ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 2 mg of exenatide.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for prolonged-release suspension for injection.

Powder: white to off-white powder.
Solvent: clear, colourless to pale yellow to pale brown solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BYDUREON is indicated for treatment of type 2 diabetes mellitus in combination with

- Metformin
- Sulphonylurea
- Thiazolidinedione
- Metformin and sulphonylurea
- Metformin and thiazolidinedione

in adults who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies.

4.2 Posology and method of administration

Posology
The recommended dose is 2 mg exenatide once weekly.

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

When BYDUREON is added to existing metformin and/or thiazolidinedione therapy, the current dose of metformin and/or thiazolidinedione can be continued. When BYDUREON is added to sulphonylurea therapy, a reduction in the dose of sulphonylurea should be considered to reduce the risk of hypoglycaemia (see section 4.4).

BYDUREON should be administered once a week on the same day each week. The day of weekly administration can be changed if necessary as long as the next dose is administered at least one day (24 hours) later. BYDUREON can be administered at any time of day, with or without meals.

If a dose is missed, it should be administered as soon as practical. Thereafter, patients can resume their once weekly dosing schedule. Two injections should not be given on the same day.

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

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

Special populations

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

Patients with renal impairment
No dose adjustment is necessary for patients with mild renal impairment (creatinine clearance 50 to 80 ml/min). Clinical experience in patients with moderate renal impairment (creatinine clearance 30 to 50 ml/min) is very limited (see section 5.2). BYDUREON is not recommended in these patients.

BYDUREON is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance < 30 ml/min) (see section 4.4).

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

Paediatric population
The safety and efficacy of BYDUREON in children and adolescents aged under 18 years have not yet been established (see section 5.2). No data are available.

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

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

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

For instructions on the suspension of the medicinal product before administration, see section 6.6 and the "Instructions for the User".

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

BYDUREON must not be administered by intravenous or intramuscular injection.

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

Renal impairment
In patients with end-stage renal disease receiving dialysis, single doses of exenatide twice daily increased frequency and severity of gastrointestinal adverse reactions therefore BYDUREON is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance < 30 ml/min). The clinical experience in patients with moderate renal impairment is very limited and the use of BYDUREON is not recommended.

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

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

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

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

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

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

Interaction with warfarin
There have been some reported cases of increased INR (International Normalized Ratio), sometimes associated with bleeding, with concomitant use of warfarin and exenatide (see section 4.5).

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

4.5 Interaction with other medicinal products and other forms of interaction

The results of a study using paracetamol as a marker of gastric emptying suggest that the effect of BYDUREON to slow gastric emptying is minor and not expected to cause clinically significant reductions in the rate and extent of absorption of concomitantly administered oral medicinal products.

Therefore, no dose adjustments for medicinal products sensitive to delayed gastric emptying are required.
When 1,000 mg paracetamol tablets were administered, either with or without a meal, following 14 weeks of BYDUREON therapy, no significant changes in paracetamol AUC were observed compared to the control period. Paracetamol C_{max} decreased by 16 % (fasting) and 5 % (fed) and t_{max} was increased from approximately 1 hour in the control period to 1.4 hours (fasting) and 1.3 hours (fed).

Sulphonylureas
The dose of a sulphonylurea may require adjustment due to the increased risk of hypoglycaemia associated with sulphonylurea therapy (see sections 4.2 and 4.4).

The following interaction studies have been conducted using 10 µg exenatide twice daily but not exenatide once weekly:
Interaction studies with exenatide have only been performed in adults.

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

Warfarin
A delay in t_{max} of about 2 h was observed when warfarin was administered 35 min after exenatide twice daily. No clinically relevant effects on C_{max} or AUC were observed. Increased INR has been reported during concomitant use of warfarin and exenatide twice daily. INR should be monitored during initiation of BYDUREON therapy in patients on warfarin and/or cumarol derivatives (see section 4.8).

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

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

4.6 Fertility, pregnancy and lactation

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

Pregnancy
There are no adequate data from the use of BYDUREON in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.
BYDUREON should not be used during pregnancy and the use of insulin is recommended.

Breastfeeding
It is unknown whether exenatide is excreted in human milk. BYDUREON should not be used during breast-feeding.

Fertility
No fertility studies in humans have been conducted.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Acute pancreatitis and acute renal failure have been reported rarely since exenatide twice daily has been marketed (see section 4.4).

Tabulated summary of adverse reactions
The frequency of adverse reactions of BYDUREON with an incidence of ≥ 1 % are summarised in Table 1 below.

The data source comprises two placebo controlled studies (10 and 15 weeks) and 3 trials comparing BYDUREON to either 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 sulphonylurea, a thiazolidinedione or a combination of oral anti-diabetic agents.

The adverse reactions observed from post-marketing and clinical trial experience with exenatide twice daily that were not observed with BYDUREON at an incidence of ≥ 1 % are listed in Table 2 below.

The reactions are listed below as MedDRA preferred term by system organ class and absolute frequency. Patient frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10000 to < 1/1000) and very rare (< 1/10000).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: The frequency of adverse reactions of BYDUREON with an incidence of ≥ 1 % in clinical trials. n= 592 total, (patients on sulphonylurea n= 135)

Very common	**Common**
Metabolism and nutrition disorder	
Hypoglycaemia (with a sulphonylurea)[1]	Decreased appetite[1]
Nervous system disorders	
	Dizziness[1]
	Headache[1]
Gastrointestinal disorders	
Constipation	Abdominal distention
Diarrhoea[1]	Abdominal pain[1]
Nausea[1]	Dyspepsia[1]
Vomiting[1]	Eructation
	Flatulence[1]
	Gastroesophageal reflux [1]
General disorders and administration site conditions	
Injection site pruritus	Fatigue[1]
	Injection site erythema
	Injection site rash
	Somnolence

[1] Frequency of reactions was the same in the exenatide twice daily treatment group.

Table 2: The adverse reactions observed from post-marketing and clinical trial experience with exenatide twice daily that were not observed with BYDUREON at an incidence of ≥ 1 % are listed below:

Common	Uncommon	Rare	Very rare
Immune system disorders			
			Anaphylactic reaction [2]
Metabolism and nutrition disorder			
		Dehydration, generally associated with nausea, vomiting and/or diarrhoea. [2]	
Nervous system disorders			
	Dysgeusia [2]		
Gastrointestinal disorders			
	Acute pancreatitis (see section 4.4). [1,3]		
Skin and subcutaneous tissue disorders			
Hyperhidrosis [1]		Macular or papular rash [2,]	
		Pruritus, and/ or urticaria [2,]	
		Angioneurotic oedema [2]	
		Alopecia [2,]	
Renal and urinary disorders			
		Altered renal function, including acute renal failure, worsened chronic renal failure, renal impairment, increased serum creatinine [2] (see section 4.4).	
General disorders and administration site conditions			
Asthenia[1]			
Feeling jittery [1]			
Investigations			
		International normalised ratio increased with concomitant warfarin use, some reports associated with bleeding (see section 4.4). [2]	

[1] Rate based on exenatide twice daily clinical trial data
[2] Rate based on exenatide twice daily spontaneous data.
[3] Events were uncommon in all treatment groups.

