Australian Government
Department of Health
Therapeutic Goods Administration

# Australian Public Assessment Report for dulaglutide rch

## Proprietary Product Name: Trulicity

## Sponsor: Eli Lilly Australia Pty Ltd

**July 2015**

TGA Health Safety Regulation

# About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and 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 <https://www.tga.gov.au>.

# About AusPARs

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

# Contents

# List of abbreviations

| Abbreviation | Meaning |
|---|---|
| ABPM | ambulatory blood pressure monitoring |
| ACPM | Advisory Committee on Prescription Medicines |
| ACSOM | Advisory Committee on the Safety of Medicines |
| ADA | anti drug antibody |
| ADCC | antibody dependent cell mediated cytotoxicity |
| AE | adverse event |
| ASA | Australian Specific Annex |
| AUC | area under the plasma concentration-time curve |
| AVB | atrioventricular block |
| BID | bis in die (twice daily) |
| BMI | body mass index |
| CI | confidence interval |
| Cmax | maximum plasma drug concentration |
| CMI | Consumer Medicine Information |
| CNS | central nervous system |
| CUI | clinical utility index |
| CV | cardiovascular |
| DBP | diastolic blood pressure |
| DPP-4 | dipeptidyl peptidase-4 |
| ECG | electrocardiograph |
| EMA | European Medicines Agency |
| $ER_{AUC}$ | exposure ratio based on AUC |
| $ER_{Cmax}$ | exposure ratio based on Cmax |
| ESRD | end stage renal disease |
| FDA | US Food and Drug Administration |

| Abbreviation | Meaning |
|---|---|
| GI | gastrointestinal |
| GLP | Good Laboratory Practice |
| GLP-1 | glucagon like peptide-1 |
| HbA1c | haemoglobin A1c |
| HCP | Host Cell Protein |
| HR | heart rate |
| IC50 | half maximal effective concentration |
| IM | intramuscular(ly) |
| ITT | Intent to Treat |
| IV | intravenous(ly) |
| $K_i$ | inhibition constant |
| MACE | major adverse cardiovascular event |
| MI | myocardial infarction |
| NOEL | no observed effect level |
| ns | native sequence |
| OPR | Office of Product Review |
| OMA | Office of Medicines Authorisation |
| PI | Product Information |
| PIP | Paediatric Investigation Plan |
| RMP | Risk Management Plan |
| SBP | systolic blood pressure |
| SC | subcutaneous(ly) |
| SmPC | Summary of Product Characteristics |
| T½ | elimination half life |
| T2DM | type 2 diabetes mellitus |
| TEAE | treatment emergent adverse event |

| Abbreviation | Meaning |
|---|---|
| Tmax | time to reach maximum plasma concentration following drug administration |

# I. Introduction to product submission

## Submission details

| | |
|---|---|
| *Type of submission:* | New chemical entity |
| *Decision*: | Approved |
| *Date of decision:* | 22 December 2014 |
| *Active ingredient:* | Dulaglutide rch |
| *Product name:* | Trulicity |
| *Sponsor's name and address:* | Eli Lilly Australia Pty Ltd<br>112 Wharf Road<br>West Ryde<br>NSW 2114 |
| *Dose forms:* | Solution for injection single use pen and prefilled syringe |
| *Strength:* | 1.5 mg/0.5mL |
| *Containers:* | Pen, syringe |
| *Pack sizes:* | 1, 2 or 4 single use pens or prefilled syringes |
| *Approved therapeutic use:* | Trulicity is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus:<br>• As monotherapy<br>• In combination with the following oral glucose-lowering medications (metformin, metformin and sulfonylurea, metformin and thiazolidinedione)<br>• In combination with prandial insulin, with or without metformin. |
| *Route of administration:* | Subcutaneous |
| *Dosage:* | The recommended dose is 1.5 mg per week. Administer once weekly, at any time of day, independently of meals. |
| *ARTG numbers:* | 217964, 217965 |

## Product background

This AusPAR describes the application by Eli Lilly Australia Pty Ltd to register a new biological agent dulaglutide [rch] (trade name Trulicity, originally Apleavo). Dulaglutide is a long acting human glucagon like peptide-1 (GLP-1) receptor agonist. The proposed indication is as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus (T2DM):

- As monotherapy

- In combination with the following oral glucose lowering medications (metformin, metformin and sulfonylurea, metformin and thiazolidinedione)
- In combination with prandial insulin, with or without metformin.

The submission proposes registration of the following dosage forms and strengths:

- 1.5 mg/0.5 mL solution for injection in single use pen injector
- 1.5 mg/0.5 mL solution for injection in prefilled syringe.

It should be administered once weekly. The dose can be administered at any time of the day, with or without meals, and can be injected subcutaneously (SC) in the abdomen, thigh or upper arm. Trulicity should not be administered intravenously (IV) or intramuscularly (IM).

T2DM is one of the most common non communicable diseases and is a global health problem. In 2011, the estimated number of people with T2DM was 366 million (8.3% of the world population), with an estimated increase to 552 million (9.9% of total world population) by 2030. There are 183 million people with undiagnosed diabetes.

T2DM has a complex pathophysiology that is characterised by deficient insulin activity arising from decreased insulin secretion secondary to β cell failure, compromised insulin action in peripheral target tissues (insulin resistance), or a combination of the two abnormalities. This abnormal metabolic state is exacerbated by excess glucagon secretion, excess hepatic glucose production, altered metabolism of protein and lipids, and abnormalities within the incretin system. All of these factors contribute to chronic hyperglycaemia which, if left untreated, can increase the risk of microvascular and macrovascular complications.

For many years, there have been several classes of antihyperglycaemic agents available that target one or more of the pathophysiologic deficiencies associated with T2DM, including metformin, sulfonylureas, thiazolidinediones, and insulins. These drugs can have undesirable side effects and/or limited usefulness in certain populations. For example, MET is contraindicated in patients with renal insufficiency, while thiazolidinediones are known to exacerbate congestive heart failure in some patients. Insulin and insulin analogues as well as sulfonylureas are often associated with hypoglycaemia and weight gain. More recently, incretin based therapies, including dipeptidyl peptidase-4 (DPP-4) inhibitors and GLP-1 receptor agonists, have become available and are being prescribed for patients with T2DM. Compared with the DPP-4 inhibitors, GLP-1 receptor agonists are injected and commonly associated with gastrointestinal (GI) side effects; however, in head-to-head trials they have demonstrated more robust glycosylated haemoglobin A1c (HbA1c) lowering and the added advantage of weight loss. Compared to the other commonly used injectable, insulin, the mechanism of action of GLP-1 receptor agonists, with glucose dependent insulin secretion, has the potential to decrease the risk of hypoglycaemia while providing reduction in HbA1c and weight loss. Among the available GLP-1 receptor agonists, there are differences in duration of action; frequency, timing of dosing, and ease of administration, effectiveness, tolerability, and immunogenicity.

Despite the currently available agents, a substantial proportion of patients with T2DM remain under poor glycaemic control. This suggests there continues to be a medical need, necessitating continued development of additional treatment options for patients with T2DM. There is still the opportunity to optimise the benefit-risk profile within the GLP-1 receptor agonist class.

## Regulatory status

Table 1 describes the international status of current regulatory submissions at the time of submission to the TGA. There has not been a withdrawal or rejection in any country.

**Table 1: International regulatory status for Trulicity.**

| Country | Submission Date | Decision Date |
|---|---|---|
| Australia | 4th December 2013 | Submitted |
| Brazil | 30th April 2014 | Submitted |
| Canada | 22nd January 2014 | Submitted |
| Europe | 26th September 2013 | Positive CHMP Opinion 25th September 2014 |
| India | 28th April 2014 | Submitted |
| Japan | July 2014 | Submitted |
| Korea | 27th June 2014 | Submitted |
| South Africa | 16th April 2014 | Submitted |
| Switzerland | 25th November 2013 | Positive Opinion 16th October 2014 |
| Taiwan | 29th January 2014 | Submitted |
| USA | 17th September 2013 | Approved 18th September 2014 |

### Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <www.tga.gov.au/product-information-pi>.

# II. Quality findings

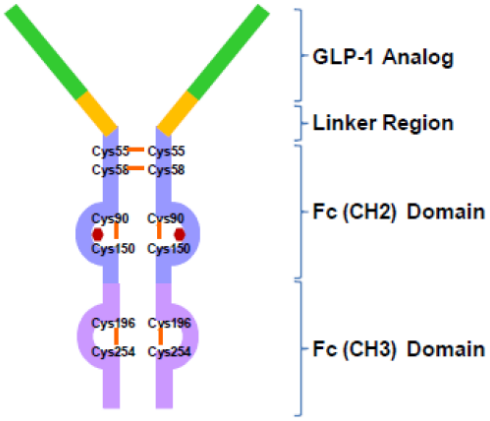
### Introduction (if applicable)

Dulaglutide is a disulphide linked peptide homodimer and is a GLP-1 receptor agonist. Two presentations of the product are proposed for registration: a single use prefilled syringe, and a single use pen.

### Drug product

Dulaglutide is produced as a disulphide linked, two chain molecule (homodimer). The overall structure of dulaglutide is shown schematically in Figure 1.

**Figure 1: A schematic diagram of dulaglutide.**




The GLP-1 analog, linker region, and IgG4 Fc CH2 and CH3 domains are depicted. The 12 Cys residues that are involved in the inter chain and intra chain disulphide bonding are also shown. The red hexagonal symbol in Figure 1 represents the N-linked glycosylation at Asn126 in each polypeptide chain.

nDulaglutide for injection (also referred to as dulaglutide injection) is supplied as 1.5 mg/0.5 mL and is a clear, colourless, essentially free from particles, sterile, and non pyrogenic parenteral solution for SC administration. The dulaglutide drug product is contained in a 1 mL long, Type I borosilicate glass, syringe with a bromobutyl plunger. The container closure system filled with drug product is referred to as the semi finished syringe. The drug product is available to patients as a semi finished syringe assembled into either a single use pen or a prefilled syringe with a plunger rod and backstop for administration.

## Biopharmaceutics

Only the prefilled syringe was used in Phase III clinical studies. The following biopharmaceutic studies were provided in support of the application to register the proposed product (Table 2).

**Table 2: Biopharmaceutic studies provided.**

| Study ID | Description | Population | Dosing Regimen |
|---|---|---|---|
| GBDR | Absolute BA of SC and relative BA of IM versus SC | Healthy Subjects | Single IV 0.1 mg, Single SC 0.75-mg and 1.5-mg dose Single IM 0.75-mg dose |
| GBCN | Effect of injection site (abdomen, arm, thigh) on BA | Healthy Subjects with Low and High BMI | Single 1.5-mg dose |
| GBDT | Comparative PK of single-use pen vs. prefilled syringe | Healthy Subjects | Single 1.5-mg dose |

Abbreviations: BA = bioavailability; BMI = body mass index; GBCN = Study H9X-MC-GBCN; GBDR = H9X-MC-GBDR; GBDT = H9X-MC-GBDT; ID = identifier; IM = intramuscular; IV = intravenous; PK = pharmacokinetics; SC = subcutaneous.

Regarding evaluation of the biopharmaceutic studies, the Submission Assessment Form included the following statement:

> *Although the submission includes three possible bioavailability studies, as per current practice of the Pharmaceutical Chemistry Section, these will not be evaluated by the Pharmaceutical Chemistry Section. The bioanalytical method will be evaluated by Biochemistry and the study design and interpretation of the results by the clinician. That would only leave the statistical calculations for the Pharmaceutical Chemistry Section to evaluate, and on a risk management basis for these types of studies, these can be accepted without repeat.*

Consistent with this statement, the claimed results of the biopharmaceutic studies are presented below without further evaluation.

**GBDR: A study to evaluate the safety, tolerability, and absolute bioavailability of subcutaneous LY2189265**

An open label, three part study was conducted in 30 healthy subjects to determine the absolute bioavailability of dulaglutide after SC injection. Relative bioavailability after IM injection was also determined as patients may accidentally self administer by this route rather than the intended SC route. The SC and IM injections were performed using prefilled, single use syringes.

In Part A, 3 male and 3 female subjects received an IV infusion of 0.1 mg dulaglutide over 30 minutes. The IV dose was well tolerated and provided measurable concentrations for analysis.

In Part B, 12 male and 4 female subjects received an IV infusion of 0.1 mg dulaglutide over 30 minutes and a SC injection of 1.5 mg dulaglutide in a randomly assigned order with at least 28 days between treatments. The results were as shown in Table 3, with the mean absolute bioavailability of a 1.5 mg SC dose of dulaglutide reported as 44.3% (90% confidence interval [CI] 39.5-49.7%).

**Table 3: Results from the GBDR study, Part B.**

| | Geometric LS Means (90% CI)[a] | | Absolute Bioavailability |
|---|---|---|---|
| Parameter [a] (units) | 1.5 mg Dulaglutide SC (N=16) | 0.1 mg Dulaglutide IV (N=16) | Ratio of Geometric LS Means; SC: IV [b] (90% CI) |
| AUC(0-∞) (ng·h/mL)/(mg) | 10256 (8964, 11734) | 23150 (20234, 26485) | 0.443 (0.395, 0.497) |
| AUC(0-168) (ng·h/mL)/(mg) | 6287 (5667, 6975) | 16956 (15283, 18813) | 0.371 (0.335, 0.410) |

Abbreviations: AUC(0-168) = area under the concentration versus time curve (AUC) from time zero to 168 hours postdose; AUC(0-∞) = AUC from zero to infinity; CI = confidence interval; IV = intravenous; LS = least squares; N = number of subjects; SC = subcutaneous.
Model: Log(PK) = Subject(Sequence) + Sequence + Treatment + Period + Random error.
[a] Parameters are shown dose normalized by the respective doses; ratio is the ratio of dose-normalized AUCs
[b] Includes data for subjects from Part B only.

In Part C, 5 male and 3 female subjects received a SC injection of 0.75 mg dulaglutide and an IM injection of 0.75 mg dulaglutide in a randomly assigned order with at least 28 days between treatments. The results are shown in Table 4, with the mean relative bioavailability of a 0.75 mg IM dose of dulaglutide reported as 95.8% (90% CI 85.8-108%) compared to a 0.75 mg SC dose.

**Table 4: Results from the GBDR study, Part C.**

| | Geometric LS Means (90% CI) | | Ratio of Geometric LS Means |
|---|---|---|---|
| Parameter (units) | 0.75 mg Dulaglutide IM (N=7) | 0.75 mg Dulaglutide SC (N=8) | IM:SC (90% CI) |
| AUC(0-∞) (ng·h/mL) | 9828 (7525, 12837) | 10215 (7832, 13323) | 0.962[a] (0.858, 1.08) |
| $C_{max}$ (ng/mL) | 56.9 (48.4, 67.0) | 54.2 (46.3, 63.5) | 1.05 (0.924, 1.19) |

Abbreviations: AUC(0-∞) = area under the plasma concentration versus time curve from zero to infinity; CI = confidence interval; $C_{max}$ = maximum observed drug concentration; IM = intramuscular; LS = least squares; N = number of subjects; SC = subcutaneous.
Model: Log(PK) = Subject(Sequence) + Sequence + Treatment + Period + Random error.
[a] This value is the relative bioavailability of dulaglutide.

The data from the three parts of the study were also combined and used to develop a population PK model. This model estimated absolute bioavailability for 0.75 mg and 1.5 mg doses of dulaglutide of 64.7% and 47.0%, respectively.

**GBCN: The effect of injection site on the relative bioavailability of LY2189265 in subjects with low and high body mass index**

An open label study was conducted in 45 healthy subjects (29 male and 16 female) to determine the bioavailability of dulaglutide injections into the upper arm and thigh relative to the abdominal wall. The injections were performed using prefilled single use syringes. Twenty subjects with high body mass index (BMI) (30.7-44.7 kg/m$^2$) and twenty five with low BMI (19.4-27.0 kg/m$^2$) received three single SC injections of 1.5 mg dulaglutide in the upper arm, thigh, and abdomen in a randomly assigned order with at least 28 days between treatments. The results were as shown in Table 5, with no statistically significant differences in absolute bioavailability, rate of absorption, or rate of elimination between injection sites reported.

**Table 5: Results from the GBCN study.**

| BMI Group | Parameter (units) | Location of Administration | Geometric LS Means (90% CI) | Ratio of Geometric LS Means (vs. Abdomen) (90% CI) |
|---|---|---|---|---|
| Overall | AUC(0-∞) | Abdomen (N=43) | 14959 (14225, 15730) | |
| | (ng·h/mL) | Arm (N=40) | 14557 (13834, 15319) | 0.973 (0.941, 1.01) |
| | | Thigh (N=39) | 14800 (14064, 15574) | 0.989 (0.956, 1.02) |
| | AUC(0-168) | Abdomen (N=43) | 9317 (8869, 9788) | |
| | (ng·h/mL) | Arm (N=40) | 9129 (8678, 9605) | 0.980 (0.934, 1.03) |
| | | Thigh (N=44) | 8580 (8169, 9010) | 0.921 (0.879, 0.964) |
| | $C_{max}$ | Abdomen (N=43) | 76.0 (71.8, 80.5) | |
| | (ng/mL) | Arm (N=40) | 74.8 (70.5, 79.4) | 0.984 (0.925, 1.05) |
| | | Thigh (N=44) | 67.7 (63.9, 71.6) | 0.890 (0.838, 0.944) |

Abbreviations: AUC(0-∞) = area under the plasma concentration-time curve from time zero to infinity; AUC(0-168) = area under the plasma concentration-time curve from time zero up to 168 hours postdose; CI = confidence interval; $C_{max}$ = maximum observed plasma concentration; LS = least squares; N = number of subjects.

Model: Log(PK) = Subject within Sequence and BMI Group + Sequence + BMI Group + Period + Location + BMI Group*Location + Random Error.

Analysis included the entire range of body mass index.

**GBDT: Comparative pharmacokinetics of dulaglutide after administration via an auto injector and a manual syringe in healthy subjects**

An open label study was conducted in 50 healthy subjects (40 male and 10 female) to establish comparability between single use pens (auto injectors) and prefilled syringes (manual syringes). Subjects received two single SC injections of 1.5 mg dulaglutide performed using a single use pen and a prefilled syringe in a randomly assigned order with at least 28 days between treatments. The results were as shown in Table 6, with area under the plasma concentration-time curve (AUC, mean ratio 1.02, 90% CI 0.998-1.04), maximum plasma drug concentration (Cmax, mean ratio 1.02, 90% CI 0.983-1.06), and time to reach maximum plasma concentration following drug administration (Tmax) (median difference 0 hours, 90% CI 0-12.0 hours) reported to be comparable.

**Table 6: Results from the GBDT study.**

| Parameter (units) | Device | N | Geometric LS Means | Ratio of Geometric LS Means Auto-injector:Manual Syringe (90% CI for the ratio) |
|---|---|---|---|---|
| AUC(0-∞) (ng·h/mL) | Auto-injector | 47 | 16483 | 1.02 (0.998, 1.04) |
| | Manual Syringe | 47 | 16150 | |
| $C_{max}$ (ng/mL) | Auto-injector | 47 | 90.8 | 1.02 (0.983, 1.06) |
| | Manual Syringe | 48 | 88.8 | |
| Parameter (units) | Device | N | Median | Median difference Auto-injector - Manual Syringe (90% CI for the difference) |
| $t_{max}$ (h) | Auto-injector | 45 | 48.0 | 0 (0, 12.0) |
| | Manual Syringe | 45 | 48.0 | |

Abbreviations: AUC(0-∞) = area under the concentration versus time curve from zero to infinity; CI = confidence interval; $C_{max}$ = maximum observed drug concentration; h = hours; LS = least squares; N = number of subjects; $t_{max}$ = time of $C_{max}$.

Model for AUC(0-∞) and $C_{max}$: Log(PK) = Subject(Sequence) + Sequence + Device + Period + BMI + Random Error.

$t_{max}$ was analyzed using the method outlined by Hauschke et al. 1990.

