Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for exenatide

Proprietary Product Name: Byetta

Sponsor: Eli Lilly Australia Pty Ltd[1]

First round CER: November 2011

Second round CER: May 2012

TGA Health Safety Regulation

[1] 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>.

About the Extract from the Clinical Evaluation Report

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

Contents

List of abbreviations

Abbreviation	Meaning
ADA	American Diabetes Association
AE	Adverse event
AGI	Alpha-glucosidase inhibitor
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BG	Blood glucose
BUN	Blood urea nitrogen
CER	Clinical evaluation report
CRF	Case report form
CRP	C-reactive protein
CSR	Clinical study report
DBP	Diastolic blood pressure
DPP-4	Dipeptidyl peptidase 4
FAS	Full analysis set
FPG	Fasting plasma glucose
IVRS	Interactive voice response system
LDL	Low-density lipoprotein
HDL	High-density lipoprotein
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
MDRD	Modification of diet in renal disease
MI	Myocardial infarction
MMRM	Mixed model repeated measures
NS	Not (statistically) significant

Abbreviation	Meaning
NYHA	New York Heart Association
OAM	Oral anti-hyperglycaemic medication
SAE	Serious AE
SBP	Systolic blood pressure
SMBG	Self-monitored blood glucose
Study GWCO	Study H8O-US-GWCO
Study IOPB	Study F3Z-US-IOPB
TG	Triglycerides
TZD	Thiazolidinedione
T2DM	Type 2 diabetes mellitus
ULN	Upper limit of normal

1. Clinical rationale

It is proposed to extend use of the established drug exenatide to T2DM patients who are already being treated with insulin (and possibly metformin and/or a thiazolidinedione).

When target glycaemic control cannot be achieved and maintained with 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 hypothesized that adding exenatide to insulin would improve overall glycaemic control, as measured by HbA1c.

The application appears to be consistent with the therapeutic principles outlined in NHMRC (2009).

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The submission contained the following clinical information:

- 1 pivotal efficacy/safety study
- 1 other efficacy/safety study

2.2. Paediatric data

The submission did not include paediatric data.

2.3. Good clinical practice

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

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

None submitted.

3.2. Summary of pharmacokinetics

Not applicable.

3.3. Evaluator's overall conclusions on pharmacokinetics

Not applicable.

4. Pharmacodynamics

4.1. Studies providing pharmacodynamic data

None submitted.

4.2. Summary of pharmacodynamics

Not applicable.

4.3. Evaluator's overall conclusions on pharmacodynamics

Not applicable.

5. Dosage selection for the pivotal studies

Byetta was given at the standard approved dosage.

6. Clinical efficacy

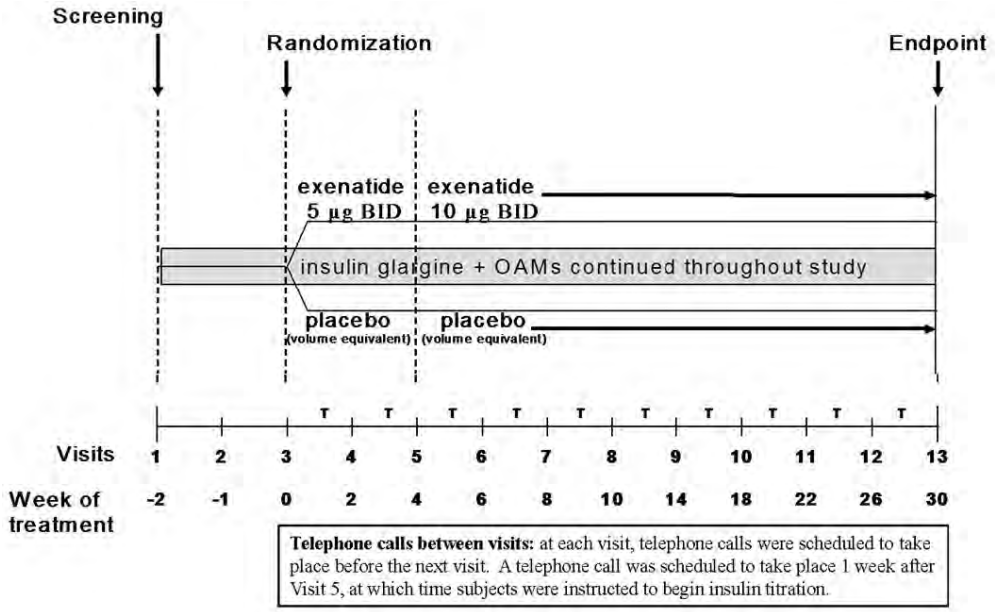
6.1. Pivotal efficacy study: GWCO

6.1.1. Study design, objectives, locations and dates

6.1.1.1. Design

This was a multicentre, randomised, parallel-group, double-blind, placebo-controlled study. The study compared exenatide with placebo in subjects with T2DM who had not met glycaemic targets with insulin glargine with or without metformin, pioglitazone, or both. It was designed to allow comparison of exenatide with placebo regarding when added to existing insulin therapy, with or without OAMs, in patients undergoing insulin dose titration to achieve optimal fasting glucose. The overall study design is outlined in Figure 1.

Figure 1: Study GWCO: overall design.



