

## PRODUCT MONOGRAPH

 **BYETTA™**

exenatide injection

250 µg/mL

1.2 mL prefilled pen (60 doses of 5 µg/dose)

and

2.4 mL prefilled pen (60 doses of 10 µg/dose)

**Antihyperglycemic Agent**

Blood Glucose Lowering Drug

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Date of Preparation:  
January 11, 2011

Submission Control No: 128932

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exenatide injection

## **PART I: HEALTH PROFESSIONAL INFORMATION**

### **SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Clinically Relevant Nonmedicinal Ingredients*</b>
Subcutaneous	Solution for injection / 250 µg/mL	<i>m</i> -cresol, Mannitol

\*For a complete listing see *Dosage Forms, Composition and Packaging* section.

### **INDICATIONS AND CLINICAL USE**

BYETTA™ (exenatide) injection is indicated in combination with metformin, and/or a sulfonylurea to improve glycemic control in patients with type 2 diabetes mellitus, when maximally tolerated doses of these oral therapies in addition to diet and exercise do not provide adequate glycemic control.

Management of type 2 diabetes should also include nutritional counselling, weight reduction as needed, and exercise.

#### **Geriatrics (≥ 65 years of age):**

BYETTA was studied in a limited number of patients 65 years of age or older and in few patients 75 years of age or older. A greater sensitivity of some older individuals cannot be ruled out (see **WARNINGS AND PRECAUTIONS- Geriatrics**).

#### **Pediatrics (< 18 years of age):**

The safety and efficacy of BYETTA have not been established in pediatric patients. Therefore, BYETTA should not be used in this patient population.

### **CONTRAINDICATIONS**

BYETTA is contraindicated in patients with known hypersensitivity to this product or any of its components. For a complete listing of ingredients, see the **DOSAGE FORMS, COMPOSITION and PACKAGING** section of the product monograph.

BYETTA should not be used in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min), including patients receiving dialysis (see **WARNINGS AND**

PRECAUTIONS; ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

BYETTA is contraindicated in patients with diabetic ketoacidosis, diabetic coma/precoma or type 1 diabetes mellitus.

## WARNINGS AND PRECAUTIONS

**Based on postmarketing data, BYETTA has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. After initiation of BYETTA, and after dose increases, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting). If pancreatitis is suspected, BYETTA should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, BYETTA should not be restarted. Consider antidiabetic therapies other than BYETTA in patients with a history of pancreatitis or in patients with other risk factors for pancreatitis (e.g. gallstones, alcoholism, or hypertriglyceridemia).**

### **General**

BYETTA is not indicated for use in patients with type 2 diabetes mellitus who require insulin therapy.

BYETTA is not a substitute for insulin. There have been reports of acute hyperglycemia and/or ketoacidosis in insulin-dependent patients who switched from insulin to BYETTA.

There is limited clinical trial experience with BYETTA in patients with BMI  $\leq 25$  kg/m<sup>2</sup>.

### **Carcinogenesis and Mutagenesis**

#### **Risk of thyroid C-cell tumours**

In female rats given exenatide for 2 years, there was an apparent numerical increase in benign thyroid C-cell adenomas observed at the highest dose representing a systemic exposure 130 times the human exposure resulting from the maximum recommended dose of 20 µg/day, based on AUC. This incidence was not statistically significant when adjusted for survival. There was no tumorigenic response in male rats or either sex of mice at systemic exposures  $\geq 95$  times the human exposure resulting from the maximum recommended dose of 20 µg/day, based on AUC (See Part II: TOXICOLOGY section).

Other GLP-1 receptor agonists have been shown to cause thyroid C-cell tumours (adenomas and/or carcinomas) at clinically relevant exposures in rats and mice. The relevance of these results to humans has not yet been determined. Until further long-term data in humans are available, BYETTA should not be used in patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

## **Cardiovascular**

In pivotal clinical trials for BYETTA, patients with moderate to severe congestive heart failure (New York Heart Association (NYHA) Class III and above) and patients with a clinically significant history of cardiac disease or presence of active cardiac disease within 1 year were excluded. Therefore, BYETTA should be used with caution in this population.

**Heart Rate Increase:** An increase in mean heart rate of up to 10 bpm was reported with BYETTA treatment in a clinical trial in healthy volunteers undergoing serial ECG monitoring. In patients with diabetes undergoing 24 hour heart rate monitoring, changes from baseline in heart rate averaged over 24 h at 12 weeks were +2 bpm and –1 bpm for BYETTA and placebo, respectively. Because of limited clinical experience in patients who have cardiac conditions that might be worsened by an increase in heart rate, such as ischemic heart disease and tachyarrhythmias, caution should be observed in these patients (see **DRUG INTERACTIONS**).

**PR Interval Prolongation:** A prolongation of the mean PR interval of up to 7 ms was reported with BYETTA treatment in a single-dose clinical trial in healthy volunteers. In this study, during the 24-hour observation period, the incidence of first degree atrioventricular (AV) block was higher with BYETTA than with placebo. The clinical significance of these changes is not fully known; however, because of limited clinical experience in patients with pre-existing conduction system abnormalities (e.g., marked first-degree AV block or second- or third-degree AV block) and rhythm disturbances (e.g., tachyarrhythmia), caution should be observed in these patients (see **DRUG INTERACTIONS**). Cases of second and third degree heart block have been reported during post-market use of BYETTA (see **ADVERSE REACTIONS**).

See **ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology** for discussion of all findings related to cardiac electrophysiology.

**General:** Physicians who prescribe drugs that increase heart rate and/or prolong the PR interval should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug.

## **Endocrine and Metabolism**

### **Hypoglycemia**

*Use with a sulfonylurea:* When BYETTA was used in combination with a sulfonylurea the incidence of hypoglycemia was increased over that of placebo in combination with a sulfonylurea (see **ADVERSE REACTIONS**). To reduce the risk of hypoglycemia associated with the use of a sulfonylurea, a decrease in the dose of sulfonylurea may be considered (see **DOSAGE AND ADMINISTRATION**).

*Use with metformin and a sulfonylurea:* When BYETTA was used in combination with metformin and a sulfonylurea, the incidence of hypoglycemia was lower in subjects who had a reduction in their dose of sulfonylurea prior to starting BYETTA. To reduce the risk of hypoglycemia associated with the use of a sulfonylurea, a decrease in the dose of sulfonylurea may be considered (see **DOSAGE AND ADMINISTRATION**).

*Use with metformin:* When BYETTA was used in combination with metformin, no increase in the incidence of hypoglycemia was observed over that of placebo in combination with metformin.

BYETTA should be administered with caution in the following situations, due to risk of hypoglycemia:

- Hypophysis cerebri failure or adrenal function failure
- Malnourishment, starvation state, irregular dietary intake, dietary intake deficiency, or state of debility
- Intense muscular exercise
- Excessive alcohol intake

### **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.

### **Loss of control of blood glucose**

When a patient, stabilized on BYETTA is exposed to stress such as fever, trauma, infection, or surgery, a loss of control of blood glucose may occur. At such times, it may be necessary to temporarily discontinue BYETTA and administer insulin.

### **Gastrointestinal**

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 diarrhea. Therefore, the use of BYETTA is not recommended in patients with severe gastrointestinal disease.

BYETTA can slow gastric emptying, which can reduce the rate of absorption of orally administered drugs (see **Drug-Drug Interactions**).

### **Hepatic/Biliary/Pancreas**

See **WARNINGS AND PRECAUTIONS, Bold Warning**.

No pharmacokinetic study has been performed in patients with acute or chronic hepatic insufficiency. See also **Pharmacokinetics, Special Populations and Conditions**.

### **Immune**

Some patients develop anti-exenatide antibodies following treatment with BYETTA, consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals. These patients may be at greater risk of developing adverse events such as injection site reactions. Other allergic adverse reactions have occurred in patients with unknown antibody status. There have been postmarketing reports of serious hypersensitivity reactions (e.g. anaphylaxis and angioedema) in patients treated with BYETTA. If a hypersensitivity reaction occurs, the patient should discontinue BYETTA and promptly seek medical advice. See **Post-market Adverse Drug Reactions**.

### **Peri-operative considerations**

See **Endocrine and Metabolism section - Loss of control of blood glucose.**

### **Renal**

There have been spontaneously reported events of altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring hemodialysis or kidney transplantation. Some of these events occurred in patients receiving one or more pharmacologic agents known to affect renal function or hydration status, such as angiotensin converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, or diuretics. Some events occurred in patients who had been experiencing nausea, vomiting, or diarrhea, with or without dehydration. Reversibility of altered renal function has been observed in many cases with supportive treatment and discontinuation of potentially causative agents, including BYETTA.

Since treatment with BYETTA may induce nausea and vomiting with transient hypovolemia, which may worsen renal function, caution should be applied when initiating or escalating doses of BYETTA from 5 µg to 10 µg in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min). BYETTA should be used with caution in patients with renal transplantation. See **CONTRAINDICATIONS.**

### **Skin**

Rashes and injection site reactions have been reported in subjects receiving BYETTA. See **ADVERSE REACTIONS.**

### **Special Populations**

**Pregnant Women:** There are no adequate and well-controlled studies in pregnant women. BYETTA is not recommended for use in pregnancy.

Based on animal data, BYETTA may cause fetal harm (see Part II: **TOXICOLOGY** section).

**Nursing Women:** There are no adequate and well-controlled studies in nursing women. BYETTA is not recommended for use in nursing women (see Part II: **TOXICOLOGY** section).

**Pediatrics (< 18 years of age):** The safety and efficacy of BYETTA have not been established in pediatric patients. BYETTA is not recommended for use in this population.

**Geriatrics (≥ 65 years of age):** BYETTA was studied in a limited number of patients 65 years of age or older and in few patients 75 years of age or older. In clinical trials with BYETTA, there was a higher incidence of adverse events, including hypoglycaemia and nausea in subjects over 65 years of age compared to younger subjects. Greater sensitivity cannot be ruled out in this population. See also **DOSAGE AND ADMINISTRATION, Dosing Considerations.**

### **Cardiovascular- Patients with Congestive Heart Failure or Other Cardiac Disease:**

BYETTA should be used with caution in patients with moderate to severe congestive heart failure (New York Heart Association (NYHA) Class III and above) and/or clinically significant

history of cardiac disease or presence of active cardiac disease within 1 year. See **WARNINGS AND PRECAUTIONS, Cardiovascular**.

### **Monitoring and Laboratory Tests**

Assessment of renal function is recommended prior to initiation of BYETTA and periodically thereafter, as appropriate.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

Three randomized, double-blind, placebo-controlled, 30-week pivotal trials were conducted to evaluate the efficacy and safety of BYETTA in patients with type 2 diabetes and BMI 27 to 45 kg/m<sup>2</sup>, inclusive, whose glycemic control was inadequate with maximally effective doses of metformin alone (study 112), sulfonylurea alone (study 113) or metformin in combination with a sulfonylurea (study 115).

In the three placebo-controlled pivotal clinical trials, the most commonly observed adverse reactions in BYETTA-treated patients were: nausea, hypoglycemia, vomiting, diarrhea, feeling jittery, dizziness, headache and dyspepsia. Adverse reactions were usually mild to moderate in intensity. In the pivotal studies, the incidence of nausea was dose-dependent and most common in the initial weeks of exenatide treatment or after an increase in exenatide dose.

In the three pivotal trials, the incidence of withdrawal due to treatment-emergent adverse events (TEAEs) was higher in BYETTA treated patients than placebo-treated patients: study 112 (4.9 % vs. 0.9%); study 113 (8.7% vs. 3.3%); study 115 (7.0% vs. 4.0%). Among BYETTA-treated patients, gastrointestinal disorders were the most common TEAEs leading to withdrawal (3.1%, 4.7% and 3.9% for studies 112, 113 and 115, respectively). Nausea was the most-common gastrointestinal disorder leading to withdrawal within the three pivotal trials (1.8%, 3.1% and 2.7% in studies 112, 113 and 115 respectively).

### **Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Table 1 lists treatment-emergent adverse events reported in the three pivotal trials, regardless of causality assessment. Adverse events reported in  $\geq 2\%$  and reported in greater frequency in BYETTA-treated patients (5  $\mu\text{g}$  and/or 10  $\mu\text{g}$ ) than in placebo-treated patients in at least one of these trials, are included in the table.

**Table 1:** Treatment-emergent adverse events reported in  $\geq 2\%$  and reported more frequently in BYETTA-treated patients than in placebo-treated patients in 3 placebo-controlled 30 week trials.

