSURs).

***OPR reviewer's comments in regard to the pharmacovigilance plan and the appropriateness of milestones***

The assessment of the pharmacovigilance plan for this submission has been focused primarily on new proposed studies that have not been previously evaluated, and pertaining to indications sought in this current submission (that is, Byetta only).

One remaining outstanding issue was raised by the RMP evaluator in the review of the previous RMP for potential cardiovascular risk, specifically on QT prolongation. The Sponsor has previously stated that there was no evidence to suggest that exenatide is associated with cardiovascular events and QT prolongation, and that the proposed or completed studies to evaluate these events were done as part of the general recommendations made by FDA<sup>6</sup> for all new anti diabetic drugs to treat T2DM (sponsor's response, dated 20 April 2011), and had noted the following:

- A previously published meta analysis on the effects of exenatide twice daily on cardiovascular events<sup>7</sup> indicated that there is no increase risk for major adverse cardiovascular events, with a relative risk of 0.7 as calculated by Mantel-Haenszel method and stratified by study. A summary of this study design:
  - This was a pooled meta analysis of 12 previously completed (8 blinded, 4 open label), controlled, randomised 12-52 weeks clinical trials comparing exenatide twice daily treatment versus comparator (placebo or insulin).
  - Primary study outcomes: CV mortality, stroke, myocardial infarction, acute coronary syndrome and revascularisation procedures.
  - Secondary study outcomes: all CV adverse events.
  - Data included ~4000 T2DM patients, with 2316 patients treated with exenatide (equivalent to 1072 person-years at 2.5 µg, 5 µg or 10 µg, with data pooled for analysis due to low CV events), 658 patients treated with insulin and 971 patients in the placebo group (equivalent to 780 person years exposure in insulin/placebo group as comparators).
  - The reported exposure-adjusted incidence rate: 18.73/1000 person-years for exenatide group and 23.17/1000 person-years for pooled comparator group.
  - Caveats discussed: retrospective analysis of events identified by physicians blinded to treatment as studies not specifically designed to assess CV risk, low number of CV events, short exposure time ( $\leq 1$  year) and a single comparator (insulin).
  - Cited a previous finding that there is no strong evidence to suggest that there is a clinically significant QTc prolongation in healthy volunteers treated with exenatide twice daily as compared to placebo.<sup>8</sup>

The information above on CV events as provided by the sponsor to support the argument that there is no increase risk for CV events, and particularly for QT prolongation appears reasonable unless specific concerns are raised from the clinical evaluation by OMA. The

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<sup>6</sup> US Food and Drug Administration, "Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes", December 2008, Web, accessed 18 February 2013 <[www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf)>.

<sup>7</sup> Ratner R, et al. (2011) Cardiovascular safety of exenatide BID: an integrated analysis from controlled clinical trials in participants with type 2 diabetes. *Cardiovasc Diabetol*. 10: 22.

<sup>8</sup> Linnebjerg H, et al. (2011) A thorough QT study to evaluate the effects of singledose exenatide 10 µg on cardiac repolarization in healthy subjects. *Int J Clin Pharmacol Ther*. 49: 594-604.

sponsor has also proposed to investigate the effects of suprathereapeutic plasma exenatide concentrations on QT interval, which might be achieved with exenatide once weekly formulations in patients with mild or moderate renal impairment. A copy of the protocol – BCB112: Phase 1 randomised, three period, double blind, placebo and positive controlled crossover study on the effects of exenatide at therapeutic and suprathereapeutic concentrations on the 12-lead electrocardiogram QT interval in healthy subject – has previously been provided (sponsor’s response, dated 20 April 2011). A search on the website [clinicaltrials.gov](http://clinicaltrials.gov) has indicated that the Study BCB112 is estimated for completion in August 2011.<sup>9</sup> Unless specific concerns are raised from the clinical evaluation by OMA, the pharmacovigilance plan as proposed is considered acceptable.