6.1.1.1.1. Continuous glucose monitoring addendum

Continuous glucose monitoring (CGM) was conducted to evaluate glucose variability in a subgroup of subjects at selected US sites. Twenty-nine subjects were enrolled in the CGM addendum. These subjects were asked to perform CGM on 3 consecutive days between Visit 2 (Week -1) and Visit 3 (Week 0; for a total of 72 hours). These subjects performed another CGM on 3 consecutive days (for a total of 72 hours) within 2 weeks prior to Visit 13 (Week 30). Subjects were asked to perform their 7-point SMBG profiles in the main study on the same days as the CGM and to continue these measurements until the CGM period was complete. Twenty-three subjects (exenatide BID: n=11; placebo: n=12) completed the CGM addendum (that is, 23/29 subjects had evaluable data). The results do not appear to be relevant to the present application.

6.1.1.2. Objectives

6.1.1.2.1. Primary

To test the hypothesis that twice daily exenatide plus titration of insulin is superior to placebo plus titration of insulin on glycaemic control, as measured by change in HbA1c from baseline to Week 30, with or without OAMs, in adult subjects with T2DM whose disease was sub-optimally controlled (HbA1c ≥7.1% and ≤10.5%).

6.1.1.2.2. Secondary

To compare the efficacy and safety of exenatide to placebo when added to insulin glargine, with or without OAMs, with respect to:

- percentage of subjects with HbA1c ≤7.0% and HbA1c ≤6.5% at Week 30
- change from baseline in FPG
- 7-point SMBG profiles and mean blood glucose measurements based on 7-point SMBG profiles
- change from baseline in fasting total cholesterol, LDL cholesterol, HDL cholesterol, and TG
- change from baseline in body weight
- change from baseline in waist circumference
- change from baseline in insulin dose
- change from baseline in seated systolic and diastolic blood pressure
- safety, as measured by:
  - self-reported hypoglycaemic episodes
  - treatment-emergent AEs

6.1.1.3. Locations and dates

Subjects were enrolled at 59 centres (all specialist clinics) in 5 countries (2 Greece, 3 Israel, 3 Mexico, 5 UK and 46 USA). The study initiation date was 29 October 2008 and completion date 4 January 2010.

6.1.2. Inclusion and exclusion criteria

Subjects diagnosed with T2DM, at least 18 years old, with a stable body weight for ≥3 months prior to study entry and with a BMI ≤45 kg/m^2. HbA1c was required to be between 7.1% and 10.5% and subjects were required to be taking insulin glargine ≥20 U/day alone or in combination with an approved OAM regimen (metformin and/or pioglitazone).

Full inclusion and exclusion criteria are listed below.

Inclusion criteria:

- Have T2DM (as defined by WHO classification)
- Age ≥18 years
- Taking basal insulin glargine at a dose of ≥20 units/day for ≥3 months prior to Visit 1.
- Receiving glargine alone or in combination with one of the following OAM regimens for the 3 months prior to Visit 1:
- metformin at a stable dose for 6 weeks prior to Visit 1 (minimum 500 mg/day)
- pioglitazone at a stable dose for 6 weeks prior to Visit 1 (minimum 15 mg/day)
- a combination of metformin and a pioglitazone at a stable dose for 6 weeks prior to Visit 1 (minimum as in (a) and (b))
- AND do not meet the first exclusion criterion below
- HbA1c ≥7.1% and ≤10.5%.
- BMI ≤45 kg/m^2.
- Show no evidence of cardiovascular disease as determined by a normal ECG.
- Stable body weight (not varying by >5% for at least 3 months prior to screening).
- Liver enzyme tests (ALT; AST) are ≤ 1.5 times the upper limit of the reference range.
- Serum creatinine ≤1.4 mg/dL (female) or ≤1.5 mg/dL (male).

Exclusion criteria:

- Currently taking a dose or combination of OAM that is not allowed with concurrent use of insulin glargine per local product label.
- Have taken any glucose-lowering medications other than insulin glargine, metformin or pioglitazone in the 3 months prior to Visit 1 for more than 1 week or within 1 month of screening.
- Have had >1 episode of major hypoglycaemia [defined], within 6 months prior to Visit 1.
- Have used a drug for weight loss (for example, prescription drugs such as orlistat, sibutramine, phenylpropanolamine, or similar over-the-counter medications) within 3 months prior to Visit 1 for > 1 week or within 1 month of screening.
- Currently on a supervised weight-loss program or have been on a weight-loss program within 3 months prior to Visit 1.
- Have had a blood transfusion or severe blood loss within 3 months prior to Visit 1 or have known haemoglobinopathy, haemolytic anaemia, or sickle cell anaemia, or any other condition known to interfere with the HbA1c methodology.
- Receiving chronic (lasting > 2 weeks) systemic glucocorticoid therapy (excluding topical, intraocular, and inhaled preparations) or have received such therapy within the 8 weeks immediately preceding Visit 1.
- If on metformin and have contraindication to metformin use, including known metabolic or lactic acidosis, or any condition associated with hypoperfusion, hypoxaemia, dehydration, or sepsis.
- If on metformin, have had a radiologic contrast study performed within 48 hours prior to Visit 1.

- If on pioglitazone, have a contraindication to pioglitazone, including NYHA Class II-IV congestive heart failure, or are at a dose of pioglitazone that is contraindicated for use with insulin in that country.
- History of pancreatitis.
- Routine exclusions relating to reproductive potential in women, various serious diseases, drug abuse, drug allergies, administrative matters, etc.