System Organ Class/Preferred Term	Study 112 <sup>a</sup> (N=336)			Study 113 <sup>b</sup> (N=377)			Study 115 <sup>c</sup> (N=733)		
	Placebo (N=113)	5 $\mu$ g (N=110)	10 $\mu$ g (N=113)	Placebo (N=123)	5 $\mu$ g (N=125)	10 $\mu$ g (N=129)	Placebo (N=247)	5 $\mu$ g (N=245)	10 $\mu$ g (N=241)
	%			%			%		
<b>Ear and labyrinth disorders</b>									
Ear pain	2.7	0.9	1.8	0.8	2.4	1.6	0.8	0.4	0.0
<b>Eye disorders</b>									
Cataract unilateral	0.0	0.0	0.0	0.8	0.0	2.3	0.4	0.0	0.0
<b>Gastrointestinal disorders</b>									
Abdominal distension	0.9	0.9	1.8	0.8	0.8	1.6	0.8	0.8	2.9
Abdominal pain NOS	0.9	1.8	1.8	3.3	0.0	0.8	0.4	2.0	2.1
Abdominal pain upper	3.5	0.9	1.8	0.0	2.4	1.6	0.8	0.8	1.7
Constipation	3.5	2.7	3.5	3.3	1.6	9.3	3.6	3.7	2.9
Diarrhoea NOS	8.0	11.8	15.9	4.1	11.2	8.5	6.5	10.2	17.4
Dyspepsia	5.3	1.8	4.4	1.6	4.8	4.7	2.8	6.5	7.9
Flatulence	0.9	2.7	0.0	1.6	0.0	2.3	1.2	2.4	1.2
Gastritis NOS	1.8	0.0	1.8	0.8	0.0	3.1	0.0	0.4	1.2
Gastroesophageal reflux disease	0.9	3.6	3.5	0.0	1.6	2.3	0.8	2.9	3.3
Nausea	23.0	36.4	45.1	7.3	39.2	51.2	20.6	39.2	48.5
Vomiting NOS	3.5	10.9	11.5	2.4	9.6	13.2	4.5	14.7	13.7
<b>General disorders and administration site conditions</b>									
Chest pain	0.0	0.9	0.9	0.8	0.8	2.3	0.8	0.8	0.8
Fatigue	3.5	1.8	3.5	3.3	4.8	2.3	3.2	6.5	4.6
Feeling jittery	0.9	4.5	1.8	1.6	12.0	14.7	6.9	8.6	11.6
Influenza like illness	1.8	4.5	0.9	2.4	2.4	3.1	2.4	3.3	2.5
Injection site bruising	7.1	5.5	2.7	4.9	4.0	5.4	2.8	5.7	5.4
Injection site pruritus	0.0	1.8	0.0	0.0	2.4	1.6	0.4	1.2	0.0
Malaise	0.9	1.8	0.9	0.0	0.8	4.7	0.4	0.4	0.8
Pyrexia	1.8	4.5	1.8	1.6	2.4	0.8	0.8	2.0	0.8
Rigors	0.0	0.0	0.9	0.0	0.0	3.9	0.8	0.4	0.4
Weakness	0.0	1.8	1.8	3.3	5.6	1.6	1.6	4.5	3.3
<b>Immune system disorders</b>									
Seasonal allergy	0.0	0.0	1.8	0.8	0.8	2.3	0.4	1.6	0.8
<b>Infections and infestations</b>									
Gastroenteritis NOS	0.9	1.8	2.7	0.8	0.8	4.7	4.0	0.4	1.7
Gastroenteritis viral NOS	1.8	3.6	1.8	1.6	3.2	4.7	1.2	4.1	2.1
Influenza	1.8	2.7	2.7	0.8	2.4	3.9	4.5	2.4	1.7
Nasopharyngitis	9.7	9.1	4.4	8.1	8.8	5.4	8.1	7.3	6.6
Sinusitis NOS	5.3	4.5	6.2	4.1	8.8	4.7	6.9	6.5	4.1

System Organ Class/Preferred Term	Study 112 <sup>a</sup> (N=336)			Study 113 <sup>b</sup> (N=377)			Study 115 <sup>c</sup> (N=733)		
	Placebo (N=113)	5 µg (N=110)	10 µg (N=113)	Placebo (N=123)	5 µg (N=125)	10 µg (N=129)	Placebo (N=247)	5 µg (N=245)	10 µg (N=241)
	%			%			%		
Upper respiratory tract infection NOS	10.6	13.6	9.7	9.8	9.6	10.9	19.4	11.4	17.4
Upper respiratory tract Infection viral NOS	0.0	0.0	0.0	1.6	4.0	0.8	0.0	0.4	0.4
Urinary tract infection NOS	3.5	2.7	0.0	2.4	2.4	2.3	2.0	4.1	2.9
Vaginitis**	0.0	0.0	2.2	4.3	0.0	0.0	0.9	1.0	0.0
Vaginosis fungal NOS**	2.2	1.9	4.4	0.0	3.9	0.0	1.8	1.0	2.0
<b>Investigations</b>									
Alanine aminotransferase increased	4.4	1.8	0.0	0.8	0.8	0.0	0.8	0.8	2.9
Blood creatine phosphokinase increased	3.5	1.8	2.7	0.8	6.4	3.1	3.2	2.0	1.7
<b>Metabolism</b>									
Appetite decreased NOS	0.9	0.0	1.8	0.0	0.8	0.8	0.0	2.0	1.7
Hypoglycaemia NOS	5.3	4.5	5.3	3.3	14.4	35.7	12.6	19.2	27.8
<b>Musculoskeletal and connective tissue disorders</b>									
Arthralgia	9.7	1.8	5.3	3.3	4.0	1.6	3.6	3.3	3.3
Back pain	2.7	2.7	6.2	3.3	2.4	2.3	2.8	2.0	2.9
Muscle cramps	1.8	0.0	0.0	1.6	2.4	3.9	1.2	2.9	1.7
Myalgia	1.8	1.8	2.7	0.0	0.8	0.8	2.4	0.8	0.8
Pain in limb	6.2	0.9	4.4	4.9	6.4	3.1	4.5	3.7	2.9
Tendonitis	0.0	2.7	0.9	0.0	0.8	0.8	0.4	0.4	1.7
<b>Nervous system disorders</b>									
Dizziness	6.2	9.1	4.4	6.5	15.2	14.7	6.1	6.1	6.6
Headache NOS	7.1	6.4	6.2	6.5	8.8	7.8	4.9	11.0	7.5
Hypoaesthesia	0.9	0.0	2.7	2.4	0.8	0.0	0.4	1.6	1.7
<b>Psychiatric disorders</b>									
Anxiety	1.8	0.9	3.5	2.4	0.0	3.9	1.6	1.2	0.8
Depression	0.9	2.7	0.0	1.6	1.6	3.1	0.8	0.8	1.7
<b>Reproductive system and breast disorders</b>									
Artificial menopause**	0.0	0.0	0.0	0.0	2.0	0.0	0.0	0.0	0.0
Endometriosis**	0.0	0.0	0.0	0.0	2.0	0.0	0.0	0.0	0.0
Erectile dysfunction NOS*	0.0	1.8	0.0	1.3	1.4	2.7	0.0	0.0	0.7
Menstruation irregular**	0.0	0.0	0.0	0.0	0.0	0.0	0.0	3.0	1.0
Uterine haemorrhage**	0.0	1.9	2.2	0.0	0.0	0.0	0.0	0.0	0.0
Vaginal haemorrhage**	0.0	1.9	0.0	0.0	2.0	0.0	0.0	0.0	0.0
<b>Respiratory, thoracic and</b>									

System Organ Class/Preferred Term	Study 112 <sup>a</sup> (N=336)			Study 113 <sup>b</sup> (N=377)			Study 115 <sup>c</sup> (N=733)		
	Placebo (N=113)	5 µg (N=110)	10 µg (N=113)	Placebo (N=123)	5 µg (N=125)	10 µg (N=129)	Placebo (N=247)	5 µg (N=245)	10 µg (N=241)
	%			%			%		
<b>mediastinal disorders</b>									
Cough	2.7	4.5	3.5	2.4	0.8	2.3	2.8	3.3	2.5
Nasal congestion	0.9	1.8	2.7	0.8	2.4	0.0	0.4	1.2	0.4
Paranasal sinus hypersecretion	0.0	0.0	0.0	0.0	0.0	2.3	0.0	0.0	0.0
Pharyngitis	6.2	5.5	3.5	0.8	3.2	3.9	2.4	2.9	3.3
Sinus congestion	0.0	4.5	2.7	4.1	0.0	1.6	2.8	2.9	1.7
<b>Skin and subcutaneous tissue disorders</b>									
Dermatitis contact	0.9	0.0	2.7	0.8	0.8	0.0	0.0	1.2	0.8
Pruritus NOS	1.8	0.9	0.0	1.6	2.4	2.3	0.8	0.0	0.4
Rash pruritic	0.0	0.0	0.0	1.6	3.2	0.0	0.0	0.4	0.0
Sweating increased	2.7	0.9	1.8	0.8	2.4	7.8	0.8	3.3	2.9
<b>Vascular disorders</b>									
Hypertension aggravated	0.9	0.0	1.8	4.9	4.0	2.3	1.2	4.9	2.1
Hypertension NOS	1.8	2.7	0.9	0.0	3.2	3.1	0.8	0.8	0.4

<sup>a</sup>Study 112: BYETTA + metformin

<sup>b</sup>Study 113: BYETTA + sulfonylurea

<sup>c</sup>Study 115: BYETTA + metformin and sulfonylurea

\* Indicates that the preferred term is only observed in male population. Study 112: The total male population for placebo=67, 5µg=57, and 10µg=68. Study 113: The total male population for placebo=77, 5µg=74, and 10µg=74. Study 115: The total male population for placebo=138, 5µg=145, and 10µg=143.

\*\* Indicates that the preferred term is only observed in female population. Study 112: The total female population for placebo=46, 5µg=53, and 10µg=45. Study 113: The total female population for placebo=46, 5µg=51, and 10µg=55. Study 115: The total female population for placebo=109, 5µg=100, and 10µg=98.

In three open-label extension studies following the three pivotal placebo-controlled studies, subjects treated with BYETTA and metformin and/or sulfonylurea for up to an additional 52 weeks experienced similar types of adverse reactions to those observed in the 30-week placebo-controlled pivotal studies.

### **Less Common Clinical Trial Adverse Drug Reactions**

The following is a list of less common treatment-emergent adverse events reported in the three pivotal trials. Adverse events reported in ≥1% and <2% and reported in greater frequency in BYETTA-treated patients (5 µg and/or 10 µg) than in placebo-treated patients are included in the listing.

#### **In combination with metformin (Study 112)**

**Cardiac disorders:** Palpitations.

**Endocrine disorders:** Hypogonadism male\*.

**Eye disorders:** Vision blurred.

**Gastrointestinal disorders:** Abdominal distension, Abdominal pain NOS, Abdominal pain lower, Dyspepsia aggravated.

**General disorders and administration site conditions:** Injection site pruritus, Injection site rash, Injection site swelling, Malaise, Weakness.

**Immune system disorders:** Seasonal allergy.

**Infections and infestations:** Cellulitis, Fungal infection NOS, Herpes simplex, Lymph gland infection, Nail fungal infection NOS, Pneumonia NOS, Skin and subcutaneous tissue abscess NOS, Viral infection NOS.

**Injury, poisoning and procedural complications:** Back injury NOS, Sunburn.

**Investigations:** Blood phosphorus increased, Blood uric acid increased.

**Metabolism and nutrition disorders:** Appetite decreased NOS, Hyperlipidaemia NOS.

**Nervous system disorders:** Migraine NOS, Neuropathy NOS, Sciatica.

**Renal and urinary disorders:** Haematuria.

**Reproductive system and breast disorders:** Dysfunctional uterine bleeding\*\*, Erectile dysfunction NOS\*, Prostatomegaly\*, Uterine disorder NOS\*\*, Vaginal haemorrhage\*\*.

**Respiratory, thoracic and mediastinal disorders:** Respiratory tract congestion.

**Skin and subcutaneous tissue disorders:** Callus, Folliculitis.

**Vascular disorders:** Hypertension aggravated.

\*Study 112: indicates that the preferred term is only observed in the male population. The total male population for placebo =67, 5µg=57, 10µg=68. \*\* indicates that the preferred term is only observed in female population. The total female population for placebo=46, 5µg=53, and 10µg=45

### **In combination with a sulfonyleurea (Study 113)**

**Eye disorders:** Conjunctivitis, Diabetic retinopathy, Vision blurred.

**Gastrointestinal disorders:** Abdominal distension, Dry mouth, Dyspepsia aggravated, Eructation, Loose stools, Oesophageal reflux aggravated, Tooth disorder NOS, Toothache.