### Quality summary and conclusions

The Quality evaluator recommended that:

- Trulicity dulaglutide rch 1.5mg/0/5mL solution for injection prefilled pen (AUST R 217965); and
- Trulicity dulaglutide rch 1.5mg/0/5mL solution for injection prefilled syringe (AUST R 217964)

should be approved.

# III. Nonclinical findings

### Introduction

The sponsor has applied to register a new chemical entity, dulaglutide, a GLP-1 receptor agonist, proposed to be used as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM:

- as monotherapy
- in combination with the following oral glucose lowering medications (metformin, metformin and sulfonylurea, metformin and thiazolidinedione)
- in combination with prandial insulin, with or without metformin

The proposed dosing regimen is 1.5 mg once weekly by SC injection. Dulaglutide consists of a modified human GLP-1(7-37) sequence covalently linked to a modified human IgG4 Fc fragment.

The overall quality of the nonclinical dossier was high, with all pivotal studies conducted under GLP conditions. No studies assessing potential pharmacodynamic, pharmacokinetic or toxicological interactions of dulaglutide with other anti diabetic agents were submitted. While this is a limitation of the dossier, it is not considered to be a major deficiency provided adequate clinical safety data are available. Furthermore, other GLP-1 receptor agonists are already approved for use with the proposed combinations.

Drug material used in the nonclinical studies is considered to be adequately representative of the proposed commercial product.

## Pharmacology

### Primary pharmacology

GLP-1 is an intestinally derived peptide hormone that is secreted after ingestion of glucose or a mixed meal. GLP-1 receptor agonists, such as dulaglutide, are expected to lower post prandial glucose levels via retardation of gastric emptying, a stimulation of insulin biosynthesis and secretion by pancreatic β cells and inhibition of glucagon secretion from pancreatic α cells.[1]

*In vitro*, dulaglutide was shown to bind to the human GLP-1 receptor with nanomolar affinity (inhibition constant [$K_i$], 4.2 nM). It was demonstrated to act as a full agonist of the receptor in cell based assays, and the potency for receptor activation was similar to that of GLP-1(7-37). Dulaglutide dose and glucose dependently enhanced insulin secretion from rat and Cynomolgus monkey pancreatic islet cells. The insulinotropic effect of dulaglutide on rat cells was abolished in the presence of a GLP-1 receptor antagonist. The *in vitro* data indicates that dulaglutide activates GLP-1 receptors in a similar manner to the native peptide.

Dulaglutide showed glucose dependent insulinotropic activity *in vivo* in both rats and Cynomolgus monkeys after SC administration. The minimal efficacious dose in rats (0.179 mg/kg; equivalent to 1.07 mg/m$^2$) is similar to the intended clinical dose (1.5 mg; equivalent to 0.99 mg/m$^2$ for a 50 kg individual) on a body surface area. Insulinotropic activity was still evident in monkeys 7 days after dosing (consistent with detectable serum dulaglutide levels), confirming a long duration of pharmacological action. There were no studies submitted that assessed the anti hyperglycaemic activity of dulaglutide in diabetic animals. However, a published paper reported that twice weekly administration of dulaglutide (0.626 mg/kg [10 nmol/kg] SC) to diabetic mice resulted in consistently lowered plasma glucose over the 4 week treatment period; there was also a small but significant reduction in body weight.[2]

Together, the pharmacology data indicate that dulaglutide is a long acting GLP-1 receptor agonist, with animal data supporting efficacy in the proposed monotherapy indication and at the proposed clinical dose.

#### *Secondary pharmacodynamics and safety pharmacology*

Like GLP-1(7-36)-$NH_2$, dulaglutide was highly selective for the human GLP-1 receptor over gastric inhibitory polypeptide (GIP) and glucagon receptors (>166 times and >324 times). No studies were submitted that specifically assessed interactions of dulaglutide with Fc receptors; however, the Fc region of IgG4 (with modifications) was chosen to reduce potential interactions with high affinity Fc receptors. Furthermore, dulaglutide did not induce antibody dependent cell mediated cytotoxicity (ADCC) on cells expressing human GLP-1 receptors, suggesting minimal adverse antibody specific interactions from the Fc region.

Specialised safety pharmacology studies were restricted to the cardiovascular system; central nervous system (CNS) and respiratory assessments were made in the general toxicity studies. Some inhibition of hERG K+ tail current was observed *in vitro* (by 33% at 15.2 µg/mL, the highest concentration tested), and prolongation of the QTc interval[3] seen in Cynomolgus monkeys that received 10 mg/kg SC dulaglutide (NOEL, 1 mg/kg). The half

[1] Meier JJ. (2012) GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. *Nat. Rev. Endocrinol.* 8: 728-742.
[2] Glaesner W, et al. (2010) Engineering and characterization of the long-acting glucagon-like peptide-1 analogue LY2189265, an Fc fusion protein. *Diabetes/Metabolism Res. Rev.* 26: 287-296.
[3] In cardiology, the QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle.

maximal effective concentration (IC50) for inhibition of the hERG K+ channel exceeds the clinical Cmax by >133 times, and the estimated plasma Cmax in monkeys at the NOEL is 46 times the clinical Cmax.[4] Based on these margins, QT prolongation is not predicted with clinical use.

In the specialised safety pharmacology study, increased heart rate and elevated left ventricular inotropic state were seen in monkeys given ≥1 mg/kg SC dulaglutide. Increased heart rate was also seen in repeat dose toxicity studies in monkeys (at 8.15 mg/kg SC dulaglutide) and has been reported in other animal studies with GLP-1 receptor agonists. The exposure ratio based on Cmax ($ER_{Cmax}$) at the NOEL for elevate heart rate in monkeys in the repeat dose toxicity studies (1.63 mg/kg) is >100. While the safety margin from animal studies appears large, increased heart rate is a class effect, and may be seen in the clinical setting.

CNS and respiratory function were unaffected in Cynomolgus monkeys that received ≤8.15 mg/kg SC dulaglutide twice weekly ($ER_{Cmax}$, 645). Accordingly, no specific hazard to the respiratory and CNS during clinical use is indicated by the animal data.

### Pharmacokinetics

Absorption of dulaglutide was slow following SC injection, with peak plasma levels typically reached 12 h post dose in mice, 12-24 h in rats, 10-16 h in monkeys and 48 h in patients. The half life was long in Cynomolgus monkeys (5.5-6.7 days) and human subjects (4.7 days) and shorter in rats (~20 h). Peak and overall exposure (Cmax and AUC) to dulaglutide was generally dose proportional in the three laboratory animal species, and there were no consistent sex differences in pharmacokinetic parameters. Exposures in mice were lower following repeat dosing for 6 months. Anti drug antibodies (ADAs) were not monitored in rodents, but the lower exposure with repeat dosing is suggestive of antibody formation. In contrast, there was some evidence of accumulation in rats and monkeys with repeated twice weekly dosing and in human subjects with weekly dosing. In most studies, no ADAs were detected in treated monkeys, so the pharmacokinetic data are not affected by antibody development.

No tissue distribution studies were submitted. As expected for this type of large molecular weight drug, the volume of distribution in monkeys and humans was lower than total body water, suggesting limited extravascular distribution.

No metabolism studies were submitted. Some of the changes made to the GLP-1 analogue portion were intended to reduce the rate of hydrolysis by DPP-4. No studies were submitted that assessed whether dulaglutide was a substrate for DPP-4. Published data indicate that the change of Ala to Gly at the second amino acid residue of GLP-1(7-37) (a modification included in dulaglutide) results in a peptide that is still a substrate for DPP-4, albeit a poorer one than native GLP-1(7-37).[5] Therefore, it may be assumed that dulaglutide is, at least to some extent, hydrolysed by DPP-4. This may have implications in interpreting exposure levels, although pharmacology studies indicated a long duration of pharmacological action. The remainder of dulaglutide would be degraded by proteases.

No excretion studies were submitted, which is considered acceptable given the nature of the drug.

Overall, the pharmacokinetic profile of dulaglutide is seen to be sufficiently similar in humans and the species used in toxicity studies (rats and monkeys) for these species to serve as appropriate models for toxicity. ADA production in mice limits the utility of this

[4] Based on day 1 data for monkeys in Study P00054 (5-week repeat-dose toxicity study).
[5] Deacon CF, et al. (1998) Dipeptidyl peptidase IV resistant analogues of glucagon-like peptide-1 which have extended metabolic stability and improved biological activity. *Diabetologia* 41: 271-278.

species somewhat, predominantly due to the impact on drug exposure levels in the long term study.

### Pharmacokinetic drug interactions

No pharmacokinetic drug interaction studies were submitted. Given the protein nature of dulaglutide, pharmacokinetic drug interactions involving CYP450 enzymes are not expected.

## Toxicology

### Acute toxicity

No single dose toxicity studies were submitted. This is considered acceptable given that adequate information can be gained from the repeat dose toxicity studies. In those studies, initial dosing at up to 100 mg/kg in mice, 20 mg/kg in rats, and 10 mg/kg in monkeys produced no mortality. These doses are ~120-300 times greater than the clinical dose on a body surface area basis.

### Repeat dose toxicity

Repeat dose toxicity studies of up to 6 months duration were conducted in rats and up to 9 months duration in Cynomolgus monkeys. A 5 week repeat dose toxicity study was also conducted in mice, to support dose selection for a subsequent carcinogenicity study. The clinical route (SC) was used in all studies, and dosing was twice weekly (compared with proposed weekly clinical dosing). The choice of species for the pivotal studies is considered acceptable (both rats and monkeys are pharmacologically responsive to dulaglutide). The dosing regimen and duration of dosing are also considered appropriate (according to guidelines).[6] The doses used were appropriate, based on high relative exposures (see below) and significant suppression of body weight gain (or body weight loss) at the highest doses. The conduct of the studies is consistent with the relevant guidelines.[7]

#### *Relative exposure*

Animal:human exposure ratios have been calculated by comparing the achieved steady state plasma levels ($AUC_{0\text{-}96\ h}$/96 h) in animals with clinical steady state plasma levels ($AUC_{0\text{-}168\ h}$/168 h). Animal $AUC_{0\text{-}96\ h}$ data from the final dose in each study, averaged across sexes, were used for comparative purposes. Very high relative exposures were achieved in all repeat dose toxicity studies (Table 7).

[6] European Medicines Agency, "ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals (EMA/CHMP/ICH/731268/1998)", June 2011.
[7] European Medicines Agency, "Guideline on repeated dose toxicity (CPMP/SWP/1042/99 Rev 1 Corr*)", 18 March 2010; European Medicines Agency, "ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals (EMA/CHMP/ICH/731268/1998)", June 2011.

**Table 7: Relative exposure in repeat dose toxicity and carcinogenicity studies.**

| Species | Study duration | Dose (mg/kg); twice weekly | $AUC_{0-96\,h}$ (µg·h/mL) | Exposure ratio[#] |
|---|---|---|---|---|
| **Mouse** (001178-W; CByB6F1-Tg(HRAS)2Jic) | 5 weeks *(Study 8224143)* | 1 | 99 | 12 |
| | | 10 | 1145 | 143 |
| | | 100 | 8696 | 1087 |
| | 26 weeks [carcinogenicity] *(Study 8224144)* | 0.3 | 8.63 | 1.1 |
| | | 1 | 23.3 | 3 |
| | | 3 | 37.0 | 5 |
| **Rat** (SD) | 5 weeks *(Study R00359)* | 2 | 237 | 30 |
| | | 6 | 739 | 92 |
| | | 20 | 1724 | 215 |
| | 13 weeks *(Study 7608-191)* | 1.63 | 124 | 16 |
| | | 4.89 | 278 | 35 |
| | | 16.29 | 1181 | 148 |
| | 6 months [pivotal] *(Study 7608-236)* | 1.63 | 121 | 15 |
| | | 4.89 | 298 | 37 |
| | | 16.29 | 1295 | 162 |
| | 93 weeks [carcinogenicity] *(Study 8203405)* | 0.05 | 4.1 | 0.5 |
| | | 0.5 | 60 | 7 |
| | | 1.5 | 159 | 20 |
| | | 5 | 465 | 58 |
| **Monkey** (Cynomolgus) | 5 weeks *(Study P00054)* | 1 | 360 | 45 |
| | | 3 | 1072 | 134 |
| | | 10 | 3921 | 490 |
| | 13 weeks *(Study 7608-192)* | 0.41 | 155 | 19 |
| | | 1.63 | 682 | 85 |
| | | 8.15 | 3034 | 379 |
| | 9 months [pivotal] *(Study 7608-235)* | 0.41 | 205 | 26 |
| | | 1.63 | 719 | 90 |
| | | 8.15 | 3792 | 474 |
| **Human** (Patients with type 2 diabetes) | steady state | [1.5 mg once weekly] | [$AUC_{0-168\,h}$ = 14 µg·h/mL] | – |

[#] = (animal $AUC_{0-96\,h}$ / 96) ÷ (human $AUC_{0-168\,h}$ / 168)

### *Major toxicities*

The chief findings in the toxicity studies were typical of the drug class, comprising effects associated with the primary pharmacological action (reduced food consumption, lower body weight gain [or body weight loss]), effects secondary to these (effects on red blood cell parameters, reproductive organs and lymphoid tissues) and proliferative changes in the thyroid (rodents only).

GLP-1 receptor agonists delay gastric emptying and reduce appetite. Hence, reduced food consumption with lower body weight gain (or body weight loss) was observed at all doses in mice, rats and monkeys. The effects on food consumption were most prominent after the first dose, with a trend to tolerance observed with ongoing treatment. At high doses, the effects on body weights were noticeably adverse, leading to secondary changes in internal organs. There was also a trend to reduced serum triglyceride and glucose levels in rats (at ≥1.63 mg/kg SC twice weekly), likely associated with the pharmacological action of dulaglutide. Vomiting, probably as a result of the action of dulaglutide to delay stomach emptying, was observed in monkeys at all doses. All of these effects were reversible. Reduced food consumption, body weight loss and vomiting may be seen during clinical use.

At high doses, with severe decrements in body weight gain, the following secondary effects were seen:

- atrophy of the reproductive organs of male rats at 20 mg/kg twice weekly for 5 weeks

  - NOEL, 6 mg/kg twice weekly; exposure ratio based on AUC ($ER_{AUC}$), 92
- abnormal oestrous cycling in female rats at ≥6 mg/kg twice weekly for 5 weeks
  - NOEL, 2 mg/kg twice weekly; $ER_{AUC}$, 30
- reduced red blood cell parameters in mice (but no other species) at ≥0.3 mg/kg twice weekly
  - no NOEL established in mice ($ER_{AUC}$, <1.1)
  - NOELs of 16.29 and 8.15 mg/kg twice weekly in rats and monkeys; $ER_{AUC}$, 162-474
- lymphoid depletion in monkeys at 10 mg/kg twice weekly for 5 weeks
  - NOEL, 3 mg/kg twice weekly; $ER_{AUC}$, 134.

The findings in the 5 week rat and monkey studies were absent in the pivotal studies in the two species (6 or 9 months duration). Based on this and the large exposure margins at the NOELs, none of these findings are expected to be clinically relevant.

Microscopic changes were seen in the thyroid of rodents in the carcinogenicity studies. An increased incidence of thyroid C cell hyperplasia and thyroid C cell tumours was seen in rats that received ≥0.5 mg/kg SC dulaglutide twice weekly for 93 weeks (NOEL, 0.05 mg/kg; $ER_{AUC}$, 0.5) and an increased incidence of thyroid C cell cytoplasmic hypertrophy (increased calcitonin staining) was seen in transgenic mice that received ≥0.3 mg/kg SC dulaglutide twice weekly ($ER_{AUC}$, 1.1; NOEL not established). Similar proliferative thyroid lesions (with similar safety margins) have been seen in rodent carcinogenicity studies with other long acting GLP-1 receptor agonists. This is discussed further below (see 'Carcinogenicity'). There appears to be no greater risk for proliferative thyroid lesions with dulaglutide compared with currently registered GLP-1 receptor agonists.

Marketed GLP-1 receptor agonists have potentially been associated with acute pancreatitis. There was no evidence of pancreatitis with dulaglutide in the standard repeat dose toxicity studies nor in a specialised 12 month investigative study in Cynomolgus monkeys at very high doses (8.15 mg/kg SC twice weekly; estimated $ER_{AUC}$, 474). In a 3-month investigative study, there were modest elevations in total amylase and pancreatic amylase activities in the serum of diabetic rats (by 12-33% at ≥0.5 mg/kg SC twice weekly; $ER_{AUC}$, 2.7) but without an increase in lipase activity. Elevated amylase levels were not always associated with pancreatic lesions. Microscopic changes in the pancreas included an increased incidence and severity of increased ductal epithelium and neutrophilic periductal inflammation, an increased incidence and severity of acinar atrophy (sometimes associated with mixed cell inflammation), an increase in the severity of islet cell hyperplasia (at ≥0.5 mg/kg SC twice weekly; $ER_{AUC}$, 2.7), and an increased incidence of neutrophilic inflammation in acinar tissue (at 5 mg/kg SC twice weekly; $ER_{AUC}$, 30). While the changes in serum amylase and lipase activities and the lesions observed were not strongly suggestive of pancreatitis, the combined evidence suggests that dulaglutide treatment leads to an increased severity of spontaneous lesions of the pancreas in diabetic (but not normal) rats.

### Genotoxicity

No genotoxicity studies were submitted, which is considered acceptable for this type of product (in accordance with published guidelines).[8] As a high molecular weight protein, dulaglutide is not expected to interact with DNA or other chromosomal material.

[8] European Medicines Agency, "ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals (EMA/CHMP/ICH/731268/1998)", June 2011.

### Carcinogenicity

The carcinogenic potential of dulaglutide was investigated in a 6 month study in transgenic Tg.rasH2 mice and a 93 week (21.5 month) study in rats. The clinical route (SC) was used and dosing was twice weekly (compared to weekly clinical doses). Group sizes and the duration of dosing were appropriate.[9] A concurrent positive control group was included in the transgenic mouse study and produced the expected results, confirming the validity of the model. Dose levels in the rat study were appropriate, with exposures >25 times the anticipated clinical exposure at the highest dose level, in accordance with published guidelines.[10] However, exposures in the mouse study were unexpectedly lower ($ER_{AUC}$, 5 at the highest tested dose). Doses in the mouse carcinogenicity study were chosen following a pilot 5 week study and, based on exposures measured in that pilot study, adequate exposures would have been predicted. Unfortunately, significantly lower exposures were observed in the mice with long term dosing, most likely as a result of antibody formation; the plasma AUC obtained at the high dose level was ~80% lower in Week 26 compared with Day 1. While no treatment related tumours were observed in transgenic mice treated with dulaglutide (≤3 mg/kg SC twice weekly; $ER_{AUC}$, ≤5), the predictive value of the study is considered to be limited due to the low exposure ratios achieved.

As indicated in the repeat dose toxicity section, proliferative thyroid lesions were observed with dulaglutide in the rat carcinogenicity study. There was an increased incidence of thyroid C cell hyperplasia (diffuse and focal) and thyroid C cell adenomas at ≥0.5 mg/kg SC twice weekly ($ER_{AUC}$, ≥7), and a higher incidence of thyroid C cell carcinomas compared to concurrent controls was observed at 5 mg/kg SC twice weekly ($ER_{AUC}$, 58). While the incidence of thyroid C cell carcinoma was still within the historical control range, given the presence of precursor lesions (hyperplasia and adenomas), the higher incidence of malignant tumours in this dose group is reasonably considered drug related. Exposure at the NOEL for carcinogenicity in the rat is subclinical (0.05 mg/kg SC twice weekly; $ER_{AUC}$, 0.5).

There was no evidence of proliferative changes in the thyroid of Cynomolgus monkeys that received 8.15 mg/kg SC dulaglutide twice weekly for 12 months (investigative study; estimated $ER_{AUC}$, 474), suggesting rats may be particularly sensitive to such effects. Thyroid C cell tumours have been reported in rodent carcinogenicity studies with other GLP-1 receptor agonists. The current view is that these proliferative lesions occur via a non genotoxic, receptor mediated mechanism and, due to species differences in GLP-1 receptor expression in the thyroid, are unlikely to be clinically relevant (see the AusPARs for Liraglutide (rys) [Victoza] and Exenatide [Byetta; Bydureon] for further discussion). However, the relevance of the tumours cannot be completely excluded and pharmacovigilance activities regarding thyroid cancer are warranted.

