

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 the 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 immediate-release (Byetta) to prolonged-release (Bydureon) exenatide, may experience transient elevations in blood glucose concentrations, which generally improve within the first two weeks after initiation of therapy.

When prolonged-release exenatide is added to existing metformin and/or thiazolidinedione therapy, the current dose of metformin and/or thiazolidinedione can be continued. When prolonged-release exenatide 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).

Prolonged-release exenatide 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. Prolonged-release exenatide 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. For the next injection patients can return to their chosen injection day. However, only one injection should be taken in a 24-hour period.

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

If a different glucose-lowering treatment is started after the discontinuation of prolonged-release exenatide, consideration should be given to the prolonged release of the product (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).

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). Prolonged-release exenatide is not recommended in these patients.

Prolonged-release exenatide 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).

Hepatic impairment

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

Paediatric population

The safety and efficacy of prolonged-release exenatide in children and adolescents aged under 18 years have not yet been established. Currently available data are described in section 5.2 but no recommendation on a posology can be made.

Method of administration

Prolonged-release exenatide is for self-administration by the patient. Each kit should be used by one person only and is for single use.

Prior to initiation of prolonged-release exenatide, it is strongly recommended that patients and caregivers be trained by their healthcare professional. The "Instructions for the User", provided in the carton, must be followed carefully.

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 listed in section 6.1.

4.4 Special warnings and precautions for use

Prolonged-release exenatide should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Prolonged-release exenatide must not be administered by intravenous or intramuscular injection.

Renal impairment

In patients with end-stage renal disease receiving dialysis, single doses of immediate-release exenatide increased frequency and severity of gastrointestinal adverse reactions; therefore, prolonged-release exenatide 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 prolonged-release exenatide is not recommended.

There have been uncommon 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

Prolonged-release exenatide 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 prolonged-release exenatide is not recommended in patients with severe gastrointestinal disease.

Acute pancreatitis

Use of GLP-1 receptor agonists has been associated with a risk of developing acute pancreatitis. There have been spontaneously reported events of acute pancreatitis with prolonged-release exenatide. Resolution of pancreatitis has been observed with supportive treatment, but very rare cases of necrotising or haemorrhagic pancreatitis and/or death have been reported. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. If pancreatitis is suspected, prolonged-release exenatide should be discontinued; if acute pancreatitis is confirmed, prolonged-release exenatide should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Concomitant medicinal products

The concurrent use of prolonged-release exenatide 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 prolonged-release and immediate-release exenatide has not been studied and is not recommended.

Interaction with warfarin

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

Hypoglycaemia

The risk of hypoglycaemia was increased when prolonged-release exenatide 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. Patients with rapid weight loss should be monitored for signs and symptoms of cholelithiasis.

Discontinuation of treatment

After discontinuation, the effect of prolonged-release exenatide 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.

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

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).

Gastric emptying

The results of a study using paracetamol as a marker of gastric emptying suggest that the effect of prolonged-release exenatide 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 prolonged-release exenatide 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).

The following interaction studies have been conducted using 10 mcg immediate-release exenatide but not prolonged-release exenatide:

Warfarin

A delay in t_{max} of about 2 h was observed when warfarin was administered 35 min after immediate-release exenatide. No clinically relevant effects on C_{max} or AUC were observed. Increased INR has been spontaneously reported during concomitant use of warfarin and prolonged-release exenatide. INR should be monitored during initiation of prolonged-release exenatide therapy in patients on warfarin and/or coumarin derivatives (see sections 4.4 and 4.8).

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 immediate-release exenatide was administered concomitantly with a single dose of lovastatin (40 mg) compared with lovastatin administered alone. In 30-week placebo-controlled clinical trials with immediate-release exenatide, 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.

Digoxin and lisinopril

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

Ethinyl estradiol and levonorgestrel

Administration of a combination oral contraceptive (30 mcg ethinyl estradiol plus 150 mcg levonorgestrel) one hour before immediate-release exenatide 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.

Paediatric population

Interaction studies with exenatide have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

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

Breast-feeding

It is unknown whether exenatide is excreted in human milk. Prolonged-release exenatide 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

Prolonged-release exenatide has minor influence on the ability to drive and use machines. When prolonged-release exenatide 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 reactions were mainly gastrointestinal related (nausea which was the most frequent reaction and associated with the initiation of treatment and decreased over time, and diarrhoea). In addition, injection site reactions (pruritus, nodules, erythema), hypoglycaemia (with a sulphonylurea), and headache occurred. Most adverse reactions associated with prolonged-release exenatide were mild to moderate in intensity.

Since immediate-release exenatide has been marketed, acute pancreatitis has been reported with a frequency not known and acute renal failure has been reported uncommonly (see section 4.4).

Tabulated summary of adverse reactions

The frequency of adverse reactions of prolonged-release exenatide identified from clinical trials and spontaneous reports (not observed in clinical trials, frequency not known) are summarised in Table 1 below.

The exenatide clinical trials data source comprises 18 placebo-controlled trials, 21 active comparator and 2 open-label trials. Background therapies included diet and exercise, metformin, a sulphonylurea, a thiazolidinedione or a combination of oral glucose-lowering agents.

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

Table 1: Adverse reactions of prolonged-release exenatide identified from clinical trials and spontaneous reports

System organ class /adverse reaction terms	Frequency of occurrence					
	Very common	Common	Uncommon	Rare	Very rare	Not known
Immune system disorders						
Anaphylactic reaction				X ¹		
Metabolism and nutrition disorders						
Hypoglycaemia (with a sulphonylurea)	X ¹					
Decreased appetite		X ¹				
Dehydration			X ¹			
Nervous system disorders						
Headache		X ¹				
Dizziness		X ¹				
Dysgeusia			X ¹			
Somnolence			X ¹			
Gastrointestinal disorders						
Intestinal obstruction			X ¹			
Acute pancreatitis (see section 4.4)						X ²
Nausea	X ¹					
Vomiting		X ¹				
Diarrhoea	X ¹					
Dyspepsia		X ¹				
Abdominal pain		X ¹				
Gastroesophageal reflux disease		X ¹				
Abdominal distension		X ¹				
Eructation			X ¹			
Constipation		X ¹				
Flatulence		X ¹				
Skin and subcutaneous tissue disorders						
Macular and papular rash						X ²
Pruritus, and/ or urticaria		X ¹				
Angioneurotic oedema						X ²
Injection site abscesses and cellulitis						X ²
Hyperhidrosis			X ¹			
Alopecia			X ¹			
Renal and urinary disorders						
Altered renal function, including acute renal failure, worsened chronic renal failure, renal impairment, increased serum creatinine (see section 4.4).			X ¹			

System organ class /adverse reaction terms	Frequency of occurrence					
	Very common	Common	Uncommon	Rare	Very rare	Not known
General disorders and administration site conditions						
Injection site pruritus		X ¹				
Fatigue		X ¹				
Injection site erythema		X ¹				
Injection site rash			X ¹			
Asthenia		X ¹				
Feeling jittery				X ¹		
Investigations						
International normalised ratio increased (see section 4.4)						X ²

¹ Rate based on prolonged-release exenatide completed long-term efficacy and safety studies n=2868 total (patients on sulphonylurea n=1002).

² Rate based on prolonged-release exenatide spontaneous reports data (unknown denominator).

Description of selected adverse reactions

Hypoglycaemia

The incidence of hypoglycaemia was increased when prolonged-release exenatide was used in combination with a sulphonylurea (24.0 % versus 5.4 %) (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).

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

Across 11 studies of prolonged-release exenatide most episodes (99.9 % n=649) 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 prolonged-release exenatide, generally 20 % reported at least one episode of nausea compared to 34 % of immediate-release exenatide 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 prolonged-release exenatide treated patients, 5 % for immediate-release exenatide 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 prolonged-release exenatide treated patients and 1 % for immediate-release exenatide treated patients.

Injection site reactions

Injection site reactions were observed more frequently in prolonged-release exenatide 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. In postmarketing experiences, cases with injection site abscesses and cellulitis have been reported.

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 prolonged-release exenatide. 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 prolonged-release exenatide, 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 prolonged-release exenatide was absent at the end of the controlled period of studies; 2.6 % of patients showed no glucose improvement with higher titre antibodies whereas 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 prolonged-release exenatide 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 prolonged-release exenatide 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).

Increased heart rate

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Effects of overdoses with exenatide (based on immediate-release exenatide 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: Glucagon-like peptide-1 (GLP-1) analogues, ATC code: A10BJ01.

Mechanism of action

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

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

Glycaemic control

In two studies prolonged-release exenatide 2 mg once weekly has been compared to immediate-release exenatide 5 mcg given twice daily for 4 weeks followed by immediate-release exenatide 10 mcg given twice daily. 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 prolonged-release exenatide 2 mg once weekly, for a further 7 years (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).

Prolonged-release exenatide resulted in a statistically significant reduction in HbA_{1c} compared to patients receiving immediate-release exenatide (Table 2).

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

Clinically and statistically significantly more subjects on prolonged-release compared to immediate-release exenatide patients achieved an HbA_{1c} reduction of $\leq 7\%$ or $< 7\%$ in the two studies ($p < 0.05$ and $p \leq 0.0001$ respectively).

