ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

BYETTA 5 micrograms solution for injection, prefilled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose contains 5 micrograms (µg) exenatide in 20 microlitres(µl), (0.25 mg exenatide per ml).

Excipients:
Each dose contains 44 µg metacresol.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection), pre-filled pen.

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BYETTA is indicated for treatment of type 2 diabetes mellitus in combination with:
- metformin
- sulphonylureas
- thiazolidinediones
- metformin and a sulphonylurea
- metformin and a thiazolidinedione

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

BYETTA is also indicated as adjunctive therapy to basal insulin with or without metformin and/or pioglitazone in adults who have not achieved adequate glycaemic control with these agents.

4.2 Posology and method of administration

Posology
BYETTA therapy should be initiated at 5 µg exenatide per dose administered twice daily (BID) for at least one month in order to improve tolerability. The dose of exenatide can then be increased to 10 µg BID to further improve glycaemic control. Doses higher than 10 µg BID are not recommended.

BYETTA is available as either a 5 µg or a 10 µg exenatide per dose pre-filled pen.

BYETTA can be administered at any time within the 60-minute period before the morning and evening meal (or two main meals of the day, approximately 6 hours or more apart). BYETTA **should not** be administered after a meal. If an injection is missed, the treatment should be continued with the next scheduled dose.

BYETTA is recommended for use in patients with type 2 diabetes mellitus who are already receiving metformin, a sulphonylurea, pioglitazone and/or a basal insulin. One can continue to use BYETTA when a basal insulin is added to existing therapy. When BYETTA is added to existing metformin and/or pioglitazone therapy, the current dose of metformin and/or pioglitazone can be continued as no increased risk of hypoglycaemia is anticipated, compared to metformin or pioglitazone alone. When

BYETTA 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.). When BYETTA is used in combination with basal insulin, the dose of basal insulin should be evaluated. In patients at increased risk of hypoglycaemia consider reducing the dose of basal insulin (see section 4.8).

The dose of BYETTA does not need to be adjusted on a day-by-day basis depending on self-monitored glycaemia. However, blood glucose self-monitoring may become necessary to adjust the dose of sulphonylureas or the dose of basal insulin.

Specialpopulations

Elderly
BYETTA should be used with caution and dose escalation from 5 µg to 10 µg should proceed conservatively in patients >70 years. The clinical experience in patients >75 years is very limited.

Patients with renal impairment
No dosage adjustment of BYETTA is necessary in patients with mild renal impairment (creatinine clearance 50 – 80 ml/min).

In patients with moderate renal impairment (creatinine clearance:30-50 ml/min), dose escalation from 5 µg to 10 µg should proceed conservatively (see section 5.2).

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

Patients with hepatic impairment
No dosage adjustment of BYETTA is necessary in patients with hepatic impairment (see section 5.2).

Paediatric population
The safety and effectiveness of exenatide have not been established in patients under 18 years of age. (see section 5.2).
Currently available data are described in section 5.2 but no recommendation on a posology can be made.

Method of administration
Each dose should be administered as a subcutaneous injection in the thigh, abdomen, or upper arm. BYETTA and basal insulin must be administered as two separate injections.

For instructions for using the pen, see section 6.6 and the instructions included with the leaflet.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

BYETTA must not be administered by intravenous or intramuscular injection.

Renal impairment
In patients with end-stage renal disease receiving dialysis, single doses of BYETTA 5 µg increased frequency and severity of gastrointestinal adverse reactions. BYETTA 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 (see section 4.2).

There have been rare, spontaneously reported events of altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring hemodialysis. 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, nonsteroidal anti-inflammatory medicinal products and diuretics. Reversibility of altered renal function has been observed with supportive treatment and discontinuation of potentially causative medicinal products, including BYETTA.

Severe gastrointestinal disease
BYETTA 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 BYETTA is not recommended in patients with severe gastrointestinal disease.

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

Concomitant medicinal products
The effect of BYETTA to slow gastric emptying may reduce the extent and rate of absorption of orally administered medicinal products. BYETTA should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption and medicinal products with a narrow therapeutic ratio. Specific recommendations regarding intake of such medicinal products in relation to BYETTA is given in section 4.5.

The concurrent use of BYETTA with D-phenylalanine derivatives (meglitinides), alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors or other GLP-1 receptor agonists has not been studied and cannot be recommended.

Patients with BMI ≤25
The experience in patients with BMI ≤25 is limited.

Rapid weight loss
Weight loss greater than 1.5 kg per week has been observed in approximately 5 % of clinical trial patients treated with exenatide. Weight loss of this rate may have harmful consequences.

Hypoglycaemia
When BYETTA was used in combination with a sulphonylurea, the incidence of hypoglycaemia was increased over that of placebo in combination with a sulphonylurea. 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.

Excipients
This medicinal product contains less than 1 mmol sodium per dose, i.e. essentially “sodium-free”.

This medicinal product contains metacresol, which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

The effect of BYETTA to slow gastric emptying may reduce the extent and rate of absorption of orally administered medicinal products. Patients receiving medicinal products of either a narrow therapeutic ratio or medicinal products that require careful clinical monitoring should be followed closely. These medicinal products should be taken in a standardised way in relation to BYETTA injection. If such medicinal products are to be administered with food, patients should be advised to, if possible, take them with a meal when BYETTA is not administered.

For oral medicinal products that are particularly dependent on threshold concentrations for efficacy, such as antibiotics, patients should be advised to take those medicinal products at least 1 hour before BYETTA injection.

Gastroresistant formulations containing substances sensitive for degradation in the stomach, such as proton pump inhibitors, should be taken at least 1 hour before or more than 4 hours after BYETTA injection.

Digoxin, lisinopril and warfarin
A delay in t_{max} of about 2 h was observed when digoxin, lisinopril or warfarin was administered 30 min after exenatide. No clinically relevant effects on C_{max} or AUC were observed. However, since market introduction, increased INR (International Normalized Ratio) has been reported during concomitant use of warfarin and BYETTA. INR should be closely monitored during initiation and dose increase of BYETTA therapy in patients on warfarin and/or cumarol derivatives (see section 4.8).

Metformin or sulphonylureas
BYETTA is not expected to have any clinically relevant effects on the pharmacokinetics of metformin or sulphonylureas. Hence no restriction in timing of intake of these medicinal products in relation to BYETTA injection are needed.

Paracetamol
Paracetamol was used as a model medicinal product to evaluate the effect of exenatide on gastric emptying. When 1000 mg paracetamol was given with 10 µg BYETTA (0 h) and 1 h, 2 h and 4 h after BYETTA injection, paracetamol AUCs were decreased by 21 %, 23 %, 24 % and 14 % respectively; C_{max} was decreased by 37 %, 56 %, 54 % and 41 %, respectively; t_{max} was increased from 0.6 h in the control period to 0.9 h, 4.2 h, 3.3 h, and 1.6 h, respectively. Paracetamol AUC, C_{max} and t_{max} were not significantly changed when paracetamol was given 1 hour before BYETTA injection. No adjustment to paracetamol dosing is required based on these study results.

Hydroxy Methyl Glutaryl Coenzyme A (HMG CoA) reductase inhibitors
Lovastatin AUC and C_{max} were decreased approximately 40 % and 28 %, respectively, and T_{max} was delayed about 4 h when BYETTA (10 µg BID) was administered concomitantly with a single dose of lovastatin (40 mg) compared with lovastatin administered alone. In the 30-week placebo-controlled clinical trials, concomitant use of BYETTA and HMG CoA reductase inhibitors was not associated with consistent changes in lipid profiles (see section 5.1). Although no predetermined dose adjustment is required, one should be aware of possible changes in LDL-C or total cholesterol. Lipid profiles should be monitored regularly.

Ethinyl estradiol and levonorgestrel
Administration of a combination oral contraceptive (30 µg ethinyl estradiol plus 150 µg levonorgestrel) one hour before BYETTA (10 µg BID) did not alter the AUC, C_{max} or C_{min} of either ethinyl estradiol or levonorgestrel. Administration of the oral contraceptive 30 minutes after BYETTA did not affect AUC but resulted in a reduction of the C_{max} of ethinyl estradiol by 45 %, and C_{max} of levonorgestrel by 27-41 %, and a delay in t_{max} by 2-4 h due to delayed gastric emptying. The reduction in C_{max} is of limited clinical relevance and no adjustment of dosing of oral contraceptives is required.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
If a patient wishes to become pregnant, or pregnancy occurs, treatment with BYETTA should be discontinued.

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

Breastfeeding
It is unknown whether exenatide is excreted in human milk. BYETTA should not be used if breast feeding.

Fertility
No fertility studies in humans have been conducted.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. When BYETTA is used in combination with a sulphonylurea or a basal insulin, 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, vomiting and diarrhoea). The most frequently reported single adverse reaction was nausea which was associated with the initiation of treatment and decreased over time. Patients may experience hypoglycaemia when BYETTA is used with a sulphonylurea. Most adverse reactions associated with BYETTA were mild to moderate in intensity.

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

Tabulated list of adverse reactions
Table 1 lists adverse reactions reported from Phase 3 studies. The table presents adverse reactions that occurred with an incidence ≥5 % and more frequently among BYETTA-treated patients than insulin- or placebo-treated patients. The table also includes adverse reactions that occurred with an incidence ≥1 % and with a statistically significantly higher and/or ≥2X incidence among BYETTA-treated patients than insulin- or placebo-treated patients.

The reactions are listed below as MedDRA preferred term by system organ class and absolute frequency. Patient frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (>1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data), including isolated reports.

Table 1: Adverse reactions reported in long term phase 3 controlled studies[1] and spontaneous adverse reactions[3]

System organ class /adverse reaction terms	**Frequency of occurrence**					
	Very common	Common	Uncommon	Rare	Very rare	not known
Immune system disorders						
Anaphylactic reaction					X[3]	
Metabolism and nutrition disorders						
Hypoglycaemia (with metformin and a sulphonylurea) [2]	X[1]					
Hypoglycaemia (with a sulphonylurea)	X[1]					
Decreased appetite		X[1]				
Dehydration, generally associated with nausea, vomiting and/or diarrhoea.				X[3]		
Nervous system disorders						
Headache [2]		X[1]				
Dizziness		X[1]				
Dysgeusia			X[3]			
Somnolence				X[3]		
Gastrointestinal disorders						
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]				
Acute pancreatitis				X[3]		
Eructation			X[3]			
Constipation			X[3]			
Flatulence			X[3]			
Skin and subcutaneous tissue disorders						
Hyperhidrosis [2]		X[1]				
Alopecia				X[3]		
Macular and papular rash				X[3]		
Pruritus, and/ or urticaria				X[3]		
Angioneurotic oedema				X[3]		
Renal and urinary disorders						
Altered renal function, including acute renal failure, worsened chronic				X[3]		

renal failure, renal impairment, increased serum creatinine						
General disorders and administration site conditions						
Feeling jittery		X[1]				
Asthenia [2]		X[1]				
Injection site reactions		X[1,3]				
Investigations						
Weight decreased		X[1]				
International normalised ratio increased with concomitant warfarin, some reports associated with bleeding						X

[1] Data from Phase 3 comparator-controlled studies versus placebo, insulin glargine or 30 % soluble insulin aspart/ 70 % insulin aspart protamine crystals (biphasic insulin aspart) in which patients also received metformin, thiazolidinediones or sulphonylurea in addition to BYETTA or comparator. (N= 1788 BYETTA-treated intent-to-treat (ITT) patients.)

