Product Information
BYDUREON®

(exenatide)

NAME OF THE MEDICINE

BYDUREON (exenatide) powder for injection vial with diluent syringe.

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.

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

Description

BYDUREON is an extended release microspheres formulation of exenatide. BYDUREON is supplied in a single dose kit containing a vial of powder, a prefilled syringe of diluent, a vial connector and two needles (one spare). BYDUREON is a sterile, white to off-white powder in a glass vial. The active ingredient in BYDUREON is exenatide. The powder is suspended using the diluent supplied. The diluent is a clear, colourless to pale yellow to pale brown solution. 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.

Bydureon consists of exenatide (5%) and sucrose (2%) encapsulated within biodegradable polyglactin microspheres that are designed to release exenatide over an extended period of time. During dose preparation, a custom diluent is added to these microspheres, which are dispersed into the diluent to create a suspension. Following administration of the suspension, the polymer biodegrades over time, providing extended release of exenatide into the circulation. The diluent contains carmellose sodium, sodium chloride, polysorbate 20, sodium phosphate - monobasic, sodium phosphate - dibasic, and water for injections.

PHARMACOLOGY

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.

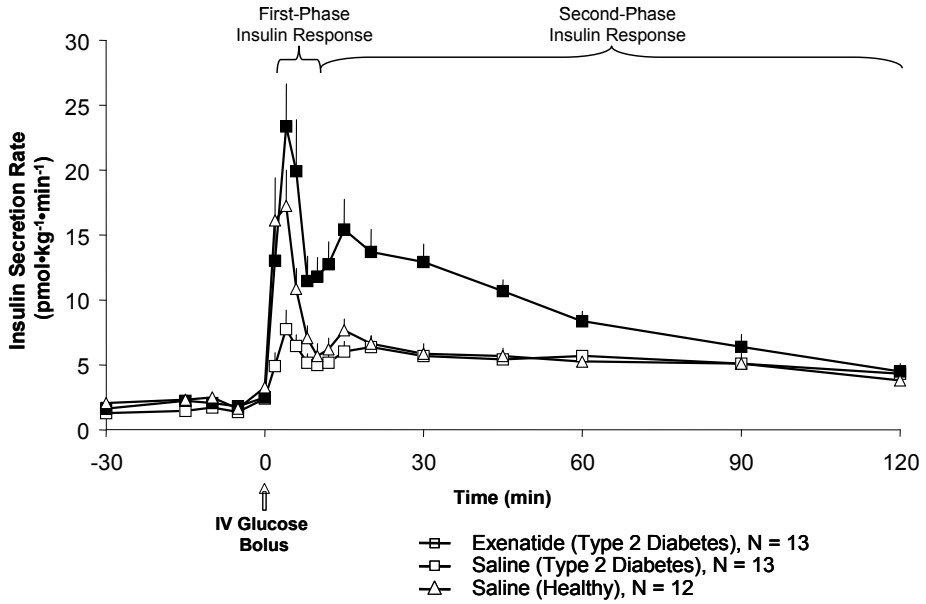
Exenatide slows gastric emptying thereby reducing the rate at which meal-derived glucose appears in the circulation.

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 euglycemia. Exenatide does not impair the normal glucagon response to hypoglycemia.

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.

Pharmacokinetics

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

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:

