Byetta

Generic Name: exenatide
Dosage Form: injection

Indications and Usage for Byetta

Type 2 Diabetes Mellitus

Byetta (exenatide) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus [see *Clinical Studies (14)*].

Important Limitations of Use

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

The concurrent use of Byetta with prandial 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.

Byetta Dosage and Administration

Recommended Dosing

Byetta should be initiated at 5 mcg administered twice daily (BID) 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. Do not mix Byetta with insulin. Do not transfer Byetta from the pen to a syringe or a vial. 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.

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

Contraindications

Hypersensitivity

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

Warnings and Precautions

Never Share a Byetta Pen Between Patients

Byetta pens should never be shared between patients, even if the needle is changed. Pen-sharing poses a risk for transmission of blood-borne pathogens.

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.

Use with Medications Known to Cause Hypoglycemia

The risk of hypoglycemia is increased when Byetta is 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.

When Byetta is used in combination with insulin, the dose of insulin should be evaluated. In patients at increased risk of hypoglycemia consider reducing the dose of insulin [see *Adverse Reactions (6.1)*]. The concurrent use of Byetta with prandial insulin has not been studied and cannot be recommended. 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)*.

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 to 10 mcg in patients with moderate renal impairment (creatinine clearance 30-50 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 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.

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.

Immunogenicity

Patients may develop antibodies to exenatide following treatment with Byetta. Antibody levels were measured in 90% of subjects in the 30-week, 24-week, and 16-week placebo-controlled studies and the 30-week comparator-controlled study of Byetta. In 3%, 4%, 1%, and 1% of these patients, respectively, antibody formation was associated with an attenuated glycemic response. If there is worsening glycemic control or failure to achieve targeted glycemic control, alternative antidiabetic therapy should be considered [see *Adverse Reactions (6.1)*].

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)*].

Macrovascular Outcomes

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

Adverse Reactions

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

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

Table 1: Incidence (%) and Rate of Hypoglycemia when Byetta was used as Monotherapy or with Concomitant Antidiabetic Therapy in Six Placebo-Controlled Clinical Trials*

	Placebo BID	Byetta 5 mcg BID	Byetta 10 mcg BID
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	not evaluated	121
% Overall	7.1%	not evaluated	10.7%
Rate (episodes/patient-years)	0.56	not evaluated	0.98
% Severe	0.0%	not evaluated	0.0%
With Insulin Glargine with or without Metformin and/or Thiazolidinedione (30 Weeks)†			
N	122	not evaluated	137
% Overall	29.5%	not evaluated	24.8%
Rate (episodes/patient-years)	1.58	not evaluated	1.61
% Severe	0.8%	not evaluated	0.0%

*A hypoglycemic episode was recorded if a patient reported symptoms of hypoglycemia with or without a blood glucose value consistent with hypoglycemia. Severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia requiring the assistance of another person and associated with either a documented blood glucose value <54 mg/dL or prompt recovery after treatment for hypoglycemia.

† When Byetta was initiated in combination with insulin glargine, the dose of insulin glargine was decreased by 20% in patients with an HbA1c ≤8.0% to minimize the risk of hypoglycemia. See Table 9 for insulin dose titration algorithm.

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

Immunogenicity

Antibodies were assessed in 90% of subjects in the 30-week, 24-week, and 16-week studies of Byetta. In the

30-week controlled trials of Byetta add-on to metformin and/or sulfonylurea, antibodies were assessed at 2- to 6-week intervals. The mean antibody titer peaked at week 6 and was reduced by 55% by week 30. Three hundred and sixty patients (38%) had low titer antibodies (<625) to exenatide at 30 weeks. The level of glycemic control (HbA_{1c}) in these patients was generally comparable to that observed in the 534 patients (56%) without antibody titers. An additional 59 patients (6%) had higher titer antibodies (≥625) at 30 weeks. Of these patients, 32 (3% overall) had an attenuated glycemic response to Byetta; the remaining 27 (3% overall) had a glycemic response comparable to that of patients without antibodies [see *Warnings and Precautions (5.6)*].

In the 16-week trial of Byetta add-on to thiazolidinediones, with or without metformin, 36 patients (31%) had low titer antibodies to exenatide at 16 weeks. The level of glycemic control in these patients was generally comparable to that observed in the 69 patients (60%) without antibody titer. An additional 10 patients (9%) had higher titer antibodies at 16 weeks. Of these patients, 4 (4% overall) had an attenuated glycemic response to Byetta; the remaining 6 (5% overall) had a glycemic response comparable to that of patients without antibodies [see *Warnings and Precautions (5.6)*].

