HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BYETTA safely and effectively. See full prescribing information for BYETTA.
BYETTA® (exenatide) Injection
Initial U.S. Approval: 2005

----------RECENT MAJOR CHANGES----------

Indications and Usage	10/2009
Monotherapy and Combination Therapy (1.1)	
Important Limitations of Use	10/2009
History of Pancreatitis (1.2)	
Warnings and Precautions	10/2009
Pancreatitis (5.1)	
Renal Impairment (5.3)	
Macrovascular Outcomes (5.7)	

----------INDICATIONS AND USAGE----------

BYETTA is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Important Limitations of Use

- BYETTA is not a substitute for insulin. BYETTA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis (1.2).
- The concurrent use of BYETTA with insulin has not been studied and cannot be recommended (1.2).
- BYETTA has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis (1.2).

----------DOSAGE AND ADMINISTRATION----------

- Inject subcutaneously within 60 minutes prior to morning and evening meals (or before the two main meals of the day, approximately 6 hours or more apart) (2.1).
- Initiate at 5 mcg per dose twice daily; increase to 10 mcg twice daily after 1 month based on clinical response (2.1).

----------DOSAGE FORMS AND STRENGTHS----------

BYETTA is supplied as 250 mcg/mL exenatide in:

- 5 mcg per dose, 60 doses, 1.2 mL prefilled pen
- 10 mcg per dose, 60 doses, 2.4 mL prefilled pen

----------CONTRAINDICATIONS----------

- History of severe hypersensitivity to exenatide or any product components (4.1).

----------WARNINGS AND PRECAUTIONS----------

- Pancreatitis: Postmarketing reports, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. *Discontinue BYETTA promptly. BYETTA should not be restarted.* Consider other antidiabetic therapies in patients with a history of pancreatitis (5.1).
- Hypoglycemia: Increased risk when BYETTA is used in combination with a sulfonylurea. Consider reducing the sulfonylurea dose (5.2).
- Renal Impairment: Postmarketing reports, sometimes requiring hemodialysis and kidney transplantation. BYETTA should *not* be used in patients with severe renal impairment or end-stage renal disease and should be used with caution in patients with renal transplantation. Caution should be applied when initiating BYETTA or escalating the dose of BYETTA in patients with moderate renal failure (5.3).
- Severe Gastrointestinal Disease: Use of BYETTA is not recommended in patients with severe gastrointestinal disease (e.g., gastroparesis) (5.4).
- Hypersensitivity: Postmarketing reports of hypersensitivity reactions (e.g. anaphylaxis and angioedema). The patient should discontinue BYETTA and other suspect medications and promptly seek medical advice (5.6).
- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with BYETTA or any other antidiabetic drug (5.7).

----------ADVERSE REACTIONS----------

- Most common (≥5%) and occurring more frequently than placebo in clinical trials: nausea, hypoglycemia, vomiting, diarrhea, feeling jittery, dizziness, headache, dyspepsia. Nausea usually decreases over time (5.2; 6).
- Postmarketing reports of increased international normalized ratio (INR) with concomitant use of warfarin, sometimes with bleeding (6.2).

To report SUSPECTED ADVERSE REACTIONS contact Amylin Pharmaceuticals, Inc. and Eli Lilly and Company at 1-800-868-1190 and www.byetta.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

- Warfarin: Postmarketing reports of increased INR sometimes associated with bleeding. Monitor INR frequently until stable upon initiation or alteration of BYETTA therapy (7.2).

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, BYETTA may cause fetal harm. BYETTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. To report drug exposure during pregnancy call 1-800-633-9081 (8.1).
- Nursing Mothers: Caution should be exercised when BYETTA is administered to a nursing woman (8.3).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2009

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Type 2 Diabetes Mellitus

BYETTA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

1.2 Important Limitations of Use

BYETTA is not a substitute for insulin. BYETTA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

The concurrent use of BYETTA with insulin has not been studied and cannot be recommended.

Based on postmarketing data BYETTA has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. BYETTA has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using BYETTA. Other antidiabetic therapies should be considered in patients with a history of pancreatitis.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

BYETTA should be initiated at 5 mcg administered twice daily 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. Based on clinical response, the dose of BYETTA can be increased to 10 mcg twice daily after 1 month of therapy. Initiation with 5 mcg reduces the incidence and severity of gastrointestinal side effects. Each dose should be administered as a subcutaneous (SC) injection in the thigh, abdomen, or upper arm. No data are available on the safety or efficacy of intravenous or intramuscular injection of BYETTA.

Use BYETTA only if it is clear, colorless and contains no particles.

3 DOSAGE FORMS AND STRENGTHS

BYETTA is supplied as a sterile solution for subcutaneous injection containing 250 mcg/mL exenatide in the following packages:

- 5 mcg per dose, 60 doses, 1.2 mL prefilled pen
- 10 mcg per dose, 60 doses, 2.4 mL prefilled pen

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4 CONTRAINDICATIONS

4.1 Hypersensitivity

BYETTA is contraindicated in patients with prior severe hypersensitivity reactions to exenatide or to any of the product components.

5 WARNINGS AND PRECAUTIONS

5.1 Acute Pancreatitis

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.

5.2 Hypoglycemia

The risk of hypoglycemia is increased when BYETTA is used in combination with a sulfonylurea (hypoglycemia can also occur when other antidiabetic agents are used in combination with a sulfonylurea). Therefore, patients receiving BYETTA and a sulfonylurea may require a lower dose of the sulfonylurea to reduce the risk of hypoglycemia. It is also possible that the use of BYETTA with other glucose-independent insulin secretagogues (e.g. meglitinides) could increase the risk of hypoglycemia.

For additional information on glucose dependent effects see *Mechanism of Action (12.1)*.

5.3 Renal Impairment

BYETTA should not be used in patients with severe renal impairment (creatinine clearance < 30 mL/min) or end-stage renal disease and should be used with caution in patients with renal transplantation *[see Use in Specific Populations (8.6)]*. In patients with end-stage renal disease receiving dialysis, single doses of BYETTA 5 mcg were not well-tolerated due to gastrointestinal side effects. Because BYETTA may induce nausea and vomiting with transient hypovolemia, treatment may worsen renal function. Caution should be applied when initiating or escalating doses of BYETTA from 5 mcg to 10 mcg in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min).

There have been postmarketing reports 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

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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. Exenatide has not been found to be directly nephrotoxic in preclinical or clinical studies.

5.4 Gastrointestinal Disease

BYETTA has not been studied in patients with severe gastrointestinal disease, including gastroparesis. Because BYETTA is commonly associated with gastrointestinal adverse reactions, including nausea, vomiting, and diarrhea, the use of BYETTA is not recommended in patients with severe gastrointestinal disease.

5.5 Immunogenicity

Patients may develop antibodies to exenatide following treatment with BYETTA, consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals. In a small proportion of patients, the formation of antibodies to exenatide at high titers could result in failure to achieve adequate improvement in glycemic control. If there is worsening glycemic control or failure to achieve targeted glycemic control, alternative antidiabetic therapy should be considered *[see Adverse Reactions (6.1)]*.

5.6 Hypersensitivity

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 other suspect medications and promptly seek medical advice *[see Adverse Reactions (6.2)]*.

5.7 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with BYETTA or any other antidiabetic drug.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Hypoglycemia

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Table 1 summarizes the incidence and rate of hypoglycemia with BYETTA in five placebo-controlled clinical trials.