[2] In insulin-comparator controlled studies in which metformin and a sulphonylurea were concomitant medicinal products, the incidence for these adverse reactions was similar for insulin- and BYETTA-treated patients.

[3] Post marketing reports

When BYETTA was used in combination with basal insulin therapy the incidence and types of other adverse events observed were similar to those seen in the controlled clinical trials with exenatide as monotherapy, with metformin and/or sulphonylurea or a thiazolidinedione, with or without metformin.

Description of selected adverse reactions

Hypoglycaemia

In studies in patients treated with BYETTA and a sulphonylurea (with or without metformin), the incidence of hypoglycaemia was increased compared to placebo (23.5 % and 25.2 % versus 12.6 % and 3.3 %) and appeared to be dependent on the doses of both BYETTA and the sulphonylurea.

There were no clinically relevant differences in incidence or severity of hypoglycaemia with exenatide compared to placebo, in combination with a thiazolidinedione, with or without metformin. Hypoglycaemia was reported in 11 % and 7 % of patients treated with exenatide and placebo respectively.

Most episodes of hypoglycaemia were mild to moderate in intensity, and resolved with oral administration of carbohydrate.

In a 30 week study, when BYETTA or placebo was added to existing basal insulin therapy(insulin glargine), the dose of basal insulin was decreased by 20 % in patients with an $HbA_{1c} \leq 8.0$ %, per protocol design in order to minimize the risk of hypoglycaemia. Both treatment arms were titrated to achieve target fasting plasma glucose levels (see section 5.1). There were no clinically significant differences in the incidence of hypoglycaemic episodes in the BYETTA compared to the placebo group (25% and 29% respectively). There were no episodes of major hypoglycaemia in the BYETTA arm.

In a 24 week study, where either insulin lispro protamine suspension or insulin glargine was added to existing therapy of BYETTA and metformin or metformin plus thiazolidinedione the incidence of patients with at least one minor hypoglycaemic episode was 18% and 9% respectively and one patient

reported major hypoglycaemia. In patients where existing therapy also included a sulphonylurea the incidence of patients with at least one minor hypoglycaemic episode was 48% and 54% respectively and one patient reported major hypoglycaemia.

Nausea
The most frequently reported adverse reaction was nausea. In patients treated with 5 µg or 10 µg BYETTA, generally 40-50 % reported at least one episode of nausea. Most episodes of nausea were mild to moderate and occurred in a dose-dependent fashion. With continued therapy, the frequency and severity decreased in most patients who initially experienced nausea.

The incidence of withdrawal due to adverse events was 8 % for BYETTA-treated patients, 3 % for placebo-treated and 1 % for insulin-treated patients in the long-term controlled trials (16 weeks or longer). The most common adverse events leading to withdrawal for BYETTA-treated patients were nausea (4 % of patients) and vomiting (1 %). For placebo-treated or insulin-treated patients, <1 % withdrew due to nausea or vomiting.

BYETTA-treated patients in the open-label extension studies at 82 weeks experienced similar types of adverse events observed in the controlled trials.

Injection site reactions
Injection site reactions have been reported in approximately 5.1 % of subjects receiving BYETTA in long-term (16 weeks or longer) controlled trials. These reactions have usually been mild and usually did not result in discontinuation of BYETTA.

Immunogenicity
Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients may develop anti-exenatide antibodies following treatment with BYETTA. In most patients who develop antibodies, antibody titres diminish over time and remain low through 82 weeks.

Overall the percentage of antibody positive patients was consistent across clinical trials. Patients who develop 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 anti-exenatide antibodies. In the three placebo-controlled trials (n=963) 38 % of patients had low titre anti-exenatide antibodies at 30 weeks. For this group, the level of glycaemic control (HbA_{1c}) was generally comparable to that observed in those without antibody titres. An additional 6 % of patients had higher titre antibodies at 30 weeks. About half of this 6 % (3 % of the total patients given BYETTA in the controlled studies), had no apparent glycaemic response to BYETTA. In two insulin-comparator controlled trials (n=475) comparable efficacy and adverse events were observed in BYETTA-treated patients regardless of antibody titre.

Examination of antibody-positive specimens from one long-term uncontrolled study revealed no significant cross-reactivity with similar endogenous peptides (glucagon or GLP-1).

4.9 Overdose

Signs and symptoms of overdose may include severe nausea, severe vomiting and rapidly declining blood glucose concentrations. In the event of overdose, appropriate supportive treatment (possibly given parenterally) should be initiated according to the patient's clinical signs and symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

Exenatide increases, on a glucose-dependent basis, the secretion of insulin from pancreatic beta cells. As blood glucose concentrations decrease, insulin secretion subsides. When exenatide was used in combination with metformin alone, no increase in the incidence of hypoglycaemia was observed over that of placebo in combination with metformin which may be due to this glucose-dependent insulinotropic mechanism. (see section 4.4).

Exenatide suppresses glucagon secretion which is known to be inappropriately elevated in type 2 diabetes. Lower glucagon concentrations lead to decreased hepatic glucose output. However, exenatide does not impair the normal glucagon response and other hormone responses to hypoglycaemia.

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

Pharmacodynamic effects

BYETTA improves glycaemic control through the immediate and sustained effects of lowering both postprandial and fasting glucose concentrations in patients with type 2 diabetes.

Clinical efficacy

Studies of BYETTA with metformin, a sulphonylurea or both as background therapy

The clinical studies comprised 3945 subjects (2997 treated with exenatide), 56 % men and 44 % women, 319 subjects (230 treated with exenatide) were ≥70 years of age and 34 subjects (27 treated with exenatide) were ≥75 years of age.

BYETTA reduced HbA_{1c} and body weight in patients treated for 30 weeks in three placebo-controlled studies, whether the BYETTA was added to metformin, a sulphonylurea or a combination of both. These reductions in HbA_{1c} were generally observed at 12 weeks after initiation of treatment. See Table 2. The reduction in HbA_{1c} was sustained and the weight loss continued for at least 82 weeks in the subset of 10 µg BID patients completing both the placebo-controlled studies and the uncontrolled study extensions (n=137).

Table 2: Combined results of the 30 week placebo controlled studies (intent to treat patients)

	Placebo	BYETTA 5 µg BID	BYETTA 10 µg BID
N	483	480	483
Baseline HbA_{1c}(%)	8.48	8.42	8.45
HbA_{1c}(%) change from base line	0.08	-0.59	-0.89
Proportion of patients (%) achieving HbA_{1c} ≤7%	7.9	25.3	33.6
Proportion of patients (%) achieving HbA_{1c} ≤7% (patients completing studies)	10.0	29.6	38.5
Baseline weight(kg)	99.26	97.10	98.11
Change of weight from baseline(kg)	-0.65	-1.41	-1.91

In insulin-comparator studies BYETTA (5 µg BID for 4 weeks, followed by 10 µg BID) in combination with metformin and sulphonylurea significantly (statistically and clinically) improved glycaemic control, as measured by decrease in HbA_{1c}. This treatment effect was comparable to that of insulin glargine in a 26-week study (mean insulin dose 24.9 IU/day ,range 4-95 IU/day, at the end of study) and biphasic insulin aspart in a 52-week study (mean insulin dose 24.4 IU/day, range 3-78 IU/day, at the end of study). BYETTA lowered HbA_{1c} from 8.21 (n=228) and 8.6 % (n=222) by 1.13 and 1.01 % while insulin glargine lowered from 8.24 (n=227) by 1.10 % and biphasic insulin aspart from 8.67 (n=224) by 0.86 %. Weight loss of 2.3 kg (2.6 %) was achieved with BYETTA in the 26 week study and a loss of 2.5 kg (2.7 %) in a 52-week study whereas treatment with insulin was associated with weight gain. Treatment differences (BYETTA minus comparator) were -4.1 kg in the 26-week study and –5.4 kg in the 52-week study. Seven-point self monitored blood glucose profiles (before and after meals and at 3 am) demonstrated significantly reduced glucose values compared to insulin in the postprandial periods after BYETTA injection. Premeal blood glucose concentrations were generally lower in patients taking insulin compared to BYETTA. Mean daily blood glucose values were similar between BYETTA and insulin. In these studies the incidence of hypoglycaemia was similar for BYETTA and insulin treatment.

Studies of BYETTA with metformin, a thiazolidinedione or both as background therapy

Two placebo-controlled studies were conducted: one of 16 and one of 26 weeks duration, with 121 and 111 BYETTA and 112 and 54 placebo treated patients respectively, added to existing thiazolidinedione treatment, with or without metformin. Of the BYETTA patients, 12% were treated with a thiazolidinedione and BYETTA and 82% were treated with a thiazolidinedione, metformin and BYETTA. BYETTA (5 µg BID for 4 weeks, followed by 10 µg BID) resulted in statistically significant reductions from baseline HbA_{1c} compared to placebo (-0.7% versus +0.1%) as well as significant reductions in body weight (-1.5 versus 0 kg) in the 16 week study. The 26 week study showed similar results with statistically significant reductions from baseline HbA_{1c} compared to placebo (-0.8% versus -0.1%). There was no significant difference in body weight between treatment groups in change from baseline to endpoint (-1.4 versus -0.8 kg).
When BYETTA was used in combination with a thiazolidinedione, the incidence of hypoglycaemia was similar to that of placebo in combination with a thiazolidinedione. The experience in patients > 65 years and in patients with impaired renal function is limited. The incidence and type of other adverse events observed were similar to those seen in the 30-week controlled clinical trials with a sulphonylurea, metformin or both.

Studies of BYETTA in combination with basal insulin

In a 30 week study, either BYETTA (5 µg BID for 4 weeks, followed by 10 µg BID) or a placebo was added to insulin glargine (with or without metformin, pioglitazone or both). During the study both

treatment arms titrated insulin glargine using an algorithm reflecting current clinical practice to a target fasting plasma glucose of approximately 5.6 mmol/l. The mean age of subjects was 59 years and the mean duration of diabetes was 12.3 years.

At the end of the study, BYETTA (n=137) demonstrated a statistically significant reduction in the HbA_{1c} and weight compared to placebo (n=122). BYETTA lowered HbA_{1c} by 1.7 % from a baseline of 8.3 % while placebo lowered HbA_{1c} by 1.0 % from a baseline of 8.5 %. The proportion of patients achieving HbA_{1c} <7% and HbA_{1c} ≤6.5% was 56 % and 42 % with BYETTA and 29 % and 13 % with placebo. Weight loss of 1.8 kg from a baseline of 95 kg was observed with BYETTA whereas a weight gain of 1.0 kg from a baseline of 94kg was observed with placebo.

In the BYETTA arm the insulin dose increased by 13 units/day compared to 20 units/ day on the placebo arm. BYETTA reduced fasting serum glucose by 1.3 mmol/l and placebo by 0.9 mmol/l. BYETTA arm compared to placebo had significantly lowered postprandial blood glucose excursions at the morning meal (- 2.0 versus - 0.2 mmol/l) and evening meal (- 1.6 versus + 0.1 mmol/l), there was no difference between treatments at midday.

In a 24 week study, where either insulin lispro protamine suspension or insulin glargine was added to existing therapy of BYETTA and metformin, metformin and sulphonylurea or metformin and pioglitazone, HbA1c was lowered by 1.2 % (n=170) and by 1.4 % (n=167) respectively from a baseline of 8.2 %. Weight increase of 0.2 kg was observed for patients on insulin lispro protamine suspension and 0.6 kg for insulin glargine treated patients from a baseline of 102 kg and 103 kg respectively.

Fasting lipids
BYETTA has shown no adverse effects on lipid parameters. A trend for a decrease in triglycerides has been observed with weight loss.