### Reproductive toxicity

A standard set of reproductive toxicity studies was submitted, examining fertility (in rats), embryofoetal development (in rats and rabbits) and pre/postnatal development (in rats). Adequate animal numbers were used and treatment periods were appropriate. Adequate dose levels were used, with significant effects on body weight and body weight gain at the highest doses tested. Significant exposures were achieved in rats, with lower, but acceptable, exposures in rabbits (Table 8). Dosing was by the clinical route (SC) at a more

[9] Morton D, et al. (2002) The Tg rasH2 mouse in cancer hazard identification. *Toxicol. Pathol.* 30: 139-146; MacDonald J, et al. (2004) The utility of genetically modified mouse assays for identifying human carcinogens: a basic understanding and path forward. *Toxicol. Sci.* 77: 188-194.

[10] European Medicines Agency, "ICH Topic S1C(R2) Dose Selection for Carcinogenicity Studies of Pharmaceuticals, Step 5: Note for Guidance on Dose Selection for Carcinogenicity Studies of Pharmaceuticals (EMEA/CHMP/ICH/383/1995)", October 2008.

frequent dosing interval (every 3 days compared to once weekly clinically), which is considered acceptable.

**Table 8: Relative exposure in reproductive toxicity studies.**

| Species | Study | | Dose (mg/kg); every 3 days | AUC (µg·h/mL) | | Exposure ratio# |
|---|---|---|---|---|---|---|
| Rat (SD) | Fertility | ♂ | 1.63 | 121[a] | | 15 |
| | | | 4.89 | 298[a] | [0–96h] | 37 |
| | | | 16.3 | 1295[a] | | 162 |
| | | ♀ | 2 | 237[b] | | 30 |
| | | | 6 | 739[b] | [0–96h] | 92 |
| | | | 20 | 1724[b] | | 216 |
| | Embryofetal development | | 0.49 | 35 | | 4.4 |
| | | | 1.63 | 110 | [0–96h] | 14 |
| | | | 4.89 | 348 | | 44 |
| | Pre-/postnatal development | | 0.2 | 15 | | 1.9 |
| | | | 0.49 | 36 | [0–96h] | 4.5 |
| | | | 1.63 | 131 | | 16 |
| Rabbit (NZW) | Embryofetal development | | 0.04 | 4.8 | | 0.8 |
| | | | 0.12 | 22 | [0–72h] | 3.6 |
| | | | 0.41 | 65 | | 11 |
| Human (Patients with type 2 diabetes) | steady state | | [1.5 mg once weekly] | 14 | [0–168h] | – |

# = animal $AUC_{0\text{-}96\,h}$ / 96 ÷ human $AUC_{0\text{-}168\,h}$ / 168 for rats and animal $AUC_{0\text{-}72\,h}$ / 72 ÷ human $AUC_{0\text{-}168\,h}$ / 168 for rabbits; a = based on data from Study 7608-236 (6-month, rat); b = based on data from Study R00359 (5-week, rat)

No treatment related effect on the fertility index was observed in male rats treated with dulaglutide (≤16.3 mg/kg every 3 days; $ER_{AUC}$, 162). Decreased reproductive organ weights (at ≥4.89 mg/kg; denoting likely atrophic changes) and a slight reduction in the mating index (at 16.3 mg/kg) were seen, though; there was no overt effect on sperm quality or number. In female rats, abnormal oestrus cycling with decreased corpora lutea (signifying inhibition of ovulation) was seen with treatment at ≥6 mg/kg every 3 days ($ER_{AUC}$, 92). The NOEL for effects on female fertility is 2 mg/kg every 3 days ($ER_{AUC}$, 30). These findings are considered likely secondary to pharmacologically mediated effects on body weight. Given the large safety margins, no adverse effects on fertility are predicted in patients.

No studies were conducted to assess potential placental transfer of dulaglutide. As dulaglutide possesses an Fc domain, it is likely to undergo placental transfer, which may be a difference between dulaglutide and currently registered GLP-1 receptor agonists. No adverse embryofoetal effects were seen in rats and rabbits at 0.49 mg/kg and ≤0.12 mg/kg SC dulaglutide, respectively ($ER_{AUC}$, ~4). Adverse effects on embryofoetal development were observed in both species at higher doses, but only in the context of maternotoxicity, with significant suppression of maternal body weight gain seen. These effects included:

- decreased foetal body weight (≥1.63 mg/kg; $ER_{AUC}$, 14), increased post implantation loss and a higher incidence of delayed ossification (at 4.89 mg/kg; $ER_{AUC}$, 44) in rat foetuses
- an increased incidence of rib abnormalities, other skeletal variations, costal cartilage anomalies and lobular agenesis of the lungs in rabbit foetuses (at 0.41 mg/kg; ERAUC, 11).

In a pre/postnatal development study in rats, birth weight and postnatal body weight gain were reduced (both sexes) and sexual development was delayed (males only) in pups of dams treated with 1.63 mg/kg SC dulaglutide every 3 days from gestation day 6 and throughout lactation ($ER_{AUC}$, 16). Delayed pup development has been reported in pre/postnatal studies with other GLP-1 receptor agonists and is likely at least partly

secondary to pharmacologically mediated effects on maternal body weight. Increased locomotor activity and changes in response to an acoustic startle stimulus, tested immediately post weaning in these pups, were attributed to the delayed development. While the body weight effects continued into adulthood, there was no persistent effect on locomotor activity or acoustic startle response. During a memory probe, female pups of dams that had received 1.63 mg/kg SC dulaglutide every 3 days had a longer mean escape time and a higher mean number of errors relative to the concurrent control during the second trial of the memory evaluation (assessed at 10 weeks of age); these effects were considered drug related and adverse. No treatment related differences were noted in this group during learning or in the first memory trial and no effects on memory were evident in male pups. The sponsor states that a juvenile rat study is planned. Findings from this study may help to understand the role of dulaglutide in the memory deficits observed in this study. No such deficits have been reported with other GLP-1 receptor agonists. The NOEL for effects on postnatal development in the rat is 0.49 mg/kg SC every 3 days ($ER_{AUC}$, 4.5).

### *Pregnancy classification*

The sponsor has proposed Pregnancy Category B3.[11] This is considered appropriate given the increase in post implantation loss, foetal growth retardation and foetal anomalies observed in the embryofoetal development studies.

## Local tolerance

Dosing solutions for SC injection used in the repeat dose toxicity studies contained dulaglutide at concentrations up to 3.3 (mouse), 5.4 (rat) or 13.5 times (monkey) the clinical strength (3 mg/mL). Injection site reactions in animals were generally minimal to slight in severity and not always significantly different from control sites. Minimal injection site reactions are predicted with clinical use.

## Immunotoxicity and immunogenicity

Dulaglutide did not induce ADCC *in vitro* (using cells expressing the human GLP-1 receptor as the target cells and human peripheral blood mononuclear cells as the effector cells), and there was no evidence of complement activation in a 5 week study in Cynomolgus monkeys (based on C3a and Bb complement split products), suggesting minimal interaction of the Fc domain of dulaglutide with the immune system.

There was no evidence of immunotoxicity in the repeat dose toxicity studies. The effects on the lymphoid tissues were secondary to body weight effects and are not considered to be clinically relevant. After 9 months treatment, lower circulating B and CD4+ T cell levels were reported for some treated monkeys, but there was no clear dose response and the effects were not consistent across sexes. Furthermore, the T cell dependent antibody response was unaffected in Cynomolgus monkeys that received ≤8.15 mg/kg SC dulaglutide twice weekly for 9 months ($ER_{AUC}$, 474). Taken together, no significant immunotoxic risk is predicted for patients.

The assessment for ADAs was limited; they were only examined (but not quantitated) in Cynomolgus monkeys. ADAs were detected in treated monkeys in the 5 week study, but not the longer term 13 week and 9 month studies, suggesting low immunogenicity. Neutralising ability was not assessed. There was some indication of ADA production in mice and rabbits, with lower drug exposures observed with repeated dosing; such a

[11] Pregnancy Category B3: "Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans."

scenario was not seen in rats. The presence of ADAs (or their potential presence) in the toxicity studies is not expected to significantly affect the safety assessment, though their presence resulted in lower than expected exposures in the mouse carcinogenicity study.

### Paediatric use

Dulaglutide is not proposed for paediatric use and no specific studies in juvenile animals were submitted. As indicated above, a juvenile animal toxicity study is planned. This study should be submitted for evaluation to the TGA in any future submission.

## Nonclinical summary and conclusions

### Summary

The overall quality of the nonclinical dossier was high. All pivotal safety-related studies were GLP compliant.

- Dulaglutide incorporates a GLP-1 analogue sequence linked to a modified human IgG4 heavy chain fragment. The drug was shown to bind to the human GLP-1 receptor with nanomolar affinity and act as a full agonist of the receptor. Dose and glucose dependent enhancement of insulin secretion from rat and monkey pancreatic islet cells was demonstrated for the drug in vitro. In vivo, dulaglutide showed glucose dependent insulinotropic activity in both rats and Cynomolgus monkeys. Long lasting activity was evident in monkeys.
- Like native GLP-1, dulaglutide showed high selectivity for the human GLP-1 receptor over glucagon and GIP receptors. The drug did not induce ADCC against cells expressing human GLP-1 receptors and there was no evidence of complement activation in treated monkeys.
- CNS and respiratory function were unaffected in Cynomolgus monkeys at high exposures. Some inhibition of hERG K+ tail current was observed in vitro with prolongation of the QTc interval seen in Cynomolgus monkeys, but only at very high (plasma) concentrations. Increased heart rate was also observed in studies in monkeys, and is a class effect.
- The pharmacokinetics of dulaglutide in laboratory animal species (mice, rats and Cynomolgus monkeys) were characterised by slow absorption from the SC injection site and a long plasma half life. As with human subjects, there was some evidence of accumulation in rats and monkeys. Lower exposures were seen in mice following repeated dosing, suggestive of ADA production in this species. No distribution, metabolism, excretion or pharmacokinetic interaction studies were submitted. Limited tissue distribution is expected.
- Repeat-dose toxicity studies were conducted in mice, rats and Cynomolgus monkeys using the clinical route (SC) and achieving high exposure multiples. The chief findings in toxicity studies were similar to those seen with other GLP-1 receptor agonists, comprising effects associated with the primary pharmacological action (reduced food consumption, lower body weight gain [or body weight loss]), effects secondary to these (abnormal oestrous cycling, atrophy of the male reproductive organs and lymphoid depletion), and proliferative changes in the thyroid (rodents only). There was some evidence that dulaglutide exacerbated spontaneous lesions of the pancreas in diabetic (but not normal) rats.
- No genotoxicity studies were submitted, which is considered acceptable for this type of product. No drug related increase in tumour incidence was seen in a 6 month carcinogenicity study in transgenic mice, but exposures were lower than optimal. A

treatment related increase in the incidence of thyroid C cell adenomas and thyroid C cell carcinomas was seen in rats treated with dulaglutide in a 21.5 month study.

- Fertility was unaffected in male and female rats treated with dulaglutide at exposure levels ≥30 times the clinical AUC. Increased post implantation loss, decreased foetal weight, impaired ossification (rats), and increased skeletal and visceral abnormalities (rabbits) were seen in embryofoetal development studies, but only in the context of significant maternotoxicity. Lower birth weight, delayed growth and development, and memory deficits (in females) were evident in pups of rats treated with dulaglutide during pregnancy and lactation.
- Injection site reactions in animals were generally minimal to slight in severity and not always significantly different from control sites.

**Conclusions and recommendation**

- Primary pharmacology studies, showing potent and long lasting effects mediated by GLP-1 receptor activation, support use in T2DM.
- Overall, the toxicity profile of dulaglutide is similar to that of currently registered GLP-1 receptor agonists. The following animal findings are considered to be potentially clinically relevant:
  - increased heart rate
  - emesis, reduced food consumption and body weight loss
- A risk for thyroid carcinogenicity cannot be completely dismissed but there is no greater risk with dulaglutide compared to currently registered long acting GLP-1 receptor agonists. Available data support that rodents are particularly sensitive to proliferative thyroid changes induced by this drug class. The absence of thyroid changes in monkeys treated with dulaglutide for 12 months at a dose estimated to yield close to 500 times the clinical exposure offers support for likely limited clinical relevance of the rodent thyroid carcinogenicity findings.
- Adverse effects on embryofetal and pre/postnatal development observed in animals most likely occurred secondary to maternotoxicity. The underlying cause for memory deficits in female rats following maternal dosing is unknown. The sponsor states that a juvenile rat study is planned. This study should be provided to the TGA in a subsequent submission.
- There are no objections on nonclinical grounds to the proposed monotherapy indication. No studies were submitted to support combination use; this needs to rely solely on clinical data.

# IV. Clinical findings

## Introduction

### Guidance

The TGA has adopted the following guidance documents related to this product:

- Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Diabetes Mellitus CPMP/EWP/1080/00 30 May 2002,[12] adopted by TGA 23 October 2002;
- Points to Consider on Applications with 1. Meta-analyses; 2. One Pivotal Study CPMP/EWP/2330/99,[13] adopted by TGA 22 March 2002.

### Contents of the clinical dossier

The submission contained the following clinical information:

- 20 clinical pharmacology studies, including 16 that provided pharmacokinetic data and 8 that provided pharmacodynamic data (some studies included both pharmacokinetics and pharmacodynamics);
- 5 studies that provided information on use, injection site location and different delivery devices;
- 2 population pharmacokinetic analyses;
- 5 pivotal efficacy/safety studies;
- 3 other efficacy/safety studies;
- 1 meta-analysis on cardiovascular risk.

### Paediatric data

The submission did not include paediatric data.

A Paediatric Investigation Plan (PIP) was agreed in Europe. A waiver of the requirement to conduct studies in paediatric patients younger than 10 years of age was granted in the EU in January 2011 (PIP decision P/37/2011). Study of dulaglutide in paediatric patients aged from 10 to 18 years was deferred. In October 2013, the sponsor requested a modification to the PIP in Europe which included the request that the PIP include a juvenile toxicology study which would delay the initiation of the clinical study in paediatric patients.

The FDA has agreed that clinical studies in paediatric patients could be delayed until completion of the juvenile toxicology study and until FDA agrees that there is sufficient evidence of efficacy and safety in adults. A waiver has also been requested in children aged 0 to <10 years.

### Good clinical practice

The clinical study reports state that all clinical trials in the dulaglutide clinical development program were conducted in accordance with:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and The Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
- the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guideline E6[14] and
- applicable laws and regulations.

[12] European Medicines Agency, "Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (CPMP/EWP/1080/00 Rev. 1)", 14 May 2012.
[13] European Medicines Agency, "Points to Consider on Applications with 1. Meta-analyses; 2. One Pivotal Study (CPMP/EWP/2330/99)", 31 May 2001.
[14] ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6, 10 June 1996.

Clinical trials conducted outside of the EU meet the ethical requirements of Directive 2001/20/EC.

## Pharmacokinetics

### Studies providing pharmacokinetic data

Table 9 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

**Table 9: Submitted pharmacokinetic studies.**

| PK topic | Subtopic | Study ID | Primary aim |
|---|---|---|---|
| **PK in healthy adults** | General PK - Single dose | GBCA | PK/PD |
| | | GBDR | IM vs SC |
| | | GBDT | Auto-injector vs syringe |
| | | GBCN | Injection site and high and low BMI |
| | | GBCB | PD |
| | - Multi-dose | GBCL | PD |
| | | GBCZ | Dose response |
| | | GBCD | PD |
| | Bioavailability - Single dose | GBCN | Injection site and high and low BMI |
| | | GBDR | IM vs SC |
| | - Multi-dose | | |
| | Device | GBDT | Auto-injector vs syringe |
| **PK in special populations** | Target population § - Single dose | GBCB | PK/PD Japanese |
| | | GBCD | PK/PD |
| | - Multi-dose | GBCL | PK/PD Japanese |
| | | GBCD | PK/PD |
| | Hepatic impairment | GBDO | PK |
| | Renal impairment | GBCM | PK |
| | Elderly | GBCT | PK |
| **PK interactions** | Lisinopril | GBCO | interaction |
| | Atorvastatin | GBCP | interaction |
| | Oral contraceptive | GBCQ | interaction |
| | Digoxin | GBCR | interaction |
| | Warfarin | GBCS | interaction |
| | Sitagliptin | GBDW | interaction |
| **Population PK analyses** | Healthy subjects | Pop-1 | Pop PK/PD |
| | Target population | Pop-1 | Pop PK/PD |
| | | Pop-2 | Pop PK/PD |

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

### Evaluator's conclusions on pharmacokinetics

An extensive pharmacokinetic programme was conducted and the studies were all appropriately designed and conducted. After a single SC 1.5 mg dose, PK results were generally similar between healthy subjects and patients with T2DM. The main PK parameters were: Cmax = 114 ng/mL, Tmax = 48 hours (range 24 to 72 hours), mean $AUC_{0\text{-}168h}$ = 1400 ng•hr/mL, T½ = 4.7 days. Steady state was reached between the 2nd and 4th doses of dulaglutide. The exposure to dulaglutide increased less than proportionally with increasing dose in the 0.5 mg to 1.5 mg dose range. Accumulation after 1.5 mg

multiple dose administration was approximately 1.56 fold and was predictable from single dose data.

No dose adjustment of dulaglutide is needed based on body weight, age, sex, race, ethnicity, or renal or hepatic impairment. The mean effects of intrinsic factors on pharmacokinetic parameters (AUC and Cmax) were generally within the inter subject pharmacokinetic variability of dulaglutide.

Dulaglutide did not have any significant drug interactions with the drugs studied. Therefore no dose adjustment is recommended for any of the commonly used drugs when co-administered with dulaglutide.

## Pharmacodynamics

### Studies providing pharmacodynamic data

Table 10 shows the studies relating to each pharmacodynamic topic and the location of each study summary.

**Table 10: Submitted pharmacodynamic studies.**

| PD Topic | Subtopic | Study ID | Primary aim |
|---|---|---|---|
| **Primary Pharmacology** | Effect on glycaemic control | GBCA | Single dose - HS |
| | | GBCI | Insulin secretion |
| | | GBCB | Single dose T2DM |
| | | GBCL | Multiple dose – T2DM |
| | | GBCZ | Dose response – T2DM |
| | | GBCD | Dose response – T2DM |
| | Effect on gastric emptying | GBCH | PK - HS |
| | | GBDM | PK - T2DM |
| **Secondary Pharmacology** | Effect on QT interval | GBCC | Effect on QTc<br>Meta-analysis |
| **Population PK-PD analyses** | Target population | Pop-1 | Pop PK/PD |
| | | Pop-2 | Pop PK/PD |

HS = healthy subjects; T2DM = type 2 diabetes mellitus.

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

### Evaluator's conclusions on pharmacodynamics

The pharmacodynamic clinical studies documented the expected GLP-1 mediated effects, including glucose dependent increases in insulin secretion, inhibition of glucagon secretion, delay in gastric emptying and modest weight loss. These mechanisms work in concert to reduce fasting and post prandial plasma glucose concentrations by modulating both glucose appearance (slowing of gastric emptying, inhibition of glucagon secretion) and glucose disposal (β cell effects), thereby leading to reduction in HbA1c and overall glycaemic benefit.

## Dosage selection for the pivotal studies

Dosing for the efficacy studies was based on the results of the clinical pharmacology studies in healthy subjects and patients with T2DM, pharmacokinetic modelling and simulation and dulaglutide dose concentration response relations of pharmacodynamics and safety measures. The initial clinical pharmacokinetic studies studied dulaglutide in the 0.05 to 12 mg dose range and established that the maximum tolerated dose was 3 mg

dulaglutide once weekly. The selection of the doses used in the Phase III studies was determined by data from Study GBCF and confirmed by the population PK/PD dose response analyses of the data.