Table 1: Incidence (%) and Rate of Hypoglycemia When BYETTA was Used as Monotherapy or With Concomitant Antidiabetic Therapy in Five Placebo-Controlled Clinical Trials*

	BYETTA		
	Placebo twice daily	**5 mcg twice daily**	**10 mcg twice daily**
Monotherapy (24 Weeks)			
N	77	77	78
% Overall	1.3%	5.2%	3.8%
Rate (episodes/patient-year)	0.03	0.21	0.52
% Severe	0.0%	0.0%	0.0%
With Metformin (30 Weeks)			
N	113	110	113
% Overall	5.3%	4.5%	5.3%
Rate (episodes/patient-year)	0.12	0.13	0.12
% Severe	0.0%	0.0%	0.0%
With a Sulfonylurea (30 Weeks)			
N	123	125	129
% Overall	3.3%	14.4%	35.7%
Rate (episodes/patient-year)	0.07	0.64	1.61
% Severe	0.0%	0.0%	0.0%
With Metformin and a Sulfonylurea (30 Weeks)			
N	247	245	241
% Overall	12.6%	19.2%	27.8%
Rate (episodes/patient-year)	0.58	0.78	1.71
% Severe	0.0%	0.4%	0.0%
With a Thiazolidinedione (16 Weeks)			
N	112	Dose not studied	121
% Overall	7.1%	Dose not studied	10.7%
Rate (episodes/patient-years)	0.56	Dose not studied	0.98
% Severe	0.0%	Dose not studied	0.0%

* For the 30-week trials, a hypoglycemia episode was recorded if the patient reported symptoms consistent with hypoglycemia and was recorded as severe if the subject required the assistance of another person to treat the event. For the other trials, a hypoglycemic episode was recorded if a patient reported signs or symptoms of hypoglycemia or had a blood glucose value consistent with hypoglycemia regardless of associated symptoms or treatment and was recorded as severe if the subject required the assistance of another person to treat the event. The requirement for assistance had to be accompanied by a blood glucose measurement of <50 mg/dL or prompt recovery after administration of oral carbohydrate.

N = The number of Intent-to-Treat subjects in each treatment group.

Immunogenicity

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In the 30-week controlled trials of BYETTA add-on to metformin and/or sulfonylurea, 38% of patients had low titer antibodies to exenatide at 30 weeks. For this group, the level of glycemic control (hemoglobin A1c [HbA_{1c}]) was generally comparable to that observed in those without antibody titers. An additional 6% of patients had higher titer antibodies at 30 weeks. In about half of this 6% (3% of the total patients given BYETTA in the 30-week controlled studies), the glycemic response to BYETTA was attenuated; the remainder had a glycemic response comparable to that of patients without antibodies.

In the 16-week trial of BYETTA add-on to thiazolidinediones, with or without metformin, 9% of patients had higher titer antibodies at 16 weeks. In the 24-week trial of BYETTA used as monotherapy, 3% of patients had higher titer antibodies at 24 weeks. Compared with patients who did not develop antibodies to BYETTA, on average the glycemic response in patients with higher titer antibodies was attenuated *[see Warnings and Precautions (5.5)]*.

Other Adverse Reactions

Monotherapy

For the 24-week placebo-controlled study of BYETTA used as a monotherapy, Table 2 summarizes adverse reactions (excluding hypoglycemia) occurring with an incidence ≥2% and occurring more frequently in BYETTA-treated patients compared with placebo-treated patients.

Table 2: Treatment-Emergent Adverse Reactions ≥2% Incidence With BYETTA Used as Monotherapy (Excluding Hypoglycemia)*

Monotherapy	Placebo BID N = 77 %	All BYETTA BID N = 155 %
Nausea	0	8
Vomiting	0	4
Dyspepsia	0	3

* In a 24-week placebo-controlled trial.
BID = twice daily.

Adverse reactions reported in ≥1.0 to <2.0% of patients receiving BYETTA and reported more frequently than with placebo included decreased appetite, diarrhea, and dizziness. The most frequently reported adverse reaction associated with BYETTA, nausea, occurred in a dose-dependent fashion.

Two of the 155 patients treated with BYETTA withdrew due to adverse reactions of headache and nausea. No placebo-treated patients withdrew due to adverse reactions.

Combination Therapy

<u>Add-on to metformin and/or sulfonylurea</u>

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In the three 30-week controlled trials of BYETTA add-on to metformin and/or sulfonylurea, adverse reactions (excluding hypoglycemia) with an incidence ≥2% and occurring more frequently in BYETTA-treated patients compared with placebo-treated patients *[see Warnings and Precautions (5.2)]* are summarized in Table 3.

Table 3: Treatment-Emergent Adverse Reactions ≥2% Incidence and Greater Incidence With BYETTA Treatment Used With Metformin and/or a Sulfonylurea (Excluding Hypoglycemia)*

	Placebo BID N = 483 %	**All BYETTA BID N = 963 %**
Nausea	18	44
Vomiting	4	13
Diarrhea	6	13
Feeling Jittery	4	9
Dizziness	6	9
Headache	6	9
Dyspepsia	3	6
Asthenia	2	4
Gastroesophageal Reflux Disease	1	3
Hyperhidrosis	1	3

* In three 30-week placebo-controlled clinical trials.
BID = twice daily.

Adverse reactions reported in ≥1.0 to <2.0% of patients receiving BYETTA and reported more frequently than with placebo included decreased appetite. Nausea was the most frequently reported adverse reaction and occurred in a dose-dependent fashion. With continued therapy, the frequency and severity decreased over time in most of the patients who initially experienced nausea. Patients in the long-term uncontrolled open-label extension studies at 52 weeks reported no new types of adverse reactions than those observed in the 30-week controlled trials.

The most common adverse reactions leading to withdrawal for BYETTA-treated patients were nausea (3% of patients) and vomiting (1%). For placebo-treated patients, <1% withdrew due to nausea and none due to vomiting.

<u>Add-on to thiazolidinedione with or without metformin</u>

For the 16-week placebo-controlled study of BYETTA add-on to a thiazolidinedione, with or without metformin, Table 4 summarizes the adverse reactions (excluding hypoglycemia) with an incidence of ≥2% and occurring more frequently in BYETTA-treated patients compared with placebo-treated patients.

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Table 4: Treatment-Emergent Adverse Reactions ≥2% Incidence With BYETTA Used With a Thiazolidinedione, With or Without Metformin (Excluding Hypoglycemia)*

With a TZD or TZD/MET	Placebo N = 112 %	All BYETTA BID N = 121 %
Nausea	15	40
Vomiting	1	13
Dyspepsia	1	7
Diarrhea	3	6
Gastroesophageal Reflux Disease	0	3

* In a 16-week placebo-controlled clinical trial.
BID = twice daily.

Adverse reactions reported in ≥1.0 to <2.0% of patients receiving BYETTA and reported more frequently than with placebo included decreased appetite. Chills (n = 4) and injection-site reactions (n = 2) occurred only in BYETTA-treated patients. The two patients who reported an injection-site reaction had high titers of antibodies to exenatide. Two serious adverse events (chest pain and chronic hypersensitivity pneumonitis) were reported in the BYETTA arm. No serious adverse events were reported in the placebo arm.

The most common adverse reactions leading to withdrawal for BYETTA-treated patients were nausea (9%) and vomiting (5%). For placebo-treated patients, <1% withdrew due to nausea.

6.2 Post-Marketing Experience

The following additional adverse reactions have been reported during post-approval use of BYETTA. 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.