In the 24-week trial of Byetta used as monotherapy, 40 patients (28%) had low titer antibodies to exenatide at 24 weeks. The level of glycemic control in these patients was generally comparable to that observed in the 101 patients (70%) without antibody titers. An additional 3 patients (2%) had higher titer antibodies at 24 weeks. Of these patients, 1 (1% overall) had an attenuated glycemic response to Byetta; the remaining 2 (1% overall) had a glycemic response comparable to that of patients without antibodies [see *Warnings and Precautions (5.6)*].

Antibodies to exenatide were not assessed in the 30-week trial of Byetta used in combination with insulin glargine.

In the 30-week comparator-controlled trial of Byetta used in combination with insulin glargine and metformin, 60 patients (20%) had low titer antibodies to exenatide at 30 weeks. The level of glycemic control in these patients was generally comparable to that observed in the 234 patients (77%) without antibody titers. An additional 10 patients (3%) had higher titer antibodies at 30 weeks. Of these patients, 2 (1% overall) had an attenuated glycemic response to Byetta; the remaining 8 (3% overall) had a glycemic response comparable to that of patients without antibodies [see *Warnings and Precautions (5.5)*].

Two hundred and ten patients with antibodies to exenatide in the Byetta clinical trials were tested for the presence of cross-reactive antibodies to GLP-1 and/or glucagon. No treatment-emergent cross-reactive antibodies were observed across the range of titers.

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

Monotherapy	Placebo BID N = 77 %	All Byetta BID N = 155 %
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

Add-On to Metformin and/or Sulfonylurea

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 (5.3)*] 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.

Add-On to Thiazolidinedione with or without Metformin

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.

Table 4: Treatment-Emergent Adverse Reactions ≥2% Incidence with Byetta used with a Thiazolidinedione (TZD), with or without Metformin (MET) (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.

Add-On to Insulin Glargine with or without Metformin and/or Thiazolidinedione (Placebo-Controlled)

For the 30-week placebo-controlled study of Byetta as add-on to insulin glargine with or without oral antihyperglycemic medications, Table 5 summarizes adverse reactions (excluding hypoglycemia) occurring with an incidence ≥2% and occurring more frequently in Byetta-treated patients compared with placebo-treated patients.

Table 5: Treatment-Emergent Adverse Reactions ≥2% Incidence with Byetta used with Insulin Glargine with or without Oral Antihyperglycemic Medications (excluding Hypoglycemia)*

With Insulin Glargine	Placebo N = 122 %	All Byetta BID N = 137 %
Nausea	8	41
Vomiting	4	18
Diarrhea	8	18
* In a 30-week placebo-controlled clinical trial.		
BID = twice daily.		

With Insulin Glargine	Placebo N = 122 %	All Byetta BID N = 137 %
Headache	4	14
Constipation	2	10
Dyspepsia	2	7
Asthenia	1	5
Abdominal Distension	1	4
Decreased Appetite	0	3
Flatulence	1	2
Gastroesophageal Reflux Disease	1	2
* In a 30-week placebo-controlled clinical trial.		
BID = twice daily.		

The most frequently reported adverse reactions leading to withdrawal for Byetta-treated patients were nausea (5.1%) and vomiting (2.9%). No placebo-treated patients withdrew due to nausea or vomiting.

Postmarketing Experience

The following additional adverse reactions have been reported during postapproval 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 (5.7)*].

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 *Indications and Usage (1.2)* and *Warnings and Precautions (5.2)*].

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 hemodialysis), kidney transplant and kidney transplant dysfunction [see *Warnings and Precautions (5.4)*].

Skin and Subcutaneous Tissue Disorders: alopecia

Drug Interactions

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)*].

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.

USE IN SPECIFIC POPULATIONS

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 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 to 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

A Pregnancy Registry has been implemented to monitor pregnancy outcomes of women exposed to exenatide during pregnancy. Physicians are encouraged to register patients by calling 1-800-633-9081.

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.

Pediatric Use

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

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.

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 50-80 mL/min). Caution should be applied when initiating or escalating doses of Byetta from 5 to 10 mcg in patients with moderate renal impairment (creatinine clearance 30-50 mL/min) [see *Clinical Pharmacology (12.3)*].

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)*].

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.

Byetta 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 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).

Byetta - Clinical Pharmacology

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.