The first efficacy study (GBCF) was a 104 week, adaptive, inferentially seamless, placebo controlled study comparing the efficacy of dulaglutide to sitagliptin in patients with T2DM on metformin. The purpose of the first, dose finding stage of Study GBCF was to identify an optimal or maximal utility dose based on a clinical utility index (CUI), using pre specified measures of efficacy (HbA1c and weight) and safety (diastolic blood pressure [DBP] and heart rate [HR]). A second dose was also selected, to mitigate the potential risk if a safety signal was subsequently observed with the maximal utility dose. The second dose level was required to have a CUI ≥0.6 and be ≤50% of the maximal utility dose, to ensure minimum overlap of dulaglutide exposure. The study's initial dose finding portion assessed seven doses of dulaglutide (0.25, 0.5, 0.75, 1.0, 1.5, 2.0, and 3.0 mg).

Dulaglutide 1.5 mg was selected as the dose with the optimal benefit-risk profile, and dulaglutide 0.75 mg was selected as the lower dose to be continued for the purposes of confirmation of long term safety and efficacy in Study GBCF and subsequent Phase III studies.

The once weekly dosing regimen was supported by the PK data: maximum concentrations of dulaglutide are reached at ~48 hours and the half life is ~4.7 days; apparent clearance is 0.107 L/hr. This extended pharmacokinetic profile makes dulaglutide suitable for once weekly administration. Steady state plasma dulaglutide concentrations were achieved between 2 and 4 weeks of once weekly administration. Consistent with its pharmacokinetic profile, dulaglutide has a pharmacodynamic profile suitable for once weekly administration.

## Efficacy

### Studies providing efficacy data

The following pivotal efficacy studies provided data:

- Study H9X-MC-GBCF: A Phase 2/3 Placebo Controlled, Efficacy and Safety Study of Once Weekly, Subcutaneous LY2189265 [Dulaglutide] Compared to Sitagliptin in Patients with Type 2 Diabetes Mellitus.
- Study H9X-MC-GBDA: A Randomised, Placebo-Controlled Comparison of the Effects of Two Doses of LY2189265 or Exenatide on Glycaemic Control in Patients with Type 2 Diabetes on Stable Doses of Metformin and Pioglitazone (AWARD-1: Assessment of Weekly AdministRation of LY2189265 in Diabetes-1)
- Study H9X-MC-GBDB: A Randomised, Open-Label, Parallel-Arm, Non-inferiority Comparison of the Effects of Two Doses of LY2189265 and Insulin Glargine on Glycaemic Control in Patients with Type 2 Diabetes on Stable Doses of Metformin and Glimepiride (AWARD-2: Assessment of Weekly AdministRation of LY2189265 in Diabetes-2)
- Study M9X-MC-GBDC: The Impact of Weekly Administration of LY2189265 versus Metformin on Glycaemic Control in Early Type 2 Diabetes Mellitus (AWARD-3: Assessment of Weekly AdministRation of LY189265 in Diabetes-3)
- Study M9X-MC-GBDD: The Impact of LY2189265 versus Insulin Glargine Both in Combination with Insulin Lispro for the Treatment to Target of Type 2 Diabetes Mellitus (AWARD-4: Assessment of Weekly AdministRation of LY2189265 in Diabetes-4)

The following other efficacy studies provided data:

- Study M9X-MC-GBCJ: The Effect of Dose Titration of LY2189265 (GLP-1 analog IV-Fc) in Overweight and Obese Patients with Type 2 Diabetes Mellitus (The EGO Study)
- Study M9X-MC-GBCK: Assessment of Dose-Dependent Effects of LY2189265 on Glycaemic Control in Patients with Type 2 Diabetes Treated only with Lifestyle Interventions
- Study M9X-MC-GBDN: The Effect of LY2189265 on Blood Pressure and Heart Rate, as Assessed by Ambulatory Blood Pressure Monitoring, in Patients with Type 2 Diabetes Mellitus

### Evaluator's conclusions on efficacy

An extensive clinical program was conducted to support the indication being requested. There is strong consistency across the studies. The studies were conducted such that they covered the different stages in the continuum of treatment and included: monotherapy in treatment naïve patients (Study GBDC), combination therapy as add on to metformin (Study GBCF), metformin and exenatide (Study GBDA), metformin and glimepride (Study GBDB) and metformin and insulin (Study GBDD).

At all primary time points in the 5 pivotal studies, once weekly dulaglutide 1.5 mg was superior to the active comparator with a corresponding greater proportion of patients reaching an HbA1c of <7% and <6.5%. Dulaglutide administered once weekly 0.75 mg was superior to active comparator in 4 of the 5 pivotal studies and non inferior to insulin glargine in 1 study. The observed reductions in HbA1c, resulting in superior HbA1c control for all studied comparators for dulaglutide 1.5 mg (in all 5 Phase 3 studies) and dulaglutide 0.75 mg (in 4 of 5 Phase III studies [non inferior in Study GBDB]), represent a dose dependent clinical benefit of improved glycaemic control with dulaglutide 1.5 mg once weekly across different stages in the clinical progression of T2DM.

The observed HbA1c reductions are consistent with that seen with the other marketed GLP-1 receptor agonists exenatide and liraglutide.

Reductions in fasting blood glucose are consistent with the HbA1c changes. The reduction in body weight is modest.

## Safety

### Studies providing safety data

The following studies provided evaluable safety data:

#### *Efficacy studies*

In the efficacy studies, the following safety data were collected:

- General adverse events (AEs) were assessed by collection of treatment emergent adverse events (TEAEs) at each visit regardless of relationship to study drug
- AEs of particular interest, including acute pancreatitis, hyperglycaemia, hypoglycaemia, thyroid neoplasms, cardiovascular events were evaluated by review of the TEAEs and further investigation for definitive diagnosis if necessary
- Laboratory tests, including chemistry panel, complete blood cell count, urinalysis, albumin/creatinine ratio, amylase, lipase, calcitonin, and lipids, were performed at each study visit
- Body weight, BMI, waist circumference

- Vital signs (blood pressure and pulse rate)
- Electrocardiographs (ECGs) according to study schedule
- Immunogenicity was assessed by collection of blood at specified times during the studies and assessed by testing for antibody formation. Positive anti LY2189265 antibody samples were evaluated for their ability to neutralise the activity of LY2189265. Any anti LY2189265 antibody samples found to be neutralising to the activity of LY2189265 were also tested for cross reactivity with native GLP-1.

***Studies that assessed safety as a primary outcome***

Study GBDN was a study that assessed safety as a primary outcome.

***Dose response and non pivotal efficacy studies***

The dose response and non pivotal efficacy studies provided safety data similar to the pivotal studies.

**Patient exposure**

The sponsor has evaluated the safety by integrating the data from the efficacy studies into 2 datasets that allowed a detailed analysis of the potential safety concerns:

- Analysis set 1 (AS1): comparison to placebo using trials with placebo duration of 26 weeks
- Analysis set 3 (AS3): long term safety (overall dulaglutide) and differential dose (1.5 mg versus 0.75 mg) for up to 104 weeks.

The trials included in each analysis set are shown in the table below and it is noted that there is overlap between the datasets.

The full safety dataset comprises 6,005 patients included in the efficacy studies, of who 4,006 received at least 1 dose of dulaglutide (Tables 11-13).

**Table 11: Summary of total treatment duration categories and analysis sets used.**

| Study | Dulaglutide vs. Placebo | Dulaglutide 1.5 mg and 0.75 mg | Total duration |
|---|---|---|---|
| GBCJ[a] | 16 weeks | | 16 weeks |
| GBCK[a] | 12 weeks | | 12 weeks |
| GBCZ[a] | 12 weeks | | 12 weeks |
| GBDN[a] | 26 weeks | x | 26 weeks |
| GBCF[b] | 26 weeks | x | 104 weeks |
| GBDA[b] | 26 weeks | x | 52 weeks |
| GBDB[b] | | x | 78 weeks |
| GBDC[b] | | x | 52 weeks |
| GBDD[b] | | x | 52 weeks |

Light shading (AS1): Integrated assessment of Dula_1.5 and Dula_0.75 (combined and separately) vs. placebo for placebo-controlled studies of planned duration ≥26 weeks.

Dark shading (AS3): Integrated assessment of Dula_1.5 vs. Dula_0.75 at full duration (26-104 weeks).

a, Phase II Studies.

b, Phase III Studies.

**Table 12: Exposure to dulaglutide and comparators in clinical studies.**

| | Exposure to Study Drug[a] | | Time on Observation | |
|---|---|---|---|---|
| | N | Patient-Years | N | Patient-Years |
| **Safety Population** | **6005** | **5536.6** | **6005** | **6194.0** |
| **Dulaglutide** | 4006 | 3531.2 | 4006 | 3983.7 |
| Dulaglutide <0.75 | 191 | 42.9 | 191 | 60.3 |
| Dulaglutide 0.75 | 1765 | 1724.2 | 1765 | 1932.8 |
| Dulaglutide 0.75 only | 1706 | 1695.1 | 1706 | 1898.1 |
| Dulaglutide 0.75 after Placebo[b,c] | 59 | 29.1 | 59 | 34.6 |
| Dulaglutide ~1.0 | 175 | 47.2 | 175 | 55.2 |
| Dulaglutide 1.5 | 1762 | 1689.1 | 1762 | 1900.6 |
| Dulaglutide 1.5 only | 1700 | 1661.0 | 1700 | 1865.3 |
| Dulaglutide 1.5 after Placebo[b,c] | 62 | 28.1 | 62 | 35.3 |
| Dulaglutide >1.5 | 113 | 27.7 | 113 | 34.9 |
| **Placebo[d]** | 703 | 283.9 | 703 | 324.3 |
| **Active Comparator** | | | | |
| Metformin | 268 | 226.7 | 268 | 254.8 |
| Sitagliptin | 439 | 637.3 | 439 | 680.6 |
| Sitagliptin only | 315 | 475.5 | 315 | 507.2 |
| Sitagliptin after Placebo[c] | 124 | 161.8 | 124 | 173.5 |
| Exenatide | 276 | 236.3 | 276 | 274.8 |
| Insulin Glargine | 558 | 621.2 | 558 | 675.7 |

N, Number of patients in the specified treatment group.

a, For some studies (GBDA, GBDB, GBDC, GBDD), if a patient ceased study drug during the study, the patient was requested to remain in the study. "Treatment exposure" does not include any time after cessation of study drug.

b, This group excludes patients in GBDA Placebo/Dula who discontinued study treatment while on Placebo, yet continued in study into the Dula portion of the study (n=3 Dula_0.75, n=0 Dula_1.5).

c, This group includes patients who received Placebo prior to receiving Dulaglutide or Sitagliptin.

d, This group includes patients who received Placebo only, and those who subsequently received Dulaglutide or Sitagliptin.

**Table 13: Exposure to dulaglutide in clinical studies according to dose and duration.**

| Total Treatment Duration (Cumulative) | All Dulaglutide-treated patients n | Dulaglutide 0.75 mg n | Dulaglutide 1.5 mg n |
|---|---|---|---|
| ≥ 1 day[a] | 4006 | 1671 | 1671 |
| ≥ 26 weeks[b] | 2761 | 1404 | 1357 |
| ≥ 52 weeks[c] | 1595 | 813 | 782 |
| ≥ 78 weeks[c] | 642 | 319 | 323 |
| ≥ 100 weeks[c] | 369 | 182 | 187 |
| ≥ 104 weeks[c] | 157 | 74 | 83 |

a, Exposure for primary safety population based on the Phase 2 and Phase 3 studies (GBCJ, GBCK, GBCZ, GBDN, GBCF, GBDA, GBDB, GBDC, GBDD).

b, Phase II and Phase III studies with 0.75 mg and 1.5 mg Dulaglutide Groups Safety Population, Studies GBCF, GBDA, GBDB, GBDC, GBDD, GBDN

c, All exposures beyond 26 weeks are from Phase 3 trials.

Note: Due to nature of 104 week treatment duration GBCF study visit schedule and visit windows, patients may have completed the treatment period in slightly less than 104 weeks therefore reporting ≥100 weeks gives a greater reflection of the number of patients completing the studies.

## Safety issues with the potential for major regulatory impact

### *Cardiovascular safety*

Studies have shown that GLP-1 receptor agonists may be associated with increased HR and stable or reduced systolic blood pressure (SBP).

Study GBCC studied the effect of dulaglutide on QT interval. Results from this study confirmed that dulaglutide did not cause a prolongation in QTc at supratherapeutic doses of 4 mg or 7 mg in healthy male and female subjects.

The overall effects of dulaglutide on SBP, DBP, and heart rate have varied across the clinical pharmacology and early efficacy studies. To address this, a large (N = 755), randomised, placebo controlled prospective study using 24 hour ambulatory blood pressure monitoring (ABPM) was conducted (Study GBDN) to evaluate the effects of dulaglutide on BP and heart rate. The results showed that dulaglutide 1.5 mg demonstrated a statistically significant 2.8 mm Hg reduction in mean 24 hour SBP compared to placebo, and a neutral effect on mean 24 hour DBP. Small increases in heart rate were observed in the dulaglutide 1.5 mg group compared to placebo at 16 weeks (2.84 bpm) and 26 weeks (3.50 bpm).

The integrated analyses confirmed the results reported in Study GBDN. Dulaglutide was associated with dose dependent mean increases in heart rate from baseline of 2 to 4 bpm. These increases in heart rate from baseline were evident at the earliest time points of measurement, were maximal by 8 weeks, and declined after 26 weeks. Associated with this waning of the increase in heart rate, the dulaglutide 1.5 mg and dulaglutide 0.75 mg doses were no longer significantly different by 39 weeks of therapy. The small mean increases in heart rate were not associated with increased reporting of specific tachyarrhythmia AEs.

In the integrated analyses, dulaglutide 1.5 mg is associated with a small decrease in mean SBP of approximately 2 mm Hg at 26 weeks. There is no clinically meaningful difference between dulaglutide 1.5 mg and 0.75 mg in reducing SBP. No other effects were observed with dulaglutide 1.5 mg on other cardiovascular (CV) parameters except small increases in PR interval[15] (2 to 3 msec) with 2.4% incidence of first degree, but not higher degrees, of atrioventricular block (AVB).

In accordance with FDA and European Medicines Agency (EMA) guidelines, the sponsor conducted a meta analysis of CV data (meta analysis report) from the completed dulaglutide clinical studies to assess the cardiovascular risk of dulaglutide. The primary objective of the meta analysis was to compare the time from randomisation to the first occurrence of any independently adjudicated event of the 4 composite CV endpoints: death due to CV causes, nonfatal myocardial infarction (MI), nonfatal stroke, or hospitalisation for unstable angina (that is, 4 component major adverse cardiovascular event [MACE]). Patients treated with dulaglutide in the 9 completed clinical efficacy studies were compared with patients who were administered comparators (placebo and active comparators combined) to demonstrate that the upper bound of the (adjusted) 95% CI for the HR was <1.8. A total of 51 patients (dulaglutide: 26 [N = 3885]; all comparators: 25 [N = 2125]) experienced at least one adjudicated 4 component MACE endpoint in the 9 studies. Based on the pre specified alpha spending function, and the number of unique events included in this meta analysis, the alpha spent is 0.0198 and the corresponding significance level is 98.02%. The meta analysis results demonstrated an estimated hazard ratio: 0.57; adjusted [98.02%] CI: 0.30, 1.10; p=0.046) for dulaglutide versus all comparators (active and placebo) indicating that treatment with dulaglutide is not associated with an increase in the risk of experiencing a 4 component MACE endpoint compared with control therapies. The 1.10 value for the upper bound of the CI for the hazard ratio satisfies the FDA stipulated limit of 1.8 and thereby meets the criterion set forth for submission of a new diabetes drug. Various sensitivity analyses using different populations, analysis methodologies, and additional types of CV events (for example,

[15] The PR interval is the period, measured in milliseconds, that extends from the beginning of the P wave (the onset of atrial depolarisation) until the beginning of the QRS complex (the onset of ventricular depolarisation); it is normally between 120 and 200ms in duration.

coronary revascularisation procedures or hospitalisation for heart failure) showed similar conclusions that dulaglutide is not associated with an increased risk of experiencing a CV event.

### *Immunogenicity*

*Anti drug antibodies (ADAs)*

All patients in all the clinical pharmacology and efficacy and safety studies had blood collected at specified times to test for antibodies to dulaglutide.

The overall incidence of treatment emergent dulaglutide ADAs was low: 1.6% as compared to 0.7% observed in patients treated with placebo or non GLP-1 comparators. In Study GBDA, the incidence of treatment emergent exenatide ADAs in exenatide twice daily (bis is die; BID) treated patients was 44.6%.

In the majority of dulaglutide exposed patients who developed treatment emergent dulaglutide ADAs, the intensity of immune response, as measured by absolute antibody titre and/or change in titre, was mild. Four patients had a high (≥1:128) treatment emergent dulaglutide ADA titre. One patient had progressive increases in antibody titre over time, but the titre remained in the low range (<128) until the completion of the trial. No dose effect was observed with respect to the incidence of treatment emergent dulaglutide ADAs across the range of dulaglutide doses included in efficacy dulaglutide studies.

Among the 64 patients with treatment emergent dulaglutide ADAs, approximately half (34; 0.9% of the overall population) had dulaglutide neutralising ADAs. There were also 4 patients with treatment emergent dulaglutide ADAs, with neutralising activity against native sequence (ns)GLP-1 (0.1% of the overall population).

Overall, no obvious pattern was detected in the relationship between the presence of dulaglutide ADAs and change in HbA1c from baseline.

The GLP-1 analogue portion of dulaglutide is ~90% homologous to native human GLP-1(7-37) and contains amino acid substitutions designed to optimise its clinical profile, including protection from DPP-4 inactivation and reduction of immunogenicity. The IgG4-Fc portion of the molecule was also modified to prevent half antibody formation and to reduce the potential for interaction with high affinity Fc receptors that may result in activation of immunologic cytotoxicity. The results for dulaglutide indicate that the structural modifications in the GLP-1 and Fc parts of the dulaglutide molecule together with high homology with native GLP-1 and native Fc resulted in low immunogenicity and low risk of immune mediated adverse events.

*Hypersensitivity reactions*

The incidence of systemic hypersensitivity AEs was low in dulaglutide treated patients and was similar to the incidence with placebo (dulaglutide 7 patients [0.3%]; placebo 5 patients [0.7%]). In the long term studies, the incidence of systemic hypersensitivity adverse events was greater in the dulaglutide 0.75 mg treated patients (13, 0.8%) than dulaglutide 1.5 mg treated patient (3, 0.2%). There were no systemic hypersensitivity adverse events in any of the 64 dulaglutide treated patients with treatment emergent dulaglutide ADAs, including patients with high or progressive treatment emergent dulaglutide titres. Overall, these data do not indicate an increased risk of systemic hypersensitivity AEs with dulaglutide treatment.

### *Malignancy*

In the dulaglutide clinical program, there was no increased reporting of malignancy in general, nor any specific type of malignancy, associated with dulaglutide compared with placebo or active comparators.

Two categories of special interest with dulaglutide, and other GLP-1 receptor agonists, are thyroid and pancreatic malignancies.

- One case of medullary thyroid cancer occurred but the cancer appeared to have been pre-existing prior to dulaglutide treatment
- Two cases of pancreatic cancer were reported. One patient was diagnosed within 1 week of his first and only dose of dulaglutide, strongly suggesting a pre-existing condition. The second case was diagnosed 5 months after randomisation to dulaglutide. Assessment of this tumour determined it to be large, locally advanced, and unresectable. Given the patient's abbreviated time on study drug, the sponsor determined that this tumour was likely to be pre-existing.

### Postmarketing data

Not applicable.

### Evaluator's conclusions on safety

The safety assessment of dulaglutide included a large number of patients (over 4,000) in a large number of independent studies. The duration of most trials was relatively short but sufficient patients were treated over 1-2 years.