Description of selected adverse reactions

Hypoglycaemia
The incidence of hypoglycaemia was increased when BYDUREON was used in combination with a sulphonylurea (15.9 % versus 2.2 %) (see section 4.4). To reduce the risk of hypoglycaemia associated with the use of a sulphonylurea, reduction in the dose of sulphonylurea may be considered (see sections 4.2 and 4.4).

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

Across all studies most episodes (96.8 % n=32) of hypoglycaemia were minor, and resolved with oral administration of carbohydrate. One patient was reported with major hypoglycaemia since he had a low blood glucose value (2.2 mmol/l) and requested assistance with oral carbohydrate treatment which resolved the event.

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

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

Injection site reactions
Injection site reactions were observed more frequently in BYDUREON-treated patients versus comparator treated patients (16 % versus range of 2-7 %) during the 6 month controlled phase of studies. These injection site reactions were generally mild and usually did not lead to withdrawal from studies. Patients may be treated to relieve symptoms, while continuing treatment. Subsequent injections should use a different site of injection each week.
Small subcutaneous injection site nodules were observed very frequently in clinical trials, consistent with the known properties of poly (D,L-lactide co-glycolide) polymer microsphere formulations. Most individual nodules were asymptomatic, did not interfere with study participation and resolved over 4 to 8 weeks.

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

The presence of antibodies (high or low titres) is not predictive of glycaemic control for an individual patient.
In clinical studies of BYDUREON, approximately 45 % of patients had low titre antibodies to exenatide at study endpoint. Overall the percentage of antibody positive patients was consistent across clinical trials. Overall, the level of glycaemic control (HbA_{1c}) was comparable to that observed in those without antibody titres. On average in the phase 3 studies, 12 % of the patients had higher titre antibodies. In a proportion of these the glycaemic response to BYDUREON was absent at the end of the controlled period of studies; 2.6 % of patients showed no glucose improvement with higher titre antibodies while 1.6 % showed no improvement while antibody negative.

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

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

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

Rapid weight loss
In a 30-week study, approximately 3 % (n=4/148) of BYDUREON-treated patients experienced at least one time period of rapid weight loss (recorded body weight loss between two consecutive study visits of greater than 1.5 kg/week).

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, other blood glucose lowering drugs, excl. insulins, ATC code: A10BX04.

Mechanism of action
Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist that exhibits several antihyperglycaemic actions of glucagon-like peptide-1 (GLP-1). The amino acid sequence of exenatide partially overlaps that of human GLP-1. Exenatide has been shown to bind to and activate the known human GLP-1 receptor *in vitro*, its mechanism of action mediated by cyclic AMP and/or other intracellular signaling pathways.
Exenatide increases, on a glucose-dependent basis, the secretion of insulin from pancreatic beta cells. As blood glucose concentrations decrease, insulin secretion subsides. When exenatide was used in combination with metformin and/or a thiazolidinedione, no increase in the incidence of hypoglycaemia was observed over that of placebo in combination with metformin and/or a thiazolidinedione which may be due to this glucose-dependent insulinotropic mechanism (see section 4.4).
Exenatide suppresses glucagon secretion which is known to be inappropriately elevated in patients with type 2 diabetes. Lower glucagon concentrations lead to decreased hepatic glucose output. However, exenatide does not impair the normal glucagon response and other hormone responses to hypoglycaemia.
Exenatide slows gastric emptying thereby reducing the rate at which meal-derived glucose appears in the circulation.
Administration of exenatide has been shown to reduce food intake, due to decreased appetite and increased satiety.

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

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

Clinical efficacy

The results of long term clinical studies of BYDUREON are presented below, these studies comprised 1628 subjects (804 treated with BYDUREON), 54 % men and 46 % women, 281 subjects (141 treated with BYDUREON) were ≥ 65 years of age.

Glycaemic control

In two studies BYDUREON 2 mg once weekly has been compared to exenatide twice daily 5 µg for 4 weeks followed by exenatide twice daily 10 µg . One study was of 24 weeks in duration (n= 252) and the other of 30 weeks (n= 295) followed by an open labelled extension where all patients were treated with BYDUREON 2 mg once weekly for a further 22 weeks (n= 243). 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).

BYDUREON resulted in a statistically significant reduction in HbA_{1c} compared to patients receiving exenatide twice daily (Table 3).

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

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

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

Further reductions in HbA_{1c} and sustained weight loss were observed for at least 52 weeks in the patients completing both the controlled 30 week study and the uncontrolled study extension. The evaluable patients who switched from exenatide twice daily to BYDUREON (n= 121) achieved the same improvement in $HbA_{1c}$of - 2.0 % , at the end of the 22 week extension compared to the initial baseline, as the patients treated with BYDUREON for 52 weeks.

Table 3: Results of two trials of BYDUREON versus exenatide twice daily in combination with diet and exercise alone, metformin and/or sulphonylurea and metformin and/or thiazolidinedione (intent to treat patients).

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

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

A study of 26 week duration has been conducted, in which BYDUREON 2 mg is compared to insulin glargine QD. BYDUREON demonstrated a superior change in HbA_{1c} compared to insulin glargine. Compared with insulin glargine treatment, BYDUREON treatment significantly lowered mean body weight and was associated with fewer hypoglycaemic events (Table 4).

Table 4: Results of one 26 week trial of BYDUREON versus insulin glargine in combination with metformin and/or sulphonylurea (intent to treat patients).

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

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

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

In a 26 week double blind study BYDUREON was compared to maximum daily doses of sitagliptin and pioglitazone in subjects also using metformin. All treatment groups had a significant reduction in HbA_{1c} compared to baseline. BYDUREON demonstrated superiority to both sitagliptin and pioglitazone with respect to change in HbA_{1c} from baseline.
BYDUREON demonstrated significantly greater weight reductions compared to sitagliptin. Patients on pioglitazone gained weight (Table 5).

Table 5: Results of one 26 week trial of BYDUREON versus sitagliptin and versus pioglitazone in combination with metformin (intent to treat patients).

