BYETTA™

exenatide

Solution for injection

Name of the medicinal product

BYETTA 5 micrograms solution for injection, prefilled pen
BYETTA 10 micrograms solution for injection, prefilled pen

Qualitative and quantitative composition

The active ingredient in BYETTA is exenatide.
BYETTA 5 microgram prefilled pen: Each dose contains 5 micrograms (µg) synthetic exenatide in 20 microlitres (µl), (0.25 mg exenatide per ml).
BYETTA 10 microgram prefilled pen: Each dose contains 10 micrograms (µg) synthetic exenatide in 40 microlitres (µl), (0.25 mg exenatide per ml).

Excipients:
BYETTA 5 microgram: Each dose contains 44 µg metacresol.
BYETTA 10 microgram: Each dose contains 88 µg metacresol.
This medicinal product contains less than 1mmol sodium per dose, i.e. essentially "sodium-free".
For a full list of excipients, see section *List of excipient*.

Pharmaceutical form

Solution for injection, prefilled pen.
Clear, colourless solution.

Therapeutic indications

BYETTA is indicated as an adjunct to diet and exercise for treatment of type 2 diabetes mellitus in combination with:
- metformin
- sulphonylureas
- metformin and a sulphonylureas

in patients 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 in adults who have not achieved adequate glycaemic control with these agents

Posology and method of administration

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 prefilled 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.

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.

BYETTA is recommended for use in patients with type 2 diabetes mellitus who are already receiving metformin, a sulphonylurea, 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, the current dose of metformin can be continued as no increased risk of hypoglycaemia is anticipated, compared to metformin 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 *Special warnings and precautions for use.*). 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 *Undesirable effects).*

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.

Limited experience exists concerning the combination of BYETTA with thiazolidinediones (see *Pharmacodynamic properties*).

Specific patient groups
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 *Pharmacokinetic properties*).

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

Patients with hepatic impairment
No dosage adjustment of BYETTA is necessary in patients with hepatic impairment (see *Pharmacokinetic properties*).

Children and adolescents
There is no experience in children and adolescents below 18 years.

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

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.

Intravenous or intramuscular injection of BYETTA is not recommended.

In patients with end-stage renal disease receiving dialysis, single doses of BYETTA 5 µg increased frequency and severity of undesirable gastrointestinal effects. 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.

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 pharmacological agents known to affect renal function/hydration status. Concomitant agents 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 agents, including BYETTA.

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.

There have been rare, spontaneously reported events of acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed with supportive treatment, but very rare cases of necrotizing or 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.

The experience in patients with BMI ≤25 is limited.

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

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.

Interactions
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 *Interaction with other medicinal products and other forms of interaction*.

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.

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.

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.

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 (0h) and 1h, 2h and 4h 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 0.6h in the control period to 0.9h, 4.2h, 3.3h, and 1.6h, 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.

HMG CoA reductase inhibitors: Lovastatin AUC and C_{max} were decreased approximately 40% and 28%, respectively, and T_{max} was delayed about 4h 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.

Digoxin, lisinopril and warfarin: A delay in T_{max} of about 2h 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 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 *Undesirable effects*).

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.

Pregnancy and lactation

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

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

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.

Undesirable effects

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) and common (≥1/100, <1/10).

Table 1: Adverse reactions reported in long term phase 3 controlled studies[1*]

Body system/adverse reaction terms	**Frequency of occurrence**		
Reactions	**Common**	**Very common**	**Not Known**
Blood and lymphatic system disorders			
Drug-induced thrombocytopenia			X[3]
Metabolism and nutrition disorders			
Hypoglycaemia (with metformin and a sulphonylurea)[2]		X	
Hypoglycaemia (with a sulphonylurea)		X	
Decreased appetite	X		
Nervous system disorders			
Headache[2]	X		

Dizziness	X		
Gastrointestinal disorders			
Nausea		X	
Vomiting		X	
Diarrhoea		X	
Dyspepsia	X		
Abdominal pain	X		
Gastroesophageal reflux disease	X		
Abdominal distension	X		
Skin and subcutaneous tissue disorders			
Hyperhidrosis[2]	X		
General disorders and administrative site conditions			
Feeling jittery	X		
Asthenia[2]	X		
Investigation			
Weight decrease	X		

*N = 1788 BYETTA-treated intent-to-treat (ITT) patients.

