AUSTRALIAN PRODUCT INFORMATION
BYDUREON® (exenatide)

1. NAME OF THE MEDICINE

Exenatide.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BYDUREON BCise suspension for injection in autoinjector (BYDUREON BCise autoinjector)

Each autoinjector delivers a dose of 2 mg of exenatide in 0.85 mL.

BYDUREON powder for injection in pre-filled pen (BYDUREON pen)

Each pre-filled pen contains 2 mg of exenatide. After suspension, each pen delivers a dose of 2 mg in 0.65 mL.

BYDUREON powder for injection in vial with diluent syringe (BYDUREON kit)

Each vial contains 2 mg of exenatide. After suspension, a dose of 2 mg in 0.65 mL is delivered.

BYDUREON is an extended release microspheres formulation of exenatide. When the product is prepared as instructed, the resulting suspension contains 2 mg exenatide. The suspension is intended for subcutaneous use only, once per week.

For a full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

BYDUREON is supplied in the following presentations:

BYDUREON BCise autoinjector

Extended-release suspension for injection.

White to off-white opaque suspension.

BYDUREON pen

Powder and diluent for extended-release suspension for injection.

Powder: White to off-white powder.

Diluent: Clear, colourless to pale yellow to pale brown solution.

BYDUREON kit

Powder and diluent for extended-release suspension for injection.

Powder: White to off-white powder.

Diluent: Clear, colourless to pale yellow to pale brown solution.

Exenatide is also available in an immediate-release formulation (BYETTA). For information related to this formulation, please refer to the BYETTA Product Information.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

BYDUREON is indicated for the treatment of type 2 diabetes mellitus to improve glycaemic control in combination with other glucose-lowering medicinal products when the therapy in use, together with diet and exercise, does not provide adequate glycaemic control (see Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials for available data on different combinations).

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended BYDUREON dose is 2 mg exenatide once weekly. Titration is not required. BYDUREON is for single-use in one patient only. Discard any residue.

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

After suspension, use BYDUREON only if the mixture is white to off-white and cloudy. Each dose should be administered in the abdomen as a subcutaneous injection immediately after suspension of the powder in the diluent. BYDUREON 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.

BYDUREON kit and pen must be injected immediately after suspension of the powder in the diluent. BYDUREON BCise autoinjector must be injected immediately after mixing the suspension.

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).

If a dose is missed and the next regularly scheduled dose is due 1 or 2 days later, the patient should not administer the missed dose and instead resume BYDUREON with the next regularly scheduled dose.

Use in combination therapy

BYDUREON is recommended for use in patients with type 2 diabetes mellitus who are already receiving metformin and/or a sulfonylurea.

When BYDUREON is added to existing metformin therapy, the current dose of metformin can be continued as no increased risk of hypoglycaemia is anticipated, compared to metformin alone.

When BYDUREON is added to sulfonylurea therapy, a reduction in the dose of sulfonylurea should be considered to reduce the risk of hypoglycaemia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

When BYDUREON is added to dapagliflozin, no dose adjustment is required.

When BYDUREON was added to a basal insulin, no initial dose adjustment of insulin was required if the fasting blood glucose level was in the target range.

BYDUREON can be used in addition to metformin and basal insulin. In a clinical trial with basal insulin, patients ceased therapy with a sulfonylurea – there are no data on the risk/benefit of continuing sulfonylurea therapy.

Switching from BYETTA to BYDUREON

Patients switching from BYETTA (10 mcg exenatide twice daily) to BYDUREON (2 mg exenatide once weekly) may experience transient elevations in blood glucose concentrations, which generally improve within the first two weeks after initiation of therapy.

Switching between BYDUREON kit or pen to BYDUREON BCise autoinjector

Patients switching between BYDUREON kit or pen and BYDUREON BCise autoinjector may do so, with minimal expected effect on blood glucose concentrations.

Monitoring

The use of BYDUREON does not require additional self-monitoring. However, when used in combination with a sulfonylurea, or insulin, blood glucose self-monitoring may be necessary to monitor for hypoglycaemia and to titrate the doses of insulin or sulfonylurea.

Discontinuation

Following discontinuation, consideration should be given to the prolonged release of exenatide (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Specific patient groups

<u>Elderly</u>

BYDUREON can be given to adults of all ages including the elderly (>65 years of age) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 5.2 PHARMACOKINETIC PROPERTIES).

Patients with renal impairment

BYDUREON can be given to patients with mild or moderate renal impairment (creatinine clearance 30 – 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 5.2 PHARMACOKINETIC PROPERTIES).

Patients with hepatic impairment

BYDUREON can be given to patients with hepatic impairment (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Children and adolescents

The safety and efficacy of exenatide have not yet been established in children under 18 years of age (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Instructions for use and handling

BYDUREON is for use by one person only.

The instructions for the user containing the complete preparation and administration instructions must be followed carefully.

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

BYDUREON should be used only with the supplied custom needles.

BYDUREON kit and pen must be injected immediately after suspension of the powder in the diluent. BYDUREON BCise autoinjector must be injected immediately after mixing the suspension.

BYDUREON that has been frozen must not be used.

BYDUREON should not be used past the expiration date.

The patient should be instructed to discard the syringe, pen, or autoinjector with the needle still attached after each injection in an appropriate needle bin and return, along with any unused medicinal product or waste material to pharmacists or diabetes nurse educators for disposal. The patient does not need to put the cover back on the needle or to save any part of the single-use kit, single-use pen, or single-use autoinjector.

4.3 CONTRAINDICATIONS

BYDUREON is contraindicated in patients with known hypersensitivity to this product or any of its components (see Section 6.1 LIST OF 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.

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

The concurrent use of BYDUREON with prandial insulin, D-phenylalanine derivatives, meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors (“gliptins”), orlistat, opioids, and anticholinergics has not been studied. The concomitant use of BYDUREON and other GLP-1 receptor agonists is not recommended (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Hypoglycaemia

As would be expected for a blood glucose lowering agent, when exenatide was used in combination with a sulfonylurea; the incidence of hypoglycaemia was increased over that of placebo in combination with a sulfonylurea. In the clinical studies including patients on a sulfonylurea combination, those 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 sulfonylurea, reduction in the dose of sulfonylurea may be considered (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Exenatide did not alter the counter-regulatory hormone response to insulin-induced hypoglycaemia in a randomised, double-blind, controlled study in healthy subjects.

Interaction with warfarin

Since market introduction there have been some spontaneously reported cases of increased INR (International Normalized Ratio) with concomitant use of warfarin and exenatide, sometimes associated with bleeding (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Altered renal function

There have been rare, spontaneously reported events of acute renal failure, worsened chronic renal failure, renal impairment, or increased serum creatinine

among patients using exenatide. These events mostly occurred in patients also receiving one or more pharmacologic agents known to potentially affect renal function or hydration status and/or experiencing events of nausea, vomiting, diarrhoea, and/or dehydration. Concomitant agents included angiotensin converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, and diuretics. Reversibility of altered renal function has been observed with supportive treatment and discontinuation of potentially causative agents, including exenatide (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Pancreatitis

Recognised risk factors for pancreatitis include a past history of pancreatitis, gallstones, alcoholism and severe hypertriglyceridaemia. Clinical judgement should be exercised when selecting anti-diabetic treatments, including BYDUREON, for these patients. The change in risk of recurrent pancreatitis in patients with a past history of pancreatitis who receive BYDUREON is not known. There have been rare, spontaneously reported events of acute pancreatitis, including fatal cases of haemorrhagic or necrotising pancreatitis in patients who have received BYETTA. Cases of haemorrhagic or necrotising pancreatitis have been reported across the adult age range (18 years and over, including the elderly). There are no early signs or symptoms that distinguish cases that will become acute haemorrhagic or necrotising pancreatitis from the less severe form of pancreatitis. This potential should be considered in patients treated with BYDUREON who manifest symptoms and signs suggestive of pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Patients and their caregivers should be advised to report immediately to their doctor such abdominal pain particularly if associated with vomiting or diarrhoea. Generally, resolution of pancreatitis has been observed with supportive treatment. If pancreatitis is suspected, exenatide and other potentially suspect medications should be discontinued and not recommenced unless pancreatitis has been excluded.

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.

Injection site reactions

There have been post-market reports of serious injection site reactions, including abscesses, cellulitis, ulcers and necrosis.

Immunogenicity

Patients may develop antibodies to exenatide. If there is worsening glycaemic control or failure to achieve target glycaemic control, alternative antidiabetic therapy should be considered (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

Use in renal impairment

No clinically meaningful differences were observed in steady state exenatide concentrations or tolerability in patients with mild to moderate renal impairment (creatinine clearance 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 (creatinine clearance <30 mL/min) or for patients with end-stage renal disease receiving dialysis (see Section 4.3 CONTRAINDICATIONS).

Use in the elderly

Population pharmacokinetic analysis of patients ranging from 22 to 73 years of age suggests that age does not influence the pharmacokinetic properties of exenatide (see Section 5.1 PHARMACODYNAMIC PROPERTIES). In the 30 week and 26 week trials, BYDUREON was studied in 46 patients and BYETTA in 24 patients, who were at least 65 years old. In separate trials, BYETTA was studied in 282 patients at least 65 years old, and in 16 patients at least 75 years old. No differences in safety or effectiveness were observed between these patients and younger patients. In a large cardiovascular outcomes trial, 2 mg exenatide once weekly was studied in 2,959 patients (40.3%) who were at least 65 years old and of those, 605 patients (8.2%) were at least 75 years old. Similar results were observed between the 2 mg exenatide once weekly and placebo groups with respect to safety outcomes. Because elderly patients are more likely to have decreased renal function, care should be taken when initiating BYDUREON in the elderly based on renal function.

Paediatric use

The safety and effectiveness of exenatide has not been established in children under 18 years of age.

Effects on laboratory tests

No data available.