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

Pharmacodynamics

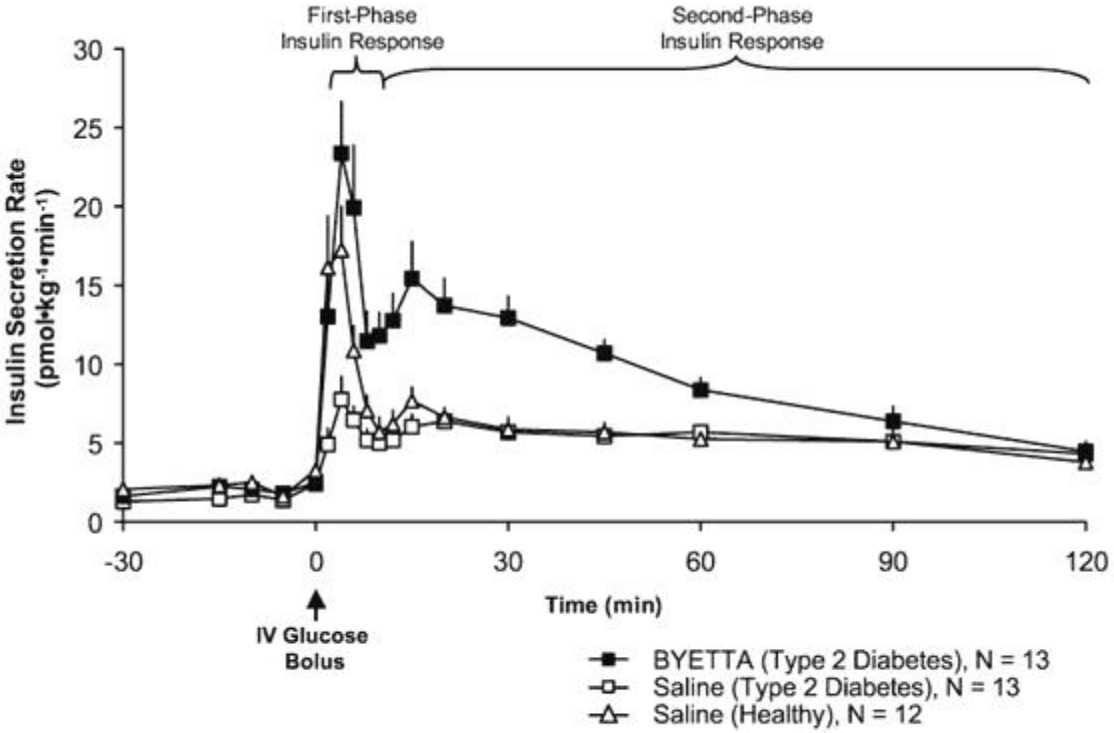
Glucose-Dependent Insulin Secretion

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).

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 BYETTA 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.

Gastric Emptying

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

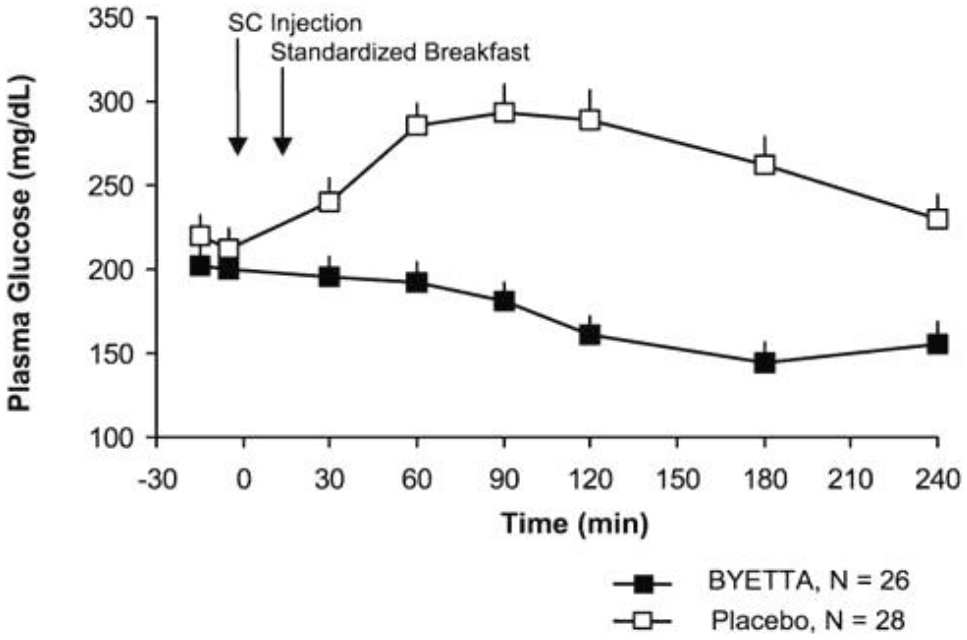
Food Intake

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

Postprandial Glucose

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

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)