[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.). Data from a 30-week study comparing BYETTA with insulin lispro when added to existing basal insulin therapy (insulin glargine) was not included

[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.

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, with or without metformin

Drug-induced thrombocytopenia

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

Hypoglycaemia: 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. Most episodes of hypoglycaemia were mild to moderate in intensity, and all 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 *Pharmacodynamic properties).* 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 developed anti-exenatide antibodies had 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 three insulin-comparator controlled trials (n=790) 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).

Spontaneous reports
Since market introduction of BYETTA, the following additional adverse reactions have been reported:

Immune system disorders: anaphylactic reaction, very rarely.

Metabolism and nutritional disorders: dehydration, generally associated with nausea, vomiting and/or diarrhoea.

Nervous system disorders: dysgeusia, somnolence.

Gastrointestinal disorders: eructation, constipation, flatulence, acute pancreatitis (see *Special warnings and precautions for use*).

Renal and urinary disorders: altered renal function, including acute renal failure, worsened chronic renal failure, renal impairment, increased serum creatinine (see *Special warnings and precautions for use*).

Skin and subcutaneous tissue disorders: alopecia (rarely), macular rash, papular rash, pruruitis, urticaria, angioneurotic oedema.

Investigations: international normalised ratio increased with concomitant warfarin, some reports associated with bleeding (see *Interaction with medicinal products and other forms of interaction*).

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.

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: 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 *Special warnings and precautions for use*).

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

The experience in patients >65 years and in patients with impaired renal function is limited.

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 in combination with basal insulin

In a 30-week study, either BYETTA (5 mcg BID for 4 weeks, followed by 10 mcg 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 $HbA_{1c} \leq 6.5\%$ 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 94 kg 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.

In a 30-week, open-label, active comparator-controlled, noninferiority study, the safety and efficacy of BYETTA (n=315) versus titrated insulin lispro three times daily (n=312) on a background of optimized basal insulin glargine and metformin in patients with type 2 diabetes was evaluated.

Following a basal insulin optimization (BIO) phase, patients with $HbA_{1c} > 7.0\%$ were randomized to add either BYETTA or insulin lispro to their existing regimen of insulin glargine and metformin. In both treatment groups, subjects continued to titrate their insulin glargine doses using an algorithm reflecting current clinical practice.

All patients assigned to BYETTA initially received 5 mcg BID for four weeks. After four weeks, their dose was increased to 10 mcg BID. Patients in the BYETTA-treated group with an HbA1c ≤8.0% at the end of the BIO phase decreased their insulin glargine dose by at least 10%.

BYETTA lowered HbA_{1c} by 1.1% from a baseline of 8.3% and insulin lispro lowered HbA_{1c} by 1.1% from a baseline of 8.2% and noninferiority of BYETTA to titrated lispro was demonstrated. The proportion of patients achieving $HbA_{1c} < 7\%$ was 47.9% with BYETTA and 42.8% with insulin lispro. Weight loss of 2.6 kg from a baseline of 89.9 kg was observed with BYETTA whereas a weight gain of 1.9 kg from a baseline of 89.3 kg was observed with insulin lispro

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

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.

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.

Pharmacokinetic properties

Absorption

Following subcutaneous administration to patients with type 2 diabetes, exenatide reaches median peak plasma concentrations in 2h. Mean peak exenatide concentration (C_{max}) was 211 pg/ml and overall mean area under the curve ($AUC_{0-\infty}$) 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.

Metabolism 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 2.4h. 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 *Posology and method of administration*).

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: Data in elderly are limited, but suggest no marked changes in exenatide exposure with increased age up to about 75 years old. There are no pharmacokinetic data in patients >75 years.

Children and adolescents: Pharmacokinetics of exenatide has not been investigated in children and adolescents below 18 years of age.

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.

Pharmaceutical particulars

List of excipients

Metacresol
Mannitol
Glacial acetic acid
Sodium acetate trihydrate
Water for injections

Incompatibilities

This medicinal product must not be mixed with other medicinal products.

Shelf life

3 years.
Shelf life for pen in use: 30 days.

Special precautions for storage

Store in a refrigerator (2ºC – 8ºC).
Do not freeze. Protect from light.
In use
The pen should be returned to the refrigerator after each use. However the pen can be stored between 5ºC and 25ºC during the 30 days patient in-use period.
The pen should not be stored with the needle attached.
Replace cap on pen in order to protect from light.