Carcinogenicity

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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The results of a study using paracetamol as a marker of gastric emptying suggest that the effect of BYDUREON to slow gastric emptying is not expected to cause clinically significant relevant changes in C_{max} or AUC of concomitantly administered oral medicines. Therefore, no dose adjustments of oral medicines are necessary when used concomitantly with BYDUREON. However, the dose of a sulfonylurea may require adjustment due to the increased risk of hypoglycaemia associated with sulfonylurea therapy (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Hypoglycaemia).

Paracetamol

Paracetamol was used as a model medicinal product to evaluate the effect of exenatide on gastric emptying.

When 1000 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). In the same study, when paracetamol was administered with a meal 15 minutes after BYETTA, AUC and C_{max} decreased by 20% and 21% respectively, and T_{max} increased to 2 hours. Given that concomitant BYDUREON administration with oral paracetamol, a marker of gastric emptying, did not alter AUC and resulted in a minor reduction in C_{max}, no dosage adjustments are recommended with concomitant oral drugs, except when used with a sulfonylurea.

The following interaction studies have been conducted using BYETTA, but not BYDUREON.

HMG CoA reductase inhibitors

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

Warfarin

In a controlled clinical pharmacology study in healthy volunteers, a delay in warfarin T_{max} of about 2 h was observed when warfarin was administered 35 min after BYETTA. No clinically relevant effects on C_{max} or AUC were observed (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). INR should be monitored during initiation of BYDUREON therapy in patients on warfarin and/or cumarol derivatives (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Digoxin and lisinopril

In interaction studies of the effect of BYETTA 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 µg ethinyl estradiol plus 150 µg levonorgestrel) one hour before BYETTA did not alter the AUC, C_{max} or C_{min} of either ethinyl estradiol or levonorgestrel. Administration of the oral contraceptive

30 minutes after BYETTA 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

Effects on fertility

Animal studies did not indicate direct harmful effects with respect to fertility. Male and female fertility were unaffected in mice treated with exenatide at SC doses up to 760 µg/kg/day, almost 150 times the clinical exposure at 2 mg/week based on AUC.

No fertility studies in humans have been conducted

Use in pregnancy – Category C

BYDUREON 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 fetus/new born child. To date, no other relevant epidemiological data are available.

Potential embryofetal effects were assessed with SC doses of exenatide during organogenesis in mice at 6, 68 and 760 µg/kg/day and in rabbits at 0.2, 2, 22, 156 and 260 µg/kg/day, giving respective exposures approximately 1.2, 8.6 and 148 times (mouse) and 0.1, 1.7, 79, 545 and 1323 times (rabbit) the clinical exposure at 2 mg/week. A low incidence of abortions and decreased fetal growth occurred in mice and rabbits at ≥68 and 22 µg/day, respectively, which also caused a decrease in food consumption and body weight gain in dams. Alterations of skeletal ossification were observed in rabbits at ≥2 µg/kg/day as a result of decreased food intake. Wavy ribs were seen in mice at 760 µg/kg/day. Fetal umbilical hernias were increased in rabbits at ≥22 µg/kg/day. There was minimal placental transfer of exenatide in animal studies *in vivo* or in human placental tissues *in vitro*. The fetal findings were probably secondary to effects on the dam.

High doses of exenatide administered to mice during gestation and lactation caused stillbirths, an increase in neonatal deaths and a decrease in neonatal growth at exposures almost 150 times the clinical exposure at 2 mg/week. The no observable effect level for peri-neonatal effects was 68 µg/kg/day, giving exposures 18 times the clinical exposure.

Use in lactation

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 (2.5% of plasma level). Neonatal deaths were increased in lactating mice at high doses (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION - Use in pregnancy). BYDUREON should be administered to nursing women only if the potential benefit to the mother justifies the potential risk to the infant.

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 sulfonylurea, or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The most common adverse reactions ≥5% of exenatide 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 pruritis, hypoglycaemia and headache were common. Most adverse reactions associated with exenatide were mild to moderate in intensity.

Acute pancreatitis and acute renal failure have been reported rarely since exenatide has been marketed (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Tabulated summary of adverse effects

BYDUREON kit and pen

The frequency of adverse reactions of 2 mg exenatide once weekly and 10 µg exenatide twice daily with an incidence of ≥2% are summarised in the table below (Table 1).

The tabulation summarises event data from 5 trials comparing 2 mg exenatide once weekly to either 10 µg exenatide twice daily (a 30 week study), sitagliptin and pioglitazone (a 26 week study), and insulin glargine (a 26 week study). Background therapies included diet and exercise, metformin, a sulfonylurea or a combination of oral anti-diabetic agents.

Table 1 Summary of Treatment Emergent Adverse Events Reported in ≥2% Exenatide Treated Patients (2 mg Once Weekly or 10 µg Twice Daily), Active Comparator-Controlled Studies (intent to treat patients)

System Organ Class Preferred Term	Exenatide QW N=592 %	Exenatide BID N=145 %	Pioglitazone N=165 %	Sitagliptin N=166 %	Insulin Glargine N=223 %
Gastrointestinal Disorders					
Nausea	20	34	5	10	2
Diarrhoea	13	13	7	10	4)
Vomiting	8	19	3	2	1
Constipation	6	6	1	2	2
Dyspepsia	4	3	2	4	1
Gastro-oesophageal Reflux Disease	3	4	1	1	1

System Organ Class Preferred Term	Exenatide QW N=592 %	Exenatide BID N=145 %	Pioglitazone N=165 %	Sitagliptin N=166 %	Insulin Glargine N=223 %
Abdominal Discomfort	2	1	0	0	<1
Abdominal Pain	2	2	1	4	1
Abdominal Pain Upper	2	1	1	4	1
Toothache	1	2	2	1	2
General Disorders and Administration Site Conditions					
Injection Site Pruritus	8	1	1	5	<1
Injection Site Erythema	4	0	0	2	<1
Fatigue	4	3	3	0	<1
Injection Site Haematoma	2	11	2	1	1
Injection Site Induration	4	0	1	1	0
Injection Site Nodule	3	0	1	1	0
Injection Site Pain	1	2	0	1	<1
Infections and Infestations					
Nasopharyngitis	19	6	3	2	18
Upper Respiratory Tract Infection	4	17	10	9	1
Sinusitis	3	7	7	1	2
Urinary Tract Infection	5	8	4	5	<1
Gastroenteritis Viral	3	6	0	1	<1
Influenza	2	2	3	1	3
Gastroenteritis	2	0	1	2	2
Injury Poisoning and Procedural Complications					
Joint Pain	1	2	0	0	0
Procedural Pain	<1	3	0	0	<1
Metabolism and Nutrition Disorders					
Hypoglycaemia	15	19	6	9	43
Decreased Appetite	3	1	0	1	0
Anorexia	2	1	0	1	0
Hypokalaemia	1	3	0	0	0
Musculoskeletal and Connective Tissue Disorders					
Back Pain	4	4	3	4	3
Arthralgia	4	4	2	5	3
Pain in Extremity	2	1	1	2	1
Musculoskeletal Pain	2	0	2	1	3
Muscle Spasms	1	2	1	1	<1
Nervous System Disorders					
Headache	8	5	4	9	9
Dizziness	3	6	4	5	1
Diabetic Neuropathy	<1	2	0	1	0
Psychiatric Disorders					
Depression	1	3	0	2	<1
Insomnia	1	3	1	1	<1
Anxiety	1	2	1	1	1
Reproductive System and Breast Disorders					
Erectile Dysfunction	<1	3	1	0	0

System Organ Class Preferred Term	Exenatide QW N=592 %	Exenatide BID N=145 %	Pioglitazone N=165 %	Sitagliptin N=166 %	Insulin Glargine N=223 %
Respiratory, Thoracic and Mediastinal Disorders					
Cough	2	1	3	1	4
Oropharyngeal Pain	2	1	1	1	4
Skin and Subcutaneous Tissue Disorders					
Alopecia	<1	2	0	0	0
Vascular Disorders					
Hypertension	3	3	1	3	3

Abbreviations: QW: once weekly; BID: twice daily

BYDUREON BCise autoinjector

The frequency of adverse effects of 2 mg exenatide once weekly suspension in autoinjector with an incidence of ≥2% are summarised in the table below (Table 2).

The tabulation summarises event data from 2 trials (both 28 weeks duration) comparing exenatide 2 mg once weekly suspension in autoinjector to exenatide 10 mcg twice daily, sitagliptin, and placebo (controlled treatment period only). Background therapies included diet and exercise, alone or in combination with metformin, a sulfonylurea, a thiazolidinedione or a combination of oral anti-diabetic agents.

Table 2 Summary of Treatment Emergent Adverse Events Reported in ≥2% Exenatide Treated Patients (2 mg Once Weekly Suspension in Autoinjector or 10 mcg Twice Daily), Active Comparator- and Placebo-Controlled Studies*

System Organ Class Preferred Term	Exenatide QWS N=410 %	Exenatide BID N=146 %	Sitagliptin N=122 %	Placebo N=61 %
General Disorders and Administration Site Conditions				
Injection Site Nodule	12	1	0	0
Injection Site Pruritis	4	1	0	0
Injection Site Bruising	3	0	0	0
Injection Site Erythema	3	1	0	0
Injection Site Pain	2	0	0	0
Injection Site Induration	2	0	0	0
Gastrointestinal Disorders				
Nausea	9	21	2	0
Diarrhoea	4	12	2	2
Vomiting	3	6	0	0
Constipation	2	3	1	2
Gastrooesophageal Reflux Disease	2	1	1	0
Infections and Infestations				
Upper Respiratory Tract Infection	4	3	0	3

System Organ Class Preferred Term	Exenatide QWS N=410 %	Exenatide BID N=146 %	Sitagliptin N=122 %	Placebo N=61 %
Urinary Tract Infection	2	2	3	3
Musculoskeletal and Connective Tissue Disorders				
Pain in Extremity	2	3	0	2
Back Pain	2	3	3	2
Nervous System Disorders				
Headache	5	6	2	2
Dizziness	3	4	1	0

Abbreviations: QWS: once weekly suspension; BID: twice daily

* Includes all adverse events with onset during the 28-week controlled period, with the exception of hypoglycaemia, which was analysed separately

Description of selected adverse effects

Hypoglycaemia

As would be expected, the incidence of hypoglycaemia was increased when exenatide was used in combination with a sulfonylurea (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). To reduce the risk of hypoglycaemia associated with the use of a sulfonylurea, reduction in the dose of sulfonylurea may be considered (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Most episodes of hypoglycaemia were mild to moderate in intensity, and all resolved with oral administration of carbohydrate.