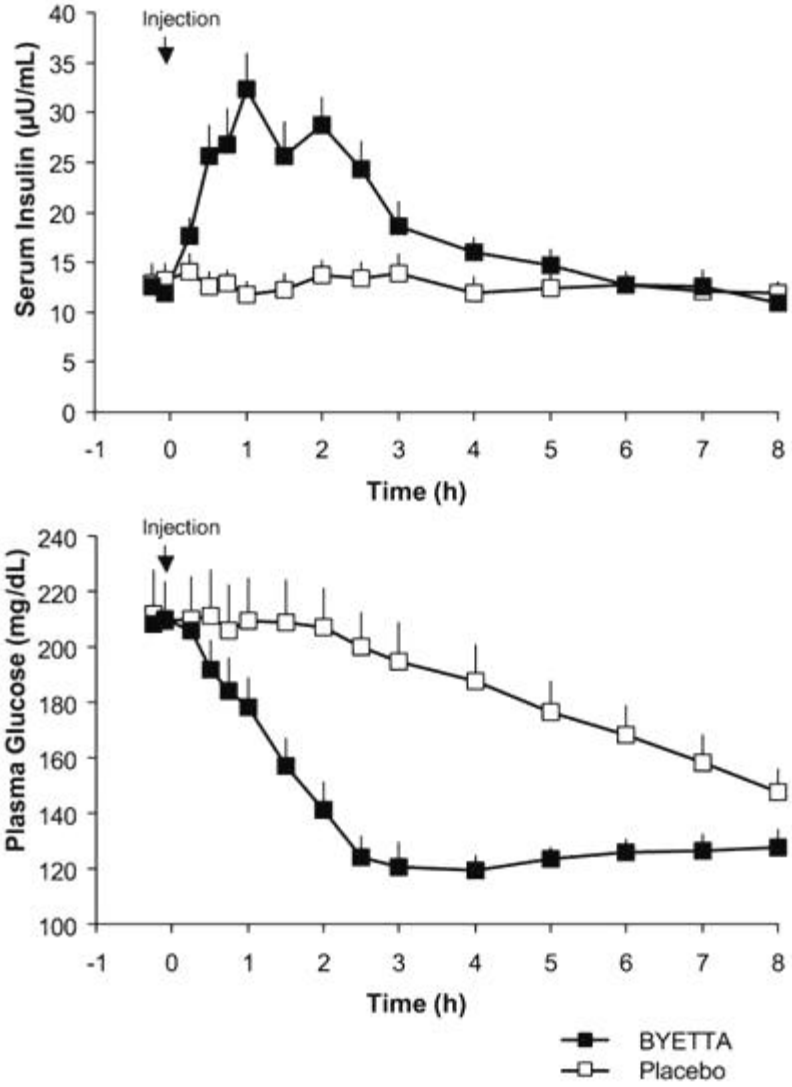


[a]Mean dose (7.8 mcg based on body weight) was administered by subcutaneous (SC) injection.

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).

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)



[a] BYETTA administration was based on body weight at baseline, mean dose was 9.1 mcg.

Cardiac Electrophysiology

The effect of exenatide 10 µg subcutaneously on QTc interval was evaluated in a randomized, placebo-, and active-controlled (moxifloxacin 400 mg) crossover thorough QTc study in 62 healthy subjects. In this study with demonstrated ability to detect small effects, the upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTc was below 10 msec. Thus, Byetta (10 mcg single dose) was not associated with clinically meaningful prolongation of the QTc interval.

Pharmacokinetics

Absorption

Following SC administration to patients with type 2 diabetes, exenatide reaches median peak plasma concentrations in 2.1 hours. 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 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.

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/hour and the mean terminal half-life is 2.4 hours. These pharmacokinetic characteristics of exenatide are independent of the dose. In most individuals, exenatide concentrations are measurable for approximately 10 hours post-dose.

Drug Interactions

Acetaminophen

When 1000 mg acetaminophen elixir was given with 10 mcg Byetta (0 hour) 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 once daily) 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 (5-20 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-hour mean systolic and diastolic blood pressure.

Oral Contraceptives

The effect of Byetta (10 mcg BID) on single and on multiple doses of a combination oral contraceptive (30 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 30-80 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)*].

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.

Nonclinical Toxicology

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.

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.

Clinical Studies

Byetta has been studied as monotherapy and in combination with metformin, a sulfonylurea, a thiazolidinedione, a combination of metformin and a sulfonylurea, a combination of metformin and a thiazolidinedione, or in combination with insulin glargine with or without metformin and/or thiazolidinedione.

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% to 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% West Asian, 3% Hispanic, 3% Black, and 0.4% 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 6).

Table 6: 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.

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

Combination Therapy with Oral Antihyperglycemic Medicines

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%) Hispanic, and 174 (12%) 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% Hispanic, and 3% 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 7 summarizes the study results for the 30- and 16-week clinical trials.

Table 7: 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			

	Placebo BID	Byetta 5 mcg BID	Byetta 10 mcg* BID
Baseline	194	180	178
Change at Week 30†	+6	−5	−11
Difference from placebo† (95% CI)		−11 [−25, 3]	−17 [−30, −3]
	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 aThiazolidinedione 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 HbA1c 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.