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 5 microgram prefilled pen contains 60 doses of sterile preserved solution (approximately 1.2 ml)

Each 10 microgram prefilled pen contains 60 doses of sterile preserved solution (approximately 2.4 ml)
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.

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.

Pack size
Box, 1 pre-filled pen @ 60 doses (1.2 ml) Reg. No.: DKI1859602443A1
Box, 1 pre-filled pen @ 60 doses (2.4 ml) Reg. No.: DKI1859602443A1

HARUS DENGAN RESEP DOKTER

Manufactured by:
Baxter Pharmaceutical Solutions LLC
927 South Curry Pike
Bloomington, Indiana 47403, USA
Released by:
AstraZeneca UK Ltd.
Silk Road Business Park
Macclesfield, UK

Imported by:
PT AstraZeneca Indonesia,
Cikarang, Bekasi – Indonesia

Date of revision of the text
As on approval date
GEL Ref.:

INFORMASI PRODUK UNTUK PASIEN
BYETTA®
exenatide injection

Brosur ini adalah ringkasan informasi produk dan tidak menjelaskan BYETTA secara detail. Jika Anda memiliki pertanyaan tentang BYETTA silahkan hubungi Dokter atau Apoteker Anda.

INFORMASI UMUM TENTANG BYETTA

Apa kegunaan BYETTA:

BYETTA diindikasikan sebagai terapi tambahan terhadap diet dan olahraga untuk pengobatan diabetes melitus tipe 2 dalam kombinasi dengan:
- metformin
- sulphonylurea
- metformin dan sulphonylurea

pada pasien yang kadar gula darahnya belum terkontrol oleh pemberian dosis maksimal terapi obat oral tersebut diatas.

BYETTA juga diindikasikan sebagai terapi tambahan terhadap terapi basal insulin dengan atau tanpa metformin pada pasien dewasa yang kadar gula darahnya belum terkontrol dengan penggunaan terapi oral tersebut diatas

Bagaimana cara kerja BYETTA:

BYETTA membantu tubuh untuk melepaskan insulin ketika kadar gula dalam darah tinggi. Hal ini membantu meningkatkan kontrol gula darah Anda.

Kapan BYETTA tidak boleh digunakan:

• Jangan gunakan BYETTA jika Anda alergi terhadap exenatide atau zat lainnya yang tercantum dalam informasi zat tambahan pada brosur informasi produk BYETTA.
• Jangan gunakan BYETTA jika Anda memiliki penyakit ginjal parah atau sedang dalam terapi dialysis.
• Jangan gunakan BYETTA jika Anda mengalam *diabetic ketoacidosis* (akumulasi keton dalam darah dan urin).
• Jangan gunakan BYETTA jika Anda memiliki diabetes tipe 1

Apa zat aktif BYETTA:

Exenatide

Apa zat tambahan BYETTA:

m-cresol, mannitol, glacial acetic acid, sodium acetate trihydrate and water for injection.

Apa bentuk sediaan BYETTA:
BYETTA adalah larutan injeksi subkutan dan dikemas dalam *prefilled injection pens.*
BYETTA tersedia dalam dua *prefilled pens* yang terdiri dari 60 dosis 5 µg atau 10 µg exenatide per dosis.

CARA PENGGUNAAN OBAT
Anda disarankan membaca *Pen User Manual* terkait instruksi cara pakai dan cara injeksi BYETTA Pen.

Jarum untuk Pen tidak termasuk dalam kemasan. Tanyakan Dokter atau Apoteker Anda spesifikasi jarum yang baik untuk Anda. Anda harus mengacu pada "**New Pen Setup**" ketika menggunakan prefilled BYETTA Pen yang baru. **Jangan mengulang "New Pen Setup" setiap kali injeksi**, karena Anda dapat kehabisan obat sebelum 30 hari.

Gunakan BYETTA sesuai dengan apa yang diresepkan Dokter Anda. Jangan pernah menambahkan dosis diluar resep Dokter.
BYETTA diinjeksikan dibawah kulit (subkutan) pada paha atas, area perut (abdomen), atau lengan atas. Jika Anda menggunakan BYETTA dan basal insulin, jangan mencampurkan dua produk tersebut. BYETTA dan basal insulin harus diberikan sebagai dua injeksi terpisah di dua tempat injeksi yang berbeda.