BYDUREON kit and pen

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

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.

Table 3 summarises the occurrence of treatment-emergent hypoglycaemia by sulfonylurea use in clinical trials of 2 mg exenatide once weekly.

Table 3 Incidence (%) of Hypoglycaemia by Concomitant Sulfonylurea Use in Exenatide Treated Patients (2 mg Once Weekly or 10 µg Twice Daily), Comparator Controlled Studies

	Exenatide QW N=592 %	Exenatide BID N=145 %	Pioglitazone N=165 %	Sitagliptin N=166 %	Insulin N=223 %
With Sulfonylurea					
Major Hypoglycaemia	0.0	0.0	0.0	0.0	1.5
Minor Hypoglycaemia	15.9	18.9	0.0	0.0	41.8
Without Sulfonylurea					
Major Hypoglycaemia	0.2	0.0	0.0	0.0	0.6
Minor Hypoglycaemia	2.0	1.1	0.6	3.0	19.2

Abbreviations: QW: once weekly; BID: twice daily

BYDUREON BCise autoinjector

There were no events of major hypoglycaemia with exenatide once weekly suspension in autoinjector. The overall incidence of minor hypoglycaemia was 6.3%. This incidence was increased when it was used in combination with a sulfonylurea (26.1%) compared to no sulfonylurea (0.9%) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Nausea

BYDUREON kit and pen

Nausea has been described in studies of GLP-1 receptor agonists. In clinical trials of 2 mg exenatide once weekly, the most frequently reported adverse reaction was nausea. In patients treated with 2 mg exenatide once weekly, generally 20% reported at least one episode of nausea compared to 34% of 10 µg 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 from clinical trials due to adverse events was approximately 5% for exenatide once weekly treated patients and 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 approximately 1% for exenatide once weekly treated patients and exenatide twice daily treated patients.

BYDUREON BCise autoinjector

During the controlled period of the clinical trial comparing exenatide once weekly suspension in autoinjector with exenatide twice daily, nausea was reported in 9.6% and 20.5% of patients in each respective group. Overall, 9.3% of patients treated with exenatide once weekly in autoinjector reported nausea during the controlled period of both clinical trials. Most episodes of nausea were mild to moderate, associated with the initiation of treatment and decreased over time.

Immunogenicity

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

BYDUREON kit and pen

In the clinical trials of exenatide once weekly, approximately 45% of patients had low titre antibodies to exenatide at study endpoint. Consistent with exenatide twice daily clinical trial results, the level of glycaemic control (HbA_{1c}) was generally comparable to that observed in those without antibody titres (51% of patients). Approximately 5% of patients had higher titre antibodies at study endpoint. In one-third of these (2% overall), the glycaemic response to exenatide once weekly was attenuated; the remaining 4% had a glycaemic response comparable to that of patients without antibodies.

Overall the percentage of antibody positive patients was consistent across clinical trials. 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 26 week studies was approximately 10%. 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).

BYDUREON BCise autoinjector

Anti-exenatide antibodies were measured at prespecified intervals in 393 exenatide once weekly suspension-treated patients in the two comparator-controlled studies for exenatide once weekly suspension in autoinjector. At the study endpoint, approximately 43.4% of patients had low titre antibodies to exenatide and approximately 13.9% of patients had high titre antibodies.

Consistent with exenatide twice daily and exenatide once weekly clinical trial results, change in HbA_{1c} from baseline in exenatide once weekly suspension in autoinjector treated patients with low titre antibodies at the last visit (-1.1 to -1.5%) was generally comparable to that observed in antibody-negative patients at the last visit (-1.1 to -1.4%). While patients with high titre antibodies at the last visit had an attenuated HbA_{1c} response, HbA_{1c} reductions in these patients were clinically relevant (-0.6 to -0.7%).

Amongst exenatide once weekly suspension in autoinjector treated patients evaluable for antibodies (N=393), the incidence of potentially immunogenic injection site reactions (most commonly injection site nodule) during the 28-week studies was

approximately 19.6%. These reactions were less commonly observed in antibody-negative patients (15.7%) and patients with low titre antibodies (16.3%) compared with those with high titre antibodies (27.2%).

Injection site reactions

Injection site reactions were observed more frequently (approximately 2-fold) in exenatide treated patients versus comparator treated patients. These injection site reactions were generally mild and usually did not lead to withdrawal from studies.

Injection site reactions were higher in exenatide once weekly treated patients (16%) compared to exenatide twice daily treated patients (2-7%). The reactions were pruritus (8%), erythema (4%), induration (4%) and nodule (3%). There was also asymptomatic nodule formation (up to 77%). Approximately 73% of the first incidence of treatment emergent injection site reactions resolved within 60 days.

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.

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 sensitising drug.

Adverse drug reactions

Adverse drug reactions (ADRs) are listed below as MedDRA preferred term by system organ class and absolute frequency. Patient frequencies are defined as follows: 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).

Pooled clinical trial data and post-marketing data

ADRs of BYDUREON kit and pen identified from pooled clinical trial data or from post-marketing data are shown below (Table 4). The pooled BYDUREON kit and pen 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 sulfonylurea, a thiazolidinedione, or a combination of oral anti-diabetic agents.

ADRs of BYDUREON BCise autoinjector identified from pooled clinical trial data are shown below (Table 4). The pooled BYDUREON BCise autoinjector clinical trials data set comprises 2 studies of 6-12 months duration. The follow-up and extension

phases of studies are included in the pool. BYDUREON BCise autoinjector background therapies included diet and exercise, alone or in combination with metformin, a sulfonylurea, a thiazolidinedione or a combination of oral anti-diabetic agents.

Across these mono- and combination therapy studies, the types of ADRs observed with BYDUREON kit and pen and BYDUREON BCise autoinjector were similar.

Table 4 Adverse drug reactions of BYDUREON kit or pen and BYDUREON BCise autoinjector identified from mono- and combination therapy pooled clinical trial data, and from post-marketing data

System Organ Class	Frequency of occurrence	Adverse reaction term	
		BYDUREON kit and pen,†**	**BYDUREON BCise autoinjector***,†
Blood and lymphatic system disorders	Not known[b]	Drug-induced thrombocytopenia	Drug-induced thrombocytopenia
Gastrointestinal disorders	Very common	Nausea; Diarrhoea	
	Common	Vomiting; Constipation; Dyspepsia; Gastroesophageal reflux disease; Abdominal pain; Abdominal distension; Flatulence	Nausea; Diarrhoea Vomiting; Constipation; Dyspepsia; Gastroesophageal reflux disease; Abdominal distension; Abdominal pain
	Uncommon	Eructation; Acute pancreatitis	Flatulence
	Rare		
	Not known[b]	Ileus; Ischaemic colitis; Gut ischaemia	Acute pancreatitis[g]; Eructation[g]; Ileus; Ischaemic colitis; Gut ischaemia
General disorders and	Common	Injection site pruritus; Injection site erythema; Fatigue; Asthenia[a]	Injection site pruritus; Injection site erythema; Fatigue

System Organ Class	Frequency of occurrence	Adverse reaction term	
		BYDUREON kit and pen,†**	**BYDUREON BCise autoinjector***,†
administration site conditions	Uncommon	Injection site reaction; Injection site rash	Injection site reaction; Asthenia; Injection site rash
	Rare	Feeling jittery	
	Not known[b]		Feeling jittery[g]
Immune system disorders	Rare	Anaphylactic reaction	
	Not known[b]		Anaphylactic reaction[g]
Investigations	Uncommon	Weight decreased	Weight decreased
	Not known[b]	INR increased with concomitant warfarin	INR increased with concomitant warfarin[g]
Metabolism and nutrition disorders	Very Common	Hypoglycaemia (with a sulfonylurea)[c, d]	Hypoglycaemia (with a sulfonylurea)[h, i]
	Common	Hypoglycaemia (with insulin)[d,e] Decreased appetite; Hypoglycaemia (without a sulfonylurea)[c, d]	
	Uncommon	Dehydration, generally associated with nausea, vomiting and/or diarrhoea	Hypoglycaemia (without a sulfonylurea)[h,i] Decreased appetite; Dehydration, generally associated with nausea, vomiting and/or diarrhoea;
Nervous system disorders	Common	Headache[a]; Dizziness	Headache; Dizziness
	Uncommon	Somnolence; Dysgeusia	Dysgeusia
	Not known[b]		Somnolence[g]
Renal and urinary disorders	Uncommon	Altered renal function[f]	Altered renal function[f]
	Common	Pruritus	

System Organ Class	Frequency of occurrence	Adverse reaction term	
		BYDUREON kit and pen,†**	**BYDUREON BCise autoinjector***,†
Skin and subcutaneous tissue disorders	Uncommon	Urticaria; Alopecia; Hyperhidrosis[a]; Angioedema	Urticaria; Hyperhidrosis; Macular or papular rash; Pruritus
	Rare	Injection site abscesses and cellulitis; Macular or papular rash	
	Not known[b]	Necrosis	Alopecia[g]; Angioedema[g]; Injection site abscesses and cellulitis[g]; Necrosis

** Rate based on BYDUREON kit and pen completed safety and efficacy studies (n=2,868); includes follow up within seventy days of the last dose received and extension period.

