

BYETTA[®]

(exenatide)

NAME OF THE MEDICINE

BYETTA (exenatide) Injection, Solution.

The active ingredient in BYETTA is exenatide. Exenatide is a 39-amino acid peptide amide. It has the empirical formula $C_{184}H_{282}N_{50}O_{60}S$ and molecular weight of 4186.6 Daltons. The amino acid sequence for exenatide is shown below.

H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH₂.

The CAS number for exenatide is 141732-76-5.

DESCRIPTION

BYETTA is a clear colourless solution.

BYETTA is supplied as a sterile, preserved solution for subcutaneous injection in a glass cartridge that has been assembled in an injector pen. Each millilitre contains 250 µg of synthetic exenatide. The excipients in BYETTA are meta-Cresol, mannitol, acetic acid - glacial, sodium acetate, and water for injections.

Two presentations of pre-filled pens are available, to deliver doses of either 5 µg or 10 µg. Each pre-filled pen will deliver 60 doses, providing 30 days of bid (twice daily) administration.

PHARMACOLOGY

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*. This leads to an increase in both the glucose-dependent insulin synthesis and secretion from pancreatic beta-cells, by mechanisms involving cyclic AMP and/or other intracellular signalling pathways. As blood glucose concentrations decrease, insulin secretion subsides thereby reducing the potential risk of hypoglycaemia (see **PRECAUTIONS**).

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

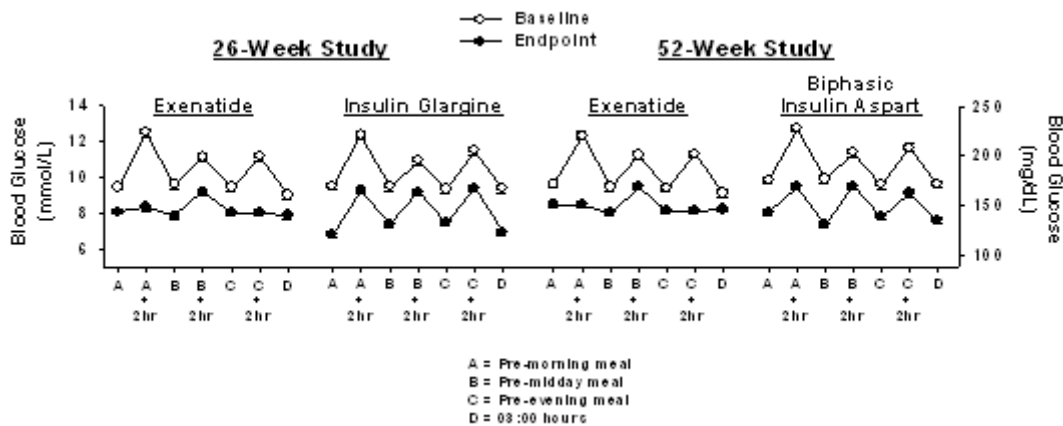
BYETTA slows gastric emptying thereby reducing the rate at which meal-derived glucose appears in the circulation.

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.

In the insulin-comparator controlled studies, BYETTA was associated with a significant reduction in postprandial blood glucose excursions compared with insulin glargine ($P < 0.0001$) and biphasic insulin aspart ($p < 0.0001$).

Figure 1: Summary of 7-point self-monitored blood glucose profiles at baseline and study endpoint in the insulin-comparator controlled studies



26-week study (ITT patients (n = 549)) and 52-week study (ITT patients (n = 501), last observation carried forward)

Beta-cell function: Clinical studies with BYETTA have demonstrated improvements in beta-cell function, using indicators such as the homeostasis model assessment for beta-cell function (HOMA-B) and the proinsulin to insulin ratio. In the 52-week insulin comparator study BYETTA (5 µg bid for 4 weeks, followed by 10 µg bid) in combination with metformin and a sulphonylurea improved HOMA-B by 32%. This result is comparable to that seen in the placebo-controlled studies. A significant reduction of 0.38 (from a baseline of 0.74) in the proinsulin/insulin ratio was observed in the 10 µg bid treatment arm of the combined placebo-controlled studies at 30 weeks. BYETTA has also shown improvement in beta-cell function in patients by restoration of first-phase insulin secretion and improved second-phase insulin secretion, in response to an intravenous bolus of glucose.

Pharmacokinetics

Absorption

Following subcutaneous administration to patients with type 2 diabetes, exenatide reaches median peak plasma concentrations in 2.1 h. Exenatide pharmacokinetics were measured in a crossover study in patients with type 2 diabetes in which single dose injections of 10 µg were administered subcutaneously in the abdomen, thigh or arm. Similar exposure was achieved with subcutaneous administration of exenatide in the abdomen, thigh, or arm. Mean (90% confidence intervals) of the three subcutaneous sites combined yielded peak exenatide concentration (C_{max}) of 211 pg/mL (100-385 pg/mL) and overall mean area under the curve (AUC_{0-inf}) of 1036 pg*h/mL (552-1928 pg*h/mL).

Based on a meta-analysis, exenatide exposure (AUC) increased proportionally over the therapeutic dose range of 5 µg to 10 µg. The C_{max} values increased less than proportionally over the therapeutic dose range of 5 µg to 10 µg.

Distribution

The mean apparent volume of distribution of exenatide following subcutaneous administration of a single dose of exenatide is 28.3 L

Metabolism and Elimination

Nonclinical studies have shown that exenatide is predominantly eliminated by glomerular filtration with subsequent proteolytic degradation. The mean apparent clearance of exenatide in humans is 9.1 L/h and the mean terminal half-life is 2.4 h. These pharmacokinetic characteristics of exenatide are independent of the dose. In most individuals, exenatide concentrations are measurable for approximately 10 h post-dose.

