1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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 6.1.

3. PHARMACEUTICAL FORM

Solution for 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, and/or sulphonylureas in patients who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies.

4.2 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 10µg 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.

Each dose should be administered as a subcutaneous injection in the thigh, abdomen, or upper arm.

BYETTA is recommended for use in patients with type 2 diabetes mellitus who are already receiving metformin and/or a sulphonylurea. When BYETTA is added to existing metformin therapy, 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 4.4.).

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 section 5.1).

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 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).

Children and adolescents

The safety and effectiveness of exenatide have not been established in patients under 18 years of age. (see section 5.2).

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 should not be used in type 2 diabetes patients who require insulin therapy due to betacell failure.

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 concurrent use of BYETTA with insulin, D-phenylalanine derivatives (meglitinides), or alpha-glucosidase inhibitors has not been studied and cannot be recommended.

The experience in patients with BMI ≤25 is limited.

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

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 4.5.

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.

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 1000mg paracetamol was given with 10 µg BYETTA (0 h) 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 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.

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 section 4.8).

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 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.

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, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines.

4.8 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), common (≥1/100, <1/10) and uncommon (≥1/1,000 to <1/100).

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

Body system/adverse reaction terms	**Frequency of occurrence**		
Reactions	Very common	Common	Uncommon
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	
Acute pancreatitis			X[3]
Skin and subcutaneous tissue disorders			
Hyperhidrosis [2]		X	
General disorders and administrative site conditions			
Feeling jittery		X	
Asthenia [2]		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.

[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] Does not conform to criteria previously cited; acute pancreatitis events were uncommon in all treatment groups.

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.

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 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).

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.

Renal and urinary disorders: altered renal function, including acute renal failure, worsened chronic renal failure, renal impairment, increased serum creatinine (see section 4.4).

Skin and subcutaneous tissue disorders: macular rash, papular rash, pruruitis, urticaria, angioneurotic oedema.

Investigations: international normalised ratio increased with concomitant warfarin, some reports associated with bleeding (see section 4.5).

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: Other blood glucose lowering drugs, excl. insulins, ATC code: A10BX04.

Mechanism of action

Exenatide is an incretin mimetic 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

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 5µg BID	BYETTA 10µg 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 a placebo-controlled study of 16 weeks duration, BYETTA (n=121) or placebo (n=112) was added to existing thiazolidinedione treatment, with or without metformin. BYETTA (5 µg BID for 4 weeks, followed by 10 µg BID) resulted in statistically significant reductions from baseline HbA_{1c} compared to placebo (-0.8% versus +0.1%) as well as significant reductions in body weight (-1.5 versus -0.2 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.

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.

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 2.4kg versus 1.7kg) 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.

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.

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 2.4 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

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

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 Cmax (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

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

6.3 Shelf life

2 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

The pen should be returned to the refrigerator after each use. However, chemical and physical in use stability at ≤25ºC has been demonstrated for 7 days (168 hours), during the 30 day in use period.

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 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)

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 - 0.33mm) and 12.7, 8 or 5mm 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.

Manufactured by:
LILLY PHARMA FERTIGUNG UND DISTRIBUTION GMBH & CO. KG 35387 GIESSEN, GERMANY