*** Rate based on BYDUREON BCise autoinjector completed safety and efficacy studies (n=526); 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 sulfonylurea were concomitant medicinal products, the incidence for these adverse reactions was similar for insulin- and exenatide BID (BYETTA)-treated patients.

b Cannot be estimated from the available data.

c Frequencies reported in pooled data from the controlled periods of the 11 BYDUREON kit and pen studies. Eleven BYDUREON kit or pen studies included two studies of <6 months duration, and nine of 6-12 months duration.

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 <3 mmol/L or 3. Result in symptoms consistent with hypoglycaemia with a concomitant glucose <3 mmol/L prior to treatment.

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

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

g Adverse drug reactions which have been identified with BYDUREON kit and pen, but have not been identified from pooled clinical trial data with BYDUREON BCise autoinjector.

h Frequencies reported in pooled data from the controlled periods of the two BYDUREON BCise autoinjector studies.

i Based on hypoglycaemic events that have symptoms consistent with hypoglycaemia with a concomitant glucose <3 mmol/L prior to treatment.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Effects of overdoses with 10 µg exenatide twice daily in 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 information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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*. This leads to an increase in both the glucose-dependent insulin synthesis and secretion from pancreatic beta-cells, by mechanisms involving cyclic AMP and/or other intracellular signalling pathways. As blood glucose concentrations decrease, insulin secretion subsides thereby reducing the potential risk of hypoglycaemia. When exenatide was used in combination with metformin, no increase in the incidence of hypoglycaemia was observed over that of placebo in combination with metformin which may be due to this glucose-dependent insulinotropic mechanism.

Exenatide suppresses glucagon secretion which is known to be inappropriately elevated in 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.

Pharmacodynamic effects

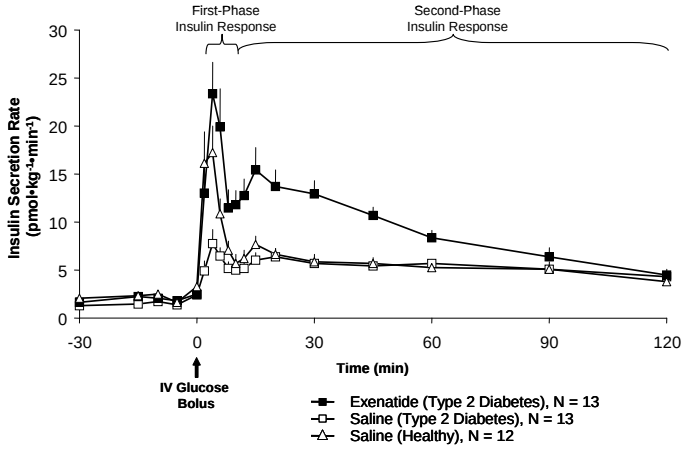
Exenatide improves glycaemic control through the immediate and sustained effects of lowering both postprandial and fasting glucose concentrations in patients with type 2 diabetes. These pharmacodynamic actions occur through various mechanisms including stimulation of insulin secretion during hyperglycaemia, suppression of glucagon, and slowing of gastric emptying. 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 euglycaemia. Exenatide does not impair the normal glucagon response to hypoglycaemia.

First phase insulin response: In healthy individuals, robust 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. The loss of the first-phase insulin response is an early beta-cell defect in type 2 diabetes. Administration of exenatide at therapeutic plasma concentrations restored first phase insulin response to an IV bolus of glucose in patients with type 2 diabetes (Figure 1). Both first-phase insulin secretion and second-phase insulin secretion were significantly increased in patients with type 2 diabetes treated with exenatide compared with saline ($p<0.001$ for both).



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

Figure 1 Mean (SE) Insulin Secretion Rate During Infusion of Exenatide or Saline in Patients With Type 2 Diabetes and During Infusion of Saline in Healthy Patients

Glucagon secretion: In patients with type 2 diabetes, exenatide moderates glucagon secretion and lowers serum glucagon concentrations during periods of hyperglycaemia. Lower glucagon concentrations lead to decreased hepatic glucose output and decreased insulin demand.

Beta-cell function: Exenatide stimulates insulin release – clinical trial data with exenatide twice daily show that this happens acutely with benefits in glycosylated haemoglobin evident within six weeks. No clinical data are available to suggest an improvement over time in beta-cell function. In studies of exenatide twice daily, most clinical benefit in glycaemic control was seen within 12 weeks of commencement. An increase in pancreatic islet cell mass has not been consistently demonstrated in animal models.

Clinical trials

Both improvement of glycaemic control and reduction of cardiovascular morbidity and mortality are an integral part of the treatment of type 2 diabetes.

BYDUREON kit and pen

Patients with Type 2 diabetes participated in 4 long term, randomised, comparator controlled, clinical studies of 2 mg exenatide once weekly up to 52 weeks duration (3 studies were open label and 1 was double-blind). These studies were conducted to evaluate the efficacy and safety of 2 mg exenatide once weekly compared to either 10 µg exenatide twice daily, insulin glargine once daily, or pioglitazone or sitagliptin once daily, in both treatment naive patients and those on background therapy with metformin and/or sulfonylurea and/or thiazolidinedione. A total of 1628 patients were included across the 5 studies, 804 of which were treated with 2 mg exenatide once weekly, 54% of all study participants were men and 141 patients treated with 2 mg exenatide once weekly were ≥65 years of age.

In addition, a double-blind, placebo-controlled cardiovascular outcome study (EXSCEL) enrolled 14,752 subjects with type 2 diabetes and any level of CV risk when added to the current usual care.

Glycaemic control

In 24 week and 30 week clinical trials, 2 mg exenatide once weekly was compared to 5 µg exenatide twice daily for 4 weeks followed by 10 µg exenatide twice daily (see Section 5.2 PHARMACOKINETIC PROPERTIES - Absorption for information on relative systemic exposures). A 22 week open labelled extension period followed the 30 week study where all patients were treated with 2 mg exenatide once weekly. 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, $p<0.0001$ in the 24 weeks study and $p<0.05$ in the 30 weeks study respectively.

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

In a 26 week study 2 mg exenatide once weekly was compared to insulin glargine once daily. Both treatment groups had a significant reduction in HbA_{1c}, ($p<0.001$) while exenatide once weekly demonstrated a superior change in HbA_{1c} compared to insulin glargine ($p=0.017$).

In a 26 week double blind study, 2 mg exenatide once weekly was compared to maximum daily doses of sitagliptin and pioglitazone in subjects also using maximal or near maximal doses of metformin. All treatment groups had a significant reduction in HbA_{1c} compared to baseline. Exenatide once weekly demonstrated superiority to both sitagliptin ($p<0.00001$) and pioglitazone ($p=0.0165$) with respect to change in HbA_{1c} from baseline.

Table 5 shows HbA_{1c} results for each of the comparator-controlled studies.

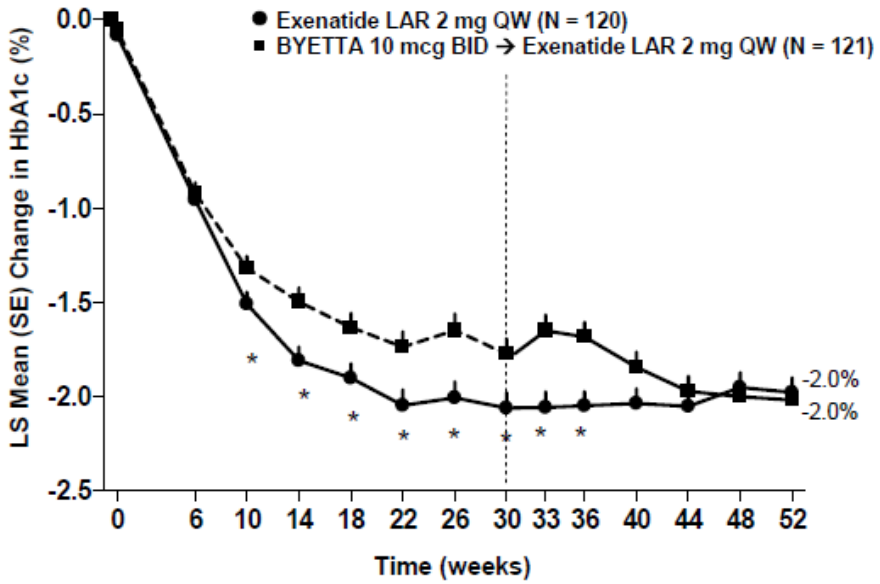
Table 5 Summary of Change in HbA1c from Baseline to Endpoint for Exenatide 2 mg Once Weekly Comparator Controlled Studies (intent to treat patients)

		Mean change from baseline to endpoint (± Standard Error)
Study	**N**	**HbA_{1c}**
2 mg exenatide once weekly vs. exenatide twice daily – 24 weeks of treatment		
2 mg exenatide once weekly (QW)	129	-1.6 (±0.1)
10 µg exenatide twice daily (BID)	123	-0.9 (±0.1)
Mean difference (95% CI QW-BID)		-0.7 (-0.9, -0.4)*
2 mg exenatide once weekly vs. exenatide twice daily – 30 weeks of treatment		
2 mg exenatide once weekly (QW)	148	-1.9 (±0.08)
10 µg exenatide twice daily (BID)	147	-1.5 (±0.08)
Mean difference (95% CI QW-BID)		-0.33 (-0.54, -0.12)*
2 mg exenatide once weekly vs. insulin glargine once daily – 26 weeks of treatment		
2 mg exenatide once weekly (QW)	233	-1.5 (±0.05)
Insulin glargine (IG)#	223	-1.3 (±0.06)
Mean difference (95% CI QW-IG)		-0.16 (-0.29, -0.03)*
2 mg exenatide once weekly vs. sitagliptin or pioglitazone – 26 weeks of treatment		
2 mg exenatide once weekly (QW)	160	-1.6 (±0.10)
100 mg sitagliptin (SG)	166	-0.9 (±0.10)
45 mg pioglitazone (Pio)	165	-1.23 (±0.10)
Mean difference (95% CI SG)^		0.63 (0.37, 0.89)*
Mean difference (95% CI Pio) ^		0.32 (0.06, 0.57)*

* statistically significant

insulin glargine was dosed using the algorithm described by Yki-Järvinen et al. 2007. 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

^ based on pairwise comparison using exenatide QW



Abbreviations: BID, twice daily; LAR, long-acting release; LS, least squares; QW, once weekly; SE, standard error.