	BYDUREON 2 mg	**Sitagliptin 100 mg**	**Pioglitazone 45 mg**
N	160	166	165
Mean HbA_{1c} (%)			
Baseline	8.6	8.5	8.5
Change from baseline(± SE)	-1.4 (± 0.1)*	-0.8 (± 0.1)*	-1.1 (± 0.1)*
Mean difference change from baseline between treatments(95 % CI) versus sitagliptin	-0.63 (, -0.89, -0.37)**		
Mean difference change from baseline between treatments(95 % CI) versus pioglitazone	-0.32 (-0.57, -0.06,)*		
Patients (%) achieving $HbA_{1c} \leq$ 7 %	62	36	49
Change in fasting serum glucose (mmol/l) (± SE)	-1.8 (± 0.2)	-0.9 (± 0.2)	-1.5 (± 0.2)
Mean body weight (kg)			
Baseline	89	87	88
Change from baseline(± SE)	-2.3 (± 0.3)	-0.8 (± 0.3)	+2.8 (± 0.3)
Mean difference change from baseline between treatments(95 % CI) versus sitagliptin	-1.54 (-2.35, -0.72)*		
Mean difference change from baseline between treatments(95 % CI) versus pioglitazone	-5.10 (-5.91 , -4.28)**		

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

Body weight
A reduction in body weight compared to baseline has been observed in all BYDUREON studies. This reduction in body weight was seen in patients treated with BYDUREON irrespective of the occurrence of nausea although the reduction was larger in the group with nausea (mean reduction - 2.9 kg to - 5.2 kg with nausea versus - 2.2 kg to -2.9 kg without nausea).
The proportion of patients who had both a reduction in weight and HbA_{1c} ranged from 70 to 79 % (the proportion of patients who had a reduction of HbA_{1c} ranged from 88 to 96 %).

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

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

Blood pressure
A reduction in systolic blood pressure was observed in BYDUREON studies (2.9 mmHg to 4.7 mmHg). In the 30 week exenatide twice daily comparator study both BYDUREON and exenatide twice daily significantly reduced systolic blood pressure from base line (4.7±1.1 mmHg and 3.4±1.1 mmHg respectively) the difference between the treatments was not significant. Improvements in blood pressure were maintained through 52 weeks.

Fasting lipids
BYDUREON has shown no adverse effects on lipid parameters.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with BYDUREON in one or more subsets of the paediatric population in type 2 diabetes mellitus (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

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

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

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

Special populations
Patients with renal impairment
Population pharmacokinetic analysis of renal impaired patients receiving 2 mg BYDUREON indicate that there may be an increase in systemic exposure of approximately 74 % and 23 % (median prediction in each group) in moderate (N=10) and mild (N=56) renal impaired patients, respectively as compared to normal (N=84) renal function patients.

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

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

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

In a pharmacokinetic study of exenatide twice daily in patients with type 2 diabetes, administration of exenatide (10 µg) 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).

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

5.3 Preclinical safety data

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
poly (D,L-lactide-co-glycolide)
sucrose

Solvent
carmellose sodium
sodium chloride
polysorbate 20
monobasic sodium phosphate, monohydrate
dibasic sodium phosphate, heptahydrate
water for injections

6.2 Incompatibilities

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

6.3 Shelf life

2 years

<u>After reconstitution</u>
The suspension must be injected immediately.

6.4 Special precautions for storage

Store in a refrigerator (2ºC - 8ºC).
Do not freeze.
The kit may be kept for up to 4 weeks below 30ºC prior to use.

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

6.5 Nature and contents of container

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

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

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

Pack size of 4 single dose kits and a multipack consisting of 3 x 4 single-dose kits. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

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

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

BYDUREON that has been frozen must not be used.

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

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V., Grootslag 1-5, NL-3991 RA Houten, The Netherlands.

8. MARKETING AUTHORISATION NUMBER(S)

EU/X/XX/XXX/XXX

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

DD month YYYY

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. Manufacturing authorisation holder responsible for batch release

Name and address of the manufacturer responsible for batch release

Lilly Pharma Fertigung und Distribution GmbH & Co.Kg
Teichweg 3
35396 Giessen
Germany

B. Conditions of the marketing authorisation

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable

- **OTHER CONDITIONS**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as described in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The MAH commits to perform the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 15 rev.14 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON - 4 single-dose kits

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 2 mg exenatide

3. LIST OF EXCIPIENTS

Excipients:
Powder
poly (D,L-lactide-co-glycolide)
sucrose

Solvent
carmellose sodium
sodium chloride
polysorbate 20
monobasic sodium phosphate, monohydrate
dibasic sodium phosphate, heptahydrate
water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for prolonged-release suspension for injection.
Each carton contains 4 single-dose kits:
1 single-dose kit contains:
1 vial of 2 mg exenatide
1 pre-filled syringe of 0.65 ml solvent
1 vial connector
2 injection needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet and user instructions before use.
Subcutaneous use.
BYDUREON must be injected immediately after suspension of the powder in the solvent.
Once weekly

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

If the box is open before first use, contact your pharmacist.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
The kit may be kept for up to 4 weeks below 30 ºC prior to use.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Grootslag 1-5, 3991 RA Houten
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/X/XX/XXX/XXX

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

BYDUREON

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

CARTON 3 x (4 single-dose kits) – with no blue box

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 2 mg exenatide

3. LIST OF EXCIPIENTS

Excipients:
Powder
poly (D,L-lactide-co-glycolide)
sucrose

Solvent
carmellose sodium
sodium chloride
polysorbate 20
monobasic sodium phosphate, monohydrate
dibasic sodium phosphate, heptahydrate
water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for prolonged-release suspension for injection.
Part of a multi-pack of 3 x (4 single dose kits). Do not sell separately.
Each carton contains 4 single-dose kits:
1 single-dose kit contains:
1 vial of 2 mg exenatide
1 pre-filled syringe of 0.65 ml solvent
1 vial connector
2 injection needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet and user instructions before use.
Subcutaneous use.
BYDUREON must be injected immediately after suspension of the powder in the solvent.
Once weekly

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

If the box is open before first use, contact your pharmacist.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
The kit may be kept for up to 4 weeks below 30 ºC prior to use.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Grootslag 1-5, 3991 RA Houten
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/X/XX/XXX/XXX

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

BYDUREON

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton multipack of 3 x (4 single-dose kits) - including the blue box

