NEW ZEALAND DATA SHEET

1. PRODUCT NAME

BYDUREON® 2 mg powder and solvent for prolonged-release suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial or pre-filled pen contains 2 mg of exenatide.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for prolonged-release suspension for injection.

Powder: white to off-white powder.

Solvent: clear, colourless to pale yellow to pale brown solution.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

BYDUREON is indicated for treatment of type 2 diabetes mellitus in adults to improve glycaemic control in combination with other glucose-lowering medicinal products, when therapy in use, together with diet and exercise, does not provide adequate glycaemic control (see section 5.1 Pharmacodynamic Properties – Clinical Efficacy and Safety for available data on different combinations).

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

The recommended BYDUREON dose is 2 mg exenatide once weekly.

BYDUREON can be administered at any time of day, with or without meals.

When BYDUREON is added to existing metformin and/or thiazolidinedione therapy, the current dose of metformin and/or thiazolidinedione can be continued as it is unlikely that the dose of metformin and/or thiazolidinedione will require adjustment due to hypoglycaemia when used with exenatide.

When BYDUREON is added to sulphonylurea therapy, a reduction in the dose of sulphonylurea should be considered to reduce the risk of hypoglycaemia (see section 4.4 – Special Warning and Precautions for Use).

The use of BYDUREON does not require additional self-monitoring. Blood glucose self-monitoring may be necessary to adjust the dose of sulphonylurea.

Changing Weekly Dosing Schedule

The day of weekly administration can be changed if necessary as long as the last dose was administered 3 or more days before.

Missed Dose

If a dose is missed, it should be administered as soon as noticed, provided the next regularly scheduled dose is due at least 3 days later. Thereafter, patients can resume their usual dosing schedule of once every 7 days (weekly).

Switching from BYETTA to BYDUREON

Patients switching from exenatide twice daily (BYETTA) to BYDUREON may experience transient elevations in blood glucose concentrations, which generally improve within the first two weeks after initiation of therapy.

Discontinuation

If a different antidiabetic treatment is started after the discontinuation of BYDUREON, consideration should be given to the prolonged release of BYDUREON (see section 5.2 – Pharmacokinetic Properties).

Special populations

Elderly

No dose adjustment is required based on age. However, as renal function generally declines with age, consideration should be given to the patient's renal function (see patients with renal impairment). The clinical experience in patients > 75 years is very limited (see section 5.2 - Pharmacokinetic Properties).

Patients with renal impairment

No dose adjustment is necessary for patients with mild or moderate renal impairment (creatinine clearance 30 to 80 mL/min) (see section 5.2 - Pharmacokinetic Properties).

BYDUREON is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance < 30 mL/min) (see section 4.4 – Special Warnings and Precautions for Use).

Patients with hepatic impairment

No dose adjustment is necessary for patients with hepatic impairment (see section 5.2 - Pharmacokinetic Properties).

Paediatric population

The safety and efficacy of BYDUREON in children and adolescents aged under 18 years have not yet been established (see section 5.2 -Pharmacokinetic Properties).

Method of administration

BYDUREON is for self-administration by the patient. Each kit or pen should be used by one person only and is for single use.

BYDUREON is administered as a subcutaneous injection and must not be administered intravenously or intramuscularly.

When used in combination with insulin, BYDUREON and insulin must be administered as two separate injections. It is acceptable to inject BYDUREON and insulin in the same region of the body, but the injections should not be adjacent to each other

Appropriate training is recommended for non-healthcare professionals administering the product. The “Instructions for the User”, provided in the carton, must be followed carefully by the patient.

Each dose should be administered in the abdomen, thigh, or the back of the upper arm as a subcutaneous injection immediately after suspension of the powder in the solvent.

For instructions on the suspension of the medicinal product before administration, see section 6.6 Special Precautions for Disposal and Other Handling and the “Instructions for the User”.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

BYDUREON 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

BYDUREON should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

BYDUREON must not be administered by intravenous or intramuscular injection.

This medicine contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially “sodium-free”.

Renal impairment

In patients with end-stage renal disease receiving dialysis, single doses of exenatide twice daily increased frequency and severity of gastrointestinal adverse reactions therefore BYDUREON is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance < 30 ml/min) – see section 4.3 - Contraindications.

Altered Renal Function

There have been rare, spontaneously reported events of altered renal function with exenatide, including increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring haemodialysis. Some of these events occurred in patients experiencing events that may affect hydration, including nausea, vomiting, and/or diarrhoea and/or receiving medicinal products known to affect renal function/hydration status. Concomitant medicinal products included angiotensin converting enzymes inhibitors, angiotensin-II antagonists, non-steroidal anti-inflammatory medicinal products and diuretics. Reversibility of altered renal function has been observed with supportive treatment and discontinuation of potentially causative agents, including exenatide.

Severe gastrointestinal disease

BYDUREON has not been studied in patients with severe gastrointestinal disease, including gastroparesis. Its use is commonly associated with gastrointestinal adverse reactions, including nausea, vomiting, and diarrhoea. Therefore, the use of BYDUREON is not recommended in patients with severe gastrointestinal disease.

Acute pancreatitis

There have been spontaneously reported events of acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed with supportive treatment, but very rare cases of necrotizing or haemorrhagic pancreatitis and/or death have been reported. If pancreatitis is suspected, BYDUREON and other potentially suspect medicinal products should be discontinued. Treatment with BYDUREON should not be resumed after pancreatitis has been diagnosed.

Concomitant medicinal products

The concurrent use of BYDUREON with prandial insulin, D-phenylalanine derivatives (meglitinides), alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors or other GLP-1 receptor agonists has not been studied. The concurrent use of BYDUREON and other GLP-1 receptor agonists is not recommended.

Hypoglycaemia

The risk of hypoglycaemia was increased when BYDUREON was used in combination with a sulphonylurea in clinical trials. Furthermore, in the clinical studies, patients on a sulphonylurea combination, with mild renal impairment had an increased incidence of hypoglycaemia compared to patients with normal renal function. To reduce the risk of hypoglycaemia associated with the use of a sulphonylurea, reduction in the dose of sulphonylurea should be considered.

Rapid weight loss

Rapid weight loss at a rate of >1.5 kg per week has been reported in patients treated with exenatide. Weight loss of this rate may have harmful consequences.

Interaction with warfarin

Since market introduction, there have been some spontaneously reported cases of increased INR (International Normalized Ratio), sometimes associated with bleeding, with concomitant use of warfarin and exenatide (see section 4.5 – Interactions and 4.8 – Undesirable Effects).

Discontinuation of treatment

After discontinuation, the effect of BYDUREON may continue as plasma levels of exenatide decline over 10 weeks. Choice of other medicinal products and dose selection should be considered accordingly, as adverse reactions may continue and efficacy may, at least partly, persist until exenatide levels decline.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Effects of other medicinal products on BYDUREON

The results of a study using paracetamol as a marker of gastric emptying suggest that the effect of BYDUREON to slow gastric emptying is minor and not expected to cause clinically significant reductions in the rate and extent of absorption of concomitantly administered oral medicinal products. Therefore, no dose adjustments for medicinal products sensitive to delayed gastric emptying are required.