Overall the safety profile with dulaglutide is consistent with those of marketed GLP-1 receptor agonists. The most commonly reported adverse events are GI related, including nausea, vomiting, and diarrhoea. The onset of nausea and vomiting usually occurs early after drug initiation and attenuates quickly. These GI related AEs are, for dulaglutide fixed dose 1.5 mg, similar to dose titrated exenatide BID in a head-to-head comparison.

There was convincing evidence presented that dose titration was not necessary and the fixed dose of 1.5 mg was appropriate.

Dulaglutide demonstrated a dose dependent effect for increase in pancreatic enzymes. These increases were observed shortly after initiation of therapy, persisted for the duration of exposure and declined towards baseline with dulaglutide cessation. In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone, noted in routine serial assessment, were not predictive of acute pancreatitis.

Dulaglutide did not increase mean serum calcitonin levels over time compared with placebo and there was no increased reporting of potential C cell hyperplasia defined by unstimulated calcitonin measurements in dulaglutide treated patients compared with placebo or active comparator treated patients. There was one report of medullary thyroid carcinoma in a patient who received dulaglutide 2 mg for approximately 6 months in the dose finding stage of Study GBCF, but this cancer appeared to be pre-existing.

Differences in the hypoglycaemia risk for dulaglutide (either 1.5 mg or 0.75 mg) are mostly attributable to the known difference in the risk between concomitant insulin secretagogues versus concomitant non secretagogues, and are consistent with the differences in the mechanism of action on glucose metabolism.

High homology with native GLP-1 and native Fc was preserved whilst implementing structural modifications in these components of the dulaglutide molecule appear to minimise immunogenicity against dulaglutide. This was confirmed by the finding of only 1.6% of dulaglutide treated patients developing treatment emergent dulaglutide ADAs. Incidences of treatment emergent dulaglutide ADAs were lower in dulaglutide treated patients compared to treatment emergent exenatide ADAs in exenatide BID treated patients (Study GBDA: 1.6% versus 44.6%). Few dulaglutide treated patients had dulaglutide neutralising ADAs (0.9%) and/or developed neutralising ADAs for nsGLP

(0.1%). The incidence of systemic hypersensitivity adverse events was low in dulaglutide-treated patients and was similar to the incidence with placebo.

Dulaglutide had no detrimental or dose dependent effects on renal or hepatic function. There was no increased reporting of malignancy but the studies were insufficient in size and duration to fully assess the effects of dulaglutide to induce or promote these types of cancers.

## First round benefit-risk assessment

### First round assessment of benefits

The benefits of dulaglutide in the proposed usage are:

- Robust improvements in glycaemic control as measured by significant decreases in HbA1c and the percentage of patients achieving a HbA1c target of <7%
- Modest weight loss
- Sustained efficacy through 104 weeks
- Low risk of hypoglycaemia
- Low immunogenicity
- No dose adjustments for elderly patients or those with renal or hepatic impairment
- Convenient once weekly injection using easy to use single use pen or prefilled syringe.

### First round assessment of risks

The risks of dulaglutide in the proposed usage are:

- Risk consistent with other drugs in the GLP-1 receptor agonist class
- Hypoglycaemic episodes particularly in combination with insulin secretagogues or an insulin regimen
- Increases in pancreatic enzymes of similar magnitude to those observed with active comparators
- Systemic hypersensitivity reactions and immune mediated injection site adverse events but incidence low.

### First round assessment of benefit-risk balance

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

## First round recommendation regarding authorisation

Based on the clinical data included, it is recommended the application is approved.

## Clinical questions

No questions submitted.

## Second round evaluation

N/A

### Second round benefit-risk assessment

N/A

### Second round recommendation regarding authorisation

N/A

# V. Pharmacovigilance findings

### Risk management plan

The sponsor submitted a core Risk Management Plan (RMP), version 2, dated 12 November 2013 and Australian Specific Annex (ASA) dated 2 December 2013 and EU-RMP, version 4, dated 17 April 2014 and ASA, version 3, which were reviewed by the TGA's Office of Product Review (OPR).

### Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 14.

**Table 14: Ongoing safety concerns.**

| Summary of Safety Concerns | |
|---|---|
| **Important Identified Risks** | Hypoglycemia |
| **Important Potential Risks** | Acute pancreatitis<br>Effects on thyroid C-cells<br>Hypersensitivity<br>Pancreatic malignancy |
| **Missing Information** | Confirmation of memory deficits in directly dosed immature rats (for more details, see Part II, Module SII) |

### Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities for all ongoing safety concerns except for the missing information of "Conformation of memory deficits in directly dosed immature rats" for which no routine pharmacovigilance activities are proposed.

The sponsor describes additional pharmacovigilance for the missing information of "Confirmation of memory deficits in directly dosed immature rats" in form of a rat toxicology study.

Additional pharmacovigilance activities related to understanding effects of dulaglutide on thyroid C cells are proposed to be carried out in the US after approval of the product in this jurisdiction.

Furthermore, additional pharmacovigilance activities are proposed for the risk of acute pancreatitis.

### Risk minimisation activities

The sponsor concludes that routine risk minimisation activities are sufficient to mitigate the risk for the product.

**Reconciliation of issues outlined in the RMP report**

Reconciliation of issues outlined in the RMP report is as follows.

***Recommendation #1 in RMP evaluation report***

Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated Section 31 request and/or the nonclinical and clinical evaluation reports, respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.

***Sponsor response***

The nonclinical evaluator recommended the RMP section on Reproductive and Developmental Safety be amended as follows:

> *"Similar to Victoza, Byetta, and Bydureon, high doses of dulaglutide during midgestation in pregnant rats and rabbits caused reduced fetal growth and/or skeletal effects in association with maternal effects (decreased maternal food intake and decreased weight gain), but there was no evidence of ~~fetal malformations~~ direct teratogenicity."*

As it is now a requirement to provide the EU-RMP document, which has not currently adopted this change, the recommendation has been incorporated in the ASA.

No changes are required as a result of the clinical evaluation.

***OPR evaluator's comment***

The sponsor's response has been noted.

***Recommendation #2 in RMP evaluation report***

It is brought to the Delegate's attention that the use of the product as monotherapy, which is a proposed indication in Australia, is not indicated in EU or US.

***Sponsor response***

The indication proposed for the Australian PI is based on the 5 pivotal Phase III studies, 1 of which included a dulaglutide versus metformin monotherapy study (H9X-MC-GBDC [Study GBDC]). In Study GBDC, once weekly dulaglutide 1.5 mg and dulaglutide 0.75 mg monotherapy were superior to metformin in reduction in HbA1c from baseline at the primary endpoint (26 weeks). Of note, both nonclinical and clinical evaluators accept the use of dulaglutide as monotherapy.

Nonclinical Evaluation Report, page 6: "There are no objections on nonclinical grounds to the proposed monotherapy indication."

Clinical Evaluation Report, page 98: "An extensive clinical program was conducted to support the indication being requested. There is strong consistency across the studies. The studies were conducted such that they covered the different stages in the continuum of treatment and included: monotherapy in treatment naive patients (Study GBDC), combination therapy as add on to metformin (Study H9X-MC-GBCF), metformin and exenatide (Study H9X-MC-GBDA), metformin and glimepride (Study H9X-MCGBDB), and metformin and insulin (Study H9X-MC-GBDD).

***OPR evaluator's comment***

The sponsor's response has been noted.

***Recommendation #3 in RMP evaluation report***

As outlined in the TGA document "Mandatory requirements for an effective application", version 2.1, dated April 2014, the sponsor should submit the current EU-RMP for evaluation. A summary outlining any differences between the submitted core RMP and the current EU-RMP, and the rational for any differences, should also be submitted.

***Sponsor response***

The current version of the EU-RMP has been submitted for evaluation. A version of the EU-RMP has been provided with changes tracked to highlight the main difference between the core RMP and the current EU-RMP. In addition to the highlighted changes, the EU-RMP differs from the core RMP by inclusion of Section VI, Summary of Activities in the Risk Management Plan by Product, and by inclusion of different annexes.

The EU review of this document is ongoing and thus content in the current version is subject to change.

The ASA has also been revised to reflect that it is now an annex to the EU-RMP rather than an annex to the core RMP.

***OPR evaluator's comment***

The ASA refers to the core RMP rather than the EU-RMP; this should be corrected in a future update to the ASA.

***Recommendation #4.1 in RMP evaluation report***

Changes to the table of ongoing safety concerns as outlined: pharmacovigilance and risk minimisation activities should be assigned to these potential risks/missing information as appropriate.

The product is derived in the GS-CHO K1SV cell line which is of Hamster origin. Consequently, hypersensitivity to Hamster protein should be included as potential risk in the table of ongoing safety concerns.

***Sponsor response***

While the GS-CHO K1SV cell line produces Host Cell Protedesigned to remove the Host Cell Protein (HCP) to low levels. Therefore, the potential risk of developing hypersensitivity to the HCP is very low. In addition, hypersensitivity is already included as an 'Important Identified Risk' irrespective of the underlying cause and would capture any such unlikely reactions.

***OPR evaluator's comment***

The sponsor's justification for not including "Hypersensitivity to Hamster Proteins" as an ongoing safety concern in the RMP has been noted.

However, it is recommended to the Delegate that the sponsor adds the following to the PI and Consumer Medicine Information (CMI):

- Describes the origin of the cell line used in the production of the product in the PI
- Adds a warning statement for individuals who are allergic to hamster proteins in the CMI.

This will ensure safer use of the product in patients with known sensitivity to hamster proteins. Please also refer to the Advisory Committee on the Safety of Medicines (ACSOM) advice regarding this point.

***Recommendation #4.2 in RMP evaluation report***

It appears that antibiotics are used in the production process of the product. Consequently, hypersensitivity to the relevant antibiotics should be included as potential risk in the table of ongoing safety concerns.

***Sponsor response***

Antibiotics are not used in the production of dulaglutide and consequently hypersensitivity to antibiotics should not be listed as an ongoing safety concern.

***OPR evaluator's comment***

The sponsor's response has been noted.

***Recommendation #4.3 in RMP evaluation report***

It appears that bovine serum albumin is used in the production process of the product. Consequently, transmission of infectious agents of bovine origin should be included as potential risk in the table of ongoing safety concerns.

***Sponsor response***

Module 3.2.R addresses the requirements for preventing transmission of infectious agents according to the guidance provided by the TGA.[16] The risk of infection has been assessed by the Biological Sciences Section of the TGA and information provided has been found to comply with the adopted European Commission (2011C 73/01) note for guidance on minimising the risk of Transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01).[17] Therefore, it is established that there is no potential risk of transmission of infectious agents associated with dulaglutide, and thus is not included in the table of ongoing safety concerns.

***OPR evaluator's comment***

The sponsor's response has been noted.

***Recommendation #4.4 in RMP evaluation report***

"Safety in paediatrics" should be added as missing information in the table of ongoing safety concerns.

***Sponsor response***

The sponsor agrees to include patients <18 years of age as "Missing Information" in the appropriate sections and tables in the RMP as in practice these subpopulations may well be part of the target population despite the proposed wording in the Australian PI.

***OPR evaluator's comment***

This is considered acceptable.

***Recommendation #4.5 in RMP evaluation report***

As the product will be provided in ready to use devices (pen or prefilled syringe), and there is limited information available about the safety of this product in a home treatment setting, "Medication errors in the home treatment setting" should be included in the table of ongoing safety as potential risk.

***Sponsor response***

Consistent with the sponsor's risk management process, all risks associated with design, manufacture and use/labelling of these delivery systems have been assessed using

[16] Therapeutic Goods Administration, "Guidance 10: Adventitious agent safety of medicines", 9 August 2013.
[17] European Commission, "Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3)" 5 March 2011.

established risk analysis methodologies. Identified risks (for example, underdose, no dose, overdose, injection site bruising) were mitigated such that they were acceptable from a patient safety point of view.

Dulaglutide 1.5 mg is available as a single use, one dose, prefilled pen or a single use, one dose, prefilled syringe. This should sufficiently minimise the risk of accidental overdose and medication error. Comprehensive instructions for use will be made available to patients with every device as a PI. These instructions explain how to use the product correctly, and include diagrams showing the correct injection site and technique which further reduces the risk of error at home. A similar approach has been taken by manufacturers of other GLP-1 receptor agonists to sufficiently mitigate potential medication errors.

***OPR evaluator's comment***

The sponsor's response has been noted.

However, as there is limited information available about the use of the product in a home treatment setting, the RMP evaluator maintains the opinion that "Medication errors in a home treatment setting" should be added as potential risk. Pharmacovigilance and risk minimisation activities should be assigned to this potential risk as appropriate.

***Recommendation #4.6 in RMP evaluation report***

The following patient groups were excluded from the clinical development program and therefore, should be included in the table of ongoing safety concerns as missing information:

A) Women who were pregnant or breastfeeding,

B) Patients with severe GI disease

C) Patients with a personal or family history of medullary thyroid carcinoma

D) Patients with personal or family history of multiple endocrine neoplasia type 2.

***Sponsor response***

A) The sponsor agrees to include patients who are pregnant and/or breastfeeding as "Missing Information" in the appropriate sections and tables in the RMP as in practice these subpopulations may well be part of the target population despite the proposed wording in the Australian PI.

B) However, the sponsor disagrees that patients with severe GI disease should also be included in this category.

The sponsor has referred to the current definition of "Missing Information" as defined in Good Vigilance Practice Guideline (Revision 2) – December 2013, specifically: Gaps in knowledge related to safety or particular patient populations, which could be clinically significant. This is consistent with the concept of "important missing information" proposed in the ICH E2E guideline (Pharmacovigilance Planning) in 2004, a guideline upon which EU RMP principles have been based for the last 10 years.[18] It is also consistent with the more recent ICH E2C(R2) definition which is: 'critical gaps in knowledge for specific safety issues or populations that use the marketed product' (that is, the intent is that missing information constitutes an important gap in knowledge with respect to predicting the safety of the product as it will be used in the market place).

There is no commonly agreed definition of the term "severe GI disease". In the dulaglutide clinical development program, the patient was considered to have "severe GI disease," if a clinically significant gastric emptying abnormality (such as severe diabetic gastroparesis

[18] ICH Harmonised Tripartite Guideline: Pharmacovigilance Planning E2E, 18 November 2004.

or gastric outlet obstruction) was present, the patient previously underwent gastric bypass (bariatric) surgery, or the patient chronically took drugs that directly affected GI motility.

The proposed language in the original Australian PI provides specific language for each of the aforementioned conditions and appropriately reflects the fact that there is insufficient data to recommend the use of dulaglutide in these populations. The PI is also consistent with other medicines in the GLP-1 receptor agonist class.

As a result of this clear advice in the PI and the well known GI effects of this class of drugs, it is highly unlikely that a clinician would prescribe them in patients with underlying severe GI disease. Neither are we aware of any evidence that this is occurring in practice. As a result of these considerations, the fact that severe GI disease was an exclusion criterion in the clinical development program would not of itself warrant missing information as this subpopulation is not expected to be part of the target population in real world clinical practice, unlike children/adolescents.

C & D) The sponsor disagrees that patients with a personal or family history of medullary thyroid carcinoma and multiple endocrine neoplasia type 2 should be added as "Missing Information". Routine pharmacovigilance activities will capture the use of dulaglutide in any patient who may have a personal or family history of medullary thyroid carcinoma and multiple endocrine neoplasia type 2; therefore, there is no reason to include this as "Missing Information." Additionally, the sponsor will perform ongoing monthly reviews and periodic aggregate reviews of adverse events of thyroid cancer. Lilly does not believe that information regarding medullary thyroid carcinoma and multiple endocrine neoplasia type 2 constitutes a gap in knowledge with respect to predicting safety as patients with these disorders are not intended to use dulaglutide.

***OPR evaluator's comment***

A) This is considered acceptable.

B) Pending agreement of the sponsor's justification by the Office of Medicines Authorisation (OMA), this is considered acceptable.

C & D) The RMP evaluator maintains the opinion that these two patient groups should be added as missing information in the RMP. Pharmacovigilance and risk minimisation activities should be assigned as appropriate. In particular, it is recommended to the Delegate that the sponsor adds a statement in the PI describing that there is no experience in using the product in these patient groups.

***Recommendation #4.7 in RMP evaluation report***

"Rapid weight loss" should be added as potential risk.

***Sponsor response***

The sponsor disagrees that rapid weight loss should be an "Important Potential Risk" for dulaglutide.

> *RMP evaluator's comment: The sponsor has in detail elaborated on this aspect and provided data from clinical trials. For full details, please refer to the sponsor's Section 31 response.*

***OPR evaluator's comment***

Pending agreement of the sponsor's justification by OMA, this is considered acceptable.

***Recommendation #4.8 in RMP evaluation report***

The sponsor states: The clinical experience with dulaglutide in patients ≥75 years of age is limited. Consequently, "Safety in the very elderly (≥75 years old)" should be added as missing information.

***Sponsor response***

The sponsor agrees to add the use of dulaglutide in patients aged ≥75 years as "Missing Information" in the appropriate sections and tables in the RMP. While the data are limited in the population aged 75 years and older, efficacy and safety data support the similarity of PK profiles in older patients compared with younger patients; therefore no dosage adjustment is necessary for this population. The sponsor believes it is appropriate to inform prescribers of the limited clinical data in the oldest age demographic category.

***OPR evaluator's comment***

Addition of "Use of dulaglutide in patients aged ≥75 years" as missing information to the RMP is considered acceptable.

The statement in the PI is considered acceptable, pending the Delegate's approval.

***Recommendation #4.9 in RMP evaluation report***

The sponsor states: There is limited experience in patients with severe renal impairment or end stage renal disease. Consequently, "Safety in patients with severe renal impairment or end stage renal disease" should be added as missing information to the table of ongoing safety concerns.

***Sponsor response***

The sponsor accepts that due to limited exposure in patients with severe renal impairment and end stage renal disease (ESRD), these will be added as "Missing Information" to the RMP for dulaglutide.

The wording proposed in the original Australian PI states: Dosage and Administration: Use in Renal Impairment - No dosage adjustment is required in patients with renal impairment. There is limited experience in patients with severe renal impairment (eGFR [by CKD EPI] <30 ml/min/1.73 $m^2$) or ESRD.

***OPR evaluator's comment***

Addition of "Patients with severe renal impairment and end stage renal disease (ESRD)" as missing information is considered acceptable.

However, it is noted that the following statement is included in the Australian PI in section "Special Populations": No dose adjustment is needed based on age, gender, race, ethnicity, body weight, or renal or hepatic impairment. It is recommended to the Delegate that the sponsor amends this statement to specify that this recommendation is based on limited information for

1) Paediatric patients,

2) Very elderly patients, and

3) Patients with severe renal disease.

Please also note the ACSOM advice regarding this statement in the PI.

***Recommendation #4.10 in RMP evaluation report***

The sponsor states: There are limited data on patients with hepatic impairment, as patients with signs or symptoms of liver disease, current or historical chronic/acute hepatitis, and elevated alanine aminotransferase (>2.5x or >3x upper limit of normal) were excluded from participation in completed Phase II and Phase III dulaglutide studies.

Consequently, "Patients with hepatic impairment" should be included as missing information.

***Sponsor response***

The sponsor has referred to the current definition of "Missing Information" as defined in Good Vigilance Practice Guideline (Revision 2) – December 2013, specifically: Gaps in knowledge, related to safety or particular patient populations, which could be clinically significant.

In this context, the sponsor does not consider data in hepatic impairment to constitute a potentially clinically significant gap in knowledge in this population. Dulaglutide is a large peptide that is presumed to undergo proteolytic degradation to component amino acids independently of the hepatic cytochrome (CYP) P450 family of enzymes. Therefore, presence of hepatic disease in patients treated with dulaglutide is not expected to have a clinically significant impact on its metabolism.