Notes: Mean baseline HbA1c was 8.2% and 8.3% for the BYETTA and exenatide LAR groups, respectively.
- Vertical dashed line indicates the timing of the switch from BYETTA to exenatide LAR.
- Subjects treated with BYETTA initiated treatment with 5 mcg BID through Week 4.

*p <0.05, exenatide LAR versus BYETTA→exenatide LAR.

Figure 2 LS Mean (SE) Change in HbA1c (%) from Baseline to Week 52

Further reductions in HbA_{1c} were observed for at least 52 weeks in the patients completing both the 22 week uncontrolled study extension. The evaluable patients who switched from exenatide twice daily to 2 mg exenatide once weekly (n=121) achieved the same improvement in HbA_{1c} of -2.0%, at the end of the extension period compared to the initial baseline, as the patients treated with 2 mg exenatide once weekly for 52 weeks.

Proportion of patients achieving target

As shown in Table 6, clinically and statistically significantly more patients on 2 mg exenatide once weekly compared to exenatide twice daily patients achieved an HbA_{1c} reduction of ≤7% or <7% in the 24 week and 30 week studies ($p<0.0001$ and $p<0.05$ respectively). Significantly more patients on 2 mg exenatide once weekly achieved an HbA_{1c} reduction of ≤ 7% compared to those receiving 100 mg sitagliptin ($p<0.0001$) and 45 mg pioglitazone ($p<0.05$).

Table 6 Proportion of Subjects (%) Achieving HbA1c less than or equal to 7% for Exenatide 2 mg Once Weekly Comparator Controlled Studies (intent to treat patients)

Study		Proportion of Patients achieving HbA_{1c} target (%)
2 mg exenatide once weekly vs. exenatide twice daily - 24 weeks of treatment		
	N	**HbA_{1c} <7%**
2 mg exenatide once weekly (QW)	129	58
10 µg exenatide twice daily (BID)	123	30*
2 mg exenatide once weekly vs. exenatide twice daily - 30 weeks of treatment		
	N	**HbA_{1c} ≤7%**
2 mg exenatide once weekly (QW)	148	73
10 µg exenatide twice daily (BID)	147	57*
2 mg exenatide once weekly vs. insulin glargine once daily – 26 weeks of treatment		
	N	**HbA_{1c} ≤7%**
2 mg exenatide once weekly (QW)	233	62
Insulin glargine (IG)[#]	223	54
2 mg exenatide once weekly vs. sitagliptin or pioglitazone – 26 weeks of treatment		
	N	**HbA_{1c} ≤7%**
2 mg exenatide once weekly (QW)	160	62
100 mg sitagliptin (SG)	166	36*
45 mg pioglitazone (Pio)	165	49*

* statistically significant

[#] insulin glargine was dosed using the algorithm described by Yki-Järvinen et al. 2007. 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

Body weight

A reduction in body weight compared to baseline has been observed in all 2 mg exenatide once weekly studies. This reduction in body weight was seen in patients treated with 2 mg 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 versus -2.2 kg to -2.9 kg).

In studies comparing 2 mg exenatide once weekly to 10 µg exenatide twice daily, both treatment arms achieved a reduction in body weight from baseline, although the difference in the treatment groups was not significant.

When compared with insulin glargine treatment, 2 mg exenatide once weekly treatment significantly lowered mean body weight ($p<0.001$) and was associated with fewer hypoglycaemic events. Significantly greater weight reduction was also achieved compared to sitagliptin ($p=0.0002$). Patients on pioglitazone gained weight ($p<0.0001$) (see Table 7).

Table 7 Change in Body Weight from Baseline to Endpoint for Exenatide 2 mg Once Weekly Comparator Controlled Studies (intent to treat patients)

Study	N	Mean change from baseline to endpoint (± Standard Error) Kg
2 mg exenatide once weekly vs. exenatide twice daily - 24 weeks of treatment		
2 mg exenatide once weekly (QW)	129	-2.3 (±0.4)
10 µg exenatide twice daily (BID)	123	-1.4 (±0.4)
Mean difference (95% CI QW-BID)		-1.0 (-1.9, 0.01)
2 mg exenatide once weekly vs. exenatide twice daily - 30 weeks of treatment		
2 mg exenatide once weekly (QW)	148	-3.67 (±0.47)
10 µg exenatide twice daily (BID)	147	-3.59 (±0.47)
Mean difference (95% CI QW-BID)		-0.08 (-1.29, 1.12)
2 mg exenatide once weekly vs. insulin glargine once daily – 26 weeks of treatment		
2 mg exenatide once weekly (QW)	207	-2.63 (±0.20)
Insulin glargine (IG)[#]	209	1.42 (±0.20)
Mean difference (95% CI QW-IG)		-4.05 (-4.57, -3.52)*
2 mg exenatide once weekly vs. sitagliptin or pioglitazone – 26 weeks of treatment		
2 mg exenatide once weekly (QW)	160	-2.3 (±0.3)
100 mg sitagliptin (SG)	166	-0.8 (±0.3)
45 mg pioglitazone (Pio)	165	2.8 (±0.3)
Mean difference (95% CI SG)^		-1.5 (-2.4, -0.7)*
Mean difference (95% CI Pio)^		-5.1 (-5.9, -4.3)*

*statistically significant

[#] insulin glargine was dosed using the algorithm described by Yki-Järvinen et al. 2007. 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

^ based on pairwise comparison using exenatide QW

The proportion of patients who had a reduction of HbA_{1c} ranged from 89 to 96%, 70 to 79% of patients had a reduction in HbA_{1c} and weight.

Plasma/serum glucose

Treatment with 2 mg 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.

Fasting Lipids

BYDUREON did not have adverse effects on lipid parameters.

Patient outcomes

Exenatide once weekly consistently improved patient satisfaction as measured by the diabetes treatment satisfaction questionnaires.

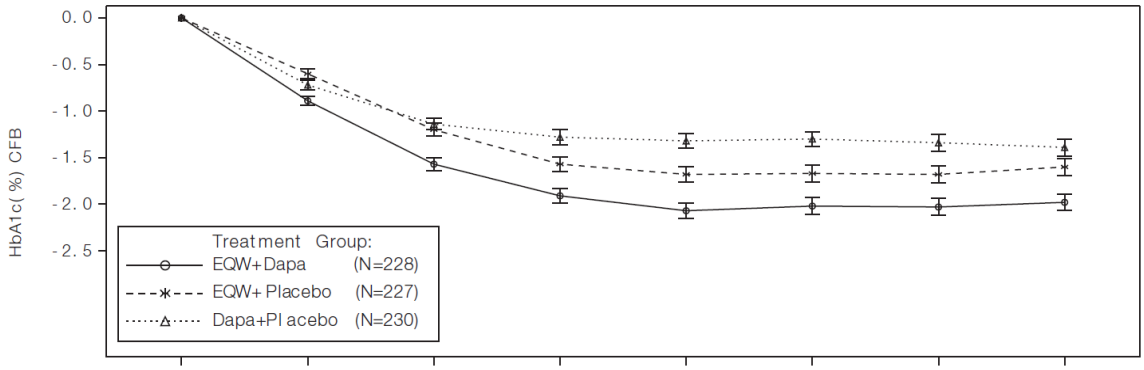
Concomitant Initiation of Exenatide Once Weekly and Dapagliflozin vs. Exenatide Once Weekly Alone and Dapagliflozin Alone, as Add-On to Metformin

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 once daily, exenatide 2 mg once weekly alone or dapagliflozin 10 mg once daily alone. During the treatment period, patients continued on the same type and dose of metformin as when they entered the study. Randomisation was stratified by HbA_{1c} at baseline (<9.0% or ≥9.0%) and patients were regularly monitored every 4 weeks in this study.

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

At baseline, patients had a mean age of 54.2 years and a BMI of 32.73 kg/m^2. The primary endpoint was the change in HbA_{1c} from baseline to Week 28 (Figure 3). Compared to exenatide 2 mg once weekly alone and dapagliflozin 10 mg once daily alone, concomitant initiation of exenatide 2 mg once weekly and dapagliflozin 10 mg once daily resulted in statistically significant reductions in HbA_{1c} from baseline at Week 28 (Table 8).



P Value							
EQW+Dapa vs EQW+Placebo	<0.001	<0.001	0.001	<0.001	0.003	0.004	0.003
EQW+Dapa vs Dapa+Placebo	0.008	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

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

Figure 3 Change in HbA_{1c} over Time, LS Mean (SE) – 28-Week Treatment Period (Intent-to-Treat Analysis Set)

Table 8 28-Week Active-Controlled Trial of Exenatide Once Weekly and Dapagliflozin 10 mg 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)[c]	**228**	**227**	**230**
Mean HbA_{1c} (%)			
Baseline	9.3	9.3	9.3
Change from baseline (±SE)[a]	-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%[b]	45%	27%	19%
Mean body weight (kg)			
Baseline	92	89	91
Change from baseline (±SE)[a]	-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)		
Mean fasting plasma glucose (mmol/L)			
Baseline	10.9	10.5	10.5
Change from baseline (±SE)[a]	-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)		
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)[a]	-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)		

	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)[c]	**228**	**227**	**230**
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)[a]	-4.3 (±0.80)	-1.2 (±0.82)	-1.8 (±0.79)
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] 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.