**General disorders and administration site conditions:** Fall, Injection site erythema, Injection site haemorrhage, Injection site pain, Oedema peripheral, Pain NOS.

**Infections and infestations:** Eye infection NOS, Fungal infection NOS, Pharyngitis streptococcal, Vaginitis bacterial NOS\*\*, Vulvovaginitis NOS\*\*.

**Injury, poisoning and procedural complications:** Accidental overdose, Joint dislocation, Road traffic accident.

**Investigations:** Blood in stool, Blood potassium increased, Blood uric acid increased, Gamma-glutamyltransferase increased, Monocyte count increased, Prostatic specific antigen increased\*, Pulse abnormal NOS, Weight increased.

**Musculoskeletal and connective tissue disorders:** Chest wall pain, Osteoarthritis aggravated.

**Neoplasms benign, malignant and unspecified (incl cysts and polyps):** Prostate cancer NOS\*.

**Nervous system disorders:** Dysgeusia, Headache NOS aggravated, Syncope.

**Psychiatric disorders:** Nervousness, Psychogenic erectile dysfunction\*.

**Renal and urinary disorders:** Haematuria.

**Reproductive system and breast disorders:** Prostate induration\*.

**Respiratory, thoracic and mediastinal disorders:** Asthma aggravated, Laryngitis NOS, Upper respiratory tract congestion.

**Skin and subcutaneous tissue disorders:** Cold sweat.

\*Study 113: indicates that the preferred term is only observed in the male population. The total male population for placebo =77, 5µg=74, 10µg=74. \*\* indicates that the preferred term is only observed in the female population. The total female population for placebo =46, 5µg=51, 10µg=55.

### **In combination with metformin and a sulfonylurea (Study 115)**

**Cardiac disorders:** Palpitations.

**Gastrointestinal disorders:** Abdominal pain upper, Dyspepsia aggravated, Gastritis NOS, Loose stools.

**General disorders and administration site conditions:** Feeling hot, Injection site pain, Injection site pruritus, Lethargy.

**Immune system disorders:** Drug hypersensitivity, Seasonal allergy.

**Infections and infestations:** Bronchitis acute NOS, Fungal infection NOS, Herpes simplex, Nail fungal infection NOS, Pharyngitis streptococcal, Pneumonia NOS, Vaginitis\*\*, Vaginitis fungal NOS\*\*.

**Injury, poisoning and procedural complications:** Abrasion NOS, Blister, Limb injury NOS.

**Investigations:** Aspartate aminotransferase increased, Blood uric acid increased, Gamma-glutamyltransferase increased, Haematocrit decreased, Haemoglobin decreased.

**Metabolism and nutrition disorders:** Diabetes mellitus inadequate control.

**Musculoskeletal and connective tissue disorders:** Muscle spasms, Neck pain, Rotator cuff syndrome, Tendonitis.

**Neoplasms benign, malignant and unspecified (incl cysts and polyps):** Ovarian cancer NOS\*\*.

**Nervous system disorders:** Hypoaesthesia, Paraesthesia, Sinus headache, Tremor.

**Psychiatric disorders:** Confusion, Depression, Insomnia, Stress symptoms.

**Reproductive system and breast disorders:** Amenorrhoea NOS\*\*, Dysmenorrhoea\*\*, Genital pruritus female\*\*, Menorrhagia\*\*, Postmenopausal haemorrhage\*\*, Uterine prolapse\*\*, Vaginal cyst\*\*, Vaginal discharge\*\*.

**Respiratory, thoracic and mediastinal disorders:** Nasal congestion, Rhinitis allergic NOS.

**Skin and subcutaneous tissue disorders:** Contusion, Dermatitis contact, Dry skin, Rash NOS.

**Social circumstances:** Menopause\*\*.

\*Study 115: indicates that the preferred term is only observed in the male population. The total male population for placebo =138, 5µg=145, 10µg=143. \*\* indicates that the preferred term is only observed in the female population. The total female population for placebo =109, 5µg=100, 10µg=98.

### **Rare Serious Treatment-Emergent Adverse Events**

The following is a list of **serious** treatment-emergent adverse events reported in <1% and reported in greater frequency in BYETTA-treated patients (5µg and/or 10µg) than in placebo-treated patients.

### **In combination with metformin (Study 112)**

**Gastrointestinal disorders:** Gastritis NOS.

**Heptobiliary disorders:** Cholelithiasis.

**Infections and infestations:** Cellulitis, Pyelonephritis NOS.

**Injury, poisoning and procedural complications:** Therapeutic agent poisoning.

**Musculoskeletal and connective tissue disorders:** Spondylosis.

**Vascular disorders:** Iliac artery thrombosis.

### **In combination with a sulfonylurea (Study 113)**

**Gastrointestinal disorders:** Diverticulitis NOS.

**Heptobiliary disorders:** Cholelithiasis.

**Metabolism and nutrition disorders:** Hypokalaemia.

**Musculoskeletal and connective tissue disorders:** Intervertebral disc herniation.

**Neoplasms benign, malignant and unspecified (incl cysts and polyps):** Acute myeloid leukaemia NOS.

**Nervous system disorders:** Cerebrovascular accident, Convulsions NOS, Syncope.

**Reproductive system and breast disorders:** Endometriosis\*\*.

\*\* indicates that the preferred term is only observed in the female population. The total female population for placebo =46, 5µg=51, 10µg=55.

### **In combination with metformin and a sulfonylurea (Study 115)**

**Cardiac disorders:** Angina pectoris, Angina unstable, Coronary artery disease NOS, Coronary artery disease aggravated, Ventricular tachycardia.

**Ear and labyrinth disorders:** Vertigo.

**Gastrointestinal disorders:** Appendicitis, Appendicitis perforated, Diverticulitis NOS, Gastrointestinal haemorrhage NOS, Pancreatitis acute, Upper gastrointestinal haemorrhage, Vomiting NOS.

**Heptobiliary disorders:** Cholecystitis acute NOS.

**Infections and infestations:** Cellulitis, Kidney infection NOS, Staphylococcal sepsis.

**Injury, poisoning and procedural complications:** Limb injury NOS, tendon rupture.

**Neoplasms benign, malignant and unspecified (incl cysts and polyps):** Brain neoplasm NOS, Colon cancer NOS, Gastric cancer NOS, Ovarian cancer NOS.

**Nervous system disorders:** Dizziness, Transient ischaemic attack.

**Reproductive system and breast disorders:** Uterine prolapse\*\*.

\*\* indicates that the preferred term is only observed in the female population. The total female population for placebo =109, 5µg=100, 10µg=98

### **Immunogenicity**

At week 30, 43.2%, 40.8% and 48.5% of exenatide treated patients in studies 112, 113 and 115 respectively, had a treatment emergent positive antibody titer. The highest incidence of treatment-emergent anti-exenatide antibodies was observed at week 18 for all three studies (48.6%, 48.2%, and 49.8% respectively).

The impact of anti-exenatide antibodies on efficacy of BYETTA has not been established; however, if there is a worsening glycemic control or failure to achieve targeted glycemic control, alternative antihyperglycemic therapy should be considered. See also **WARNINGS AND PRECAUTIONS, Immune**.

### **Injection Site Reactions**

In study 112 injection site related adverse events were experienced in 9.7% placebo vs. 9.4% BYETTA-treated subjects (intent to treat population). In study 113, 6.5% placebo vs. 9.8% BYETTA-treated subjects experienced injection site related adverse events (injection site bruising, pruritus, erythema, haemorrhage, pain, and swelling). In study 115, 4.5% placebo vs. 7.4% BYETTA-treated subjects experienced injection site related adverse events (injection site bruising, burning, haemorrhage, pain, and pruritus). The most common injection site related event observed for all treatment groups across the three studies was injection site bruising. No subject was withdrawn due to an adverse event resulting from an injection site reaction.

### **Post-Market Adverse Drug Reactions**

The following serious and unexpected adverse events of interest not previously listed in the clinical trial adverse reactions section of the Product Monograph have been reported. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Cardiac Disorders:** Acute coronary syndrome, Acute myocardial infarction, Aortic valve incompetence, Aortic valve stenosis, Arrhythmia, Arteriosclerosis coronary artery, Atrial fibrillation, Atrial flutter, Atrial tachycardia, Atrioventricular block, Atrioventricular block complete, Atrioventricular dissociation, Bradycardia, Bundle branch block left, Bundle branch block right, Cardiac aneurysm, Cardiac arrest, Cardiac disorder, Cardiac failure, Cardiac failure congestive, Cardiac flutter, Cardiac tamponade, Cardiac valve disease, Cardiac ventricular disorder, Cardiogenic shock, Cardiopulmonary failure, Cardio-respiratory arrest, Cardiomegaly, Cardiomyopathy, Cardiovascular disorder, Congestive cardiomyopathy, Cor pulmonale, Coronary artery insufficiency, Coronary artery occlusion, Coronary artery stenosis, Coronary artery thrombosis, Electromechanical dissociation, Extrasystoles, Intracardiac thrombus, Ischaemic cardiomyopathy, Left ventricular dysfunction, Mitral valve disease, Mitral valve incompetence, Myocardial infarction, Myocardial ischaemia, Myocarditis, Pericarditis, Pericardial effusion, Pericardial haemorrhage, Sick sinus syndrome, Sinus arrest, Sinus arrhythmia, Sinus tachycardia, Stress cardiomyopathy, Supraventricular extrasystoles, Supraventricular tachycardia, Tachyarrhythmia, Tachycardia, Ventricular dysfunction, Ventricular extrasystoles, Ventricular fibrillation, Ventricular hypertrophy, Ventricular hypokinesia, Ventricular tachycardia, Wolff-Parkinson-White syndrome.

**General disorders and administration site conditions:** Cardiac death, Sudden cardiac death.

**Investigations:** Blood calcitonin increased, Blood creatine phosphokinase increased, Blood pressure decreased, Blood pressure increased, Catheterisation cardiac, Electrocardiogram ambulatory abnormal, Electrocardiogram poor R-wave progression, Electrocardiogram ST segment, Heart rate abnormal, Heart rate decreased, Heart rate increased, Heart rate irregular, Pulse absent, Pulse pressure decreased.

**Neoplasms benign, malignant and unspecified (incl cysts and polyps):** Adenocarcinoma pancreas, Benign neoplasm of thyroid gland, Benign pancreatic neoplasm, Pancreatic carcinoma, Pancreatic carcinoma metastatic, Pancreatic neoplasm, Pancreatic neuroendocrine tumour, Thyroid cancer, Thyroid cancer metastatic, Thyroid neoplasm.

**Nervous system disorders:** Cardiac autonomic neuropathy.

**Surgical and medical procedures:** Aortic valve replacement, Cardiac ablation, Cardiac operation, Cardiac pacemaker insertion, Coronary artery bypass, Coronary arterial stent insertion, Coronary revascularization.

A causal relationship has been established for the following serious adverse reactions.

**Gastrointestinal disorders:** Abdominal distension, Abdominal pain, Acute pancreatitis, Constipation, Flatulence, Hemorrhagic and necrotizing pancreatitis sometimes resulting in death.

**General Disorders and Administration Site Conditions:** Injection-site reactions.

**Immune System Disorders:** Anaphylactic reaction.

**Investigations:** INR increased with concomitant warfarin use, some reports associated with bleeding.

**Metabolism and Nutrition Disorders:** Dehydration (generally associated with nausea, vomiting and/or diarrhea), weight decreased.

**Nervous System Disorders:** Dysgeusia, Somnolence.

**Renal and Urinary Disorders:** Altered renal function, including acute renal failure, worsened chronic renal failure (sometimes requiring hemodialysis), renal impairment, kidney transplant and kidney transplant dysfunction.

**Skin and Subcutaneous Tissue Disorders:** Alopecia, Angioedema, Generalized pruritus and/or urticaria, Macular or papular rash.

## DRUG INTERACTIONS

### Overview

BYETTA can slow gastric emptying, which can reduce the rate of absorption of orally administered drugs. BYETTA should be used with caution in patients receiving oral medications that require rapid gastrointestinal absorption. Patients should be advised to take oral medications that depend on threshold concentrations for efficacy, such as antibiotics, at least 1 hour before BYETTA injection. If such drugs are to be administered with food, patients should be advised to take them with a meal or snack when BYETTA is not administered.

Drug interactions between BYETTA and metformin or sulfonylurea have not been studied in specific pharmacokinetic drug-drug interaction studies.

### Drug-Drug Interactions

**Drugs that Increase Heart Rate:** BYETTA caused an increase in heart rate of up to 10 bpm in a clinical trial in healthy volunteers with a single-dose of exenatide (see **ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology**). The impact on heart rate of co-administration of BYETTA with other drugs that increase heart rate (e.g., sympathomimetic drugs) has not been evaluated in drug-drug interaction studies. As a result, co-administration of BYETTA with these drugs should be undertaken with caution.