6.1.3. Study treatments

Subjects self-administered their study drug (exenatide or placebo) within 60 minutes prior to breakfast and dinner, and continued to follow their prestudy OAM regimens. Subjects recorded SMBG values, insulin doses, hypoglycemic episodes, and concomitant medications in study diaries, and were in contact with study investigators by phone or in person every week during the first 10 weeks following randomization, and then every 2 weeks for the last 20 weeks of the study, as outlined in the study protocol. Based on laboratory measures at Visit 1 (Week -2), subjects with an HbA1c ≤8.0% decreased their prestudy dose of insulin glargine by 20% and subjects with an HbA1c ≥8.1% maintained their current dose of insulin glargine at Visit 3 (Week 0). One week after Visit 5 (Week 4), the investigator contacted subjects and instructed them to begin titrating their insulin glargine dose (based on the algorithm described below).

6.1.3.1. Insulin titration

In subjects with an HbA1c ≤8.0% at Visit 1 (Week -2), insulin doses were reduced by 20% at Visit 3 (Week 0 - start of exenatide placebo treatment), and then at the telephone call that occurred 1 week after Visit 5 (Week 4), insulin doses were titrated toward predefined fasting glucose targets, according to the dose titration algorithm shown in Table 1.

Table 1: Insulin dose titration algorithm.

FPG (mg/dL)	Dose change (U)
< 56[1]	-4
56 to 72[1]	-2
73 to 99[2]	0
100 to 119[2]	+2
120 to 139[2]	+4
140 to 179[2]	+6
≥ 180[2]	+8

[1] Value for at least 1 FPG measurement since the last assessment.
[2] Based on the average of fasting plasma glucose measurements during the last 3 to 7 days. The increase in the total daily dose should not exceed 10 units per day or 10% of the current total daily dose, whichever is greater.

Subjects with a baseline HbA1c ≥8.1% did not change their insulin dose at Visit 3 (Week 0) and began titration as instructed at the telephone call that occurred 1 week after Visit 5 (Week 4), according to the dose titration algorithm. Investigators were instructed to maintain all subjects' insulin doses during the first 5 weeks following randomisation unless changes were deemed medically necessary. Investigators were to adjust insulin doses at least weekly, as applicable, from Week 5 through Week 10, and then every 2 weeks for the remainder of the study. A 1-time dose adjustment was not to exceed 10 U or 10% of the total daily dose, whichever was greater.

6.1.4. Efficacy variables and outcomes

6.1.4.1. Primary

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

6.1.4.2. Secondary

The percentage of subjects with A1C ≤ 7.0% and A1C ≤ 6.5% will be analyzed using the categorical repeated measures approach. The following variables will be analyzed by the same MMRM model as used for the primary analysis:

- Change in fasting glucose.
- Change in glucose value before and after each meal and at bedtime from self-monitored glucose.
- Change in SBP and DBP.
- Change in fasting total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides.
- Change in weight
- Change in waist circumference
- Change in insulin dose (24-hour total IU and total units/kg body weight).

6.1.5. Randomisation and blinding methods

At Visit 3 (Week 0), all eligible subjects were randomly assigned in a 1:1 ratio to 1 of the 2 treatment groups using an IVRS. To achieve between-group comparability for baseline HbA1c within each study site, allocation was stratified by screening HbA1c (≤8.0%, ≥8.1%) at the site level, and randomisation was carried out using permutation blocks.

6.1.6. Analysis populations

Datasets were defined as shown below.

Table 2: Datasets used in Study GWCO.

Dataset name	Description
All Randomised	All subjects assigned to a randomized medication, regardless of whether a study drug dose was received.
Full Analysis Set†	All data from all randomised subjects receiving at least 1 dose of study drug.
Full analysis set, Addendum Subject Population	Subjects enrolled in the Continuous Glucose Monitoring Addendum with nonmissing baseline value and at least 1 nonmissing postbaseline value of the response variable.

† The precise definition of this set is unclear:
Protocol, section 8.2.1: See section 7.1.8 below.
CSR, page 89: "Efficacy and safety analyses were conducted on the full analysis set (FAS), which followed a slightly modified intent-to-treat (ITT) principle. This set included all available data from all randomized subjects who received at least 1 dose of the study drug according to the treatment the subjects actually received."
CSR, page 95 (among changes made prior to database lock): "The definition for the FAS dataset was updated to include all data from all randomized subjects receiving at least 1 dose of randomized study drug from the previous definition of all data from all randomized subjects receiving at least 1 dose of study drug *according to the treatment the subjects actually received.*

Efficacy and safety analyses were conducted on the full analysis set.

Except for the LOCF analysis, no adjustments for missing data were performed.

6.1.7. Sample size

Approximately 260 subjects with T2DM taking basal insulin glargine with or without metformin and/or pioglitazone will be randomized to either placebo or exenatide. Assuming a 20% dropout rate, approximately 104 subjects per group will complete the study. With an anticipated mean difference of 0.5% in A1C between the two treatment groups, and a standard deviation of 1.1% [estimated from previous studies], 104 completers per group will provide

approximately 90% power to detect a significant difference in A1C between the two treatment groups at 30 weeks at a 2-sided alpha level of 0.05 using a 2-sample t-test.

6.1.8. Statistical methods

Efficacy and safety analyses will be conducted on the full analysis set (FAS) following a slightly modified intent-to-treat principle. This set includes all data from all randomized subjects receiving at least one dose of the study drug according to the treatment the subjects actually received.

Investigators with fewer than 2 randomized subjects per treatment group will be pooled for statistical analysis purposes.

All tests of treatment effects will be conducted at a two-sided alpha level of 0.05, unless otherwise stated. As there is only one primary analysis, no adjustment for multiplicities will be made.