Both prolonged-release and immediate-release exenatide patients achieved a reduction in weight compared to baseline, although the difference between the two treatment arms was not significant.

In the uncontrolled study extension, evaluable patients who switched from immediate release to prolonged-release exenatide at week 30 (n=121), achieved the same improvement in HbA_{1c} of -2.0% at week 52 compared to baseline as patients treated with prolonged-release exenatide. For all patients completing the uncontrolled study extension of 7 years (n=122 of 243 patients included in the extension phase), HbA_{1c} gradually increased over time from week 52 onwards, but was still reduced compared to baseline after 7 years (-1.1%). Weight loss was sustained over 7 years in these patients.

Table 2: Results of two trials of prolonged-release versus immediate-release exenatide in combination with diet and exercise alone, metformin and/or sulphonylurea and metformin and/or thiazolidinedione (intent to treat patients)

24-Week Study	Prolonged-release exenatide 2 mg	Immediate-release exenatide 10 mcg twice daily
N	129	123
Mean HbA_{1c} (%)		
Baseline	8.5	8.4
Change from baseline (\pm 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) (\pm SE)	-1.4 (± 0.2)	-0.3 (± 0.2)
Mean body weight (kg)		
Baseline	97	94
Change from baseline (\pm 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 (\pm SE)	-1.9 (± 0.1)*	-1.5 (± 0.1)

24-Week Study	Prolonged-release exenatide 2 mg	Immediate-release exenatide 10 mcg twice daily
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 prolonged-release exenatide 2 mg is compared to insulin glargine once daily. Prolonged-release exenatide demonstrated a superior change in HbA_{1c} compared to insulin glargine. Compared with insulin glargine treatment, prolonged-release exenatide treatment significantly lowered mean body weight and was associated with fewer hypoglycaemic events (Table 3).

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

	Prolonged-release exenatide 2 mg	Insulin glargine¹
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} ≤ 7 %	62	54
Change in fasting serum glucose (mmol/l) (± SE)	-2.1 (± 0.2)	-2.8 (± 0.2)
Mean body weight (kg)		
Baseline	91	91
Change from baseline (± SE)	-2.6 (± 0.2)	+1.4 (±0.2)
Mean difference change from baseline between treatments (95 % CI)	-4.05 (-4.57, -3.52)*	

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

¹ Insulin glargine was dosed to a target glucose concentration of 4.0 to 5.5 mmol/l (72 to 100 mg/dl).

The mean dose of insulin glargine at the beginning of treatment was 10.1 IU/day rising to 31.1 IU/day for insulin glargine-treated patients.

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

In a 26-week double-blind study prolonged-release exenatide 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. Prolonged-release exenatide demonstrated superiority to both sitagliptin and pioglitazone with respect to change in HbA_{1c} from baseline.

Prolonged-release exenatide demonstrated significantly greater weight reductions compared to sitagliptin. Patients on pioglitazone gained weight (Table 4).

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

	Prolonged-release exenatide 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)	-1.6 (± 0.1)*	-0.9 (± 0.1)*	-1.2 (± 0.1)*
Mean difference change from baseline between treatments (95 % CI) versus sitagliptin	-0.63 (-0.89, -0.37)**		
Mean difference change from baseline between treatments (95 % CI) versus pioglitazone	-0.32 (-0.57, -0.06)*		
Patients (%) achieving HbA_{1c} ≤ 7 %	62	36	49
Change in fasting serum glucose (mmol/l) (± SE)	-1.8 (± 0.2)	-0.9 (± 0.2)	-1.5 (± 0.2)
Mean body weight (kg)			
Baseline	89	87	88
Change from baseline (± SE)	-2.3 (± 0.3)	-0.8 (± 0.3)	+2.8 (± 0.3)
Mean difference change from baseline between treatments (95 % CI) versus sitagliptin	-1.54 (-2.35, -0.72)*		
Mean difference change from baseline between treatments (95 % CI) versus pioglitazone	-5.10 (-5.91, -4.28)**		

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

Body weight

A reduction in body weight compared to baseline has been observed in all prolonged-release exenatide studies. This reduction in body weight was seen in patients treated with prolonged-release exenatide 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 prolonged-release exenatide 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 prolonged-release exenatide 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 prolonged-release exenatide studies (2.9 mmHg to 4.7 mmHg). In the 30-week immediate-release exenatide comparator study both

prolonged-release and immediate-release exenatide 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

Prolonged-release exenatide 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 prolonged-release exenatide 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 prolonged-release exenatide 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 prolonged-release exenatide, 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 prolonged-release exenatide therapy, mean plasma exenatide concentrations fell below minimal detectable concentrations.

Special populations

Renal impairment

Population pharmacokinetic analysis of renal impaired patients receiving 2 mg prolonged-release exenatide 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.

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 immediate-release exenatide in patients with type 2 diabetes, administration of exenatide (10 mcg) resulted in a mean increase of exenatide AUC by 36 % in 15 elderly subjects aged 75 to 85 years compared to 15 subjects aged 45 to 65 years likely related to reduced renal function in the older age group (see section 4.2).

Paediatric population

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

In a 104-week carcinogenicity study with prolonged-release exenatide a statistically significant increase in thyroid C-cell tumour incidence (adenomas and / or carcinomas) was observed in rats at all doses (1.4- to 26-fold the human clinical exposure with prolonged-release exenatide). 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
sodium dihydrogen phosphate monohydrate
disodium 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

3 years

After suspension

The suspension must be injected immediately after mixing the powder and the solvent.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze.

The kit may be kept for up to 4 weeks below 30°C prior to use.
Store in the original package in order to protect from light.
For storage conditions after mixing of the medicinal product, see section 6.3.

6.5 Nature and contents of container

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

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

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

Pack size of 4 single-dose kits and a multipack consisting of 12 (3 packs of 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 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, the mixture should only be used if it is white to off white and cloudy.

Prolonged-release exenatide must be injected immediately after suspension of the powder in the solvent.

Prolonged-release exenatide 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

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/696/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 June 2011
Date of latest renewal: 18 Feb 2016

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>

1. NAME OF THE MEDICINAL PRODUCT

Bydureon 2 mg powder and solvent for prolonged-release suspension for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the 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 immediate-release (Byetta) to prolonged-release exenatide may experience transient elevations in blood glucose concentrations, which generally improve within the first two weeks after initiation of therapy.

When prolonged-release exenatide is added to existing metformin and/or thiazolidinedione therapy, the current dose of metformin and/or thiazolidinedione can be continued. When prolonged-release exenatide 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).

Prolonged-release exenatide 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. Prolonged-release exenatide 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. For the next injection patients can return to their chosen injection day. However, only one injection should be taken in a 24-hour period.

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

If a different glucose-lowering treatment is started after the discontinuation of prolonged-release exenatide, consideration should be given to the prolonged release of the product (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).

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). Prolonged-release exenatide is not recommended in these patients.

Prolonged-release exenatide 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).

Hepatic impairment

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

Paediatric population

The safety and efficacy of prolonged-release exenatide in children and adolescents aged under 18 years have not yet been established. Currently available data are described in section 5.2 but no recommendation on a posology can be made.

Method of administration

Prolonged-release exenatide is for self-administration by the patient. Each pen should be used by one person only and is for single use.

Prior to initiation of prolonged-release exenatide, it is strongly recommended that patients and caregivers be trained by their healthcare professional. The "Instructions for the User", provided in the carton, must be followed carefully.

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 listed in section 6.1.

4.4 Special warnings and precautions for use

Prolonged-release exenatide should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Prolonged-release exenatide must not be administered by intravenous or intramuscular injection.

Renal impairment

In patients with end-stage renal disease receiving dialysis, single doses of immediate-release exenatide increased frequency and severity of gastrointestinal adverse reactions; therefore, prolonged-release exenatide 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 prolonged-release exenatide is not recommended.

There have been uncommon 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

Prolonged-release exenatide 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 prolonged-release exenatide is not recommended in patients with severe gastrointestinal disease.

Acute pancreatitis

Use of GLP-1 receptor agonists has been associated with a risk of developing acute pancreatitis. There have been spontaneously reported events of acute pancreatitis with prolonged-release exenatide. Resolution of pancreatitis has been observed with supportive treatment, but very rare cases of necrotising or haemorrhagic pancreatitis and/or death have been reported. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. If pancreatitis is suspected, prolonged-release exenatide should be discontinued; if acute pancreatitis is confirmed, prolonged-release exenatide should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Concomitant medicinal products

The concurrent use of prolonged-release exenatide 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 prolonged-release exenatide and immediate-release exenatide has not been studied and is not recommended.

Interaction with warfarin

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

Hypoglycaemia

The risk of hypoglycaemia was increased when prolonged-release exenatide 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. Patients with rapid weight loss should be monitored for signs and symptoms of cholelithiasis.

Discontinuation of treatment

After discontinuation, the effect of prolonged-release exenatide 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.

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

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).

Gastric emptying

The results of a study using paracetamol as a marker of gastric emptying suggest that the effect of prolonged-release exenatide 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 prolonged-release exenatide 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).