**Drugs that Cause PR Interval Prolongation:** BYETTA caused an increase in the PR interval of up to 7 ms in a clinical trial in healthy volunteers with a single-dose of exenatide (see **ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology**). The impact on the PR interval of co-administration of BYETTA with other drugs that prolong the PR interval (including antiarrhythmics, calcium channel blockers, beta-adrenergic blockers, digitalis glycosides, HIV protease inhibitors) has not been evaluated. As a result, co-administration of BYETTA with these drugs should be undertaken with caution.

**General:** Current information sources should be consulted for a comprehensive list of all approved drugs that increase heart rate, prolong the PR interval or cause electrolyte disturbances.

**Digoxin:** Coadministration of repeated doses of BYETTA (10 µg BID) decreased the  $C_{max}$  of oral digoxin (0.25 mg QD) by 17% and delayed the  $T_{max}$  by approximately 2.5 h; however, the overall steady-state pharmacokinetic exposure (AUC) was not changed.

**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.

**Lisinopril:** In patients with mild to moderate hypertension stabilized on lisinopril (5 to 20 mg/day), BYETTA (10 µg BID) did not alter steady-state  $C_{max}$  or AUC of lisinopril. Lisinopril steady-state  $T_{max}$  was delayed by 2 h. There were no changes in 24-h mean systolic and diastolic blood pressure.

**Acetaminophen:** When 1000 mg acetaminophen elixir was given with 10 µg BYETTA (0 h and 1 h, 2 h, and 4 h after BYETTA injection, acetaminophen AUCs were decreased by 21%, 23%, 24%, and 14%, respectively;  $C_{max}$  was decreased by 37%, 56%, 54%, and 41%, respectively;  $T_{max}$  was increased from 0.6 h in the control period to 0.9 h, 4.2 h, 3.3 h, and 1.6 h, respectively. Acetaminophen AUC,  $C_{max}$  and  $T_{max}$  were not significantly changed when acetaminophen was given 1 h before BYETTA injection.<sup>2</sup>

**Warfarin:** In a controlled clinical pharmacology study in healthy volunteers, a delay in warfarin  $T_{max}$  of about 2 hours was observed when warfarin was administered 35 minutes after BYETTA. No clinically relevant effects on  $C_{max}$  or AUC were observed and BYETTA did not have a significant effect on INR. However there have been spontaneously reported cases of increased INR, sometimes associated with bleeding, with concomitant use of warfarin and BYETTA. Closer monitoring of INR is recommended after initiation or alteration of BYETTA therapy in patients taking warfarin.

**Combination Oral Contraceptives (ethinyl estradiol and levonorgestrel):** In healthy females, the administration of a combination oral contraceptive, ethinyl estradiol and levonorgestrel, 30 min after BYETTA resulted in a 45% reduction of the  $C_{max}$  of ethinyl estradiol, a 27% to 41% reduction in  $C_{max}$  of levonorgestrel, and a delay in  $T_{max}$  of up to approximately 4.5; however, BYETTA did not affect AUC of ethinyl estradiol or levonorgestrel. When the oral contraceptive was administered 1 hour before BYETTA, pharmacokinetic profiles of ethinyl estradiol or levonorgestrel were not altered.

### **Drug-Food Interactions**

Interactions with food have not been studied.

### **Drug-Herb Interactions**

Interactions with herbal products have not been established.

### **Drug-Laboratory Interactions**

Interactions with laboratory tests have not been established.

### **Drug-Lifestyle Interactions**

When exenatide is used in combination with a sulfonylurea, patients should be advised to take precautions to avoid hypoglycaemia while driving or using machinery.

## DOSAGE AND ADMINISTRATION

### **Dosing Considerations**

Initiation with 5 µg may reduce the incidence and severity of gastrointestinal side effects.

When BYETTA is added to sulfonylurea therapy, a decrease in the dose of sulfonylurea may be considered to reduce the risk of hypoglycemia (see **WARNINGS AND PRECAUTIONS, Hypoglycemia**).

BYETTA can slow gastric emptying, which can reduce the rate of absorption of orally administered drugs. See **DRUG INTERACTIONS**.

### **Renal Impairment**

BYETTA should not be used in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min), including patients receiving dialysis. Caution should be applied when using BYETTA in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min). BYETTA should be used with caution in patients with renal transplantation. See **Recommended Dose and Dosage Adjustment**, below.

### **Geriatrics (≥ 65 years of age)**

A greater sensitivity of some older individuals cannot be ruled out. Caution should be applied when initiating or escalating doses of BYETTA from 5 µg to 10 µg in patients 65 years of age or older. See **WARNINGS AND PRECAUTIONS, Geriatrics**.

### **Recommended Dose and Dosage Adjustment**

BYETTA can be administered at any time within the 60-minute period **before** the morning and evening meal (or before the two main meals of the day, at least 6 hours or more apart). BYETTA **should not** be administered after a meal.

BYETTA should be initiated at 5 µg per dose administered twice daily in patients with type 2 diabetes mellitus who are already receiving metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea. Based on clinical response, the dose of BYETTA can be increased to 10 µg BID after 1 month of therapy to further improve glycemic control, as tolerated. The maximum dose is 10 µg BID. If no improvement in blood glucose control is seen after 3-4 months, alternative therapies should be considered.

### **Renal Impairment**

No dosage adjustment of BYETTA is required in patients with mild renal impairment (creatinine clearance 50 to 80 mL/min). Caution should be applied when initiating or escalating doses of BYETTA from 5 µg to 10 µg in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min). See also **Dosing Considerations**, above.

### **Missed Dose**

If a dose of BYETTA is missed, the missed dose should be skipped and treatment should be resumed with the next scheduled dose.

### **Administration**

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

### **OVERDOSAGE**

Signs and symptoms of overdose that have been observed at doses of 100 µg (10 times the maximum recommended dose) 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 and should include close monitoring of plasma glucose, hydration status and renal function.

**For management of a suspected drug overdose, contact your regional Poison Control Centre.**

### **ACTION AND CLINICAL PHARMACOLOGY**

Exenatide is a 39-amino acid peptide amide. The amino acid sequence of exenatide partially overlaps that of the endogenous incretin glucagon-like peptide-1 (GLP-1).<sup>6</sup>

#### **Mechanism of Action**

Incretins, such as GLP-1, enhance glucose-dependent insulin secretion and exhibit other glucoregulatory actions following their release into the circulation from the gut.<sup>11,23</sup>

Exenatide is a GLP-1 receptor agonist that mimics several antihyperglycemic actions of incretins.<sup>17,18</sup> Exenatide has been shown to bind to and activate the known human GLP-1 receptor in vitro.<sup>10</sup> This stimulates in vivo secretion of insulin from pancreatic beta cells by mechanisms involving cyclic AMP and/or other intracellular signaling pathways.<sup>10,12</sup> As blood glucose concentrations decrease, insulin secretion subsides.

BYETTA improves glycemic control by reducing fasting and postprandial glucose concentrations in patients with type 2 diabetes through multiple mechanisms of action.<sup>8, 14</sup> BYETTA enhances glucose-dependent insulin secretion and restores first-phase insulin secretion. BYETTA suppresses glucagon secretion during periods of hyperglycemia in patients with type 2 diabetes.<sup>19</sup> BYETTA also slows gastric emptying.<sup>2</sup> These actions work together to reduce fasting and postprandial glucose concentrations by modulation of both glucose appearance and glucose disposal.

**Glucose-dependent insulin secretion:** BYETTA has been shown to enhance insulin secretion in the presence of hyperglycemia in individuals with type 2 diabetes.<sup>14</sup>

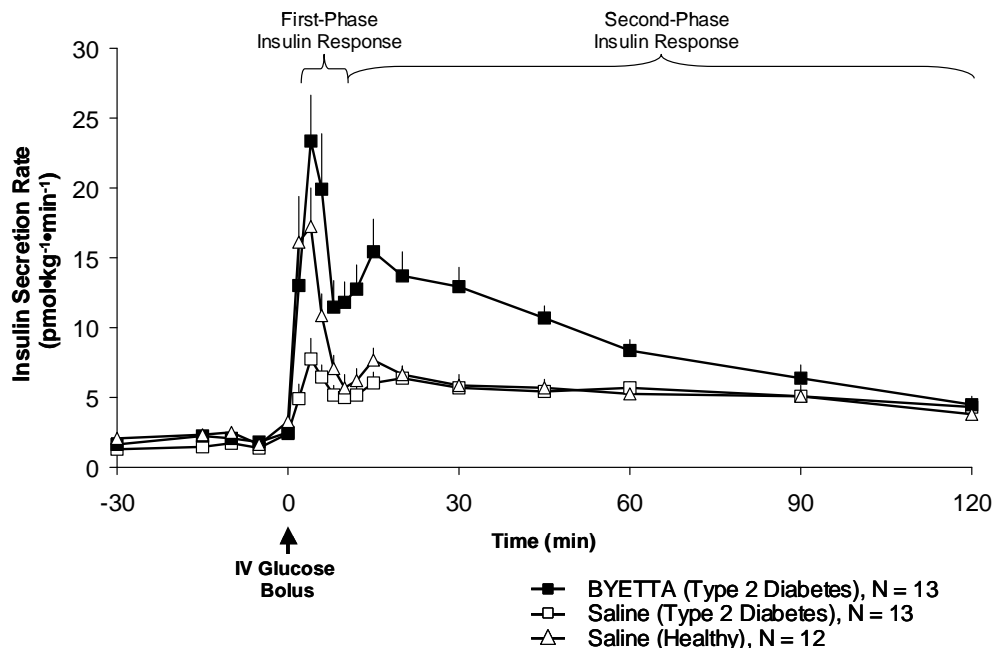
**Beta-cell function:** In healthy individuals, robust insulin secretion occurs during the first 10 minutes following intravenous (IV) glucose administration. This secretion, known as the

“first-phase insulin response,” is characteristically absent in patients with type 2 diabetes. The loss of the first-phase insulin response is an early beta-cell defect in type 2 diabetes.<sup>4</sup>

Intravenous administration of BYETTA at therapeutic plasma concentrations restored first-phase insulin response to an IV bolus of glucose in patients with type 2 diabetes (Figure 1). Both first-phase insulin secretion and second-phase insulin secretion were significantly increased in patients with type 2 diabetes treated with BYETTA compared with saline ( $p < 0.001$  for both).<sup>7</sup>

In some clinical trials BYETTA improved fasting insulin response (as measured by the homeostasis model assessment for beta-cell function [HOMA-B])<sup>16</sup> and insulin procession (proinsulin to insulin ratio).<sup>20</sup>

**Figure 1: Mean (+SEM) Insulin Secretion Rate During Infusion of BYETTA or Saline in Patients With Type 2 Diabetes and During Infusion of Saline in Healthy Subjects**



Patients received an IV infusion of insulin for 6.5 h (discontinued at time [t] = -30 min) to normalize plasma glucose concentrations and a continuous IV infusion of either exenatide or saline for 5 h beginning 3 h prior to an IV bolus of glucose (0.3 g/kg over 30 sec) at t = 0 min.

Glucagon secretion: In patients with type 2 diabetes, BYETTA moderates glucagon secretion and lowers serum glucagon concentrations during periods of hyperglycemia. Lower glucagon concentrations lead to decreased hepatic glucose output and decreased insulin demand.<sup>22</sup> However, BYETTA does not impair the normal glucagon response to hypoglycemia.