Allergy/Hypersensitivity: injection-site reactions, generalized pruritus and/or urticaria, macular or papular rash, angioedema, anaphylactic reaction *[see Warnings and Precautions (5.6)]*.

Drug Interactions: International normalized ratio (INR) increased with concomitant warfarin use sometimes associated with bleeding *[see Drug Interactions (7.2)]*.

Gastrointestinal: nausea, vomiting, and/or diarrhea resulting in dehydration; abdominal distension, abdominal pain, eructation, constipation, flatulence, acute pancreatitis, hemorrhagic and necrotizing pancreatitis sometimes resulting in death *[see Limitations of Use (1.2) and Warnings and Precautions (5.1)]*.

Neurologic: dysgeusia; somnolence

Renal and Urinary Disorders: altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure or acute renal failure (sometimes requiring

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hemodialysis), kidney transplant and kidney transplant dysfunction *[see Warnings and Precautions (5.3)]*.

7 DRUG INTERACTIONS

7.1 Orally Administered Drugs

The effect of BYETTA to slow gastric emptying can reduce the extent and rate of absorption of orally administered drugs. BYETTA should be used with caution in patients receiving oral medications that have narrow therapeutic index or require rapid gastrointestinal absorption *[see Adverse Reactions (6.2)]*. For oral medications that are dependent on threshold concentrations for efficacy, such as contraceptives and antibiotics, patients should be advised to take those drugs 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 *[see Clinical Pharmacology (12.3)]*.

7.2 Warfarin

There are postmarketing reports of increased INR sometimes associated with bleeding, with concomitant use of warfarin and BYETTA *[see Adverse Reactions (6.2)]*. In a drug interaction study, BYETTA did not have a significant effect on INR *[see Clinical Pharmacology (12.3)]*. In patients taking warfarin, prothrombin time should be monitored more frequently after initiation or alteration of BYETTA therapy. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on warfarin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of BYETTA use in pregnant women. In animal studies, exenatide caused cleft palate, irregular skeletal ossification and an increased number of neonatal deaths. BYETTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Female mice given SC doses of 6, 68, or 760 mcg/kg/day beginning 2 weeks prior to and throughout mating until gestation day 7 had no adverse fetal effects. At the maximal dose, 760 mcg/kg/day, systemic exposures were up to 390 times the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on AUC *[see Nonclinical Toxicology (13.3)]*.

In developmental toxicity studies, pregnant animals received exenatide subcutaneously during organogenesis. Specifically, fetuses from pregnant rabbits given SC doses of 0.2, 2, 22, 156, or

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260 mcg/kg/day from gestation day 6 through 18 experienced irregular skeletal ossifications from exposures 12 times the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on AUC. Moreover, fetuses from pregnant mice given SC doses of 6, 68, 460, or 760 mcg/kg/day from gestation day 6 through 15 demonstrated reduced fetal and neonatal growth, cleft palate and skeletal effects at systemic exposure 3 times the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on AUC *[see Nonclinical Toxicology (13.3)]*.

Lactating mice given SC doses of 6, 68, or 760 mcg/kg/day from gestation day 6 through lactation day 20 (weaning), experienced an increased number of neonatal deaths. Deaths were observed on postpartum days 2-4 in dams given 6 mcg/kg/day, a systemic exposure 3 times the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on AUC *[see Nonclinical Toxicology (13.3)]*.

Pregnancy Registry

Amylin Pharmaceuticals, Inc. maintains a Pregnancy Registry to monitor pregnancy outcomes of women exposed to exenatide during pregnancy. Physicians are encouraged to register patients by calling 1-800-633-9081.

8.3 Nursing Mothers

It is not known whether exenatide is excreted in human milk. However, exenatide is present at low concentrations (less than or equal to 2.5% of the concentration in maternal plasma following subcutaneous dosing) in the milk of lactating mice. Many drugs are excreted in human milk and because of the potential for clinically significant adverse reactions in nursing infants from exenatide, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account these potential risks against the glycemic benefits to the lactating woman. Caution should be exercised when BYETTA is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of BYETTA have not been established in pediatric patients.

8.5 Geriatric Use

Population pharmacokinetic analysis of patients ranging from 22 to 73 years of age suggests that age does not influence the pharmacokinetic properties of exenatide *[see Clinical Pharmacology (12.3)]*. BYETTA was studied in 282 patients 65 years of age or older and in 16 patients 75 years of age or older. No differences in safety or effectiveness were observed between these patients and younger patients. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly based on renal function.

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8.6 Renal Impairment

BYETTA is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance < 30 mL/min) and should be used with caution in patients with renal transplantation. 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 mcg to 10 mcg in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min) *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No pharmacokinetic study has been performed in patients with a diagnosis of acute or chronic hepatic impairment. Because exenatide is cleared primarily by the kidney, hepatic dysfunction is not expected to affect blood concentrations of exenatide *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

In a clinical study of BYETTA, three patients with type 2 diabetes each experienced a single overdose of 100 mcg SC (10 times the maximum recommended dose). Effects of the overdoses included severe nausea, severe vomiting, and rapidly declining blood glucose concentrations. One of the three patients experienced severe hypoglycemia requiring parenteral glucose administration. The three patients recovered without complication. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

11 DESCRIPTION

BYETTA (exenatide) is a synthetic peptide that was originally identified in the lizard *Heloderma suspectum*. Exenatide differs in chemical structure and pharmacological action from insulin, sulfonylureas (including D-phenylalanine derivatives and meglitinides), biguanides, thiazolidinediones, alpha-glucosidase inhibitors, amylinomimetics and dipeptidyl peptidase-4 inhibitors.

Exenatide is a 39-amino acid peptide amide. Exenatide 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-NH_2

BYETTA is supplied for SC injection as a sterile, preserved isotonic solution in a glass cartridge that has been assembled in a pen-injector (pen). Each milliliter (mL) contains 250 micrograms (mcg) synthetic exenatide, 2.2 mg metacresol as an antimicrobial preservative, mannitol as a tonicity-adjusting agent, and glacial acetic acid and sodium acetate trihydrate in water for

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injection as a buffering solution at pH 4.5. Two prefilled pens are available to deliver unit doses of 5 mcg or 10 mcg. Each prefilled pen will deliver 60 doses to provide for 30 days of twice daily administration (BID).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Incretins, such as glucagon-like peptide-1 (GLP-1), enhance glucose-dependent insulin secretion and exhibit other antihyperglycemic actions following their release into the circulation from the gut. BYETTA is a GLP-1 receptor agonist that enhances glucose-dependent insulin secretion by the pancreatic beta-cell, suppresses inappropriately elevated glucagon secretion, and slows gastric emptying.

The amino acid sequence of exenatide partially overlaps that of human GLP-1. Exenatide has been shown to bind and activate the human GLP-1 receptor in vitro. This leads to an increase in both glucose-dependent synthesis of insulin, and in vivo secretion of insulin from pancreatic beta cells, by mechanisms involving cyclic AMP and/or other intracellular signaling pathways. Exenatide promotes insulin release from pancreatic beta cells in the presence of elevated glucose concentrations.

BYETTA improves glycemic control by reducing fasting and postprandial glucose concentrations in patients with type 2 diabetes through the actions described below.

Glucose-dependent insulin secretion: BYETTA has acute effects on pancreatic beta-cell responsiveness to glucose leading to insulin release predominantly in the presence of elevated glucose concentrations. This insulin secretion subsides as blood glucose concentrations decrease and approach euglycemia. However, BYETTA does not impair the normal glucagon response to hypoglycemia.

