Bydureon 2mg

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 reconstitution suspension, each pen delivers a dose of 2 mg in 0.65 ml.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for prolonged-release suspension for injection.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Bydureon is indicated in adults 18 years and older with type 2 diabetes mellitus to improve glycaemic control in combination with other glucose-lowering medicinal products including basal insulin, when the therapy in use, together with diet and exercise, does not provide adequate glycaemic control (see section 4.4, 4.5 and 5.1 for available data on different combinations).

4.2 Posology and method of administration

Posology
The recommended dose is 2 mg exenatide once weekly.

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

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

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

If a dose is missed, it should be administered as soon as practical. 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 BYDUREON does not require additional self-monitoring. Blood glucose self-monitoring is necessary to adjust the dose of sulphonylurea and of insulin, particularly when BYDUREON therapy is started and insulin is reduced. A stepwise approach to insulin dose reduction is recommended.

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

Special populations

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

Renal impairment
No dose adjustment is necessary for patients with mild renal impairment (creatinine clearance 50 to 80 ml/min). Bydureon should be used with caution in patients with renal transplantation. Use BYDUREON with caution in patients with moderate renal impairment (creatinine clearance 30-50 mL/min).

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

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

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

Method of administration
Subcutaneous use
BYDUREON 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 BYDUREON, 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.

When used with insulin, BYDUREON and insulin must be administered as two separate injections.

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

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

BYDUREON is not a substitute for insulin. Diabetic ketoacidosis has been reported in insulin-dependent patients after rapid discontinuation or dose reduction of insulin (see section 4.2).

BYDUREON must not be administered by intravenous or intramuscular injection.

Renal impairment
In patients with end-stage renal disease receiving dialysis, single doses of exenatide twice daily increased frequency and severity of gastrointestinal adverse reactions therefore BYDUREON is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance < 30 ml/min). Use BYDUREON with caution in patients with moderate renal impairment (creatinine clearance 30-50 mL/min).

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

Acute pancreatitis
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 BYDUREON. 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. Resolution of pancreatitis has been observed with supportive treatment, but very rare cases of necrotizing or haemorrhagic pancreatitis and/or death have been reported. If pancreatitis is suspected, BYDUREON should be discontinued; if acute pancreatitis is confirmed, BYDUREON should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Drug-Induced Thrombocytopenia
Serious bleeding, which may be fatal, from drug-induced immune-mediated thrombocytopenia has been reported in the post-marketing setting with exenatide use. Drug-induced thrombocytopenia is an immune-mediated reaction, with exenatide-dependent anti-platelet antibodies. In the presence of exenatide, these

antibodies cause platelet destruction. If drug-induced thrombocytopenia is suspected, discontinue BYDUREON immediately and do not re-expose the patient to exenatide. Upon discontinuation, thrombocytopenia can persist due to the prolonged exenatide exposure from BYDUREON (about 10 weeks).

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

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

Rapid weight loss
Rapid weight loss at a rate of >1.5 kg per week has been reported in patients treated with exenatide. Weight loss of this rate may have harmful consequences. Patients with rapid weight loss should be monitored for signs and symptoms of cholelithiasis.

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

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 BYDUREON to slow gastric emptying is minor and not expected to cause clinically significant reductions in the rate and extent of absorption of concomitantly administered oral medicinal products. Therefore, no dose adjustments for medicinal products sensitive to delayed gastric emptying are required.

When 1,000 mg paracetamol tablets were administered, either with or without a meal, following 14 weeks of BYDUREON therapy, no significant changes in paracetamol AUC were observed compared to the

control period. Paracetamol C_{max} decreased by 16 % (fasting) and 5 % (fed) and t_{max} was increased from approximately 1 hour in the control period to 1.4 hours (fasting) and 1.3 hours (fed).

The following interaction studies have been conducted using 10 µg exenatide 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 exenatide twice daily. INR should be monitored during initiation of BYDUREON therapy in patients on warfarin and/or cumarol 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 exenatide twice daily was administered concomitantly with a single dose of lovastatin (40 mg) compared with lovastatin administered alone. e. 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 exenatide twice daily on digoxin and lisinopril there were no clinical relevant effects on C_{max} or AUC, however a delay in t_{max} of about 2 h was observed.

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

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 BYDUREON, women of childbearing potential should use contraception during treatment with BYDUREON. BYDUREON should be discontinued at least 3 months before a planned pregnancy.