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 7).

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 7).

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-hour 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).

Combination with Insulin Glargine

30-Week Placebo-Controlled Trial

A 30-week, double-blind, placebo-controlled trial was conducted to evaluate the efficacy and safety of Byetta (n=137) versus placebo (n=122) when added to titrated insulin glargine, with or without metformin and/or thiazolidinedione, in patients with type 2 diabetes with inadequate glycemic control.

All patients assigned to Byetta initially received 5 mcg BID for 4 weeks. After 4 weeks, those patients assigned to Byetta 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. Patients with an HbA_{1c} ≤8.0% decreased their prestudy dose of insulin glargine by 20% and patients with an HbA_{1c} ≥8.1% maintained their current dose of insulin glargine. Five weeks after initiating randomized treatment, insulin doses were titrated with guidance from the investigator toward predefined fasting glucose targets according to the dose titration algorithm provided in Table 9. The majority of patients (78%) were Caucasian, 10% American Indian or Alaska Native, 9% Black, 3% Asian, and 0.8% of multiple origins.

The primary endpoint was the change in HbA_{1c} from baseline to Week 30. Compared to placebo, Byetta 10 mcg BID resulted in statistically significant reductions in HbA_{1c} from baseline at Week 30 (Table 8) in patients receiving titrated insulin glargine.

Table 8: 30-Week Placebo-Controlled Trial of Byetta Used in Combination with Insulin Glargine with or without Metformin and/or Thiazolidinediones

	Placebo BID + Titrated Insulin Glargine	Byetta 10 mcg* BID + Titrated Insulin Glargine

	Placebo BID + Titrated Insulin Glargine	Byetta 10 mcg* BID + Titrated Insulin Glargine
Intent-to-Treat Population (N)	122	137
HbA_{1c} (%), Mean		
Baseline	8.5	8.3
Change at Week 30†	−1.0	−1.7
Difference from placebo† (95% CI)		−0.7 [−1.0, −0.5]¶
Proportion Achieving HbA_{1c} <7%	30%	57%
Body Weight (kg), Mean		
Baseline	93.8	95.4
Change at Week 30‡	1.0	−1.8
Difference from placebo‡ (95% CI)		−2.7 [−3.7, −1.7]¶
Fasting Serum Glucose§ (mg/dL), Mean		
Baseline	133	132
Change at Week 30‡	−16	−23
Difference from placebo‡ (95% CI)		−7 [−18, 3]

* Byetta 5 mcg twice daily for 1 month followed by 10 mcg BID for 5 months for the 30-week trial.

† Least squares means are based on a mixed model adjusting for treatment, pooled investigator, visit, baseline HbA1c value, and treatment by visit, where subject is treated as a random effect.

‡ Least squares means are based on a mixed model adjusting for treatment, pooled investigator, visit, baseline HbA1c stratum, baseline value of the dependent variable (where applicable), and treatment by visit, where subject is treated as a random effect.

§ Patients in both groups titrated insulin glargine dose to achieve optimal fasting glucose concentrations.

¶ p <0.01, treatment vs. placebo.

BID = twice daily.

Table 9: Dosing Algorithm for Titration of Insulin Glargine*

Fasting Plasma Glucose Values (mg/dL)	Dose Change (U)
<56†	−4
56 to 72†	−2
73 to 99‡	0
100 to 119‡	+2
120 to 139‡	+4
140 to 179‡	+6
≥180‡	+8

Abbreviations: U = units.

* Adapted from Riddle et al. 2003.

† Value for at least 1 fasting plasma glucose measurement since the last assessment.

‡ Based on the average of fasting plasma glucose measurements taken over the prior 3 to 7 days. The increase in the total daily dose should not have exceeded more than 10 units per day or 10% of the current total daily dose, whichever was greater.

30-Week Comparator-Controlled Noninferiority Trial

A 30 week, open-label, active comparator-controlled, noninferiority study was conducted to evaluate the safety and efficacy of Byetta (n=315) versus titrated insulin lispro (n=312) on a background of optimized basal insulin glargine and metformin in patients with type 2 diabetes with inadequate glycemic control.

Following a 12-week basal insulin optimization (BIO) phase, subjects with an HbA_{1c} >7.0% entered a 30-week intervention phase and were randomized to add either Byetta or insulin lispro to their existing regimen of insulin glargine and metformin. Insulin glargine was titrated to a target fasting plasma glucose of 72 to 100 mg/dL.

All patients assigned to Byetta initially received 5 mcg BID for four weeks. After four weeks, their dose was increased to 10 mcg BID. Patients in the Byetta-treated arm with an HbA_{1c} ≤8.0% at the end of the BIO phase decreased their insulin glargine dose by at least 10%.