First-phase insulin response: 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. 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).

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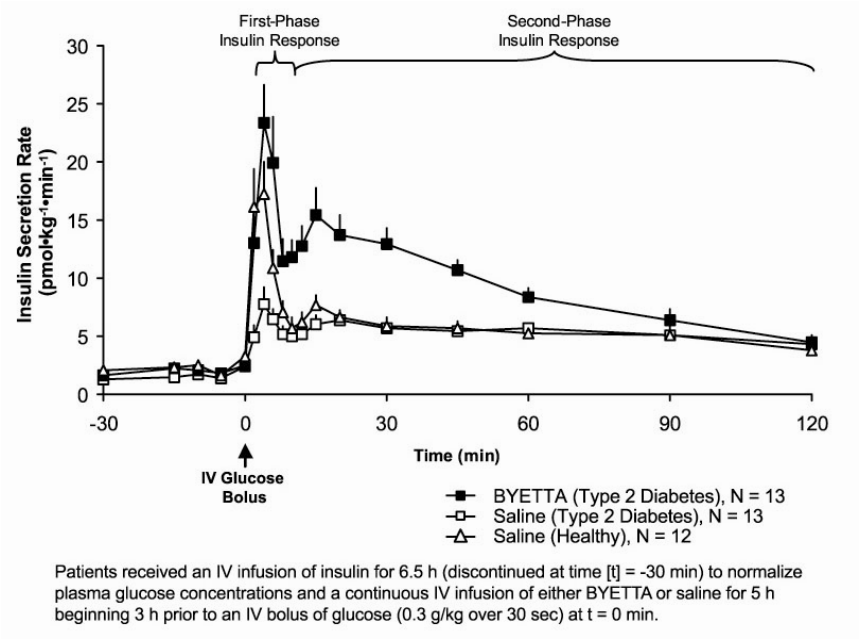

Figure 1: Mean (+SEM) Insulin Secretion Rate During Infusion of BYETTA or Saline in Patients With Type 2 Diabetes and During Infusion of Saline in Healthy Subjects

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.

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

Food intake: In both animals and humans, administration of exenatide has been shown to reduce food intake.

12.2 Pharmacodynamics

Postprandial Glucose

In patients with type 2 diabetes, BYETTA reduces postprandial plasma glucose concentrations (Figure 2).

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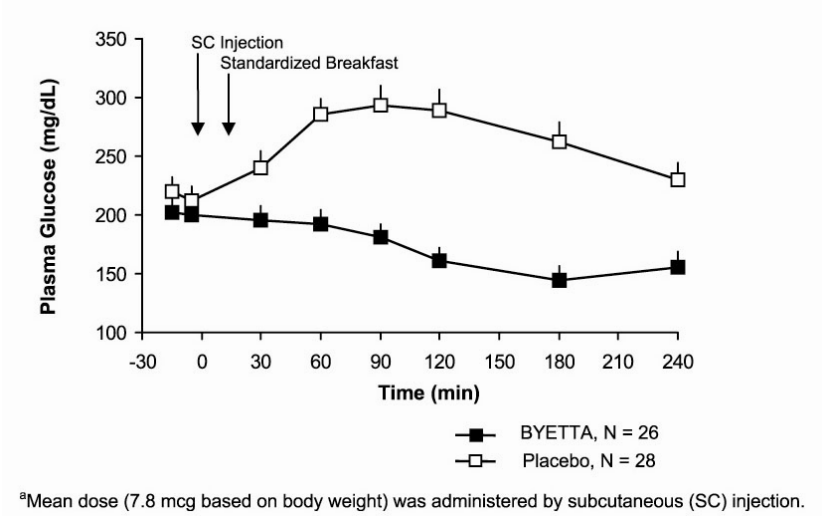

Figure 2: Mean (+SEM) Postprandial Plasma Glucose Concentrations on Day 1 of BYETTA[a] Treatment in Patients With Type 2 Diabetes Treated With Metformin, a Sulfonylurea, or Both (N = 54)

Fasting Glucose

In a single-dose crossover study in patients with type 2 diabetes and fasting hyperglycemia, immediate insulin release followed injection of BYETTA. Plasma glucose concentrations were significantly reduced with BYETTA compared with placebo (Figure 3).

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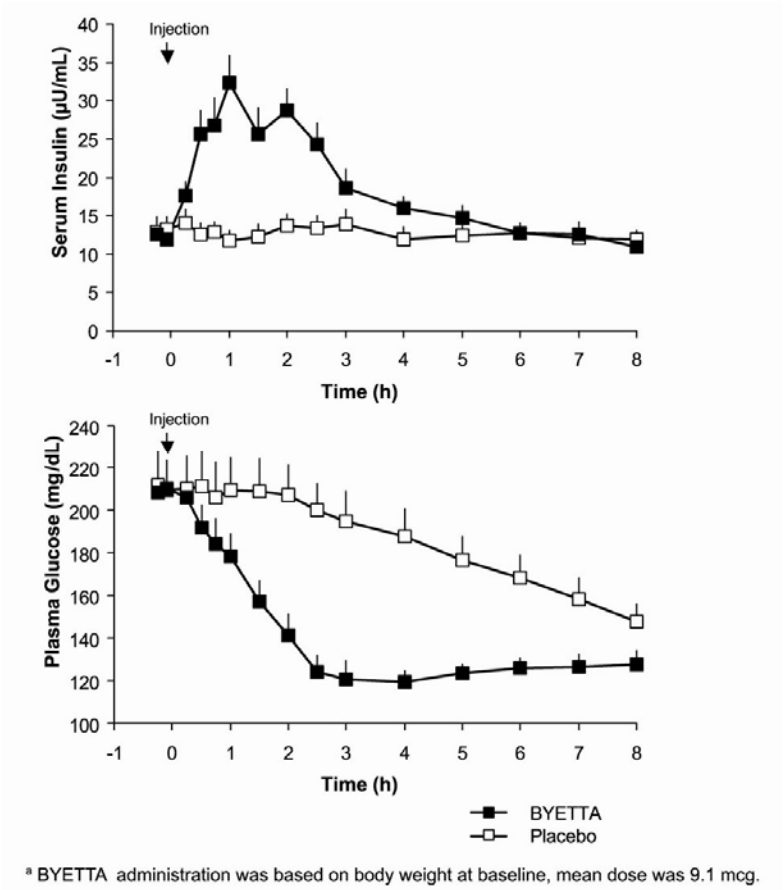

Figure 3: Mean (+SEM) Serum Insulin and Plasma Glucose Concentrations Following a One-Time Injection of BYETTA[a] or Placebo in Fasting Patients With Type 2 Diabetes (N = 12)

12.3 Pharmacokinetics

Absorption

Following SC administration to patients with type 2 diabetes, exenatide reaches median peak plasma concentrations in 2.1 h. The mean peak exenatide concentration (C_{max}) was 211 pg/mL and overall mean area under the time-concentration curve ($AUC_{0\text{-}inf}$) was 1036 pg•h/mL following SC administration of a 10-mcg dose of BYETTA. Exenatide exposure (AUC) increased proportionally over the therapeutic dose range of 5 mcg to 10 mcg. The C_{max} values increased less than proportionally over the same range. Similar exposure is achieved with SC administration of BYETTA in the abdomen, thigh, or upper arm.