Beta-cell function
Clinical studies with BYETTA have indicated improved beta-cell function, using measures such as the homeostasis model assessment for beta-cell function (HOMA-B) and the proinsulin to insulin ratio. A pharmacodynamic study 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.

Body weight
A reduction in body weight was seen in patients treated with BYETTA irrespective of the occurrence of nausea although the reduction was larger in the group with nausea (mean reduction 2.4 kg versus 1.7 kg) in the long term controlled studies of up to 52 weeks.

Administration of exenatide has been shown to reduce food intake, due to decreased appetite and increased satiety.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with BYETTA 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

Absorption
Following subcutaneous administration to patients with type 2 diabetes, exenatide reaches median peak plasma concentrations in 2 h. Mean peak exenatide concentration (C_{max}) was 211 pg/ml and overall mean area under the curve (AUC_{0-inf}) was 1036 pg •h/ml following subcutaneous administration of a 10 µg dose of exenatide. Exenatide exposure increased proportionally over the therapeutic dose range of 5 µg to 10 µg. Similar exposure is achieved with subcutaneous administration of exenatide in the abdomen, thigh, or arm.

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. In clinical studies the mean apparent clearance of exenatide is 9 l/h and the mean terminal half-life is 2.4 h. These pharmacokinetic characteristics of exenatide are independent of the dose.

Special populations
Patients with renal impairment
In patients with mild (creatinine clearance 50 to 80 ml/min) or moderate renal impairment (creatinine clearance 30 to 50 ml/min), exenatide clearance was mildly reduced compared to clearance in individuals with normal renal function (13 % reduction in mild and 36 % reduction in moderate renal impairment). Clearance was significantly reduced by 84 % in patients with end-stage renal disease receiving dialysis (see section 4.2).

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

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

Elderly
Long-term controlled 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 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 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.

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.

In female rats given exenatide for 2 years, an increased incidence of benign thyroid C–cell adenomas was observed at the highest dose, 250 µg/kg/day, a dose that produced an exenatide plasma exposure 130-fold the human clinical exposure. This incidence was not statistically significant when adjusted for survival. There was no tumorigenic response in male rats or either sex of mice.

Animal studies did not indicate direct harmful effects with respect to fertility or pregnancy. High doses of exenatide during mid-gestation caused skeletal effects and reduced foetal growth in mice and reduced foetal growth in rabbits. Neonatal growth was reduced in mice exposed to high doses during late gestation and lactation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

metacresol
mannitol
glacial acetic acid
sodium acetate trihydrate
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.
Shelf life for pen in use: 30 days.

6.4 Special precautions for storage

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

In use
Store below 25 ºC.

The pen should not be stored with the needle attached.
Replace cap on pen in order to protect from light.

6.5 Nature and contents of container

Type I glass cartridge with a (bromobutyl) rubber plunger, rubber disc, and aluminium seal. Each cartridge is assembled into a disposable pen-injector (pen).

Each pre-filled pen contains 60 doses of sterile preserved solution (approximately 1.2 ml)

Pack size of 1 and 3 pens. Not all pack sizes may be marketed.

Injection needles are not included. The following are examples of disposable needles that can be used with the BYETTA pen: 29, 30 or 31 gauge (diameter 0.25 - 0.33 mm) and 12.7, 8 or 5 mm length.

6.6 Special precautions for disposal and other handling.

The patient should be instructed to discard the needle after each injection.

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

Instructions for use
BYETTA is for use by one person only.
The instructions for using the pen, included with the leaflet, must be followed carefully.
The pen is stored without needle.

BYETTA should not be used if particles appear or if the solution is cloudy and/or coloured.

BYETTA that has been frozen must not be used.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/362/001 –2

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 November 2006
Date of latest renewal: 20 November 2011

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

BYETTA 10 micrograms solution for injection, prefilled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose contains 10 micrograms (µg) exenatide in 40 microlitres(µl), (0.25 mg exenatide per ml).

Excipients:
Each dose contains 88 µg metacresol.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection), pre-filled pen.

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BYETTA is indicated for treatment of type 2 diabetes mellitus in combination with:
-metformin
-sulphonylureas
-thiazolidinediones
-metformin and a sulphonylurea
-metformin and a thiazolidinedione
in adults who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies.

BYETTA is also indicated as adjunctive therapy to basal insulin with or without metformin and/or pioglitazone in adults who have not achieved adequate glycaemic control with these agents.

4.2 Posology and method of administration

Posology
BYETTA therapy should be initiated at 5 µg exenatide per dose administered twice daily (BID) for at least one month in order to improve tolerability. The dose of exenatide can then be increased to 10 µg BID to further improve glycaemic control. Doses higher than 10 µg BID are not recommended.

BYETTA is available as either a 5 µg or a 10 µg exenatide per dose pre-filled pen.

BYETTA can be administered at any time within the 60-minute period before the morning and evening meal (or two main meals of the day, approximately 6 hours or more apart). BYETTA **should not** be administered after a meal. If an injection is missed, the treatment should be continued with the next scheduled dose.

BYETTA is recommended for use in patients with type 2 diabetes mellitus who are already receiving metformin, a sulphonylurea , pioglitazone and/or a basal insulin. One can continue to use BYETTA when a basal insulin is added to existing therapy. When BYETTA is added to existing metformin and/or pioglitazone therapy, the current dose of metformin and/or pioglitazone can be continued as no increased risk of hypoglycaemia is anticipated, compared to metformin or pioglitazone alone. When BYETTA 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.). When BYETTA is used in combination with basal insulin, the dose of basal insulin should be evaluated. In patients at increased risk of hypoglycaemia consider reducing the dose of basal insulin (see section 4.8).

The dose of BYETTA does not need to be adjusted on a day-by-day basis depending on self-monitored glycaemia. However, blood glucose self-monitoring may become necessary to adjust the dose of sulphonylureas or the dose of basal insulin.

Special populations

Elderly
BYETTA should be used with caution and dose escalation from 5 µg to 10 µg should proceed conservatively in patients >70 years. The clinical experience in patients >75 years is very limited.

Patients with renal impairment
No dosage adjustment of BYETTA is necessary in patients with mild renal impairment (creatinine clearance 50 – 80 ml/min).

In patients with moderate renal impairment (creatinine clearance:30-50 ml/min), dose escalation from 5 µg to 10 µg should proceed conservatively (see section 5.2).

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

Patients with hepatic impairment
No dosage adjustment of BYETTA is necessary in patients with hepatic impairment (see section 5.2).

Paediatric population
The safety and effectiveness of exenatide have not been established in patients under 18 years of age. (see section 5.2).
Currently available data are described in section 5.2 but no recommendation on a posology can be made.

Method of administration
Each dose should be administered as a subcutaneous injection in the thigh, abdomen, or upper arm. BYETTA and basal insulin must be administered as two separate injections.

For instructions for using the pen, see section 6.6 and the instructions included with the leaflet.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

BYETTA must not be administered by intravenous or intramuscular injection.

Renal impairment
In patients with end-stage renal disease receiving dialysis, single doses of BYETTA 5 µg increased frequency and severity of gastrointestinal adverse reactions. BYETTA 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 (see section 4.2).

There have been rare, spontaneously reported events of altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometimes

requiring hemodialysis. 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, nonsteroidal anti-inflammatory medicinal products and diuretics. Reversibility of altered renal function has been observed with supportive treatment and discontinuation of potentially causative medicinal products, including BYETTA.

Severe gastrointestinal disease
BYETTA 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 BYETTA is not recommended in patients with severe gastrointestinal disease.

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

Concomitant medicinal products
The effect of BYETTA to slow gastric emptying may reduce the extent and rate of absorption of orally administered medicinal products. BYETTA should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption and medicinal products with a narrow therapeutic ratio. Specific recommendations regarding intake of such medicinal products in relation to BYETTA is given in section 4.5.

The concurrent use of BYETTA with D-phenylalanine derivatives (meglitinides), alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors or other GLP-1 receptor agonists has not been studied and cannot be recommended.

Patients with BMI ≤25
The experience in patients with BMI ≤25 is limited.

Rapid weight loss
Weight loss greater than 1.5 kg per week has been observed in approximately 5 % of clinical trial patients treated with exenatide. Weight loss of this rate may have harmful consequences.

Hypoglycaemia
When BYETTA was used in combination with a sulphonylurea, the incidence of hypoglycaemia was increased over that of placebo in combination with a sulphonylurea. 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.

Excipients
This medicinal product contains less than 1 mmol sodium per dose, i.e. essentially “sodium-free”.

This medicinal product contains metacresol, which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

The effect of BYETTA to slow gastric emptying may reduce the extent and rate of absorption of orally administered medicinal products. Patients receiving medicinal products of either a narrow therapeutic ratio or medicinal products that require careful clinical monitoring should be followed closely. These

medicinal products should be taken in a standardised way in relation to BYETTA injection. If such medicinal products are to be administered with food, patients should be advised to, if possible, take them with a meal when BYETTA is not administered.

For oral medicinal products that are particularly dependent on threshold concentrations for efficacy, such as antibiotics, patients should be advised to take those medicinal products at least 1 hour before BYETTA injection.

Gastroresistant formulations containing substances sensitive for degradation in the stomach, such as proton pump inhibitors, should be taken at least 1 hour before or more than 4 hours after BYETTA injection.

Digoxin, lisinopril and warfarin
A delay in t_{max} of about 2 h was observed when digoxin, lisinopril or warfarin was administered 30 min after exenatide. No clinically relevant effects on C_{max} or AUC were observed. However, since market introduction, increased INR (International Normalized Ratio), has been reported during concomitant use of warfarin and BYETTA. INR should be closely monitored during initiation and dose increase of BYETTA therapy in patients on warfarin and/or cumarol derivatives (see section 4.8).

Metformin or sulphonylureas
BYETTA is not expected to have any clinically relevant effects on the pharmacokinetics of metformin or sulphonylureas. Hence no restriction in timing of intake of these medicinal products in relation to BYETTA injection are needed.

Paracetamol
Paracetamol was used as a model medicinal product to evaluate the effect of exenatide on gastric emptying. When 1000 mg paracetamol was given with 10 µg BYETTA (0 h) and 1 h, 2 h and 4 h after BYETTA injection, paracetamol AUCs were decreased by 21 %, 23 %, 24 % and 14 % respectively; C_{max} was decreased by 37 %, 56 %, 54 % and 41 %, respectively; t_{max} was increased from 0.6 h in the control period to 0.9 h, 4.2 h, 3.3 h, and 1.6 h, respectively. Paracetamol AUC, C_{max} and t_{max} were not significantly changed when paracetamol was given 1 hour before BYETTA injection. No adjustment to paracetamol dosing is required based on these study results.

Hydroxy Methyl Glutaryl Coenzyme A (HMG CoA) reductase inhibitors
Lovastatin AUC and C_{max} were decreased approximately 40 % and 28 %, respectively, and T_{max} was delayed about 4 h when BYETTA (10 µg BID) was administered concomitantly with a single dose of lovastatin (40 mg) compared with lovastatin administered alone. In the 30-week placebo-controlled clinical trials, concomitant use of BYETTA and HMG CoA reductase inhibitors was not associated with consistent changes in lipid profiles (see section 5.1). Although no predetermined dose adjustment is required, one should be aware of possible changes in LDL-C or total cholesterol. Lipid profiles should be monitored regularly.