Special populations

Patients with renal impairment

In patients with mild to moderate renal impairment (creatinine clearance 30 to 80 mL/min), exenatide clearance was only mildly reduced compared to clearance in individuals with normal renal function. Clearance was significantly reduced to 0.9 l/h in patients with end-stage renal disease receiving dialysis compared with 9.1 l/h in healthy subjects (see **PRECAUTIONS, CONTRAINDICATIONS** and **DOSAGE AND ADMINISTRATION**).

Patients with hepatic insufficiency

No pharmacokinetic study has been performed in patients with a diagnosis of acute or chronic hepatic insufficiency. Exenatide is cleared primarily by the kidney; therefore hepatic dysfunction is not expected to affect blood concentrations of exenatide.

Age, gender, race, obesity

Age, gender, race or obesity has no significant influence on exenatide pharmacokinetics.

CLINICAL TRIALS

Efficacy of BYETTA in treatment of type 2 diabetes has been established in 5 pivotal placebo- or active comparator-controlled clinical trials, involving 2,496 patients, 1,498 of whom received BYETTA.

BYETTA treatment results in durable improvement in glycaemic control with progressive reduction of body weight. Administration of BYETTA has been shown to reduce food intake, due to decreased appetite and increased satiety.

The clinical trial data demonstrate that BYETTA significantly improves fasting and postprandial glycaemic control when used in patients with type 2 diabetes using metformin, sulfonylurea, or a combination of both. The treatment effect of BYETTA is comparable to that of insulin glargine and biphasic insulin aspart (see Table 1 and 2)

Table 1: Summary of Efficacy Results for Exenatide Active-Comparator Controlled Studies (ITT Subjects)

| Study | N | Change From Baseline to Endpoint Least Squares Mean ± Standard Error | | |
|--|-----|---|-------------------------------------|----------------------|
| | | HbA _{1c} (%) [1] | Fasting Plasma Glucose (mmol/L) [1] | Body Weight (kg) [2] |
| H80-MC-GWAA (metformin + sulphonylurea) – 26 weeks of treatment | | | | |
| Insulin glargine | 260 | -1.05 ± 0.06* | -2.86 ± 0.19* | 1.75 ± 0.21* |
| BYETTA 10 µg [3] | 275 | -1.00 ± 0.06* | -1.22 ± 0.19* | -2.3 ± 0.21 * |
| LS Mean Difference | | 0.05 | 1.64 ** | -4.07 ** |
| 95% CI (E-I) | | -0.09 to 0.20 | 1.21 to 2.08 | -4.63 to 3.51 |
| H80-MC-GWAD (metformin + sulphonylurea) – 52 weeks of treatment | | | | |
| Biphasic insulin aspart | 246 | -0.88 ± 0.07* | -1.64 ± 0.19* | 2.92 ± 0.17* |
| BYETTA 10 µg [3] | 248 | -0.98 ± 0.07* | -1.75 ± 0.19* | -2.54 ± 0.17* |
| LS Mean Difference | | -0.10 | -0.11 | - 5.45 ** |
| 95% CI (E-I) | | -0.28 to 0.08 | -0.06 to 0.37 | -5.89 to 5.02 |

Abbreviations: N = number of subjects; SE = standard error of the mean; LS = least squares

Note: The last observation carried forward method was applied to impute missing values for HbA_{1c} and fasting glucose.

[1] Based on a general linear model with treatment, country, and baseline value of the dependent variable as fixed effects.

[2] Based on a mixed model repeated measures analysis with treatment, baseline weight, country, time and the interaction of time and treatment as fixed effects and with patient as a random effect (compound symmetry covariance structure).

[3] BYETTA 10 µg is BYETTA 5 µg bid (4 weeks) followed by BYETTA 10 µg bid for the remaining duration of the study.

CI (E-I) = the 2-sided, 95% Confidence Interval for the least squares (LS) mean difference between treatments (BYETTA-Insulin).

*p <0.0001 for difference within treatment, **p <0.0001 difference between treatment

Table 2: Summary of Efficacy Results in Placebo-Controlled Studies (ITT Subjects)

| | N | Change From Baseline to Week 30 (LS Mean ± SE)[1] | | |
|--|-----|--|---------------------------------|------------------|
| | | HbA _{1c} (%) | Fasting Plasma Glucose (mmol/L) | Body Weight (kg) |
| <u>2993-112 (Metformin)</u> | | | | |
| Placebo | 113 | 0.00 ± 0.106 | 0.79 ± 0.26 | -0.2 ± 0.42 |
| BYETTA 5 µg [2] | 110 | -0.46 ± 0.112** | -0.29 ± 0.28* | -1.3 ± 0.45* |
| BYETTA 10 µg [3] | 113 | -0.86 ± 0.110** | -0.56 ± 0.27* | -2.6 ± 0.44* |
| <u>2993-113 (Sulphonylurea)</u> | | | | |
| Placebo | 123 | 0.06 ± 0.115 | 0.32 ± 0.29 | -0.8 ± 0.32 |
| BYETTA 5 µg [2] | 125 | -0.51 ± 0.111** | -0.29 ± 0.28 | -1.1 ± 0.30 |
| BYETTA 10 µg [3] | 129 | -0.91 ± 0.110** | -0.60 ± 0.28* | -1.6 ± 0.30 * |
| <u>2993-115 (Metformin + Sulphonylurea)</u> | | | | |
| Placebo | 247 | 0.12 ± 0.079 | 0.72 ± 0.20 | -0.9 ± 0.21 |
| BYETTA 5 µg [2] | 245 | -0.66 ± 0.079** | -0.60 ± 0.20* | -1.6 ± 0.21* |
| BYETTA 10 µg [3] | 241 | -0.88 ± 0.080** | -0.68 ± 0.20* | -1.6 ± 0.21* |

Abbreviations: N = number of subjects; OAD = oral antidiabetic agent(s); SE = standard error of the mean; SU = sulphonylurea.