When 1,000 mg paracetamol tablets were administered, either with or without a meal, following 14 weeks of BYDUREON therapy, no significant changes in paracetamol AUC were observed compared to the control period. Paracetamol C_{max} decreased by 16 % (fasting) and 5 % (fed)

and t_{max} was increased from approximately 1 hour in the control period to 1.4 hours (fasting) and 1.3 hours (fed).

Sulphonylureas

The dose of a sulphonylurea may require adjustment due to the increased risk of hypoglycaemia associated with sulphonylurea therapy (see sections 4.2 – Dose and Method of Administration and 4.4 – Special Warnings and Precautions for Use).

The following interaction studies have been conducted using 10 mcg exenatide twice daily but not exenatide once weekly.

Interaction studies with exenatide have only been performed in adults.

Hydroxy Methyl Glutaryl Coenzyme A reductase inhibitors

Lovastatin AUC and C_{max} were decreased approximately 40 % and 28 %, respectively, and t_{max} was delayed about 4 h when exenatide twice daily was administered concomitantly with a single dose of lovastatin (40 mg) compared with lovastatin administered alone. In exenatide twice daily 30-week placebo-controlled clinical trials, concomitant use of exenatide and HMG CoA reductase inhibitors was not associated with consistent changes in lipid profiles (see section 5.1 – Pharmacodynamic Properties). No predetermined dose adjustment is required; however lipid profiles should be monitored as appropriate.

Warfarin

A delay in t_{max} of about 2 h was observed when warfarin was administered 35 min after exenatide twice daily. No clinically relevant effects on C_{max} or AUC were observed. Increased INR has been reported during concomitant use of warfarin and exenatide once weekly. INR should be monitored during initiation of BYDUREON therapy in patients on warfarin and/or cumarol derivatives (see sections 4.4 – Special Warnings and Precautions for Use and 4.8 – Undesirable Effects).

Digoxin and lisinopril

In interaction studies of the effect of exenatide twice daily on digoxin and lisinopril there were no clinical relevant effects on C_{max} or AUC, however a delay in t_{max} of about 2 h was observed.

Ethinyl estradiol and levonorgestrel

Administration of a combination oral contraceptive (30 mcg ethinyl estradiol plus 150 mcg levonorgestrel) one hour before exenatide twice daily did not alter the AUC, C_{max} or C_{min} of either ethinyl estradiol or levonorgestrel. Administration of the oral contraceptive 35 minutes after exenatide did not affect AUC but resulted in a reduction of the C_{max} of ethinyl estradiol by 45 %, and C_{max} of levonorgestrel by 27-41 %, and a delay in t_{max} by 2-4 h due to delayed gastric emptying. The reduction in C_{max} is of limited clinical relevance and no adjustment of dosing of oral contraceptives is required.

4.6 FERTILITY, PREGNANCY AND LACTATION

Women of childbearing potential

Due to the long washout period of BYDUREON, women of childbearing potential should use contraception during treatment with BYDUREON. BYDUREON should be discontinued at least 3 months before a planned pregnancy.

Pregnancy

Exenatide is not recommended for use during pregnancy. No specific studies have been conducted in pregnant women. Data on a limited number of exposed pregnancies indicate no adverse effects of exenatide on pregnancy or on the health of the foetus/new born child.

Breastfeeding

It is unknown whether exenatide is excreted in human milk. In lactating mice given high doses of exenatide, low concentrations of exenatide were detected in milk. Exenatide should be administered to nursing women only if the potential benefit to the mother justifies the potential risk to the infant.

Fertility

No fertility studies in humans have been conducted.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of the ability to drive and use machines have been performed. When BYDUREON is used in combination with a sulphonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines.

4.8 UNDESIRABLE EFFECTS

Summary of the safety profile

The most frequent adverse drug reactions (≥ 5 % of BYDUREON treatment) were gastrointestinal related (nausea, vomiting, diarrhoea and constipation). The most frequently reported adverse reaction was nausea which was associated with the initiation of treatment and decreased over time. In addition, injection site reactions (pruritus, nodules, erythema), hypoglycaemia (with a sulphonylurea), and headache occurred. Most adverse reactions associated with BYDUREON were mild to moderate in intensity.

Tabulated summary of adverse reactions

The frequency of adverse reactions of BYDUREON identified from pooled clinical trial data or from post-marketing data are shown below (Table 1). The pooled BYDUREON clinical trials data set comprises 12 studies. The twelve trials included two studies of < 6 months duration, eight studies of 6-12 months duration and two studies of > 12 months duration. The follow-up and extension phases of studies are included in the pool.

Background therapies included diet and exercise, alone or in combination with metformin, a sulphonylurea, a thiazolidinedione or a combination of oral anti-diabetic agents.

The reactions are listed below as MedDRA preferred term by system organ class and absolute frequency. Patient frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10000 to < 1/1000), very rare (< 1/10000)) and not known (cannot be estimated from the available data).

Table 1: Adverse drug reactions of exenatide once weekly identified from mono- and combination therapy pooled clinical trial data, and from post-marketing data

System Organ Class	Frequency of occurrence	Adverse reaction term Exenatide once weekly *,†
Blood and lymphatic system disorders	Not known[b]	Drug-induced thrombocytopenia
Gastrointestinal disorders	Very common	Nausea; Diarrhoea
	Common	Vomiting; Constipation; Dyspepsia; Gastroesophageal reflux disease; Abdominal pain; Abdominal distension; Flatulence
	Uncommon	Eructation; Acute pancreatitis
General disorders and administration site conditions	Common	Injection site pruritus; Injection site erythema; Fatigue; Asthenia[a]
	Uncommon	Injection site reaction; Injection site rash
	Rare	Feeling jittery
Immune system disorders	Rare	Anaphylactic reaction
Investigations	Uncommon	Weight decreased
	Not known[b]	INR increased with concomitant warfarin
Metabolism and nutrition disorders	Very Common	Hypoglycaemia (with a sulphonylurea)[c, d]
	Common	Hypoglycaemia (with insulin)[d,e] Decreased appetite; Hypoglycaemia (without a sulphonylurea)[c, d]
	Uncommon	Dehydration, generally associated with nausea, vomiting and/or diarrhoea
Nervous system disorders	Common	Headache[a]; Dizziness
	Uncommon	Somnolence; Dysgeusia
Renal and urinary disorders	Uncommon	Altered renal function[f]
Skin and subcutaneous tissue disorders	Common	Pruritus
	Uncommon	Urticaria; Alopecia; Hyperhidrosis[a]; Angioedema
	Rare	Injection site abscesses and cellulitis; Macular or papular rash

* Rate based on exenatide once weekly completed safety and efficacy studies (n=2868); includes follow up within seventy days of the last dose received and extension period.