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

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

Fertility
No fertility studies in humans have been conducted.

4.7 Effects on ability to drive and use machines

BYDUREON has minor influence on the ability to drive and use machines. When BYDUREON is used in combination with a sulphonylurea, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines.

4.8 Undesirable effects

Summary of the safety profile
The most frequent adverse 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 BYDUREON were mild to moderate in intensity.

Tabulated summary of adverse reactions
The frequency of adverse reactions of BYDUREON identified from clinical trials and spontaneous reports (not observed in clinical trials, frequency not known) are summarised in Table 1 below.

In the BYDUREON clinical trials, background therapies included diet and exercise, metformin, a sulphonylurea, a thiazolidinedione or a combination of oral glucose-lowering agents or a basal insulin.

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

Table 1: Adverse reactions of BYDUREON 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
Blood and lymphatic system disorders						
Drug-induced thrombocytopenia						X[4]
Immune system disorders						
Anaphylactic reaction				X[1]		
Metabolism and nutrition disorders						
Hypoglycaemia (with a sulphonylurea)	X[1]					
Hypoglycaemia (with insulin)		X[2,3]				
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[1]			
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[4]
Pruritus, and/ or urticaria		X[1]				
Angioneurotic oedema						X[4]
Injection site abscesses and cellulitis						X[4]
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]			
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[4]

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

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

consciousness or behaviour and has glucose value of <54 mg/dL (3 mmol/L) OR 3. Result in symptoms consistent with hypoglycaemia with a concomitant glucose <54 mg/dL (3 mmol/L) prior to treatment.
[3] Frequency reported from the 28-week controlled treatment period of the prolonged-release exenatide as add-on to insulin glargine study **(**N=232).
[4] Rate based on prolonged-release exenatide spontaneous reports data (unknown denominator).

Description of selected adverse reactions

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

Hypoglycaemia
The incidence of hypoglycaemia was increased when BYDUREON was used in combination with a sulphonylurea (24.0%versus5.4%) (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).

BYDUREON 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 12 studies of BYDUREON 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.

When BYDUREON was added to basal insulin, no initial dose adjustment of insulin was required. Prolonged-release exenatide in combination with basal insulin showed no clinically significant differences in the incidence of hypoglycaemic episodes compared to insulin. There were no episodes of major hypoglycaemia in the prolonged-release exenatide with insulin group.

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

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

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

use a different site of injection each week. In post marketing 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 BYDUREON. In most patients who develop antibodies, antibody titres diminish over time.

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

In clinical studies of BYDUREON, approximately 45 % of patients had low titre antibodies to exenatide at study endpoint. Overall the percentage of antibody positive patients was consistent across clinical trials. Overall, the level of glycaemic control (HbA_{1c}) was comparable to that observed in those without antibody titres. On average in the phase 3 studies, 12 % of the patients had higher titre antibodies. In a proportion of these the glycaemic response to BYDUREON was absent at the end of the controlled period of studies; 2.6 % of patients showed no glucose improvement with higher titre antibodies 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 BYDUREON-treated patients, the incidence of potentially immunogenic injection site reactions (most commonly pruritus with or without erythema) during the 30-week and the two 26-week studies, was 9 %. These reactions were less commonly observed in antibody-negative patients (4 %) compared with antibody-positive patients (13 %), with a greater incidence in those with higher titre antibodies.

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

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

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 BYDUREON clinical studies. Fifteen percent of BYDUREON 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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, 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, BYDUREON has a pharmacokinetic and pharmacodynamic profile in humans suitable for once weekly administration.

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

Clinical efficacy and safety

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

Glycaemic control

In two studies prolonged-reease exenatideBYDUREON 2 mg once weekly has been compared to exenatide twice daily 5 µg given twice daily for 4 weeks followed by immediate-release exenatide 10 µg 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 BYDUREON 2 mg once weekly for a further 7 years (n= 258). In both studies, decreases in HbA_{1c} were evident in both treatment groups as early as the first post-treatment HbA_{1c} measurement (weeks 4 or 6).

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 exenatidetreated 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 exenatidepatients achieved an HbA_{1c} reduction of ≤ 7 % or < 7 % in the two studies ($p < 0.05$ and $p =< 0.0001$ 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 258 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.