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 2 mg exenatide

3. LIST OF EXCIPIENTS

Excipients:
Powder
poly (D,L-lactide-co-glycolide)
sucrose

Solvent
carmellose sodium
sodium chloride
polysorbate 20
monobasic sodium phosphate, monohydrate
dibasic sodium phosphate, heptahydrate
water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for prolonged-release suspension for injection.
Multi-pack of 3 x (4 single dose kits). Do not sell separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet and user instructions before use.
Subcutaneous use.
BYDUREON must be injected immediately after suspension of the powder in the solvent.
Once weekly

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

If the box is open before first use, contact your pharmacist.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
The kit may be kept for up to 4 weeks below 30 ºC prior to use.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Grootslag 1-5, 3991 RA Houten
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/X/XX/XXX/XXX

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

BYDUREON

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

BYDUREON 2 mg powder for injection
exenatide
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 mg

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SOLVENT LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for BYDUREON

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.65 ml

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

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

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What BYDUREON is and what it is used for
2. Before you use BYDUREON
3. How to use BYDUREON
4. Possible side effects
5. How to store BYDUREON
6. Further information

1. WHAT BYDUREON IS AND WHAT IT IS USED FOR

BYDUREON is an injectable medicine used to improve blood sugar control in adults with type 2 diabetes mellitus.

BYDUREON is used in combination with the following diabetes medicines: metformin, sulphonylureas and thiazolidinediones. Your doctor is now prescribing BYDUREON as an additional medicine to help control your blood sugar. Continue to follow your food and exercise plan.

You have diabetes because your body does not make enough insulin to control the level of sugar in your blood or your body is not able to use the insulin properly. BYDUREON helps your body to increase the production of insulin when your blood sugar is high.

2. BEFORE YOU USE BYDUREON

Do not use BYDUREON

- If you are allergic (hypersensitive) to exenatide or any of the other ingredients of BYDUREON, listed in section 6.

Take special care with BYDUREON

- When using it in combination with a sulphonylurea, as low blood sugar (hypoglycaemia) can occur. Test your blood glucose levels regularly. Ask your doctor or pharmacist if you are not sure if any of your other medicines contain a sulphonylurea.
- BYDUREON should not be used if you have type 1 diabetes or diabetic ketoacidosis.
- BYDUREON should be injected into the skin and not into a vein or into the muscle.
- If you have severe problems with your stomach emptying (including gastroparesis) or food digestion, the use of BYDUREON is not recommended. BYDUREON slows stomach emptying so food passes more slowly through your stomach.
- Tell your doctor if you have ever had pancreatitis (see section 4).
- If you lose weight too quickly (more than 1.5 kg per week) talk to your doctor about it since this may not be good for you.

- There is little experience with BYDUREON in patients with kidney problems. The use of BYDUREON is not recommended if you have severe kidney disease or you are on dialysis.
- There is no experience with BYDUREON in children and adolescents less than 18 years and, therefore, use of BYDUREON is not recommended in this age group.

Using other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including warfarin and including medicines obtained without a prescription.

The use of BYDUREON with insulins, and other medicines that are used to treat type 2 diabetes that work like BYDUREON (for example:liraglutide and Byetta [exenatide twice daily]), is not recommended.

Using BYDUREON with food and drink

Use BYDUREON at any time of day, with or without meals.

Pregnancy and breast-feeding

Women of childbearing potential should use contraception during treatment with BYDUREON. It is not known if BYDUREON may harm your unborn child. Tell your doctor if you are, you think you might be, or are planning to become pregnant as BYDUREON should not be used during pregnancy and for at least three months before a pregnancy.

It is not known if BYDUREON passes into your milk. BYDUREON should not be used if breast-feeding.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

If you use BYDUREON in combination with a sulphonylurea, low blood sugar (hypoglycaemia) can occur. Hypoglycaemia may reduce your ability to concentrate. Please keep this possible problem in mind in all situations where you might put yourself and others at risk (e.g. driving a car or operating machines).

Important information about some of the ingredients of BYDUREON

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

3. HOW TO USE BYDUREON

Always use BYDUREON exactly as your doctor or diabetes nurse has told you. You should check with your doctor, diabetes nurse or pharmacist if you are unsure.

BYDUREON 2 mg should be injected once a week, at any time of day, with or without meals.

BYDUREON is injected into the skin (subcutaneous injection) of your stomach area (abdomen), upper leg (thigh), or the back of your upper arm.
Each week you can use the same area of your body. But be sure to choose a different injection site in that area.

Test your blood glucose levels regularly, it is particularly important to do this if you are also using a sulphonylurea.

Follow the Instructions for the User provided in the carton to inject BYDUREON

Your health care professional should teach you how to inject BYDUREON before you use it for the first time.

Check that the liquid in the syringe is clear and free of particles before you begin. After mixing use the suspension only if the mixture is white to off white and cloudy. If you see clumps of dry powder on the sides or bottom of the vial, the medicine is NOT mixed well. Shake vigorously again until well mixed.

BYDUREON should be injected immediately after mixing the powder and the solvent.

Use a new injection needle for each injection and dispose of it after each use.

If you are not sure you have taken the full dose of BYDUREON:

If you are not sure if you have taken all your dose, do not inject another dose of BYDUREON, just take it next week as planned.

If you use more BYDUREON than you should

If you use too much BYDUREON you may need medical treatment. Too much BYDUREON can cause nausea, vomiting, dizziness, or symptoms of low blood sugar (see section 4).

If you forget to use BYDUREON

You might like to choose a day that you always plan to make your BYDUREON injection. If you miss your injection that day, take your injection as soon as possible after you notice. For your next injection you can return to your chosen injection day as long as the next injection is at least one day (24 hours) later. You can also change your chosen injection day. Do not take two injections on the same day.

If you stop using BYDUREON

If you feel you should stop using BYDUREON please consult your doctor first. If you stop using BYDUREON this can affect your blood sugar levels.
If you have any further questions on the use of this medicine, ask your doctor, diabetes nurse or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, BYDUREON can have side effects although not everybody gets them.

The frequency of possible side effects listed below is defined using the following convention:
very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
very rare (affects less than 1 user in 10,000)
not known (frequency cannot be estimated from the available data).

Severe allergic reactions (anaphylaxis) have been reported very rarely in patients receiving a product that has the same active ingredient as BYDUREON.

You should see your doctor immediately if you experience symptoms such as
- Swollen face, tongue or throat
- Difficulty with swallowing

- Hives and difficulty with breathing

Cases of inflammation of the pancreas (pancreatitis) have been reported rarely in patients receiving a product that has the same active ingredient as BYDUREON. Pancreatitis can be a serious, potentially life-threatening medical condition.

- Tell your doctor if you have had pancreatitis, gallstones, alcoholism or very high triglycerides. These medical conditions can increase your chance of getting pancreatitis, or getting it again, whether or not you are taking BYDUREON.