Gastric emptying: BYETTA slows gastric emptying thereby reducing the rate at which meal-derived glucose appears in the circulation.<sup>15</sup>

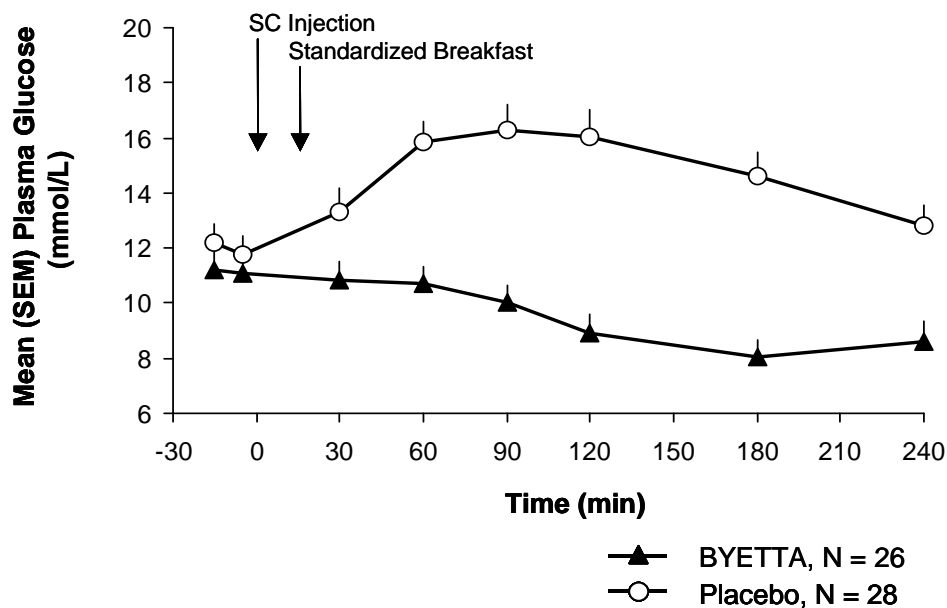
## **Pharmacodynamics**

BYETTA improves glycemic control through the immediate and sustained effects of lowering both postprandial and fasting glucose concentrations in patients with type 2 diabetes.<sup>14, 15</sup>

### **Postprandial Glucose**

In patients with type 2 diabetes, exenatide reduces the postprandial plasma glucose concentrations (Figure 2).<sup>8</sup>

**Figure 2: Mean (+SEM) Postprandial Plasma Glucose Concentrations on Day 1 of BYETTA<sup>a</sup> Treatment in Patients With Type 2 Diabetes Treated With Metformin, a Sulfonylurea, or Both (N = 54)**

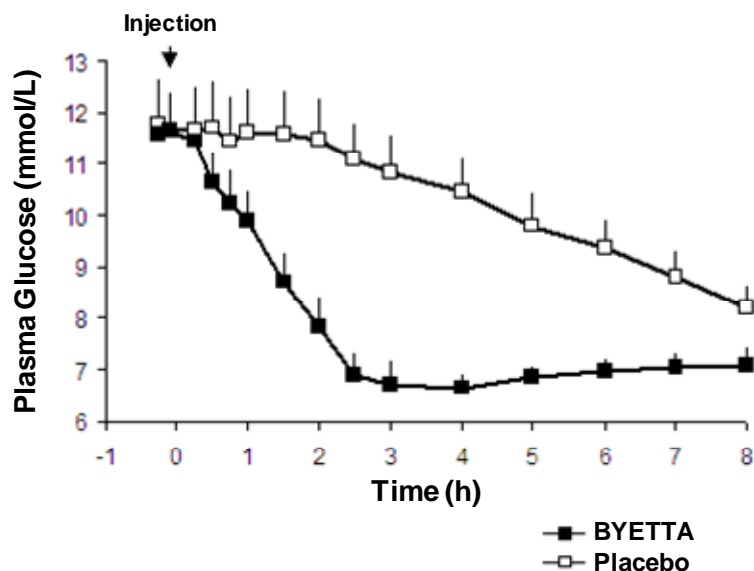


<sup>a</sup> Mean dose (7.8  $\mu$ g based on body weight) was administered by subcutaneous (SC) injection.

### **Fasting Glucose**

In a single-dose crossover trial in patients with type 2 diabetes, plasma glucose concentrations under fasting conditions were significantly reduced with exenatide compared with placebo (Figure 3).<sup>14</sup>

**Figure 3: Mean (+SEM) Plasma Glucose Concentrations Following a One-Time Injection of BYETTA<sup>a</sup> or Placebo in Fasting Patients With Type 2 Diabetes (N = 12)**

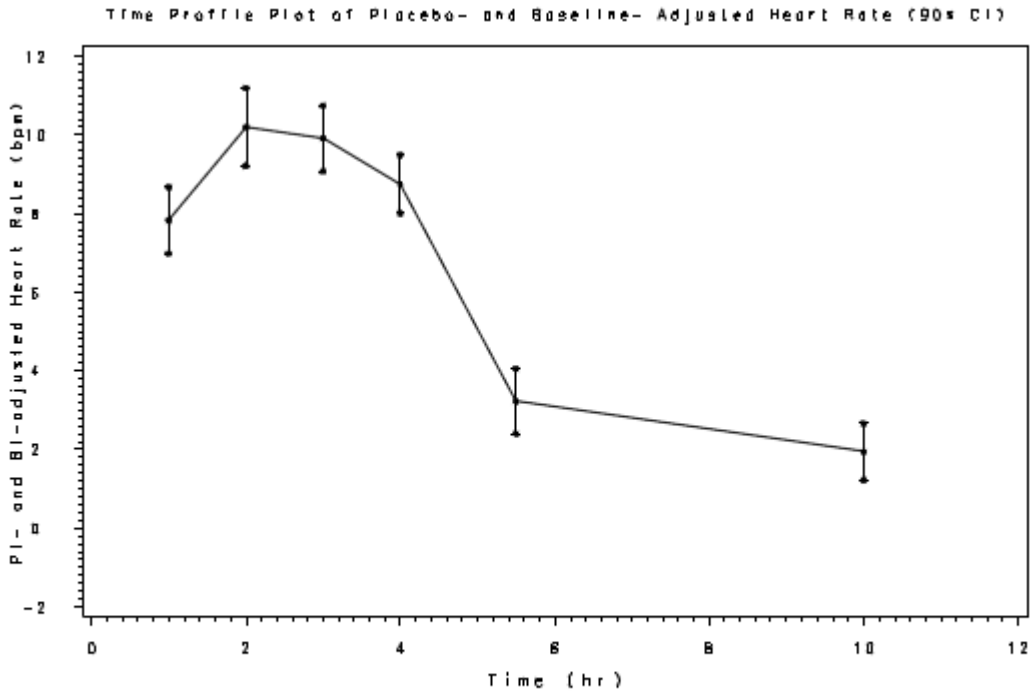


<sup>a</sup> BYETTA administration was based on body weight at baseline; mean dose was 9.1  $\mu$ g.

### **Cardiac Electrophysiology:**

A randomized, double-blind, double-dummy, 3-period crossover, placebo-controlled trial was performed in 62 healthy volunteers (39 Male/23 Female, 18-63 years). Following randomization, subjects in the exenatide treatment arm received a single 10  $\mu$ g subcutaneous (s.c.) dose of exenatide. Subjects randomized to the placebo arm had a placebo s.c. injection. Steady-state effects were not studied.

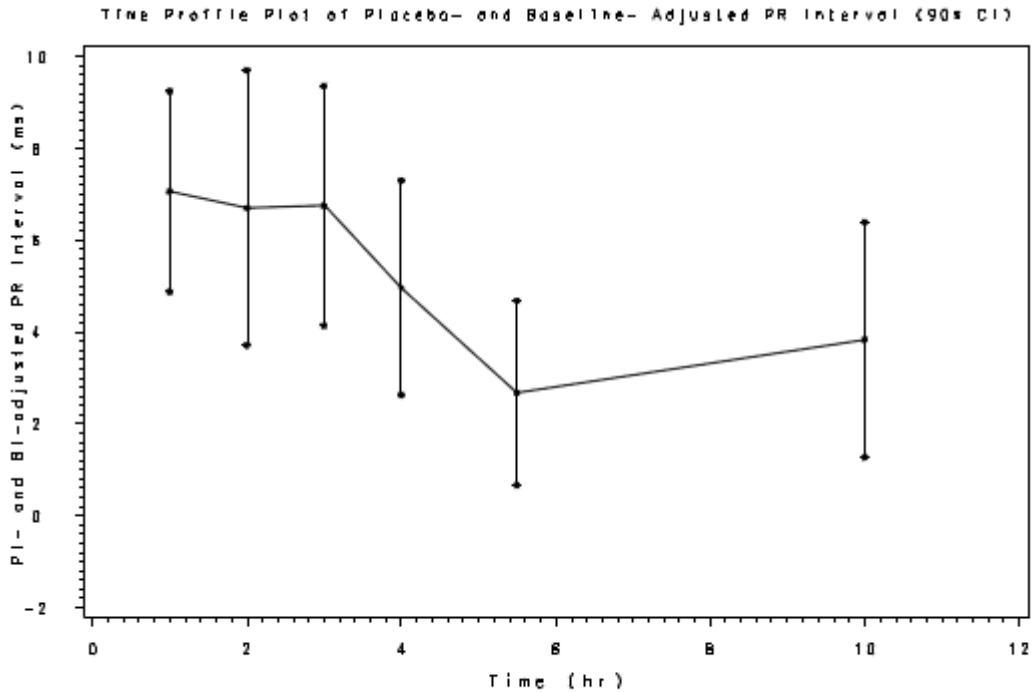
*Heart Rate:* Exenatide 10  $\mu$ g s.c. was associated with small statistically significant increases in heart rate from 1 to 10 hours post-dosing in healthy subjects. The maximum mean placebo- and baseline-adjusted increase was 10.21 (90% 8.58, 11.83) bpm at 2 hours post-dosing. The incidence of subjects with heart rates greater than 90 bpm was 4.8% (3 subjects) for exenatide 10  $\mu$ g s.c. versus 1.6% (1 subject) for placebo.



**Time profile plot of the placebo- and baseline-adjusted heart rate (90% CI) as a function of time for exenatide 10 mcg**

A 12 week study in patients with type 2 diabetes (N=28 on exenatide, N=26 on placebo) showed that changes from baseline in heart rate averaged over 24 hours at 12 weeks were +2 bpm and -1 bpm for Byetta and placebo, respectively. These patients were receiving exenatide or placebo as an add-on to oral antihyperglycemic agents.

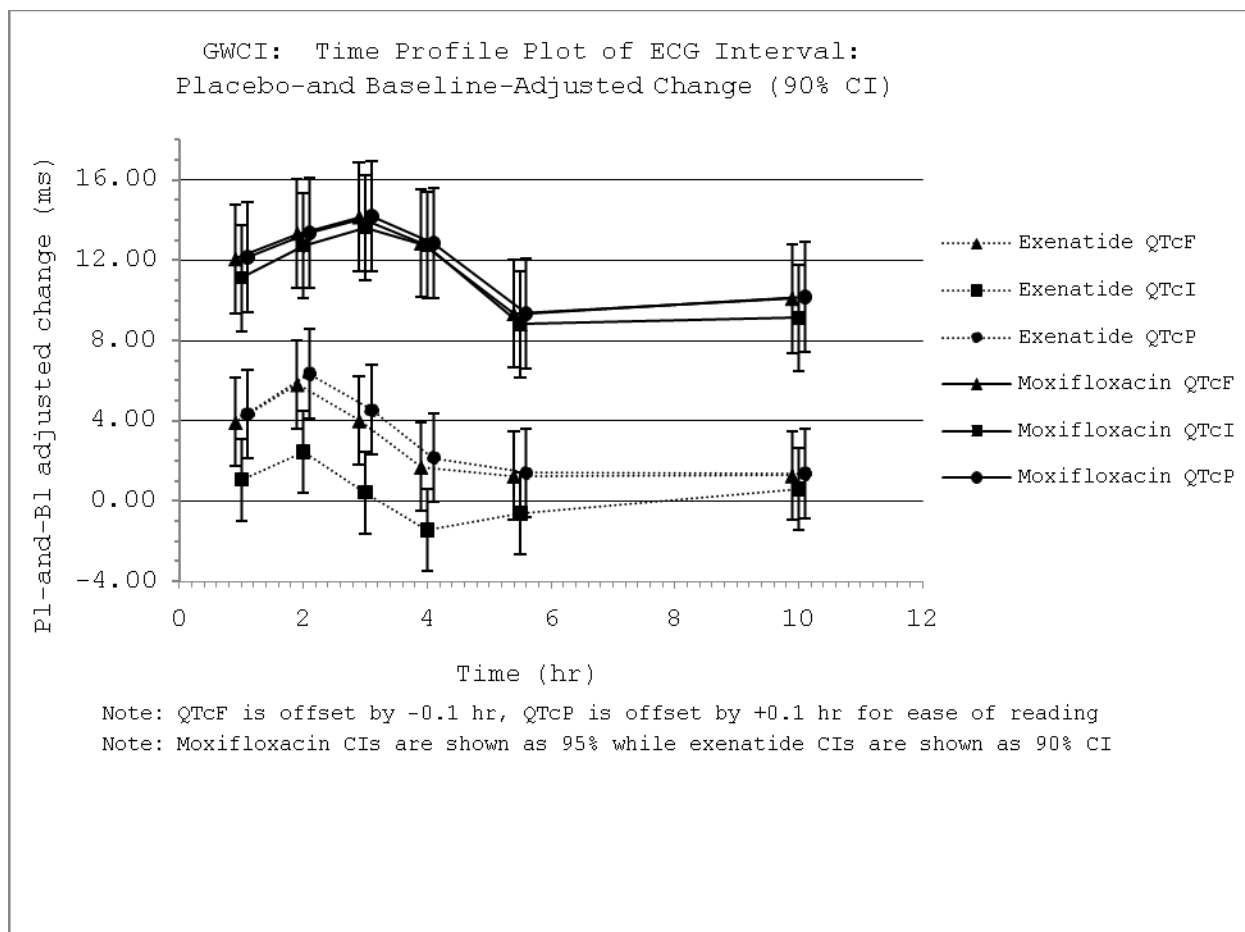
*PR Interval:* Exenatide 10 µg s.c. was associated with statistically significant increases in the PR interval from 1 to 10 hours post-dosing in healthy subjects. The maximum increase in the mean PR interval occurred at the 1 h time point and was 7.13 (90% CI: 4.89, 9.37) ms. The incidence of subjects with PR intervals >200 ms that appeared during treatment was 19% for exenatide versus 11% for placebo.