The following interaction studies have been conducted using 10 mcg immediate-release exenatide but not prolonged-release exenatide:

Warfarin

A delay in t_{\max} of about 2 h was observed when warfarin was administered 35 min after immediate-release exenatide. No clinically relevant effects on C_{\max} or AUC were observed. Increased INR has been spontaneously reported during concomitant use of warfarin and prolonged-release exenatide. INR should be monitored during initiation of prolonged-release exenatide therapy in patients on warfarin and/or coumarin derivatives (see sections 4.4 and 4.8).

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 immediate-release exenatide was administered concomitantly with a single dose of lovastatin (40 mg) compared with lovastatin administered alone. In 30-week placebo-controlled clinical trials with immediate-release exenatide, 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.

Digoxin and lisinopril

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

Ethinyl estradiol and levonorgestrel

Administration of a combination oral contraceptive (30 mcg ethinyl estradiol plus 150 mcg levonorgestrel) one hour before immediate-release exenatide 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.

Paediatric population

Interaction studies with exenatide have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

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

Breast-feeding

It is unknown whether exenatide is excreted in human milk. Prolonged-release exenatide 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

Prolonged-release exenatide has minor influence on the ability to drive and use machines. When prolonged-release exenatide 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 reactions were mainly gastrointestinal related (nausea which was the most frequent reaction and associated with the initiation of treatment and decreased over time, and diarrhoea). In addition, injection site reactions (pruritus, nodules, erythema), hypoglycaemia (with a sulphonylurea), and headache occurred. Most adverse reactions associated with prolonged-release exenatide were mild to moderate in intensity.

Since immediate-release exenatide has been marketed, acute pancreatitis has been reported with a frequency not known and acute renal failure has been reported uncommonly (see section 4.4).

Tabulated summary of adverse reactions

The frequency of adverse reactions of prolonged-release exenatide identified from clinical trials and spontaneous reports (not observed in clinical trials, frequency not known) are summarised in Table 1 below.

The exenatide clinical trials data source comprises 18 placebo-controlled trials, 21 active comparator and 2 open-label trials. Background therapies included diet and exercise, metformin, a sulphonylurea, a thiazolidinedione or a combination of oral glucose-lowering agents.

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

Table 1: Adverse reactions of prolonged-release exenatide identified from clinical trials and spontaneous reports

System organ class /adverse reaction terms	Frequency of occurrence					
	Very common	Common	Uncommon	Rare	Very rare	Not known
Immune system disorders						
Anaphylactic reaction				X ¹		
Metabolism and nutrition disorders						
Hypoglycaemia (with a sulphonylurea)	X ¹					
Decreased appetite		X ¹				
Dehydration			X ¹			
Nervous system disorders						
Headache		X ¹				
Dizziness		X ¹				
Dysgeusia			X ¹			
Somnolence			X ¹			
Gastrointestinal disorders						
Intestinal obstruction			X ¹			
Acute pancreatitis (see section 4.4)						X ²
Nausea	X ¹					
Vomiting		X ¹				
Diarrhoea	X ¹					
Dyspepsia		X ¹				
Abdominal pain		X ¹				
Gastroesophageal reflux disease		X ¹				
Abdominal distension		X ¹				
Eructation			X ¹			
Constipation		X ¹				
Flatulence		X ¹				
Skin and subcutaneous tissue disorders						
Macular and papular rash						X ²
Pruritus, and/ or urticaria		X ¹				
Angioneurotic oedema						X ²
Injection site abscesses and cellulitis						X ²
Hyperhidrosis			X ¹			
Alopecia			X ¹			
Renal and urinary disorders						
Altered renal function, including acute renal failure, worsened chronic renal failure, renal impairment, increased serum creatinine (see section 4.4).			X ¹			

System organ class /adverse reaction terms	Frequency of occurrence					
	Very common	Common	Uncommon	Rare	Very rare	Not known
General disorders and administration site conditions						
Injection site pruritus		X ¹				
Fatigue		X ¹				
Injection site erythema		X ¹				
Injection site rash			X ¹			
Asthenia		X ¹				
Feeling jittery				X ¹		
Investigations						
International normalised ratio increased (see section 4.4)						X ²

¹ Rate based on prolonged-release exenatide completed long-term efficacy and safety studies n=2868 total (patients on sulphonylurea n=1002).

² Rate based on prolonged-release exenatide spontaneous reports data (unknown denominator).

Description of selected adverse reactions

Hypoglycaemia

The incidence of hypoglycaemia was increased when prolonged-release exenatide was used in combination with a sulphonylurea (24.0 % versus 5.4 %) (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).

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

Across 11 studies of prolonged-release exenatide most episodes (99.9 % n=649) 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 prolonged-release exenatide, generally 20 % reported at least one episode of nausea compared to 34 % of immediate-release exenatide 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 prolonged-release exenatide treated patients, 5 % for immediate-release exenatide 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 prolonged-release exenatide treated patients and 1 % for immediate-release exenatide treated patients.

Injection site reactions

Injection site reactions were observed more frequently in prolonged-release exenatide 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. In postmarketing experiences, cases with injection site abscesses and cellulitis have been reported.

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 prolonged-release exenatide. 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 prolonged-release exenatide, 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 prolonged-release exenatide was absent at the end of the controlled period of studies; 2.6 % of patients showed no glucose improvement with higher titre antibodies whereas 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 prolonged-release exenatide 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 prolonged-release exenatide 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).

Increased heart rate

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Effects of overdoses with exenatide (based on immediate-release exenatide 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: Glucagon-like peptide-1 (GLP-1) analogues, ATC code: A10BJ01.

Mechanism of action

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

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

Glycaemic control

In two studies prolonged-release exenatide 2 mg once weekly has been compared to immediate-release exenatide 5 mcg given twice daily for 4 weeks followed by immediate-release exenatide 10 mcg given twice daily. 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 prolonged-release exenatide 2 mg once weekly for a further 7 years (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).

Prolonged-release exenatide resulted in a statistically significant reduction in HbA_{1c} compared to patients receiving immediate-release exenatide (Table 2).

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

Clinically and statistically significantly more subjects on prolonged-release compared to immediate-release exenatide patients achieved an HbA_{1c} reduction of $\leq 7\%$ or $< 7\%$ in the two studies ($p < 0.05$ and $p \leq 0.0001$ respectively).

Both prolonged-release and immediate-release exenatide patients achieved a reduction in weight compared to baseline, although the difference between the two treatment arms was not significant.

In the uncontrolled study extension, evaluable patients who switched from immediate release to prolonged-release exenatide at week 30 (n=121), achieved the same improvement in HbA_{1c} of -2.0% at week 52 compared to baseline as patients treated with prolonged-release exenatide. For all patients completing the uncontrolled study extension of 7 years (n=122 of 243 patients included in the extension phase), HbA_{1c} gradually increased over time from week 52 onwards, but was still reduced compared to baseline after 7 years (-1.1%). Weight loss was sustained over 7 years in these patients.

Table 2: Results of two trials of prolonged-release versus immediate-release exenatide in combination with diet and exercise alone, metformin and/or sulphonylurea and metformin and/or thiazolidinedione (intent to treat patients)

24-Week Study	Prolonged-release exenatide 2 mg	Immediate-release exenatide 10 mcg twice daily
N	129	123
Mean HbA_{1c} (%)		
Baseline	8.5	8.4
Change from baseline (\pm 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) (\pm SE)	-1.4 (± 0.2)	-0.3 (± 0.2)
Mean body weight (kg)		
Baseline	97	94
Change from baseline (\pm 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 (\pm SE)	-1.9 (± 0.1)*	-1.5 (± 0.1)

24-Week Study	Prolonged-release exenatide 2 mg	Immediate-release exenatide 10 mcg twice daily
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 prolonged-release exenatide 2 mg is compared to insulin glargine once daily. Prolonged-release exenatide demonstrated a superior change in HbA_{1c} compared to insulin glargine. Compared with insulin glargine treatment, prolonged-release exenatide treatment significantly lowered mean body weight and was associated with fewer hypoglycaemic events (Table 3).

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

	Prolonged-release exenatide 2 mg	Insulin glargine¹
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} ≤ 7 %	62	54
Change in fasting serum glucose (mmol/l) (± SE)	-2.1 (± 0.2)	-2.8 (± 0.2)
Mean body weight (kg)		
Baseline	91	91
Change from baseline (± SE)	-2.6 (± 0.2)	+1.4 (±0.2)
Mean difference change from baseline between treatments (95 % CI)	-4.05 (-4.57, -3.52)*	

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

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

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

In a 26-week double-blind study prolonged-release exenatide 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. Prolonged-release exenatide demonstrated superiority to both sitagliptin and pioglitazone with respect to change in HbA_{1c} from baseline.

Prolonged-release exenatide demonstrated significantly greater weight reductions compared to sitagliptin. Patients on pioglitazone gained weight (Table 4).