For any variable, baseline value is defined as the last nonmissing value prior to or at randomization. The mixed model will be used for variables with repeated measurements (MMRM) to account for the missing values.2 This model produces an unbiased estimate of the treatment effect when missing values are random.

6.1.9. Major protocol violations/deviations

Significant violations were unlikely to affect the overall conclusions from the study.

6.1.10. Baseline data

6.1.10.1. Demographic data

Demographic data is shown in Table 3.

Table 3: Demographic data.

	Exen N=137	Pbo N=122	Total N=259
Age: mean (sd)†	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)

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

6.1.10.2. Baseline data relating to disease state and treatment

Baseline data relating to disease state and treatment is shown in Table 4.

Table 4: Baseline data relating to disease state and treatment.

	Exen N=137	Pbo N=122	Total 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)

[2] The ANCOVA MMRM model used included visit, treatment group, pooled investigator site, and treatment group-by-visit interaction as factors, and baseline value of the dependent variable as a covariate.

6.1.11. Results for the primary efficacy outcome

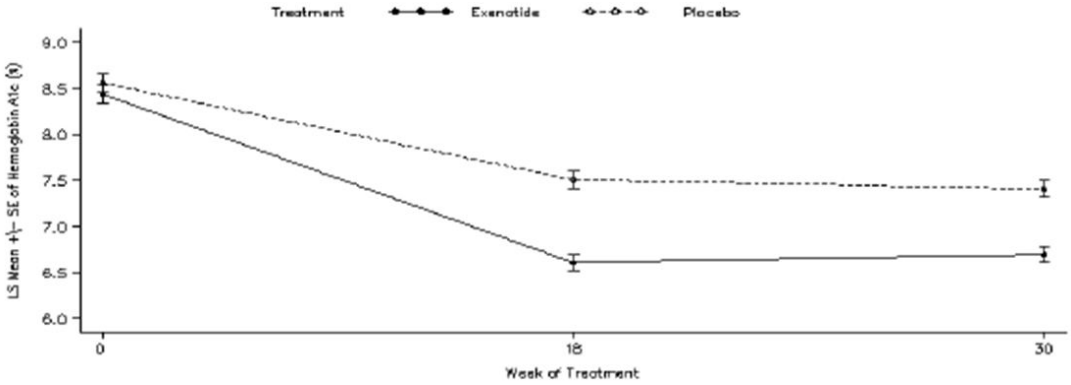
Results for the primary efficacy outcome are shown in Table 5.

Table 5: Primary efficacy outcome.

HbA1c (%)	Exen N=137	Pbo N=122
All patients with observations recorded		
n		
Baseline: LS Mean (SE)	8.33 (0.08)	8.54 (0.09)
n	115	105
Week 18: LS Mean (SE)	6.61 (0.09)	7.51 (0.09)
n	115	103
Week 30: LS Mean (SE)	6.70 (0.09)	7.41 (0.09)
n	112	100
LS Mean change from baseline (SE)	-1.71 (0.09)	-1.00 (0.09)
Difference from control		
Mean	-0.71	
95% CI	(-0.95, -0.47)	
P-Value	< 0.001	

The mean change from baseline over time during the 30-week treatment period is shown in Figure 2.

Figure 2: Mean change from baseline over time during the 30-week treatment period.



6.1.11.1.1. Subgroup analysis

Results of this analysis are of particular interest because randomisation was stratified by baseline HbA1c:

> *"For subjects with a baseline HbA1c ≤8.0%, baseline mean HbA1c was 7.56% for the exenatide BID group (n=56) and 7.48% for the placebo group (n=38). By Week 30, mean HbA1c for subjects with a baseline HbA1c ≤8.0% decreased to 6.51% for the exenatide BID group (n=50; change of -1.04%) and to 6.97% for the placebo group (n=33; change of -0.49%). For subjects with a baseline HbA1c >8.0%, mean HbA1c at baseline was 8.93% for the exenatide BID group (n=75) and 9.06% for the placebo group (n=75). By Week 30, mean HbA1c for subjects with a baseline HbA1c >8.0% decreased to 6.92% for the exenatide BID group (n=62; change of -1.98%) and to 7.76% for the placebo group (n=67; change of -1.31%)."*

6.1.12. Results for other efficacy outcomes

The *CSR* states:

> *"The secondary analysis of highest priority was the treatment difference for change in weight from baseline. This measure was tested in a gatekeeping manner with the primary*

objective, where, if the primary objective was met, the objective of next priority would be the test of treatment differences for change in weight from baseline. Otherwise, no additional adjustments for multiplicity were made."

However, the *Protocol* made no mention of any proposed gatekeeping procedure.

In view of the *Protocol's* silence on this matter, the clinical evaluator believes the gatekeeping aspect of the analysis is invalid. All the results from secondary efficacy outcomes must be recognised as resulting from multiple comparisons, and their significance discounted accordingly.

The results of the main planned secondary efficacy analyses are shown in Tables 6-8.

Table 6: Achievement of HbA1c targets (Study GWCO).

Variable	Exen N=137	Pbo N=122	p-value†
Number (%) of patients achieving HbA1c ≤7 at endpoint	74/127 (58.3)	33/106 (31.1)	<0.001
Number (%) of patients achieving HbA1c ≤6.5 at endpoint	55/131 (42.0)	15/113 (13.3)	<0.001

† Calculated using Cochran-Mantel-Haenszel test, adjusting for HbA1c stratum.