Ethinyl estradiol and levonorgestrel
Administration of a combination oral contraceptive (30 µg ethinyl estradiol plus 150 µg levonorgestrel) one hour before BYETTA (10 µg BID) did not alter the AUC, C_{max} or C_{min} of either ethinyl estradiol or levonorgestrel. Administration of the oral contraceptive 30 minutes after BYETTA did not affect AUC but resulted in a reduction of the C_{max} of ethinyl estradiol by 45 %, and C_{max} of levonorgestrel by 27-41 %, and a delay in t_{max} by 2-4 h due to delayed gastric emptying. The reduction in C_{max} is of limited clinical relevance and no adjustment of dosing of oral contraceptives is required.

4.6 Fertility pregnancy and lactation

Women of childbearing potential
If a patient wishes to become pregnant, or pregnancy occurs, treatment with BYETTA should be discontinued.

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

Breastfeeding
It is unknown whether exenatide is excreted in human milk. BYETTA should not be used if breast feeding.

Fertility
No fertility studies in humans have been conducted.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. When BYETTA is used in combination with a sulphonylurea or a basal insulin, 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, vomiting and diarrhoea). The most frequently reported single adverse reaction was nausea which was associated with the initiation of treatment and decreased over time. Patients may experience hypoglycaemia when BYETTA is used with a sulphonylurea. Most adverse reactions associated with BYETTA were mild to moderate in intensity.

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

Tabulated list of adverse reactions
Table 1 lists adverse reactions reported from Phase 3 studies. The table presents adverse reactions that occurred with an incidence ≥5 % and more frequently among BYETTA-treated patients than insulin- or placebo-treated patients. The table also includes adverse reactions that occurred with an incidence ≥1 % and with a statistically significantly higher and/or ≥2X incidence among BYETTA-treated patients than insulin- or placebo-treated patients.

The reactions are listed below as MedDRA preferred term by system organ class and absolute frequency. Patient frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (>1/10,000 to <1/1,000),very rare (<1/10,000) and not known (cannot be estimated from the available data), including isolated reports.

Table 1: Adverse reactions reported in long term phase 3 controlled studies[1] and spontaneous adverse reactions [3]

System organ class /adverse reaction terms	**Frequency of occurrence**					
	Very Common	Common	Uncommon	Rare	Very rare	not known
Immune system disorders						
Anaphylactic reaction					X[3]	
Metabolism and nutrition disorders						
Hypoglycaemia (with metformin and a sulphonylurea) [2]	X[1]					
Hypoglycaemia (with a sulphonylurea)	X[1]					
Decreased appetite		X[1]				
Dehydration, generally associated with nausea, vomiting and/or diarrhoea				X[3]		
Nervous system disorders						
Headache [2]		X[1]				
Dizziness		X[1]				
Dysgeusia			X[3]			
Somnolence				X[3]		
Gastrointestinal disorders						
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]				
Acute pancreatitis				X[3]		
Eructation			X[3]			
Constipation			X[3]			
Flatulence			X[3]			
Skin and subcutaneous tissue disorders						
Hyperhidrosis [2]		X[1]				
Alopecia				X[3]		
Macular and papular rash				X[3]		
Pruritus, and/or urticaria				X[3]		
Angioneurotic oedema				X[3]		
Renal and urinary disorders						
Altered renal function,				X[3]		

including acute renal failure, worsened chronic renal failure, renal impairment, increased serum creatinine						
General disorders and administration site conditions						
Feeling jittery		X[1]				
Asthenia [2]		X[1]				
Injection site reactions		X[1,3]				
Investigations						
Weight decreased		X[1]				
International normalised ratio increased with concomitant warfarin, some reports associated with bleeding						X

[1] Data from Phase 3 comparator-controlled studies versus placebo, insulin glargine or 30 % soluble insulin aspart/ 70 % insulin aspart protamine crystals (biphasic insulin aspart) in which patients also received metformin, thiazolidinediones or sulphonylurea in addition to BYETTA or comparator. (N= 1788 BYETTA-treated intent-to-treat (ITT) patients.)

[2] In insulin-comparator controlled studies in which metformin and a sulphonylurea were concomitant medicinal products, the incidence for these adverse reactions was similar for insulin- and BYETTA-treated patients.

[3] Post marketing reports.

When BYETTA was used in combination with basal insulin therapy the incidence and types of other adverse events observed were similar to those seen in the controlled clinical trials with exenatide as monotherapy, with metformin and/or sulphonylurea or a thiazolidinedione, with or without metformin.

Description of selected adverse reactions

Hypoglycaemia
In studies in patients treated with BYETTA and a sulphonylurea (with or without metformin), the incidence of hypoglycaemia was increased compared to placebo (23.5 % and 25.2 % versus 12.6 % and 3.3 %) and appeared to be dependent on the doses of both BYETTA and the sulphonylurea.

There were no clinically relevant differences in incidence or severity of hypoglycaemia with exenatide compared to placebo, in combination with a thiazolidinedione, with or without metformin. Hypoglycaemia was reported in 11% and 7% of patients treated with exenatide and placebo respectively.

Most episodes of hypoglycaemia were mild to moderate in intensity, and resolved with oral administration of carbohydrate.

In a 30 week study, when BYETTA or placebo was added to existing basal insulin therapy(insulin glargine), the dose of basal insulin was decreased by 20 % in patients with an $HbA_{1c} \leq 8.0$ %, per protocol design in order to minimize the risk of hypoglycaemia. Both treatment arms were titrated to achieve target fasting plasma glucose levels (see section 5.1). There were no clinically significant differences in the incidence of hypoglycaemic episodes in the BYETTA compared to the placebo group (25 % and 29 % respectively). There were no episodes of major hypoglycaemia in the BYETTA arm.

In a 24 week study, where either insulin lispro protamine suspension or insulin glargine was added to existing therapy of BYETTA and metformin or metformin plus thiazolidinedione the incidence of patients with at least one minor hypoglycaemic episode was 18% and 9% respectively and one patient reported major hypoglycaemia. In patients where existing therapy also included a sulphonylurea the incidence of patients with at least one minor hypoglycaemic episode was 48% and 54% respectively and one patient reported major hypoglycaemia.

Nausea
The most frequently reported adverse reaction was nausea. In patients treated with 5 µg or 10 µg BYETTA, generally 40-50 % reported at least one episode of nausea. Most episodes of nausea were mild to moderate and occurred in a dose-dependent fashion. With continued therapy, the frequency and severity decreased in most patients who initially experienced nausea.

The incidence of withdrawal due to adverse events was 8 % for BYETTA-treated patients, 3 % for placebo-treated and 1 % for insulin-treated patients in the long-term controlled trials (16 weeks or longer). The most common adverse events leading to withdrawal for BYETTA-treated patients were nausea (4 % of patients) and vomiting (1 %). For placebo-treated or insulin-treated patients, <1 % withdrew due to nausea or vomiting.

BYETTA-treated patients in the open-label extension studies at 82 weeks experienced similar types of adverse events observed in the controlled trials.

Injection site reactions
Injection site reactions have been reported in approximately 5.1 % of subjects receiving BYETTA in long-term (16 weeks or longer) controlled trials. These reactions have usually been mild and usually did not result in discontinuation of BYETTA.

Immunogenicity
Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients may develop anti-exenatide antibodies following treatment with BYETTA. In most patients who develop antibodies, antibody titres diminish over time and remain low through 82 weeks.

Overall the percentage of antibody positive patients was consistent across clinical trials. Patients who develop 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 anti-exenatide antibodies. In the three placebo-controlled trials (n=963) 38 % of patients had low titre anti-exenatide antibodies at 30 weeks. For this group, the level of glycaemic control (HbA_{1c}) was generally comparable to that observed in those without antibody titres. An additional 6 % of patients had higher titre antibodies at 30 weeks. About half of this 6 % (3 % of the total patients given BYETTA in the controlled studies), had no apparent glycaemic response to BYETTA. In two insulin-comparator controlled trials (n=475) comparable efficacy and adverse events were observed in BYETTA-treated patients regardless of antibody titre.

Examination of antibody-positive specimens from one long-term uncontrolled study revealed no significant cross-reactivity with similar endogenous peptides (glucagon or GLP-1).

4.9 Overdose

Signs and symptoms of overdose may include severe nausea, severe vomiting and rapidly declining blood glucose concentrations. In the event of overdose, appropriate supportive treatment (possibly given parenterally) should be initiated according to the patient's clinical signs and symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

Exenatide increases, on a glucose-dependent basis, the secretion of insulin from pancreatic beta cells. As blood glucose concentrations decrease, insulin secretion subsides. When exenatide was used in combination with metformin alone, no increase in the incidence of hypoglycaemia was observed over that of placebo in combination with metformin which may be due to this glucose-dependent insulinotropic mechanism. (see section 4.4).

Exenatide suppresses glucagon secretion which is known to be inappropriately elevated in type 2 diabetes. Lower glucagon concentrations lead to decreased hepatic glucose output. However, exenatide does not impair the normal glucagon response and other hormone responses to hypoglycaemia.

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

Pharmacodynamic effects
BYETTA improves glycaemic control through the immediate and sustained effects of lowering both postprandial and fasting glucose concentrations in patients with type 2 diabetes.

Clinical efficacy

Studies of BYETTA with metformin, a sulphonylurea or both as background therapy

The clinical studies comprised 3945 subjects (2997 treated with exenatide), 56 % men and 44 % women, 319 subjects (230 treated with exenatide) were ≥70 years of age and 34 subjects (27 treated with exenatide) were ≥75 years of age.

BYETTA reduced HbA_{1c} and body weight in patients treated for 30 weeks in three placebo-controlled studies, whether the BYETTA was added to metformin, a sulphonylurea or a combination of both. These reductions in HbA_{1c} were generally observed at 12 weeks after initiation of treatment. See Table 2. The reduction in HbA_{1c} was sustained and the weight loss continued for at least 82 weeks in the subset of 10 µg BID patients completing both the placebo-controlled studies and the uncontrolled study extensions (n=137).

Table 2: Combined results of the 30 week placebo controlled studies (intent to treat patients)

	Placebo	BYETTA 5 µg BID	BYETTA 10 µg BID
N	483	480	483
Baseline HbA_{1c}(%)	8.48	8.42	8.45
HbA_{1c}(%) change from base line	0.08	-0.59	-0.89
Proportion of patients (%) achieving HbA_{1c} ≤7%	7.9	25.3	33.6
Proportion of patients (%) achieving HbA_{1c} ≤7% (patients completing studies)	10.0	29.6	38.5
Baseline weight(kg)	99.26	97.10	98.11
Change of weight from baseline(kg)	-0.65	-1.41	-1.91

In insulin-comparator studies BYETTA (5 µg BID for 4 weeks, followed by 10 µg BID) in combination with metformin and sulphonylurea significantly (statistically and clinically) improved glycaemic control, as measured by decrease in HbA_{1c}. This treatment effect was comparable to that of insulin glargine in a 26-week study (mean insulin dose 24.9 IU/day ,range 4-95 IU/day, at the end of study) and biphasic insulin aspart in a 52-week study (mean insulin dose 24.4 IU/day, range 3-78 IU/day, at the end of study). BYETTA lowered HbA_{1c} from 8.21 (n=228) and 8.6 % (n=222) by 1.13 and 1.01 % while insulin glargine lowered from 8.24 (n=227) by 1.10 % and biphasic insulin aspart from 8.67 (n=224) by 0.86 %. Weight loss of 2.3 kg (2.6 %) was achieved with BYETTA in the 26 week study and a loss of 2.5 kg (2.7 %) in a 52-week study whereas treatment with insulin was associated with weight gain. Treatment differences (BYETTA minus comparator) were -4.1 kg in the 26-week study and –5.4 kg in the 52-week study. Seven-point self monitored blood glucose profiles (before and after meals and at 3 am) demonstrated significantly reduced glucose values compared to insulin in the postprandial periods after BYETTA injection. Premeal blood glucose concentrations were generally lower in patients taking insulin compared to BYETTA. Mean daily blood glucose values were similar between BYETTA and insulin. In these studies the incidence of hypoglycaemia was similar for BYETTA and insulin treatment.