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

	Prolonged-release exenatide 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)	-1.6 (± 0.1)*	-0.9 (± 0.1)*	-1.2 (± 0.1)*
Mean difference change from baseline between treatments (95 % CI) versus sitagliptin	-0.63 (-0.89, -0.37)**		
Mean difference change from baseline between treatments (95 % CI) versus pioglitazone	-0.32 (-0.57, -0.06)*		
Patients (%) achieving HbA_{1c} ≤ 7 %	62	36	49
Change in fasting serum glucose (mmol/l) (± SE)	-1.8 (± 0.2)	-0.9 (± 0.2)	-1.5 (± 0.2)
Mean body weight (kg)			
Baseline	89	87	88
Change from baseline (± SE)	-2.3 (± 0.3)	-0.8 (± 0.3)	+2.8 (± 0.3)
Mean difference change from baseline between treatments (95 % CI) versus sitagliptin	-1.54 (-2.35, -0.72)*		
Mean difference change from baseline between treatments (95 % CI) versus pioglitazone	-5.10 (-5.91, -4.28)**		

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

Body weight

A reduction in body weight compared to baseline has been observed in all prolonged-release exenatide studies. This reduction in body weight was seen in patients treated with prolonged-release exenatide 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 prolonged-release exenatide 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 prolonged-release exenatide 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 prolonged-release exenatide studies (2.9 mmHg to 4.7 mmHg). In the 30-week immediate-release exenatide comparator study both

prolonged-release and immediate-release exenatide 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

Prolonged-release exenatide 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 prolonged-release exenatide 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 prolonged-release exenatide 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 prolonged-release exenatide, 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 prolonged-release exenatide therapy, mean plasma exenatide concentrations fell below minimal detectable concentrations.

Special populations

Renal impairment

Population pharmacokinetic analysis of renal impaired patients receiving 2 mg prolonged-release exenatide 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.

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 immediate-release exenatide in patients with type 2 diabetes, administration of exenatide (10 mcg) resulted in a mean increase of exenatide AUC by 36 % in 15 elderly subjects aged 75 to 85 years compared to 15 subjects aged 45 to 65 years likely related to reduced renal function in the older age group (see section 4.2).

Paediatric population

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

In a 104-week carcinogenicity study with prolonged-release exenatide a statistically significant increase in thyroid C-cell tumour incidence (adenomas and / or carcinomas) was observed in rats at all doses (1.4- to 26- fold the human clinical exposure with prolonged-release exenatide). 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
sodium dihydrogen phosphate monohydrate
disodium phosphate heptahydrate
water for injections
sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

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

6.3 Shelf life

3 years

After suspension

The suspension must be injected immediately after mixing the powder and the solvent.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze.

The pens may be kept for up to 4 weeks below 30°C prior to use. At the end of this period the pens must be used or discarded.

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

For storage conditions after mixing of the medicinal product, see section 6.3.

6.5 Nature and contents of container

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

Pack size of 4 single-dose pre-filled pens and a multipack containing 12 (3 packs of 4) single-dose pre-filled pens.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Pre-filled pen is for single-use only.

The powder in one chamber must be mixed with the solvent in the other chamber of the pre-filled pen. The solvent should be visually inspected prior to use. The solvent should only be used if it is clear and free of particulate matter. After suspension, the mixture should only be used if it is white to off white and cloudy. Please see the package leaflet and "Instructions for the User" for additional information on suspension and administration.

Use only the supplied custom needles with the pen.

Prolonged-release exenatide must be injected subcutaneously immediately after mixing of the powder and the solvent.

Prolonged-release exenatide that has been frozen must not be used.

The patient should be instructed to discard the pen safely, with the needle still attached, after each injection.

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

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/696/003-004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 June 2011

Date of latest renewal: 18 Feb 2016

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. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

AstraZeneca UK Limited
Silk Road Business Park,
Macclesfield, Cheshire, SK10 2NA
United Kingdom

Swords Laboratories T/A Lawrence Laboratories
Unit 12 Distribution Centre, Shannon Industrial Estate, Shannon, Co. Clare
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines webportal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

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

sodium dihydrogen phosphate monohydrate

disodium 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 before use.

Follow the Instructions for the User to prepare and inject your dose.

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 SIGHT AND REACH OF CHILDREN
--

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY
--

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°C 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

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/11/696/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

bydureon

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA
--

PC:

SN:

NN:

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING

INNER CARTON, MULTIPACK OF 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

sodium dihydrogen phosphate monohydrate

disodium 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 before use.

Follow the Instructions for the User to prepare and inject your dose.

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 SIGHT AND REACH OF CHILDREN
--

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY
--

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°C 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

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/11/696/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

bydureon

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA
--

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

sodium dihydrogen phosphate monohydrate

disodium 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 before use.

Follow the Instructions for the User to prepare and inject your dose.

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 SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**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°C 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**

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/696/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

bydureon

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

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

AstraZeneca AB

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

AstraZeneca AB

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARTON (PACK OF 4 SINGLE-DOSE PRE-FILLED PENS)****1. NAME OF THE MEDICINAL PRODUCT**

Bydureon 2 mg powder and solvent for prolonged-release suspension for injection in pre-filled pen
exenatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 2 mg exenatide. After suspension, the delivered dose is 2 mg/0.65 ml.

3. LIST OF EXCIPIENTS

Excipients:

Powder

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

sucrose

Solvent:

carmellose sodium

sodium chloride

polysorbate 20

sodium dihydrogen phosphate monohydrate

disodium phosphate heptahydrate

water for injections

sodium hydroxide

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for prolonged-release suspension for injection.

4 single-dose pre-filled pens

1 spare injection needle

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Follow the Instructions for the User to prepare and inject your dose.

Subcutaneous use

For single-use only

Bydureon must be injected immediately after mixing.

Once weekly

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

The pre-filled pens may be kept for up to 4 weeks below 30°C 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**

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/696/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

bydureon

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**INNER CARTON MULTIPACK OF 3 X (4 SINGLE-DOSE PRE-FILLED PENS) – WITH NO BLUE BOX****1. NAME OF THE MEDICINAL PRODUCT**

Bydureon 2 mg powder and solvent for prolonged-release suspension for injection in pre-filled pen exenatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 2 mg exenatide. After suspension, the delivered dose is 2 mg/0.65 ml.

3. LIST OF EXCIPIENTS

Excipients:

Powder

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

sucrose

Solvent:

carmellose sodium

sodium chloride

polysorbate 20

sodium dihydrogen phosphate monohydrate

disodium phosphate heptahydrate

water for injections

sodium hydroxide

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for prolonged-release suspension for injection.

4 single-dose pre-filled pens. Component of a multipack, can't be sold separately.

1 spare injection needle

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Follow the Instructions for the User to prepare and inject your dose.

Subcutaneous use

For single-use only

Bydureon must be injected immediately after mixing.

Once weekly

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY
--

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

The pre-filled pens may be kept for up to 4 weeks below 30°C 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

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/11/696/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

bydureon

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA
--

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON MULTIPACK OF 3 X (4 SINGLE-DOSE PRE-FILLED PENS) - INCLUDING THE BLUE BOX****1. NAME OF THE MEDICINAL PRODUCT**

Bydureon 2 mg powder and solvent for prolonged-release suspension for injection in pre-filled pen
exenatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 2 mg exenatide. After suspension, the delivered dose is 2 mg/0.65 ml

3. LIST OF EXCIPIENTS

Excipients:

Powder

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

sucrose

Solvent:

carmellose sodium

sodium chloride

polysorbate 20

sodium dihydrogen phosphate monohydrate

disodium phosphate heptahydrate

water for injections

sodium hydroxide

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for prolonged-release suspension for injection

Multipack: 12 (3 packs of 4) single-dose pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Follow the Instructions for the User to prepare and inject your dose.

Subcutaneous use

For single-use only

Bydureon must be injected immediately after mixing.

Once weekly

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

The pre-filled pens may be kept for up to 4 weeks below 30 °C 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**

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/696/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

bydureon

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS PEN GRIP LABEL
--

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

Bydureon 2 mg powder and solvent for prolonged-release suspension 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

AstraZeneca AB

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 because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or diabetes nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist, or diabetes nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Bydureon is and what it is used for
2. What you need to know before you use Bydureon
3. How to use Bydureon
4. Possible side effects
5. How to store Bydureon
6. Contents of the pack and other information

1. What Bydureon is and what it is used for

Bydureon contains the active substance exenatide. It is an injectable medicine used to improve blood sugar control in adults with type 2 diabetes mellitus.

This medicine is used in combination with the following diabetes medicines: metformin, sulphonylureas and thiazolidinediones. Your doctor is now prescribing this medicine 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. The active substance in this medicine helps your body to increase the production of insulin when your blood sugar is high.

2. What you need to know before you use Bydureon

Do not use Bydureon:

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

Warnings and precautions

Talk to your doctor, pharmacist, or diabetes nurse before using Bydureon about the following:

- Using this medicine in combination with a sulphonylurea, as low blood sugar (hypoglycaemia) can occur. Test your blood glucose levels regularly. Ask your doctor, pharmacist, or diabetes nurse if you are not sure if any of your other medicines contain a sulphonylurea.
- If you have type 1 diabetes or diabetic ketoacidosis, as this medicine should not be used.
- How to inject this medicine. It 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, as the use of this medicine is not recommended. The active substance in this medicine slows stomach emptying so food passes more slowly through your stomach.

- If you have ever had inflammation of the pancreas (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 cause problems such as gallstones.
- If you have severe kidney disease or you are on dialysis, as the use of this medicine is not recommended. There is little experience with this medicine in patients with kidney problems.