Note: The last observation carried forward method was applied to impute missing values at Week 4 through Week 30.

[1] Based on a general linear model with treatment, baseline HbA_{1c} strata, and site as fixed effects for 2993-112 and 2993-113; based on a general linear model with treatment, baseline HbA_{1c} strata, SU management group, and site as fixed effects for 2993-115.

[2] BYETTA 5 µg is BYETTA 5 µg bid (4 weeks) followed by BYETTA 5 µg bid (26 weeks);

[3] BYETTA 10 µg is BYETTA 5 µg bid (4 weeks) followed by BYETTA 10 µg bid (26 weeks).

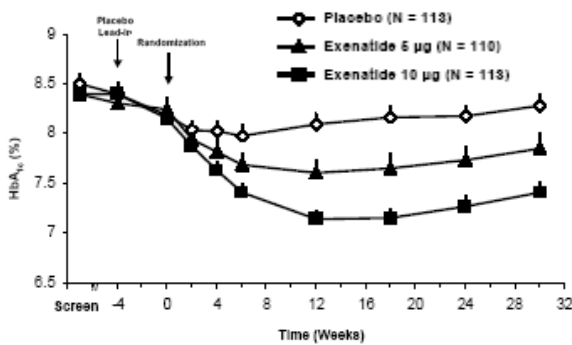
*p <0.05, **p <0.01 for difference from placebo (p-values for the HbA_{1c} endpoint are adjusted based on Fisher's Protected Testing procedure).

The glucose lowering effect of BYETTA can be seen immediately following the first injection. The average reduction in HbA_{1c} (approximately 1%) is generally observable as

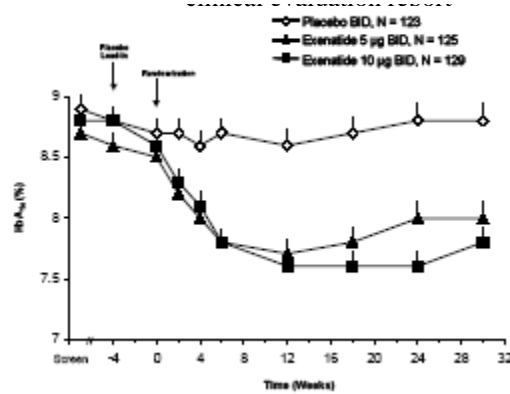
early as 12 weeks after initiation of treatment. Figure 2 shows the mean HbA_{1c} over time in patients with type 2 diabetes using BYETTA or placebo together with metformin, sulfonylurea, or a combination of both. A sustained reduction of HbA_{1c} has been shown through at least 52 weeks of therapy in a controlled study and 82 weeks in uncontrolled studies. In the 30 week placebo-controlled studies, 33.6% of patients using BYETTA 10 µg bid together with metformin, sulfonylurea or a combination of both achieved HbA_{1c} ≤ 7.0%. The ≤7.0% HbA_{1c} goal was achieved by 46.4% of exenatide-treated versus 48% of insulin glargine-treated subjects in the 26 week study and by 31.7% of exenatide-treated and 24.1% of biphasic insulin aspart-treated subjects in the 52 weeks study (see Table 3).

Figure 2: Mean (SE) HbA_{1c} by visit in placebo-comparator controlled studies of patients also taking metformin, sulfonylurea or a combination of both

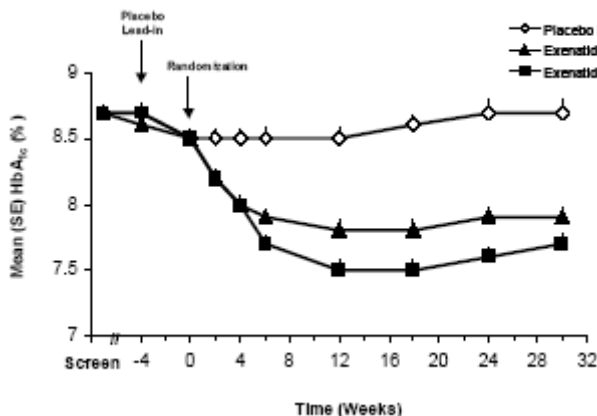
Study 2993 – 112 – Byetta with Metformin alone (ITT population, N = 336)



Study 2993- 113 – Byetta with Sulfonylurea alone (ITT population, N= 377)



Study 2993-115 – BYETTA in combination with metformin and sulfonylurea (ITT population, N= 733)



The LOCF method was applied to impute missing HbA_{1c} values at Week 4 through Week 30.

Patients randomised to exenatide 5 µg bid (4 weeks) followed by exenatide 5 µg bid (26 weeks) or exenatide 5 µg bid (4 weeks) followed by exenatide 10 µg bid (26 weeks).