### **Risk minimisation activities**

#### ***Sponsor’s conclusion in regard to the need for risk minimisation activities***

The Sponsor has proposed only routine risk minimisation activities, which include the provision of Consumer Medicine Information (CMI) and PI in every pack of Byetta. It is also stated in Module 1, Section 1.13.1 *Australian Annex* to RMP, that:

- *“Risk minimisation activities described in EU RMP included with this application are applicable to the Australian circumstances for all identified and potential risks.*
- *Activities described to address missing information are appropriate for Australia for all categories except very elderly patients (>75 years of age)... will update the Byetta PI to incorporate the instruction for caution when escalating dosing in this application. Upon final approval, the changes will be incorporated into the proposed PI for this application.”*

#### ***OPR reviewer’s comment:***

This is considered acceptable unless specific concerns are raised from the clinical evaluation by OMA.

#### ***Potential for medication errors***

##### *Medication error*

Instruction for use (User Manual) will be available to detail the step by step process to follow on how to initiate the Byetta pen and to administer each dose. The company states that it will continue to improve the usability of the Byetta pen by ongoing review of global product feedbacks that will guide future updates of patient educational materials.

To mitigate the potential for medication error, the company has proposed to provide educational presentations to HCPs (Health Care Professionals) at diabetes symposia and conferences, post education materials on appropriate use of Byetta on websites (so far, available in Germany and US), prepare Global Response Documents for distribution upon request by HCPs and set up Call Centres to receive inquiries from HCPs and patients, and provide a ‘Welcome Kit’ for patient who are newly prescribed Byetta that includes a one page Discussion Guide for the initial consultation, a Reference Booklet for detailed information and a Patient Diary to record blood glucose measurements and body weights during the first month of use. A training video may also be available to instruct patients on how to use the Byetta pen. However, this proposed risk minimisation strategy may differ from those available in Australia, for example the use of Australian websites as educational tools will not be promoted and the types of professional conferences in Australia for educational presentations on Byetta may differ from those offered in other

<sup>9</sup> <<http://clinicaltrials.gov/ct2/show/NCT01297062?term=exenatide+AND+QT&rank=1>>

jurisdictions, although the aims and content of the materials are expected to be similar (Section 1.13.1 *Australian Annex* to RMP).

*Off label use:*

Discussion was provided on the potential for off label use, including in patients with severe gastrointestinal disease, end stage renal disease or severe renal impairment, who are not recommended in the PI to use Byetta. It is stated in the RMP that no new safety concern relating to off label use has been detected so far through routine pharmacovigilance. The potential for off label use for weight loss was also discussed, with a reported incidence rate of about 0.7% as obtained from post market spontaneous reports (as of review conducted up to 31 March 2009).

It is also discussed that the company had collected up to two years of post market data for off label use in Germany, UK, France and Belgium from primary care databases, and the data did not show a significant concern with off label use, although the patient numbers with data collected were low. In addition, it is stated that the company is proposing educational presentations for HCPs at medical conferences and symposia.

***Toxicity in overdose***

It is discussed in the *Potential for Overdose* section of the RMP that the potential for overdose is low because the Byetta pen is designed to deliver a fixed dose of 5 µg or 10 µg per injection. For overdose to occur, repeated injections will have to be administered. The company considers the provision of the User Manual to be sufficient to minimise this risk. Instruction to seek immediate medical attention and the contact information for the Poisons Information Centre in Australia are also provided in the CMI. Cases of overdose from clinical trials (n=3) and spontaneous report (n=1) are described, with all cases having recovered from the incidents, in the *Overdosage* section of the PI.

***OPR reviewer's comments:***

The sponsor has previously stated that the additional risk minimisation activity proposed on collecting consumer feedback to improve the user friendliness of the pen would include data from the Australian market, as all customer feedback from Australia would be reported to the global Lilly office, and globally identified changes would be implemented and communicated through Lilly Australia (sponsor's response, dated 20 April 2011). The discussions provided by the sponsor on mitigating the potential risks of medication error, overdose and off label use are considered acceptable unless specific concerns are raised from the clinical evaluation by OMA.