- Call your doctor if you experience **severe and persistent** stomach pain, with or without vomiting, because you could have pancreatitis.

Very common side effects of BYDUREON:
- nausea, (nausea is most common when first starting BYDUREON, but decreases over time in most patients)
- vomiting
- diarrhoea or constipation
- injection site reactions

If you have an injection site reaction (redness, rash, or itching) you may like to ask your doctor for something to help relieve any signs or symptoms. You may see or feel a small bump under the skin after your injection; it should go away after 4 to 8 weeks. You should not need to stop your treatment.

- Hypoglycaemia

When BYDUREON is used with a medicine that contains a **sulphonylurea**, episodes of low blood sugar (hypoglycaemia, generally mild to moderate) can occur. The dose of your sulphonylurea medicine may need to be reduced while you use BYDUREON. The signs and symptoms of low blood sugar may include headache, drowsiness, weakness, dizziness, confusion, irritability, hunger, fast heartbeat, sweating, and feeling jittery. Your doctor should tell you how to treat low blood sugar.

Common side effects of BYDUREON:
- dizziness
- headache
- tiredness (fatigue)
- sleepiness
- pain in the stomach area
- bloating
- indigestion
- burping
- flatulence
- heartburn
- reduced appetite

BYDUREON may reduce your appetite, the amount of food you eat, and your weight.
If you lose weight too quickly (more than 1.5 kg per week) talk to your doctor about it since this may not be good for you.

In addition, some **other side effects** have been seen in patients using a product that has the same active ingredient as BYDUREON:

Common:
- sweating

Uncommon:
- unusual taste in the mouth

Rare:
- angioedema (swelling of the face and throat)

- hypersensitivity (rashes, itching and rapid swelling of the tissues of the neck, face, mouth or throat)
- decrease in kidney function
- dehydration, sometimes with a decrease in kidney function
- hair loss
- Changes in INR (measurement of blood thinning) have been reported when used together with warfarin.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE BYDUREON

Keep out of the reach and sight of children.

Do not use BYDUREON after the expiry date, which is stated on the label and the carton after EXP.

Store in a refrigerator. Do not freeze.
However, the kit may be kept for up to 4 weeks below 30 ºC prior to use.
Store in the original package in order to protect from light.
Throw away any BYDUREON kit that has been frozen.

Medicines should not be disposed of via waste water or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What BYDUREON contains:

- The active substance is exenatide. Each vial contains 2 mg of exenatide.
- The other ingredients are:
- In the powder: poly (D,L-lactide-co-glycolide) and sucrose.
- In the solvent: carmellose sodium, sodium chloride, polysorbate 20, monobasic sodium phosphate monohydrate, dibasic sodium phosphate heptahydrate and water for injections.

What BYDUREON looks like and contents of the pack:

Powder and solvent for prolonged-release suspension for injection.

The powder is white to off-white and the solvent is a clear, colourless to pale yellow to pale brown solution.

Each single-dose kit consists of one vial containing 2 mg exenatide powder, one pre-filled syringe containing 0.65 ml solvent, one vial connector, and two injection needles. One needle is a spare.

It is available in pack sizes of 4 single dose kits and 3 packs of 4 single-dose kits. Not all pack sizes may be marketed.

Marketing Authorisation Holder:
Eli Lilly Nederland B.V., Grootslag 1-5, NL-3991 RA Houten, The Netherlands.

Manufacturer:
Lilly Pharma Fertigung und Distribution GmbH & Co. KG, Teichweg 3, D - 35396 Giessen, Germany.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

Belgique/België/Belgien
Eli Lilly Benelux S.A/N.V.
Tél/Tel: +32-(0) 2 548 84 84

България
ТП "Ели Лили Недерланд" Б.В. - България
тел. + 359 2 491 41 40

Česká republika
Eli Lilly ČR, s.r.o.
Tel: + 420 234 664 111

Danmark
Eli Lilly Danmark A/S
Tlf: +45 45 26 60 00

Deutschland
Lilly Deutschland GmbH
Tel. + 49-(0) 6172 273 2222

Eesti
Eli Lilly Holdings Limited Eesti filiaal
Tel: +372 6 817 280

Ελλάδα
ΦΑΡΜΑΣΕΡΒ-ΛΙΛΛΥ Α.Ε.Β.Ε
Τηλ: +30 210 629 4600

España
Lilly S.A.
Tel: + 34 91 663 50 00

France
Lilly France SAS
Tél.: +33-(0)1 55 49 34 34

Ireland
Eli Lilly and Co. (Ireland) Limited,
Tel: +353-(0) 1 661 4377

Ísland
Icepharma hf.
Sími: + 354 540 8000

Italia
Eli Lilly Italia S.p.A.
Tel: + 39-055 42571

Luxembourg/Luxemburg
Eli Lilly Benelux S.A/N.V.
Tél/Tel: +32-(0) 2 548 84 84

Magyarország
Lilly Hungária Kft.
Tel: + 36 1 328 5100

Malta
Charles de Giorgio Ltd.
Tel: + 356 25600 500

Nederland
Eli Lilly Nederland B.V.
Tel: + 31-(0) 30 60 25 800

Norge
Eli Lilly Norge A.S
Tlf: + 47 22 88 18 00

Österreich
Eli Lilly Ges.m.b.H
Tel: +43-(0) 1 711 780

Polska
Eli Lilly Polska Sp. z o.o.
Tel.: +48 (0) 22 440 33 00

Portugal
Lilly Portugal - Produtos Farmacêuticos, Lda
Tel: +351 21 4126600

România
Eli Lilly România S.R.L.
Tel: + 40 21 4023000

Slovenija
Eli Lilly farmacevtska družba, d.o.o.
Tel: +386 (0)1 580 00 10

Slovenská republika
Eli Lilly Slovakia, s.r.o.
Tel: + 421 220 663 111

Suomi/Finland
Oy Eli Lilly Finland Ab
Puh/Tel: + 358-(0) 9 85 45 250

Κύπρος
Phadisco Ltd
Τηλ: +357 22 715000

Latvija
Eli Lilly Holdings Limited pārstāvniecība Latvijā
Tel: +371 67364000

Lietuva
Eli Lilly Holdings Limited atstovybė
Tel. +370 (5) 2649600

Sverige
Eli Lilly Sweden AB
Tel: +46 (0) 8 737 88 00

United Kingdom
Eli Lilly and Company Limited
Tel: +44-(0) 1256 315000

This leaflet was last approved in

Detailed information on this medicine is available on the website of the European Medicines Agency http://www.ema.europa.eu/

INSTRUCTIONS FOR THE USER

Your Step by Step Guide

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

If you have questions about taking BYDUREON

- Refer to the **Common Questions and Answers**

Helpful Hints

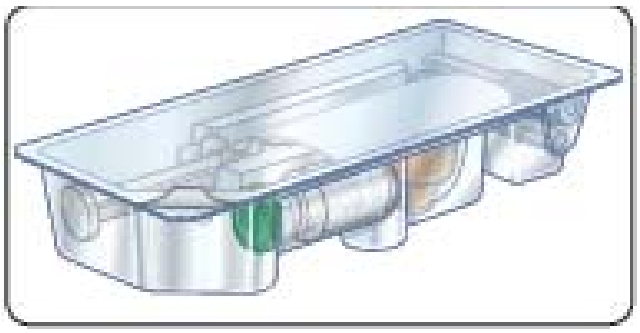
- Take your time.
- Follow these instructions step by step.
- You will need enough time to complete all the steps without stopping.
- You will probably need less time as you get used to giving yourself injections.