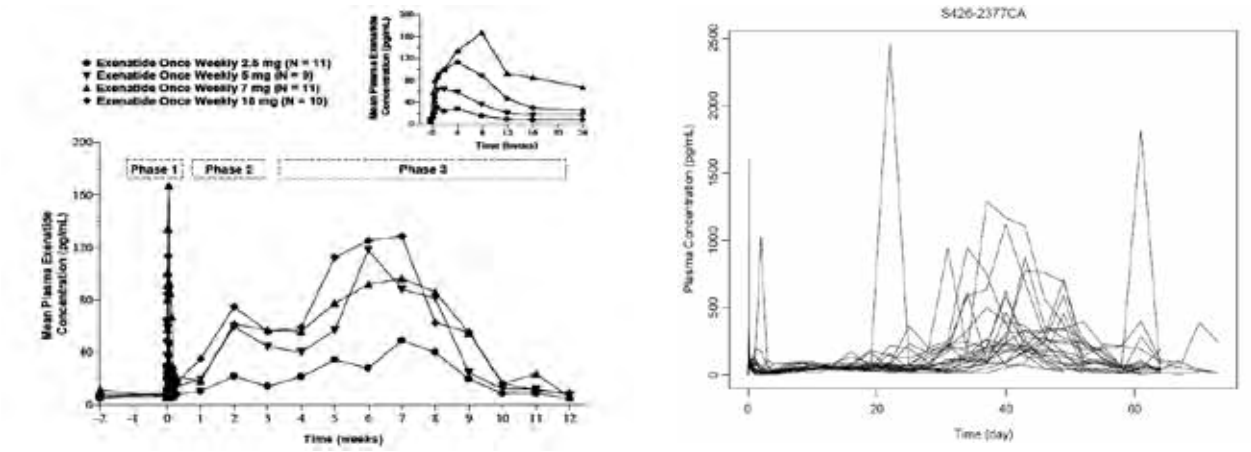


Figure 2: Extended Release Profile of Single Doses of BYDUREON, Mean (left) and Individual Plasma Concentrations (right)

Following weekly administration of 2mg 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 microgram per week) compared with the immediate release formulation, BYETTA at 10 µg bid gives an exposure of 140microgram/week.

Distribution

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

Metabolism and Elimination

Nonclinical studies have shown that exenatide is predominantly eliminated by glomerular filtration with subsequent proteolytic degradation. 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 2 mg exenatide once weekly is required for patients with mild to moderate renal impairment. Exenatide once weekly 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 **PRECAUTIONS, CONTRAINDICATIONS** and **DOSAGE AND ADMINISTRATION**).

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 10 µg exenatide twice daily 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 **DOSAGE AND ADMINISTRATION**).

CLINICAL TRIALS

Patients with Type 2 Diabetes participated in 4 long term, randomised, comparator controlled, clinical studies of 2mg 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.

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 **PHARMACOKINETICS – 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}, ($p<.001$) 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 1 shows HbA_{1c} results for each of the comparator controlled studies.

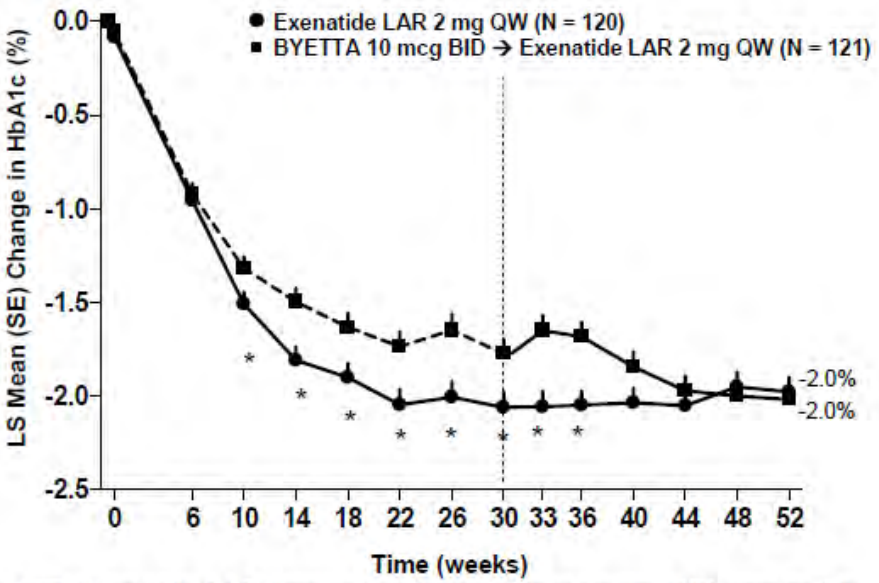
Table 1. Summary of Change in HbA1c from Baseline to Endpoint for Exenatide 2 mg Once Weekly Comparator Controlled Studies (intent to treat patients)

	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 3: 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 2, 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 2. Proportion of Subjects (%) Achieving HbA1c less than or equal to 7% for Exenatide 2 mg Once Weekly Comparator Controlled Studies (intent to treat patients)

	Proportion of Patients achieving HbA_{1c} target (%)	
Study		
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 ($p<.001$) 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 3).

Table 3. Change in Body Weight 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**	**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.

INDICATIONS

Exenatide is indicated for the treatment of type 2 diabetes mellitus in combination with:
- metformin
- sulfonylureas
- metformin and a sulfonylurea

in patients who have not achieved adequate glycaemic control.

CONTRAINDICATIONS

Exenatide is contraindicated in patients with known hypersensitivity to this product or any of its components.