Table 7: Self-monitored blood glucose (mmol/L) (Study GWCO).

	Exen N=108		Pbo N=89		
Time of Measurement	Baseline LS Mean (SE)	LS Mean (SE) Change from Baseline to Week 30	Baseline LS Mean (SE)	LS Mean (SE) Change from Baseline to Week 30	Between-Group p-value
Morning Preprandial	7.89 (0.2)	-1.58(0.1)	8.27 (0.2)	-1.48 (0.1)	.633
Morning Postprandial†	10.89 (0.2)	-3.56(0.2)	11.82 (0.2)	-1.72 (0.2)	<.001
Midday Preprandial	8.95 (0.2)	-2.23 (0.2)	9.77 (0.2)	-1.15 (0.2)	<.001
Midday Postprandial	11.35 (0.2)	-2.74 (0.2)	11.70 (0.2)	-1.38 (0.2)	<.001
Evening Preprandial	9.85 (0.2)	-2.25 (0.2)	9.99 (0.2)	-1.33 (0.2)	.004
Evening Postprandial	12.03 (0.3)	-3.87 (0.2)	11.86 (0.3)	-1.34 (0.3)	<.001
0300 hours	8.95 (0.2)	-2.27 (0.2)	9.20 (0.2)	-1.48 (0.2)	.005

† The *Protocol* stipulated that for SMBG measurements, a sample should be obtained "2 hours after" the meal (page 20), and also referred (page 43) to "2-hour postprandial glucose", but was not entirely specific about these terms. In view of the American Diabetes Association's advice (ADA 2008, at page S18) that "Postprandial glucose measurements should be made 1–2 h after the beginning of the meal", there is room for confusion here.

Table 8: Summary of other secondary efficacy results (Study GWCO).

Variable	LS Mean change from baseline		Estimated Treatment Difference (95% CI)
	Exen N=137	Pbo N=122	
Fasting serum glucose (mmol/L)	-1.28	-0.87	-0.41 (-0.99, 0.18) NS
Systolic blood pressure (mm Hg)	-2.7	1.7	-4.4 (-7.8, -1.0) p<0.05
Diastolic blood pressure (mm Hg)	-1.7	1.7	-3.4 (-5.2, -1.6) p<0.001
Total cholesterol (mmol/L)	-0.16	-0.02	-0.14 (-0.37, 0.08) NS
Body weight (kg)	-1.78	0.96	-2.74 (-3.74, -1.74) p<0.001
Waist circumference (cm)	-1.08	-0.25	-0.83 (-2.18, 0.52) NS
Daily insulin dose (U/kg)	0.15	0.20	-0.05 (-0.10, 0.00) NS

6.2. Evaluator's conclusions on clinical 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 which 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. See EMEA (2002), which advises (at page 7):

> *"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 (*Clinical Overview*, page 24) to a paper of Klonoff et al. (2008) 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 2 on exenatide.

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

7. Clinical safety

7.1. Studies providing evaluable safety data

The following studies provided evaluable safety data: GWCO; IOPB.

7.1.1. Pivotal efficacy study: GWCO

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

- General adverse events were assessed by routine inquiry at each visit.
- AEs of particular interest (hypoglycaemic events) were classified as follows:
  - Minor hypoglycaemic episodes — any time a subject experienced a sign or symptom associated with hypoglycaemia that was either self-treated by the subject or resolved on its own and had a concurrent finger stick BG <3.0 mmol/L (54 mg/dL).
  - Major hypoglycaemic episodes — any episode with symptoms consistent with hypoglycaemia that resulted in loss of consciousness or seizure that showed prompt recovery in response to administration of glucagon or glucose or documented hypoglycaemia (BG <3.0 mmol/L [54 mg/dL]) that required the assistance of another person because of severe impairment in consciousness or behaviour (whether or not symptoms of hypoglycaemia were detected by the subject).
  - Symptoms of hypoglycaemia — any reported hypoglycaemic episode that did not fit the definitions of major or minor hypoglycaemia (for example, hypoglycaemic episodes with related BG values missing were classified as symptoms of hypoglycaemia).
  - Non-nocturnal hypoglycaemia — any hypoglycaemic episode that occurred after breakfast and before bedtime.
  - Nocturnal hypoglycaemia — any hypoglycaemic episode that occurred after bedtime and before breakfast.
- No routine haematology safety testing was done. Routine biochemistry testing (creatinine, AST and ALT) was done at Visit 1 only.

7.1.2. Other study evaluable for safety only: IOPB

This was a study of T2DM patients aged 18-75 who were taking exenatide (at dosage 10 µg bd) and 1 or 2 OAMs for ≥3 months prior to the study, and had inadequate glycaemic control. The primary objective was to test the hypothesis that bedtime dosing of insulin lispro is noninferior to bedtime dosing of insulin glargine regarding glycaemic control, when added to existing therapy in these patients.

Study participants were recruited from 49 specialist centres in USA between November 2007 and December 2009. 339 patients were randomised to either lispro (171) or glargine (168) for 24 weeks, and 305 completed (154 lispro, 151 glargine).

Demographics and other important baseline characteristics of the study participants are summarised in Table 9.

Table 9: Demographics and baseline characteristics of study participants.