Abbreviations: bid = twice daily before meals in the morning and evening; SE = standard error of the mean, ITT = intention to treat

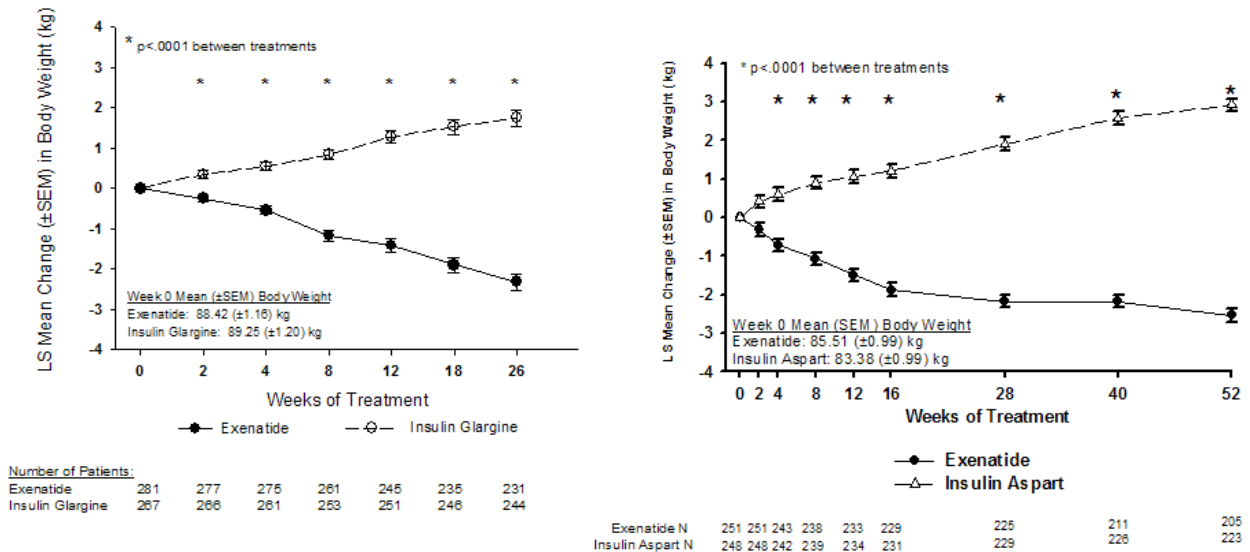
Table 3: Number and proportion of subjects achieving HbA_{1c} of ≤ 7.0% (ITT Subjects)

| Studies 2993-112, 2993-113, 2993-115 combined (30 weeks) | | Study H80-MC-GWAA (26 weeks) | | Study H80-MC-GWAD (52 weeks) | |
|--|-----------|------------------------------|------------------|------------------------------|-------------------------|
| Exenatide* | Placebo | Exenatide* | Insulin Glargine | Exenatide* | Biphasic insulin aspart |
| 152 (33.6%) | 36 (7.9%) | 117(46.4%) | 110 (48.0%) | 72 (31.7%) | 57 (24.1%) |

*Exenatide 10 µg, given as 5 µg bid for 4 weeks followed by 10 µg daily for remainder of study
Includes subjects whose baseline HbA_{1c} values were > 7%

Body weight: BYETTA significantly reduced patient body weight in Phase 3 studies (placebo and insulin comparator controlled). Patients who continued in an uncontrolled open label extension to the placebo controlled studies continued to lose weight through 82 weeks of treatment. Weight loss of 2.3 kg (2.6%, p <0.0001) was achieved in a 26-week insulin glargine comparator study and a loss of 2.5 kg (2.7%) in a 52-week biphasic insulin aspart comparator study whereas treatment with insulin was associated with weight gain. Refer to Figure 3.

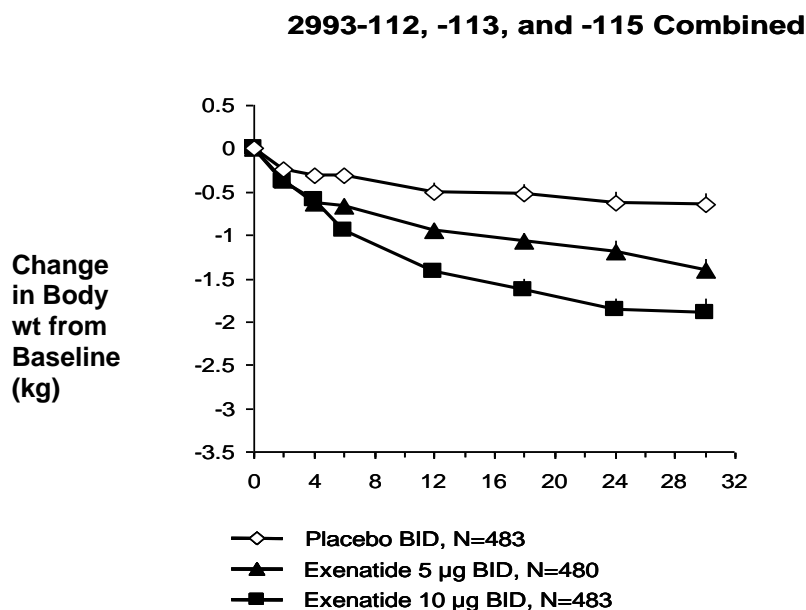
Figure 3: Least Squares Mean change in body weight in patients taking BYETTA compared with insulin glargine or insulin aspart (ITT Subjects)



A total estimated treatment difference (BYETTA minus comparator) was -4.1 kg in the 26-week study and -5.4 kg in the 52-week study.