**Time profile plot of the placebo- and baseline-adjusted PR interval (90% CI) as a function of time for exenatide 10 mcg**

*QT Interval:* Exenatide 10 µg s.c. was associated with a small but statistically significant QTc interval prolongation. The magnitude of the observed effect differed for the three heart rate correction methods used (individual-specific method (QTcI), Fridericia method (QTcF), study population-specific method (QTcP)). A maximum mean increase of 2.44 (90% CI 0.40, 4.47) ms (QTcI); 5.81(90% CI 3.62, 8.00) ms (QTcF); and 6.34 (90% CI 4.12, 8.56) ms (QTcP) was observed at 2 hours post-dosing. The QTc prolongation effect (QTcF) shows a positive correlation with exenatide plasma concentration and a negative correlation with plasma glucose. The optimal heart rate correction for the type of data available in this study is not known.

Care should be observed in patients with risk factors for torsade de pointes (e.g., congenital long QT syndrome, cardiac disease, electrolyte abnormalities).



**Time profile plot of placebo- and baseline-adjusted QTcI, QTcF and QTcP exenatide (90% confidence interval) (Study GWCI).**

### **Pharmacokinetics**

**Absorption:** Following subcutaneous administration to patients with type 2 diabetes, exenatide is rapidly absorbed, reaching median peak plasma concentrations ( $T_{max}$ ) in 2.1 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 ( $AUC$ ) increased proportionally over the therapeutic dose range of 5 µg to 10 µg. The  $C_{max}$  values increased less than proportionally over the same range. Similar exposure is achieved with subcutaneous administration of exenatide in the abdomen, thigh, or upper arm. Relative bioavailability of exenatide in the arm or thigh, as compared to the abdomen, was 93% and 97%, respectively.<sup>3</sup> Therefore, exenatide can be administered either in the abdomen, arm or thigh.

**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.

### **Special Populations and Conditions**

**Geriatrics:** Population pharmacokinetic analysis of patients (range from 22 to 73 years) suggests that age does not influence the pharmacokinetic properties of exenatide. This was based on limited data in subjects over 65 years, with no data for subjects over 73 years.

**Gender:** Population pharmacokinetic analysis of male and female patients suggests that gender has no clinically relevant influence on the distribution and elimination of exenatide.

**Race:** Population pharmacokinetic analysis of patients including Caucasian, Hispanic, Asian and Black, suggests that race has no significant influence on the pharmacokinetics of exenatide.

**Hepatic Impairment:** No pharmacokinetic study has been performed in patients with a diagnosis of acute or chronic hepatic insufficiency. Because exenatide is cleared primarily by the kidney, hepatic dysfunction is not expected to affect blood concentrations of exenatide (see Pharmacokinetics, Metabolism and Elimination).

**Renal Impairment:** In patients with mild to moderate renal impairment (creatinine clearance 30 to 80 mL/min), exenatide clearance was reduced compared to clearance in individuals with normal renal function (13% reduction in mild and 36% reduction in moderate renal impairment); in patients with end-stage renal disease receiving dialysis (creatinine clearance < 30 L/h), mean exenatide clearance is reduced to 0.9 L/h compared with 9.1 L/h in healthy subjects. Given the significant reduction in clearance coupled with poor tolerability in severe and end-stage renal disease, exenatide should not be used in these patients (creatinine clearance <30 mL/min; see **CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS, Renal**).

**Obesity:** Population pharmacokinetic analysis of obese (BMI  $\geq 30$  kg/m<sup>2</sup>) and non-obese patients suggests that obesity has no significant effect on the pharmacokinetics of exenatide; however, there is limited clinical trial experience in patients with BMI  $\leq 25$  kg/m<sup>2</sup>.

## **STORAGE AND STABILITY**

BYETTA should be protected from light. Prior to first use BYETTA must be stored refrigerated at 2°C to 8°C. Do not freeze. Do not use BYETTA if it has been frozen. After first use of the pen, BYETTA should be stored at 2°C to 25°C.

The BYETTA pen should be discarded 30 days after first use, even if some drug remains in the pen. The BYETTA pen should not be stored with the needle attached.

Keep the BYETTA pen and needles out of reach of children and pets.

## **SPECIAL HANDLING INSTRUCTIONS**

BYETTA is a clear and colourless liquid and should not be used if particles appear or if the solution is cloudy or coloured. BYETTA should not be used past the expiration date. The Pen User Manual instructions must be followed carefully.

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

BYETTA is supplied as a sterile, preserved solution for subcutaneous injection in a glass cartridge that has been assembled in a pen-injector (pen). Each milliliter (mL) contains 250 micrograms ( $\mu\text{g}$ ) exenatide in addition to the following nonmedicinal ingredients: *m*-cresol (2.20 mg), mannitol, glacial acetic acid, sodium acetate trihydrate, and water for injection.

The following BYETTA prefilled pen presentations are available:

- 1.2 mL prefilled pen, 5  $\mu\text{g}$  per dose (packaged in a carton)
- 2.4 mL prefilled pen, 10  $\mu\text{g}$  per dose (packaged in a carton)

Each prefilled pen will deliver 60 doses to provide 30 days of twice daily administration (BID).

In the absence of compatibility studies, BYETTA must not be mixed with other medicinal products.

Pen needles are not included with the pen and must be purchased separately.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

Common name: exenatide

Chemical name: Exenatide is a 39-amino acid peptide amide. The amino acid sequence of exenatide is as follows:

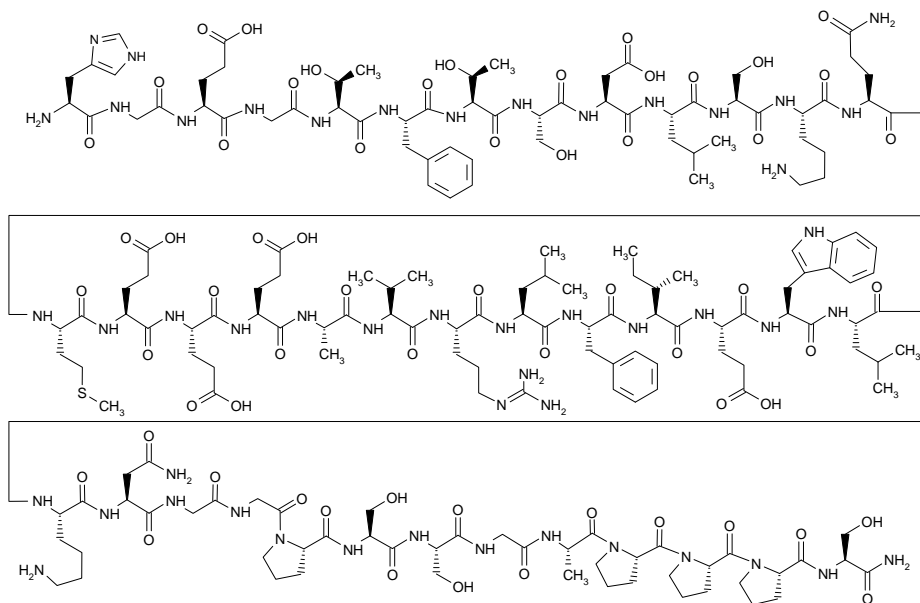
H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH<sub>2</sub>

Chemical name (USAN):

L-histidylglycyl-L-glutamylglycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-aspartyl-L-leucyl-L-seryl-L-lysyl-L-glutamyl-L-methionyl-L-glutamyl-L-glutamyl-L-alanyl-L-valyl-L-arginyl-L-leucyl-L-phenylalanyl-L-isoleucyl-L-glutamyl-L-tryptophanyl-L-leucyl-L-lysyl-L-asparaginylglycylglycyl-L-prolyl-L-seryl-L-serylglycyl-L-alanyl-L-prolyl-L-prolyl-L-prolyl-L-serinamide

Molecular formula and molecular mass: C<sub>184</sub>H<sub>282</sub>N<sub>50</sub>O<sub>60</sub>S, 4186.6 Daltons

Structural formula:



Physicochemical properties: Exenatide drug substance is a white to off-white powder. Exenatide is freely soluble in water and pH 4.5 acetate buffer.

## CLINICAL TRIALS

### Long-Term Placebo-Controlled Clinical Trials (Use with metformin and/or a sulfonylurea)

Three randomized, double-blind, placebo-controlled, 30-week pivotal trials were conducted to evaluate the efficacy and safety of BYETTA in patients with type 2 diabetes and BMI 27 to 45 kg/m<sup>2</sup>, inclusive, whose glycemic control was inadequate with maximally effective doses of metformin alone<sup>5</sup>, sulfonylurea alone<sup>1</sup>, or metformin in combination with a sulfonylurea<sup>13</sup> (Table 3).

#### Study Demographics and Trial Design

**Table 3: Summary of Patient Demographics for Long-Term Placebo-Controlled Clinical Trials of BYETTA in the Treatment of Type 2 Diabetes Mellitus**

Study #	Trial Design / Duration	Dosage <sup>a</sup> and Route of Administration	Study Subjects (N=Number)	Mean Age (Range)	Gender (Number)
112	30-week, randomized, double-blind, placebo-controlled, 3-arm parallel, multicentre	BYETTA 5 µg, BYETTA 10 µg or placebo; SC BID	Type 2 diabetes mellitus + ≥1500 mg/day metformin (N=336)	53 years (19 to 78 years)	Female (144) Male (192)
113	30-week, randomized, double-blind, placebo-controlled, 3-arm parallel, multicentre	BYETTA 5 µg, BYETTA 10 µg or placebo; SC BID	Type 2 diabetes mellitus + at least a maximally effective dose of a SFU (N=377)	55 years (22 to 76 years)	Female (152) Male (225)
115	30-week, randomized, double-blind, placebo-controlled, 3-arm parallel, multicentre	BYETTA 5 µg, BYETTA 10 µg or placebo; SC BID	Type 2 diabetes mellitus + metformin and SFU (N=733)	55 years (22 to 77 years)	Female (307) Male (426)

<sup>a</sup> Patients assigned to BYETTA 10 µg received BYETTA 5 µg for a 4-week treatment initiation period followed by BYETTA 10 µg for 26 weeks.

Abbreviations: SC, subcutaneous; BID, twice daily; SFU, sulfonylurea.

A total of 1447 (Intent-to-treat subjects=1446) patients were randomized in these three trials: 991 (68.5%) were Caucasian, 224 (15.5%) were Hispanic, and 174 (12.0%) were Black. Mean glycosylated hemoglobin (A1C) values at baseline averaged 8.4%, mean baseline BMI was approximately 34 kg/m<sup>2</sup>, and mean baseline body weight was approximately 98 kg. After a 4-week placebo lead-in period, patients were randomly assigned to receive BYETTA 5 µg BID, BYETTA 10 µg BID, or placebo BID before the morning and evening meals, in addition to their existing oral antihyperglycemic agent (metformin and/or a sulfonylurea). All patients assigned to BYETTA began a treatment initiation period with 5 µg BID for 4 weeks. After 4 weeks, those patients either continued to receive BYETTA 5 µg BID or had their dose increased to 10 µg BID for 26 weeks. Patients assigned to placebo received placebo BID throughout the study. The primary endpoint in each study was mean change in HbA1c from baseline to 30 weeks.

## Study Results

Thirty-week pivotal study results are summarized in Table 4.