† Within each frequency grouping, adverse reactions are presented in the order of decreasing frequency.

a In insulin comparator-controlled studies in which metformin and sulphonylurea were concomitant medicinal products, the incidence for these adverse reaction s was similar for insulin- and exenatide BID-treated patients.

b Cannot be estimated from the available data.

c Frequencies reported in pooled data from the controlled periods of the 11 exenatide once weekly studies and 26 exenatide twice daily studies. Eleven exenatide one weekly studies included two studies of < 6 months duration, and nine of 6-12 months duration. Twenty-six exenatide twice daily studies included ten studies of < 6 months duration, fifteen studies of 6-12 months duration and one study of > 12 months.

d Based on hypoglycaemic events that 1. Result in loss of consciousness, seizure, or coma which resolves after administration of glucagon or glucose OR 2. Require third party assistance to

resolve because of impairment in consciousness or behaviour and has glucose value of <54 mg/dL (3 mmol/L) or 3. Result in symptoms consistent with hypoglycaemia with a concomitant glucose <54 mg/dL (3 mmol/L) prior to treatment.

e Frequency reported from the 28-week controlled treatment period of the exenatide once weekly as add-on to insulin glargine study **(**N=231).

f Includes acute renal failure, worsened chronic renal failure, renal impairment, increased serum creatinine.

Description of selected adverse reactions

Hypoglycaemia

The incidence of hypoglycaemia was increased when BYDUREON was used in combination with a sulphonylurea (see section 4.4). To reduce the risk of hypoglycaemia associated with the use of a sulphonylurea, reduction in the dose of sulphonylurea may be considered (see sections 4.2 - Dose and Method of Administration and 4.4 – Special Warnings and Precautions for Use).

Exenatide once weekly was associated with a significantly lower incidence of episodes of hypoglycaemia than insulin glargine in patients also receiving metformin therapy (3 % versus 19 %) and in patients also receiving metformin plus sulphonylurea therapy (20 % versus 42 %).

When exenatide once weekly was added to a basal insulin, no initial dose adjustment of insulin was required. Exenatide once weekly in combination with basal insulin showed no clinically significant differences in the incidence of hypoglycaemic episodes compared to insulin. There were no episodes of major hypoglycaemia in the exenatide once weekly with insulin group.

Nausea

The most frequently reported adverse reaction was nausea. In patients treated with exenatide once weekly, generally 20 % reported at least one episode of nausea compared to 34 % of exenatide twice daily patients. Most episodes of nausea were mild to moderate. With continued therapy, the frequency decreased in most patients who initially experienced nausea.

The incidence of withdrawal due to adverse events during the 30-week controlled trial was 6 % for exenatide once weekly -treated patients, 5 % for exenatide twice daily -treated patients. The most common adverse events leading to withdrawal in either treatment group were nausea and vomiting. Withdrawal due to nausea or vomiting each occurred in < 1 % for exenatide once weekly -treated patients and 1 % for exenatide twice daily treated patients.

Drug-induced thrombocytopenia

Drug-induced thrombocytopenia (DITP) with exenatide-dependent anti-platelet antibodies has been reported in the post-marketing setting. DITP is an immune-mediated reaction that is caused by drug-dependent platelet-reactive antibodies. These antibodies cause destruction of platelets in the presence of the sensitizing drug.

Injection site reactions

Injection site reactions were observed more frequently in exenatide once weekly treated patients versus comparator treated patients (16 % versus range of 2-7 %) during the 6 month controlled phase of studies. These injection site reactions were generally mild and usually did not lead to withdrawal from studies. Patients may be treated to relieve symptoms, while continuing treatment. Subsequent injections should use a different site of injection each week.

Small subcutaneous injection site nodules were observed very frequently in clinical trials, consistent with the known properties of poly (D,L-lactide co-glycolide) polymer microsphere

formulations. Most individual nodules were asymptomatic, did not interfere with study participation and resolved over 4 to 8 weeks.

Immunogenicity

Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients may develop antibodies to exenatide following treatment with exenatide once weekly. In most patients who develop antibodies, antibody titres diminish over time.

The presence of antibodies (high or low titres) is not predictive of glycaemic control for an individual patient.

In clinical studies of exenatide once weekly, approximately 45 % of patients had low titre antibodies to exenatide at study endpoint. Overall the percentage of antibody positive patients was consistent across clinical trials. Overall, the level of glycaemic control (HbA_{1c}) was comparable to that observed in those without antibody titres. On average in the phase 3 studies, 12 % of the patients had higher titre antibodies. In a proportion of these the glycaemic response to exenatide once weekly was absent at the end of the controlled period of studies; 2.6 % of patients showed no glucose improvement with higher titre antibodies while 1.6 % showed no improvement while antibody negative.

Patients who developed antibodies to exenatide tend to have more injection site reactions (for example: redness of skin and itching), but otherwise similar rates and types of adverse events as those with no antibodies to exenatide.

For exenatide once weekly treated patients, the incidence of potentially immunogenic injection site reactions (most commonly pruritus with or without erythema) during the 30-week and the two 26-week studies, was 9 %. These reactions were less commonly observed in antibody-negative patients (4 %) compared with antibody-positive patients (13 %), with a greater incidence in those with higher titre antibodies.

Examination of antibody-positive specimens revealed no significant cross-reactivity with similar endogenous peptides (glucagon or GLP-1).

Increased heart rate

A mean increase in heart rate (HR) of 2.6 beats per minute (bpm) from baseline (74 bpm) was observed in pooled exenatide once weekly clinical studies. Fifteen percent of exenatide once weekly treated patients had mean increases in HR of ≥10 bpm; approximately 5% to 10% of subjects within the other treatment groups had mean increases in HR of ≥10 bpm.

REPORTING OF SUSPECTED ADVERSE REACTIONS

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via https://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSE

Effects of overdoses with exenatide (based on exenatide twice daily clinical studies) included severe nausea, severe vomiting and rapidly declining blood glucose concentrations. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Glucagon-like peptide-1 receptor (GLP-1) analogues. ATC code: A10BJ01.

Mechanism of action

Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist that exhibits several antihyperglycaemic actions of glucagon-like peptide-1 (GLP-1). The amino acid sequence of exenatide partially overlaps that of human GLP-1. Exenatide has been shown to bind to and activate the known human GLP-1 receptor *in vitro*, its mechanism of action mediated by cyclic AMP and/or other intracellular signaling pathways.

Exenatide increases, on a glucose-dependent basis, the secretion of insulin from pancreatic beta cells. As blood glucose concentrations decrease, insulin secretion subsides. When exenatide was used in combination with metformin and/or a thiazolidinedione, no increase in the incidence of hypoglycaemia was observed over that of placebo in combination with metformin and/or a thiazolidinedione which may be due to this glucose-dependent insulinotropic mechanism (see section 4.4 – Special Warnings and Precautions for Use).

Exenatide suppresses glucagon secretion which is known to be inappropriately elevated in patients with type 2 diabetes. Lower glucagon concentrations lead to decreased hepatic glucose output. However, exenatide does not impair the normal glucagon response and other hormone responses to hypoglycaemia.

Exenatide slows gastric emptying thereby reducing the rate at which meal-derived glucose appears in the circulation.

Administration of exenatide has been shown to reduce food intake, due to decreased appetite and increased satiety.

Pharmacodynamic effects

Exenatide improves glycaemic control through the sustained effects of lowering both postprandial and fasting glucose concentrations in patients with type 2 diabetes. Unlike native GLP-1, BYDUREON has a pharmacokinetic and pharmacodynamic profile in humans suitable for once weekly administration.