Results of three 30 weeks randomised triple-blind, placebo controlled trials showed significantly greater reductions from baseline in bodyweight with exenatide 5 or 10 µg bid daily than with placebo in patients receiving BYETTA and metformin alone (-1.6 kg and -2.8 kg versus -0.3 kg) or BYETTA and metformin plus a sulfonylurea (-1.6 kg and -2.8 kg vs -0.3 kg). In patients receiving BYETTA and sulfonylurea only, only patients on BYETTA 10 µg bid achieved a significantly greater reduction in body weight than placebo (-1.6 kg versus -0.6 kg) (see Figure 4).

Figure 4: Change in Body Weight Over Time for the Placebo-Controlled Studies-Combined (ITT Subjects)



In patients receiving BYETTA and metformin alone, weight reduction was statistically significant for patients with a baseline BMI < 30 kg/m² and ≥30kg/m² for exenatide 10 µg bid but not for the BYETTA 5 µg bid compared with placebo. For patients receiving BYETTA and sulfonylurea alone, the change in body weight was statistically significant in patients with a baseline BMI < 30 kg/m² for exenatide 10 µg bid compared with placebo but not for exenatide 5 µg bid or patients with a BMI ≥30 kg/m². For the BYETTA with metformin and sulfonylurea, patients, a statistically significant reduction in body weight was observed for each exenatide treatment (5 µg, bid and 10 µg, bid) compared with placebo with baseline BMI ≥30 kg/m² but not for subjects with baseline BMI < 30 kg/m².

The observed weight loss was not necessarily secondary to nausea and other gastrointestinal side effects, as weight loss was also observed in those subjects who did not experience these adverse events.

Effect on lipids: BYETTA has shown no adverse effects on lipid parameters. A trend for a decrease in triglycerides has been observed. An improvement in high density lipoprotein and an improvement in triglyceride levels have been correlated with greater weight loss at 82 weeks in BYETTA treated patients.

INDICATIONS

BYETTA is indicated as adjunctive therapy to improve glycaemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea but are not achieving adequate glycaemic control.

CONTRAINDICATIONS

BYETTA is contraindicated in patients with known hypersensitivity to this product or any of its components, including meta-Cresol.

Exenatide should not be used in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 ml/min). Compared with healthy subjects, renal clearance of Exenatide was significantly reduced in patients with end-stage renal disease receiving dialysis, resulting in poor gastrointestinal tolerability.

PRECAUTIONS

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 may be considered (see **DOSAGE AND ADMINISTRATION** and **ADVERSE EFFECTS**).

Due to the glucose-dependent insulinotropic mechanism of action of BYETTA, when used in combination with metformin alone, no increase in the incidence of hypoglycaemia was observed over that of placebo in combination with metformin (see **DOSAGE AND ADMINISTRATION** and **ADVERSE EFFECTS**).

BYETTA did not alter the counter-regulatory hormone response to insulin-induced hypoglycaemia in a randomised, double-blind, controlled study in healthy subjects.

General

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

The concurrent use of BYETTA with insulin, D-phenylalanine derivatives, meglitinides, alpha-glucosidase inhibitors, orlistat, opioids, and anticholinergics has not been studied. BYETTA in combination with a thiazolidinedione is not recommended as there is limited experience.

BYETTA is not a substitute for insulin in insulin-requiring patients. BYETTA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Since market introduction there have been some spontaneously reported cases of increased INR (International Normalized Ratio) with concomitant use of warfarin and exenatide, sometimes associated with bleeding. (see **Interaction With Other Medicines** and **ADVERSE EFFECTS, Spontaneous Data**).

Altered Renal Function

There have been rare, spontaneously reported events of acute renal failure, worsened chronic renal failure, renal impairment, or increased serum creatinine among patients using Exenatide. These events mostly occurred in patients also receiving one or more pharmacologic agents known to potentially affect renal function or hydration status and/or experiencing events of nausea, vomiting, diarrhoea, and/or dehydration. Concomitant agents included angiotensin converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, and diuretics. For many events, reversibility has been observed with appropriate treatment (see **ADVERSE EFFECTS, Spontaneous Data**).

Pancreatitis

Recognised risk factors for pancreatitis include a past history of pancreatitis, gallstones, alcoholism and severe hypertriglyceridaemia. Clinical judgement should be exercised when selecting anti-diabetic treatments, including Byetta, for these patients. The change in risk of recurrent pancreatitis in patients with a past history of pancreatitis who receive Byetta is not known. There have been rare, spontaneously reported events of acute pancreatitis, including fatal cases of haemorrhagic or necrotising pancreatitis in patients who have received Byetta. Cases of haemorrhagic or necrotising pancreatitis have been reported across the adult age range (18 years and over, including the elderly). There are no early signs or symptoms that distinguish cases that will become acute haemorrhagic or necrotising pancreatitis from the less severe form of pancreatitis. This potential should be considered in patients treated with Byetta who manifest symptoms and signs suggestive of pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Patients and their caregivers should be advised to report immediately to their doctor such abdominal pain particularly if associated with vomiting or diarrhoea. Generally, resolution of pancreatitis has been observed with supportive treatment. If pancreatitis is suspected, BYETTA and other potentially suspect medications should be discontinued and not recommenced unless pancreatitis has been excluded.

Weight Loss

Rapid weight loss at a rate of > 1.5 kg per week has been reported in patients treated with exenatide. Weight loss of this rate may have harmful consequences.