**Table 4: Results of 30-Week Placebo-Controlled Trials of BYETTA in Patients With Type 2 Diabetes Mellitus and Inadequate Glucose Control Despite the Use of Metformin, a Sulfonylurea, or Both (Intent-to-treat population)**

	Placebo BID	BYETTA 5 µg BID	BYETTA 10 µg <sup>a</sup> BID
	<b>In Combination With Metformin (Study 112)<sup>5</sup></b>		
<b>Intent-to-Treat Population (N)</b>	113	110	113
<b>HbA1c (%), LS Mean</b>			
Baseline	8.2	8.3	8.2
Change at Week 30	-0.0	-0.5*	-0.9**
<b>Proportion Achieving HbA1c ≤7%<sup>b</sup></b>	11%	27%*	40%**
<b>Fasting Plasma Glucose (mmol/L), LS Mean</b>			
Baseline	9.4	9.8	9.3
Change at Week 30	+0.8	-0.3*	-0.6*
<b>Body Weight (kg), LS Mean</b>			
Baseline	99.9	100.0	100.9
Change at Week 30	-0.2	-1.3*	-2.6**
	<b>In Combination With a Sulfonylurea (Study 113)<sup>1</sup></b>		
<b>Intent-to-Treat Population (N)</b>	123	125	129
<b>HbA1c (%), LS Mean</b>			
Baseline	8.7	8.5	8.6
Change at Week 30	+0.1	-0.5*	-0.9**
<b>Proportion Achieving HbA1c ≤7%<sup>b</sup></b>	8%	27% **	34% **
<b>Fasting Plasma Glucose (mmol/L), LS Mean</b>			
Baseline	10.8	10.0	9.9
Change at Week 30	+0.3	-0.3	-0.6*
<b>Body Weight (kg), LS Mean</b>			
Baseline	99.1	94.9	95.2
Change at Week 30	-0.8	-1.1	-1.6*
	<b>In Combination With Metformin and a Sulfonylurea (Study 115)<sup>13</sup></b>		
<b>Intent-to-Treat Population (N)</b>	247	245	241
<b>HbA1c (%), LS Mean</b>			
Baseline	8.5	8.5	8.5
Change at Week 30	+0.1	-0.7**	-0.9**
<b>Proportion Achieving HbA1c ≤7%<sup>b</sup></b>	7%	24%**	30%**
<b>Fasting Plasma Glucose (mmol/L), LS Mean</b>			
Baseline	10.0	10.1	9.9
Change at Week 30	+0.7	-0.6**	-0.7**
<b>Body Weight (kg), LS Mean</b>			
Baseline	99.1	96.9	98.4
Change at Week 30	-0.9	-1.6*	-1.6*

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<sup>a</sup> BYETTA 5 µg twice daily (BID) for 4 weeks followed by 10 µg BID for 26 weeks before the morning and evening meals.

<sup>b</sup> Patients eligible for the analysis with baseline HbA1c >7%.

\* p ≤0.05, treatment vs. placebo

\*\* p ≤0.0001, treatment vs. placebo

## HbA1c

The addition of BYETTA to a regimen of metformin, a sulfonylurea, or both, resulted in statistically significant reductions from baseline HbA1c at Week 30 compared with patients receiving placebo added to these agents in the three controlled trials (Table 5). In addition, a statistically significant dose response effect was observed between 5µg and 10µg BYETTA groups for the change from baseline HbA1c at Week 30 in the three studies.

## DETAILED PHARMACOLOGY

Exenatide is a 39-amino acid peptide amide that exhibits approximately 50% sequence identity with that of the mammalian endogenous incretin glucagon-like peptide-1 (GLP-1) secreted in response to a meal by intestinal L-cells.<sup>6</sup> In vitro pharmacology studies have shown that exenatide can bind and activate the human GLP-1 receptor leading to an increase in both synthesis and secretion of insulin from pancreatic beta-cells.<sup>10</sup> In vitro studies have also demonstrated that exenatide is not substantially degraded by the protease dipeptidyl peptidase IV (DPP-IV), which explains the longer duration of pharmacologic effects observed with exenatide.

### Pharmacodynamics

Nonclinical pharmacology studies support the concept that exenatide is a GLP-1 receptor agonist that acts through multiple mechanisms to promote lowering of plasma glucose concentrations and to lower HbA1c. Exenatide decreases fasting glucose concentrations in animal models of type 2 diabetes (rat, mouse, and monkey) and exhibits a durable effect to lower HbA1c in diabetic mice and rats.<sup>9</sup> Improvements in glycemic control are achieved via modulation of both the rate of glucose appearance in the circulation (slowing of gastric emptying, reduced food intake, and suppression of inappropriately elevated glucagon secretion) and the rate of glucose clearance (enhanced glucose-dependent insulin secretion, improved insulin sensitivity, and increased beta-cell mass). Reduced food intake in animal models of type 2 diabetes was associated with reduced weight gain.<sup>21</sup>

### Safety Pharmacology

Safety pharmacology studies examined exenatide-related cardiovascular, renal, nervous, and endocrine system effects. Exenatide produced acute, dose-dependent hemodynamic effects including increases in mean arterial blood pressure and heart rate in rats. These effects appeared to be transient and were not observed in other species. Exenatide at nominal concentrations of 5.9 and 91.1 µM did not affect hERG currents in HEK293 cells stably transfected with hERG DNA (N=3/treatment). No differences from vehicle in heart rate or electrocardiogram changes were detected in an escalating dose cardiovascular safety pharmacology study performed in free-moving conscious telemetry monkeys (N=3), receiving single subcutaneous doses of 30, 300, and 1000 µg/kg exenatide. Exenatide produced an acute, profound diuresis and natriuresis in

rats, and a mild diuresis in mice. No exenatide-related effects on renal function were detected in monkeys.

### **Pharmacokinetics**

No consistent differences in the pharmacokinetic parameters for exenatide were observed between male and female mice, rats, and monkeys. In general, for SC administration,  $C_{\max}$  and AUC increased in proportion to dose. Since clearance of peptides by renal filtration and metabolism is known to occur, this route of elimination was investigated for exenatide. The dominant role of the kidneys in the clearance of exenatide was further assessed in a renal-ligation model in rats. Following renal ligation,  $C_{\max}$ , and  $t_{1/2}$  for exenatide all significantly increased and clearance decreased. Studies performed in rats, mice, rabbits, and humans to evaluate the potential for exenatide to cross the placental barrier provide support that the fetal to maternal ratio is low.

## **TOXICOLOGY**

### **Acute Toxicity**

Single-dose toxicity studies were conducted in mice, rats, and monkeys. No lethality or serious toxicity was observed in mice, rats, or monkeys at doses up to 1500  $\mu\text{g}/\text{kg}$  (intravenous), 30,000  $\mu\text{g}/\text{kg}$  (subcutaneous), or 5000  $\mu\text{g}/\text{kg}$  (subcutaneous) respectively.

### **Repeat-Dose Toxicity**

Repeat-dose toxicity studies were conducted in mice, rats, and monkeys. Decreased body weight gain and food consumption, a known pharmacologic effect of exenatide, were observed in all repeat-dose toxicity studies. No target organ toxicities occurred in mice, rats, or monkeys at subcutaneous doses up to 760  $\mu\text{g}/\text{kg}/\text{day}$  (182 days), 250  $\mu\text{g}/\text{kg}/\text{day}$  (91 days), or 150  $\mu\text{g}/\text{kg}/\text{day}$  (273 days), respectively, with corresponding systemic exposures of up to 519, 128, and 482 times the human exposure resulting from the maximum recommended dose of 20  $\mu\text{g}/\text{day}$  based on plasma area under the curve (AUC), respectively.

### **Carcinogenicity**

A 104-week carcinogenicity study was conducted in male and female rats at doses of 18, 70, or 250  $\mu\text{g}/\text{kg}/\text{day}$  administered by bolus subcutaneous injection. An apparent numerical increase in benign thyroid C-cell adenomas was observed in female rats given the high dose of 250  $\mu\text{g}/\text{kg}/\text{day}$ , a systemic exposure 130 times the human exposure resulting from the maximum recommended dose of 20  $\mu\text{g}/\text{day}$ , based on AUC. This increased incidence was not statistically significant when adjusted for survival. There was no tumorigenic response in male rats.

In a 104-week carcinogenicity study in mice at doses of 18, 70, or 250  $\mu\text{g}/\text{kg}/\text{day}$  administered by bolus subcutaneous injection, no evidence of tumors was observed at doses up to 250  $\mu\text{g}/\text{kg}/\text{day}$ , a systemic exposure up to 95 times the human exposure based on AUC.

### **Mutagenicity**

Exenatide was not mutagenic or clastogenic, with or without metabolic activation, in the Ames bacterial mutagenicity assay or chromosomal aberration assay in Chinese hamster ovary cells. Exenatide was negative in the in vivo mouse micronucleus assay.

### **Impairment of Fertility**

In mouse fertility studies with subcutaneous doses of 6, 68 or 760 µg/kg/day, males were treated for 4 weeks prior to and throughout mating and females were treated 2 weeks prior to and throughout mating until Gestation Day 7. No adverse effect on fertility was observed at 760 µg/kg/day, a systemic exposure 390 times the human exposure resulting from the maximum recommended dose of 20 µg/day, based on AUC.

### **Teratogenicity**

In pregnant mice given subcutaneous doses of 6, 68, 460, or 760 µg/kg/day from Gestation Day 6 through 15 (organogenesis), fetal growth was slowed at doses  $\geq$  68 µg/kg/day exenatide ( $\geq$  23 times the human exposure). Administration of higher doses of exenatide ( $\geq$  460 µg/kg/day) was associated with skeletal effects known to be associated with slowed fetal growth. The NOAEL for developmental effects in mice was 6 µg/kg/day (3 times the human exposure, based on AUC).

In pregnant mice given subcutaneous doses of 6, 68, or 760 µg/kg/day from Gestation Day 6 through Lactation Day 20 (weaning), slowed neonatal growth was observed in the F1 offspring at doses  $\geq$  68 µg/kg/day ( $\geq$  23 times the human exposure resulting from the maximum recommended dose of 20 µg/kg/day, based on AUC). Increased perinatal and neonatal mortality occurred in the F1 offspring at 760 µg/kg/day (390 times the human exposure resulting from the maximum recommended dose of 20 µg/kg/day, based on AUC). The NOAEL for developmental toxicity in mice was 6 µg/kg/day (3 times the human exposure, based on AUC).

In pregnant rabbits given subcutaneous doses of 0.2, 2, 22, 156, or 260 µg/kg/day from Gestation Day 6 through 18 (organogenesis), fetal growth was slowed at doses greater than or equal to 22 µg/kg/day ( $\geq$  207 times the human exposure resulting from the maximum recommended dose of 20 µg/day, based on AUC). The NOAEL for developmental effects in rabbits was 2 µg/kg/day (12 times the human exposure, based on AUC).

## REFERENCES

1. Buse JB, Henry RR, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care*. 2004;27:2628-2635.
2. Blase E, Taylor K, Gao HY, Wintle M, Fineman M. Pharmacokinetics of an oral drug (acetaminophen) administered at various times in relation to subcutaneous injection of exenatide (exendin-4) in healthy subjects. *J Clin Pharmacol*. 2005;45:570-577.
3. Calara F, Taylor K, Han J, Zabala E, Carr E, Wintle M, Fineman M. A randomized, open-label, crossover study examining the effect of injection site on bioavailability of exenatide (synthetic exendin-4). *Clin Ther*. 2005;27:210-215.
4. Caumo A, Luzi L. First-phase insulin secretion: does it exist in real life? Considerations on shape and function. *Am J Physiol Endocrinol Metab*. 2004;287:E371-E385.
5. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes mellitus. *Diabetes Care*. 2005;28:1092-1100.
6. Eng J, Kleinman WA, Singh L, Singh G, Raufman JP. Isolation and characterization of exendin-4, an exendin-3 analogue from *Heloderma suspectum* venom. *J Biol Chem*. 1992;267:7402-7405.
7. Fehse F, Trautmann M, Holst JJ, Halseth AE, Nanayakkara N, Nielsen LL, Fineman MS, Kim DD, Nauck MA. Exenatide Augments First and Second Phase Insulin Secretion in Response to Intravenous Glucose in Subjects with Type 2 Diabetes. *J Clin Endocrinol Metab*. 2005
8. Fineman MS, Bicsak TA, Shen LZ, Taylor K, Gaines E, Varns A, Kim D, Baron AD. Effect on glycemic control of exenatide (synthetic exendin-4) additive to existing metformin and/or sulfonylurea treatment in patients with type 2 diabetes. *Diabetes Care*. 2003;26:2370-2377.
9. Gedulin B, Jodka C, Hoyt J. Exendin-4 (AC2993) decreases glucagon secretion during hyperglycemic clamps in diabetic fatty Zucker rats. *Diabetes* 1999;48(suppl 1):A199. Abstract 0864.
10. Goke R, Fehmann HC, Linn T, Schmidt H, Krause M, Eng J, Goke B. Exendin-4 is a high potency agonist and truncated exendin-(9-39)-amide an antagonist at the glucagon-like peptide-1-(7-36) amide receptor of insulin-secreting beta-cells. *J Biol Chem*. 1993;268:19650-19655.
11. Holst JJ. Therapy of type 2 diabetes mellitus based on the action of glucagon-like peptide-1. *Diabetes Metab Res Rev*. 2002; 18:430-441.