IMPORTANT:

Read and follow each step in these instructions carefully *every time* you take BYDUREON. Do not skip steps. Also read the *Package Leaflet* in your carton.

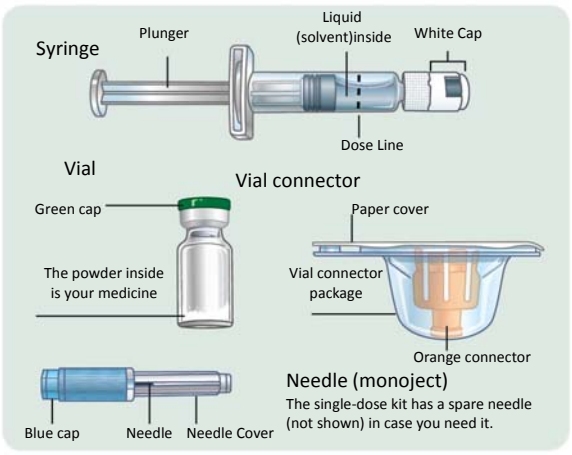
Your guide to the parts

- **Single-dose kit**



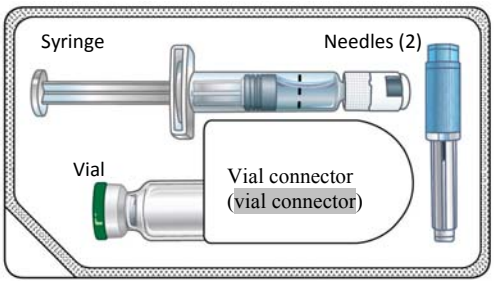
Lift here for a closer look at the parts

Keep this flap open so you can refer to it as you go through the steps



Your guide to the parts

Single-dose kit



What's inside

To take the correct dose, read <u>each</u> section so that you do <u>every</u> step in order.

This guide is divided into sections:

1 Getting started
2 Connecting the parts
3 Mixing the medicine and filling the syringe
4 Injecting the medicine
Common Questions and Answers.

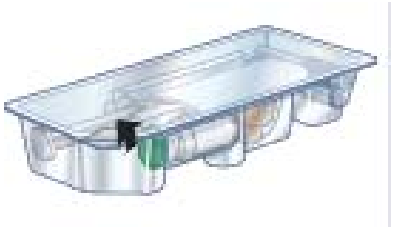
1. Getting Started

1a Take a single-dose kit from the refrigerator.

Prepare to safely dispose of used needles and syringes. Have what you need ready in order to safely dispose of used needles and syringes.

1b Wash your hands.

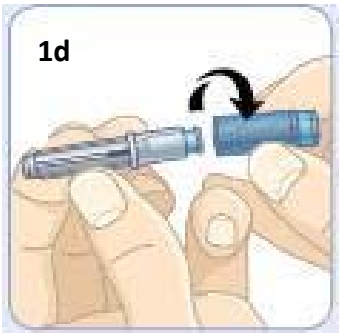
1c



Peel back the cover to open.

Remove the syringe. The liquid in the syringe should be clear and free of particles. It is okay if there are air bubbles.

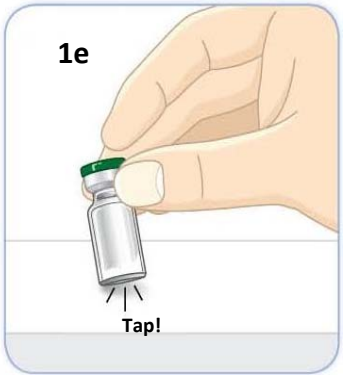
Place the needle, vial connector package, vial, and syringe on a clean, flat surface.



Pick up the needle, and <u>twist off</u> the blue cap.

Put the covered needle down. The needle is now prepared. You will need it later.

There is a spare needle in case you need it.



Pick up the vial.

Tap the vial several times against a hard surface to loosen the powder.

Use your thumb to remove the green cap.

Put the vial down.

2. Connecting the Parts

Pick up the vial connector package and peel off the paper cover. Do not touch the orange connector inside.

Hold the vial connector package.

In your other hand, hold the vial.

Press the top of the vial firmly into the orange connector.

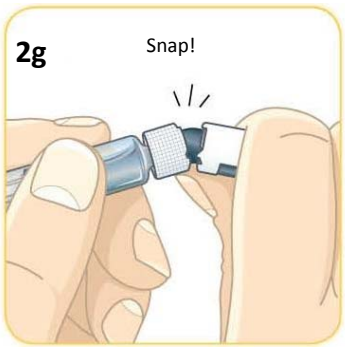
Lift the vial with the orange connector now attached out of its package.

This is what the vial should now look like.

Put it down for later.

Pick up the syringe.

With your other hand, firmly hold the 2 grey squares on the white cap.



<u>Break off the cap</u>

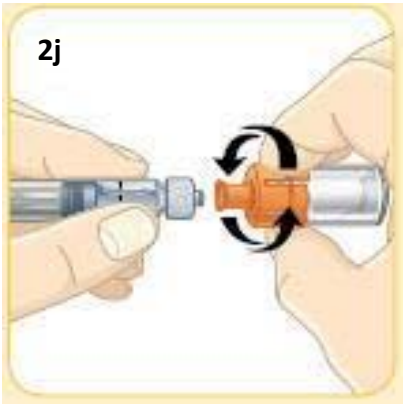
Be careful not to push in the plunger.

Just like you might break a stick, you are breaking off the cap.

This is what the broken-off cap looks like.