**Summary of recommendations**

The final RMP may need to be updated if additional safety concerns are identified by the clinical evaluator. Pending the finalisation of the clinical evaluation report by the OMA, the OPR provides the recommendation in the context that the submitted RMP is supportive to the application:

- the implementation of a RMP identified as EU RMP Version 16 (Revision 15, data lock point 31 March 2010) with the Australian specific Annex to the RMP (Revision 15\_v1.0), and any subsequent versions, be imposed as a condition of registration.

## VI. Overall conclusion and risk/benefit assessment

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

### Quality

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

### Nonclinical

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

### Clinical

Two studies are submitted.

The pivotal study, GWCO, is a multicentre randomised double blind placebo controlled study.

The evaluator mentions that exenatide was compared to placebo in patients with T2DM who did not meet the glycaemic targets with insulin glargine with or without metformin, pioglitazone or both.

Subjects diagnosed with T2DM, at least 18 years old with a stable body weight  $\geq 3$  months prior to study entry with a BMI  $\leq 45$  kg/m<sup>2</sup> were eligible. HbA1c was to be within 7.1% and 10.5%; insulin glargine of  $\geq 20$  units alone or in conjunction with metformin and or pioglitazone were inclusion criteria. Details of inclusion and exclusion criteria are found in the clinical evaluation report.

Details of dose titration in relation to insulin and other details regarding dosing are included in the clinical evaluation report.

The primary efficacy outcome was change in HbA1c from baseline to Week 30.

Randomisation details and the definition of populations analysed are included in the clinical evaluation report. These are acceptable. Statistical considerations are discussed. It is stated that the numbers were included based on an anticipated mean difference of 0.5% in HbA1c between groups. This, too, is acceptable.

The demographic details extracted from the clinical evaluation report is given in Tables 2-3.

**Table 2: Demographic details.**

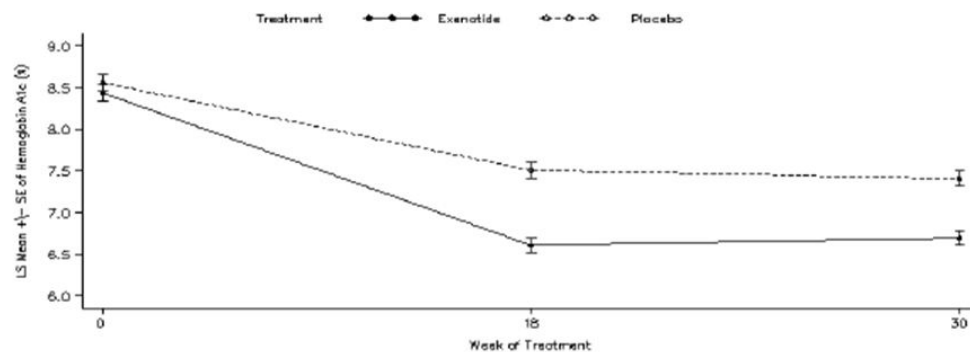
	<b>Exen</b> N=137	<b>Pbo</b> N=122	<b>Total</b> N=259
Age: mean (sd) <sup>†</sup>	58.7 (8.9)	59.4 (10.0)	59.0 (9.4)
Sex	70M, 67F	78M, 44F	148M, 111F
Weight (kg): mean (sd)	95.4 (20)	93.4 (21)	94.4 (21)
BMI: mean (sd)	33.8 (5.8)	33.1 (6.2)	33.5 (6.0)

<sup>†</sup> Of the 259 patients, 29% were aged > 65. Of these, 8 (2 on exenatide and 6 on placebo) were aged > 75.

**Table 3: Baseline data relating to disease state and treatment.**

	<b>Exen</b> N=137	<b>Pbo</b> N=122	<b>Total</b> N=259
Duration of T2DM (years): mean (sd)	12.3 (6.9)	12.4 (7.1)	12.3 (7.0)
HbA1c (%): mean (sd)	8.3 (0.85)	8.5 (0.96)	8.4 (0.91)
FPG (mmol/L): mean (sd)	7.3 (2.6) N=135	7.5 (2.6) N=119	7.4 (2.6) N=253
Daily insulin (U/kg): mean (sd)	0.51 (0.28)	0.50 (0.24)	0.51 (0.26)
Oral anti-diabetic medication: n(%)			
Metformin only	91 (66.4)	91 (74.6)	182 (70.3)
Metformin + pioglitazone	23 (16.8)	8 (6.6)	31 (12)
Pioglitazone	2 (1.5)	6 (4.9)	8 (3.1)
No oral agent	21 (15.3)	17 (13.9)	38 (14.7)

The mean change from baseline in HbA1c is given in Figure 1.