Studies of BYETTA with metformin, a thiazolidinedione or both as background therapy

Two placebo-controlled studies were conducted: one of 16 and one of 26 weeks duration, with 121 and 111 BYETTA and 112 and 54 placebo treated patients respectively, added to existing thiazolidinedione treatment, with or without metformin. Of the BYETTA patients, 12% were treated with a thiazolidinedione and BYETTA and 82% were treated with a thiazolidinedione, metformin and BYETTA. BYETTA (5 µg BID for 4 weeks, followed by 10 µg BID) resulted in statistically significant reductions from baseline HbA_{1c} compared to placebo (-0.7% versus +0.1%) as well as significant reductions in body weight (-1.5 versus 0 kg) in the 16 week study. The 26 week study showed similar results with statistically significant reductions from baseline HbA_{1c} compared to placebo (-0.8% versus -0.1%). There was no significant difference in body weight between treatment groups in change from baseline to endpoint (-1.4 versus -0.8 kg).
When BYETTA was used in combination with a thiazolidinedione, the incidence of hypoglycaemia was similar to that of placebo in combination with a thiazolidinedione. The experience in patients > 65 years and in patients with impaired renal function is limited. The incidence and type of other adverse events observed were similar to those seen in the 30-week controlled clinical trials with a sulphonylurea, metformin or both.

Studies of BYETTA in combination with basal insulin

In a 30 week study, either BYETTA (5 µg BID for 4 weeks, followed by 10 µg BID) or a placebo was added to insulin glargine (with or without metformin, pioglitazone or both). During the study both treatment arms titrated insulin glargine using an algorithm reflecting current clinical practice to a target fasting plasma glucose of approximately 5.6 mmol/l. The mean age of subjects was 59 years and the mean duration of diabetes was 12.3 years.

At the end of the study, BYETTA (n=137) demonstrated a statistically significant reduction in the HbA_{1c} and weight compared to placebo (n=122). BYETTA lowered HbA_{1c} by 1.7 % from a baseline of 8.3 % while placebo lowered HbA_{1c} by 1.0 % from a baseline of 8.5 %. The proportion of patients achieving HbA_{1c} <7% and HbA_{1c} ≤6.5% was 56 % and 42 % with BYETTA and 29 % and 13 % with placebo. Weight loss of 1.8 kg from a baseline of 95 kg was observed with BYETTA whereas a weight gain of 1.0 kg from a baseline of 94kg was observed with placebo.

In the BYETTA arm the insulin dose increased by 13 units/day compared to 20 units/ day on the placebo arm. BYETTA reduced fasting serum glucose by 1.3 mmol/l and placebo by 0.9 mmol/l. BYETTA arm compared to placebo had significantly lowered postprandial blood glucose excursions at the morning meal (- 2.0 versus - 0.2 mmol/l) and evening meal (- 1.6 versus + 0.1 mmol/l), there was no difference between treatments at midday.

In a 24 week study, where either insulin lispro protamine suspension or insulin glargine was added to existing therapy of BYETTA and metformin, metformin and sulphonylurea or metformin and pioglitazone, HbA1c was lowered by 1.2 % (n=170) and by 1.4 % (n=167) respectively from a baseline of 8.2 %. Weight increase of 0.2 kg was observed for patients on insulin lispro protamine suspension and 0.6 kg for insulin glargine treated patients from a baseline of 102 kg and 103 kg respectively.

Fasting lipids
BYETTA has shown no adverse effects on lipid parameters. A trend for a decrease in triglycerides has been observed with weight loss.

Beta-cell function
Clinical studies with BYETTA have indicated improved beta-cell function, using measures such as the homeostasis model assessment for beta-cell function (HOMA-B) and the proinsulin to insulin ratio. A pharmacodynamic study 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.

Body weight
A reduction in body weight was seen in patients treated with BYETTA irrespective of the occurrence of nausea although the reduction was larger in the group with nausea (mean reduction 2.4 kg versus 1.7 kg) in the long term controlled studies of up to 52 weeks.

Administration of exenatide has been shown to reduce food intake, due to decreased appetite and increased satiety.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with BYETTA 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

Absorption
Following subcutaneous administration to patients with type 2 diabetes, exenatide reaches median peak plasma concentrations in 2 h. Mean peak exenatide concentration (C_{max}) was 211 pg/ml and overall mean area under the curve (AUC_{0-inf}) was 1036 pg •h/ml following subcutaneous administration of a 10 µg dose of exenatide. Exenatide exposure increased proportionally over the

therapeutic dose range of 5 µg to 10 µg. Similar exposure is achieved with subcutaneous administration of exenatide in the abdomen, thigh, or arm.

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. In clinical studies the mean apparent clearance of exenatide is 9 l/h and the mean terminal half-life is 2.4 h. These pharmacokinetic characteristics of exenatide are independent of the dose.

Special populations
Patients with renal impairment
In patients with mild (creatinine clearance 50 to 80 ml/min) or moderate renal impairment (creatinine clearance 30 to 50 ml/min), exenatide clearance was mildly reduced compared to clearance in individuals with normal renal function (13 % reduction in mild and 36 % reduction in moderate renal impairment). Clearance was significantly reduced by 84% in patients with end-stage renal disease receiving dialysis (see section 4.2).

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

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

Elderly
Long-term controlled 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 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 in 13 patients with type 2 diabetes and between the ages of 12 and 16 years, administration of exenatide (5µg) resulted in slightly lower mean AUC (16 % lower) and C_{max} (25 % lower) compared to those observed in adults.

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.

In female rats given exenatide for 2 years, an increased incidence of benign thyroid C–cell adenomas was observed at the highest dose, 250 µg/kg/day, a dose that produced an exenatide plasma exposure 130-fold the human clinical exposure. This incidence was not statistically significant when adjusted for survival. There was no tumorigenic response in male rats or either sex of mice.

Animal studies did not indicate direct harmful effects with respect to fertility or pregnancy. High doses of exenatide during mid-gestation caused skeletal effects and reduced foetal growth in mice and reduced foetal growth in rabbits. Neonatal growth was reduced in mice exposed to high doses during late gestation and lactation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

metacresol
mannitol
glacial acetic acid
sodium acetate trihydrate
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.
Shelf life for pen in use: 30 days.

6.4 Special precautions for storage

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

In use
Store below 25 ºC.

The pen should not be stored with the needle attached.
Replace cap on pen in order to protect from light.

6.5 Nature and contents of container

Type I glass cartridge with a (bromobutyl) rubber plunger, rubber disc, and aluminium seal. Each cartridge is assembled into a disposable pen-injector (pen).

Each pre-filled pen contains 60 doses of sterile preserved solution (approximately 2.4ml)

Pack size of 1 and 3 pens. Not all pack sizes may be marketed.

Injection needles are not included. The following are examples of disposable needles that can be used with the BYETTA pen: 29, 30 or 31 gauge (diameter 0.25 - 0.33 mm) and 12.7, 8 or 5 mm length.

6.6 Special precautions for disposal and other handling.

The patient should be instructed to discard the needle after each injection.

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

Instructions for use
BYETTA is for use by one person only.
The instructions for using the pen, included with the leaflet, must be followed carefully.
The pen is stored without needle.

BYETTA should not be used if particles appear or if the solution is cloudy and/or coloured.

BYETTA that has been frozen must not be used.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/362/003 –4

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 November 2006
Date of latest renewal: 20 November 2011

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

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

B. CONDITIONS OF THE MARKETING AUTHORISATION

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

Medicinal product subject to medical prescription.

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

Not applicable.

- **OTHER CONDITIONS**

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

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version Revision 10 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

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

When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities

Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached

At the request of the European Medicines Agency

PSURs
The PSUR submission schedule should follow the PSUR frequency schedule for Bydureon.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON OF (Pack of 1 or 3)

1. NAME OF THE MEDICINAL PRODUCT

Byetta 5 micrograms solution for injection, prefilled pen
Exenatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dose contains 5 micrograms exenatide.

3. LIST OF EXCIPIENTS

Mannitol, glacial acetic acid, sodium acetate trihydrate, water for injections.
Contains metacresol. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection, pre-filled pen
1 pen (60 doses)
3 pens (3 x 60 doses)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Twice daily

Read the package leaflet and pen user manual before use.

Subcutaneous use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

If the seal is broken before first use, contact your pharmacist.

8. EXPIRY DATE

EXP
Discard pen 30 days after first use.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Once in use: Store below 25 ºC for 30 days.
Do not store with needle attached.
Recap pen to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/362/001
EU/1/06/362/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Byetta 5

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

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

Byetta 5 µg injection
Exenatide
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

60 doses (1.2 ml)

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF (Pack of 1 or3)

1. NAME OF THE MEDICINAL PRODUCT

Byetta 10 micrograms solution for injection, prefilled pen
Exenatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dose contains 10 micrograms exenatide.

3. LIST OF EXCIPIENTS

Mannitol, glacial acetic acid, sodium acetate trihydrate, water for injections.
Contains metacresol. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection, pre-filled pen
1 pen (60 doses)
3 pens (3 x 60 doses)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Twice daily

Read the package leaflet and pen user manual before use.

Subcutaneous use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

If the seal is broken before first use, contact your pharmacist.

8. EXPIRY DATE

EXP
Discard pen 30 days after first use.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Once in use: Store below 25 ºC for 30 days.Do not store with needle attached.
Recap pen to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/362/003
EU/1/06/362/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Byetta 10

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

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

Byetta 10 µg injection
Exenatide
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

60 doses (2.4 ml)

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

BYETTA 5 micrograms solution for injection, pre-filled pen
BYETTA 10 micrograms solution for injection, pre-filled pen
exenatide

Read all of this leaflet carefully before you start using this medicine.

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

In this leaflet:

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

1. WHAT BYETTA IS AND WHAT IT IS USED FOR

BYETTA contains the active substance exenatide and is used to improve blood sugar control in adults with type 2 (non insulin dependent) diabetes mellitus.

BYETTA is used with other diabetic medicines called metformin, sulphonylureas, thiazolidinediones and basal or long acting insulins. Your doctor is now prescribing BYETTA 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 if your body is not able to use the insulin properly. BYETTA helps your body to increase the production of insulin when your blood sugar is high.

2. BEFORE YOU USE BYETTA

Do not use BYETTA

- If you are allergic (hypersensitive) to exenatide or any of the other ingredients of BYETTA, listed at the end of this leaflet.

Take special care with BYETTA

- When using it in combination with a sulphonylurea, as low blood sugar (hypoglycaemia) can occur. Ask your doctor or pharmacist if you are not sure if any of your other medicines contain a sulphonylurea.
- BYETTA should not be used if you have type 1 diabetes or diabetic ketoacidosis (a dangerous condition that can occur in diabetes).
- BYETTA should be injected under the skin and not into a vein or into the muscle.
- If you have severe problems with your stomach emptying (including gastroparesis) or food digestion the use of BYETTA is not recommended. BYETTA slows stomach emptying so food passes more slowly through your stomach.