BYETTA hanya dapat digunakan jika larutannya bening, tak berwarna dan tidak mengandung partikel. BYETTA tidak boleh dipindahkan dari pen kedalam syringe atau vial.

Jangan menggunakan ulang atau berbagi jarum dengan orang lain, karena hal ini dapat berpotensi menularkan infeksi. BYETTA pen tidak boleh digunakan bersama dengan orang lain.

Dosis lazim awal: 5 µg dua kali sehari diinjeksikan dibawah kulit dalam 60 menit sebelum makan pagi dan makan malam (atau sebelum 2 jam makan utama dalam satu hari, setidaknya ada jeda 6 jam lebih dari penggunaan pertama ke kedua). **BYETTA tidak boleh diinjeksikan setelah makan.** Dosis BYETTA dapat ditingkatkan menjadi 10 µg dua kali sehari setelah 1 bulan perngobatan jika diperlukan untuk mengontrol kadar gula darah. Dosis maksimal adalah 10 µg dua kali sehari.

Overdose:
Jika Anda menggunakan BYETTA secara berlebihan, segera hubungi Dokter Anda atau segera pergi ke Unit Gawa Darurat Rumah Sakit terdekat. Tunjukkan BYETTA Pen pada Dokter Anda. Penggunaan BYETTA yang berlebihan dapat menyebabkan mual, muntah, pusing, atau gejala gula darah rendah.

Missed Dose:
Jika Anda lupa menggunakan BYETTA, JANGAN menambahkan dosisnya. Lakukan injeksi pada waktu injeksi berikutnya sesuai jadwal yang telah ditentukan .

EFEK SAMPING DAN APA YANG HARUS DILAKUKAN

Seperti kebanyakan obat lainnya, BYETTA dapat menyebabkan efek samping, meskipun tidak semua orang akan mengalaminya.

Reaksi alergi berat (anaphylaxis) telah dilaporkan terjadi dengan frekuensi kejadian sangat jarang (muncul pada 1 dari 1,000 orang).
Anda harus menemui Dokter Anda secepatnya jika Anda mengalami gejala sebagai berikut :

- Pembengkakan pada wajah, lidah atau kerongkongan (angioedema)
- Ruam, gatal, dan pembengkakan pada jaringan leher, wajah, mulut atau kerongkongan yang terjadi secara cepat.
- Kesulitan menelan

- Gatal-gatal dan kesulitan bernafas

Kasus inflamasi pada pancreas (pancreatitis) dilaporkan telah terjadi pada pasien yang menggunakan BYETTA dengan frekuensi kejadian tidak diketahui. Pankreatitis dapat menjadi suatu konsisi medis yang serius, dan berpotensi mengancam jiwa.

- Sampaikan pada Dokter Anda jika Anda pernah menderita pankreatitis, batu empedu, kecanduan alcohol atau kadar trigliserida tinggi. Kondisi medis yang demikian dapat meningkatkan resiko Anda untuk terkena pankreatitis atau mengidap pankreatitis lagi, meskipun Anda tidak menggunakan obat ini.
- BERHENTI menggunakan obat ini dan hubungi Dokter Anda segera jika Anda mengalami nyeri perut yang parah dan tidak mau pergi, dengan atau tanpa muntah, karena hal ini dapat mengindikasikan bahwa pancreas Anda inflamasi (pancreatitis).

Efek samping yang sangat umum terjadi (dapat terjadi pada 1 dari 10 orang):

- mual (mual tidak umum terjadi saat menggunakan obat ini, namun dapat berkurang seiring waktu pada kebanyakan pasien)
- muntah
- diare
- hipoglikemia

Ketika BYETTA digunakan bersamaan dengan obat yang mengandung sulfonylurea atau insulin, maka episode kadar gula darah rendah
(hypoglycaemia, dengan tingkat keparahan umumnya ringan hingga sedang) seringkali dapat muncul. Dosis sulfonylurea maupun insulin harus dikurangi jika hal ini terjadi. Gejala kadar gula darah rendah adalah sakit kepala, ngantuk, lemas, pusing, kebingungan, lekas marah, lapar, detak jantung cepat, berkeringat, dan gelisah. Dokter Anda akan menyampaikan pada Ada bagaimana cara mengatasi kadar gula rendah Anda.