**Figure 1: Mean change from baseline in HbA1c.**

The change was statistically significant.

Subjects were stratified based on baseline HbA1c ( $\leq 8\%$  and  $> 8\%$ ). The changes in  $> 8\%$  subjects were greater with exenatide treatment.

In relation to the secondary efficacy endpoints the evaluator contends that no adjustments were made regarding multiplicity issues. In view of this, the evaluator recommends that the results of the secondary efficacy outcomes be discounted.

Study IOPB did not contribute to efficacy as it did not address the indication sought.

## Safety

Two studies are discussed: Studies GWCO and IOPB.

The evaluator states that Study IOPB did not provide evidence of efficacy; and safety data are of "marginal" value as only 2 subjects were relevant in relation to the combination sought.

Overall, the results obtained with exenatide and insulin in GWCO is "consistent with currently approved PI".

## Overall conclusions of the evaluator

The evaluator mentions that data to support the use of exenatide with insulin glargine (without OAM) is insufficient based on Study GWCO. 14.7% of those in Study GWCO had insulin glargine only with exenatide or placebo added to their treatment.

The evaluator recommends approval as follows:

*Exenatide is indicated as adjunctive therapy to improve glycaemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, or a*



*combination of metformin and a sulfonylurea, or a combination of metformin and a basal insulin, but are not achieving adequate glycaemic control.*

The evaluator recommends rejection of concomitant use with TZDs because,

- the use of a TZD in Study GWCO is uncontrolled, so its role in any efficacy outcome cannot be discerned; and
- particularly in the absence of metformin, the number of relevant cases is insufficient.

### **Risk management plan**

The RMP evaluation is attached. Some PI and CMI amendments are proposed.

Overall, the evaluator recommends that the RMP is “supportive to the application”.

### **Risk-benefit analysis**

#### **Delegate considerations**

Exenatide in combination with TZDs was rejected by the TGA in February 2012, based essentially on insufficient safety data. This application was considered by ACPM at the 2011 December meeting; the Committee recommended rejection (Res 9609).

The current submission also includes a small data set (n=25) who were given pioglitazone in Study GWCO. The delegate agrees with the evaluator that the data are inadequate to establish efficacy or safety of combination use (TZDs and insulin) and recommend rejection.

#### **Questions to the Committee:**

1. Is the evidence of efficacy seen in the figure on page 3 compelling, considering that there was a significant placebo effect? Should this figure be included in the PI?
2. Is this (evidence of efficacy) likely to be seen in the “real world” situation?
3. There has been no comparative study versus basal bolus regimen. Thus, when there is secondary failure there is a need to cease exenatide and commence basal bolus insulin therapy. Should this be included in the PI?

#### **Proposed action**

In relation to combined use with basal insulin, the delegate agrees with the evaluator and recommends that Exenatide is indicated as adjunctive therapy to improve glycaemic control in patients with T2DM who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea, or a combination of metformin and a basal insulin, but are not achieving adequate glycaemic control.

The Committee’s advice is sought.

#### **Response from sponsor**

Eli Lilly and Company (Lilly) acknowledges receipt of the Delegate’s overview which includes the recommendation of approval of the application with an amended indication. Lilly wishes to thank the TGA for this opportunity to provide comments.

#### ***Combination use with insulin: Approval status in the US and EU***

The submission in the US included Study GWCO and was approved on 19 October 2011.

The label is published on the FDA website.

The approved indication is:

*“Byetta is a glucagon like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus.”*

The label describes the results from Study GWCO:

*“Add on to insulin glargine with or without metformin and/or thiazolidinedione.”*

The submission in the EU consisted of Studies GWCO and IOPB and was approved on 19 March 2012. Information from Studies GWCO and IOPB are provided in the label. The approved indication is:

*“Byetta is also indicated as adjunctive therapy to basal insulin with or without metformin and/or pioglitazone in adults who have not achieved adequate glycaemic control with these agents.”*

The label is published on the European Commission website.