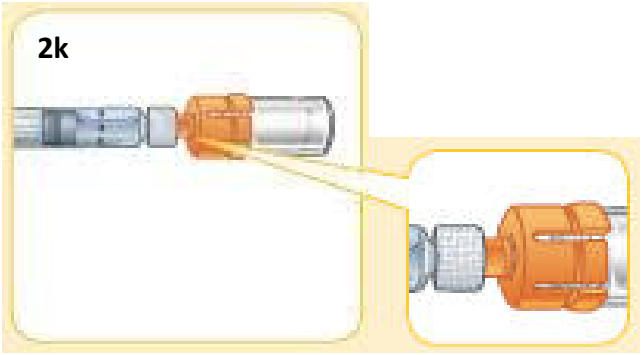
You will not need the cap and can throw it away.

This is what the syringe should now look like.



Now, pick up the vial with the orange connector attached.

Twist the orange connector onto the syringe until snug. While twisting, be sure to hold the orange connector. Do not over tighten. Be careful not to push in the plunger.

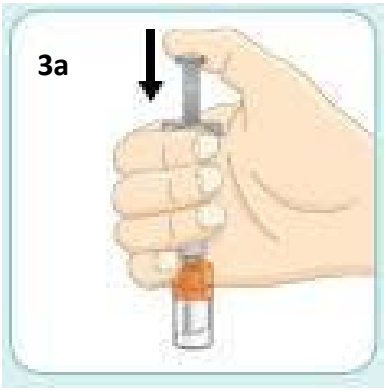


This is how the parts should now look when they are connected.

3. Mixing the Medicine and Filling the Syringe

IMPORTANT:

During these next steps, you will be mixing the medicine and filling the syringe. Once you mix the medicine, you must inject it immediately. You must not save the mixed medicine to inject at a later time.



With your thumb, push down the plunger until it stops and hold your thumb in place.

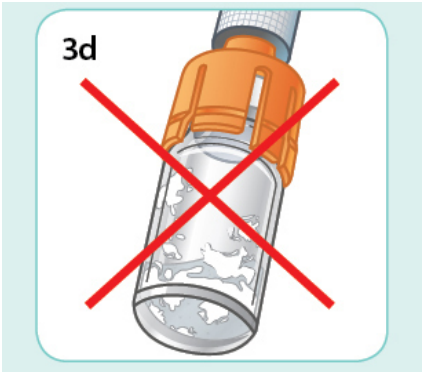
The plunger may feel like it is springing back a little.

Keep pushing down on the plunger with your thumb and <u>shake vigorously</u>. Keep shaking until the liquid and powder are mixed well.

Do not worry that the vial might come off. The orange connector will keep it attached to the syringe.

<u>Shake vigorously</u> like you would shake a bottle of oil-and-vinegar salad dressing.

When the medicine is mixed well, it should look cloudy.



If you see clumps of dry powder on the sides or bottom of the vial, the medicine is NOT mixed well.

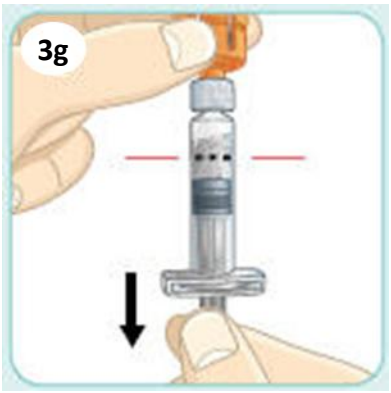
Shake vigorously again until well mixed.

Keep pushing on the plunger with your thumb while shaking.

Now, hold the vial so the syringe is pointing up. Keep pushing on the plunger with your thumb until it stops, and hold it in place.

<u>Gently</u> tap the vial with the other hand. Keep pushing on the plunger with your thumb to keep the plunger in place.

The tapping helps the medicine drip down along the sides of the vial. It is okay if there are air bubbles.

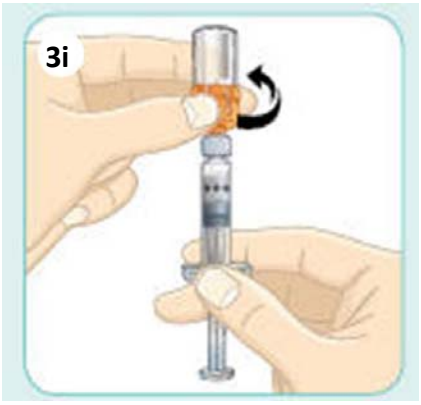


Pull the plunger down <u>beyond</u> the black dashed Dose Line.

This draws the medicine from the vial into the syringe. You may see air bubbles. This is normal.

A little bit of liquid may cling to the sides of the vial. This is also normal.

With one hand, hold the plunger in place so it does not move.



With the other hand, <u>twist</u> the <u>orange connector</u> to remove.

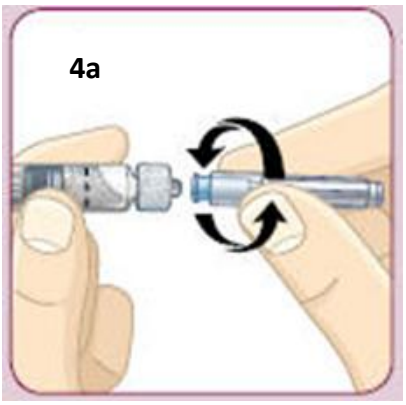
After removing the connector be careful not to push in the plunger.

This is what the syringe should now look like.

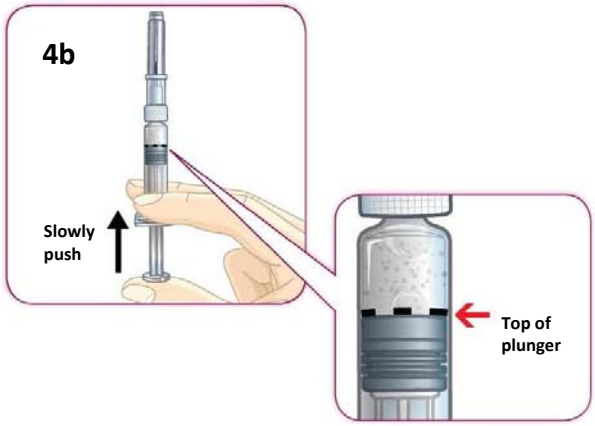
4. Injecting the Medicine

IMPORTANT:

Read the next steps carefully and look closely at the pictures.
This helps you get the correct dose of medicine.