In addition, the pharmacokinetics of dulaglutide in subjects with varying degrees of hepatic impairment, were compared to healthy patients (Study GBDO). Subjects with hepatic impairment had statistically significant decreases in dulaglutide exposure of up to 30% to 33% for Cmax and AUC, respectively, compared to healthy controls. There was a general increase in Tmax of dulaglutide with increased hepatic impairment. However, no trend in dulaglutide exposure was observed relative to the degree of hepatic impairment. Since there were no increases on dulaglutide concentrations, and therefore no safety concerns, plus concentrations remained at efficacious levels, these effects were not considered to be clinically relevant. Furthermore, a full evaluation of the hepatic safety of dulaglutide in the Phase II and Phase III clinical program did not reveal an association between dulaglutide exposure and negative effects on the liver (Summary of Clinical Safety).

Thus, based on data from the overall dulaglutide program, the sponsor concludes that "Patients with hepatic impairment" should be not be included as missing information in the RMP. The following recommendation remains in the Australian PI: Dosage and Administration: use in Hepatic impairment: *No dosage adjustment is required based on hepatic impairment.*

***OPR evaluator's comment***

Pending agreement of the sponsor's justification by OMA, this is considered acceptable.

***Recommendation #4.11 in RMP evaluation report***

It appears that the potential for co-administered drugs to influence the PK of dulaglutide was only studied with co-administration of sitagliptin. Consequently, "Potential for coadministered drugs to influence the pharmacokinetics of dulaglutide" should be listed as missing information.

***Sponsor response***

The sponsor does not agree that the "Potential for coadministered drugs to influence the pharmacokinetics of dulaglutide" should be listed as missing information. As noted in the previous point, dulaglutide is not anticipated to be eliminated intact in the urine or to be metabolised by the CYP P450 enzymes. Therefore, pharmacokinetic interactions with drugs that are primarily renally eliminated or metabolised by CYP450 enzymes are not expected.

Since dulaglutide contains a GLP-1 analog, and the activity of incretin hormones (including GLP-1) is limited by the DPP-4 enzyme, which rapidly hydrolyzes GLP-1 to produce inactive products, one plausible interaction would be with a DPP-4 inhibitor. However, dulaglutide was designed to have enhanced stability against DPP-4 inactivation, thereby increasing its duration of pharmacological activity.

A clinical pharmacology study tested the interaction between dulaglutide and sitagliptin, a DPP-4 inhibitor, thought to improve glycemic control by preventing the hydrolysis of

incretin hormones. In this study, a single dose of dulaglutide (1.5 mg) coadministered with steady state sitagliptin (100 mg) resulted in an increase in dulaglutide AUC and Cmax of approximately 38% and 27%; which are comparable to the PK variability for dulaglutide; and showed no safety concerns. Therefore these increases were considered to be not clinically relevant.

Thus, the sponsor believes that the potential for coadministered drugs to influence the PK of dulaglutide were sufficiently evaluated with the DPP-4 inhibitor, sitagliptin.

***OPR evaluator's comment***

Pending agreement of the sponsor's justification by OMA, this is considered acceptable.

***Recommendation #4.12 in RMP evaluation report***

A cardiovascular outcome study is ongoing at the time of evaluation. Consequently, it appears that cardiovascular safety has not been sufficiently established at present and therefore "Cardiovascular events" should be included in the table of ongoing safety concerns as missing information.

***Sponsor response***

The sponsor does not consider CV safety to be missing information. A CV meta analysis evaluating CV risk in the dulaglutide clinical program was performed by the sponsor. This analysis included data from the 9 dulaglutide Phase II and Phase III clinical studies with different comparators, background medications, and a broad spectrum of the T2DM population. The primary measure for the meta analysis was the time to first occurrence (after randomisation) of the 4 component MACE endpoint (death due to CV causes, nonfatal myocardial infarction, nonfatal stroke, and hospitalisation for unstable angina).

A total of 51 patients (All Comparators: 25 [1.18%]; All Dulaglutide: 26 [0.67%]) experienced a MACE endpoint in the 9 studies. These results show that treatment with dulaglutide is not associated with an increase in the risk of experiencing a MACE endpoint compared with control therapies (estimated HR: 0.57; adjusted 98.02% confidence interval (CI): [0.30, 1.10]). The upper bound of the adjusted two sided 98.02% CI for the estimated HR (1.10) was less than the FDA stipulated limits of 1.8 required for submission, and the incidence of the 4 component MACE in the All Dulaglutide group over time was consistently lower than the All Comparators group. Therefore, the primary objective of this meta analysis was met.

Consistent with the primary analysis, similar results were observed when the dulaglutide 1.5 mg dose was compared to the All Comparators group (HR: 0.59; 95% CI: [0.26, 1.30]). Analysis of the 3 component MACE (estimated HR: 0.60; 95% CI: [0.33, 1.08]) confirms the results of the primary measure. Evaluation of individual component endpoints showed no significant difference between dulaglutide and comparators for risk of death from CV causes, non fatal stroke, or hospitalisation for unstable angina. The incidence for non fatal stroke was numerically higher in the All Dulaglutide group compared to the All Comparators group, but with a HR CI that ranged from 0.42 to 6.20. The relative risk of experiencing a non fatal myocardial infarction was significantly lower with All Dulaglutide group compared with the All Comparators group. Overall, these data indicate that the incidence of major CV events is very low with dulaglutide treatment, and dulaglutide does not increase the risk of CV events.

The CV outcomes study (Study H9X-MC-GBDJ [REWIND]) is currently ongoing to assess the effect of dulaglutide on reducing MACE when added to existing antihyperglycaemic treatment in patients with T2DM who are at high risk for CV events. Patients enrolled in this study must be ≥50 years of age and have more advanced comorbidities (that is, established CV disease, documented subclinical CV disease, or multiple CV risk factors) than those typically enrolled in the studies with primary glycaemic efficacy objectives. This study completed enrolment in the third quarter of 2013. The completion of the study

is event driven with no prespecified last patient visit and thus the final study report is estimated to be available in the third quarter of 2019. This study will provide definitive data regarding the assessment of effects of long-term dulaglutide treatment with respect to the CV benefit versus risk profile.

***OPR evaluator's comment***

Pending agreement of the sponsor's justification by OMA, this is considered acceptable.

***Recommendation #5 in RMP evaluation report***

Additional pharmacovigilance activities related to understanding effects of dulaglutide on thyroid C cells are proposed to be carried out in the US after approval of the product in this jurisdiction. As the product has not yet been approved in the US, the sponsor should clarify how this ongoing safety concern will be addressed if the product would be approved in Australia but not in the US.

***Sponsor response***

The EU RMP, which will replace the core RMP, addresses the pharmacovigilance activities proposed for thyroid C cells in Europe.

Proposed Routine and Additional Pharmacovigilance Activities: 'Following the anticipated approval of dulaglutide in the US (2014), Lilly will join this surveillance programme, which is expected to end by 2025. In addition, Lilly plans to conduct a prospective database study to monitor events that are unlikely to be recorded in electronic medical records in 1 or more European countries. Lilly also proposes to conduct a retrospective database study to estimate incidence rates of adverse events in patients with T2DM treated with dulaglutide compared to other GLP-1 receptor agonists using existing databases and registries in Europe. Both studies will seek to investigate data on thyroid cancer.'

***OPR evaluator's comment***

The sponsor's response has been noted.

As the product has not yet been approved in the US or EU, it is recommended the sponsor implement additional pharmacovigilance activities in Australia, which are comparable to the currently proposed programs in the EU, if the product were approved in Australia but not in the USA and the EU. Please also refer to the ACSOM advice regarding this point.

***Recommendation #6 in RMP evaluation report***

The sponsor should provide an attachment to the ASA setting out all the forthcoming studies and the anticipated dates for their submission in Australia.

***Sponsor response***

The sponsor has provided a table of forthcoming studies as an attachment to the ASA.

It is not routine practice for sponsors to submit all studies in their clinical program to the TGA for evaluation. Submission of any of the studies included in the annex will be considered once the final study results are available. When a study adds significant value to the prescribing information, it may be submitted for inclusion in the PI; however, as the TGA process of submitting non safety related updates is exclusively via a category 1 application, there is limited opportunity to make regular updates.

Any safety related findings from the ongoing clinical program will be submitted to the TGA according to standard industry practices.

***OPR evaluator's comment***

The sponsor's response has been noted.

***Recommendation #7 in RMP evaluation report***

No protocol was provided for the "Active Surveillance Program for Cases of Medullary Thyroid Carcinoma", and the sponsor should submit a detailed outline about this additional pharmacovigilance activity as an attachment to the RMP.

***Sponsor response***

The sponsor will join an existing registry ("An Active Surveillance Program for Cases of Medullary Thyroid Carcinoma [MTC]") upon approval of dulaglutide by the FDA. The registry is part of a US, multi pharmaceutical medullary thyroid carcinoma cancer registry which utilises state cancer registries and uses a universal protocol that is already in existence. Upon dulaglutide marketing authorisation, the sponsor will join the registry, and be granted access to the full protocol.

***OPR evaluator's comment***

The sponsor's response has been noted.

***Recommendation #8 in RMP evaluation report***

It is noted that information regarding thyroid C cell malignancy is provided in the PI under the heading "Carcinogenicity". It appears that this constitutes a routine risk minimisation activity and therefore the sponsor should amend the ASA to outline that routine risk minimisation is carried out for this potential risk. The table in the ASA should also be amended to include the proposed wording in the PI for this potential risk.

***Sponsor response***

The sponsor has amended the ASA to outline that routine risk minimisation is carried out for the potential risk of thyroid C cell tumors (ASA Part III.1: Important identified risk or important potential risk or important missing information and overview of planned pharmacovigilance activities).

***OPR evaluator's comment***

This is considered acceptable.

***Recommendation #9 in RMP evaluation report***

The sponsor should provide justification as to why no routine risk minimisation is proposed for the potential risk of "Pancreatic Malignancy".

***Sponsor response***

There are no routine risk minimisation measures proposed for pancreatic neoplasm. However, the sponsor proposes ongoing monthly review of pancreatic malignancy and periodic aggregate review and reporting and these pharmacovigilance activities are described in the EU RMP.

***OPR evaluator's comment***

The sponsor's response has been noted.

However, the sponsor does not provide a justification as to why no risk minimisation activities are proposed for the ongoing safety concern of Pancreatic Cancer in the Australian PI.

It is recommended to the Delegate that the sponsor include wording in the Australian PI addressing the important potential safety concern of Pancreatic Cancer unless compelling justification can be provided for not doing so.

### *Recommendation #10 in RMP evaluation report*

The sponsor should submit a summary table as attachment to the ASA, outlining the wording, by which risk-minimisation is conducted in the EU Summary of Product Characteristics (SmPC) and the Australian PI. Justification for any significant differences in wording pertaining to the ongoing safety concerns in between the EU SmPC and the Australian PI should also be provided.

### *Sponsor response*

The ASA has been revised to include a comparison of the SmPC and Australian PI where the labelling is cited as a risk minimisation activity. The wording in the Australian PI is closely aligned with that of the SmPC; there are no significant differences.

### *OPR evaluator's comment*

This is considered acceptable.

## Summary of recommendations

It is considered that the sponsor's response to the TGA Section 31 request has not adequately addressed all of the issues identified in the RMP evaluation report.

### *Outstanding issues*

*Issues in relation to the RMP*

- The ASA refers to the core RMP rather than the EU RMP, this should be corrected in a future update to the ASA.
- It is recommended to the Delegate that the sponsor adds the following to the PI and CMI:
  - 1) Describes the origin of the cell-line used in the production of the product in the PI;
  - 2) Adds a warning statement for individuals who are allergic to hamster proteins in the CMI.

  This will ensure safer use of the product in patients with known sensitivity to hamster proteins. Please also refer to the ACSOM advice regarding this point.
- As there is limited information available about the use of the product in a home treatment setting, the RMP evaluator maintains the opinion that "Medication errors in a home treatment setting" should be added as potential risk. Pharmacovigilance and risk minimisation activities should be assigned to this potential risk as appropriate.
- Patients with a personal or family history of medullary thyroid carcinoma and multiple endocrine neoplasia type 2 should be added as missing information in the RMP. Pharmacovigilance and risk minimisation activities should be assigned as appropriate. In particular, it is recommended to the Delegate that the sponsor adds a statement in the PI describing that there is no experience in using the product in these patient groups.
- It is noted that the following statement is included in the Australian PI in section "Special Populations": No dose adjustment is needed based on age, gender, race, ethnicity, body weight, or renal or hepatic impairment. It is recommended to the delegate that the sponsor amends this statement to specify that this statement is based on limited information for
  - 1) Paediatric patients;
  - 2) Very elderly patients; and

  - 3) Patients with severe renal disease.

- Please also note the ACSOM advice regarding this statement in the PI.
- As the product has not yet been approved in the US or EU, it is recommended the sponsor implement additional pharmacovigilance activities in Australia, which are comparable to the currently proposed programs in the EU, if the product were approved in Australia but not in the US and the EU. Please also refer to the ACSOM advice regarding this point.
- It is recommended to the Delegate, the sponsor include wording in the Australian PI, addressing the important potential safety concern of Pancreatic Cancer, unless compelling justification can be provided for not doing so.

*Advice from the Advisory Committee on the Safety of Medicines (ACSOM)*

The ACSOM advice is attached to this report.

### *Comments on the safety specification of the RMP*

*Clinical Evaluation Report*

The Safety Specification in the draft RMP is satisfactory.

*Nonclinical Evaluation Report*

Results and conclusions drawn from the nonclinical program for dulaglutide detailed in the sponsor's draft RMP are in general concordance with those of the nonclinical evaluator except with regard to the claim that "there was no evidence of foetal malformations" in reproductive and developmental safety studies. Treatment with dulaglutide at the high dose level (0.41 mg/kg) in the rabbit embryofoetal development study (Study WIL-353119) is considered to be associated with various malformations (lobular agenesis of lungs, vertebral anomaly with or without associated rib anomaly, and costal cartilage anomaly), occurring in conjunction with significant maternotoxicity. The percentage of foetuses showing any malformation was 6.7 times greater with treatment with dulaglutide at this dose level compared to concurrent controls. It is suggested that the relevant statement be modified as follows:

> "Similar to Victoza, Byetta, and Bydureon, high doses of dulaglutide during midgestation in pregnant rats and rabbits caused reduced foetal growth and/or skeletal effects in association with maternal effects (decreased maternal food intake and decreased weight gain), but there was no evidence of ~~foetal malformations~~ direct teratogenicity."

It appears that the sponsor has satisfactorily addressed this recommendation in their s31 response.

### *Key changes to the updated RMP*

In their response to the TGA Section 31 requests, the sponsor provided an updated RMP (EU RMP, version 4, dated 17 April 2014). The table of ongoing safety concerns detailed in the EU RMP, version 4 differs from the table of ongoing safety concerns of core RMP, version 2 evaluated as shown in Tables 15-16.

**Table 15: Ongoing safety concerns in core RMP, version 2.**

| Summary of Safety Concerns | |
|---|---|
| **Important Identified Risks** | Hypoglycemia |
| **Important Potential Risks** | Acute pancreatitis<br>Effects on thyroid C-cells<br>Hypersensitivity<br>Pancreatic malignancy |
| **Missing Information** | Confirmation of memory deficits in directly dosed immature rats (for more details, see Part II, Module SII) |

**Table 16: Ongoing safety concerns in core RMP, version 4.**

| Summary of Safety Concerns | |
|---|---|
| **Important Identified Risks** | Hypoglycaemia |
| **Important Potential Risks** | Acute pancreatitis<br>Hypersensitivity<br>Thyroid C-cell tumours<br>Pancreatic malignancy |
| **Missing Information** | Use in children and adolescents <18 years of age<br>Use in pregnant and/or breastfeeding women<br>Use in patients with severe renal failure<br>Use in patients with congestive heart failure<br>Use in patients aged ≥75 years |

*OPR Evaluator's comments:*

It is recommended that "medication errors in a home treatment setting" be added as potential risk to the table of ongoing safety concerns.

***Suggested wording for conditions of registration***

*RMP*

Implement EU RMP, version 4, dated 17 April 2014 with ASA, version 3 and any future updates as a condition of registration.

*PSUR*

OMA to provide wording.

# VI. Overall conclusion and risk/benefit assessment

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

### Quality

The evaluator states that all outstanding chemistry and quality control issues have been resolved.

The evaluator states that, "based upon the stability profile demonstrated during the primary stability studies as well as the supporting stability studies, an expiry period of 24

months is proposed for the drug product when stored at the long term storage condition of 2-8°C with a 14 day patient in use period at not more than 30°C."

Overall, approval is recommended from a chemistry point of view.

## Nonclinical

The evaluator states that the overall quality of the nonclinical dossier was high.

The drug binds to the human GLP-1 receptor with nanomolar affinity and acts as a full agonist of the receptor. Dose and glucose dependent enhancement of insulin secretion from rat and monkeys was demonstrated for the drug *in vitro* and *in vivo*. Prolonged effect was seen in the monkey model.

The drug did not induce ADCC against cells expressing human GLP-1 receptors and there was no evidence of complement activation in treated monkeys.

Acute toxicity studies did not reveal CNS or respiratory effects in the Cynomolgus monkeys (at high doses). Some inhibition of hERG K+ tail current was observed in vitro with prolongation of the QTc interval seen in Cynomolgus monkeys, but only at very high (plasma) concentrations.

The pharmacokinetics of dulaglutide (mice, rats and Cynomolgus monkeys) were characterised by slow absorption from the SC injection site and a long plasma half life. The evaluator mentions that "lower exposures were seen in mice following repeated dosing, suggestive of anti-drug antibody production in this species". Studies on distribution, metabolism, excretion or pharmacokinetic interaction were not submitted.

Repeat dose toxicity studies in mice, rats and Cynomolgus monkeys showed similar toxicity findings to other GLP-1 receptor agonists. There was some evidence that dulaglutide exacerbated spontaneous lesions of the pancreas in diabetic (but not normal) rats.

No genotoxicity studies were submitted and this was considered acceptable by the evaluator. The evaluator mentions that:

> *a treatment related increase in the incidence of thyroid C-cell adenomas and thyroid C cell carcinomas was seen in rats treated with dulaglutide in a 21.5 month study… A risk for thyroid carcinogenicity cannot be completely dismissed but there is no greater risk with dulaglutide compared with currently registered, long acting GLP-1 receptor agonists. Available data support that rodents are particularly sensitive to proliferative thyroid changes induced by this drug class.*

Fertility was not affected in males or females treated with exposure ≥ 30 times clinical AUC. There were foetal effects only in the context of significant maternal toxicity.

There were no significant injection site reactions.

The evaluator recommends approval from a nonclinical point of view.

## Clinical

### Pharmacokinetics

The pharmacokinetic information is based on conventional pharmacokinetic studies and population pharmacokinetic studies. The latter was based on the meta analysis of 8 individual studies.

The evaluator mentions that a study on 45 healthy volunteers (GBCN) administered a single dose of 1.5 mg SC; this did not reveal any significant difference in absorption in relation to injection sites (upper arm versus thigh versus abdominal wall).

Absolute bioavailability was assessed in Study GBDR in 30 healthy adult volunteers. This study also assessed relative bioavailability of IM and SC injections. The absolute bioavailability of a 1.5 mg SC dose of dulaglutide relative to a 0.1 mg IV dose was approximately 44% based on AUC(0-∞) with a 90% CI of 39.5-49.7%. The mean relative bioavailability of an IM dose of dulaglutide compared to a SC dose based on AUC(0-∞) was 95.8% (90% CI: 85.8-108%) which showed that systemic exposure to dulaglutide was similar via both administration routes.

Dose proportionality was examined in Study GBCA which was a single dose study in 18 healthy subjects that examined a dose range of 0.1 mg to 12 mg. The evaluator mentions that "Cmax and AUC(0-∞) increased less than proportionally for each doubling of the dose". The range over 0.5 mg to 1.5 mg was also examined in the pharmacokinetic meta analysis which reflected similar results.

Volume of distribution, metabolism and excretion are discussed in the clinical evaluation report.

Study GBDO investigated the pharmacokinetics of dulaglutide in 26 subjects with varying degree of hepatic impairment. The evaluator states that this study and the population pharmacokinetics model revealed no effects. Similarly, there was no effect seen in study GBCM in relation to varying degrees of renal impairment (8 in each group), including ESRD.