Effect on Fertility

Animal studies did not indicate direct harmful effects with respect to fertility. Male and female fertility was unaffected in mice treated with exenatide at SC doses up to 760 µg/kg/day, 500 times the clinical exposure at 20 µg/day based on AUC.

Use in Pregnancy

Pregnancy Category C

Data on a limited number of exposed pregnancies indicate no adverse effects of exenatide on pregnancy or on the health of the foetus/new born child. To date, no other relevant epidemiological data are available.

Potential embryofetal effects were assessed with SC doses of exenatide during organogenesis in mice at 6, 68 and 760 µg/kg/day and in rabbits at 0.2, 2, 22, 156 and 260 µg/kg/day, giving respective exposures approximately 3, 30 and 500 times (mouse) and 0.2, 5, 200, 1400 and 3500 times (rabbit) the clinical exposure at 20 µg/day. A low incidence of abortions and decreased fetal growth occurred in mice and rabbits at ≥ 68 and 22 µg/day, respectively, which also caused a decrease in food consumption and body weight gain in dams. Alterations of skeletal ossification were observed in rabbits at ≥ 2 µg/kg/day as a result of decreased food intake. Wavy ribs were seen in mice at 760 µg/kg/day. Fetal umbilical hernias were increased in rabbits at ≥ 22 µg/kg/day. There was minimal placental transfer of exenatide in animal studies *in vivo* or in human placental tissues *in vitro*. The fetal findings were probably secondary to effects on the dam.

High doses of exenatide administered to mice during gestation and lactation caused stillbirths, an increase in neonatal deaths and a decrease in neonatal growth at

exposures 500 times the clinical exposure at 20 µg/day. The no observable effect level for peri-neonatal effects was 68 µg/kg/day, giving exposures 30 times the clinical exposure (**see Carcinogenicity, Genotoxicity, Effects on Fertility**).

Caution should be exercised when prescribing BYETTA to pregnant women. BYETTA should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus.

Use in Lactation

It is unknown whether exenatide is excreted in human milk. In lactating mice given high doses of exenatide, low concentrations of exenatide were detected in milk (2.5% of plasma level). Neonatal deaths were increased in lactating mice at high doses (see **Use in Pregnancy**). BYETTA should be administered to nursing women only if the potential benefit to the mother justifies the potential risk to the infant.

Genotoxicity

Exenatide was not genotoxic in bacterial reverse mutation assays, *in vitro* chromosomal aberration tests in Chinese hamster ovary cells or a mouse micronucleus assay.

Carcinogenicity

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 110 times the human clinical exposure at 20 µg/day. There was no tumorigenic response in male rats or either sex of mice at exposures 80 (mouse) and 110 (rat) times the human exposure.

Paediatrics

BYETTA has not been studied in patients under 18 years of age.

Use in the elderly

No dosage adjustments are necessary for use of BYETTA in elderly patients. Subjects aged up to 75 years were enrolled in the 5 placebo- and active comparator-controlled pivotal clinical studies. A total of 333 subjects aged 65 years or older received BYETTA in these studies. There were no apparent age-related differences in the change in HbA_{1c} values from baseline to endpoint for subjects treated with BYETTA during these studies.

Use in Renal Impairment

In patients with mild to moderate renal impairment (creatinine clearance >30 to 80 ml/min), exenatide clearance was only mildly reduced compared to clearance in individuals with normal renal function. Patients with moderate renal impairment (creatinine clearance >30 to 50 ml/min) have been noted to have an increase in the AUC of Exenatide. As the risk of adverse events is dose-dependant, caution is recommended in this population (**see CONTRAINDICATIONS**).

Interaction with other medicines

The effect of BYETTA to slow gastric emptying may reduce the extent and rate of absorption of orally administered medicines. BYETTA should be used with caution in patients receiving oral medications that require rapid gastrointestinal absorption or medication associated with local gastrointestinal irritation such as bisphosphonates or tetracyclines. Gastroresistant formulations containing substances sensitive to 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. For oral medications that are particularly dependent on threshold concentrations for efficacy, such as contraceptives

and antibiotics, patients should be advised to take those medicines at least 1 hour before BYETTA injection. If such medicines are to be administered with food, patients should be advised to take them with a meal or snack when exenatide is not administered.

HMG CoA reductase inhibitors

The AUC and C_{max} of lovastatin, a HMG CoA reductase inhibitor, were decreased approximately 40% and 28%, respectively, and T_{max} was delayed by 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.

Warfarin, Digoxin, Lisinopril

In a controlled clinical pharmacology study in healthy volunteers, a delay in warfarin T_{max} of about 2h was observed when warfarin was administered 30 min after exenatide. No clinically relevant effects on C_{max} or AUC were observed (see **PRECAUTIONS** and **ADVERSE EFFECTS, Spontaneous Data**).

No clinically relevant interactions were observed with digoxin, lisinopril or warfarin.

Effects on ability to drive and use machines

When BYETTA is used in combination with a sulphonylurea, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines.

ADVERSE EFFECTS

The safety of BYETTA has been evaluated in over 2500 exenatide-treated subjects in the completed clinical pharmacology, efficacy and safety studies, comprising 1729 subject years. Overall, 87% of exenatide-treated subjects experienced at least one treatment emergent adverse event, compared with 72% of insulin- and 64% of placebo-treated subjects. Among exenatide-treated subjects, nausea was the most common event (52%), followed by hypoglycaemia (27%) and vomiting (19%).