[b] 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.

[c] Patients who received at least 1 dose of study medication and had at least 1 post-baseline HbA1c assessment.

*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 (-2.3 mmol/L with exenatide once weekly + dapagliflozin vs. -1.2 mmol/L with exenatide once weekly + placebo, p <0.001).

Exenatide 2 mg Once Weekly vs. Placebo as Add-On to Basal Insulin Alone or in Combination with Metformin

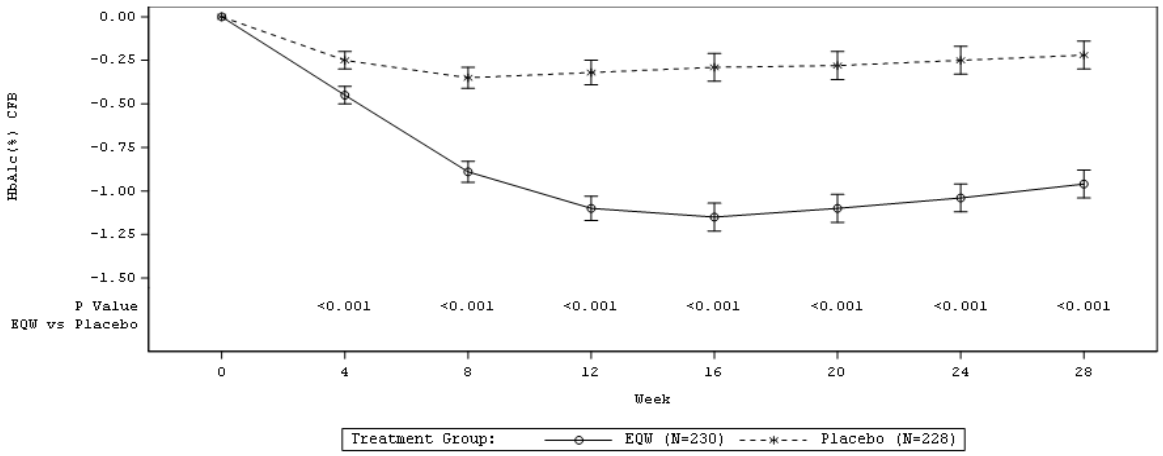
A 28-week, double-blind, placebo-controlled trial was conducted to evaluate the efficacy and safety of exenatide 2 mg once weekly (n=230) versus placebo (n=228) when added to titrated basal insulin glargine, with or without metformin, in patients with type 2 diabetes with inadequate glycaemic control.

All patients initially entered an 8-week insulin dose optimisation phase. Patients on sulfonylurea therapy discontinued sulfonylurea. The dose of insulin glargine was titrated to a target fasting plasma glucose of 4.0 to 5.5 mmol/L. Patients with HbA_{1c} ≥7.0% and ≤10.5% were then randomly assigned to receive either exenatide 2 mg

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.

At baseline, patients had a mean age of 57.7 years, a mean BMI of 33.66 kg/m^2, a mean diabetes duration of 11.29 years and a mean HbA_{1c} of 8.53%. The primary endpoint was the change in HbA_{1c} from baseline to Week 28 (Figure 4). Exenatide 2 mg once weekly achieved a significantly greater reduction in HbA_{1c} at Week 28 than that observed with placebo (Table 9).



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.

Figure 4 Change in HbA1c by Week of Treatment – ITT patients

Table 9 28-Week Placebo-Controlled Trial of Exenatide 2 mg 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
Primary endpoint		
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)	
Secondary endpoints		

	Exenatide 2 mg QW + Titrated Insulin Glargine	Placebo + Titrated Insulin Glargine
Proportion achieving HbA_{1c} <7.0%[c]	33%*	7%
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)	
Mean systolic blood pressure (mmHg)		
Baseline	132.8	132.6
Change from baseline (±SE)	-2.6 (0.93)	-0.7 (0.93)
Mean difference in change from baseline vs. placebo (95% CI)	-1.8*** (-4.0, 0.4)	
Exploratory endpoint		
Mean fasting plasma glucose (mmol/L)		
Baseline	8.22	7.99
Change from baseline (± SE)[b]	-0.66 (0.19)	-0.13 (0.19)
Mean difference in change from baseline vs. Placebo (95% CI)	-0.53** (-0.99, -0.06)	

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 HbA1c 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 <0.05 (exploratory endpoint).
Analyses exclude measurements post rescue therapy and post premature discontinuation of study medication.
*** nominal p-value=0.105.

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 2 mg 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 2 mg 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%).

Cardiovascular outcomes

EXSCEL was a multinational, placebo-controlled, double-blind, randomised, parallel group pragmatic study that evaluated cardiovascular (CV) outcomes during treatment with exenatide 2 mg once weekly in patients with type 2 diabetes and any level of CV risk when added to the current usual care.

A total of 14,752 patients were randomised 1:1 to either exenatide 2 mg once weekly or placebo and followed as in routine clinical practice for a median of 38.7 months with a median treatment duration of 27.8 months. Ninety six percent of the patients in both treatment groups completed the study in accordance with the protocol, and the vital status was known at the end of the study for 98.9% and 98.8% of the patients in the 2 mg exenatide once weekly and placebo group, respectively. The demographics and baseline characteristics were well-balanced between treatment groups.

The mean age at study entry was 62 years (21 to 92 years with 8.5% of the patients ≥75 years). Approximately 62.0% of the patients were male, 75.8% were Caucasian, 9.8% were Asian, 6.0% were Black, and 20.5% were Hispanic or Latino. The mean BMI was 32.7 kg/m^2 and the mean duration of diabetes was 13.1 years. Approximately 49.3% had mild renal impairment (estimated glomerular filtration rate [eGFR] ≥60 to ≤89 mL/min/1.73 m^2) and 21.6% had moderate renal impairment (eGFR ≥30 to ≤59 mL/min/1.73 m^2).

The mean HbA_{1c} was 8.1%. At baseline, 1.5% of patients were not treated with either oral antidiabetic medications or insulin, 42.3% were treated with one oral antidiabetic medication and 42.4% were treated with two or more oral antidiabetic medications. Usage of oral antidiabetic medications included metformin (76.6%), sulfonylurea (36.6%), DPP-4 inhibitors (14.9%), thiazolidinediones (3.9%), and SGLT-2 inhibitors (0.9%).

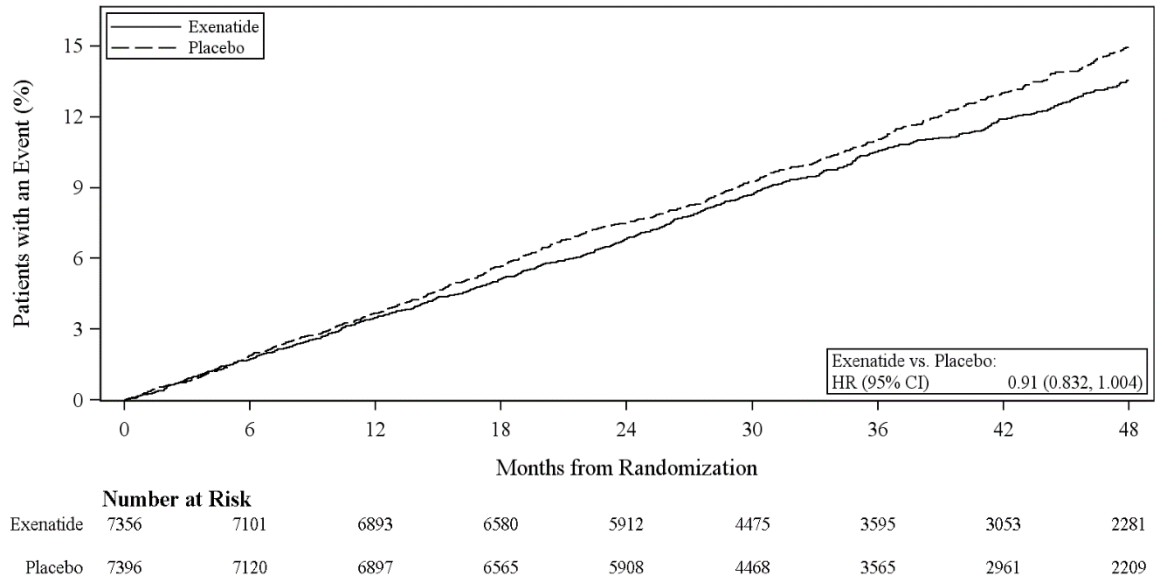
Overall insulin usage was 46.3% (13.8% with insulin alone and 32.6% with insulin and one or more oral antidiabetic medications). Overall, 26.9% of patients did not have any prior cardiovascular (CV) event, 73.1% had at least one prior CV event. The concomitant use of CV medications (e.g. ACE inhibitors, angiotensin receptor blockers, diuretics, beta blockers, calcium channel blockers, antithrombotic and anticoagulants, and lipid-lowering agents) was similar in the exenatide 2 mg once weekly and placebo groups. At baseline, the mean systolic blood pressure was 135.5 mmHg, the mean diastolic blood pressure was 78.1 mmHg, the mean LDL was 2.5 mmol/L, and the mean HDL was 1.1 mmol/L.

The primary endpoint in EXSCEL was the time to first confirmed Major Adverse Cardiac Event (MACE). A major adverse cardiac event was defined as occurrence of either a cardiovascular (CV)-related death, or a nonfatal myocardial infarction (MI) or

a nonfatal stroke. All-cause mortality, CV-related death, and fatal or nonfatal MI or stroke, hospitalisation for acute coronary syndrome, and hospitalisation for heart failure were also assessed as secondary endpoints.