A pharmacodynamic study with exenatide demonstrated in patients with type 2 diabetes (n=13) a restoration of first phase insulin secretion and improved second phase insulin secretion in response to an intravenous bolus of glucose.

Glucose-Dependent Insulin Secretion

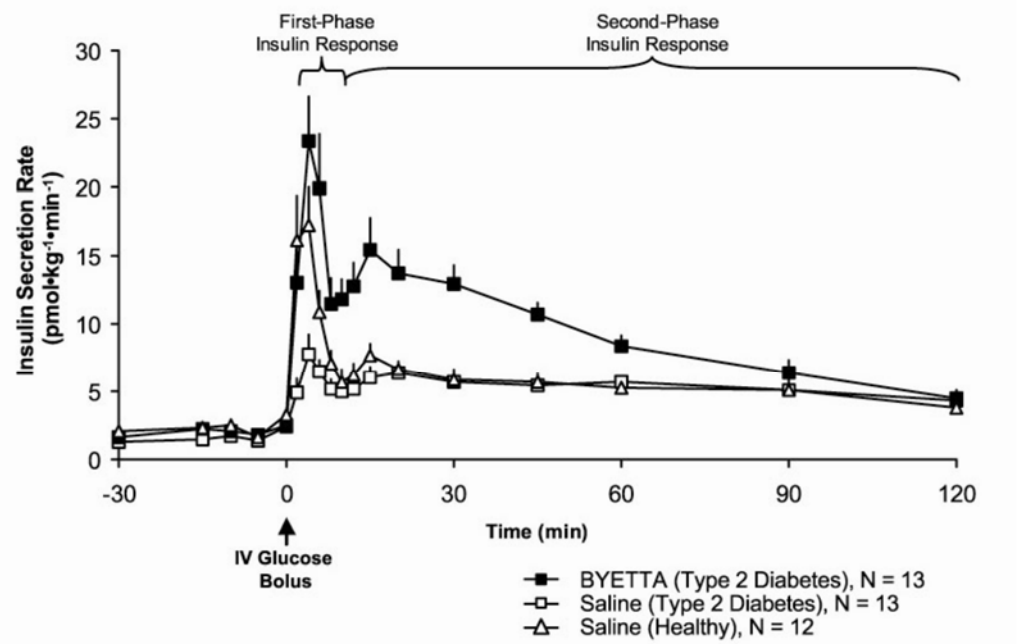
Exenatide has acute effects on pancreatic beta-cell responsiveness to glucose leading to insulin release predominantly in the presence of elevated glucose concentrations. This insulin secretion subsides as blood glucose concentrations decrease and approach euglycemia. However, exenatide does not impair the normal glucagon response to hypoglycaemia.

First-Phase Insulin Response

In healthy individuals, robust increase in insulin secretion occurs during the first 10 minutes following intravenous (IV) glucose administration. This secretion, known as the “first-phase insulin response,” is characteristically absent in patients with type 2 diabetes mellitus. The loss of the first-phase insulin response is an early beta-cell defect in type 2 diabetes mellitus. Administration of exenatide at therapeutic plasma concentrations restored first-phase insulin response to an IV bolus of glucose in patients with type 2 diabetes mellitus (Figure 1). Both first-phase insulin secretion and second-phase insulin secretion were significantly increased

in patients with type 2 diabetes mellitus treated with exenatide compared with saline ($p<0.001$ for both).

Figure 1: Mean (+SEM) Insulin Secretion Rate during Infusion of Exenatide or Saline in Patients with Type 2 Diabetes Mellitus and during Infusion of Saline in Healthy Subjects



Patients received an IV infusion of insulin for 6.5 h (discontinued at time [t] = -30 min) to normalize plasma glucose concentrations and a continuous IV infusion of either BYETTA or saline for 5 h beginning 3 h prior to an IV bolus of glucose (0.3 g/kg over 30 sec) at t = 0 min.

Glucagon Secretion

In patients with type 2 diabetes mellitus, exenatide moderates glucagon secretion and lowers serum glucagon concentrations during periods of hyperglycemia. Lower glucagon concentrations lead to decreased hepatic glucose output. Exenatide does not impair the normal glucagon response to hypoglycaemia.

Clinical Efficacy and Safety

The results of long term clinical studies of exenatide once weekly are presented below, these studies comprised 1356 subjects treated with exenatide once weekly, 52 % men and 48 % women, 230 (17%)) were ≥ 65 years of age.

Glycaemic control

In two studies exenatide 2 mg once weekly has been compared to exenatide twice daily 5 mcg for 4 weeks followed by exenatide twice daily 10 mcg. One study was of 24 weeks in duration (n= 252) and the other of 30 weeks (n= 295) followed by an open labelled extension where all patients were treated with exenatide 2 mg once weekly for a further 7 years (n= 258). In both studies, decreases in HbA_{1c} were evident in both treatment groups as early as the first post-treatment HbA_{1c} measurement (weeks 4 or 6).

Exenatide once weekly resulted in a statistically significant reduction in HbA_{1c} compared to patients receiving exenatide twice daily (Table 2).

A clinically relevant effect of exenatide once weekly and exenatide twice daily treated subjects was observed on HbA_{1c}, regardless of the background anti-diabetic therapy in both studies.

Clinically and statistically significantly more subjects on exenatide once weekly compared to exenatide twice daily patients achieved an HbA_{1c} reduction of ≤ 7 % or < 7 % in the two studies ($p < 0.05$ and $p =< 0.0001$ respectively).

Both exenatide once weekly and exenatide twice daily patients achieved a reduction in weight compared to baseline, although the difference between the two treatment arms was not significant.

In the uncontrolled study extension, evaluable patients who switched from exenatide twice daily to exenatide once weekly at week 30 (n= 121) achieved the same improvement in HbA_{1c} of - 2.0 % at week 52 compared to baseline as patients treated with exenatide once weekly.

For all patients completing the uncontrolled study extension of 7 years (n=122 of 258 patients included in the extension phase), HbA1c gradually increased over time from week 52 onwards, but was still reduced compared to baseline after 7 years (-1.1%). Weight loss was sustained over 7 years in these patients.