There were no age related (Study GBCT) effects seen; a six week study of 36 subjects aged over 65 revealed no significant difference. However, there was only 1 subject over 75 years.

Population pharmacokinetic analysis did not reveal any ethnicity related interactions.

### *Drug interaction*

The evaluator states that:

> *observations were generally consistent with those of other GLP-1 receptor agonists. Therefore, dulaglutide did not affect the exposure of co-administered acetaminophen, lisinopril, metoprolol, digoxin, oral contraceptives, atorvastatin, sitagliptin, metformin, or warfarin to any clinically relevant degree. No dose adjustment is recommended for these drugs when co-administered with dulaglutide.*

## Pharmacodynamics

Study GBCB showed in patients with T2DM, statistically significant and clinically relevant reductions of fasting and postprandial glucose (LS mean differences of up to -38 mg/dL19 and -95 mg/dL, respectively) compared to placebo were observed for 7 days after single 1 to 6 mg dulaglutide doses.

There was a rapid onset of action and the effect was sustained through the dosing period. Similar findings were also seen in Studies GBCD, GBCT and GBDM. These studies examined FPG and PPG after dulaglutide injections in T2DM patients. The evaluator mentions, that significant reductions in HbA1c were also observed after 5 or 6 weeks of once weekly dosing in these studies.

These studies also showed first and second phase insulin secretion in response to dulaglutide; the response in T2DM was greater than in healthy adults. Insulin and C peptide secretion in response to glucagon was greater than with placebo. There was also a reduction of glucagon secretion observed in the Phase 3 study, GBDC.

Study GBDM examined gastric emptying after dulaglutide. Statistically significant delays in gastric emptying rate compared to baseline were observed following each of four successive 1.5 mg dulaglutide doses. The effect was most pronounced after the first dose of dulaglutide.

There were no significant trends seen in relation to weight in the 4 pharmacology studies conducted: Studies GBCD, GBCL, GBCT and GBDM.

QT interval evaluation: Study GBCC evaluated the effect of supratherapeutic doses of dulaglutide (4 and 7 mg) on the QTc intervals in 147 healthy subjects. Dulaglutide did not prolong the QTc interval.

### Dose selection for the pivotal studies

The first study (GBCF) was a 104 week placebo controlled study comparing the efficacy of dulaglutide to sitagliptin in patients with T2DM on metformin. The first stage of this study was the initial dose finding portion (0.25, 0.5, 0.75, 1.0, 1.5, 2.0 and 3.0 mg). The optimal dose was based on a clinical utility index using efficacy (HbA1c and weight) and safety (DBP and HR). A second dose was also selected, to mitigate the potential risk if a safety signal was subsequently observed with the maximal utility dose. Dulaglutide 1.5 mg was selected as the dose with the optimal benefit-risk profile, and dulaglutide 0.75 mg was selected as the lower dose to be continued for the purposes of confirmation of long term safety and efficacy in Study GBCF and subsequent Phase III studies.

The evaluator also mentions that

> *the once weekly dosing regimen was supported by the PK data: maximum concentrations of dulaglutide are reached at approximately 48 hours and the half life is approximately 4.7 days; apparent clearance is 0.107 L/hr. This extended PK profile makes dulaglutide suitable for once weekly administration.*

### Clinical efficacy

The pivotal studies (GBCF, GBDA, GBDB, GBDC and GBDD) are discussed. They are dealt with under indications that they support.

#### *Add on to metformin: Study H9X-MC-GBCF*

This was a Phase II/III placebo controlled study of once weekly dulaglutide compared to sitagliptin in patients with T2DM. Stage 1 of this study has been discussed in the section on dose finding above, and is not further discussed. Stage 2 included the treatments of 1.5 mg, 0.75 mg dulaglutide, sitagliptin 100 mg, and placebo in a 2:2:2:1 manner. All had metformin <1500 mg/day.

Of note in the inclusion and exclusion criteria: male and female patients 18 to 74 years of age (inclusive) who had had T2DM for ≥6 months; with an HbA1c ≥8.0% to ≤9.5% at screening, for diet/exercise treated patients and ≥7.0% to ≤9.5% for all others on a qualifying diabetes therapy of diet and exercise, oral monotherapy or oral combination therapy.

Statistical methods are detailed in the report. The evaluator mentions that

> *one analysis used the 6 month data and the other used the 12 month data, separately. The 6 month data were used to compare the selected dulaglutide and*

> *sitagliptin treatment arms to placebo and the 12 month data were used to compare the selected dulaglutide arms to sitagliptin.*

A total of 1202 were randomised; dulaglutide 0.75 mg (N = 302); dulaglutide 1.5 mg (N = 341); sitagliptin (315) and placebo/sitagliptin (N = 177).

Baseline characteristics are similar across treatment groups, the mean age was 54.08 years; the mean duration of diabetes was 7.12 years; the mean body weight was 86.41 kg; mean baseline HbA1c (8.13%) was similar across treatment groups. Mean ± sd of metformin dose was 1911.5 mg (± 365.13).

The stage 1 results are not discussed further.

The primary efficacy measure was change in HbA1c from baseline to 12 months (least squares mean standard error) to assess non inferiority of dulaglutide 1.5 mg once weekly to sitagliptin 100 mg once daily (non inferiority margin 0.25%). Other efficacy endpoints relate to other presentations of HbA1c, insulin, fasting plasma glucose (FPG), etc.

The evaluator mentions that dulaglutide:

> *1.5 mg arm was non inferior to sitagliptin at 12 months (adjusted one sided p-value <0.001), meeting the primary objective of the study. It was also superior to sitagliptin at 12 months (adjusted one sided p-value <0.001). The 0.75 mg arm was non inferior to sitagliptin (adjusted one sided p-value <0.001) at 12 months, and was superior to sitagliptin (adjusted one sided p-value <0.001) at 12 months.*

The other secondary efficacy endpoints are discussed. They were in line with the primary efficacy results. Durability of effect was seen of the 12 month treatment period. The evaluator mentions that change from baseline in bodyweight was "consistently greater" in the dulaglutide 1.5 mg group than the sitagliptin group; this was seen up to 24 months.

### *Add on to metformin and pioglitazone*

This was a 12 month, Phase III, placebo controlled active comparator study where 2 doses of dulaglutide (1.5 mg or 0.75 mg) were used. Details of the design and treatment regimens are included in the evaluation. In this study the inclusion criteria also stipulated "T2DM treated with maximally tolerated concomitant oral anticancer medications, metformin and pioglitazone". The active comparator was exenatide 5 µg twice daily for 4 weeks and then 10 µg twice daily for 48 weeks.

The primary efficacy endpoint was the change from baseline in HbA1c at 26 weeks. The secondary endpoints were as per the previous study. Statistical testing is discussed and considered satisfactory.

There were 976 patients in the Intent to Treat (ITT) group; dulaglutide 1.5 group N = 279; dulaglutide 0.75 mg N = 280; placebo N = 141 and exenatide N = 276. The baseline characteristics were similar across groups with the mean duration of diabetes being 8.8 years, see page 48. The dose of metformin and pioglitazone in the subjects at baseline is not provided. **The sponsor should submit this in the pre Advisory Committee on Prescription Medicines (ACPM) response.**

Primary efficacy endpoint: Treatment with dulaglutide 1.5 mg resulted in a LS mean (SE) reduction of -1.51% (0.06) compared to -0.46% (0.08) for placebo and -0.99% (0.06) for exenatide; and dulaglutide 0.75 mg resulted in a reduction of -1.30% (0.06). Each of these reductions was statistically significant (p<0.001).

Secondary efficacy endpoint: At Week 52 (HbA1c), patients in the dulaglutide 1.5 mg and dulaglutide 0.75 mg treatment groups had a significantly greater least squares mean reduction from baseline in HbA1c of -1.39% (SE: 0.08) and -1.07% (SE: 0.08), respectively, compared to -0.80% (SE: 0.08) for exenatide.

FPG: At Week 52, the largest least squares mean decreases from baseline were also observed in the 2 dulaglutide groups, and they were statistically significant when compared to exenatide (p≤0.005, both).

In relation to body weight: At 26 weeks, both dulaglutide groups and exenatide were significantly different from placebo (p≤0.010). At 26 and 52 weeks dulaglutide 1.5 was not significantly different to exenatide but was significantly different to dulagluide 0.75 (p<0.001).

***Add on to metformin and glimepiride (Study H9X-MC-GBDB)***

This was a randomised, open label, non inferiority study (of 2 doses) of dulaglutide and insulin glargine in patients with T2DM on stable doses of metformin and glimepiride. The study consisted of a 10 week lead in period, a 52 week treatment period, a 26 week extended treatment period and a 4 week safety follow up period.

T2DM not optimally controlled with 1, 2, or 3 oral anticancer medications (at least 1 of which must have been metformin or a sulfonylurea) were eligible. This study involved a comparison of 2 doses of dulaglutide (1.5 mg and 0.75 mg), given as a once weekly SC injection versus insulin glargine titrated-to-target given as a once daily SC injection in patients with T2DM on metformin and glimepiride (metformin: at least 1500 mg/day, but not higher than the maximum approved dose in the local label in participating countries; glimepiride: at least 4 mg/day, but not higher than the maximum approved dose in the local label in participating countries).

The sample size and statistical considerations are adequate.

A total of 810 patients were randomised and 807 were included in the ITT population. There were 273 subjects in the dulaglutide 1.5 mg group; 272 in the 0.75 mg group and 262 in the insulin glargine group. The baseline characteristics were similar between groups. The mean HbA1c at baseline was 8.14% (± 0.99%), and the mean duration of T2DM was 9.10 years (± 6.04). Mean body weight (86.3 kg). The mean baseline dose of metformin and glimepiride has not been stated. This should be provided in the pre ACPM response.

The primary efficacy endpoint: Treatment with dulaglutide 1.5 mg resulted in an LS mean (SE) HbA1c (%) change from baseline of -1.08% (0.06) compared to -0.63% (0.06) for insulin glargine; dulaglutide 0.75 mg resulted in a reduction of -0.76% (0.06); each of these reductions was significant (p<0.001 for all comparisons). The LS means and nominal 95% CIs for the difference of dulaglutide 1.5 mg and 0.75 mg relative to insulin glargine at 52 weeks were: -0.45% (-0.60, -0.29) and -0.13% (-0.29, 0.02), respectively. Dulaglutide 1.5 mg was non inferior to insulin glargine at 52 weeks (adjusted one sided p-value <0.001), meeting the primary objective of the study.

The endpoints relating to HbA1C up to 78 weeks generally showed greater reduction with dulaglutide than insulin glargine. Change in FPG was greater with insulin glargine. No significant difference was seen with fasting insulin. Patients in the insulin glargine arm showed an increase in mean body weight and those in the dulaglutide arms showed a decrease, resulting in a mean difference between dulaglutide 1.5 mg and insulin of 3.3 kg at 52 weeks.

***Initial monotherapy in early T2DM (M9X-MC-GBDC)***

This was a Phase II double blind active comparator monotherapy study of dulaglutide 0.75 mg or 1.5 mg once weekly versus metformin BID for 52 weeks. The dose for metformin was 2 x 500 mg tablets 2 times daily by mouth (total dose 2,000 mg/day) or 3 x 500 mg tablets (1,500 mg/day) as tolerated by the patient.

Inclusion criteria: male and (non pregnant) female patients ≥18 years who were diagnosed with T2DM for at least 3 months and ≤5 years, with a screening HbA1c ≥6.5 to

≤9.5%, who entered the study not optimally controlled by diet and exercise and either treatment naïve or on 1 oral antihyperglycaemic medication (oral anticancer medication) (excluding thiazolidinediones) and had stable weight (± 5%) ≥3 months prior to screening (Visit 1) and a BMI between 23 kg/m$^2$ and 45 kg/m$^2$, inclusive.

The efficacy endpoints were as per previous studies (change in HbA1c at 26 weeks). Statistical testing was generally similar to previous studies.

A total of 807 subjects were randomised; dulaglutide 1.5 mg (N = 269), dulaglutide 0.75 mg (N = 270) and metformin N = 268 were included in the ITT analysis. The baseline characteristics were similar between groups. The mean (SD) HbA1c overall was 7.60% (0.87) and the mean (SD) duration of T2DM was 2.63 (1.83) years. Mean body weight was 92.3 kg, and mean BMI was 33.3 kg/m$^2$.

The primary efficacy endpoint: Least squares mean difference (95% CI) for dulaglutide minus metformin was -0.22% (-0.36%, -0.08%) adjusted p value <0.001 for non inferiority.

HbA1C at 52 weeks dulaglutide 1.5 mg was superior to metformin, and dulaglutide 0.75 mg was non inferior to metformin in reduction from baseline of HbA1c. FPG at 52 weeks also showed similar trends. In relation to fasting insulin, comparisons were significant for both doses of dulaglutide versus metformin (p≤0.002). No significant weight changes were observed in relation to the comparisons.

***Add on to insulin M9X-MC-GBDD***

This was a Phase III active comparator partially blinded trial comparing the effect of once weekly 1.5 mg dulaglutide, injected SC, to that of insulin glargine (treated-to-target) on HbA1c at 26 weeks (change from baseline) in patients with T2DM who were treated in combination with prandial insulin lispro.

These patients were on a conventional insulin regimen alone or in combination with oral anticancer medications.

A total of 884 subjects were randomised. In the ITT population, 295 were randomised to dulaglutide 1.5 mg; 293 in the dulaglutide 0.75 mg group and 296 in the insulin glargine group.

The 3 treatment groups were similar with respect to demographic and other patient characteristics at baseline, except for BMI (dulaglutide 1.5 mg: 31.99 kg/m$^2$; dulaglutide 0.75 mg: 33.08 kg/m$^2$; insulin glargine: 32.41 kg/m$^2$; p = 0.013). The patients had a long history of diabetes (mean duration: 12.7 years) and the mean HbA1c concentration was 8.5%. The mean total daily insulin dose at baseline was 56 units and was similar across the 3 treatment groups.

Dulaglutide 1.5 mg arm met criteria for both non inferiority (primary objective) and superiority to insulin glargine at 26 weeks (adjusted one sided p-value <0.001) on HbA1c change from baseline. The LS mean and nominal 95% CI for the difference of the dulaglutide 1.5 mg arm relative to insulin glargine at 26 weeks was: -0.22% (-0.38, -0.07).

*Other efficacy endpoints*

Dulaglutide 1.5 mg and dulaglutide 0.75 mg groups were superior to insulin glargine at 52 weeks on HbA1c change from baseline. The LS mean and nominal 95% CI for the difference of the dulaglutide 1.5 mg arm relative to insulin glargine at 52 weeks was: -0.25% (-0.42, -0.07). At 26 weeks and 52 weeks, the change from baseline in FSG was significantly greater with glargine compared to the dulaglutide groups. Insulin doses were stable between Week 26 and Week 52 of the treatment period. At 52 weeks, the body weight and BMI results for between group differences were similar.

### *Other efficacy studies*

Three studies are discussed and are of minimal relevance to efficacy in this submission. These studies have used doses other than proposed for marketing.

Study M9X-MC-GBCJ was a study to assess the effect of dose titration in overweight and obese subjects with T2DM.

Study M9X-MC-GBCK assessed dose dependent effects of dulaglutide in T2DM patients who were treatment naïve. There were 0.1 mg to 1.5 mg once weekly injections used over 12 weeks, where dose dependent effects were seen.

Study M9X-MC-GB DN was a study conducted to assess the effect of dulaglutide on BP and HR in patients with T2DM. This is, in essence, a safety study and is discussed in the safety section of the report.

### *Overall efficacy conclusions*

The evaluator states that there was strong consistency in efficacy findings across the studies. At all primary time points in the 5 pivotal studies, once weekly dulaglutide 1.5 mg was superior to the active comparator with a corresponding greater proportion of patients reaching an HbA1c of <7% and <6.5%. Dulaglutide 0.75 mg, administered once weekly, was superior to active comparator in 4 of the 5 pivotal studies and non inferior to insulin glargine in 1 study. The magnitude of effect in relation to HbA1c was similar to other marketed GLP-1 agents, that is, exenatide and liraglutide.

## Safety

One study (M9X-MC-GBDN) discussed safety as a primary outcome. This was a double blind placebo controlled study that assessed mean 24 hour SBP by an ABPM in patients with T2DM. The primary objective was to demonstrate that dulaglutide at doses 0.75 and 1.5 mg were non inferior to placebo at week 16. Patients were to have stable blood pressure (see inclusion criteria for details).

A total of 251 subjects were randomised to dulaglutide 1.5 mg; 254 subjects to 0.75 mg and 250 subjects to placebo. These subjects had a mean duration of diabetes for 8.1 years.

Both doses of dulaglutide were non inferior to placebo for mean 24 hour SBP at 16 weeks, using a non inferiority margin of 3 mm Hg. The dulaglutide 1.5 mg dose was shown to significantly reduce mean 24 hour SBP compared with placebo at 16 weeks (-2.8 mmHg; $p<0.001$) and at 26 weeks (-2.7 mm Hg; $p = 0.002$). Secondary endpoints are discussed; no statistically significant changes were seen in comparison with placebo.

### *Other safety information*

Overall, 4006 patients were exposed to dulaglutide; equal numbers received 0.75 mg and 1.5 mg.

The evaluator mentions that in the placebo controlled studies, “the proportion of patients reporting at least 1 TEAE was similar in the all dulaglutide group (69.8%) compared with placebo (66.7%). GI AEs including nausea (16.8% versus 5.3%), diarrhoea (10.7% versus 6.7%), and vomiting (9.3% versus 2.3%) were the most common AEs reported with dulaglutide and were reported more frequently than with placebo treated patients”. In the long term studies (26-104 weeks), the trends were similar to the placebo controlled database; GI events continued to be the most common TEAEs reported.

There were a total of 17 deaths in the clinical trials programme; 9 were on dulaglutide and 8 on comparator treatments. The individual casuality is also discussed. The evaluator states that:

> *the deaths appear to be balanced across the treatments and were primarily cardiac in nature (sudden death, cardio respiratory arrest, MI, CVA, cardiogenic shock, cardiac failure, ventricular fibrillation) which are not unexpected in this population. The events did not appear to cluster with respect to a specific event type and thus do not suggest clinical concern.*

*Serious adverse events*

Patients in the placebo (4.4%) and all dulaglutide (4.2%) groups reported a similar incidence of serious AEs. The most frequently reported serious AEs for placebo and all dulaglutide were: appendicitis, cholelithiasis, atrial fibrillation and coronary artery disease. No serious AE occurred at >1% of patients.

*Discontinuations*

Placebo controlled studies: More patients on placebo (7.0%) than on dulaglutide (4.7%) were withdrawn from studies. GI TEAEs as a reason for early withdrawal from study or study drug which was more common in dulaglutide (2.4%) than placebo (0.2%) treated patients. Nausea and vomiting were the most commonly reported events leading to study drug or study withdrawal. However, the withdrawal rates due to these events were low, 1.1% and 0.5%, respectively, in dulaglutide treated patients as compared to 0% for both events with placebo. There were similar trends with the long term studies.

The evaluator discusses the laboratory function tests in relation to the liver and kidney. There were no significant trends observed.

No haematology and biochemistry results are discussed by the evaluator. On reviewing the abnormal results listed, the Delegate did not identify any cause for concern.

The safety topics peculiar to GLP-1 are discussed.

*GI tolerability*

The most common AEs with dulaglutide treatment were GI in nature, namely nausea, vomiting, and diarrhoea, and to a lesser extent constipation and abdominal pain. These GI disorder events reported were typically mild or moderate in severity and led to discontinuation from study drug and/or study in a small proportion of patients.

*Pancreatitis*

Of the 151 adjudicated cases, 19 cases were identified by investigators as suspected or definite acute or chronic pancreatitis and 9 cases were identified. The exposure adjusted incidence rates were similar between placebo and dulaglutide; however, the numbers were small to be meaningful.