The incidence of withdrawal due to adverse events was 8% for BYETTA-treated patients and 2% for placebo-treated or insulin-treated patients in the long-term controlled trials (26 weeks or longer). The most common adverse events leading to withdrawal for BYETTA-treated patients were nausea (3% of patients) and vomiting (1%). For placebo-treated or insulin-treated patients, <1% withdrew due to nausea and 0% due to vomiting.

BYETTA-treated patients in the open-label extension studies at 82 weeks experienced similar types of adverse events to those observed in the long term controlled trials of 26 weeks or more.

Table 4 lists the adverse reactions reported from Phase 3 placebo, insulin glargine and 30% soluble insulin aspart/70% insulin aspart protamine crystal (biphasic insulin aspart) - comparator controlled studies in which the patients received metformin, a sulphonylurea or a combination of both in addition to BYETTA or comparator.

The table presents adverse reactions that occurred with an incidence $\geq 5\%$ and more frequently among BYETTA-treated patients than insulin- or placebo-treated patients. The table also includes adverse reactions that occurred with an incidence $\geq 1\%$ and

with a statistically significantly higher and/or $\geq 2X$ 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 $\geq 1/10$, common $\geq 1/100$ and $< 1/10$.

Table 4: Adverse Reactions Reported in Phase 3 Placebo or Active Comparator-Controlled Studies

| Body System/Adverse Reaction Terms | Frequency of Occurrence | |
|---|------------------------------------|-----------------------------|
| | Common ($\geq 1\%$ and $< 10\%$) | Very common ($\geq 10\%$) |
| Events | | |
| Metabolism and nutrition disorders | | |
| Hypoglycaemia (with metformin and a sulphonylurea) ¹ | | X |
| Hypoglycaemia (with a sulphonylurea) | | X |
| Decreased appetite | X | |
| Nervous system disorders | | |
| Headache ¹ | X | |
| Dizziness | X | |
| Gastrointestinal disorders | | |
| Nausea | | X |
| Vomiting | | X |
| Diarrhoea | | X |
| Abdominal pain | X | |
| Dyspepsia | X | |
| Gastroesophageal reflux disease | X | |
| Abdominal distension | X | |
| Skin and subcutaneous tissue disorders | | |
| Hyperhidrosis ¹ | X | |
| General disorders and administrative site conditions | | |
| Feeling jittery | X | |
| Asthenia ¹ | X | |

N= 1498 exenatide-treated patients in the pivotal placebo- or active comparator-controlled studies.

¹ In insulin comparator controlled studies in which metformin and a sulphonylurea were concomitant medications, the incidence for these terms was similar for insulin and BYETTA treated patients.

Hypoglycaemia Use with a sulphonylurea, metformin or both

In 30-week placebo-controlled studies in patients treated with exenatide in combination with a sulphonylurea, or exenatide in combination with a sulphonylurea and metformin, the incidence of hypoglycaemia was increased over that of placebo in combination with a sulphonylurea, or placebo in combination with a sulphonylurea and metformin (see **PRECAUTIONS**) and appeared to be dependent on the doses of both exenatide and the sulphonylurea. Most episodes of hypoglycaemia were mild to moderate in intensity, and all resolved with oral administration of carbohydrate (see Table 5). In contrast, when exenatide was used in combination with metformin, no increase in the incidence of hypoglycaemia was observed over that of placebo in combination with metformin.

Table 5: Incidence (%) of Hypoglycaemia by Concomitant Antidiabetic Therapy in 30-Week Placebo Controlled Studies

| | Placebo | | BYETTA | | Placebo | | BYETTA | | Placebo | | BYETTA | |
|---------------|----------------|----------|-----------|--------------------|----------|-----------|--------------|----------|-----------|-----|----------|-----------|
| | bid | 5 µg bid | 10 µg bid | bid | 5 µg bid | 10 µg bid | bid | 5 µg bid | 10 µg bid | bid | 5 µg bid | 10 µg bid |
| | With Metformin | | | With Sulphonylurea | | | With MET/SFU | | | | | |
| N | 113 | 110 | 113 | 123 | 125 | 129 | 247 | 245 | 241 | | | |
| Hypoglycaemia | 5.3% | 4.5% | 5.3% | 3.3% | 14.4% | 35.7% | 12.6% | 19.2% | 27.8% | | | |

BYETTA and placebo were administered before the morning and evening meals.
Abbreviations: bid, twice daily; MET/SFU, metformin and a sulphonylurea.

In the long-term active comparator (26 weeks or greater) studies in which all patients also received both metformin and a sulphonylurea the incidence of hypoglycaemia was similar for BYETTA and insulin treatment (either insulin glargine or biphasic insulin aspart). BYETTA patients reported fewer episodes of nocturnal hypoglycaemia than insulin patients in both insulin glargine-comparator study ($p < 0.001$) and the biphasic insulin aspart-comparator study ($p = 0.0384$).

To reduce the risk of hypoglycaemia associated with the use of a sulphonylurea, reduction in the dose of sulphonylurea may be considered (see **DOSAGE and ADMINISTRATION**).

Nausea

The most frequently reported adverse reaction, mild to moderate nausea, occurred in a dose-dependent fashion. With continued therapy, the frequency and severity decreased in most patients who initially experienced nausea.

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.

In the three long-term placebo controlled trials 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. In about half of this 6% (3% of the total patients given BYETTA in the controlled studies), the glycaemic response to BYETTA appeared diminished; the remainder had a glycaemic response consistent with that of patients without antibodies. Patients who developed anti-exenatide antibodies tend to have more injection site reactions (for example: redness of skin and itching), but otherwise had similar rates and types of adverse events as those with no anti-exenatide antibodies. In the insulin-comparator controlled trials comparable efficacy and adverse events were observed in exenatide-treated patients with and without antibody titres. Examination of antibody-positive specimens from one long-term uncontrolled study revealed no significant cross-reactivity with related endogenous peptides (glucagon or GLP-1).