Table 2: Results of two trials of exenatide once weekly versus exenatide twice daily in combination with diet and exercise alone, metformin and/or sulphonylurea and metformin and/or thiazolidinedione (intent to treat patients)

24 Week Study	**Exenatide 2 mg once weekly**	**Exenatide 10 mcg twice daily**
N	129	123
Mean HbA_{1c} (%)		
Baseline	8.5	8.4
Change from baseline (± SE)	-1.6 (±0.1)**	-0.9 (±0.1)
Mean difference change from baseline between treatments (95 % CI)	-0.67 (-0.94, -0.39) **	
Patients (%) achieving HbA_{1c} < 7 %	58	30
Change in fasting plasma glucose (mmol/l) (± SE)	-1.4 (±0.2)	-0.3 (±0.2)
Mean body weight (kg)		
Baseline	97	94
Change from baseline (± SE)	-2.3 (±0.4)	-1.4 (± 0.4)
Mean difference change from baseline between treatments (95 % CI)	-0.95 (-1.91, 0.01)	
30 Week Study		
N	148	147
Mean HbA_{1c} (%)		
Baseline	8.3	8.3
Change from baseline (± SE)	-1.9 (±0.1)*	-1.5 (±0.1)
Mean difference change from baseline between treatments (95 % CI)	-0.33 (-0.54, -0.12) *	
Patients (%) achieving HbA_{1c} ≤ 7 %	73	57
Change in fasting plasma glucose (mmol/l) (± SE)	-2.3 (±0.2)	-1.4 (±0.2)
Mean body weight (kg)		
Baseline	102	102
Change from baseline (± SE)	-3.7 (±0.5)	-3.6 (±0.5)
Mean difference change from baseline between treatments (95 % CI)	-0.08 (-1.29, 1.12)	

SE = standard error, CI= confidence interval), * p< 0.05, **p< 0.0001

A study of 26 week duration has been conducted, in which exenatide once weekly 2 mg is compared to insulin glargine once daily. Exenatide once weekly demonstrated a superior change in HbA_{1c} compared to insulin glargine. Compared with insulin glargine treatment,

exenatide once weekly treatment significantly lowered mean body weight and was associated with fewer hypoglycaemic events (Table 3).

Table 3: Results of one 26 week trial of exenatide once weekly versus insulin glargine in combination with metformin alone or metformin and sulphonylurea (intent to treat patients)

	Exenatide 2 mg once weekly	**Insulin Glargine**[1]
N	233	223
Mean HbA_{1c} (%)		
Baseline	8.3	8.3
Change from baseline (± SE)	-1.5 (± 0.1)*	-1.3 (± 0.1)*
Mean difference change from baseline between treatments (95 % CI)	-0.16 (-0.29, -0.03)*	
Patients (%) achieving $HbA_{1c} \leq 7$ %	62	54
Change in fasting serum glucose (mmol/l) (± SE)	-2.1 (± 0.2)	-2.8 (± 0.2)
Mean body weight (kg)		
Baseline	91	91
Change from baseline(± SE)	-2.6 (± 0.2)	+1.4 (±0.2)
Mean difference change from baseline between treatments (95 % CI)	-4.05 (-4.57, -3.52) *	

SE = standard error, CI= confidence interval), * p<0.05

[1] Insulin glargine was dosed to a target glucose concentration of 4.0 to 5.5 mmol/l (72 to 100 mg/dl). The mean dose of insulin glargine at the beginning of treatment was 10.1 IU/day rising to 31.1 IU/day for insulin glargine-treated patients.

The 156-week results were consistent with those previously reported in the 26-week interim report. Treatment with exenatide once weekly persistently significantly improved glycaemic control and weight control, compared to the insulin glargine treatment. Safety findings at 156 weeks were consistent with those reported at 26 weeks.

In a 26 week double blind study exenatide once weekly was compared to maximum daily doses of sitagliptin and pioglitazone in subjects also using metformin. All treatment groups had a significant reduction in HbA_{1c} compared to baseline. Exenatide once weekly demonstrated superiority to both sitagliptin and pioglitazone with respect to change in HbA_{1c} from baseline.

Exenatide once weekly demonstrated significantly greater weight reductions compared to sitagliptin. Patients on pioglitazone gained weight (Table 4).

Table 4: Results of one 26 week trial of exenatide once weekly versus sitagliptin and versus pioglitazone in combination with metformin (intent to treat patients)

	Exenatide 2 mg once weekly	**Sitagliptin 100 mg**	**Pioglitazone 45 mg**
N	160	166	165
Mean HbA_{1c} (%)			
Baseline	8.6	8.5	8.5
Change from baseline (± SE)	-1.6 (± 0.1)*	-0.9 (± 0.1)*	-1.2 (± 0.1)*
Mean difference change from baseline between treatments (95 % CI) versus sitagliptin	-0.63 (-0.89, -0.37)**		
Mean difference change from baseline between treatments (95 % CI) versus pioglitazone	-0.32 (-0.57, -0.06,)*		
Patients (%) achieving HbA_{1c} **≤ 7 %**	62	36	49
Change in fasting serum glucose (mmol/l) (± SE)	-1.8 (± 0.2)	-0.9 (± 0.2)	-1.5 (± 0.2)
Mean body weight (kg)			
Baseline	89	87	88
Change from baseline(± SE)	-2.3 (± 0.3)	-0.8 (± 0.3)	+2.8 (± 0.3)
Mean difference change from baseline between treatments (95 % CI) versus sitagliptin	-1.54 (-2.35, -0.72)*		
Mean difference change from baseline between treatments (95 % CI) versus pioglitazone	-5.10 (-5.91 , -4.28)**		

SE = standard error, CI= confidence interval), * p< 0.05, **p< 0.0001

Body weight

A reduction in body weight compared to baseline has been observed in all exenatide once weekly studies. In the 4 comparator controlled studies, this reduction in body weight was seen in patients treated with exenatide once weekly irrespective of the occurrence of nausea although the reduction was larger in the group with nausea (mean reduction - 2.9 kg to - 5.2 kg with nausea versus - 2.2 kg to -2.9 kg without nausea).

The proportion of patients who had both a reduction in weight and HbA_{1c} ranged from 70 to 79 % (the proportion of patients who had a reduction of HbA_{1c} ranged from 88 to 96 %).

Plasma/serum glucose

Treatment with exenatide once weekly resulted in significant reductions in fasting plasma/serum glucose concentrations, these reductions were observed as early as 4 weeks. Additional reductions in postprandial concentrations were also observed. The improvement in fasting plasma glucose concentrations was durable through 52 weeks.

Beta-cell function

Clinical studies with exenatide once weekly have indicated improved beta-cell function, using measures such as the homeostasis model assessments (HOMA-B). The durability of effect on beta-cell function was maintained through 52 weeks.

Blood pressure

A reduction in systolic blood pressure was observed in the 4 comparator controlled exenatide once weekly studies (2.9 mmHg to 4.7 mmHg). In the 30 week exenatide twice daily comparator study both exenatide once weekly and exenatide twice daily significantly reduced

systolic blood pressure from base line (4.7±1.1 mmHg and 3.4±1.1 mmHg respectively) the difference between the treatments was not significant. Improvements in blood pressure were maintained through 52 weeks.

Fasting lipids

Exenatide once weekly has shown no adverse effects on lipid parameters.