All patients assigned to insulin lispro three times daily (TID) maintained their prior total daily insulin dose at baseline; however, the initial insulin lispro dose was ⅓ to ½ of the total daily insulin dose with the insulin glargine dose reduced accordingly. The insulin lispro dose was titrated based on preprandial glucose values.

The majority of patients (87%) were Caucasian, 7% American Indian or Alaska Native, 5% Asian, and <1% African American.

The primary endpoint was the change in HbA_{1c} from baseline to Week 30. Both Byetta 10 mcg BID and titrated lispro provided a mean reduction in HbA_{1c} at Week 30 that met the pre-specified non-inferiority margin of 0.4%.

Table 10: 30-Week Comparator-Controlled Trial of Byetta used in Combination with Insulin Glargine and Metformin

	Titrated Insulin Lispro TID + Titrated Insulin Glargine	Byetta 10 mcg* BID + Titrated Insulin Glargine
Intent-to-Treat Population (N)	312	315
HbA_{1c} (%), Mean		
Baseline	8.2	8.3
Change at Week 30† #	−1.1	−1.1
Difference from Insulin Lispro† # (95% CI)		−0.0 [−0.2, 0.1]
Body Weight (kg), Mean		
Baseline	89.3	89.9
Change at Week 30† #	1.9	−2.6
Difference from Insulin Lispro† # (95% CI)		−4.5 [−5.2, −3.9]
Fasting Serum Glucose‡ (mg/dL), Mean		
Baseline	126	129
Change at Week 30† #	5	−7
Difference from Insulin Lispro† # (95% CI)		−12 [−019, −4]

*

Byetta 5 mcg BID for 1 month followed by 10 mcg BID for 5 months for the 30-week trial.

† Least squares means are based on a mixed model adjusting for treatment, country, prior use of sulfonylurea (yes/no), visit, corresponding baseline, and treatment by visit interaction, where subject is treated as a random effect.

Data at 30 weeks are available from 88% and 84% of the intent-to-treat subjects in the Lispro and BYETT groups, respectively.

‡ Patients titrated insulin glargine or insulin lispro dose to achieve prespecified target fasting and preprandial glucose concentrations.

BID = twice daily.

TID = three times daily.

How Supplied/Storage and Handling

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 0310-6512-01

10 mcg per dose, 60 doses, 2.4 mL prefilled pen, NDC 0310-6524-01

Storage and Handling

- Prior to first use, Byetta must be stored refrigerated at 36°F to 46°F (2°C to 8°C).
- After first use, Byetta can be kept at a temperature not to exceed 77°F (25°C).
- 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.
- Use a puncture-resistant container to discard the needles. Do not reuse or share needles.
- Byetta should not be used past the expiration date.

Patient Counseling Information

See FDA-approved Medication Guide.

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, 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.

Never Share a Byetta Pen Between Patients

Advise patients that they should never share a Byetta pen with another person, even if the needle is changed, because doing so carries a risk for transmission of blood-borne pathogens.

Risk of Pancreatitis

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 (5.2)*].

Risk of Hypoglycemia

The risk of hypoglycemia is increased when Byetta is 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. Patients should be informed that it is also possible that the use of Byetta with other glucose-independent insulin secretagogues (e.g., meglitinides) could increase the risk of hypoglycemia.

When Byetta is used in combination with insulin, evaluate the dose of insulin. Consider reducing the dose of insulin in patients at increased risk of hypoglycemia [see *Adverse Reactions (6.1)*]. Patients treated with Byetta should be informed that the concurrent use of Byetta with prandial insulin has not been studied and cannot be recommended.

The symptoms, treatment, and conditions that predispose to development of hypoglycemia should be explained to the patient. The patient's usual instructions for hypoglycemia management should be reviewed and reinforced when initiating Byetta therapy, particularly when concomitantly administered with a sulfonylurea or insulin [see *Warnings and Precautions (5.3)*].

Risk of Renal Impairment

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 (5.4)*].

Risk of Hypersensitivity Reactions

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 (5.7)*].

Use in Pregnancy

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

Instructions

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.

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)*].

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 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.

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AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

Byetta is a registered trademark of the AstraZeneca group of companies.

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.

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

These medical conditions can make you more likely to get pancreatitis in general. It is not known if having these conditions will lead to a higher chance of getting pancreatitis while taking Byetta.

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.

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 short acting insulin is not recommended.
- The use of Byetta with rapid acting 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	• fainting or feeling dizzy • very rapid heartbeat

• severe rash or itching	

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.
- 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: A registry has been implemented 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 1-800-633-9081.