Children and adolescents

Do not give this medicine to children and adolescents less than 18 years, as there is no experience with this medicine in this age group.

Other medicines and Bydureon

Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines, particularly:

- medicines that are used to treat type 2 diabetes, such as insulins and other medicines that work like Bydureon (e.g. liraglutide and Byetta [immediate-release exenatide]), as taking these medicines with Bydureon is not recommended.
- medicines used to thin the blood (anticoagulants), e.g. Warfarin, as you will require additional monitoring of changes in INR (measurement of blood thinning) during initiation of therapy with this medicine.

Pregnancy and breast-feeding

It is not known if this medicine may harm your unborn child, therefore you should not use it during pregnancy and for at least 3 months before a planned pregnancy.

It is not known if exenatide passes into your milk. You should not use this medicine while breast-feeding.

If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

You should use contraception if you could potentially become pregnant during treatment with this medicine.

Driving and using machines

If you use this medicine 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 using 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 this medicine exactly as your doctor, pharmacist, or diabetes nurse has told you. Check with your doctor, pharmacist, or diabetes nurse if you are not sure.

You should inject this medicine once a week, at any time of day, with or without meals.

You should inject this medicine 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. 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 doctor or diabetes nurse should teach you how to inject this medicine 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.

You should inject this medicine immediately after mixing the powder and the solvent.

Use a new injection needle for each injection and dispose of it safely after each use as instructed by your doctor or diabetes nurse.

If you use more Bydureon than you should

If you use more of this medicine than you should, you may need medical treatment. Using too much of this medicine 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 a dose it should be taken as soon as it is possible to do so. For your next injection you can return to your chosen injection day. However, only one injection should be taken in a 24-hour period. You can also change your chosen injection day. Do not take two injections on the same day.

If you are not sure you have taken the full dose of Bydureon

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

If you stop using Bydureon

If you feel you should stop using this medicine, please consult your doctor first. If you stop using this medicine this can affect your blood sugar levels.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist, or diabetes nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Severe allergic reactions (anaphylaxis) have been reported rarely (may affect up to 1 in 1000 people).

You should see your doctor immediately if you experience symptoms such as

- Swelling of the face, tongue or throat (angioedema)
- Hypersensitivity (rashes, itching and rapid swelling of the tissues of the neck, face, mouth or throat)
- Difficulty with swallowing
- Hives and difficulty with breathing

Cases of inflammation of the pancreas (pancreatitis) have been reported (frequency not known) in patients receiving this medicine. 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 the risk of getting pancreatitis, or getting it again, whether or not you are taking this medicine.
- STOP taking this medicine and contact your doctor immediately if you experience **severe and persistent** stomach pain, with or without vomiting, because you could have an inflamed pancreas (pancreatitis).

Very common side effects of Bydureon (may affect more than 1 in 10 people):

- nausea (nausea is most common when first starting this medicine, but decreases over time in most patients)
- diarrhoea
- hypoglycaemia

When this medicine 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 this medicine. 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 (may affect up to 1 in 10 people):

- dizziness
- headache
- vomiting
- loss of energy and strength
- tiredness (fatigue)
- constipation
- pain in the stomach area
- bloating
- indigestion
- flatulence (passing gas)
- heartburn
- reduced appetite

This medicine 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 cause problems such as gallstones.

- 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.

Uncommon side effects of Bydureon (may affect up to 1 in 100 people):

- decrease in kidney function
- dehydration, sometimes with a decrease in kidney function
- intestinal obstruction (blockage in intestine)
- burping
- unusual taste in the mouth
- increased sweating
- hair loss
- sleepiness

Rare side effects of Bydureon (may affect up to 1 in 1,000 people):

- feeling jittery

In addition some **other side effects** have been reported (frequency not known, cannot be estimated from the available data).

- changes in INR (measurement of blood thinning) have been reported when used together with warfarin
- skin reactions at the injection site following injection of exenatide. These include: cavity containing pus (abscess) and swollen, or red area of skin that feels hot and tender (cellulitis).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or diabetes nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system listed in Appendix V**. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Bydureon

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the label and the carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C). Do not freeze.
The kit may be kept for up to 4 weeks below 30°C prior to use.
Store in the original package in order to protect from light.
Throw away any Bydureon kit that has been frozen.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other 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, sodium dihydrogen phosphate monohydrate, disodium phosphate heptahydrate and water for injection.

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

AstraZeneca AB
SE-151 85 Södertälje
Sweden

Manufacturer

AstraZeneca UK Limited
Silk Road Business Park,
Macclesfield, Cheshire, SK10 2NA
United Kingdom

Swords Laboratories T/A Lawrence Laboratories
Unit 12 Distribution Centre, Shannon Industrial Estate, Shannon, Co. Clare
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This leaflet was last revised in

Other sources of information

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

PACKAGE LEAFLET: INFORMATION FOR THE USER

Bydureon 2 mg powder and solvent for prolonged-release suspension for injection in pre-filled pen exenatide

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or diabetes nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist, or diabetes nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Bydureon is and what it is used for
2. What you need to know before you use Bydureon
3. How to use Bydureon
4. Possible side effects
5. How to store Bydureon
6. Contents of the pack and other information

1. What Bydureon is and what it is used for

Bydureon contains the active substance exenatide. It is an injectable medicine used to improve blood sugar control in adults with type 2 diabetes mellitus.

This medicine is used in combination with the following diabetes medicines: metformin, sulphonylureas and thiazolidinediones. Your doctor is now prescribing this medicine 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. The active substance in this medicine helps your body to increase the production of insulin when your blood sugar is high.

2. What you need to know before you use Bydureon

Do not use Bydureon:

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

Warnings and precautions

Talk to your doctor, pharmacist, or diabetes nurse before using Bydureon about the following:

- Using this medicine in combination with a sulphonylurea, as low blood sugar (hypoglycaemia) can occur. Test your blood glucose levels regularly. Ask your doctor, pharmacist, or diabetes nurse if you are not sure if any of your other medicines contain a sulphonylurea.
- If you have type 1 diabetes or diabetic ketoacidosis, as this medicine should not be used.
- How to inject this medicine. It 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, as the use of this medicine is not recommended. The active substance in this medicine slows stomach emptying so food passes more slowly through your stomach.

- If you have ever had inflammation of the pancreas (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 cause problems such as gallstones.
- If you have severe kidney disease or you are on dialysis, as the use of this medicine is not recommended. There is little experience with this medicine in patients with kidney problems.

Children and adolescents

Do not give this medicine to children and adolescents less than 18 years, as there is no experience with this medicine in this age group.

Other medicines and Bydureon

Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines, particularly:

- other medicines that are used to treat type 2 diabetes such as insulins and medicines that work like Bydureon (for example: liraglutide and Byetta [immediate-release exenatide]), as taking these medicines with Bydureon is not recommended.
- medicines used to thin the blood (anticoagulants), e.g. Warfarin, as you will require additional monitoring of changes in INR (measurement of blood thinning) during initiation of therapy with this medicine.

Pregnancy and breast-feeding

It is not known if Bydureon may harm your unborn child, therefore you should not use Bydureon during pregnancy and for at least 3 months before a planned pregnancy.

It is not known if exenatide passes into your milk. You should not use this medicine while breast-feeding.

If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

You should use contraception if you could potentially become pregnant during treatment with this medicine.

Driving and using machines

If you use this medicine 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 using 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 this medicine exactly as your doctor, pharmacist, or diabetes nurse has told you. Check with your doctor, pharmacist, or diabetes nurse if you are not sure.

You should inject this medicine once a week, at any time of day, with or without meals.

You should inject this medicine 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. 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 doctor or diabetes nurse should teach you how to inject this medicine before you use it for the first time.

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

You should inject this medicine immediately after mixing the powder and the solvent.

Use a new pen for each injection. You should dispose of the pen safely, with the needle still attached, after use, as instructed by your doctor or diabetes nurse.

If you use more Bydureon than you should

If you use more of this medicine than you should, you may need medical treatment. Using too much of this medicine 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 a dose you should take it as soon as it is possible to do so. For your next injection you can return to your chosen injection day. However, only one injection should be taken in a 24-hour period. You can also change your chosen injection day. Do not take two injections on the same day.

If you are not sure you have taken the full dose of Bydureon

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

If you stop using Bydureon

If you feel you should stop using this medicine, please consult your doctor first. If you stop using this medicine this can affect your blood sugar levels.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist, or diabetes nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Severe allergic reactions (anaphylaxis) have been reported rarely (may affect up to 1 in 1000 people).

You should see your doctor immediately if you experience symptoms such as

- Swelling of the face, tongue or throat (angioedema)
- Hypersensitivity (rashes, itching and rapid swelling of the tissues of the neck, face, mouth or throat)
- Difficulty with swallowing
- Hives and difficulty with breathing

Cases of inflammation of the pancreas (pancreatitis) have been reported (frequency not known) in patients receiving this medicine. 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 the risk of getting pancreatitis, or getting it again, whether or not you are taking this medicine.
- STOP taking this medicine and contact your doctor immediately if you experience **severe and persistent** stomach pain, with or without vomiting, because you could have an inflamed pancreas (pancreatitis).