Concomitant Initiation of Exenatide Once Weekly and Dapagliflozin vs. Exenatide Once Weekly Alone and Dapagliflozin Alone, as Add-On to Metformin

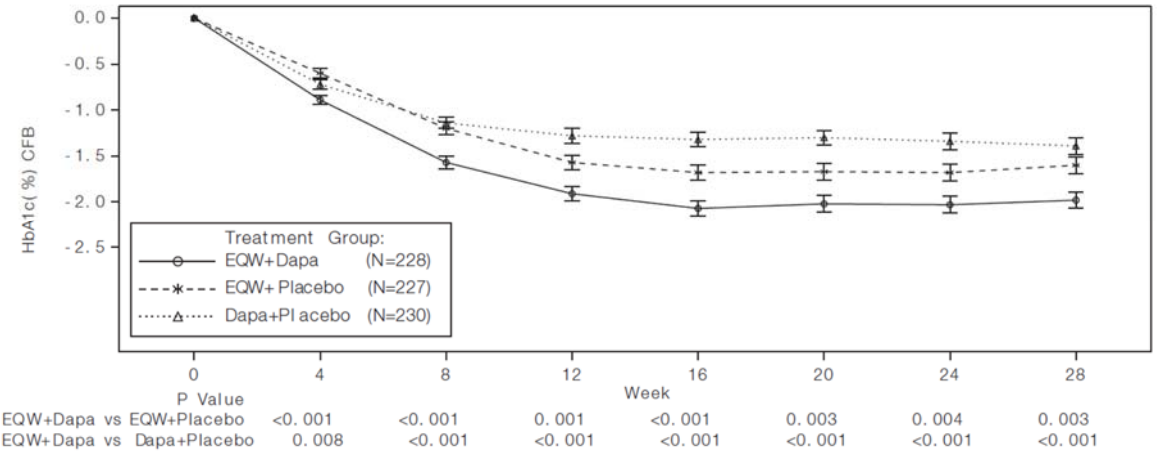
A 28-week, double-blind, active-controlled trial was conducted to evaluate the efficacy and safety of exenatide 2 mg once weekly and dapagliflozin 10 mg once daily (SGLT2 inhibitor), when initiated concomitantly, versus exenatide 2 mg once weekly alone and dapagliflozin 10 mg once daily alone, in a total of 694 patients with type 2 diabetes who were not achieving adequate glycaemic control on a background of metformin (≥1500 mg/day).

All patients entered a 1-week placebo lead-in period. Patients with HbA_{1c} ≥8.0 and ≤12.0% were randomly assigned to receive exenatide once weekly and dapagliflozin 10 mg, exenatide 2 mg once weekly alone or dapagliflozin 10 mg alone. During the treatment period, patients continued on the same type and dose of metformin as when they entered the study. Randomization was stratified by glycated hemoglobin A_{1c} (HbA_{1c}) at baseline (<9.0% or ≥9.0%).

The majority of patients (84%) were White, 14 % Black or African, 2% Other and <1% Asian and American Indian or Alaska Native.

The primary endpoint was the change in HbA_{1c} from baseline to Week 28 (Figure 2). Compared to exenatide 2 mg once weekly alone and dapagliflozin 10 mg alone, concomitant initiation of exenatide 2 mg once weekly and dapagliflozin 10 mg resulted in statistically significant reductions in HbA_{1c} from baseline at Week 28 (Table 5).

Figure 2: Change in HbA_{1c} Over Time, LS Mean (SE) – 28-Week Treatment Period (Intent-to-Treat Analysis Set)



CFB=change from baseline; EQW=BYDUREON 2 mg once weekly; Dapa=dapagliflozin 10 mg QD. Baseline is defined as Week 0.

Table 5: 28-Week Active-Controlled Trial of Exenatide Once Weekly and Dapagliflozin 10 mg versus Exenatide Once Weekly Alone and Dapaglifozin Alone, Concomitant Add-On to Metformin

	Exenatide 2 mg QW + Dapagliflozin 10 mg QD	**Exenatide 2 mg QW + Placebo QD**	**Dapagliflozin 10 mg QD + Placebo QW**
Intent-to-Treat population (N)[a]	**228**	**227**	**230**
Mean HbA_{1c} (%)			
Baseline	9.3	9.3	9.3
Change from baseline (±SE)[b]	-2.0 (±0.1)	-1.6 (±0.1)	-1.4 (±0.1)
Mean difference in change from baseline vs. exenatide QW (95% CI)	-0.38* (-0.63, -0.13)		
Mean difference in change from baseline vs. dapagliflozin (95% CI)	-0.59** (-0.84, -0.34)		
Patients (%) achieving HbA_{1c} <7.0%[c]	45%	27%	19%
Patients (%) achieving HbA_{1c} ≤6.5%	30%	19%	10%
Mean body weight (kg)			
Baseline	92	89	91
Change from baseline (±SE)[b]	-3.6 (±0.3)	-1.6 (±0.3)	-2.2 (±0.3)
Mean difference in change from baseline vs. exenatide QW (95% CI)	-2.00** (-2.79, -1.20)		
Mean difference in change from baseline vs. dapagliflozin (95% CI)	-1.33** (-2.12, -0.55)		
Proportion of patients achieving weight loss ≥5.0%[c]	33.3%	13.7%	20.0%
Difference in proportion of patients vs. exenatide QW (%)	19.7**		
Difference in proportion of patients vs. dapagliflozin (%)	13.3*		
Mean fasting plasma glucose (mmol/L)			
Baseline	10.9	10.5	10.5
Change from baseline (±SE)[b]	-3.7 (±0.2)	-2.5 (±0.2)	-2.7 (±0.2)
Mean difference in change from baseline vs. exenatide QW (95% CI)	-1.12** (-1.55, -0.68)		

	Exenatide 2 mg QW + Dapagliflozin 10 mg QD	Exenatide 2 mg QW + Placebo QD	Dapagliflozin 10 mg QD + Placebo QW
Intent-to-Treat population (N)[a]	**228**	**227**	**230**
Mean difference in change from baseline vs. dapagliflozin (95% CI)	-0.92** (-1.36, -0.49)		
Mean 2-hour postprandial plasma glucose change from baseline (mmol/L)			
Standard meal test population (n)	198	188	199
Baseline	14.9	14.8	14.5
Change from baseline (±SE)[b]	-4.9 (±0.2)	-3.3 (±0.2)	-3.4 (±0.2)
Mean difference in change from baseline vs. exenatide QW (95% CI)	-1.54** (-2.10, -0.98)		
Mean difference in change from baseline vs. dapagliflozin (95% CI)	-1.49** (-2.04, -0.93)		
Mean systolic blood pressure (mmHg)			
Baseline	130.7	129.3	129.5
Change from baseline (±SE)[b]	-4.3 (±0.80)	-1.2 (±0.82)	-1.8 (±0.8)
Mean difference in change from baseline vs. exenatide QW (95% CI)	-3.0* (-5.2, -0.9)		
Mean difference in change from baseline vs. dapagliflozin (95% CI)	-2.4# (-4.5, -0.4)		

QW=once weekly, QD=once daily, N=number of patients in treatment group, SE=standard error, CI=confidence interval.

[a] Patients who received at least 1 dose of study medication and had at least 1 post-baseline HbA_{1c} assessment.

[b] Adjusted least squares means (LS Means) and treatment group difference(s) in the change from baseline values at Week 28 are modeled using a mixed model with repeated measures (MMRM) including treatment, region, baseline HbA_{1c} stratum (< 9.0% or ≥ 9.0%), week, and treatment by week interaction as fixed factors, and baseline value as a covariate.

[c] Categories are derived from continuous measurements. All patients with missing endpoint data are imputed as non-responders. Treatment comparison is based on Cochran-Mantel-Haenszel (CMH) test stratified by baseline HbA_{1c} (<9.0% or ≥9.0%). P-values are from the general association statistics.