Exenatide should not be used in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 ml/min). Compared with healthy subjects, renal clearance of exenatide was significantly reduced in patients with end-stage renal disease receiving dialysis, resulting in poor gastrointestinal tolerability.

PRECAUTIONS

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

Exenatide must not be administered by intravenous or intramuscular injection.

Exenatide 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 exenatide is not recommended in patients with severe gastrointestinal disease including gastroparesis and dumping syndrome.

The concurrent use of exenatide with insulin, D-phenylalanine derivatives, meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase 4 (“gliptins”), orlistat, opioids, and anticholinergics has not been studied. The concomitant use of exenatide once weekly and exenatide twice daily is not recommended.

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 patients on a sulfonylurea 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 sulfonylurea, reduction in the dose of sulfonylurea may be considered (see **DOSAGE AND ADMINISTRATION** and **ADVERSE 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 **Interaction With Other Medicines** and **ADVERSE EFFECTS**, **Spontaneous Data).**

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 **ADVERSE EFFECTS, Spontaneous Data).**

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 exenatide, for these patients. The change in risk of recurrent pancreatitis in patients with a past history of pancreatitis who receive exenatide 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 exenatide twice daily. 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 exenatide once weekly 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.

Effect 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 mg/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
Pregnancy Category C

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. 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 mg/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 **Use in Pregnancy**). Exenatide should be administered to nursing women only if the potential benefit to the mother justifies the potential risk to the infant.

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
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.

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

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 **CLINICAL PHARMACOLOGY**). In the 30 week and 26 week trials, exenatide once weekly was studied in 46 patients and exenatide twice daily in 24 patients, who were at least 65 years old. In separate trials, exenatide twice daily 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. Because elderly patients are more likely to have decreased renal function, care should be taken when initiating 2 mg exenatide once weekly in the elderly based on renal function.

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 2 mg exenatide once weekly is required for patients with mild to moderate renal impairment. Exenatide once weekly 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 **CONTRAINDICATIONS).**

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 exenatide is used in combination with a sulfonylurea, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines.

INTERACTION WITH OTHER MEDICINES
The results of a study using paracetamol as a marker of gastric emptying suggest that the effect of exenatide once weekly 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 exenatide once weekly. However, the dose of a sulfonylurea may require adjustment due to the increased risk of hypoglycaemia associated with sulfonylurea therapy (see **PRECAUTIONS, Hypoglycaemia** and **DOSAGE AND ADMINISTRATION**).

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 2 mg exenatide once weekly 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 10 µg exenatide twice daily, AUC and C_{max} decreased by 20% and 21% respectively, and t_{max} increased to 2 hours. Given that concomitant 2 mg exenatide once weekly 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 10 µg exenatide twice daily but not 2 mg exenatide once weekly.

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 exenatide 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 **PHARMACODYNAMIC PROPERTIES**). 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 Exenatide. No clinically relevant effects on C_{max} or AUC were observed (*see* **PRECAUTIONS** and **ADVERSE EFFECTS, Spontaneous Data**). INR should be monitored during initiation of exenatide once weekly therapy in patients on warfarin and/or cumarol derivatives (see **PRECATUIONS** and **ADVERSE EFFECTS, Spontaneous Data**).

Digoxin and Lisinopril
In interaction studies of the effect of exenatide 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 exenatide did not alter the AUC, C_{max} or C_{min} of either ethinyl estradiol or levonorgestrel. Administration of the oral contraceptive 30 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.

ADVERSE 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 twice daily has been marketed (see **PRECAUTIONS**).

Tabulated summary of adverse reactions

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.