Very common side effects of Bydureon (may affect more than 1 in 10 people):

- nausea (nausea is most common when first starting this medicine, but decreases over time in most patients)
- diarrhoea
- hypoglycaemia

When this medicine 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 this medicine. 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 (may affect up to 1 in 10 people):

- dizziness
- headache
- vomiting
- loss of energy and strength
- tiredness (fatigue)
- constipation
- pain in the stomach area
- bloating
- indigestion
- flatulence (passing gas)
- heartburn
- reduced appetite

This medicine 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 cause problems such as gallstones.

- 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.

Uncommon side effects of Bydureon (may affect up to 1 in 100 people):

- decrease in kidney function
- dehydration, sometimes with a decrease in kidney function
- intestinal obstruction (blockage in intestine)
- burping
- unusual taste in the mouth
- increased sweating
- hair loss
- sleepiness

Rare side effects of Bydureon (may affect up to 1 in 1,000 people):

- feeling jittery

In addition some **other side effects** have been reported (frequency not known, cannot be estimated from the available data).

- changes in INR (measurement of blood thinning) have been reported when used together with warfarin
- skin reactions at the injection site following injection of exenatide. These include: cavity containing pus (abscess) and swollen, or red area of skin that feels hot and tender (cellulitis).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or diabetes nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Bydureon

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the label and the carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C). Do not freeze.

The pen may be kept for up to 4 weeks below 30°C prior to use.

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

Throw away any Bydureon pen that has been frozen.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Bydureon contains

- The active substance is exenatide. Each pre-filled pen contains 2 mg of exenatide. After suspension, the delivered dose is 2 mg/0.65 ml.
- The other ingredients are:
- In the powder: poly (D,L-lactide-co-glycolide) and sucrose.
- In the solvent: carmellose sodium, sodium chloride, polysorbate 20, sodium dihydrogen phosphate monohydrate, disodium phosphate heptahydrate, water for injection and sodium hydroxide (for pH adjustment).

What Bydureon looks like and contents of the pack

This medicine is provided as a powder and solvent (liquid) for suspension for injection in a pre-filled pen. The powder (2 mg) in one chamber, is white to off-white and the solvent (0.65 ml) in the other chamber, is a clear, colourless to pale yellow to pale brown solution. Each single-dose pre-filled pen is provided with one custom needle. Each carton also contains one spare needle.

This medicine is available in pack of 4 single-dose pre-filled pens, and a multipack containing 12 (3 packs of 4) single-dose pre-filled pens. Not all pack sizes may be marketed.

Marketing Authorisation Holder

AstraZeneca AB
SE-151 85 Södertälje
Sweden

Manufacturer

AstraZeneca UK Limited
Silk Road Business Park,
Macclesfield, Cheshire, SK10 2NA
United Kingdom

Swords Laboratories T/A Lawrence Laboratories
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This leaflet was last revised in

Other sources of information

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

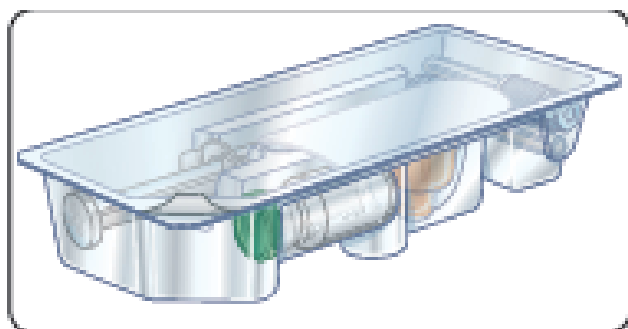
- Take your time.
- Follow these instructions step by step.
- You will need enough time to complete all the steps without stopping.
- You will probably need less time as you get used to giving yourself injections.

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.

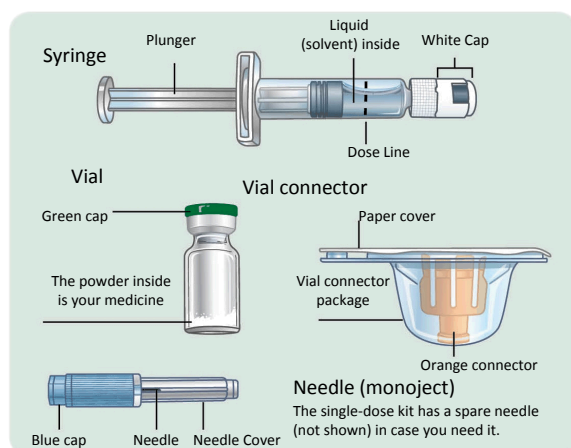
Your guide to the parts

Single-dose kit



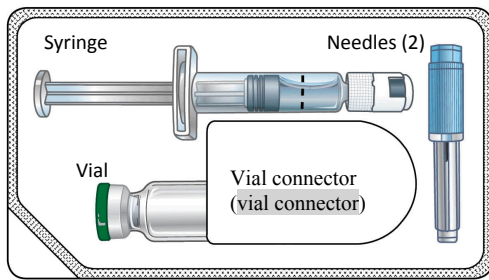
Lift here for a closer look at the parts

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 each section so that you do every 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.

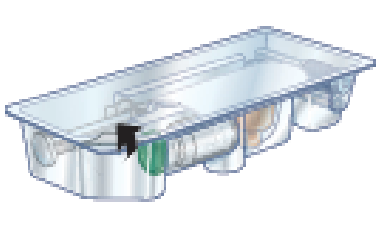
1. Getting Started

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.

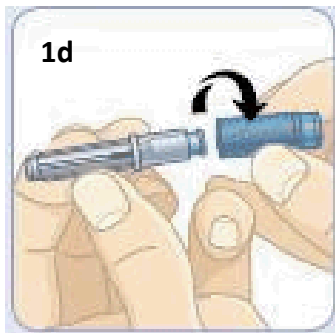
1c



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.

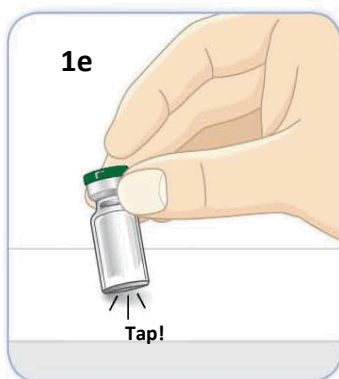
Place the needle, vial connector package, vial, and syringe on a clean, flat surface.



Pick up the needle, and twist off 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.



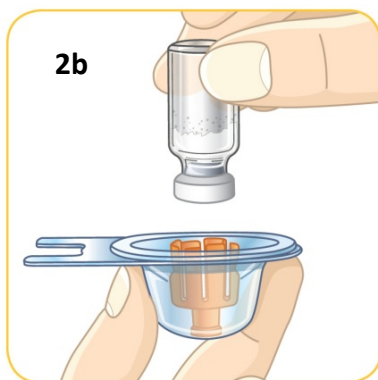
Use your thumb to remove the green cap.

Put the vial down.

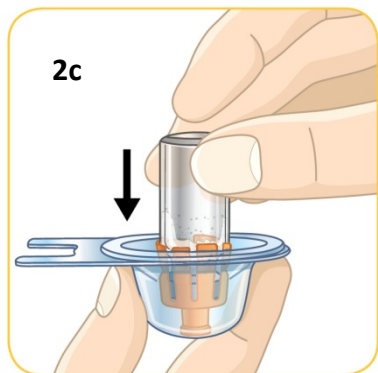
2. Connecting the parts



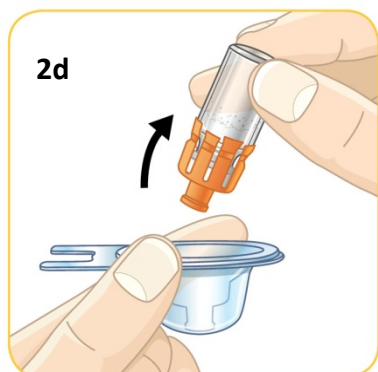
Pick up the vial connector package and peel off the paper cover. Do not touch the orange connector inside.



Hold the vial connector package. In your other hand, hold the vial.



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

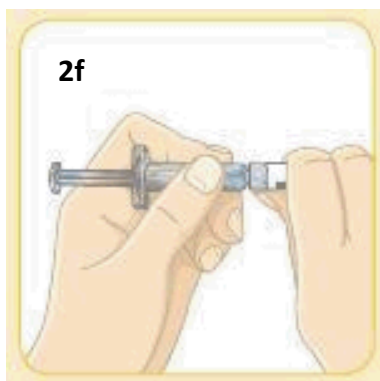


Lift the vial with the orange connector now attached out of its package.



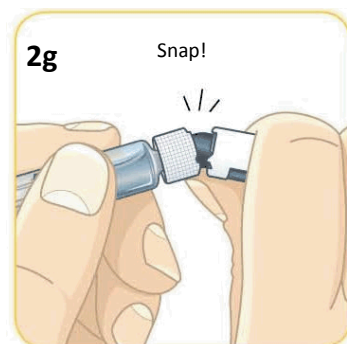
This is what the vial should now look like.

Put it down for later.



Pick up the syringe.