- Tell your doctor if you have ever had inflammation of the pancreas (pancreatitis) (see section 4).
- There is little experience with BYETTA in patients with a BMI (body mass index) ≤25.
- There is little experience with BYETTA in patients with kidney problems. The use of BYETTA is not recommended if you have severe kidney disease or you are on dialysis.

Children and adolescents

There is no experience with BYETTA in children and adolescents less than 18 years and, therefore, use of BYETTA is not recommended in this age group.

Using other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines (for example warfarin) including medicines obtained without a prescription.

Ask your doctor if the time at which you take any tablets should be changed because BYETTA slows stomach emptying and can affect medicines that need to pass through the stomach quickly.

Stomach resistant tablets or capsules (for example proton pump inhibitors) that should not stay too long in your stomach may need to be taken an hour before, or four hours after BYETTA.

Some antibiotics may need to be taken an hour before your BYETTA injection.

For tablets that you need to take with food, it may be best if they are taken at a meal at a time when BYETTA is not being administered.

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

Using BYETTA with food and drink

Use BYETTA at any time within the 60 minutes (1 hour) **before** your meal. (See 3 “How to use BYETTA”). **Do not** use BYETTA **after** your meal.

Pregnancy and breast-feeding

It is not known if BYETTA may harm your unborn child. Tell your doctor if you are, you think you might be, or are planning to become pregnant as BYETTA should not be used during pregnancy.

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

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

Driving and using machines

If you use BYETTA in combination with a sulphonylurea or insulin, 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 BYETTA

This medicine contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially “sodium-free”.
This medicine contains metacresol which may cause allergic reactions.

3. HOW TO USE BYETTA

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

Two strengths of BYETTA are available: BYETTA 5 micrograms(µg) and BYETTA 10 micrograms(µg). Your doctor may tell you to use BYETTA 5 micrograms(µg) twice a day to start with. After using BYETTA 5 micrograms(µg) twice a day for 30 days the doctor may increase your dose to BYETTA 10 micrograms(µg) twice a day.

If you are over 70 years old or have problems with your kidneys it may take longer than 30 days to tolerate the BYETTA 5 micrograms(µg) dose and so your doctor may not increase your dose.

One injection of your pre-filled pen will give you your dose. Do not change your dose unless your doctor has told you to.

BYETTA should be injected at any time within the 60 minutes (1 hour) **before** your morning and evening meals, or before your two main meals of the day, which should be about 6 hours or more apart. **Do not** use BYETTA **after** your meal.

BYETTA is injected under the skin (subcutaneous injection) of your upper leg (thigh), stomach area (abdomen), or upper arm. If you are using BYETTA and an insulin you must make two separate injections.

You will **not** need to test your sugar levels on a day-by-day basis to set the dose of BYETTA. However, if you are also using a sulphonylurea or an insulin your doctor may tell you to check your blood sugar levels to adjust the dose of sulphonylurea or insulin.

See the accompanying Pen User Manual for instructions for using the BYETTA Pen.

Your doctor or nurse must teach you how to inject BYETTA before you use it for the first time.

Injection needles are not included. The following are examples of disposable needles that can be used with your BYETTA pen:

- 29 (thin), 30 or 31 (thinner) gauge (diameter 0.25 - 0.33mm) and
- 12.7, 8 or 5mm length.

Ask your doctor or nurse, which needle gauge and length is best for you.

Use a new injection needle for each injection and dispose of it after each use. This medicine is for you; never share a BYETTA pen with others.

If you use more BYETTA than you should

If you use too much BYETTA you may need medical treatment right away. Too much BYETTA can cause nausea, vomiting, dizziness, or symptoms of low blood sugar.

If you forget to use BYETTA

If you miss a dose of BYETTA, skip that dose and take your next dose at the next prescribed time. **Do not** take an extra dose or increase the amount of your next dose to make up for the one you missed.

If you stop using BYETTA

If you feel you should stop using BYETTA consult your doctor. If you stop using BYETTA this can affect your blood sugar levels.

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

4. POSSIBLE SIDE EFFECTS

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

Some severe allergic reactions (anaphylaxis) have been reported very rarely (may affect up to 1 in 10,000 people).

You should see your doctor immediately if you experience symptoms such as
- Swollen face, tongue or throat
- Difficulty to swallow
- Hives and difficulties to breathe

Cases of inflammation of the pancreas (pancreatitis) have been reported rarely (may affect up to 1 in 1,000 people) in patients receiving BYETTA. Pancreatitis can be a serious, potentially life-threatening medical condition.

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

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

Very common side effects of BYETTA (may affect more than 1 in 10 people):
- nausea, (nausea is most common when first starting BYETTA, but decreases over time in most patients)
- vomiting
- diarrhoea
- hypoglycaemia

When BYETTA is used with a medicine that contains a **sulphonylurea or an insulin,** episodes of low blood sugar (hypoglycaemia, generally mild to moderate) can occur very commonly. The dose of your sulphonylurea or insulin medicine may need to be reduced while you use BYETTA. 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 BYETTA (may affect up to 1 in 10 people):
- dizziness
- headache
- feeling jittery
- pain in the stomach area
- bloating
- indigestion
- increased sweating
- loss of energy and strength
- heartburn
- injection site reactions (redness)
- weight decreased
- reduced appetite

BYETTA may reduce your appetite, the amount of food you eat, and your weight.

If you lose weight too quickly (more than 1.5 kg per week) talk to your doctor about it since this may not be good for you.

Uncommon side effects of BYETTA (may affect up to 1 in 100 people):
- unusual taste in the mouth
- burping
- constipation
- gas (flatulence)

Rare side effects of BYETTA:
- angiodema (swelling of the face and throat)
- hypersensitivity (rashes, itching and rapid swelling of the tissues of the neck, face, mouth or throat)
- decrease in kidney function
- dehydration, sometimes with a decrease in kidney function
- drowsiness
- hair loss

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.

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

5. HOW TO STORE BYETTA

Keep out of the reach and sight of children.

Do not use BYETTA 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 – 8 ºC). Once in use, your BYETTA pen should be kept below 25 ºC for 30 days.

Replace the cap on the pen in order to protect from light. Do not freeze. Throw away any BYETTA pen that has been frozen.

Use a BYETTA pen for only 30 days. Dispose of a used BYETTA pen after 30 days, even if some medicine remains in the pen.

Do not use BYETTA if you notice particles in the solution, or if it is cloudy or coloured.

Do not store the BYETTA pen with the needle attached. If the needle is left on, medicine may leak from the BYETTA pen or air bubbles may form in the cartridge.

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

6. FURTHER INFORMATION

What BYETTA contains

- The active substance is exenatide.
- Two pre-filled pens are available. One to deliver doses of 5 micrograms (µg) and one 10 micrograms (µg).
- Each dose of BYETTA 5 micrograms (µg) solution for injection (injection) contains 5 micrograms (µg) exenatide in 20 microlitre.
- Each dose of BYETTA 10 micrograms (µg) solution for injection (injection) contains 10 micrograms (µg) exenatide in 40 microlitre.
- Each millilitre (ml) of the solution for injection contains 0.25 milligrams (mg) of exenatide.
- The other ingredients are metacresol, (44 micrograms/dose in BYETTA 5 micrograms(µg) solution for injection and 88 micrograms/dose in BYETTA 10 micrograms(µg) solution for injection), mannitol, glacial acetic acid, sodium acetate trihydrate and water for injections.

What BYETTA looks like and contents of the pack

BYETTA is a clear and colourless liquid (solution for injection) filled in a glass cartridge within a pen. When the pen is empty, you cannot use it again. Each pen has 60 doses to provide 30 days of twice–a–day injections.
It is available in pack sizes of 1 and 3 pens. Not all pack sizes may be marketed.

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

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

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

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This leaflet was last approved in

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

PEN USER MANUAL

Section 1. **WHAT YOU NEED TO KNOW ABOUT YOUR BYETTA PEN**

Read this section completely before you begin. Then, move on to section 2 – getting started.

BYETTA 5 micrograms solution for injection, pre-filled pen
(exenatide)



Read these instructions carefully BEFORE using your BYETTA pen. Also read the BYETTA Package leaflet that comes with the BYETTA pen carton.

You need to use the pen correctly in order to get the most benefit from BYETTA. Failure to follow these instructions completely may result in a wrong dose, a broken pen or an infection.

These instructions do not take the place of talking with your healthcare professional about your medical condition or your treatment. If you are having problems using your BYETTA pen, contact your healthcare professional.

IMPORTANT INFORMATION ABOUT YOUR BYETTA PEN

- BYETTA is injected twice a day, the pen contains enough medicine for 30 days. You do not have to measure any doses, the pen measures each dose for you.
- **DO NOT TRANSFER THE MEDICINE IN THE BYETTA PEN TO A SYRINGE.**
- If any part of your pen appears broken or damaged, do not use the pen.
- **Do not share your pen or needles as this may risk transmission of infectious agents.**
- This pen is not recommended for use by people who are blind or who cannot see well enough. Help will be needed by a person trained to use the pen.
- Healthcare professionals or other caregivers should follow local or institutional policies regarding needle handling.
- **Follow the instructions for hygienic injection technique recommended by your healthcare professional.**
- Follow Section 2 only to set up a new pen before first use.
- Section 3 of this manual should be used for every injection.

ABOUT INJECTION NEEDLES

What kinds of needles can be used with my BYETTA pen?

- Injection needles are not included. The following are examples of disposable needles that can be used with your BYETTA pen:
  - 29 (thin), 30 or 31 (thinner) gauge (diameter 0.25-0.33mm) and
  - 12.7, 8 or 5mm length.

Ask your healthcare professional which needle gauge and length is best for you.

Do I use a new needle for each injection?

- Yes. Do not reuse needles.
- Remove the needle immediately after each injection. This will help prevent leakage of BYETTA, keep out air bubbles, reduce needle clogs, and decrease the risk of infection.
- Never push the injection button on the pen unless a needle is attached.

How do I throw away my needles?

- Throw away used needles in a puncture-resistant container or as recommended by your healthcare professional.
- Do not throw away the pen with a needle attached.

STORING YOUR BYETTA PEN

How do I store my BYETTA pen?

- Store in a refrigerator (2° to 8°C).
- Do not freeze. Throw away any BYETTA pen that has been frozen.
- Once in use, your BYETTA pen should be kept below 25°C.
- Replace the cap on the pen in order to protect from light.
- Do not store the BYETTA pen with the needle attached. If the needle is left on, medicine may leak from the BYETTA pen or air bubbles may form in the cartridge.

Keep your pen and needles out of the reach and sight of children.

How long can I use a BYETTA pen?

- Use a BYETTA pen for only 30 days after setting up a new pen for first use.
  Dispose of a used BYETTA pen after 30 days, even if some medicine remains in the pen.
- Mark the date when you first used your pen and the date 30 days later in the spaces below:

Date of first use

Date to throw away pen

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

How do I clean my BYETTA pen?

- If needed, wipe the outside of the pen with a clean, damp cloth.
- White particles may appear on the outside tip of the cartridge during normal use. You may remove them with an alcohol wipe or alcohol swab.

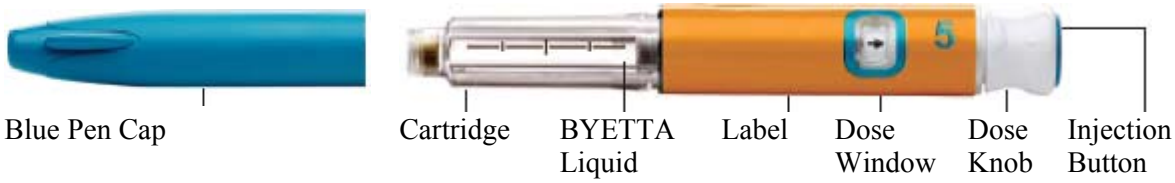
Please see the accompanying BYETTA Package Leaflet. For additional information, contact your healthcare professional.