In relation to pancreatic enzymes the evaluator states:

> *in the placebo controlled studies, dulaglutide treated patients had significant increases from baseline in pancreatic enzymes, including lipase (up to 20%), p-amylase (up to 20%), and to a lesser extent total amylase (up to 12%) compared with minimal change in placebo. The maximum increases in enzymes were evident by 4 to 8 weeks, and these levels persisted for the duration of exposure and resulted in more dulaglutide treated patients with enzyme values above the upper limit of normal (ULN) post baseline (treatment emergent) compared with placebo.*

There were similar changes in the long term studies.

*Thyroid safety*

Dulaglutide did not increase mean serum calcitonin compared with placebo. There was one report of medullary thyroid cancer in a patient who received dulaglutide 2 mg for approximately 6 months in the dose finding stage of Study GBCF. This was stated to be pre-existing by the sponsor. Two papillary thyroid carcinomas have also been reported in

the completed clinical program (one in Study GBCF and one in Study GBDB), both in patients who received dulaglutide 1.5 mg. Neither of these patients had any abnormal measurements of serum calcitonin.

*Hypoglycaemia*

The rates with dulaglutide were generally low. The addition of dulaglutide to a regimen that included sulfonylurea or insulin was associated with higher rates of total hypoglycaemia compared to studies with non secretagogues as background therapy. The highest rate of total hypoglycaemia occurred when dulaglutide was used in combination with insulin lispro (with or without metformin) (Study GBDD). There were no episodes of severe hypoglycaemia in dulaglutide patients treated with concomitant non secretagogues or with dulaglutide monotherapy.

The injection site reaction was higher with dulaglutide than with placebo.

In accordance with FDA and EU guidelines, the sponsor conducted a meta analysis of CV data from the completed dulaglutide clinical studies to assess the cardiovascular risk of dulaglutide. The meta analysis results demonstrated an estimated hazard ratio: 0.57; adjusted [98.02%] CI: 0.30, 1.10; p = 0.046) for dulaglutide versus all comparators (active and placebo) indicating that treatment with dulaglutide is not associated with an increase in the risk of experiencing a 4 component MACE endpoint compared with control therapies.

The overall incidence of treatment emergent dulaglutide ADAs was low: 1.6% as compared to 0.7% observed in patients treated with placebo or non GLP-1 comparators. Among the 64 patients with treatment emergent dulaglutide ADAs, approximately half (34; 0.9% of the overall population) had dulaglutide neutralising ADAs. There were also 4 patients with treatment emergent dulaglutide ADAs with neutralising activity against nsGLP (0.1% of the overall population). The evaluator mentions that “overall, no obvious pattern was detected in the relationship between the presence of dulaglutide ADA and change in HbA1c from baseline”.

There was no increase in hypersensitivity reactions observed.

In the dulaglutide clinical program, there was no increased reporting of malignancy in general, nor any specific type of malignancy, associated with dulaglutide compared with placebo or active comparators.

*Overall safety conclusions*

The evaluator states that the safety data were included in a large number (4000) of patients. There was adequate number included for 12 to 24 months. The safety profile was similar to other GLP-1 agents. There were no detrimental hepatic or renal effects with the proposed dose of dulaglutide. Incidences of treatment emergent dulaglutide ADAs were lower in dulaglutide treated patients compared to treatment emergent exenatide ADAs in exenatide BID treated patients (Study GBDA: 1.6% versus 44.6%). Few dulaglutide treated patients had dulaglutide neutralising ADA (0.9%) and/or developed neutralising ADA for nsGLP (0.1%). The studies were insufficient in size and duration to fully assess the effects of dulaglutide to induce or promote malignancies.

## Clinical evaluator’s recommendation

The evaluator states that the overall risk benefit profile is acceptable. There was statistically significant evidence of efficacy in relation to changes in HbA1c which was sustained is some studies to Week 104. Once weekly dosing, no adjustments in the elderly, renally or hepatic impairment was also an advantage. Risks were consistent with other drugs of this class.

## Risk management plan

Overall, pharmacovigilance and risk minimisation activities are satisfactory. The PI amendments considered relevant are included in the attachment. This submission was considered by ACSOM. ACSOM noted that a large cardiovascular outcomes study and routine pharmacovigilance was proposed for pancreatic malignancy. The evaluator recommends that a statement be included in the PI that there is no experience in patients with a personal or family history of medullary thyroid carcinoma and multiple endocrine neoplasia type 2. The evaluator also recommends a statement in the PI on the lack of information for paediatric patients and very elderly patients.

## Risk-benefit analysis

### Delegate's considerations

The data submitted provides a satisfactory risk benefit profile for approval of the requested dose for T2DM for the requested patient groups.

It has also been recommended for approval in the US and EU in September 2014.

It is noted that there is a boxed warning in the US that tumours of the thyroid gland (thyroid C cell tumours) have been observed in rodent studies with dulaglutide but that it is unknown whether dulaglutide causes thyroid C-cell tumours, including a type of thyroid cancer called medullary thyroid carcinoma in humans. It is contraindicated in patients with a personal or family history of medullary thyroid carcinoma and in patients with Multiple Endocrine Neoplasia syndrome type 2. Such a Boxed Warning is also included in the US Victoza, liraglutide PI. The sponsor should justify the lack of this in the Australian PI.

The following are the FDA's requirements regarding post market studies:

- a clinical trial to evaluate dosing, efficacy, and safety in paediatric patients;
- a study to assess potential effects on sexual maturation, reproduction, and CNS development and function in immature rats;
- a medullary thyroid carcinoma case registry of at least 15 years duration to identify any increase in medullary thyroid carcinoma incidence related to dulaglutide;
- a clinical trial comparing dulaglutide with insulin glargine on glycemic control in patients with T2DM and moderate or severe renal impairment; and
- a cardiovascular outcomes trial to evaluate the cardiovascular risk of dulaglutide in patients with high baseline risk of cardiovascular disease.

The progress and results of these studies should also be submitted to the TGA when the US FDA is informed.

### Proposed action

The Delegate proposes to register Trulicity (dulaglutide rch) 1.5 mg/0.5 mL for the treatment of T2DM, for the requested populations.

### Request for ACPM advice

Does the Committee agree with the Delegate that the risk-benefit profile is acceptable for the proposed indications?

**Response from sponsor**

Eli Lilly acknowledges receipt of the Delegate's Overview and wishes to thank the TGA for the opportunity to provide comments at this time. This response will focus on the Comments on the PI for Trulicity and include additional information requested by the Delegate.

***Comments on PI***

***Justification for Omission of a Boxed Warning***

In Australia, boxed warnings are used rarely and only where a serious, clinically significant safety issue has been identified in patients with such certainty that the issue is directly related to the product.

In US labelling, boxed warnings are used more commonly and do not imply the same level of risk as is associated with a boxed warning in Australia. The content of the boxed warning in the Trulicity US PI does not describe a known causative relationship between dulaglutide and an adverse outcome. It only describes a contraindicated population based on nonclinical data.

Most products registered in Australia carry contraindications for subpopulations; however, boxed warnings for contraindications are very rarely considered necessary. This is clearly demonstrated by comparing the contraindications in the Australian labelling of other products in the GLP-1 class (Table 17); none of which are required as a boxed warning.

**Table 17: Comparison of GLP-1 labelling: contraindications.**

| Bydureon | Byetta | Lyxumia | Victoza |
|---|---|---|---|
| Exenatide is contraindicated in patients with known hypersensitivity to this product or any of its components.<br><br>Exenatide should not be used in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min). Compared with healthy subjects, renal clearance of exenatide was significantly reduced in patients with end-stage renal disease receiving dialysis, resulting in poor gastrointestinal tolerability. | Exenatide is contraindicated in patients with known hypersensitivity to this product or any of its components, including meta-Cresol.<br><br>Exenatide should not be used in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min). Compared with healthy subjects, renal clearance of exenatide was significantly reduced in patients with end-stage renal disease receiving dialysis, resulting in poor gastrointestinal tolerability. | Lyxumia is contraindicated in patients with known hypersensitivity to lixisenatide or to any of the inactive ingredients in the formulation | Liraglutide is not to be used in:<br>- patients with hypersensitivity to liraglutide or any of its excipients.<br>- patients with a past history of GLP-1 analogue associated pancreatitis |

Furthermore, the PI of all other GLP-1's include similar preclinical data on occurrence of tumours in rodents (Table 18) without also including a contraindication for medullary thyroid cancer and Multiple Endocrine Neoplasia syndrome type 2. Therefore, based on the class labelling and relatively low level of severity conveyed in the US PI boxed warning, neither a boxed warning nor an additional contraindication is being proposed in the Australian PI. The potential risk is more than adequately addressed by the following information (consistent with class labelling) recorded under the 'Carcinogenicity' heading of the Precautions section of the proposed PI:

> *In a 93 week carcinogenicity study in rats, dulaglutide caused statistically significant, dose-related increases in the incidence of thyroid C cell tumours (adenomas and carcinomas combined) with SC administration at ≥0.5 mg/kg twice weekly, yielding ≥ 7 times the human clinical exposure following once weekly administration of 1.5 mg dulaglutide. Exposure (plasma AUC) at the no observable effect level for*

*carcinogenicity in the rat (0.05 mg/kg) was subclinical. The human relevance of these findings is unknown. There was no tumorigenic response in a 6 month carcinogenicity study in transgenic mice with SC doses ≤3 mg/kg twice weekly, yielding exposures up to 5 times higher than that in patients at the maximum recommended human dose.*

**Table 18: Comparison of GLP-1 labelling: carcinogenicity.**

| Bydureon | Byetta | Lyxumia | Victoza |
|---|---|---|---|
| In a 104 week carcinogenicity study with the extended release formulation of exenatide, a statistically significant increase in thyroid c-cell tumour incidence (adenomas and / or carcinomas) was observed in rats at all doses (0.3 to 3 mg/kg/fortnight subcutaneously; 1.4 to 26 fold the human clinical exposure with exenatide once weekly). The available evidence indicates that these tumours are mediated by a specific GLP-1 receptor mechanism to which rodents are particularly sensitive. The human relevance of these findings is currently unknown but predicted to be low. | In female rats given exenatide for 2 years, an increased incidence of benign thyroid C-cell adenomas was observed at the highest dose (250 µg/kg/day), a dose that produced an exenatide plasma exposure 110 times the human clinical exposure at 20 µg/day. There was no tumorigenic response in male rats or either sex of mice at exposures 80 (mouse) and 110 (rat) times the human exposure. | Lixisenatide caused thyroid C-cell tumours in 2-year subcutaneous carcinogenicity studies in rodents. In mice, thyroid C-cell adenoma (together with focal C-cell hyperplasia) was increased at ≥400 µg/kg/day, yielding systemic exposure levels ≥29-fold greater than in humans at the maximum recommended human dose. No treatment-related increase in tumour incidence was seen in mice at 80 µg/kg/day (relative exposure, 7). In rats, focal C-cell hyperplasia and C-cell adenoma were increased at all dose levels tested (≥80 µg/kg/day: yielding exposure ratios ≥9), and C-cell carcinoma was observed at ≥400 µg/kg/day (yielding ≥35-times the human exposure). These findings are considered to be caused by a GLP-1 receptor-mediated mechanism to which rodents are particularly sensitive. Human relevance cannot presently be completely excluded. | Liraglutide caused thyroid C-cell adenomas and carcinomas in two-year studies in mice and rats. C-cell neoplasia was observed in mice at subcutaneous doses ≥1mg/kg/day (relative exposure based on plasma AUC, ≥7.7) and in rats at all doses tested (≥0.075mg/kg/day subcutaneously; relative exposure, ≥0.5). No tumours or other C-cell proliferative changes were seen in monkeys treated with liraglutide for 20 months (≤5 mg/kg/day subcutaneously; relative exposure, ≤64). The findings in mice and rats are mediated by a specific GLP-1 receptor-mediated mechanism to which rodents are particularly sensitive. The relevance for humans is likely to be low but cannot presently be completely excluded. |

### *Contraindications*

As described above, the contraindication is not included in the proposed PI as this is not consistent with GLP-1 class labelling.

### *Clinical Trials*

The following statement has been included in the clinical trial section to clarify the primary endpoint for the efficacy trials compared to the secondary endpoints:

*Table 1 provides a summary for all five studies; change in HbA1c (%) was the primary endpoint, other important secondary outcomes included change in fasting blood glucose (FBG), percentage of patients achieving a target HbA1c <7.0%, and change in body weight at the primary and final study time points.*

Information from the US PI on immunogenicity has been included in the Australian PI with a minor amendment to the original text as follows:

*Across four Phase II and five Phase III clinical studies, 64 (1.6%) Trulicity treated patients developed ADAs to the active ingredient in Trulicity (dulaglutide). Of the 64 dulaglutide treated patients that developed dulaglutide ADAs, 34 patients (0.9% of*

*the overall population) had dulaglutide neutralising antibodies, 36 patients (0.9% of the overall population) developed antibodies against native GLP-1.*

*~~In clinical studies, treatment with dulaglutide (either 0.75 mg or 1.5 mg) was associated with a 1.6% incidence of treatment emergent dulaglutide anti drug antibodies indicating that the structural modifications in the GLP-1 and modified IgG4 parts of the dulaglutide molecule, together with high homology with native GLP-1 and native IgG4, minimise the risk of immune response against dulatglutide.~~ Patients with dulaglutide ~~anti drug antibodies~~ ADAs generally had low titres and although the number of patients developing dulaglitide ~~anti drug antibodies~~ ADAs was low, examination of the phase III data revealed no clear impact of dulaglutide ~~anti drug antibodies~~ ADAs on changes in HbA1c.*

*The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralising antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the incidence of antibodies to dulaglutide cannot be directly compared with the incidence of antibodies of other products.*

### *Precautions*

A precaution on lack of evidence for macrovascular risk reduction has been included as follows:

*There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Trulicity or any other antidiabetic drug.*

### *Use in renal impairment*

Dulaglutide is a large peptide molecule (~60 KD) and elimination is presumed to be by proteolytic degradation into its amino acid components and is not anticipated to be eliminated intact in the urine or to be metabolised by the CYP enzymes. The dulaglutide clinical trial programme enrolled a substantial number of patients with moderate renal impairment (eGFR <60 mL/min/1.73m$^2$). The risk benefit profile in these patients did not differ from the overall population.

However, as patients with severe renal impairment and end stage renal disease were not included in the clinical trial programme there is insufficient data to support use in these populations. The precautions and dosing and administration sections of the PI have been revised accordingly; Trulicity is not recommended for use in these populations.

### *Adverse reactions*

The table has been revised to align with the US PI and now includes reactions occurring in Trulicity treated patients with a frequency of ≥5%.

### *Overseas Regulatory Status – Indications*

The approved indication in the US PI is:

*1 Indications and usage*

Trulicity is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM.

*1.1 Limitations of Use*

- Trulicity is not recommended as a first line therapy for patients who have inadequate glycaemic control on diet and exercise (see Warnings and Precautions).

- Trulicity has not been studied in patients with a history of pancreatitis (see Warnings and Precautions). Consider other antidiabetic therapies in patients with a history of pancreatitis.
- Trulicity should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Trulicity is not a substitute for insulin.
- Trulicity has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis. The use of Trulicity is not recommended in patients with pre-existing severe gastrointestinal disease (see Warnings and Precautions).
- The concurrent use of Trulicity and basal insulin has not been studied.

The indication recommended for approval in the SmPC is:

*4.1 Therapeutic indications*

Trulicity is indicated in adults with T2DM to improve glycaemic control as:

*Monotherapy*

When diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications.

*Add on therapy*

In combination with other glucose lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see data with respect to different combinations).

***Baseline Pioglitazone and Metformin in Study GBDA***

In the summary of Study H9X-MC-GBDA (add on to metformin and pioglitazone), the evaluator requested that additional information be included in the pre ACPM response regarding baseline metformin and pioglitazone:

> *The dose of metformin and pioglitazone in the subjects at baseline is not provided. The sponsor should submit this in the pre ACPM response.*

In the GBDA study, patients were required to be on maximally tolerated doses (per local label) of pioglitazone and metformin throughout the study. At baseline, a majority of patients were receiving pioglitazone 45 mg (95.9%) and metformin ≥2500 mg (88.7%); please also see Clinical Safety Report Tables GBDA.14.38 and GBDA14.39, respectively. A total of 86 percent (86.2%) of patients at baseline were receiving both pioglitazone 45 mg and metformin ≥2500 mg (Clinical Safety Report Table GBDA.14.41).

***Baseline glimepiride and metformin in Study GBDB***

In the summary of Study H9X-MC-GBDB (add on to metformin and glimepiride), the evaluator requested that additional information be included in the pre ACPM response regarding baseline metformin and glimepiride dose:

> *The mean baseline dose of metformin and glimepiride has not been stated. This should be provided in the pre-ACPM response.*

In the GBDB study, the overall mean (SD) baseline doses of metformin and glimepiride were, respectively, 2403 (483) mg/day and 6.3 (1.6) mg/day. By study arm for metformin, at baseline, mean (SD) doses were 2379.03 mg (480.08), 2411.76 mg (494.93), and 2419.18 mg (475.34) for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and insulin glargine, respectively. By study arm for glimepiride, at baseline, mean (SD) doses were 6.25 mg (1.68), 6.32 mg (1.60), and 6.24 mg (1.57) for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and insulin glargine, respectively (please also see Clinical Safety Report Table GBDB 11.5).

### *Advisory Committee considerations*

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered Trulicity (formally Apleavo) solution for injection containing 1.5 mg/0.5 mL of dulaglutide rch to have an overall positive benefit-risk profile for the indication:

> *Trulicity is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM:*
>
> - *As monotherapy*
> - *In combination with the following oral glucose lowering medications (metformin, metformin and sulfonylurea, metformin and thiazolidinedione)*
> - *In combination with prandial insulin, with or without metformin.*

In making this recommendation, the ACPM:

- Noted the contraindication for familial thyroid medullary carcinoma / multiple endocrine neoplasia patients seems prima facie prudent but is not directly supported by evidence.

*Proposed conditions of registration*

The ACPM agreed with the delegate on the proposed conditions of registration and specifically advised on the following;

- Presentation to the TGA in a timely manner of the longer term studies stipulated by the FDA should be a condition of registration.

*PI/ CMI amendments*

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the following:

- A tabulation of adverse effects and frequency should be added as requested by clinical evaluator.
- The CMI needs amendments of the current trade name.

*Specific Advice*

The ACPM advised the following in response to the Delegate's specific questions on this submission:

- Does the Committee agree that the risk-benefit profile is acceptable for the proposed indications?

The ACPM advised this product has been shown to have significant efficacy in an appropriate population and the toxicity is consistent with the known class profile and is acceptable. There are imputed advantages to once weekly injections. Trulicity has a favourable benefit-risk profile.

The ACPM advised that 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 this product.

## Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of

- Trulicity (dulaglutide [rch]) 1.5 mg/0.5 mL solution for injection prefilled syringe
- Trulicity (dulaglutide [rch]) 1.5 mg/0.5 mL solution for injection prefilled pen

indicated for

> *Trulicity is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM:*
>
> - *As monotherapy*
> - *In combination with the following oral glucose-lowering medications (metformin, metformin and sulfonylurea, metformin and thiazolidinedione)*
> - *In combination with prandial insulin, with or without metformin.*

**Specific conditions of registration applying to these goods**

1. The Trulicity [dulaglutide (rch)] EU RMP, version 4, dated 17 April 2014 with ASA version 3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

2. The progress and results of the post market studies requested by the US FDA should also be submitted to the TGA when the US FDA is informed.

3. Batch Release Testing: As a minimum, the first five independent batches of Trulicity (dulaglutide (rch)) 1.5 mg/0.5 mL solution for injection in prefilled syringe and prefilled pen imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Office of Laboratories and Scientific Services (OLSS).

The sponsor should supply:

- Certificates of Analysis of all active ingredient (drug substance) and final product.
- Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents (if included).
- Evidence of the maintenance of registered storage conditions during transport to Australia.
- Five vials of each batch for testing by the OLSS together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

# Attachment 1. Product Information

The PI approved for main Trulicity at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

# Attachment 2. Extract from the Clinical Evaluation Report

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