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



Break off the cap

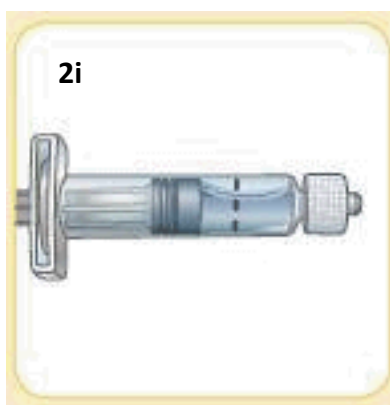
Be careful not to push in the plunger.

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

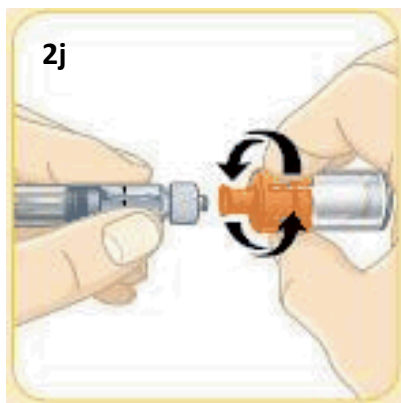


This is what the broken-off cap looks like.

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

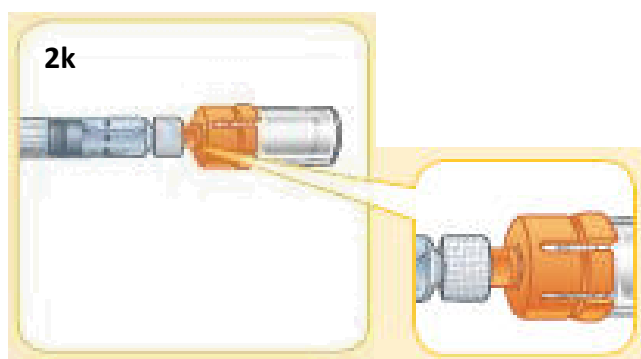


This is what the syringe should now look like.



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.

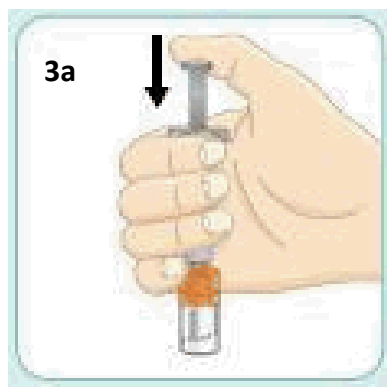


This is how the parts should now look when they are connected.

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.





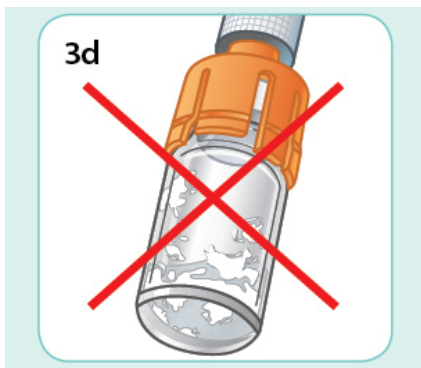
Keep pushing down on the plunger with your thumb and shake vigorously. Keep shaking until the liquid and powder are mixed well.

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

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



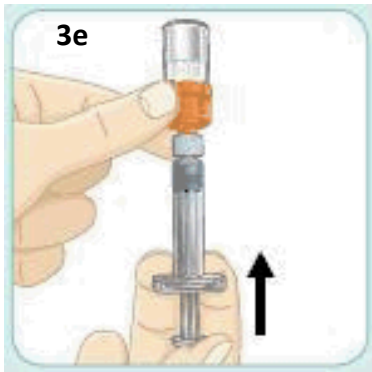
When the medicine is mixed well, it should look cloudy.



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.

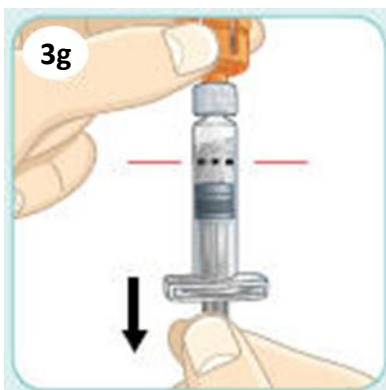


Now, hold the vial so the syringe is pointing up. Keep pushing on the plunger with your thumb until it stops, and hold it in place.



Gently 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.



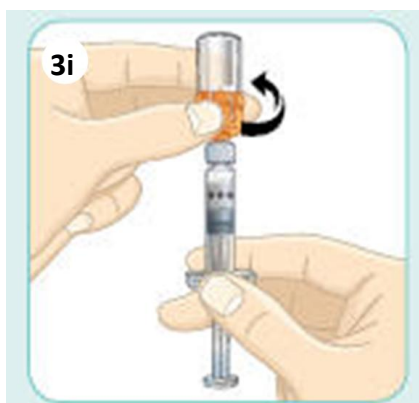
Pull the plunger down beyond the black dashed Dose Line.

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, twist the orange connector to remove.

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

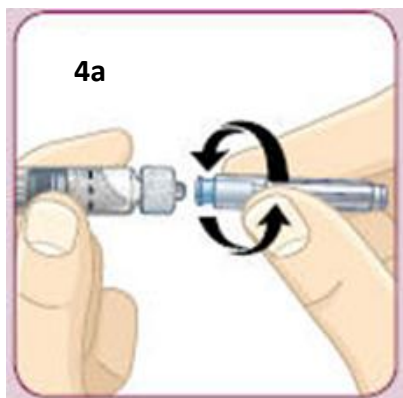


This is what the syringe should now look like.

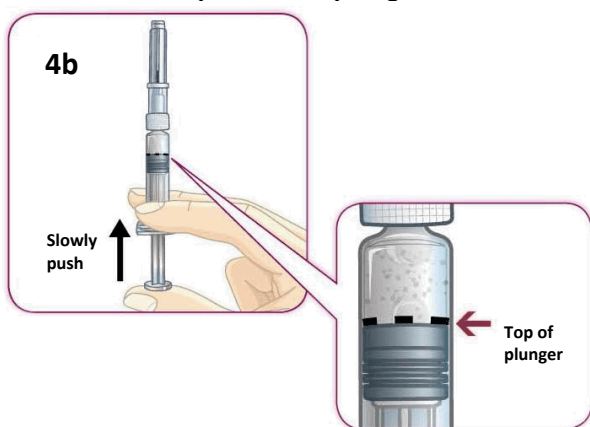
4. Injecting the medicine

IMPORTANT:

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

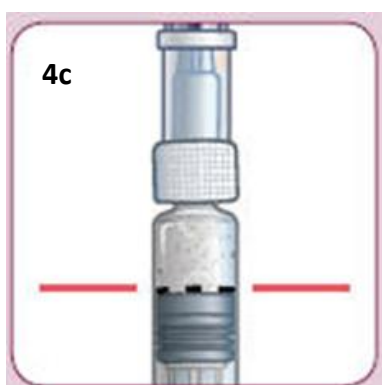


Twist the needle onto the syringe until snug. Do not remove the needle cover yet. Be careful not to push in the plunger.



Slowly 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.

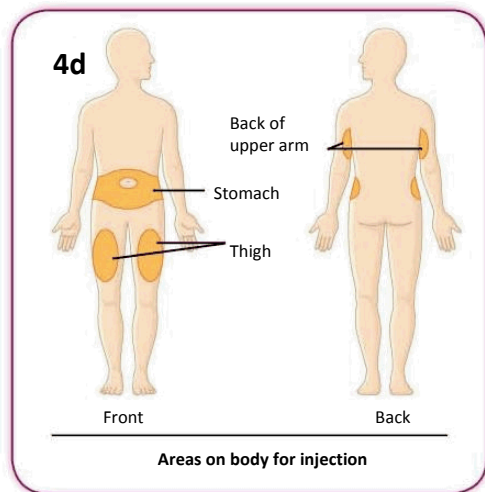
It is important to stop pushing at this point, or you will waste your medicine and you will not get the correct dose.



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.**

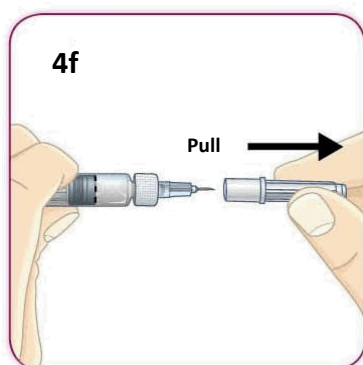


You can inject each dose of the medicine in your stomach area (abdomen), your thigh, or the back of your upper arm.

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.



Pull the needle cover straight off.
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 doctor or diabetes nurse.
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. Dispose of the syringe with the needle still attached as instructed by your doctor or diabetes nurse. DO NOT try to recap or reuse the needle.

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:

How soon to inject after mixing

Mixing the medicine

Air bubbles in syringe

Attaching the needle

Removing the needle cover

Plunger not lining up with black dashed Dose Line

Being unable to push the plunger down when injecting

See question number:

1

2

3

4

5

6

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 in Sections 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.)

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 step 1d
- Attach the needle, see step 4a
- Remove the needle cover and give the injection, see steps 4e to 4g

If you still cannot push the plunger all the way down, 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.