Section 2. GETTING STARTED

Read and follow the directions in this section only after you've read section 1-what you need to know about your BYETTA pen.

Set up your new pen just before you use it for the first time. Follow the **New Pen Setup** only **once**. For routine use, **do not repeat** the New Pen Setup. If you do, you will run out of BYETTA before 30 days of use.

BYETTA PEN PARTS



NEEDLE PARTS
(Needles Not Included)



DOSE WINDOW SYMBOLS

- ready to pull dose knob out
- ready to turn to dose position
- ready to inject 5 micrograms (µg)
- dose knob pushed in and ready to reset

NEW PEN SETUP – DO THIS ONE TIME ONLY

STEP A Check the Pen



- Wash hands prior to use.
- Check pen label to make sure it is your 5 µg pen.
- Pull off the blue pen cap.



Check BYETTA in the cartridge. The liquid should be clear, colourless, and free of particles. If it is not, do not use.
Note: A small air bubble in the cartridge is normal

STEP B Attach the Needle



- Remove paper tab from outer needle shield.
- **Push** outer needle shield containing the needle **straight** onto the pen, then **screw** needle on until secure.



- Pull off outer needle shield. **Do not** throw away. The outer needle shield will be used when you are removing the needle from the pen after the injection.



- Pull off inner needle shield and throw away. A small drop of liquid may appear. This is normal.

STEP C Dial the Dose



- Check that the  is in the dose window. If not, turn dose knob clockwise **until it stops** and the  is in the dose window.



- **Pull dose knob out until it stops** and the  is in the dose window.



- **Turn dose knob clockwise until it stops** at . Make sure that the 5 with the line under it is in the centre of the dose window.

Note: If you cannot turn the dose knob clockwise to the , see **Commonly Asked Questions**, number 8, in Section 4 of this user manual.

STEP D Prepare the Pen



- Point the needle of the pen up and away from you.



PUSH & HOLD

- **Use thumb to firmly push the injection button in until it stops**, then continue holding the injection button in while **slowly counting to 5.**
- **If you do not see a stream or several drops come from the needle tip, repeat Steps C & D.**



- Pen preparation is complete when the ▲ is in the centre of the dose window AND you have seen a stream or several drops come from the needle tip.

Note: If you do not see liquid after 4 times, see **Commonly Asked Questions**, number 3, in Section 4 of this user manual.

STEP E Complete New Pen Setup



- **Turn dose knob clockwise until it stops** and the → is in the dose window.
- New Pen Setup is now done. Do not repeat Section 2 for routine use, if you do, you will run out of BYETTA before 30 days of use.
- You are now ready for your first dose of BYETTA.
- **Go to Section 3, Step 3, for instructions on how to inject your first routine dose.**

Note: If you cannot turn the dose knob, see **Commonly Asked Questions**, number 8, Section 4 of this user manual.

Section 3. ROUTINE USE

Now that you have done the New Pen Setup, follow Section 3 for **all** of your injections.

STEP 1 Check the Pen



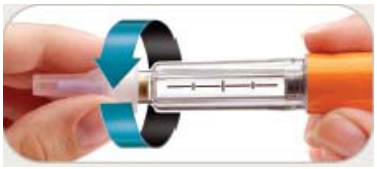
- Wash hands prior to use.
- Check pen label to make sure it is your 5 µg pen.
- Pull off the blue pen cap.



- Check BYETTA in the cartridge.
- The liquid should be clear, colourless, and free of particles. If it is not, do not use.

Note: A small air bubble will not harm you or affect your dose.

STEP 2 Attach the Needle



- Remove paper tab from outer needle shield.
- **Push** outer needle shield containing the needle **straight** onto the pen, then **screw** needle on until secure.



- Pull off outer needle shield. **Do not** throw away. The outer needle shield will be used when you are removing the needle from the pen after the injection.



- Pull off inner needle shield and throw away. A small drop of liquid may appear. This is normal.

STEP 3 Dial the Dose



- Check that the  is in the dose window. If not, turn dose knob clockwise **until it stops** and the  is in the dose window.



- **Pull dose knob out until it stops** and the  is in the dose window.



- **Turn dose knob clockwise until it stops** at . Make sure that the 5 with the line under it is in the centre of the dose window.

Note: If you cannot turn the dose knob clockwise to the , see **Commonly Asked Questions**, number 8, in Section 4 of this user manual.

STEP 4 Inject the Dose



- Grip pen firmly.
- Insert needle into skin using **hygienic** injection technique recommended by your healthcare professional.



PUSH & HOLD

- **Use thumb to firmly push injection button in until it stops**, then continue holding the injection button in while **slowly counting to 5** in order to get a full dose.
- Remove needle from skin.



- Injection is complete when the is in the centre of the dose window.
- The pen is now ready to reset.

Note: If you see several drops of BYETTA leaking from the needle after the injection, the injection button was not pushed in all the way. See **Commonly Asked Questions**, number 4, in Section 4 of this user manual.

STEP 5 Reset the Pen



- **Turn dose knob clockwise until it stops** and the is in the dose window.

Note: If you cannot turn the dose knob, or if your pen leaks, your full dose has not been delivered. See **Commonly Asked Questions**, numbers 4 and 8, in Section 4 of this user manual.

STEP 6 Remove and Dispose of the Needle



- **Remove the needle after each injection.**
- Carefully put the outer needle shield back over the needle.



- Unscrew the needle.
- Replace blue pen cap on pen before storage.



- Throw away needles in a puncture-resistant container or as recommended by your healthcare professional.

STEP 7 Store Pen for Next Dose

- Store your BYETTA pen properly. (See **Storing Your BYETTA Pen** in Section 1 of this user manual for more information.)
- When it is time for your next routine dose, go to **Section 3, Step 1**, and repeat Steps 1 - 7.

Section 4. COMMONLY ASKED QUESTIONS

1. Do I need to do the New Pen Setup before every dose?

- No. The New Pen Setup is done only **once**, just before each new pen is used for the first time.
- The purpose of the setup is to make sure that your BYETTA pen is ready to use for the next 30 days.
- **If you repeat the New Pen Setup before each routine dose, you will not have enough BYETTA for 30 days**. The small amount of BYETTA used in the New Pen Setup will not affect the 30-day supply of BYETTA.

2. Why are there air bubbles in the cartridge?

- A small air bubble is normal. It will not harm you or affect your dose.
- If the pen is stored with a needle attached, air bubbles may form in the cartridge. **Do not** store the pen with the needle attached.

3. What should I do if BYETTA does not come out of the needle tip after four tries during New Pen Setup?

- Remove the needle by carefully putting the outer needle shield back over the needle. Unscrew and dispose of properly.
- Attach a new needle and repeat **New Pen Setup, Steps B – E**, in Section 2 of this user manual. Once you see several drops or a stream of liquid coming out of the tip of the needle, the setup is complete.

4. Why do I see BYETTA leaking from my needle after I have finished my injection?

It is normal for a single drop to remain on the tip of your needle after your injection is complete. If you see more than one drop:

- You may not have received your full dose. **Do not** inject another dose. **Consult with your healthcare professional about how to handle a partial dose.**
- To prevent this, for your next dose, **firmly push and hold** the injection button in and **slowly count to 5** (see **Section 3, Step 4: Inject the Dose**).

5. What do the arrows mean?

The arrows mean you are ready for the next step. These arrows  show the direction to pull or turn the dose knob in the next step. This symbol  means the dose knob is pushed in and the pen is ready to reset.

6. How can I tell when the injection is complete?

The injection is complete when:

- You have firmly pushed the injection button in all the way **until it stops**

and

- **You have slowly counted to 5** while you are still holding the injection button in and the needle is still in your skin

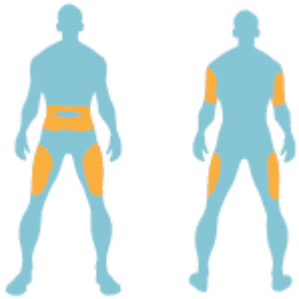
and

- The  is in the centre of the dose window.

7. Where should I inject BYETTA?

BYETTA should be injected into your abdomen, thigh, or upper arm using the injection technique recommended by your healthcare professional.

Front Back



8. What if I cannot pull, turn, or push the dose knob?
Check the symbol in the dose window. Follow the steps next to the matching symbol.

If  is in the dose window:

- Pull the dose knob out until  appears.

If  is in the dose window and the dose knob will not turn:

- The cartridge in your BYETTA pen may not have enough liquid to deliver a full dose. A small amount of BYETTA will always remain in the cartridge. If the cartridge contains a small amount or looks empty, obtain a new BYETTA pen.

If  and part of the  are in the dose window and the dose knob cannot be pushed in:

- The dose knob was not turned all the way. Continue turning the dose knob clockwise until  is in the centre of the dose window.

If part of  and part of  are in the dose window and the dose knob cannot be pushed in:

- The needle may be clogged, bent, or incorrectly attached.
- Attach a new needle. Make sure needle is on straight and screwed on all the way.
- Firmly push the injection button in all the way. BYETTA should come from needle tip.

If  is in the dose window and the dose knob will not turn:

- The injection button was not pushed in all the way and a complete dose was not delivered. **Consult with your healthcare professional about how to handle a partial dose**.
- Follow these steps to reset your pen for your next injection:
  - Firmly push the injection button in all the way **until it stops**. Keep holding the injection button in and **slowly count to 5**. Then turn the dose knob clockwise until  appears in the dose window.
  - If you cannot turn the dose knob, the needle may be clogged. Replace the needle and repeat the step above.
- For your next dose, be sure to **firmly push and hold** the injection button in and **slowly count to 5** before removing needle from skin.

Please see the accompanying Package Leaflet. For additional information contact your healthcare professional.

Pen User Manual was last approved in

PEN USER MANUAL

Section 1. **WHAT YOU NEED TO KNOW ABOUT YOUR BYETTA PEN**

Read this section completely before you begin. Then, move on to section 2 – getting started.

BYETTA 10 micrograms solution for injection, pre-filled pen
(exenatide)



Read these instructions carefully BEFORE using your BYETTA pen. Also read the BYETTA Package leaflet that comes with the BYETTA pen carton.

You need to use the pen correctly in order to get the most benefit from BYETTA. Failure to follow these instructions completely may result in a wrong dose, a broken pen or an infection.

These instructions do not take the place of talking with your healthcare professional about your medical condition or your treatment. If you are having problems using your BYETTA pen, contact your healthcare professional.

IMPORTANT INFORMATION ABOUT YOUR BYETTA PEN

- BYETTA is injected twice a day, the pen contains enough medicine for 30 days. You do not have to measure any doses, the pen measures each dose for you.
- **DO NOT TRANSFER THE MEDICINE IN THE BYETTA PEN TO A SYRINGE.**
- If any part of your pen appears broken or damaged, do not use the pen.
- **Do not share your pen or needles as this may risk transmission of infectious agents.**
- This pen is not recommended for use by people who are blind or who cannot see well enough. Help will be needed by a person trained to use the pen.
- Healthcare professionals or other caregivers should follow local or institutional policies regarding needle handling.
- **Follow the instructions for hygienic injection technique recommended by your healthcare professional.**
- Follow Section 2 only to set up a new pen before first use.
- Section 3 of this manual should be used for every injection.