Distribution

The mean apparent volume of distribution of exenatide following SC administration of a single dose of BYETTA is 28.3 L.

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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.

Drug Interactions

Acetaminophen

When 1000 mg acetaminophen elixir was given with 10 mcg BYETTA (0 h) and 1 hour, 2 hours, and 4 hours 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 hour in the control period to 0.9 hour, 4.2 hours, 3.3 hours, and 1.6 hours, respectively. Acetaminophen AUC, C_{max} and T_{max} were not significantly changed when acetaminophen was given 1 hour before BYETTA injection.

Digoxin

Administration of repeated doses of BYETTA (10 mcg BID) 30 minutes before oral digoxin (0.25 mg QD) decreased the C_{max} of digoxin by 17% and delayed the T_{max} of digoxin by approximately 2.5 hours; however, the overall steady-state pharmacokinetic exposure (e.g., AUC) of digoxin was not changed.

Lovastatin

Administration of BYETTA (10 mcg BID) 30 minutes before a single oral dose of lovastatin (40 mg) decreased the AUC and C_{max} of lovastatin by approximately 40% and 28%, respectively, and delayed the T_{max} by about 4 hours compared with lovastatin administered alone. In the 30-week controlled clinical trials of BYETTA, the use of BYETTA in patients already receiving HMG CoA reductase inhibitors was not associated with consistent changes in lipid profiles compared to baseline.

Lisinopril

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

Oral Contraceptives

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The effect of BYETTA (10 mcg BID) on single and on multiple doses of a combination oral contraceptive (35 mcg ethinyl estradiol plus 150 mcg levonorgestrel) was studied in healthy female subjects. Repeated daily doses of the oral contraceptive (OC) given 30 minutes after BYETTA administration decreased the C_{max} of ethinyl estradiol and levonorgestrel by 45% and 27%, respectively and delayed the T_{max} of ethinyl estradiol and levonorgestrel by 3.0 hours and 3.5 hours, respectively, as compared to the oral contraceptive administered alone. Administration of repeated daily doses of the OC one hour prior to BYETTA administration decreased the mean C_{max} of ethinyl estradiol by 15% but the mean C_{max} of levonorgestrel was not significantly changed as compared to when the OC was given alone. BYETTA did not alter the mean trough concentrations of levonorgestrel after repeated daily dosing of the oral contraceptive for both regimens. However, the mean trough concentration of ethinyl estradiol was increased by 20% when the OC was administered 30 minutes after BYETTA administration injection as compared to when the OC was given alone. The effect of BYETTA on OC pharmacokinetics is confounded by the possible food effect on OC in this study. Therefore, OC products should be administered at least one hour prior to BYETTA injection.

Warfarin

Administration of warfarin (25 mg) 35 minutes after repeated doses of BYETTA (5 mcg BID on days 1-2 and 10 mcg BID on days 3-9) in healthy volunteers delayed warfarin T_{max} by approximately 2 hours. No clinically relevant effects on C_{max} or AUC of S- and R-enantiomers of warfarin were observed. BYETTA did not significantly alter the pharmacodynamic properties (e.g., international normalized ratio) of warfarin *[see Drug Interactions (7.2)]*.

Specific Populations

Renal Impairment

Pharmacokinetics of exenatide was studied in subjects with normal, mild, or moderate renal impairment and subjects with end stage renal disease. In subjects with mild to moderate renal impairment (creatinine clearance 30 to 80 mL/min), exenatide exposure was similar to that of subjects with normal renal function. However, in subjects with end-stage renal disease receiving dialysis, mean exenatide exposure increased by 3.37-fold compared to that of subjects with normal renal function. *[see Use in Specific Populations (8.6)]*.

Hepatic Impairment

No pharmacokinetic study has been performed in patients with a diagnosis of acute or chronic hepatic impairment *[see Use in Specific Populations (8.7)]*.

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Age

Population pharmacokinetic analysis of patients ranging from 22 to 73 years of age suggests that age does not influence the pharmacokinetic properties of exenatide *[see Use in Specific Population (8.5)]*.

Gender

Population pharmacokinetic analysis of male and female patients suggests that gender does not influence the distribution and elimination of exenatide.

Race

Population pharmacokinetic analysis of samples from Caucasian, Hispanic, Asian, and Black patients suggests that race has no significant influence on the pharmacokinetics of exenatide.

Body Mass Index

Population pharmacokinetic analysis of patients with body mass indices (BMI) ≥30 kg/m^2 and <30 kg/m^2 suggests that BMI has no significant effect on the pharmacokinetics of exenatide.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 104-week carcinogenicity study was conducted in male and female rats at doses of 18, 70, or 250 mcg/kg/day administered by bolus SC injection. Benign thyroid C-cell adenomas were observed in female rats at all exenatide doses. The incidences in female rats were 8% and 5% in the two control groups and 14%, 11%, and 23% in the low-, medium-, and high-dose groups with systemic exposures of 5, 22, and 130 times, respectively, the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on plasma area under the curve (AUC).

In a 104-week carcinogenicity study in mice at doses of 18, 70, or 250 mcg/kg/day administered by bolus SC injection, no evidence of tumors was observed at doses up to 250 mcg/kg/day, a systemic exposure up to 95 times the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on AUC.

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.

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

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13.3 Reproductive and Developmental Toxicology

In female mice given SC doses of 6, 68, or 760 mcg/kg/day beginning 2 weeks prior to and throughout mating until gestation day 7, there were no adverse fetal effects at doses up to 760 mcg/kg/day, systemic exposures up to 390 times the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on AUC.

In pregnant mice given SC doses of 6, 68, 460, or 760 mcg/kg/day from gestation day 6 through 15 (organogenesis), cleft palate (some with holes) and irregular fetal skeletal ossification of rib and skull bones were observed at 6 mcg/kg/day, a systemic exposure 3 times the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on AUC.

In pregnant rabbits given SC doses of 0.2, 2, 22, 156, or 260 mcg/kg/day from gestation day 6 through 18 (organogenesis), irregular fetal skeletal ossifications were observed at 2 mcg/kg/day, a systemic exposure 12 times the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on AUC.

In pregnant mice given SC doses of 6, 68, or 760 mcg/kg/day from gestation day 6 through lactation day 20 (weaning), an increased number of neonatal deaths was observed on postpartum days 2-4 in dams given 6 mcg/kg/day, a systemic exposure 3 times the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on AUC.

14 CLINICAL STUDIES

BYETTA has been studied as monotherapy and in combination with metformin, a sulfonylurea, a thiazolidinedione, a combination of metformin and a sulfonylurea, or a combination of metformin and a thiazolidinedione.

14.1 Monotherapy

In a randomized, double-blind, placebo-controlled trial of 24 weeks duration, BYETTA 5 mcg BID (n = 77), BYETTA 10 mcg BID (n = 78), or placebo BID (n = 77) was used as monotherapy in patients with entry HbA_{1c} ranging from 6.5-10%. All patients assigned to BYETTA initially received 5 mcg BID for 4 weeks. After 4 weeks, those patients either continued to receive BYETTA 5 mcg BID or had their dose increased to 10 mcg BID. Patients assigned to placebo received placebo BID throughout the trial. BYETTA or placebo was injected subcutaneously before the morning and evening meals. The majority of patients (68%) were Caucasian, 26% were West Asian, 3% were Hispanic, 3% were Black, and 0.4% were East Asian.