*p < 0.01, **p < 0.001, #p < 0.05.

P-values are all adjusted p-values for multiplicity.

Analyses exclude measurements post rescue therapy and post premature discontinuation of study medication, except for systolic blood pressure analysis, which includes measurements post rescue therapy but excludes data post premature discontinuation of study medication.

Compared to exenatide once weekly alone, concomitant use of exenatide once weekly and dapagliflozin 10 mg, resulted in significantly greater reductions in fasting plasma glucose from baseline at Week 2 (-41 mg/dL [-2.3 mmol/L] with exenatide once weekly + dapagliflozin vs. -21 mg/dL [-1.2 mmol/L] with exenatide once weekly + placebo, p < 0.001).

Combination with Basal Insulin

Exenatide once weekly vs. Placebo as Add-On to Basal Insulin Alone or in Combination with Metformin

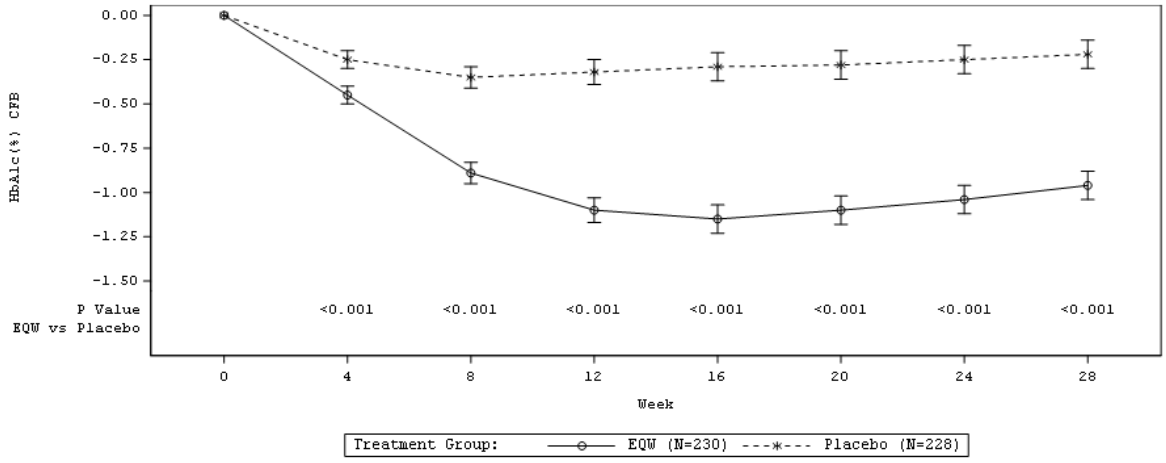
A 28-week, double-blind, placebo-controlled trial was conducted to evaluate the efficacy and safety of exenatide once weekly (n=230) versus placebo (n=228) when added to titrated basal insulin glargine, with or without metformin, in patients with type 2 diabetes with inadequate glycaemic control.

All patients initially entered an 8-week insulin dose optimization phase. Patients on sulphonylurea therapy discontinued sulphonylurea. The dose of insulin glargine was titrated to a target fasting plasma glucose of 4.0 to 5.5 mmol/L (72 to 99 mg/dL). Patients with HbA_{1c} ≥7.0% and ≤10.5% were then randomly assigned to receive either exenatide once weekly or placebo. Insulin glargine dose titration continued throughout the treatment phase of the study. Patients who had been on metformin at baseline (≥1,500 mg/day) continued on the same type and dose of metformin therapy throughout the study.

The majority of the patients (87%) were White, 10% Black or African American, 1% Asian, 1% Other, <1% American Indian or Alaska Native, and <1% Pacific Islander.

The primary endpoint was the change in HbA_{1c} from baseline to Week 28 (Figure 3). Exenatide once weekly achieved a significantly greater reduction in HbA_{1c} at Week 28 than that observed with placebo (Table 6).

Figure 3: Change in HbA_{1c} by Week of Treatment – ITT patients



EQW=exenatide once weekly + titrated basal insulin ± metformin; N=number of patients in the analysis;
Placebo=placebo + titrated basal insulin ± metformin.
CFB=Change from baseline.
Baseline is defined as Week 0.

Table 6: 28-Week Placebo-Controlled Trial of Exenatide Once Weekly as Add-On to Insulin Glargine Alone or in Combination with Metformin

	Exenatide 2 mg QW + Titrated Insulin Glargine	**Placebo + Titrated Insulin Glargine**
Intent-to-Treat Population (N)[a]	230	228
Mean HbA_{1c} (%)		
Baseline	8.5	8.5
Change from baseline (± SE)[b]	-1.0 (0.1)	-0.2 (0.1)
Mean difference in change from baseline vs. Placebo (95% CI)	-0.74* (-0.94, -0.54)	
Proportion achieving HbA_{1c} <7.0%[c]	33%*	7%
Proportion achieving HbA_{1c} ≤6.5%	21%**	5%
Mean body weight (kg)		
Baseline	94	94
Change from baseline (± SE)[b]	-1.0 (0.3)	0.5 (0.3)
Mean difference in change from baseline vs. Placebo (95% CI)	-1.52* (-2.19, -0.85)	
Mean 2-hour postprandial plasma glucose change from baseline (mmol/L)[d]		
Baseline	13.1	13.0
Change from baseline (± SE)[b]	-1.6 (0.3)	-0.1 (0.3)
Mean difference in change from baseline vs. Placebo (95% CI)	-1.54* (-2.17, -0.91)	

N=number of patients in each treatment group, SE=standard error, CI=confidence interval.

a. Patients who received at least 1 dose of study medication and had at least 1 post-baseline HbA_{1c} assessment.

b. Adjusted LS means and treatment group difference(s) in the change from baseline values at Week 28 are modeled using a mixed model with repeated measures (MMRM) including treatment, region, baseline HbA_{1c} stratum (<9.0% or ≥9.0%), baseline SU-use stratum (yes vs. no), week, and treatment by week interaction as fixed factors, and baseline value as a covariate. The absolute change in 2-hour postprandial plasma glucose at Week 28 is modeled similarly using ANCOVA.

c. Categories are derived from continuous measurements. All patients with missing endpoint data are imputed as non-responders. Treatment comparison is based on Cochran-Mantel-Haenszel (CMH) test stratified by baseline HbA_{1c} (<9.0% or ≥9.0%), and baseline SU-use stratum (yes vs. no). P-values are from the general association statistics.

d. After a standard meal tolerance test.

* p-value <0.001 (adjusted for multiplicity).
** nominal p-value <0.001 (exploratory endpoint).
Analyses exclude measurements post rescue therapy and post premature discontinuation of study medication.

The mean daily insulin dose was increased from baseline to Week 28 for both treatment groups (50.4 to 51.9 units in the exenatide once weekly group and 51.0 to 54.2 units in the placebo group). The difference in change from baseline to Week 28 in mean daily insulin dose was not statistically significant (-2.0 units, p=0.068).

Larger proportions of patients in the exenatide once weekly group (22%) achieved HbA_{1c} <7.0% at Week 28 with no weight gain and no major hypoglycaemia over 28 weeks compared to the placebo group (2%).