ABOUT INJECTION NEEDLES

What kinds of needles can be used with my BYETTA pen?

- Injection needles are not included. The following are examples of disposable needles that can be used with your BYETTA pen:
  - 29 (thin), 30 or 31 (thinner) gauge (diameter 0.25-0.33mm) and
  - 12.7, 8 or 5mm length.

Ask your healthcare professional which needle gauge and length is best for you.

Do I use a new needle for each injection?

- Yes. Do not reuse needles.
- Remove the needle immediately after each injection. This will help prevent leakage of BYETTA, keep out air bubbles, reduce needle clogs, and decrease the risk of infection.
- Never push the injection button on the pen unless a needle is attached.

How do I throw away my needles?

- Throw away used needles in a puncture-resistant container or as recommended by your healthcare professional.
- Do not throw away the pen with a needle attached.

STORING YOUR BYETTA PEN

How do I store my BYETTA pen?

- Store in a refrigerator (2° to 8°C).
- Do not freeze. Throw away any BYETTA pen that has been frozen.
- Once in use, your BYETTA pen should be kept below 25°C.
- Replace the cap on the pen in order to protect from light.
- Do not store the BYETTA pen with the needle attached. If the needle is left on, medicine may leak from the BYETTA pen or air bubbles may form in the cartridge.

Keep your pen and needles out of the reach and sight of children.

How long can I use a BYETTA pen?

- Use a BYETTA pen for only 30 days after setting up a new pen for first use.
  Dispose of a used BYETTA pen after 30 days, even if some medicine remains in the pen.
- Mark the date when you first used your pen and the date 30 days later in the spaces below:

Date of first use

Date to throw away pen

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

How do I clean my BYETTA pen?

- If needed, wipe the outside of the pen with a clean, damp cloth.
- White particles may appear on the outside tip of the cartridge during normal use. You may remove them with an alcohol wipe or alcohol swab.

Please see the accompanying BYETTA Package Leaflet. For additional information, contact your healthcare professional.

Section 2. GETTING STARTED

Read and follow the directions in this section only after you've read section 1-what you need to know about your BYETTA pen.

Set up your new pen just before you use it for the first time. Follow the **New Pen Setup** only **once**. For routine use, **do not repeat** the New Pen Setup. If you do, you will run out of BYETTA before 30 days of use.

BYETTA PEN PARTS



Blue Pen Cap | Cartridge | BYETTA Liquid | Label | Dose Window | Dose Knob | Injection Button

NEEDLE PARTS
(Needles Not Included)



Outer Needle Shield | Inner Needle Shield | Needle | Paper Tab

DOSE WINDOW SYMBOLS

- ready to pull dose knob out
- ready to turn to dose position
- ready to inject 10 micrograms (µg)
- dose knob pushed in and ready to reset

NEW PEN SETUP – DO THIS ONE TIME ONLY

STEP A Check the Pen



- Wash hands prior to use.
- Check pen label to make sure it is your 10 µg pen.
- Pull off the blue pen cap.



Check BYETTA in the cartridge. The liquid should be clear, colourless, and free of particles. If it is not, do not use.
Note: A small air bubble in the cartridge is normal

STEP B Attach the Needle



- Remove paper tab from outer needle shield.
- **Push** outer needle shield containing the needle **straight** onto the pen, then **screw** needle on until secure.



- Pull off outer needle shield. **Do not** throw away. The outer needle shield will be used when you are removing the needle from the pen after the injection.



- Pull off inner needle shield and throw away. A small drop of liquid may appear. This is normal.

STEP C Dial the Dose



- Check that the  is in the dose window. If not, turn dose knob clockwise **until it stops** and the  is in the dose window.



- **Pull dose knob out until it stops** and the  is in the dose window.



- **Turn dose knob clockwise until it stops** at . Make sure that the 10 with the line under it is in the centre of the dose window.

Note: If you cannot turn the dose knob clockwise to the , see **Commonly Asked Questions**, number 8, in Section 4 of this user manual.

STEP D Prepare the Pen



- Point the needle of the pen up and away from you.



PUSH & HOLD

- **Use thumb to firmly push the injection button in until it stops**, then continue holding the injection button in while **slowly counting to 5.**
- **If you do not see a stream or several drops come from the needle tip, repeat Steps C & D.**



- Pen preparation is complete when the  is in the centre of the dose window AND you have seen a stream or several drops come from the needle tip.

Note: If you do not see liquid after 4 times, see **Commonly Asked Questions**, number 3, in Section 4 of this user manual.

STEP E Complete New Pen Setup



- **Turn dose knob clockwise until it stops** and the  is in the dose window.
- New Pen Setup is now done. Do not repeat Section 2 for routine use, if you do, you will run out of BYETTA before 30 days of use.
- You are now ready for your first dose of BYETTA.
- **Go to Section 3, Step 3, for instructions on how to inject your first routine dose.**

Note: If you cannot turn the dose knob, see **Commonly Asked Questions**, number 8, Section 4 of this user manual.

Section 3. ROUTINE USE

Now that you have done the New Pen Setup, follow Section 3 for **all** of your injections.

STEP 1 Check the Pen



- Wash hands prior to use.
- Check pen label to make sure it is your 10 µg pen.
- Pull off the blue pen cap.



- Check BYETTA in the cartridge.
- The liquid should be clear, colourless, and free of particles. If it is not, do not use.

Note: A small air bubble will not harm you or affect your dose.

STEP 2 Attach the Needle



- Remove paper tab from outer needle shield.
- **Push** outer needle shield containing the needle **straight** onto the pen, then **screw** needle on until secure.



- Pull off outer needle shield. **Do not** throw away. The outer needle shield will be used when you are removing the needle from the pen after the injection.



- Pull off inner needle shield and throw away. A small drop of liquid may appear. This is normal.

STEP 3 Dial the Dose



- Check that the  is in the dose window. If not, turn dose knob clockwise **until it stops** and the  is in the dose window.



- **Pull dose knob out until it stops** and the  is in the dose window.



- **Turn dose knob clockwise until it stops** at . Make sure that the 10 with the line under it is in the centre of the dose window.

Note: If you cannot turn the dose knob clockwise to the , see **Commonly Asked Questions**, number 8, in Section 4 of this user manual.

STEP 4 Inject the Dose



- Grip pen firmly.
- Insert needle into skin using **hygienic** injection technique recommended by your healthcare professional.



PUSH & HOLD

- **Use thumb to firmly push injection button in until it stops**, then continue holding the injection button in while **slowly counting to 5** in order to get a full dose.
- Remove needle from skin.



- Injection is complete when the  is in the centre of the dose window.
- The pen is now ready to reset.

Note: If you see several drops of BYETTA leaking from the needle after the injection, the injection button was not pushed in all the way. See **Commonly Asked Questions**, number 4, in Section 4 of this user manual.

STEP 5 Reset the Pen



- **Turn dose knob clockwise until it stops** and the  is in the dose window.

Note: If you cannot turn the dose knob, or if your pen leaks, your full dose has not been delivered. See **Commonly Asked Questions**, numbers 4 and 8, in Section 4 of this user manual.

STEP 6 Remove and Dispose of the Needle



- **Remove the needle after each injection.**
- Carefully put the outer needle shield back over the needle.



- Unscrew the needle.
- Replace blue pen cap on pen before storage.



- Throw away needles in a puncture-resistant container or as recommended by your healthcare professional.

STEP 7 Store Pen for Next Dose

- Store your BYETTA pen properly. (See **Storing Your BYETTA Pen** in Section 1 of this user manual for more information.)
- When it is time for your next routine dose, go to **Section 3, Step 1**, and repeat Steps 1 - 7.

Section 4. COMMONLY ASKED QUESTIONS

1. Do I need to do the New Pen Setup before every dose?

- No. The New Pen Setup is done only **once**, just before each new pen is used for the first time.
- The purpose of the setup is to make sure that your BYETTA pen is ready to use for the next 30 days.
- **If you repeat the New Pen Setup before each routine dose, you will not have enough BYETTA for 30 days**. The small amount of BYETTA used in the New Pen Setup will not affect the 30-day supply of BYETTA.

2. Why are there air bubbles in the cartridge?

- A small air bubble is normal. It will not harm you or affect your dose.
- If the pen is stored with a needle attached, air bubbles may form in the cartridge. **Do not** store the pen with the needle attached.

3. What should I do if BYETTA does not come out of the needle tip after four tries during New Pen Setup?

- Remove the needle by carefully putting the outer needle shield back over the needle. Unscrew and dispose of properly.
- Attach a new needle and repeat **New Pen Setup, Steps B – E**, in Section 2 of this user manual. Once you see several drops or a stream of liquid coming out of the tip of the needle, the setup is complete.

4. Why do I see BYETTA leaking from my needle after I have finished my injection?

It is normal for a single drop to remain on the tip of your needle after your injection is complete. If you see more than one drop:

- You may not have received your full dose. **Do not** inject another dose. **Consult with your healthcare professional about how to handle a partial dose.**
- To prevent this, for your next dose, **firmly push and hold** the injection button in and **slowly count to 5** (see **Section 3, Step 4: Inject the Dose**).

5. What do the arrows mean?

The arrows mean you are ready for the next step. These arrows  show the direction to pull or turn the dose knob in the next step. This symbol  means the dose knob is pushed in and the pen is ready to reset.

6. How can I tell when the injection is complete?

The injection is complete when:

- You have firmly pushed the injection button in all the way **until it stops**

and

- **You have slowly counted to 5** while you are still holding the injection button in and the needle is still in your skin

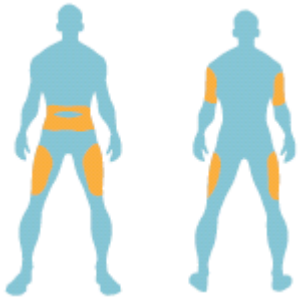
and

- The  is in the centre of the dose window.

7. Where should I inject BYETTA?

BYETTA should be injected into your abdomen, thigh, or upper arm using the injection technique recommended by your healthcare professional.

Front Back



8. What if I cannot pull, turn, or push the dose knob?
Check the symbol in the dose window. Follow the steps next to the matching symbol.

If  is in the dose window:

- Pull the dose knob out until  appears.

If  is in the dose window and the dose knob will not turn:

- The cartridge in your BYETTA pen may not have enough liquid to deliver a full dose. A small amount of BYETTA will always remain in the cartridge. If the cartridge contains a small amount or looks empty, obtain a new BYETTA pen.

If  and part of the  are in the dose window and the dose knob cannot be pushed in:

- The dose knob was not turned all the way. Continue turning the dose knob clockwise until  is in the centre of the dose window.

If part of  and part of  are in the dose window and the dose knob cannot be pushed in:

- The needle may be clogged, bent, or incorrectly attached.
- Attach a new needle. Make sure needle is on straight and screwed on all the way.
- Firmly push the injection button in all the way. BYETTA should come from needle tip.

If  is in the dose window and the dose knob will not turn:

- The injection button was not pushed in all the way and a complete dose was not delivered. **Consult with your healthcare professional about how to handle a partial dose**.
- Follow these steps to reset your pen for your next injection:
  - Firmly push the injection button in all the way **until it stops**. Keep holding the injection button in and **slowly count to 5**. Then turn the dose knob clockwise until  appears in the dose window.
  - If you cannot turn the dose knob, the needle may be clogged. Replace the needle and repeat the step above.
- For your next dose, be sure to **firmly push and hold** the injection button in and **slowly count to 5** before removing needle from skin.

Please see the accompanying Package Leaflet. For additional information contact your healthcare professional.

Pen User Manual was last approved in