Table2: 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	**BYDUREON 2 mg**	**Exenatide 10 µg twice daily**
N	129	123
Mean HbA_{1c} (%)		
Baseline	8.5	8.4
Change from baseline (± SE)	-1.6 (±0.1) **	-0.9 (±0.1)
Mean difference change from baseline between treatments (95 % CI)	-0.67 (-0.94, -0.39) **	
Patients (%) achieving HbA_{1c} < 7 %	58	30
Change in fasting plasma glucose (mmol/l) (± SE)	-1.4 (±0.2)	-0.3 (±0.2)
Mean body weight (kg)		
Baseline	97	94
Change from baseline (± SE)	-2.3 (±0.4)	-1.4 (± 0.4)
Mean difference change from baseline between treatments (95 % CI)	-0.95 (-1.91, 0.01)	
30 Week Study		
N	148	147
Mean HbA_{1c} (%)		
Baseline	8.3	8.3
Change from baseline (± SE)	-1.9 (±0.1) *	-1.5 (±0.1)
Mean difference change from baseline between treatments (95 % CI)	-0.33 (-0.54, -0.12) *	
Patients (%) achieving HbA_{1c} ≤ 7 %	73	57
Change in fasting plasma glucose (mmol/l) (± SE)	-2.3 (±0.2)	-1.4 (±0.2)
Mean body weight (kg)		
Baseline	102	102
Change from baseline (± SE)	-3.7 (±0.5)	-3.6 (±0.5)
Mean difference change from baseline between treatments (95 % CI)	-0.08 (-1.29, 1.12)	

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

A study of 26-week duration has been conducted, in which 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 and/or sulphonylurea (intent to treat patients).**

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

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

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

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).**

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

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

In a 28-week, double-blind study, the combination of prolonged-release exenatide and dapagliflozin was compared to prolonged-release exenatide alone and dapagliflozin alone in subjects also using metformin. All treatment groups had a reduction in HbA_{1c} compared to baseline. The prolonged-release exenatide and dapagliflozin treatment group showed superior reductions in HbA_{1c} from baseline compared to prolonged-release exenatide alone and dapagliflozin alone (Table 5).

The combination of prolonged-release exenatide and dapagliflozin demonstrated significantly greater weight reductions compared to either agent alone (Table 5).

Table 5: Results of one 28-week trial of prolonged-release exenatide **and dapagliflozin versus** prolonged-release exenatide **alone and dapagliflozin alone, in combination with metformin (intent to treat patient)**

	Prolonged-release exenatide 2 mg QW + Dapagliflozin 10 mg QD	Prolonged-release exenatide 2 mg QW + Placebo QD	Dapagliflozin 10 mg QD + Placebo QW
N	228	227	230
Mean HbA_{1c} (%)			
Baseline	9.3	9.3	9.3
Change from baseline (± SE) [a]	- 2 (± 0.1)	-1.6 (± 0.1)	-1.4 (± 0.1)
Mean difference in change from baseline between combination and single active agent (95 % CI)		-0.38* (-0.63, -0.13)	-0.59** (-0.84, -0.34)
Patients (%) achieving HbA1c < 7 %	45	27	19
Mean change from baseline in fasting plasma glucose (mmol/l) (±SE) [a]	-3.7 (±0.2)	-2.5 (±0.2)	-2.7 (±0.2)
Mean difference in change from baseline between combination and single active agent (95% CI)		-1.12** (-1.55, -0.68)	-0.92** (-1.36, -0.49)
Mean change from baseline in 2-hour postprandial plasma glucose (mmol/L) (±SE) [a]	-4.9 (±0.2)	-3.3 (±0.2)	-3.4 (±0.2)
Mean difference in change from baseline between combination and single active agent (95 % CI)		-1.54** (-2.10, -0.98)	-1.49** (-2.04, -0.93)
Mean body weight (kg)			
Baseline	92	89	91
Change from baseline (± SE) [a]	-3.6 (±0.3)	-1.6 (±0.3)	-2.2 (±0.3)
Mean difference in change from baseline between combination and single active agent (95 % CI)		-2.00** (-2.79, -1.20)	-1.33** (-2.12, -0.55)

QW=once weekly, QD=once daily, SE = standard error, CI= confidence interval, N=number of patients.
[a] Adjusted least squares means (LS Means) and treatment group difference(s) in the change from baseline values at Week 28 are modelled using a mixed model with repeated measures (MMRM) including treatment, region, baseline HbA1c stratum (< 9.0 % or ≥ 9.0 %), week, and treatment by week interaction as fixed factors, and baseline value as a covariate.
*p < 0.01, **p < 0.001.
P-values are all adjusted p-values for multiplicity.
Analyses exclude measurements post rescue therapy and post premature discontinuation of study medicinal product.