The primary endpoint was the change in HbA_{1c} from baseline to Week 24 (or the last value at time of early discontinuation). Compared to placebo, BYETTA 5 mcg BID and 10 mcg BID resulted in statistically significant reductions in HbA_{1c} from baseline at Week 24 (Table 5).

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Table 5: Results of 24-Week Placebo-Controlled Trial of BYETTA Used as Monotherapy

	Placebo BID	BYETTA 5 mcg BID	BYETTA 10 mcg* BID
Intent-to-Treat Population (N)	77	77	78
HbA_{1c} (%), Mean			
Baseline	7.8	7.9	7.8
Change at Week 24†	-0.2	-0.7	-0.9
Difference from placebo†(95% CI)		-0.5 [-0.9, -0.2]‡	-0.7 [-1.0, -0.3]‡
Proportion Achieving HbA_{1c} <7%	38%	48%	53%
Body Weight (kg), Mean			
Baseline	86.1	85.1	86.2
Change at Week 24†	-1.5	-2.7	-2.9
Difference from placebo†(95% CI)		-1.3 [-2.3, -0.2]	-1.5 [-2.5, -0.4]
Fasting Serum Glucose§ (mg/dL), Mean			
Baseline	159	166	155
Change at Week 24†	-5	-17	-19
Difference from placebo† (95% CI)		-12 [-23.2, -1.3]	-14 [-24.5, -2.5]

* BYETTA 5 mcg twice daily (BID) for 1 month followed by 10 mcg BID for 5 months before the morning and evening meals.

† Least squares means are adjusted for screening HbA_{1c} strata and baseline value of the dependent variable.

‡ $p < 0.01$, treatment vs. placebo.

§ Measured using the hexokinase-based glucose method.

BID = twice daily.

On average, there were no adverse effects of exenatide on blood pressure or lipids.

14.2 Combination Therapy

Three 30-week, double-blind, placebo-controlled trials were conducted to evaluate the safety and efficacy of BYETTA in patients with type 2 diabetes whose glycemic control was inadequate with metformin alone, a sulfonylurea alone, or metformin in combination with a sulfonylurea. In addition, a 16-week, placebo-controlled trial was conducted where BYETTA was added to existing thiazolidinedione (pioglitazone or rosiglitazone) treatment, with or without metformin, in patients with type 2 diabetes with inadequate glycemic control.

In the 30-week trials, after a 4-week placebo lead-in period, patients were randomly assigned to receive BYETTA 5 mcg BID, BYETTA 10 mcg BID, or placebo BID before the morning and evening meals, in addition to their existing oral antidiabetic agent. All patients assigned to BYETTA initially received 5 mcg BID for 4 weeks. After 4 weeks, those patients either continued to receive BYETTA 5 mcg BID or had their dose increased to 10 mcg BID. Patients assigned to placebo received placebo BID throughout the study. A total of 1446 patients were randomized in the three 30-week trials: 991 (69%) were Caucasian, 224 (16%) were Hispanic,

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and 174 (12%) were Black. Mean HbA_{1c} values at baseline for the trials ranged from 8.2% to 8.7%.

In the placebo-controlled trial of 16 weeks duration, BYETTA (n = 121) or placebo (n = 112) was added to existing thiazolidinedione (pioglitazone or rosiglitazone) treatment, with or without metformin. Randomization to BYETTA or placebo was stratified based on whether the patients were receiving metformin. BYETTA treatment was initiated at a dose of 5 mcg BID for 4 weeks then increased to 10 mcg BID for 12 more weeks. Patients assigned to placebo received placebo BID throughout the study. BYETTA or placebo was injected subcutaneously before the morning and evening meals. In this trial, 79% of patients were taking a thiazolidinedione and metformin and 21% were taking a thiazolidinedione alone. The majority of patients (84%) were Caucasian, 8% were Hispanic and 3% were Black. The mean baseline HbA_{1c} values were 7.9% for BYETTA and placebo.

The primary endpoint in each study was the mean change in HbA_{1c} from baseline to study end (or early discontinuation). Table 6 summarizes the study results for the 30-week and 16-week clinical trials.

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Table 6: Results of 30-Week and 16-Week Placebo-Controlled Trials of BYETTA Used in Combination with Oral Antidiabetic Agents

	Placebo BID	BYETTA 5 mcg BID	BYETTA 10 mcg* BID
	In Combination With Metformin (30 Weeks)		
Intent-to-Treat Population (N)	113	110	113
HbA_{1c} (%), Mean			
Baseline	8.2	8.3	8.2
Change at Week 30†	-0.0	-0.5	-0.9
Difference from placebo† (95% CI)		-0.5 [-0.7, -0.2]‡	-0.9 [-1.1, -0.6]‡
Proportion Achieving HbA_{1c} <7%	12%	32%	40%
Body Weight (kg), Mean			
Baseline	99.9	100.0	100.9
Change at Week 30†	-0.2	-1.3	-2.6
Difference from placebo† (95% CI)		-1.1 [-2.2, -0.0]	-2.4 [-3.5, -1.3]
Fasting Plasma Glucose§ (mg/dL), Mean			
Baseline	169	176	168
Change at Week 30†	+14	-5	-10
Difference from placebo† (95% CI)		-20 [-32, -7]	-24 [-37, -12]
	In Combination With a Sulfonylurea (30 Weeks)		
Intent-to-Treat Population (N)	123	125	129
HbA_{1c} (%), Mean			
Baseline	8.7	8.5	8.6
Change at Week 30†	+0.1	-0.5	-0.9
Difference from placebo† (95% CI)		-0.6 [-0.9, -0.3]‡	-1.0 [-1.3, -0.7]‡
Proportion Achieving HbA_{1c} <7%	10%	25%	36%
Body Weight (kg), Mean			
Baseline	99.1	94.9	95.2
Change at Week 30†	-0.8	-1.1	-1.6
Difference from placebo† (95% CI)		-0.3 [-1.1, 0.6]	-0.9 [-1.7, -0.0]
Fasting Plasma Glucose§ (mg/dL), Mean			
Baseline	194	180	178
Change at Week 30†	+6	-5	-11
Difference from placebo† (95% CI)		-11 [-25, 3]	-17 [-30, -3]

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Table 6: Results of 30-Week and 16-Week Placebo-Controlled Trials of BYETTA Used in Combination with Oral Antidiabetic Agents (continued)

	Placebo BID	BYETTA 5 mcg BID	BYETTA 10 mcg* BID
	In Combination With Metformin and a Sulfonylurea (30 Weeks)		
Intent-to-Treat Population (N)	247	245	241
HbA_{1c} (%), Mean			
Baseline	8.5	8.5	8.5
Change at Week 30†	+0.1	-0.7	-0.9
Difference from placebo† (95% CI)		-0.8 [-1.0, -0.6]‡	-1.0 [-1.2, -0.8]‡
Proportion Achieving HbA_{1c} <7%	8%	25%	31%
Body Weight (kg), Mean			
Baseline	99.1	96.9	98.4
Change at Week 30†	-0.9	-1.6	-1.6
Difference from placebo† (95% CI)		-0.7 [-1.2, -0.2]	-0.7 [-1.3, -0.2]
Fasting Plasma Glucose§ (mg/dL), Mean			
Baseline	181	182	178
Change at Week 30†	+13	-11	-12
Difference from placebo† (95% CI)		-24 [-33, -15]	-25 [-34, -16]
	In Combination With a Thiazolidinedione or a Thiazolidinedione plus Metformin (16 Weeks)		
Intent-to-Treat Population (N)	112	Dose not studied	121
HbA_{1c} (%), Mean			
Baseline	7.9	Dose not studied	7.9
Change at Week 16†	+0.1	Dose not studied	-0.7
Difference from placebo† (95% CI)		Dose not studied	-0.9 [-1.1, -0.7]‡
Proportion Achieving HbA_{1c} <7%	15%	Dose not studied	51%
Body Weight (kg), Mean			
Baseline	96.8	Dose not studied	97.5
Change at Week 16†	-0.0	Dose not studied	-1.5
Difference from placebo† (95% CI)		Dose not studied	-1.5 [-2.2, -0.7]
Fasting Serum Glucose§ (mg/dL), Mean			
Baseline	159	Dose not studied	164
Change at Week 16†	+4	Dose not studied	-21
Difference from placebo† (95% CI)		Dose not studied	-25 [-33, -16]

* BYETTA 5 mcg twice daily for 1 month followed by 10 mcg BID for 6 months for the 30-week trials or 10 mcg BID for 3 months in the 16-week trial before the morning and evening meals.