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

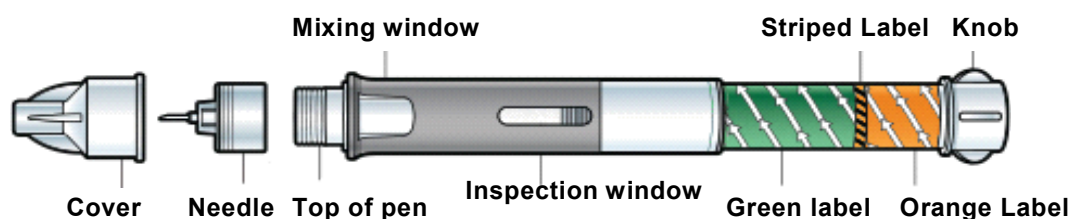
- **Talk with your doctor, pharmacist or diabetes nurse**
- **Read the Package Leaflet carefully**

INSTRUCTIONS FOR THE USER

Read these instructions carefully before use

Bydureon 2 mg powder and solvent for prolonged-release suspension for injection in pre-filled pen

How to use Bydureon pre-filled pen



Prior to use of the pen, it is recommended that you should be trained by a doctor or diabetes nurse on its proper use.

Unless a trained person can help to inject this medicine it is not recommended for people who are blind or cannot see well.

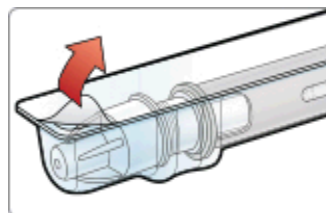
Step 1: Prepare your pen

Let your pen warm up. Remove one pen from the refrigerator and let it stand at room temperature for at least 15 minutes. **DO NOT** use a pen past its expiration date.

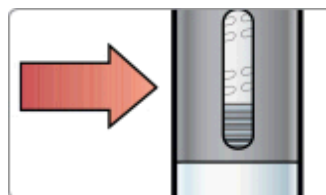


Wash your hands while the pen is warming up.

Open the tray by pulling on the corner tab. Then remove the pen and needle. **DO NOT** use your pen or needle if any parts are broken or missing.



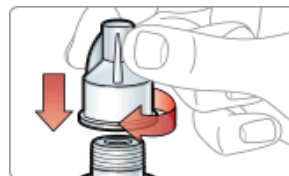
Check the liquid inside the inspection window. It should be clear and free of particles. It's normal if you see air bubbles in the liquid.



Peel off the paper tab from the needle cover.

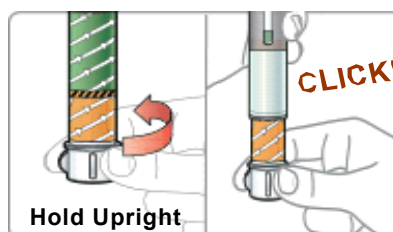


Attach the needle to the pen by pushing and screwing it onto the top of the pen until it is tight. **DO NOT** remove the needle cover yet.



Step 2: Mix your dose

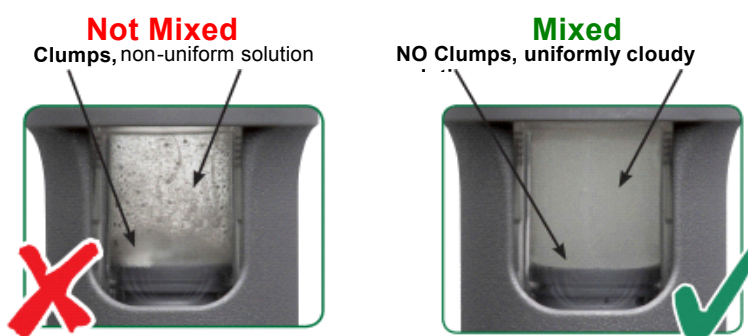
Combine the medicine. While holding the pen upright with the needle cover uppermost, **slowly** turn the knob anticlockwise. **STOP** when you hear the click and the green label disappears.



Firmly tap the pen to mix. Hold the pen by the end with the orange label and **tap the pen firmly against the palm of your hand.** **WITHOUT** twisting the knob, **ROTATE** the pen every few taps. Tap the prefilled pen firmly until a uniformly cloudy suspension with no clumps is obtained. You may need to tap 80 times or more.



Check the suspension. Hold the pen up to the light and look through both sides of the mixing window. The solution should have **NO CLUMPS** and be uniformly cloudy.



To get your full dose the medicine must be mixed well.

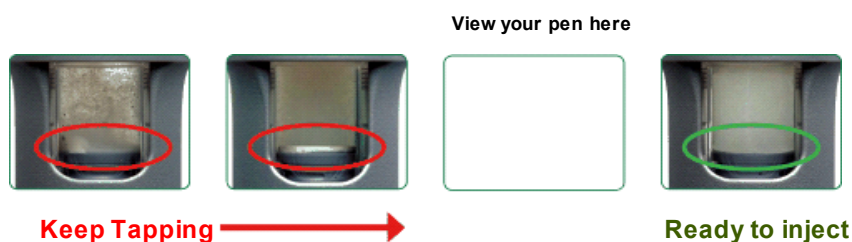
If it's not mixed well, tap longer and more firmly.



DO NOT proceed unless your medicine is mixed well

To get your full dose the medicine must be mixed well. If it's not mixed well, tap longer and more firmly. It's normal if you see air bubbles in the liquid, and they will cause no harm.

Compare both sides of the mixing window to the photos below by holding the pen against the page. Pay attention to the **bottom surface**. If you **don't** see **clumps** you are ready to inject.

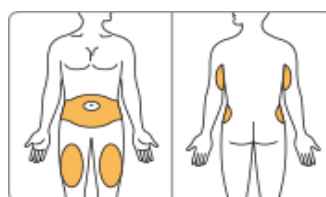


Step 3: Inject your dose

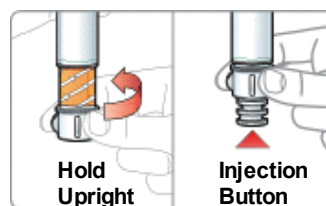
IMPORTANT Once the medicine is mixed well, you must inject the dose immediately. You cannot save it for later use.

Choose your injection site in either your stomach, thigh, or back of the arm. Each week you can use the same area of your body but choose a different injection site in that area.

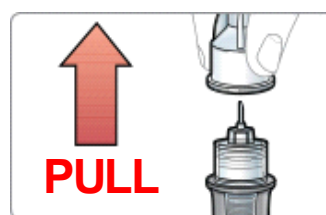
Gently clean the area with soap and water or an alcohol swab.



Twist knob to release injection button. While holding the **pen upright** with the needle cover uppermost, twist the knob anticlockwise until the orange label disappears and the injection button is released. **DO NOT** push the injection button yet.



Remove the needle cover by pulling straight off. **DO NOT** twist. You may see a few drops of liquid on the needle or in the cover.



Inject the medicine. Insert the needle into your skin (subcutaneously). Press the injection button with your thumb until you hear a click. **Hold for 10 seconds** to make sure you get the full dose.



Properly dispose of your pen, with the needle attached, in a puncture-resistant container. **DO NOT** try to recap or reuse the needle.



Common Questions and Answers

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

The medicine is mixed well when the liquid looks cloudy from both sides of the window. You should not see any clumps in the liquid. It may help to hold the pen up to the light to see in the window. If you see clumps of any size keep tapping the pen firmly against the palm of your hand until mixed.

2. I am having trouble mixing my dose. What should I do?

Remember, before preparing your dose, leave the pen out of the refrigerator for at least 15 minutes. This will let the pen warm up to room temperature. It will be easier to mix the medicine if the pen is at room temperature.

Be sure you are holding the pen at the end with the knob and the orange label. This will help you grip the pen better and tap it more firmly against your palm.

It may also help to tap the mixing window on both sides against your palm. If you see any clumps, keep tapping.

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

You must inject your dose right after mixing it. If you do not inject your dose right away, small clumps of medicine may form in the pen and you may not get your full dose.

4. I'm ready to inject my dose. What should I do if I see air bubbles in the pen?

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

5. What should I do if I cannot push the injection button all the way in when trying to inject my dose?

Check that you have fully screwed on the pen needle. Also be sure you twisted the knob until it stopped, the orange label disappeared, and the injection button appears.

If you still cannot push the button in, this may mean that the needle is clogged. Remove the needle from your skin and replace it with the spare needle from the carton. Review how to attach the needle. Then choose a different injection site and finish taking the injection.

If you still cannot push the button all the way in, remove the needle from your skin. Use a puncture-resistant container to throw away the pen with the needle still attached.

6. How do I know if I injected my full dose?

To be sure you get your full dose, press the injection button with your thumb until you hear a click. After the click, continue to hold the needle in your skin for 10 seconds. This will allow enough time for all the medicine to go from the pen to under your skin.

7. How do I dispose of my Bydureon pen?

You will need a puncture-resistant container that is large enough to hold the entire pen with a used needle attached. Be sure the container has a lid. You may use a biohazard container, another hard plastic container, or a metal container. A container is not included in the carton.

Ask your pharmacist how to safely throw away the container with used pens and needles. Do not throw the container in your household waste.