A Cox proportional hazards model was used to test for non-inferiority against the pre-specified risk margin of 1.3 for the hazard ratio of MACE and superiority on MACE if non-inferiority was demonstrated. Type-1 error was controlled across multiples tests using a hierarchical testing strategy.

Exenatide 2 mg once weekly did not increase the risk of MACE in patients with type 2 diabetes mellitus compared to placebo when added to current usual care (HR: 0.91; 95% CI: 0.832, 1.004; P<0.001 for non-inferiority (Safety hypothesis); and did not reach statistical significance for superiority (P=0.061) (Efficacy hypothesis)). The results for the primary composite endpoint are shown in Figure 5.



HR=hazard ratio, CI=confidence interval

Figure 5 Time to First Adjudicated MACE (intention to treat patients)

The incidence of MACE in patients with and without established CV disease was 13.4% in the exenatide 2 mg once weekly group versus 14.6% in the placebo group, and 6.0% (exenatide) versus 5.9% (placebo), respectively. The results for the primary composite components and secondary cardiovascular endpoints are shown in Figure 6.

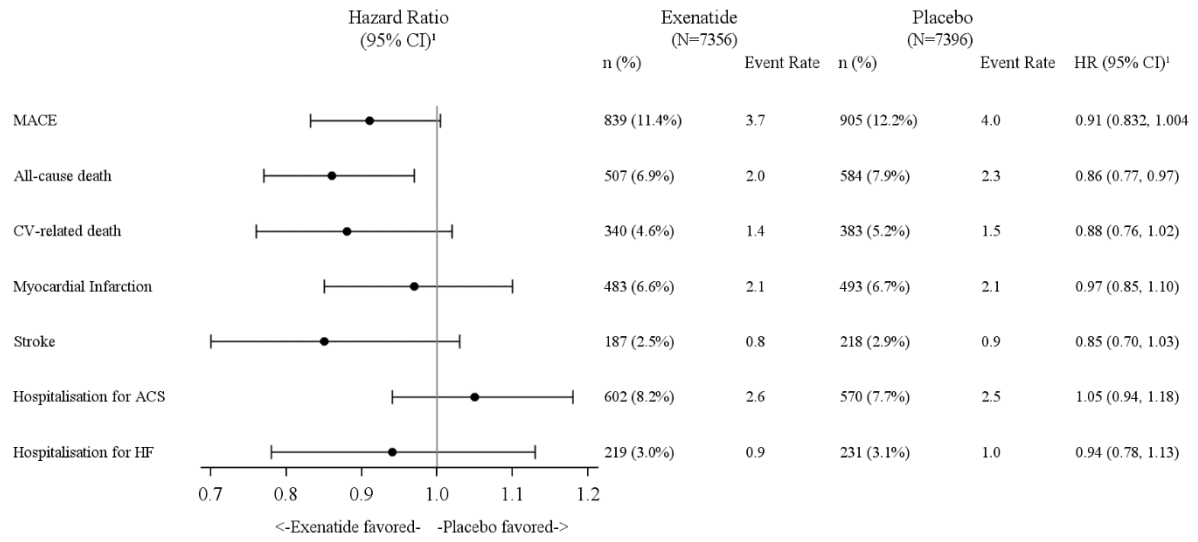


Figure 6 Forest Plot: Analysis of Primary and Secondary Endpoints (intent to treat patients)

BYDUREON BCise autoinjector

Exenatide 2 mg Once Weekly Suspension in Autoinjector vs. Exenatide 10 mcg Twice Daily as Add On to Diet and Exercise Alone or in Combination with one or any two of Metformin, Sulfonylurea, or Thiazolidinedione

A 28-week, open-label comparator-controlled trial with a 24-week open-ended extension period was conducted to evaluate the efficacy and safety of exenatide 2 mg once weekly suspension in autoinjector (n=229) versus exenatide 10 mcg twice daily (n=146) in patients with type 2 diabetes who were not achieving adequate glycaemic control on diet and exercise alone, or in combination with a stable regimen of oral antidiabetic medication (one or any two of metformin, sulfonylurea or thiazolidinedione).

All patients were randomly assigned to receive either exenatide 2 mg once weekly suspension in autoinjector or exenatide 10 mcg twice daily. Patients assigned to exenatide 10 mcg twice daily initiated treatment with 5 mcg twice daily for 4 weeks, followed by 10 mcg twice daily for 24 weeks, followed by a switch to exenatide 2 mg once weekly suspension in autoinjector for 24 weeks.

The majority of the patients (74%) were Caucasian, 16% Black or African American, 7% Asian, 1% listed as other, 1% American Indian or Alaska Native, and <1% Native Hawaiian or Other Pacific Islander.

The primary endpoint was change in HbA_{1c} from baseline to Week 28 (Figure 7). Exenatide 2 mg once weekly suspension in autoinjector achieved a statistically

significantly larger reduction in HbA_{1c} than that observed with exenatide 10 mcg twice daily (Table 10).

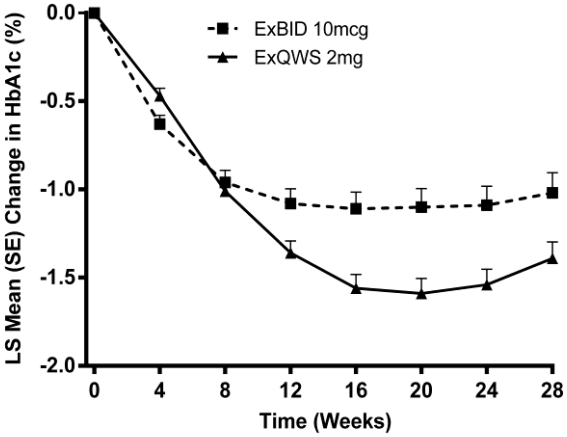


Figure 7 Change in HbA1c by week of treatment – modified ITT patients

Table 10 28-Week Comparator-Controlled Trial of Exenatide 2 mg Once Weekly Suspension in Autoinjector Versus Exenatide Twice Daily as Add-On to Diet and Exercise Alone or in Combination with one or any two of Metformin, Sulfonylurea, or Thiazolidinedione

	Exenatide 2 mg QWS	Exenatide 10 mcg BID
Modified Intent-to-Treat Population (N)	229	146
Mean HbA1c (%)		
Baseline	8.5	8.4
Change from baseline (± SE)[1]	-1.5 (0.1)	-1.1 (0.1)
Mean difference change from baseline vs. exenatide twice daily (95% CI)[1]	-0.38 (-0.64, -0.12)*	
Proportion achieving HbA1c <7.0%[2]	49%	43%
Proportion achieving HbA1c ≤6.5%[2]	36%	26%
Mean body weight (kg)		
Baseline	97	97
Change from baseline (± SE)[1]	-1.4 (0.3)	-1.8 (0.4)
Mean difference change from baseline vs. exenatide twice daily (95% CI)[1]	0.37 (-0.51, 1.25)	
Mean fasting plasma glucose (mmol/L)		
Baseline	9.9	10.4
Change from baseline (± SE)[1]	-1.8 (0.2)	-1.2 (0.3)
Mean difference change from baseline vs. exenatide twice daily (95% CI)[1]	-0.55 (-1.19, -0.10)	

	Exenatide 2 mg QWS	Exenatide 10 mcg BID
Mean 2-hour postprandial plasma glucose change from baseline (mmol/L)[2]		
Standard Meal Test Population (N)	37	31
Baseline	14.1	16.2
Change from baseline (± SE)[1]	-4.3 (0.7)	-5.8 (0.8)
Mean difference change from baseline vs. exenatide twice daily (95% CI)[1]	1.5 (-0.3, 3.3)	

CI= unadjusted confidence interval. QWS=once weekly suspension, BID=twice daily, N=treatment group patient population, SE=standard error, *p-value <0.01.
1. Least squares means.
2. LOCF.
3. Data extracted from the standard meal test which occurred at baseline and week 16.

The effects in HbA1c at Week 52 converged for both groups and appeared to reach a plateau. The LS mean change from baseline (SE) was-1.00% (0.11%) and -0.99% (0.13%) in the exenatide 2 mg once weekly suspension in autoinjector and exenatide twice daily treatment groups, respectively.

Exenatide 2 mg Once Weekly Suspension in Autoinjector vs. Sitagliptin or Placebo as Add-On to Metformin

A 28-week, open-label (oral medication blinded), comparator- and placebo-controlled trial was conducted to evaluate the efficacy and safety of exenatide 2 mg once weekly suspension in autoinjector (n=181) versus sitagliptin (n=122) and placebo (n=61) in patients with type 2 diabetes who were not achieving adequate glycemic control with ≥1500 mg metformin daily.

All patients were randomly assigned to receive either exenatide 2 mg suspension once weekly in autoinjector, sitagliptin once daily or placebo once daily.

The majority of the patients (81%) were Caucasian, 14% Black or African American, 4% Asian and <1% American Indian or Alaska Native, and Native Hawaiian or Other Pacific Islander.

The primary endpoint was change in HbA_{1c} from baseline to Week 28 (Figure 8). Exenatide 2 mg once weekly suspension in autoinjector achieved a statistically significantly larger reduction in HbA_{1c} than that observed with sitagliptin and placebo (Table 11).