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 4: 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	118 (20)	50 (34)	8 (5)	16 (10)	4 (2)
Diarrhoea	76 (13)	19 (13)	12 (7)	16 (10)	8 (4)
Vomiting	46 (8)	27 (19)	5 (3)	4 (2)	3 (1)
Constipation	34 (6)	9 (6)	2 (1)	3 (2)	4 (2)
Dyspepsia	24 (4)	4 (3)	4 (2)	6 (4)	2 (1)
Gastrooesophageal Reflux Disease	19 (3)	6 (4)	2 (1)	2 (1)	2 (1)
Abdominal Discomfort	13 (2)	2 (1)	0 (0)	0 (0)	1 (<1)
Abdominal Pain	13 (2)	3 (2)	2 (1)	6 (4)	2 (1)
Abdominal Pain Upper	12 (2)	2 (1)	2 (1)	6 (4)	2 (1)
Toothache	6 (1)	3 (2)	4 (2)	2 (1)	4 (2)
General Disorders and Administration Site Conditions					
Injection Site Pruritus	47 (8)	2 (1)	2 (1)	8 (5)	1 (<1)
Injection Site Erythema	24 (4)	0 (0)	0 (0)	4 (2)	1 (<1)
Fatigue	23 (4)	4 (3)	5 (3)	0 (0)	1 (<1)
Injection Site Haematoma	14 (2)	16 (11)	4 (2)	2 (1)	2 (1)
Injection Site Induration	23 (4)	0 (0)	1 (1)	1 (1)	0 (0)
Injection Site Nodule	19 (3)	0 (0)	1 (1)	2 (1)	0 (0)
Injection Site Pain	6 (1)	3 (2)	0 (0)	2 (1)	1 (<1)
Infections and Infestations					
Nasopharyngitis	51 (19)	8 (6)	5 (3)	4 (2)	40 (18)
Upper Respiratory Tract Infection	23 (4)	25 (17)	17 (10)	15 (9)	3 (1)
Sinusitis	17 (3)	10 (7)	11 (7)	2 (1)	5 (2)
Urinary Tract Infection	30 (5)	12 (8)	6 (4)	9 (5)	1 (<1)
Gastroenteritis Viral	17 (3)	8 (6)	0 (0)	2 (1)	9 (<1)
Influenza	13 (2)	3 (2)	5(3)	2 (1)	7 (3)

System Organ Class Preferred Term	Exenatide QW N=592 (%)	Exenatide BID N=145 (%)	Pioglitazone N=165 (%)	Sitagliptin N=166 (%)	Insulin Glargine N=223 (%)
Gastroenteritis	12 (2)	0 (0)	1 (1)	3 (2)	4 (2)
Injury Poisoning and Procedural Complications					
Joint Pain	3 (1)	3 (2)	0 (0)	0 (0)	0 (0)
Procedural Pain	1 (<1)	5 (3)	0 (0)	0 (0)	1 (<1)
Metabolism and Nutrition Disorders					
Hypoglycaemia	90 (15)	28 (19)	10 (6)	15 (9)	97 (43)
Decreased Appetite	15 (3)	1 (1)	0 (0)	2 (1)	0 (0)
Anorexia	12 (2)	1 (1)	0 (0)	1 (1)	0 (0)
Hypokalaemia	3 (1)	4 (3)	0 (0)	0 (0)	0 (0)
Musculoskeletal and Connective Tissue Disorders					
Back Pain	24 (4)	6 (4)	5 (3)	7 (4)	7 (3)
Arthralgia	21 (4)	6 (4)	3 (2)	8 (5)	6 (3)
Pain in Extremity	13 (2)	1 (1)	2 (1)	4 (2)	2 (1)
Musculoskeletal Pain	11 (2)	0 (0)	3 (2)	2 (1)	7 (3)
Muscle Spasms	5 (1)	3 (2)	1 (1)	2 (1)	1 (<1)
Nervous System Disorders					
Headache	50 (8)	7 (5)	7 (4)	15 (9)	20 (9)
Dizziness	15 (3)	9 (6)	6 (4)	8 (5)	3 (1)
Diabetic Neuropathy	2 (<1)	3 (2)	0 (0)	1 (1)	0 (0)
Psychiatric Disorders					
Depression	6 (1)	4 (3)	0 (0)	3 (2)	1 (<1)
Insomnia	4 (1)	4 (3)	2 (1)	1 (1)	1 (<1)
Anxiety	5 (1)	3 (2)	1 (1)	2 (1)	3 (1)
Reproductive System and Breast Disorders					
Erectile Dysfunction	1 (<1)	4 (3)	1 (1)	0 (0)	0 (0)
Respiratory, Thoracic and Mediastinal Disorders					
Cough	11 (2)	2 (1)	5 (3)	2 (1)	8 (4)
Oropharyngeal Pain	12 (2)	2(1)	1 (1)	1 (1)	8 (4)
Skin and Subcutaneous Tissue Disorders					
Alopecia	1 (<1)	3 (2)	0 (0)	0 (0)	0 (0)
Vascular Disorders					
Hypertension	16 (3)	4 (3)	2 (1)	5 (3)	7 (3)

Abbreviations: QW: once weekly; BID: twice daily

Hypoglycaemia

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

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%).

Table 5 summarises the occurrence of treatment-emergent hypoglycaemia by sulfonylurea use in clinical trials of 2 mg exenatide once weekly.