† Least squares means are adjusted for baseline HbA_{1c} strata or value, investigator site, baseline value of the dependent variable (if applicable), and background antihyperglycemic therapy (if applicable).

‡ $p < 0.01$, treatment vs. placebo.

§ Measured using the hexokinase-based glucose method.

BID = twice daily.

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HbA_{1c}

The addition of BYETTA to a regimen of metformin, a sulfonylurea, or both, resulted in statistically significant reductions from baseline in HbA_{1c} compared with patients receiving placebo added to these agents in the three controlled trials (Table 6).

In the 16-week trial of BYETTA add-on to thiazolidinediones, with or without metformin, BYETTA resulted in statistically significant reductions from baseline in HbA_{1c} compared with patients receiving placebo (Table 6).

Postprandial Glucose

Postprandial glucose was measured after a mixed meal tolerance test in 9.5% of patients participating in the 30-week add-on to metformin, add-on to sulfonylurea, and add-on to metformin in combination with sulfonylurea clinical trials. In this pooled subset of patients, BYETTA reduced postprandial plasma glucose concentrations in a dose-dependent manner. The mean (SD) change in 2-h postprandial glucose concentration following administration of BYETTA at Week 30 relative to baseline was -63 (65) mg/dL for 5 mcg BID (n=42), -71 (73) mg/dL for 10 mcg BID (n=52), and +11 (69) mg/dL for placebo BID (n=44).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

BYETTA is supplied as a sterile solution for subcutaneous injection containing 250 mcg/mL exenatide.

The following packages are available:
5 mcg per dose, 60 doses, 1.2 mL prefilled pen, NDC 66780-210-07
10 mcg per dose, 60 doses, 2.4 mL prefilled pen, NDC 66780-212-01

16.2 Storage and Handling

Prior to first use, BYETTA must be stored refrigerated at 36ºF to 46ºF (2ºC to 8ºC). After first use, BYETTA can be kept at a temperature not to exceed 77ºF (25ºC). Do not freeze. Do not use BYETTA if it has been frozen. BYETTA should be protected from light. The pen should be discarded 30 days after first use, even if some drug remains in the pen. BYETTA should not be used past the expiration date. **BYETTA pens are not to be shared with other patients.**

17 PATIENT COUNSELING INFORMATION

Patients should be advised that BYETTA pens are never to be shared with another patient.

Patients should be informed of the potential risks and benefits of BYETTA and of alternative modes of therapy. Patients should also be fully informed about self-management practices,

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including the importance of proper storage of BYETTA, injection technique, timing of dosage of BYETTA and concomitant oral drugs, adherence to meal planning, regular physical activity, periodic blood glucose monitoring and HbA_{1c} testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications.

Patients should be advised to inform their physicians if they are pregnant or intend to become pregnant.

Each dose of BYETTA should be administered as a SC injection in the thigh, abdomen, or upper arm 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 a dose is missed, the treatment regimen should be resumed as prescribed with the next scheduled dose.

The risk of hypoglycemia is increased when BYETTA is used in combination with an agent that induces hypoglycemia, such as a sulfonylurea. The symptoms, treatment, and conditions that predispose to development of hypoglycemia should be explained to the patient. While the patient's usual instructions for hypoglycemia management do not need to be changed, these instructions should be reviewed and reinforced when initiating BYETTA therapy, particularly when concomitantly administered with a sulfonylurea *[see Warnings and Precautions (5.2)]*.

Patients should be advised that treatment with BYETTA may result in a reduction in appetite, food intake, and/or body weight, and that there is no need to modify the dosing regimen due to such effects. Treatment with BYETTA may also result in nausea, particularly upon initiation of therapy *[see Adverse Reactions (6)]*.

Patients should be informed that persistent severe abdominal pain that may radiate to the back and which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Patients should be instructed to promptly discontinue BYETTA and contact their physician if persistent severe abdominal pain occurs *[see Warnings and Precautions (5.1)]*.

Patients treated with BYETTA should be informed of the potential risk for worsening renal function and informed about associated signs and symptoms of renal dysfunction, as well as the possibility of dialysis as a medical intervention if renal failure occurs *[see Warnings and Precautions (5.3)]*.

Patients should be informed that serious hypersensitivity reactions have been reported during postmarketing use of BYETTA. If symptoms of hypersensitivity reactions occur, patients must stop taking BYETTA and seek medical advice promptly *[see Warnings and Precautions (5.6)]*.

The patient should read the Medication Guide and the Pen User Manual before starting BYETTA therapy and review them each time the prescription is refilled. The patient should be instructed

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on proper use and storage of the pen, emphasizing how and when to set up a new pen and noting that only one setup step is necessary at initial use. The patient should be advised not to share the pen and needles.

Patients should be informed that pen needles are not included with the pen and must be purchased separately. Patients should be advised which needle length and gauge should be used.

Manufactured for Amylin Pharmaceuticals, Inc., San Diego, CA 92121

Marketed by Amylin Pharmaceuticals, Inc. and Eli Lilly and Company
1-800-868-1190

http://www.BYETTA.com

Literature Revised October 2009

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Medication Guide

BYETTA® (bye-A-tuh)
(exenatide)
Injection

Read this Medication Guide and the Pen User Manual that come with BYETTA before you start using it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your treatment. If you have questions about BYETTA after reading this information, ask your healthcare provider or pharmacist.

What is the most important information I should know about BYETTA?

Serious side effects can happen in people who take BYETTA, including inflammation of the pancreas (pancreatitis) which may be severe and lead to death.

Certain medical conditions make you more likely to get pancreatitis.

Before taking BYETTA, tell your healthcare provider if you have had:

- pancreatitis.
- stones in your gallbladder (gallstones).
- a history of alcoholism.
- high blood triglyceride levels.

While taking BYETTA:

Call your healthcare provider right away if you have pain in your stomach area (abdomen) that is severe, and will not go away. The pain may happen with or without vomiting. The pain may be felt going from your abdomen through to your back. These may be symptoms of pancreatitis.

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What is BYETTA?

- BYETTA is an injectable prescription medicine that may improve blood sugar (glucose) control in adults with type 2 diabetes mellitus, when used with a diet and exercise program.
- BYETTA is not insulin.
- You should not take BYETTA instead of insulin.
- The use of BYETTA with insulin is not recommended.
- BYETTA is not for people with type 1 diabetes or people with diabetic ketoacidosis.
- It is not known if BYETTA is safe and effective in children.
- BYETTA has not been studied in people who have pancreatitis.
- BYETTA should not be used in people who have severe kidney problems.