	Lispro N=171	Glargine N=168	Total N=339
Age: mean (sd)	56.5 (9.7)	56.2 (9.3)	56.4 (9.5)
Sex	76M, 95F	93M, 75F	169M, 170F
Weight (kg): mean (sd)	101.6 (19)	102.3 (20)	101.9 (19)
BMI: mean (sd)	34.9 (5.2)	34.8 (5.2)	34.8 (5.2)
Duration of T2DM (years): mean (sd)	9.5 (6.0)	10.3 (6.6)	9.9 (6.3)
HbA1c (%): mean (sd)	8.2 (0.79)	8.2 (0.80)	8.2 (0.79)
Oral anti-diabetic medication: n(%)			
Metformin only	40 (23.4)	47 (28.0)†	87 (25.7)
Metformin + sulfonylurea	105 (61.4)	104 (61.9)	209 (61.6)
Metformin + TZD	22 (12.9)	10 (5.9)†	32 (9.4)
Sulfonylurea only	0	1 (0.6)	1 (0.3)
Sulfonylurea + TZD	1 (0.6)	0	1 (0.3)
Metformin + sulfonylurea + TZD	2 (1.2)	5 (3.0)	7 (2.1)

† See below.

Only the 2 patient groups marked with a dagger in the table above comprise patients treated with the combination of drugs for which approval is now being sought. But even these patients are not members of the population to which the indication sought would apply: the proposed indication relates to patients who have exhibited inadequate glycaemic control while on glargine; the patients in Study IOPB were not on insulin before recruitment. Thus, in my opinion, Study IOPB provides no evidence of efficacy for the purposes of the present application, and the safety data it provides are of marginal value.

7.2. Pivotal studies that assessed safety as a primary outcome

None submitted.

7.3. Patient exposure

Patient exposures are shown in Tables 10-11.

Table 10: Exposure to exenatide and comparators in clinical studies included in this dossier.

Study type	Controlled studies		Uncontrolled studies	Total Exen
	Exen	Placebo	Exen	
• Pivotal	137	122	0	137
• Other			337	337
TOTAL	**137**	**122**	**337**	**474**

Table 11: Exposure to exenatide in clinical studies according to dose and duration.

Study type	Proposed dose				Higher dose			
	≥ 3 mo.	≥ 6 mo.	≥ 12 mo.	Any dur'n	≥ 3 mo.	≥ 6 mo.	≥ 12 mo.	Any dur'n
• Placebo-controlled		137		137				0
• Active-controlled				0				0
• Uncontrolled	337			337				0
TOTAL	**337**			**474**				**0**

7.4. Adverse events

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

7.4.1.1. Pivotal study: GWCO

Table 12 shows adverse events from Study GWCO. No case of pancreatitis was reported.

Table 12: Adverse events from Study GWCO.

SOC Preferred Term[1]	Exenatide N=137 n (%)	Placebo N=122 n (%)
Number of patients with any AE	109 (79.6)	86 (70.5)
Blood and lymphatic system	1 (0.7)	1 (0.8)
Cardiac disorders	6 (4.4)	6 (4.9)
Ear and labyrinth disorders	2 (1.5)	2 (1.6)
Endocrine disorders	1 (0.7)	0 (0.0)
Eye disorders	6 (4.4)	4 (3.3)
Gastrointestinal disorders	79 (57.7)	33 (27.0)
Abdominal distension	5 (3.6)	1 (0.8)
Abdominal pain	4 (2.9)	4 (3.3)
Abdominal pain upper	3 (2.2)	3 (2.5)
Constipation	14 (10.2)	2 (1.6)
Diarrhoea	25 (18.2)	10 (8.2)
Dyspepsia	9 (6.6)	2 (1.6)
Flatulence	3 (2.2)	1 (0.8)
GORD	3 (2.2)	1 (0.8)
Nausea	56 (40.9)	10 (8.2)
Toothache	4 (2.9)	4 (3.3)
Vomiting	25 (18.2)	5 (4.1)
General disorders and admin site	19 (13.9)	15 (12.3)
Asthenia	7 (5.1)	1 (0.8)
Chest pain	2 (1.5)	4 (3.3)
Fatigue	5 (3.6)	3 (2.5)
Oedema peripheral	2 (1.5)	4 (3.3)
Pain	3 (2.2)	1 (0.8)
Hepatobiliary disorders	0 (0.0)	1 (0.8)
Immune system disorders	2 (1.5)	1 (0.8)
Infections and infestations	35 (25.5)	42 (34.4)
Bronchitis	4 (2.9)	3 (2.5)
Influenza	2 (1.5)	4 (3.3)
Nasopharyngitis	8 (5.8)	6 (4.9)
Sinusitis	3 (2.2)	2 (1.6)
URTI	11 (8.0)	9 (7.4)
Injury, poisoning and procedural	17 (12.4)	10 (8.2)
Contusion	3 (2.2)	0 (0.0)
Joint sprain	3 (2.2)	1 (0.8)
Procedural pain	1 (0.7)	3 (2.5)
Investigations	2 (1.5)	3 (2.5)
Metabolism and nutrition	14 (10.2)	6 (4.9)
Anorexia	5 (3.6)	0 (0.0)
Appetite ↓	4 (2.9)	0 (0.0)
Musculoskeletal and connective tissue	26 (19.0)	15 (12.3)
Arthralgia	3 (2.2)	1 (0.8)
Back pain	9 (6.6)	2 (1.6)
Muscle spasms	1 (0.7)	3 (2.5)
Musculoskeletal pain	4 (2.9)	0 (0.0)
Myalgia	3 (2.2)	3 (2.5)
Pain in extremity	3 (2.2)	2 (1.6)
Neoplasms	1 (0.7)	1 (0.8)
Nervous system disorders	32 (23.4)	22 (18.0)
Dizziness	6 (4.4)	7 (5.7)
Headache	19 (13.9)	5 (4.1)
Hypoaesthesia	3 (2.2)	1 (0.8)
Tremor	2 (1.5)	3 (2.5)
Psychiatric disorders	2 (1.5)	4 (3.3)
Renal and urinary disorders	3 (2.2)	1 (0.8)
Reproductive system and breast	3 (2.2)	3 (2.5)
Respiratory, thoracic and mediastinal	18 (13.1)	15 (12.3)
Cough	7 (5.1)	7 (5.7)
Dyspnoea	3 (2.2)	0 (0.0)
Oropharyngeal pain	2 (1.5)	5 (4.1)
Skin and subcutaneous tissue	9 (6.6)	9 (7.4)
Pruritus	1 (0.7)	3 (2.5)
Surgical and medical procedures	4 (2.9)	2 (1.6)
Tooth extraction	3 (2.2)	1 (0.8)
Vascular disorders	3 (2.2)	5 (4.1)
Hypertension	3 (2.2)	4 (3.3)