Table 5: 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 (0.0)	0 (0.0)	1 (1.5)
Minor Hypoglycaemia	22 (15.9)	10 (18.9)	0 (0.0)	0 (0.0)	28 (41.8)
Without Sulfonylurea					
Major Hypoglycaemia	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Minor Hypoglycaemia	9 (2.0)	1 (1.1)	1 (0.6)	5 (3.0)	30 (19.2)

Abbreviations: QW: once weekly; BID: twice daily

Nausea

Nausea has been described in studies of GLP-1 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.

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.

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).

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 exenatide BID 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.

SPONTANEOUS DATA

General: Common (³ 1% and <10%): injection-site reactions.

Gastrointestinal disorders: Uncommon (³ 0.1% and < 1%): abdominal distension, abdominal pain, eructation, constipation, flatulence. Rare (³ 0.01% and <0.1%): acute pancreatitis. Very rare (<0.01%): Cases of ileus, ischaemic colitis and gut ischaemia have been reported.

Nervous System disorders: Uncommon (³ 0.1% and < 1%): dysgeusia.
Rare (³ 0.01% <0.1%): somnolence.

Investigations: Rare (³ 0.01% <0.1%) INR increased with concomitant warfarin use, some reports associated with bleeding (*see* **PRECAUTIONS** and **Interaction With Other Medicines**).

Immune system disorder: Very rare (<0.01%): anaphylactic reaction.

Skin and subcutaneous disorders: Rare (³ 0.01% and <0.1%): angioedema, generalized pruritus and/or urticaria, macular or papular rash, alopecia.

Metabolism and nutritional disorders: Rare (³ 0.01% and <0.1%): dehydration, generally associated with nausea, vomiting, and/or diarrhoea, weight decreased (see **PRECAUTIONS, Weight Loss**).

Renal and urinary disorders: Rare (>0.01% and <0.1%): acute renal failure, chronic renal failure, renal impairment, increased serum creatinine. See **PRECAUTIONS.**

DOSAGE AND ADMINISTRATION

The recommended BYDUREON dose is 2 mg exenatide once weekly. Titration is not required.

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.

The day of weekly administration can be changed if necessary as long as the next dose is administered at least one day later than the last dose.

If a dose is missed, it should be administered as soon as noticed. Thereafter, patients can resume their once weekly dosing schedule on next preferred day of the week, as long as the next dose is administered at least one day later than the last dose. Two injections should not be given on the same day.

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

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

When exenatide once weekly is added to sulfonylurea therapy, a reduction in the dose of sulfonylurea should be considered to reduce the risk of hypoglycaemia (see **PRECAUTIONS**).

BYDUREON' s safety and efficacy in use with thiazolidinediones has not been shown.

Patients switching from 10 µg exenatide twice daily to 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.

The use of 2 mg exenatide once weekly does not require additional self-monitoring. When used in combination with a sulfonylurea, blood glucose self-monitoring may be necessary to adjust the dose of sulfonylurea.

Following discontinuation, consideration should be given to the prolonged release of exenatide (see **PHARMACOKINETICS**).

Specific patient groups
Elderly
Exenatide can be given to adults of all ages including the elderly (> 65 years of age). The clinical experience in patients > 75 years is very limited (see **PHARMACOKINETICS**).

Patients with renal impairment

Exenatide can be given to patients with mild or moderate renal impairment (creatinine clearance 30 – 80 ml/min) (see **PHARMACOKINETICS**).

Exenatide is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance < 30 ml/min) (see **PRECAUTIONS**).

Patients with hepatic impairment

Exenatide can be given to patients with hepatic impairment (see **PHARMACOKINETICS**).

Children and adolescents

The safety and efficacy of exenatide have not yet been established in children under 18 years of age (see **PHARMACOKINETICS**).

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 must be injected immediately after suspension of the powder in the diluent.

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 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.

Incompatibilities

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

OVERDOSAGE

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.

PRESENTATION AND STORAGE CONDITIONS

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 aluminum seal with a plastic flip-off cap.

The diluent 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).

Storage

During the 2 year shelf life, the entire kit should be stored at 2ºC to 8ºC. However, the kit may be kept for 4 weeks below 30ºC during the 2 year shelf life. Refrigerate. Do not freeze. Store in the original pack to protect from light.

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

NAME AND ADDRESS OF SPONSOR

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AUSTRALIA

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20 December 2012

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