Efek samping yang umum terjadi (dapat terjadi pada 1 dari 10 orang):

- Pusing
- Sakit kepala
- Gelisah
- Nyeri di area perut
- Distensi abdomen
- Dyspepsia
- Hiperhidrosis
- *Gastroesophageal reflux*
- Kehilangan energi dan kekuatan
- Penurunan berat badan
- Penurunan nafsu makan

Obat ini dapat menyebabkan penurunan nafsu makan Anda, jumlah makanan yang Anda makan, dan berat badan Anda.
Jika Anda kehilangan berat badan terlalu cepat (lebih dari 1,5 kg per minggu) bicarakan pada Dokter Anda tentang hal tersebut karena hal tersebut dapat menyebabkan masalah seperti batu empedu.

Efek samping yang tidak diketahui (frekuensi tidak dapat diperkirakan dari data yang tersedia)
Selain itu **efek samping** yang telah terjadi :

- Pendarahan atau lebam lebih mudah terjadi dari biasanya karena kadar trombosit darah yang rendah.

PERINGATAN DAN PERHATIAN

Kasus inflamasi pada pankreas (pankreatitis) telah dilaporkan terkait penggunaan BYETTA. Pankreatitis merupakan kondisi medis yang serius dan berpotensi mengancam jiwa.
(Lihat – EFEK SAMPING DAN APA YANG HARUS DILAKUKAN.)

Tidak ada pengalaman penggunaan BYETTA pada anak-anak dan penderita dengan usia kurang dari 18 tahun sehingga pengunaan BYETTA pada penderita usia tersebut tidak direkomendasikan.

BYETTA dapat meningkatkan detak jantung atau menyebabkan perubahan pada ritme jantung.
Jarang adanya obat-obat dengan efek tersebut yang menyebabkan pusing, palpitasi (detak jantung yang terasa tidak teratur, cepat atau berdebar). Perubahan ritme jantung ini kemungkinan terjadi jika Anda memiliki penyakit jantung atau jika Anda menggunakan obat-obatan tertentu.
Secara umum, orang dengan usia 65 tahun keatas memiliki resiko yang lebih tinggi untuk mengalami hal tersebut. Lihat **EFEK SAMPING DAN APA YANG HARUS DILAKUKAN**. Jika Anda mengalami pusing, palpitasi (sensasi detak jantung yang tidak beraturan, cepat atau berdebar), pingsan, atau kejang, maka Anda harus segera mencari pertolongan medis.

SEBELUM menggunakan BYETTA sampaikan pada Dokter dan Apoteker Anda jika Anda:
• Memiliki masalah serius dengan lambung Anda (*gastroparesis*) atau masalah pencernaan. BYETTA memperlambat pengosongan lambung sehingga makanan dicerna lebih lambat dalam lambung Anda.
• Mengalami muntah parah dan/atau diare dan/atau dehidrasi.
• Memiliki riwayat pankreatitis (inflamasi pankreas), batu di empedu, riwayat kecanduan alkohol, atau kadar trigliserida tinggi dalam darah.
• Menggunakan sulfonylurea (seperti: glyburide, gliclazide, glimepiride) atau insulin karena tipe obat-obatan ini dapat meningkatkan resiko hipoglikemia (kadar gula darah rendah) jika digunakan sebagai kombinasi dengan BYETTA. Berhati-hatilah untuk menghindari kadar gula rendah ketika mengemudi atau mengoperasikan mesin.
• Pernah menjalani transplantasi ginjal atau mengalami kelainan ginjal.
• Hamil atau berencana untuk hamil
• Menyusui atau berencana untuk menyusui.
• Mengalami atau pernah mengalami gagal jantung atau penyakit jantung lainnya seperti angina atau gangguan ritme jantung, atau serangan jantung.
• Memiliki riwayat pingsan.
• Memiliki laju jantung yang tinggi (berdetak cepat) atau mengalami suatu kondisi yang disebut *heart block*.
• memiliki gangguan elektrolit (sebagai contoh kadar kalium atau magnesium dalam darah rendah) atau megalami kondisi yang dapat menyebabkan gangguan elektrolit (seperti muntah, diare, dehidrasi).

Dan bicaralah dengan Dokter atau Apoteker Anda sebelum menggunakan BYETTA jika Anda:
• Didiagnosa mengidap gagal ginjal (*pituitary* atau *adrenal failure)*
• Mengalami gangguan makan (*eating disorders)*, atau sedang dalam program diet special, atau sering melewatkan waktu makan.
• Berolahraga secara regular atau seringkali
• Meminum alkohol dalam jumlah banyak
Kondisi-kondisi tersebut diatas dapat meningkatkan resiko kadar gula darah rendah jika Anda menggnakan BYETTA.