[1] SOC totals are exhaustive, but for Preferred Terms only AEs occurring in > 2 patients in any group are shown. Multiple instances of the same AE in the same patient are counted only once. Different AEs in the same SOC in the same patient are counted only once in the SOC total.

7.4.1.2. Other study: IOPB

Table 13 shows adverse events from Study IOPB.

Table 13: Adverse events from Study IOPB.

SOC Preferred Term[1]	Lispro N=170 n (%)	Glargine N=167 n (%)
Number of patients with any AE	86 (50.6)	110 (65.9)
Cardiac disorders	3 (1.8)	2 (1.2)
Ear and labyrinth disorders	2 (1.2)	1 (0.6)
Endocrine disorders	1 (0.6)	0 (0.0)
Eye disorders	2 (1.2)	5 (3.0)
Gastrointestinal disorders	33 (19.4)	36 (21.6)
Abdominal discomfort	6 (3.5)	4 (2.4)
Diarrhoea	9 (5.3)	12 (7.2)
Dyspepsia	1 (0.6)	4 (2.4)
Nausea	12 (7.1)	10 (6.0)
Vomiting	6 (3.5)	8 (4.8)
General disorders and admin site	11 (6.5)	18 (10.8)
Fatigue	2 (1.2)	3 (1.8)
Pain	1 (0.6)	3 (1.8)
Pyrexia	1 (0.6)	5 (3.0)
Hepatobiliary disorders	3 (1.8)	1 (0.6)
Immune system disorders	1 (0.6)	2 (1.2)
Infections and infestations	49 (28.8)	55 (32.9)
Bronchitis	1 (0.6)	5 (3.0)
Gastroenteritis	3 (1.8)	2 (1.2)
Gastroenteritis viral	2 (1.2)	12 (7.2)
Influenza	4 (2.4)	3 (1.8)
Nasopharyngitis	11 (6.5)	9 (5.4)
Sinusitis	7 (4.1)	9 (5.4)
URTI	11 (6.5)	9 (5.4)
UTI	5 (2.9)	2 (1.2)
Injury, poisoning and procedural	10 (5.9)	14 (8.4)
Fall	0 (0.0)	4 (2.4)
Joint sprain	3 (1.8)	2 (1.2)
Procedural pain	3 (1.8)	2 (1.2)
Investigations	8 (4.7)	3 (1.8)
Weight ↑	3 (1.8)	0 (0.0)
Metabolism and nutrition	3 (1.8)	2 (1.2)
Musculoskeletal and connective tissue	19 (11.2)	27 (16.2)
Arthralgia	8 (4.7)	5 (3.0)
Back pain	3 (1.8)	3 (1.8)
Muscle spasms	3 (1.8)	1 (0.6)
Musculoskeletal pain	2 (1.2)	3 (1.8)
Myalgia	0 (0.0)	4 (2.4)
Pain in extremity	3 (1.8)	5 (3.0)
Tendonitis	0 (0.0)	3 (1.8)
Neoplasms	4 (2.4)	1 (0.6)
Nervous system disorders	18 (10.6)	19 (11.4)
Headache	11 (6.5)	14 (8.4)
Sinus headache	3 (1.8)	1 (0.6)
Psychiatric disorders	4 (2.4)	5 (3.0)
Stress	1 (0.6)	3 (1.8)
Renal and urinary disorders	2 (1.2)	1 (0.6)
Reproductive system and breast	1 (0.6)	4 (2.4)
Respiratory, thoracic and mediastinal	16 (9.4)	22 (13.2)
Cough	4 (2.4)	5 (3.0)
Nasal congestion	3 (1.8)	8 (4.8)
Oropharyngeal pain	3 (1.8)	7 (4.2)
Sinus congestion	6 (3.5)	1 (0.6)
Skin and subcutaneous tissue	8 (4.7)	5 (3.0)
Social circumstances	0 (0.0)	1 (0.6)
Surgical and medical procedures	4 (2.4)	6 (3.6)
Vascular disorders	1 (0.6)	2 (1.2)

[1] As for previous table.

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

7.4.2.1. Pivotal study: GWCO

AEs classified by trialists as possibly related to study drug are shown in Table 14.

Table 14: Treatment-related adverse events (Study GWCO).