### **Study GWCO secondary endpoints**

The evaluator comments that since no adjustments were made regarding multiplicity issues the results of the secondary efficacy outcomes should be discounted.

Lilly acknowledges the evaluator’s comment on the lack of multiplicity adjustment for the secondary endpoints, however, the summaries of the secondary variables provide valuable clinical information to potential prescribers of exenatide in combination with insulin.

Healthcare providers and patients are concerned about weight gain as a result of insulin use; therefore, this information is useful to convey. A disadvantage of current insulin therapy is that intensive glucose lowering is almost always accompanied by weight gain, which may confound detection of macrovascular benefit. With exenatide, improved glycaemic control is achieved without weight gain (even when used in combination with long acting insulin) and with added benefits of modest improvements in blood pressure and lipid profiles. Maintenance of body weight (or for subjects who are overweight or obese, modest weight loss), especially in subjects receiving insulin therapy, may further reduce attendant long term risks of diabetes.

A physician may benefit from considering the effects of exenatide on reducing post breakfast and post dinner glucose excursions. These are the main secondary efficacy endpoints of Study GWCO, which was purposely designed to evaluate the complementary effects of basal insulin and exenatide on fasting and postprandial glucose (PPG), respectively. All patients in the Intetnt to Treat (ITT) population (N=259) assessed self monitored blood glucose (SMBG) at study midpoint and endpoint. The data demonstrated significant differences between the exenatide and placebo treated patients at 6 of the 7 time points, showing significant reductions in blood glucose excursions after the morning and evening meals when exenatide was administered.

Lilly believes these data are appropriate for inclusion in the exenatide label as they demonstrate the robustness of the exenatide mechanism of action (for example, glucose dependent insulin secretion, glucagon suppression, and slowing of gastric emptying) and its effects on PPG. The PPG effects of a diabetes product are used by prescribing physicians both in selecting therapies, and as a clinical target for improving glycaemic control. The American Diabetes Association and the European Association for the Study of Diabetes (ADA and EASD) have both issued guidelines for treatment that include recommendations for PPG control. The proportional contribution of PPG to overall hyperglycaemia increases



as patients near commonly utilised HbA1c targets, making the understanding of PPG effects a useful element of the decision making process.<sup>10</sup>

To address the evaluator's concerns regarding multiplicity adjustment with a large number of secondary endpoints, the company is proposing to limit the number of included variables in the PI to only those of highest clinical interest to healthcare providers and patients: weight, SMBG, FSG and will delete the endpoints of SBP, DBP and HR. Lilly proposes to amend Table 4 of the PI to include headings to clearly indicate the primary and secondary endpoints. Lastly, Lilly proposes to delete the *p* values from Table 4 of the PI for the secondary clinical efficacy variables, and will only provide the observed changes in each treatment group and the 95% confidence intervals for the observed changes.

### **Study IOPB relevant patients**

The evaluator indicates that only two patients were on the therapy described by the proposed indication.

This is not correct.

In Study IOPB, 7 subjects out of 339 (2%) were on combination therapy of metformin plus an sulphonylurea (SU) plus a TZD; 209 (62%) were on an SU plus metformin; 32 (9%) were on a TZD plus metformin; 1 (0.3%) was on an SU plus a TZD; 87 (26%) were on metformin alone; 1 (0.3%) was on an SU alone; and no subjects were on a TZD alone.

### **Indication**

The evaluator proposes to reject the use of TZD with insulins and Byetta and proposes the following amended indication:

“Exenatide is indicated as adjunctive therapy to improve glycaemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulphonylurea, or a combination of metformin and a sulphonylurea, or a combination of metformin and a basal insulin.”

Lilly agrees with this proposal.