Who should not use BYETTA?

Do not use BYETTA if:

- you have had an allergic reaction to exenatide or any of the other ingredients in BYETTA. See the end of this Medication Guide for a complete list of ingredients in BYETTA.

Symptoms of a severe allergic reaction with BYETTA may include:

- swelling of your face, lips, tongue, or throat
- problems breathing or swallowing
- severe rash or itching
- fainting or feeling dizzy
- very rapid heartbeat

What should I tell my healthcare provider before using BYETTA?

Before taking BYETTA, tell your healthcare provider if you:

- have or have had pancreatitis, stones in your gallbladder (gallstones), a history of alcoholism, or high blood triglyceride levels.
- have severe problems with your stomach, such as delayed emptying of your stomach (gastroparesis) or problems with digesting food.

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- have or have had kidney problems, or have had a kidney transplant.
- have any other medical conditions.
- are pregnant or plan to become pregnant. It is not known if BYETTA will harm your unborn baby.

  Pregnancy Registry: Amylin Pharmaceuticals, Inc. has a registry for women who take BYETTA during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. If you take BYETTA at any time during pregnancy you may enroll in this registry by calling (800) 633-9081.
- are breastfeeding or plan to breast-feed. It is not known if BYETTA passes into your breast milk. You and your healthcare provider should decide if you will take BYETTA or breast-feed. You should not do both without talking with your healthcare provider first.

Tell your healthcare provider about all the medicines you take including prescription and nonprescription medicines, vitamins, and herbal supplements. BYETTA slows stomach emptying and can affect medicines that need to pass through the stomach quickly. BYETTA may affect the way some medicines work and some other medicines may affect the way BYETTA works.

Especially tell your healthcare provider if you take:

- insulin, or any other anti-diabetes medicines.
- birth control pills that are taken by mouth (oral contraceptives). BYETTA may lower the amount of the medicine in your blood from your birth control pills and they may not work as well to prevent pregnancy. Take your birth control pills at least one hour before your injection of BYETTA. If you must take your birth control pills with food, take it with a meal or snack where you do not also take BYETTA.
- an antibiotic. Take antibiotic medicines at least one hour before taking BYETTA. If you must take your antibiotic with food, take it with a meal or snack where you do not also take BYETTA.
- warfarin sodium (Coumadin®, Jantoven®).
- a blood pressure medicine.
- a water pill (diuretic).

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- a pain medicine.
- lovastatin (Altoprev®, Mevacor®, Advicor®).

Ask your healthcare provider if you are not sure if your medicine is listed above.

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

How should I use BYETTA?

See the Pen User Manual that comes with BYETTA for instructions for using the BYETTA Pen and injecting BYETTA.

- Your healthcare provider may prescribe BYETTA alone or with certain other medicines to help control your blood sugar.
- BYETTA comes in a prefilled pen.
- Use BYETTA exactly as prescribed by your healthcare provider. Do not change your dose unless your healthcare provider has told you to change your dose.
- Your healthcare provider must teach you how to inject BYETTA before you use it for the first time. If you have questions or do not understand the instructions, talk to your healthcare provider or pharmacist.
- Pen needles are not included. You may need a prescription to purchase pen needles from your pharmacist. Ask your healthcare provider which needle length and gauge is best for you.
- Inject your dose of BYETTA under the skin (subcutaneous injection) of your upper leg (thigh), stomach area (abdomen), or upper arm as instructed by your healthcare provider. **Do not inject into a vein or muscle**.
- BYETTA is injected two times each day, at any time within the 60 minutes (1 hour) **before** your morning and evening meals (or before the two main meals of the day, approximately 6 hours or more apart). **Do not take BYETTA after your meal**.
- If you miss a dose of BYETTA, skip that dose and take your next dose at the next prescribed time. Do not take an extra dose or

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increase the amount of your next dose to make up for a missed dose.

- If you use too much BYETTA, call your healthcare provider or poison control center right away. Too much BYETTA can cause your blood sugar to drop quickly and you may have symptoms of low blood sugar. You may need medical treatment right away. Too much BYETTA can also cause severe nausea and vomiting.
- Follow your healthcare provider's instructions for diet, exercise, and how often to test your blood sugar. If you see your blood sugar increasing during treatment with BYETTA, talk to your healthcare provider because you may need to adjust your current treatment plan for your diabetes.
- Talk to your healthcare provider about how to manage high blood sugar (hyperglycemia) and low blood sugar (hypoglycemia), and how to recognize problems that can happen with your diabetes.
- Never share your BYETTA pen with another person. You may give an infection to them, or get an infection from them, and BYETTA may harm them.

What are the possible side effects of BYETTA?

BYETTA can cause serious side effects.

See "What is the most important information I should know about BYETTA?"

It is not known whether BYETTA, or other anti-diabetes medications, increase your risk of a heart attack or stroke.

- **Low blood sugar (hypoglycemia).** Your risk for getting low blood sugar is higher if you take BYETTA with another medicine that can cause low blood sugar, such as a sulfonylurea. The dose of your sulfonylurea medicine may need to be lowered while you use BYETTA. Signs and symptoms of low blood sugar may include:

  - headache
  - drowsiness
  - weakness
  - dizziness
  - confusion
  - irritability
  - hunger
  - fast heart beat
  - sweating
  - feeling jittery

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Talk with your healthcare provider about how to treat low blood sugar.

- **Kidney problems.** BYETTA may cause new or worse problems with kidney function, including kidney failure. Dialysis or kidney transplant may be needed.
  - **While taking BYETTA:**
    Call your healthcare provider right away if you have nausea, vomiting, or diarrhea that will not go away, or if you cannot take liquids by mouth. You may be at increased risk for kidney problems.
- **Severe allergic reactions**. Severe allergic reactions can happen with BYETTA. Stop taking BYETTA, and get medical help right away if you have any symptom of a severe allergic reaction. See "Who should not take BYETTA?"

The most common side effects with BYETTA include:

- nausea. Nausea most commonly happens when first starting BYETTA, but may become less over time.
- vomiting.
- diarrhea.
- dizziness.
- headache.
- feeling jittery.
- acid stomach.

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

These are not all the side effects with BYETTA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store BYETTA?

- Store your new, unused BYETTA Pen in the original carton in a refrigerator at 36°F to 46°F (2°C to 8ºC).

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- After first use, keep your BYETTA Pen at a temperature cooler than 77°F (25°C).
- Do not freeze your BYETTA Pen. Do not use BYETTA if it has been frozen.
- Protect BYETTA from light.
- Use a BYETTA Pen for only 30 days. Throw away a used BYETTA Pen after 30 days, even if there is some medicine left in the pen.
- Do not use BYETTA 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.
- See the BYETTA Pen User Manual for instructions about the right way to throw away your BYETTA Pen.
- **Keep your BYETTA Pen, pen needles, and all medicines out of the reach of children.**

General information about BYETTA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use BYETTA for a condition for which it was not prescribed. Do not give BYETTA to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide includes the most important information you should know about using BYETTA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about BYETTA that is written for health professionals.

For more information about BYETTA, go to http://www.BYETTA.com or call BYETTA Customer Service at 1-800-868-1190.

What are the ingredients in BYETTA?

Active Ingredient: exenatide

Inactive Ingredients: metacresol, mannitol, glacial acetic acid, and sodium acetate trihydrate in water for injection.

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