- 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:

- other anti-diabetes medicines, especially sulfonylurea medicines or insulin.
- 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).
- 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. Do not reuse or share needles with another person.
- 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.**
- **Do not** mix Byetta and insulin in the same syringe or vial even if you take them at the same time.
- 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 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 at 1-800-222-1222 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.
- Do not share your Byetta pen with another person, even if the needle is changed. You may give another person an infection, or get an infection from 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 or insulin. The dose of your sulfonylurea or insulin medicine may need to be lowered while you use Byetta. Signs and symptoms of low blood sugar may include:

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

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 use 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
- feeling jittery
- dizziness
- headache
- acid stomach
- constipation
- weakness

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 8°C).
- 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. **Do not reuse or share needles.**
- **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 www.Byetta.com or call Byetta Customer Service at 1-800-236-9933.

What are the ingredients in Byetta?

Active Ingredient: exenatide

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

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Distributed by:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

Revised: December 2014

PEN USER MANUAL
Byetta® exenatide injection
250 mcg/mL, 1.2 mL
5 mcg

5 mcg PEN USER MANUAL

Section 1

Read this section completely before you begin. Then, move on to Section 2–Getting Started.

WHAT YOU NEED TO KNOW ABOUT YOUR Byetta PEN

PEN USER MANUAL

Read these instructions carefully BEFORE using your Byetta Pen. For complete dosing and safety information, also read the Byetta *Medication Guide* that comes with the Byetta Pen carton.

It is important that you use your pen correctly. Failure to follow these instructions completely may result in a wrong dose, a broken pen or an infection.

These instructions do not take the place of talking with your healthcare provider about your medical condition or your treatment. If you are having problems using your Byetta Pen, call toll free 1-800-236-9933.

IMPORTANT INFORMATION ABOUT YOUR Byetta PEN

- Each Byetta Pen contains enough medicine for injection two times each day for 30 days. You do not have to measure any doses, the pen measures each dose for you.
- **Do not transfer the medicine in the Byetta Pen to a syringe or vial.**
- **Do not** mix Byetta and insulin in the same syringe or vial even if you take them at the same time.
- If any part of your pen appears broken or damaged, do not use the pen.
- This Byetta Pen is not recommended for use by people who are blind or have vision problems without the help of a person trained in the proper use of the pen.
- **Follow the injection method explained to you by your healthcare provider.**
- Follow Section 2 only to set up a new pen before first use.
- Section 3 of this manual should be used for every injection.

ABOUT PEN NEEDLES

What kinds of needles can be used with my Byetta Pen?

- **Pen needles are not included with your pen.** You may need a prescription to get them from your pharmacist.
- Use 29 (thin), 30, or 31 (thinner) gauge disposable pen needles with your Byetta Pen. Ask your healthcare provider which needle gauge and length is best for you.

Do I use a new needle for each injection?

- Yes. Do not reuse or share needles with another person.
- Remove the needle from the pen immediately after you complete each injection. This will help prevent leakage of Byetta, keep out air bubbles, reduce needle clogs, and decrease the risk of infection.
- Do not push the injection button on your pen unless a needle is attached to the pen.

How do I throw away my needles?

- Do not throw away the pen with a needle attached.
- Place used needles in a closeable, puncture-resistant container. You may use a sharps container (such as a red biohazard container), a hard plastic container (such as a detergent bottle), or a metal container (such as an empty coffee can). Ask your healthcare provider for instructions on the right way to throw away (dispose of) your used pens and the container. There may be state and local laws about how you should throw away used pens and needles.
- Do not throw the disposal container in the household trash. Do not recycle.
- Always keep the puncture-proof container out of reach of children.

Do not share your Byetta pen with another person, even if the needle is changed. You may give another person an infection, or get an infection from them.

STORING YOUR Byetta PEN

How do I store my Byetta Pen?

- Prior to first use, store your unused Byetta Pen in the original carton in a refrigerator at 36°F to 46°F (2°C to 8°C).
- After first use, your Byetta Pen can be kept at a temperature not to exceed 77°F (25°C).
- Do not freeze. Do not use Byetta if it has been frozen. Byetta should be protected from light.
- When carrying the pen away from home, store the pen at a temperature between 36°F to 77°F (2°C to 25°C) and

keep dry.

- Do not store the pen with the needle attached. If the needle is left on the pen, Byetta may leak from the pen and air bubbles may form in the cartridge.

Keep your pen and needles out of the reach of children.

How long can I use a Byetta Pen?

- You can use your Byetta Pen for up to 30 days after setting up a new pen for first use. **After 30 days, throw away the Byetta Pen, even if it is not completely empty.**
- Mark the date when you first used your pen and the date 30 days later in the spaces below:

Date of First Use _____ Date to Throw Away Pen _____

- Byetta should not be used after the expiration date printed on the pen label.

How do I clean my Byetta Pen?

- Wipe the outside of the pen with a clean, damp cloth.
- White particles may appear on the outside tip of the cartridge during normal use. You may remove them with an alcohol wipe or alcohol swab.