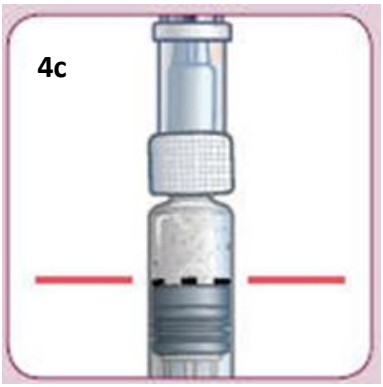


<u>Twist</u> the needle onto the syringe until snug. Do not remove the needle cover yet.
Be careful not to push in the plunger.



<u>Slowly</u> push in the plunger so the top of the plunger lines up with the black dashed Dose Line. Then, take your thumb off the plunger.

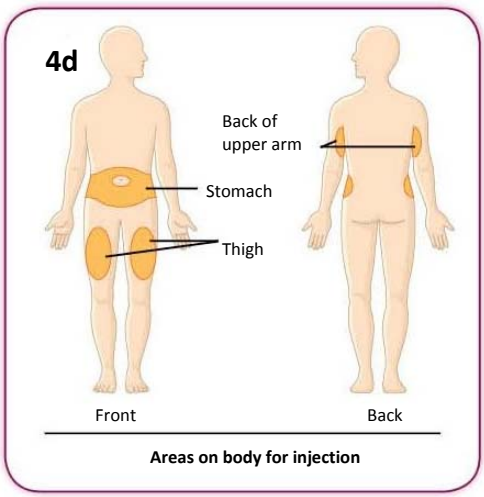
<u>It is important to stop pushing at this point, or you will waste your medicine and you will not get the correct dose.</u>



The top of the plunger must stay lined up with the black dashed Dose Line as you go through the next steps. This will help you get the correct dose of medicine.

IMPORTANT:

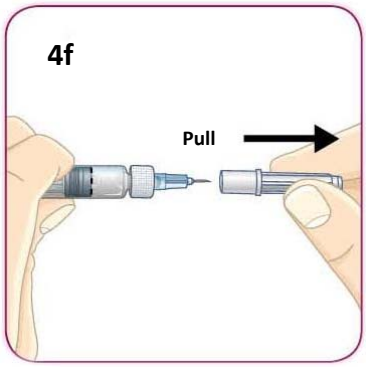
It is normal to see a few air bubbles in the mixture.
The air bubbles will not harm you or affect your dose.



You can inject each dose of the medicine in your stomach area (abdomen), your thigh, or the back of your upper arm.

Each week you can use the same area of your body. But be sure to choose a different injection site in that area.

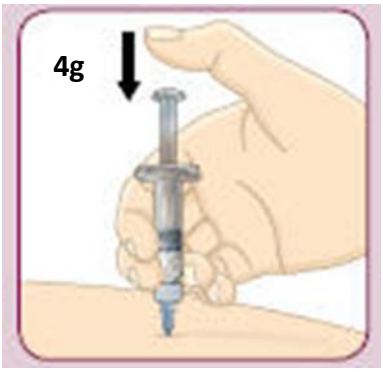
Hold the syringe near the black dashed Dose Line.



<u>Pull the needle cover straight off</u>.
Do not twist.

Be careful not to push in the plunger.

When you remove the cover, you may see 1 or 2 drops of liquid. This is normal.



Be sure to use the injection technique recommended by your healthcare professional.
Remember: You must take your injection of **BYDUREON** immediately after mixing it

Insert the needle into your skin (subcutaneously). To inject your full dose, push down on the plunger with your thumb until it stops.

Withdraw the needle.

Refer to the package leaflet (section 3) on what to do if you are not sure if you have received a complete dose.

4h. Put the cover back on the needle. Dispose of the syringe with the covered needle still attached as instructed by your healthcare professional.
You do not have to save any parts. Each single-dose kit has everything you need for your weekly dose of BYDUREON.

Medicines should not be disposed of via waste water or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

When it is time for your next weekly dose, start again at step 1.

Common Questions and Answers

If your question is about:	*See question number*:
How soon to inject after mixing	**1**
Mixing the medicine	**2**
Air bubbles in syringe	**3**
Attaching the needle	**4**
Removing the needle cover	**5**
Plunger not lining up with black dashed Dose Line	**6**
Being unable to push the plunger down when injecting	**7**

Common Questions and Answers

1. After I mix the medicine, how long can I wait before taking the injection?

You must take your injection of **BYDUREON** immediately after mixing it. If you do not inject **BYDUREON** immediately, the medicine will start to form small clumps in the syringe. These clumps could clog the needle when you take the injection (see question 7).

2. How do I know that the medicine is mixed well?

When the medicine is mixed well, it should look cloudy. There should not be any dry powder on the sides or bottom of the vial. If you do see any dry powder, shake vigorously while continuing to push

down on the plunger with your thumb. (This question relates to the steps shown on page X, Section 3a to 3d).

3. I'm ready to take the injection. What should I do if I see air bubbles in the syringe?

It is normal for air bubbles to be in the syringe. The air bubbles will not harm you or affect your dose. **BYDUREON** is injected into your skin (subcutaneously). Air bubbles are not a problem with this type of injection.

4. What should I do if I have trouble attaching the needle?

First, be sure you have removed the blue cap. Then, twist the needle onto the syringe until snug. To prevent losing medicine, do not push in the plunger while attaching the needle. For more information on injection techniques talk with your health care professional.
(This question relates to step 4a.)

5. What should I do if I have trouble removing the needle cover?

With one hand, hold the syringe near the black dashed Dose Line. With your other hand, hold the needle cover. Pull the needle cover straight off. Do not twist it. (This question relates to step 4f page X.)

6. I am at step 4c. What should I do if the top of the plunger has been pushed past the black dashed Dose Line?

The black dashed Dose Line shows the correct dose. If the top of the plunger has been pushed past the line, you should continue from step 4d and take the injection. Before your next injection in 1 week, carefully review the instructions for steps 3a to 4h.

7. When I inject, what should I do if I cannot push the plunger all the way down?

This means the needle has become clogged. Remove the needle and replace it with the spare needle from your kit. Then choose a different injection site and finish taking the injection.

To review how to:
- Remove the blue cap of the needle, see page X (step 1d)
- Attach the needle, see page X (step 4a)
- Remove the needle cover and give the injection, see page X (steps 4e to 4g)

If you still cannot push the plunger all the way down, withdraw the needle. Carefully put the needle cover back on the needle. Refer to the package leaflet (section 3) on what to do if you are not sure if you have received a complete dose.

To prevent a clogged needle, always mix the medicine very well, and inject immediately after mixing.

BYDUREON only needs to be taken once a week.

Make a note that you have taken your **BYDUREON** today and mark your calendar for when you are due for your next injection.

Where to learn more about BYDUREON

- **Talk with your healthcare professional**

Read the Package Leaflet carefully

Instructions for the User was last approved in