12. Idris I, Patiag D, Gray S, Donnelly R. Exendin-4 increases insulin sensitivity via a PI-3-kinase-dependent mechanism: contrasting effects of GLP-1. *Biochem Pharmacol.* 2002;63:993-996.
13. Kendall DM, Riddle MC, Rosenstock J, Zhuang D, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes mellitus treated with metformin and a sulfonylurea. *Diabetes Care.* 2005;28:1083-1091.
14. Kolterman OG, Buse JB, Fineman MS, Gaines E, Heintz S, Bicsak TA, Taylor K, Kim D, Aisporna M, Wang Y, Baron AD. Synthetic exendin-4 (AC2993) significantly reduces postprandial and fasting plasma glucose in subjects with type 2 diabetes. *J Clin Endocrinol Metab.* 2003;88:3082-3089.
15. Kolterman OG, Kim DD, Shen L, Ruggles JA, Nielsen LL, Fineman MS, Baron AD. Pharmacokinetics, pharmacodynamics, and safety of exenatide in patients with type 2 diabetes mellitus. *Amer J Health Sys Pharmacy.* 2005;62:173-181.
16. Levy JC, Matthews DR, Hermans MP. Correct homeostasis model assessment (HOMA) evaluation uses the computer program. *Diabetes Care* 1998;21:2191-2.
17. Nielsen LL, Baron AD. Pharmacology of exenatide (synthetic exendin-4) for the treatment of type 2 diabetes. *Curr Opin Invest Drugs.* 2003;4:401-405.
18. Parkes DG, Pittner R, Jodka C, Smith P, Young A. Insulinotropic actions of exendin-4 and glucagon-like peptide-1 in vivo and in vitro. *Metabolism.* 2001;50:583-589.
19. Reaven GM, Chen YD, Golay A, Swislocki AL, Jaspan JB. Documentation of hyperglucagonemia throughout the day in nonobese and obese patients with noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 1987;64:106-10.
20. Roder ME, Porte D Jr, Schwartz RS, Kahn SE. Disproportionately elevated proinsulin levels reflect the degree of impaired B cell secretory capacity in patients with noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 1998;83:604-8.
21. Szayna M, Doyle ME, Betkey JA, Holloway HW, Spencer RGS, Greig NH, Egan JM. Exendin-4 decelerates food intake, weight gain, and fat deposition in Zucker rats. *Endocrinology.* 2000;141:1936-1941.
22. Unger RH, Orci L. The role of glucagon in the endogenous hyperglycemia of diabetes mellitus. *Annu Rev Med* 1977;28:119-30.
23. Vilsbøll T, Holst JJ. Incretins, insulin secretion and type 2 diabetes mellitus. *Diabetologia.* 2004;47:357-366.

**PART III: CONSUMER INFORMATION**

**BYETTA™**  
exenatide injection

www.lilly.ca

This leaflet is part III of a three-part "Product Monograph" published when BYETTA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about BYETTA. Contact your doctor or pharmacist if you have any questions about the drug.

**ABOUT THIS MEDICATION**What BYETTA is used for:

BYETTA is used to improve blood sugar control in adults with type 2 diabetes in combination with metformin and/or a sulfonyleurea when metformin and/or a sulfonyleurea plus diet and exercise have failed to adequately control blood sugar levels. Continue to follow your diet and exercise plan.

What BYETTA does:

BYETTA helps your body release more insulin when your blood sugar is high. This help to improve your blood sugar control.

When BYETTA should not be used:

- Do not use BYETTA if you are allergic to exenatide or any of the other ingredients in BYETTA listed in the "nonmedicinal ingredients" section below.
- Do not use BYETTA if you have severe kidney disease or are on dialysis.
- Do not use BYETTA if you have diabetic ketoacidosis (accumulation of ketones in the blood and urine).
- Do not use BYETTA if you have type 1 diabetes.

What the medicinal ingredient is:

exenatide

What the nonmedicinal ingredients are:

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

What dosage forms BYETTA comes in:

BYETTA is a solution for injection under the skin (subcutaneous injection) and is available as prefilled injection pens. There are two prefilled pens that provide 60 doses of either 5 µg or 10 µg exenatide per dose.

**WARNINGS AND PRECAUTIONS**

**Cases of inflammation of the pancreas (pancreatitis) have been reported in patients receiving Byetta. Pancreatitis can be a serious, potentially life-threatening medical condition. (See below - Serious Side Effects and What to do About Them.)**

BYETTA should not be used in patients with type 2 diabetes who require insulin.

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

BYETTA may increase heart rate or cause changes in heart rhythm. Rarely drugs with these effects could result in dizziness, palpitations (a feeling of rapid, pounding, or irregular heart beat), fainting, or death. These heart rhythm changes are more likely if you have heart disease or if you are taking certain other drugs. In general, people more than 65 years in age are at higher risk. See SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM. If you experience dizziness, palpitations (sensation of rapid, pounding, or irregular heart beat), fainting, or seizures, you should seek immediate medical attention.

BEFORE you use BYETTA talk to your doctor or pharmacist if you:

- Have severe problems with your stomach (gastroparesis) or food digestion. BYETTA slows stomach emptying so food passes more slowly through your stomach.
- Have severe vomiting and/or diarrhea and/or dehydration.
- Have a history of pancreatitis (inflammation of the pancreas), stones in your gallbladder (gallstones), a history of alcoholism, or high blood triglyceride levels.
- Are receiving treatment with a sulfonyleurea (e.g. Diabeta, Diamicon, Amaryl) since these types of drugs can increase the risk of hypoglycaemia (low blood sugar) if used in combination with BYETTA. Take precautions to avoid low blood sugar while driving or using machinery.
- Have had kidney disorder or kidney transplant.
- Are pregnant or planning to become pregnant.
- Are breastfeeding or plan to breastfeed.
- Have current or history of heart failure or other heart disease, such as angina or heart rhythm disturbances, or if you have ever had a myocardial infarction (heart attack).
- Have a personal history of fainting spells.
- Have high heart rate (fast pulse) or a condition called heart block.
- Have electrolyte disturbances (e.g., low blood potassium or magnesium levels) or conditions that could lead to electrolyte disturbances (e.g., vomiting, diarrhea, dehydration).
- if you or a member of your family have ever had medullary thyroid cancer.

- if you have Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

Also talk to your doctor or pharmacist before you use BYETTA if you:

- have been diagnosed with pituitary or adrenal failure
- have any eating disorders, are on a special diet, or often skip meals
- exercise regularly or intensely
- drink alcohol excessively

These conditions may increase your risk of low blood sugar if you take BYETTA.

Your blood sugar may get too high (hyperglycaemia) if you have fever, infection, surgery, or trauma (stress conditions). In such cases contact your doctor as your medication may need to be adjusted.

## INTERACTIONS WITH THIS MEDICATION

**Tell your doctor or pharmacist about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements.**

In particular, tell your doctor or pharmacist if you are taking:

- a birth control pill (oral contraceptive), this medication should be taken at least 1 hour before taking BYETTA
- an antibiotic, this medication should be taken at least 1 hour before taking BYETTA
- warfarin (blood thinner)
- digoxin (heart medication)
- lisinopril (blood pressure medication)
- acetaminophen (pain and fever medication)
- lovastatin (cholesterol medication)
- any of the following drugs that may increase the risk of heart rhythm disturbances:
  - drugs to treat heart rhythm disturbances
  - antivirals to treat HIV infection
  - diuretics (water pills)
  - drugs to treat hypertension (high blood pressure)
  - drugs to treat heart failure

BYETTA slows stomach emptying and can affect medicines that need to pass through the stomach quickly. Ask your doctor or pharmacist if the time at which you take any of your oral medicines (for example, birth control pills, antibiotics) should be changed.

If you must take other medications with food, take them with meals or a snack when you do not also take BYETTA.

Know the medicines you take. Keep a list of them with you to show your doctor or pharmacist each time you get a new medicine.

## PROPER USE OF THIS MEDICATION

**You should read the Pen-User Manual for instructions to use the BYETTA Pen and how to inject BYETTA.** Pen needles are not included. Ask your doctor or pharmacist which needle length and gauge is best for you.

You must do a “**New Pen Set-Up**” when starting a new prefilled BYETTA Pen. **Do not repeat a “New Pen Set-Up” before each injection**, you will run out of medication before 30 days.

Use BYETTA exactly as prescribed by your doctor. Never exceed the prescribed dose.

BYETTA is to be injected under the skin (subcutaneous injection) of your upper leg (thigh), stomach area (abdomen), or upper arm.

Usual starting dose: 5 µg twice a day to be injected under the skin at any time within the 60 minute period **before** your morning and evening meals (or before the two main meals of the day, at least 6 hours or more apart). **BYETTA should not be injected after a meal.** The dose of BYETTA may be increased to 10 µg twice daily after a month if required to improve blood sugar control. Maximum is 10 µg twice daily.

### Overdose:

If you use too much BYETTA, immediately contact your doctor or regional poison control centre or go to your nearest hospital emergency department. Show the doctor your BYETTA Pen. Too much BYETTA can cause nausea, vomiting, dizziness, or symptoms of low blood sugar.

### Missed Dose:

If you miss a dose of BYETTA, **DO NOT** take an extra dose or increase the amount of your next dose. Skip the dose you missed. Take your next dose at the next prescribed time.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects with BYETTA include nausea, vomiting, diarrhea, feeling jittery, dizziness, headache, acid stomach and heartburn.

When BYETTA is used with a medicine that contains a sulfonyleurea, low blood sugar (hypoglycemia) is also common. The dose of your sulfonyleurea medicine may need to be reduced while you use BYETTA. The signs and symptoms of low blood sugar may include headache, drowsiness, weakness, dizziness, confusion, irritability, hunger, fast heartbeat, sweating, and feeling jittery. Discuss with your doctor or pharmacist how to treat low blood sugar.

BYETTA may cause new or worsening problems with kidney function, including kidney failure. Dialysis or kidney transplant may be needed. See also **Serious side effects** table, below.

Injection site reactions (e.g. rash, itching, bruising) have been reported in subjects receiving BYETTA

Talk to your doctor or pharmacist about any side effect that bothers you or that does not go away.

<b>SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM</b>				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Rare*	Prolonged severe abdominal pain which may be accompanied by vomiting. These may be symptoms of pancreatitis.			✓
Rare*	Prolonged nausea, vomiting and/or diarrhea, or cannot take liquids by mouth. These may increase the risk of kidney problems.			✓
Rare*	Sudden swelling of the face, lips, tongue or throat, problems breathing or swallowing, severe rash or itching, fainting, very rapid heartbeat. These may be symptoms of angioedema or severe allergic reactions, including anaphylaxis.			✓

\*frequency from postmarketing reports

If you experience any symptoms of a possible heart rhythm disturbance, such as dizziness, palpitations, fainting, or seizures, you should seek immediate medical attention.

***This is not a complete list of side effects. For any unexpected effects while taking BYETTA, contact your doctor or pharmacist.***

## HOW TO STORE IT

- Store your new, unused BYETTA Pen in the original carton in a refrigerator at 2°C to 8°C protected from light. Do not freeze. Throw away any BYETTA Pen that has been frozen.
- After first use, your BYETTA Pen should be kept at or below 25°C.
- Use a BYETTA Pen for only 30 days. Throw away a used BYETTA Pen after 30 days, even if some medicine remains in the pen.
- BYETTA should not be used after the expiration date printed on the label.
- Do not store the BYETTA Pen with the needle attached. If the needle is left on, medicine may leak from the BYETTA Pen or air bubbles may form in the cartridge.
- Keep your BYETTA Pen, pen needles, and all medicines out of the reach of children and pets.
- Throw away used needles in a puncture-resistant container or as recommended by your healthcare professional. Do not throw away the pen with a needle attached. Dispose of pen as directed by your healthcare professional.

## REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program  
Health Canada  
Postal Locator 0701D  
Ottawa, ON K1A0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

*Note: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

## MORE INFORMATION

For more information, please contact your doctor or pharmacist first, or Eli Lilly Canada Inc. at: 1-888-545-5972, or visit the website at [www.lilly.ca](http://www.lilly.ca).

This leaflet was prepared by Eli Lilly Canada Inc., Toronto,

Ontario, M1N 2E8.

Last revised: January 11, 2011

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