The change from baseline to Week 28 in seated systolic blood pressure was -2.6 mmHg for the exenatide once weekly group and -0.7 mmHg for the placebo group.

The change from baseline to Week 28 in fasting plasma glucose was –11 mg/dL (-0.6 mmol/L) for the exenatide once weekly group and -2 mg/dL (-0.1 mmol/L) for the placebo group.

5.2 PHARMACOKINETIC PROPERTIES

The absorption properties of exenatide reflect the extended release properties of the BYDUREON formulation. Once absorbed into the circulation, exenatide is distributed and eliminated according to its known systemic pharmacokinetic properties (as described in this section).

Absorption

Following weekly administration of 2 mg BYDUREON, mean exenatide concentrations exceeded minimal efficacious concentrations (~ 50 pg/mL) in 2 weeks with gradual increase in the average plasma exenatide concentration over 6 to 7 weeks. Subsequently, exenatide concentrations of approximately 300 pg/mL were maintained indicating that steady-state was achieved. Steady-state exenatide concentrations are maintained during the one week interval between doses with minimal peak to trough fluctuation from this average therapeutic concentration.

Distribution

The mean apparent volume of distribution of exenatide following subcutaneous administration of a single dose of exenatide is 28 L.

Biotransformation and elimination

Nonclinical studies have shown that exenatide is predominantly eliminated by glomerular filtration with subsequent proteolytic degradation. The mean apparent clearance of exenatide is 9 L/h. These pharmacokinetic characteristics of exenatide are independent of the dose. Approximately 10 weeks after discontinuation of BYDUREON therapy, mean plasma exenatide concentrations fell below minimal detectable concentrations.

Special populations

Patients with renal impairment

No clinically meaningful differences were observed in steady state exenatide concentrations or tolerability in patients with mild to moderate renal impairment (CLcr 30 to 80 mL/min) compared to those with normal renal function. No dosage adjustment of BYDUREON is required for patients with mild to moderate renal impairment. BYDUREON is not recommended for patients with severe renal impairment (CLcr <30 mL/min) or for patients with end-stage renal disease receiving dialysis (see section 4.4 Special Warnings and Precautions for Use).

Patients with hepatic insufficiency

No pharmacokinetic study has been performed in patients with hepatic insufficiency. Exenatide is cleared primarily by the kidney, therefore hepatic dysfunction is not expected to affect blood concentrations of exenatide.

Gender, race and body weight

Gender, race and body weight have no clinically relevant influence on exenatide pharmacokinetics.

Elderly

Data in elderly are limited, but suggest no marked changes in exenatide exposure with increased age up to about 75 years old.

In a pharmacokinetic study of exenatide twice daily in patients with type 2 diabetes, administration of exenatide (10 mcg) resulted in a mean increase of exenatide AUC by 36 % in 15 elderly subjects aged 75 to 85 years compared to 15 subjects aged 45 to 65 years likely related to reduced renal function in the older age group (see section 4.2 – Dose and Method of Administration).

Paediatric population

In a single-dose pharmacokinetic study of exenatide twice daily in 13 patients with type 2 diabetes and between the ages of 12 and 16 years, administration of exenatide (5 mcg) resulted in slightly lower mean AUC (16 % lower) and C_{max} (25 % lower) compared to those observed in adults. No pharmacokinetics study of BYDUREON has been conducted in the paediatric population.

5.3 PRECLINICAL SAFETY DATA

Non-clinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, or genotoxicity conducted with exenatide twice daily or exenatide once weekly.

In a 104-week carcinogenicity study with exenatide once weekly a statistically significant increase in thyroid c - cell tumour incidence (adenomas and / or carcinomas) was observed in rats at all doses (1.4 - to 26 - fold the human clinical exposure with exenatide once weekly). The human relevance of these findings is currently unknown.

Animal studies with exenatide did not indicate harmful effects with respect to fertility; high doses of exenatide caused skeletal effects and reduced foetal and neonatal growth.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Powder
Poly (D,L-lactide-co-glycolide)
Sucrose

Solvent
Carmellose sodium
Sodium chloride
Polysorbate 20
Monobasic sodium phosphate, monohydrate
Dibasic sodium phosphate, heptahydrate
Water for injections
Sodium hydroxide (pen only)

6.2 INCOMPATIBILITIES

In the absence of compatibility studies this medicinal product must not be mixed with other medicinal products.

6.3 SHELF LIFE

3 years

After reconstitution the suspension must be injected immediately.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator (2ºC - 8ºC).

Do not freeze.

The kit and pen may be kept for up to 4 weeks below 30ºC prior to use.

Store in the original package in order to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Pre-filled pen.

Each dual-chamber pen contains exenatide powder and solvent in a Type 1 glass cartridge sealed at one end with a chlorobutyl rubber stopper and an aluminium seal, and at the other end with a chlorobutyl rubber piston. The two chambers are separated by a second chlorobutyl rubber piston. There is one needle supplied per pen. Each carton also contains one spare needle. Use only the supplied needles with the pen.

Pack size of 4 single dose pre-filled pens.

Single Dose Kit (vial with diluent syringe)

The powder is packaged in a 3 mL Type I glass vial sealed with a chlorobutyl rubber stopper and an aluminum seal with a plastic flip-off cap.

The solvent is packaged in a 1.5 mL Type 1 glass pre-filled syringe sealed with a bromobutyl rubber cap and a rubber plunger.

Each single-dose kit contains one vial of 2 mg exenatide, one pre-filled syringe of 0.65mL solvent, one vial connector, and two injection needles (one spare).

Pack size of 4 single dose kits.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

BYDUREON that has been frozen must not be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

BYDUREON must be injected immediately after suspension of the powder in the solvent.

The instruction manual must be followed carefully.

Pre-filled Pen

The pre-filled pen is for single-use only.

The pen must be removed from the refrigerator 15 minutes prior to injection. The powder in one chamber must be mixed with the solvent in the other chamber of the pre-filled pen. The solvent should be visually inspected prior to use. The solvent should only be used if it is clear and free of particulate matter. After suspension, BYDUREON should only be used if it is white to off white and cloudy.

Use only the supplied custom needles with the pen. Do no reuse or share needles.

The patient should be instructed to use a puncture-resistant container to discard the pen safely, with the needle still attached after each injection .

Single Dose Kit

The solvent should be visually inspected prior to use. The solvent should only be used if it is clear and free of particulate matter. After suspension, BYDUREON should only be used if the mixture is white to off white and cloudy.

The patient should be instructed to discard the syringe safely, with the needle still attached after each injection. The patient should recap the needle. The patient does not need to save any part of the single-use kit.

7 MEDICINE SCHEDULE

Prescription Medicine.

8. NAME AND ADDRESS

AstraZeneca Limited
PO Box 87453
Meadowbank
Auckland 1742.
Telephone: (09) 306 5650

9. DATE OF FIRST APPROVAL

8 September 2016

10. DATE OF REVISION OF TEXT

18 November 2019

CDS 270619

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8	New information regarding drug-induced thrombocytopenia.
5.1	Combination with basal insulin study data updated.
8	Postal address updated.