Kadar gula darah Anda dapat menjadi tinggi (hiperglikemi) jika Anda mengalami demam, infeksi, operasi, atau trauma (kondisi stress). Disarankan agar Anda segera menghubungi Dokter Anda jika mengalami kondisi tersebut diatas sehingga pengobatan Anda dapat disesuaikan dengan kondisi Anda.

BYETTA tidak boleh disuntikkan ke vena atau otot.

Penggunaan BYETTA dengan rapid-acting atau short-acting insulin tidak direkomendasikan.

INTERAKSI OBAT

Beritahu Dokter atau Apoteker Anda tentang obat,vitamin, dan suplemen herbal yang sedang Anda gunakan.

Khususnya jika Anda menggunakan:
• Pil untuk mengontrol kelahiran (pil KB), pil KB digunakan setidaknya 1 jam sebelum menggunakan BYETTA
• Antibiotik, obat ini digunakan setidaknya 1 jam sebelum menggunakan BYETTA
• warfarin (pengencer darah)
• digoxin (obat jantung)
• lisinopril (obat antihipertensi)
• parasetamol (obat Pereda nyeri dan demam)
• lovastatin (obat antikolesterol)
• obat-obatan dibawah ini dapat meningkatkan resiko gangguan ritme jantung:
  - obat-obatan untuk mengobati gangguan ritme jantung
  - antivirus untuk infeksi HIV.
  - diuretik (*water pills*)
  - obat-obatan untuk mengobati tekanan darah tinggi/hipertensi
  - obat-obatan untuk mengobati gagal jantung.
- Obat untuk menurunkan asam lambung (proton pump inhibitor). Obat ini digunakan setidaknya 1 jam sebelum atau 4 jam setelah menggunakan BYETTA.

BYETTA memperlambat pengosongan lambung dan dapat berdampak pada obat yang memerlukan penyerapan cepat di lambung. Tanyakan kepada Dokter atau Apoteker Anda sekiranya jadwal konsumsi obat (seperti pil KB, antibiotic) Anda perlu dirubah.

Jika Anda perlu mengkonsumsi obat bersamaan dengan makanan, maka silahkan konsumsi obat tersebut bersamaan dengan makanan ringan ketika Anda tidak menggunakan BYETTA.

Kenalilah obat yang Anda kosumsi. Buatlah daftar obat-obat tersebut dan tunjukan pada Dokter atau Apoteker Anda setiap kali Anda mendapatkan obat baru.

BAGAIMANA CARA PENYIMPANAN BYETTA

• Simpan BYETTA Pen Anda baik baru maupun yang sudah terpakai dalam kartonnya dan masukkan dalam lemari es bersuhu 2°C to 8°C dan terlindung dari cahaya. Buang BYETTA Pen yang telah membeku.
• Setelah penggunaan pertama, BYETTA Pen Anda harus disimpan dalam lemari pendingin atau pada suhu 2°C to 25°C.
• Gunakan BYETTA Pen hanya untuk 30 hari. Buang BYETTA Pen setelah digunakan selama 30 hari, meskipun masih ada yang tersisa didalam pen.
• BYETTA tidak boleh digunakan setelah tanggal kadaluarsa yang tertera pada label dan karton.
• Jangan menyimpan BYETTA Pen dengan jarum yang masih tertancap. Hal tersebut dapat menyebabkan kebocoran atau menimbulkan gelembung udara dalam cartridge.
• Pastikan BYETTA Pen, jarum, dan obat-obatan jauh dari jangkauan anak-anak dan hewan peliharaan.
• Buang jarum sudah pakai dalam kemasan anti tusuk yang dianjurkan oleh Dokter atau Apoteker Anda. Jangan membuang pen dengan jarum yang masih tertancap. Buang pen dengan cara yang disarankan oleh Dokter atau Apoteker Anda.

Kemasan :
Box, 1 pre-filled pen @ 60 doses (1.2 ml) Reg. No.: DKI1859602443A1

Box, 1 pre-filled pen @ 60 doses (2.4 ml) Reg. No.: DKI1859602443A1

HARUS DENGAN RESEP DOKTER

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