Preferred Term[1]	Exenatide N=137 n (%)	Placebo N=122 n (%)
Number of patients with such AE	69 (50.4)	25 (20.5)
Nausea	47 (34.3)	9 (7.4)
Vomiting	21 (15.3)	2 (1.6)
Diarrhoea	15 (10.9)	3 (2.5)
Dyspepsia	7 (5.1)	2 (1.6)
Headache	9 (6.6)	0
Constipation	5 (3.6)	2 (1.6)
Abdominal distension	5 (3.6)	1 (0.8)
Fatigue	5 (3.6)	1 (0.8)
Anorexia	5 (3.6)	0
Abdominal pain	3 (2.2)	1 (0.8)
Appetite ↓	4 (2.9)	0
Dizziness	2 (1.5)	2 (1.6)
URTI	3 (2.2)	1 (0.8)
Abdominal discomfort	1 (0.7)	2 (1.6)
Abdominal pain upper	0	3 (2.5)
Weight ↑ abnormal	1 (0.7)	2 (1.6)
Hyperhidrosis	1 (0.7)	2 (1.6)
Vertigo	1 (0.7)	2 (1.6)
Vision blurred	2 (1.5)	1 (0.8)
Accidental overdose	2 (1.5)	0
Asthenia	2 (1.5)	0
Flatulence	2 (1.5)	0
Urticaria	0	2 (1.6)

[1] Only AEs occurring in >1 patient in any treatment group are listed

7.4.2.2. Other study: IOPB

The clinical evaluator believes there is no point presenting here the list of AEs classified by trialists as "possibly related to study drug", as this phrase (quoted from the sample CRF) would probably be interpreted as referring to the test drug (insulin lispro), and possibly also to the comparator (insulin glargine), but not to other drugs which the patient was taking (such as exenatide). The *Protocol* and associated documents were not specific on this.

7.4.3. Deaths and other serious adverse events

7.4.3.1. Pivotal study: GWCO

Deaths: 1 (in placebo group – myocardial infarction)

Other SAEs:

- Exenatide: 8/137 reported SAEs. 1 patient reported an SAE considered possibly related to study drug: accidental overdose.
- Placebo: 11/122 reported SAEs. 1 patient reported an SAE considered possibly related to study drug: urticaria.

7.4.3.2. Other study: IOPB

Deaths: 0

14/337 reported other SAEs

7.4.4. Discontinuation due to adverse events

7.4.4.1. Pivotal study: GWCO

Table 15 shows discontinuations due to adverse events.

Table 15: Discontinuations due to adverse events (Study GWCO).

Exenatide 12 (6 nausea; 4 vomiting; 1 headache; 1 diarrhoea[1]) **Placebo** 2 (1 joint swelling; 1 myocardial infarction[2])
[1] Onset before trial [2] Died.

7.4.4.2. Other study: IOPB

No data specific to exenatide.

7.5. Laboratory tests

7.5.1. Clinical chemistry

7.5.1.1. Pivotal study: GWCO

Routine biochemistry testing (creatinine, AST and ALT) was done at Visit 1 only.

7.5.1.2. Other study: IOPB

Routine biochemistry testing (creatinine, AST and ALT) was done at Visit 1 only. "Data is not available for analysis from the local laboratory assessments performed for the inclusion/exclusion criteria."

7.5.2. Haematology

7.5.2.1. Pivotal study: GWCO

No routine haematology testing was done.

7.5.2.2. Other study: IOPB

No routine haematology testing was done.

7.6. Post-marketing experience

No data.

7.7. Other safety issues

7.7.1. Hypoglycaemic episodes

Hypoglycaemia events reported in Study GWCO are shown in Table 16.

Table 16: Hypoglycaemia events (Study GWCO).

	Exenatide N=137 n (%) Events	Placebo N=122 n (%) Events
Major Hypoglycaemia	0	1 (0.82) 2
Minor Hypoglycaemia	34 (24.8) 92	35 (28.7) 82
Symptoms of Hypoglycaemia[1]	78 (56.9) 419	71 (58.2) 340

[1] An additional event of symptoms of hypoglycaemia was reported as an AE [in the placebo group].

7.8. Evaluator's overall conclusions on clinical 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.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

The benefits of exenatide in the proposed usage (as modified in accordance with section 7.2 above) 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.

8.2. 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 (as modified in accordance with section 7.2 above) appear similar to those of the usage which has already been approved.

8.3. 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 in Section 9 are adopted.

9. 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 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.*

10. Clinical questions

10.1. Pharmacokinetics

None.

10.2. Pharmacodynamics

None.

10.3. Efficacy

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

10.4. 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: "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?

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

None.

12. Second round benefit-risk assessment

12.1. Second round assessment of benefits

The assessment is unchanged from the first round assessment.

12.2. Second round assessment of benefits

The assessment is unchanged from the first round assessment.

12.3. Second round assessment of benefit-risk balance

The assessment is unchanged from the first round assessment.

13. Second round recommendation regarding authorisation

This recommendation is identical to the first round recommendation – please see Section 9 for this recommendation.

14. References

14.1. Studies presented in the dossier

Study no.	Title
H8O-US-GWCO	A Randomized Trial Comparing Exenatide with Placebo in Subjects with Type 2 Diabetes on Insulin Glargine with or without Oral Antihyperglycemic Medications
F3Z-US-IOPB	A Randomized Trial Comparing Insulin Lispro Protamine Suspension with Insulin Glargine in Subjects with Type 2 Diabetes on Oral Antihyperglycemic Medications and Exenatide

14.2. Other references

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

Therapeutic Goods Administration

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