### **Evidence of efficacy and Figure 3**

In Study GWCO, 29% of placebo treated subjects achieved target HbA1c <7% at study endpoint. Part of the improvement in glycaemic control in the placebo subjects can be attributed to study effect. In addition, investigators were requested to titrate insulin glargine to a target value for fasting plasma glucose concentrations of 5.6 mmol/L.<sup>11</sup> As expected, HbA1c concentrations decreased in both groups. However, despite continued optimisation of insulin dose in the placebo treated patients, the reduction in HbA1c was ~0.7% greater in subjects treated with exenatide than in the placebo treated subjects.

Lilly considers that the evidence of efficacy of exenatide versus titrated insulin alone is compelling and that Figure 3 could be included in the PI to convey the comparative efficacy profiles over time to healthcare providers and patients.

<sup>10</sup> Balkau B, *et al.* (2002) Frequency of the WHO metabolic syndrome in European cohorts, and an alternative definition of an insulin resistance syndrome. *Diabetes Metab.* 28: 364-376; Gerich JE. (2003) Clinical significance, pathogenesis, and management of postprandial hyperglycemia. *Arch Intern Med.* 163: 1306-16; Monnier L, *et al.* (2003) Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). *Diabetes Care* 26: 881-885.

<sup>11</sup> Riddle MC, *et al.* (2003) The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* 26: 3080-3086.

***Is this (evidence of efficacy) likely to be seen in the “real world” situation?***

Lilly is providing the literature review as discussed in the clinical overview, while the Committee is considering the Delegate’s question:

Although use of exenatide in combination with basal insulin has not received regulatory approval in any geography, (at the timing of writing this overview) numerous clinicians have explored the therapeutic potential of this combined therapy by applying it in patient care (see literature review).

Recently, Nayak and colleagues<sup>12</sup> and Thong and colleagues<sup>13</sup> have reported results of audits conducted in the United Kingdom. The larger of the observational studies was the report from the Association of British Clinical Diabetologists (ABCD).<sup>14</sup> A total of 6717 patients with diabetes were included in the audit with 4857 patients having baseline and follow up treatment. Most of the patients were on background OAD therapy (SUs, metformin, TZDs). More than 25% of the audited patients (n=1921) were taking exenatide plus insulin therapy. Among the exenatide plus insulin treated patients, approximately two thirds (n=1257) had added exenatide to insulin (similar to the design of Study GWCO) whereas the remaining one third (n=664) of patients had added insulin to exenatide therapy (similar to design of Study IOPB). The patients who had added exenatide to insulin were taking mean 120 U/day of insulin at exenatide initiation (higher than the dose in Study GWCO) and this dose was decreased to 78 U/day at the end of follow up. Furthermore, 34% of patients who continued exenatide plus insulin had an HbA1c reduction of  $\geq 1.0\%$  and a mean weight loss of 6 kg. This large study generally is concordant with the observations from Study GWCO and supports the concept that exenatide use (added to OAD therapies) with insulin has favourable glycaemic and weight effects, and perhaps insulin dose reductions.

In addition, Nayak and colleagues reported on the effects of adding exenatide to insulin in 160 patients also treated with metformin. This study had an obese cohort (body mass index [BMI]  $>40$  kg/m<sup>2</sup>). The purpose of the study was to determine whether exenatide use would be associated with insulin sparing effects and a corresponding reduction in weight. Mean weight loss over 6 months was  $>10$  kg and insulin doses were decreased from a mean of 144 U/day to 51 U/day. There was, however, no significant change in HbA1c. Nonetheless, these data support the efficacy of exenatide even when added to large doses of insulin in obese subjects.

Tzefos and Olin<sup>15</sup> reviewed the literature on this topic and reported on 10 studies of combined exenatide and insulin use that included approximately 700 patients. These studies varied in design: prospective versus retrospective; efficacy and/or safety data collection; basal insulin, bolus insulin, or basal plus bolus insulin users; order of combining exenatide and insulin use. Overall, the efficacy results of these studies showed minor to no effect of combined exenatide and insulin treatment on HbA1c. In contrast, most subjects demonstrated statistically significant weight loss. Total insulin doses tended to decrease when exenatide was added to the

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<sup>12</sup> Nayak UA, et al. (2010) Exenatide therapy in insulin-treated type 2 diabetes and obesity. *QJM* 103: 687-694.