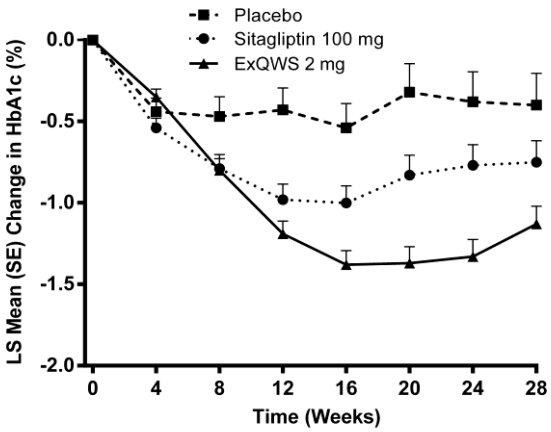


Figure 8 Change in HbA_{1c} by week of treatment – modified ITT patients

Table 11 28-Week Comparator- and Placebo-Controlled Trial of Exenatide 2 mg Once Weekly Suspension in Autoinjector Versus Sitagliptin and Placebo as Add-On to Metformin

	Exenatide 2 mg QWS	Sitagliptin 100 mg QD	Placebo QD
Modified Intent-to-Treat Population (N)	181	122	61
Mean HbA1c (%)			
Baseline	8.4	8.4	8.4
Change from baseline (± SE)[1]	-1.0 (0.1)	-0.6 (0.1)	-0.3 (0.2)
Mean difference change from baseline vs. exenatide suspension 2 mg once weekly (95% CI)[1]		0. 40 (0.07, 0.73)*	0.75 (0.32, 1.18)**
Proportion achieving HbA1c <7.0%[2]	43%[4,5,*]	32%	25%
Proportion achieving HbA1c ≤6.5%[2]	27%[4,5]	22%	13%
Mean body weight (kg)			
Baseline	88	87	87
Change from baseline (± SE)[1]	-1.2 (0.3)	-1.3 (0.3)	0.1 (0.5)
Mean difference change from baseline vs. exenatide suspension 2 mg once weekly (95% CI)[1]		-0.07 (-0.87, 0.73)	1.30 (0.24, 2.37)
Mean fasting plasma glucose (mmol/L)			
Baseline	9.7	9.7	9.1
Change from baseline (± SE)[1]	-1.1 (0.2)	-0.6 (0.3)	0.6 (0.4)
Mean difference change from baseline vs. exenatide suspension 2 mg once weekly (95% CI)[1]		0.56 (-0.09, 1.20)	1.7 (0.83, 2.58)

	Exenatide 2 mg QWS	Sitagliptin 100 mg QD	Placebo QD
Mean 2-hour postprandial plasma glucose change from baseline (mmol/L)[3]			
Standard Meal Test Population (N)	44	31	15
Baseline	14.2	15.4	12.3
Change from baseline (± SE)[1]	-3.7 (0.6)	-1.7 (0.8)	-2.3 (1.0)
Mean difference change from baseline vs. exenatide suspension 2 mg once weekly (95% CI)[1]		1.98 (0.18, 3.77)	1.43 (-0.80, 3.66)

CI = unadjusted confidence interval, QWS=once weekly suspension, QD=once daily N = number of patients in each treatment group, SE=standard error, *p-value <0.05, **p-value <0.01.
1: Least Squares Means.
2: LOCF.
3: Data extracted from the standard meal test which occurred at baseline and week 16.
4. Comparing to placebo.
5. Comparing to sitagliptin.

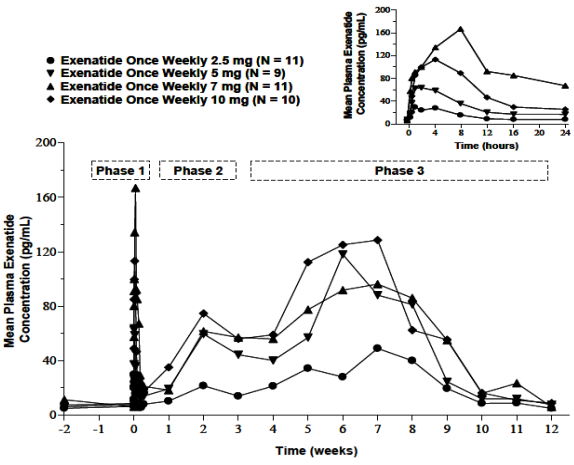
5.2 PHARMACOKINETIC PROPERTIES

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

<u>BYDUREON kit and pen</u>

A single dose of BYDUREON exhibits multiphasic release over an approximately 10 week period. This is interpretable as an initial period involving the release of surface-bound exenatide followed by 2 subsequent peaks representing the hydration and erosion of the microspheres. However, there are significant interindividual variations in release as shown below in terms of mean (figure left) and individual plasma levels (figure right) reflecting large inherent variability in release from the dose form:



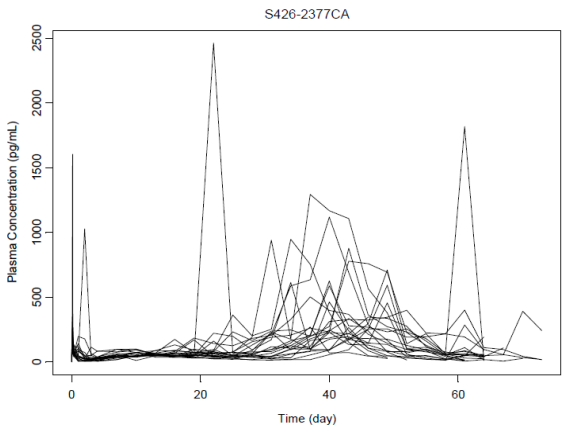


Figure 9 Extended Release Profile of Single Doses of BYDUREON, Mean (left) and Individual Plasma Concentrations (right)

Following weekly administration of 2 mg exenatide once weekly to patients with type 2 diabetes, mean drug 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 drug concentrations are maintained during the one week interval between doses with minimal peak to trough fluctuation from this average therapeutic concentration. The bioavailability of BYDUREON was approximately 25% (i.e. systemic exposure is 500 mcg/week) compared with the immediate release formulation, BYETTA at 10 mcg twice daily, which gives an exposure of 140 mcg/week.

BYDUREON BCise autoinjector

Following weekly administration of 2 mg exenatide once weekly suspension in autoinjector, mean drug concentrations exceeded minimal efficacious concentrations (~ 50 pg/mL) in 2 weeks with gradual increase in the average plasma exenatide concentration up to week 8. Subsequently, exenatide concentrations of approximately 208 pg/mL were maintained indicating that steady-state was achieved.

Distribution

The mean apparent volume of distribution of exenatide following subcutaneous administration of a single dose of exenatide is 28.3 L.

Metabolism

Nonclinical studies have shown that exenatide is predominantly eliminated by glomerular filtration with subsequent proteolytic degradation.

Excretion

The mean apparent clearance of exenatide in humans is 9.1 L/h and the mean terminal half-life is 2.4 h. These pharmacokinetic characteristics of exenatide are independent of the dose. Approximately 10 weeks after discontinuation of exenatide once weekly 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 (creatinine clearance 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 (creatinine clearance <30 mL/min) or for patients with end-stage renal

disease receiving dialysis (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Patients with hepatic insufficiency

No pharmacokinetic study has been performed in patients with a diagnosis of acute or chronic 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 BYETTA 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).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Exenatide was not genotoxic in bacterial reverse mutation assays, *in vitro* chromosomal aberration tests in Chinese hamster ovary cells or a mouse micronucleus assay.

Carcinogenicity

Refer to Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

BYDUREON BCise autoinjector

Powder

Polyglactin, sucrose.

Vehicle

Medium chain triglycerides.

BYDUREON kit and pen

Powder

Polyglactin, sucrose.

Diluent

Carmellose sodium, sodium chloride, polysorbate 20, monobasic sodium phosphate monohydrate, dibasic sodium phosphate (as heptahydrate), water for injections.

Sodium hydroxide may be added during manufacture of the BYDUREON pre-filled pen for pH adjustment.

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

During the shelf life, BYDUREON should be stored at 2°C to 8°C. However, BYDUREON may be kept for up to 4 weeks below 30°C during the shelf life. Refrigerate. Do not freeze. Store flat and in the original pack to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

BYDUREON BCise autoinjector

BYDUREON BCise (exenatide suspension for injection autoinjector) for weekly subcutaneous administration is supplied in cartons containing 4 single dose autoinjectors or 1 single dose autoinjector.

The suspension is packaged in a 2 mL Type 1 glass cartridge, sealed at one end with a rubber seal/cap combination, and at the other end with a rubber plunger. The finished drug product is comprised of the suspension filled cartridge assembled into the autoinjector device. The autoinjector contains an integrated needle.

BYDUREON pen

BYDUREON (exenatide powder and solvent for injection pre-filled pen) for weekly subcutaneous administration is supplied in cartons containing either 4 single dose dual-chamber pens or 1 single dose dual-chamber pen.

Each pre-filled pen contains exenatide powder and solvent for suspension for injection. The powder and solvent are packaged in a Type 1 glass cartridge sealed at one end with a rubber stopper and an aluminium seal, and at the other end with a rubber piston. The two chambers are separated by a second rubber piston.

There is one needle supplied per pen. Each carton also contains one spare needle. Use only the supplied needles with the pen.

BYDUREON kit

BYDUREON (exenatide powder for injection vial with diluent syringe) for weekly subcutaneous administration is supplied in cartons containing 4 single dose kits.

Exenatide powder for injection is packaged in a 3 mL Type I glass vial sealed with a rubber stopper and an aluminium seal with a plastic flip-off cap.

The diluent (solvent) is packaged in a 1.5 mL Type 1 glass syringe sealed with a rubber tip cap and a rubber plunger.

Each single-dose kit contains one vial of exenatide powder for suspension for injection, one pre-filled syringe of diluent for injection, one vial connector, and two needles (one spare).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The active ingredient in BYDUREON is exenatide. Exenatide is a 39-amino acid peptide amide. It has the empirical formula $C_{184}H_{282}N_{50}O_{60}S$ and molecular weight of 4186.6 Daltons. The amino acid sequence for exenatide is shown below.

H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2.

CAS number

The CAS number for exenatide is 141732-76-5.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8. SPONSOR

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Telephone: 1800 805 342

9. DATE OF FIRST APPROVAL

20 December 2012

10. DATE OF REVISION

3 November 2020

Summary table of changes

Section changed	Summary of new information
4.8	Update and reformat of adverse drug reaction data.
5.1	Update to data associated with DURATION-7 study.