Injection site reactions

Injection site reactions have been reported in approximately 5.7% of subjects receiving BYETTA in long term (26 weeks or longer) controlled clinical trials. These reactions have usually been mild and usually did not result in discontinuation of BYETTA.

SPONTANEOUS DATA

General: Common ($\geq 1\%$ and $<10\%$): injection-site reactions.

Gastrointestinal disorders: Uncommon ($\geq 0.1\%$ and $< 1\%$): abdominal distension, eructation, constipation, flatulence. Rare ($\geq 0.01\%$ and $<0.1\%$): acute pancreatitis. Very rare ($<0.01\%$): Cases of ileus, ischaemic colitis and gut ischaemia have been reported.

Nervous System disorders: Uncommon ($\geq 0.1\%$ and $< 1\%$): dysgeusia.
Rare ($\geq 0.01\%$ $<0.1\%$): somnolence.

Investigations: Rare ($\geq 0.01\%$ $<0.1\%$) INR increased with concomitant warfarin use, some reports associated with bleeding (see **PRECAUTIONS** and **Interaction With Other Medicines**).

Immune system disorder: Very rare ($<0.01\%$): anaphylactic reaction.

Skin and subcutaneous disorders: Rare ($\geq 0.01\%$ and $<0.1\%$): angioedema, generalized pruritus and/or urticaria, macular or papular rash, alopecia.

Metabolism and nutritional disorders: Rare ($\geq 0.01\%$ and $<0.1\%$): dehydration, generally associated with nausea, vomiting, and/or diarrhoea, weight decreased (see **PRECAUTIONS, Weight Loss**)

Renal and urinary disorders: Rare ($>0.01\%$ and $<0.1\%$): acute renal failure, chronic renal failure, renal impairment, increased serum creatinine. See **PRECAUTIONS**.

DOSAGE AND 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 BYETTA can then be increased to 10 μg bid to further improve glycaemic control. Doses higher than 10 μg bid are not recommended.

BYETTA can be administered at any time within the 60-minute period before the morning and evening meals (or before the 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 of BYETTA should be administered as a subcutaneous injection in the thigh, abdomen, or upper arm. BYETTA is not recommended to be administered by intravenous or intramuscular injection.

BYETTA is recommended for use in patients with type 2 diabetes mellitus who are already receiving metformin, a sulphonylurea, or both. When BYETTA is added to 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 may be considered to reduce the risk of hypoglycaemia (see **PRECAUTIONS**).

Specific patient groups

Gender, age, race or obesity

No dosage adjustment is necessary for gender, for age, for race or for obese patients (BMI>30 kg/m²) (see **Pharmacokinetics**).

Patients with renal impairment

No dosage adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 to 80 mL/min) (see **Pharmacokinetics**).

In patients with moderate renal impairment (creatinine clearance: 30-50 mL/min), dose escalation from 5 µg to 10 µg should proceed conservatively. (see **PRECAUTIONS and Pharmacokinetics**).

BYETTA should not be used in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min) (see **CONTRAINDICATIONS and Pharmacokinetics**).

Patients with hepatic impairment

No pharmacokinetic study has been performed in patients with a diagnosis of acute or chronic hepatic insufficiency (see **Pharmacokinetics**).

Children and adolescents

BYETTA has not been studied in children and adolescents below 18 years.

Instructions for use and handling

Each BYETTA pen is for use by one person only. The instructions for using the pen must be followed carefully.

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

BYETTA that has been frozen must not be used.

The patient should be advised to discard the needle after each injection. The pen is stored without the needle attached. The cartridge must not be refilled.

Incompatibilities

BYETTA must not be mixed with other medicines.

OVERDOSAGE

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.

PRESENTATION AND STORAGE CONDITIONS

BYETTA is supplied for subcutaneous injection as a sterile, preserved isotonic solution in a glass cartridge that has been assembled into a disposable pen-injector (pen).

A BYETTA 5 µg pre-filled pen contains 60 doses of sterile, preserved solution (approximately 1.2 mL). Each dose contains 5 µg exenatide in 20 microlitres (0.25 mg synthetic exenatide per mL).

A BYETTA 10 µg pre-filled pen contains 60 doses of sterile, preserved solution (approximately 2.4 mL). Each dose contains 10 µg exenatide in 40 microlitres (0.25 mg synthetic exenatide per mL).

Pack size of 1 BYETTA pen.

Storage

Store at 2 °C to 8 °C. Refrigerate. Do not freeze. Protect from light.

Once in use the BYETTA pen should be kept below 25°C and away from direct heat and light.

The BYETTA pen should not be stored with the needle attached.

Shelf life for pen in use is 30 days. The pen should be discarded 30 days after use, even if some medicine remains in the pen.

NAME AND ADDRESS OF SPONSOR

Eli Lilly and Company (NZ) Limited
Level 3, Axon House
414-422 Khyber Pass Road
Newmarket
Auckland
NEW ZEALAND

POISON SCHEDULE OF MEDICINE

S4

DATE of PREPARATION

17 January 2012

BYETTA® is a registered trademark of Amylin Pharmaceuticals, Inc. and is used under licence by Eli Lilly Australia Pty Limited and Eli Lilly and Company (NZ) Limited.