In a 28-week double-blind study, prolonged-release exenatide added to insulin glargine alone or with metformin was compared to placebo added to insulin glargine alone or with metformin. Insulin glargine was dosed targeting a fasting plasma glucose of 4.0 to 5.5 mmol/l (72 to 99 mg/dl). prolonged-release exenatide demonstrated superiority to placebo in reducing HbA_{1c} from baseline to Week 28 (Table 6). prolonged-release exenatide was superior to placebo in reducing body weight at Week 28 (Table 6).

Table 6: Results of one 28-week trial of prolonged-release exenatide **versus placebo in combination with insulin glargine alone or with metformin (intent to treat patients)**

	Prolonged-release exenatide 2 mg + Insulin glargine [a]	**Placebo + Insulin glargine [a]**
N	231	230
Mean HbA1c (%)		
Baseline	8.5	8.5
Change from baseline (± SE) [b]	- 1.0 (± 0.1)	-0.2 (± 0.1)
Mean difference in change from baseline between treatments (95% CI)	-0.73* (-0.93, -0.53)	
Patients (%) achieving HbA1c ≤7% [c]	33*	7
Mean body weight (kg)		
Baseline	94	94
Change from baseline (± SE) [b]	-1.0 (±0.3)	0.5 (±0.3)
Mean difference in change from baseline between treatments (95% CI)	-1.50* (-2.17, -0.84)	
Change from baseline in 2-hour postprandial plasma glucose (mmol/l) (± SE) [b,d]	-1.6 (±0.3)	-0.1 (±0.3)
Mean difference in change from baseline between treatments (95% CI)	-1.52* (-2.15, -0.90)	

N=number of patients in each treatment group, SE = standard error, CI= confidence interval, *p-value <0.001 (adjusted for multiplicity).

a. The LS means change in mean daily insulin dose was 1.6 units for the prolonged-release exenatide group and 3.6 units for the placebo group.

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

c. All patients with missing endpoint data are imputed as non-responders.

d. After a standard meal tolerance test.

Analyses exclude measurements post rescue therapy and post premature discontinuation of study medication.

Body weight

A reduction in body weight compared to baseline has been observed in all prolonged-release exenatide studies. In the 4 comparator-controlled 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).

In the 4 comparator-controlled studies, 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. In the placebo-controlled study with insulin glargine, the change from baseline to Week 28 in fasting plasma glucose was -0.7 mmol/l for the prolonged-release exenatide group and -0.1 mmol/l for the placebo group. 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 the 4 comparator-controlled 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 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.

In the placebo-controlled study with insulin glargine, the change from baseline to Week 28 in systolic blood pressure was -2.6 mmHg for the prolonged-release exenatide group and -0.7 mmHg for the placebo group.

Treatment with prolonged-release exenatide and dapagliflozin combination at Week 28 resulted in a significant mean change reduction of -4.3±0.8 mmHg in systolic blood pressure compared to prolonged-release exenatide alone of -1.2±0.8 mmHg ($p<0.01$) or to dapagliflozin alone of -1.8±0.8 mmHg ($p<0.05$).

Fasting lipids
prolonged-release exenatide has shown no adverse effects on lipid parameters.

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

Paediatric population

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

In a 104-week carcinogenicity study with immediate-release exenatide a statistically significant increase in thyroid c -cell tumor incidence (adenomas and / or carcinomas) was observed in rats at all doses (1.4 - to 26 - fold the human clinical exposure with immediate-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

5050 DL 4AP Polymer (poly (D,L-lactide-co-glycolide))

Sucrose
Solvent
Carmellose Sodium
Sodium Chloride
Polysorbate 20
Monobasic Sodium Phosphate Monohydrate
Dibasic Sodium Phosphate Heptahydrate
sodium hydroxide (for pH adjustment)
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

The expiry date of the product is indicated on the packaging materials.

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 (2ºC - 8ºC).
Do not freeze.
The pens may be kept for up to 4 weeks below 30ºC prior to use. At the end of this period Bydureon should 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 aluminum 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.

Bydureon must be injected subcutaneously immediately after mixing of the powder and the solvent BYDUREON 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. MANUFACTURER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. LICENSE HOLDER

Astra Zeneca Israel Ltd
1 Atirei Yeda St., Kfar Saba 4464301.

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