<sup>13</sup> Thong KY, et al. (2011) Safety, efficacy and tolerability of exenatide in combination with insulin in the Association of British Clinical Diabetologists nationwide exenatide audit. *Diabetes Obes Metab.* 13: 703-710.

<sup>14</sup> Thong KY, et al. (2011) Safety, efficacy and tolerability of exenatide in combination with insulin in the Association of British Clinical Diabetologists nationwide exenatide audit. *Diabetes Obes Metab.* 13: 703-710.

<sup>15</sup> Tzefos M, Olin JL. (2010) Glucagon-like peptide-1 analog and insulin combination therapy in the management of adults with type 2 diabetes mellitus. *Ann Pharmacother.* 44: 1294-1300.

treatment regimen but these changes were largely attributable to removal or reduction of bolus insulin doses without substantive changes in basal doses. These studies found safety and tolerability with combined exenatide and insulin treatment similar to that of existing indications for exenatide plus OAD(s). Specifically, the most frequently noted events were gastrointestinal in nature, some of which led to withdrawal from the studies. Mild hypoglycaemic episodes were reported as well as a case of severe hypoglycaemia.

In 2009, the ABCD determined that the benefit of using exenatide in combination with insulin outweighed the potential for worsening of glycaemic control if insulin were stopped with initiation of exenatide, particularly in obese patients with marginal glycaemic control.<sup>16</sup> **Consequently, the Association of British Clinical Diabetologists made the following recommendation for use of exenatide by specialist diabetologists:**

***Possible role in combination with insulin in carefully controlled situations especially where insulin sparing and weight loss could benefit comorbidity, for example, sleep apnoea. Reduction in insulin dose of 20-50% on initiation of exenatide.***

***When there is secondary failure, there is a need to cease exenatide and commence basal bolus insulin therapy. Should this be indicated in the PI?***

It is not common practice in a PI to provide recommendations for the next therapy. Currently basal bolus insulin therapy is the likely next step for a patient not achieving sufficient glucose control using basal insulin and exenatide; however, this may change with the introduction of new anti diabetes agents. It is more appropriate to discuss treatment steps within treatment guidelines.

The PI has been amended as recommended in the RMP evaluation report to include the following statement:

*“The concurrent use of exenatide with prandial insulin has not been studied and cannot be recommended.”*

This may address the Delegate’s comment if it concerns the fact that no information is currently available on the use of exenatide and bolus insulin.

### **Advisory Committee Considerations**

The Advisory Committee on Prescription Medicines (ACPM), taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered these products to have an overall positive benefit-risk profile for the following indication:

*Exenatide is indicated as adjunctive therapy to improve glycaemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea, or a combination of metformin and a basal insulin.*

The ACPM also agreed with the delegate that there was insufficient evidence to support the use of exenatide with TZD with insulin.

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

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<sup>16</sup> Edwards CMB, Winocour PH. (2009) ABCD position statement on incretin mimetics and DPP-4 inhibitors – 2009. *Pract Diab Int*. 26: 191-194.

*- a statement in the Dosage and Administration section of the CMI to clarify the use of the term "separately" as the intent is to advise on the use of separate administration sites and not dosage times.*

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

### **Outcome**

Based on a review of quality, safety and efficacy, TGA approved the registration of Byetta (exenatide) 5 µg/20 µl and 10 µg/40 µl solution for injection. The improved indication reads as follows:

*Exenatide is indicated as adjunctive therapy to improve glycaemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea, or a combination of metformin and a basal insulin, but are not achieving adequate glycaemic control.*

### **Specific conditions of registration applying to these therapeutic goods:**

1. The implementation in Australia of the Byetta (exenatide) (EU RMP version 16 (Revision 15; data lock point 31 March 2010) with the Australian specific Annex to the RMP Revision 15\_v1.0), included with the submission PM 2011-01931-3-5, and any subsequent revisions, as agreed with the TGA and its OPR.

## **Attachment 1. Product Information**

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

## **Attachment 2. Extract from the Clinical Evaluation Report**

## **Therapeutic Goods Administration**

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