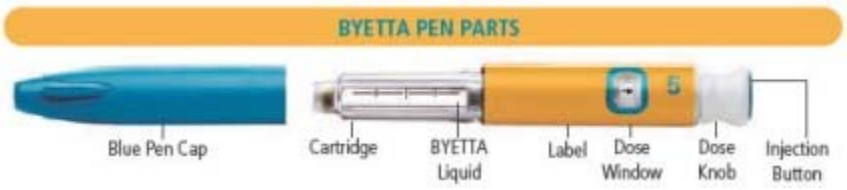
See the complete Byetta *Medication Guide* that comes with Byetta. For more information, call toll free 1-800-236-9933 or visit www.Byetta.com

Section 2

Read and follow the directions in this section only after you've read Section 1—What You Need To Know About Your Byetta Pen.

GETTING STARTED

Set up your new pen just before you use it the first time. For routine use, do not repeat this one-time-only new pen setup. If you do, you will run out of Byetta before 30 days of use.



ONE-TIME-ONLY NEW PEN SETUP

STEP A Check the Pen

		**Note:** A small air bubble in the cartridge is normal.
• Wash hands prior to use. • Check pen label to make sure it is your 5 mcg pen. • Pull off the blue pen cap.	• Check Byetta in the cartridge. The liquid should be clear, colorless, and free of particles. If not, do not use.	

STEP B Attach the Needle

		
• Remove paper tab from outer needle shield. • **Push** outer needle shield containing the needle **straight** onto the pen, then **screw** needle on until secure.	• Pull off outer needle shield. **Do not** throw away.	• Pull off inner needle shield and throw away. A small drop of liquid may appear. This is normal.

STEP C Dial the Dose

		
• Check that the ➔ is in the dose window. If not, turn dose knob away from you (clockwise) **until it stops** and the ➔ is in the dose window.	• **Pull dose knob out until it stops** and the ↑ is in the dose window.	• **Turn dose knob away from you until it stops** at 5. Make sure that the 5 with the line under it is in the center of the dose window.

Note: If you cannot turn the dose knob away from you to the 5, see **Commonly Asked Questions,** number 7, in Section 4 of this user manual.

STEP D Prepare the Pen

		
• Point the needle of the pen up and away from you.	**PUSH & HOLD** • **Use thumb to firmly push injection button in until it stops,** then continue holding the injection button in while **slowly counting to 5.** • **If you do not see a stream or several drops come from the needle tip, repeat Steps C & D.**	• Pen preparation is complete when the ▲ is in the center of the dose window AND you have seen a stream or several drops come from the needle tip.

Note: If you do not see liquid after 4 times, see **Commonly Asked Questions,** number 3, in Section 4 of this user manual.

STEP E Complete New Pen Setup

	• **For routine use,** do not repeat this one-time-only new pen setup. If you do, you will run out of Byetta before 30 days of use.	• You are now ready for your first dose of Byetta. • **Go to Section 3, Step 3, for instructions on how to inject your first routine dose.**
• **Turn dose knob away from you**		

until it stops and the is in the dose window.		

Note: If you cannot turn the dose knob, see **Commonly Asked Questions,** number 7, in Section 4 of user manual.

Section 3
Now that you have done the one-time-only new pen setup, follow Section 3 for all of your injections.

ROUTINE USE

STEP 1 Check the Pen

		**Note:** A small air bubble will not harm you or affect your dose.
• Wash hands prior to use. • Check pen label to make sure it is your 5 mcg pen. • Pull off the blue pen cap.	• Check Byetta in the cartridge. • The liquid should be clear, colorless, and free of particles. If it is not, do not use.	

STEP 2 Attach the Needle

		
• Remove paper tab from outer needle shield. • **Push** outer needle shield containing the needle **straight** onto pen, then **screw** needle on until secure.	• Pull off outer needle shield. **Do not** throw away.	• Pull off inner needle shield and throw away. A small drop of liquid may appear. This is normal.

STEP 3 Dial the Dose

		
• Check that the → is in the dose window. If not, turn dose knob away from you (clockwise) **until it stops** and the → is in the dose window.	• **Pull dose knob out until it stops** and the ▲ is in the dose window.	• **Turn dose knob away from you until it stops** at 5. Make sure that the 5 with the line under it is in the center of the dose window.

Note: If you cannot turn the dose knob away from you to the 5, see **Commonly Asked Questions,** number 7, in Section 4 of this user manual.

STEP 4 Inject the Dose

			
• Grip pen firmly. • Insert needle into skin using the under-the-skin (subcutaneous) injection method explained by your healthcare provider.	**PUSH & HOLD** • **Use thumb to firmly push injection button in until it stops.** Continue holding in the injection button while **slowly counting to 5** to get a full dose. • Remove needle from skin.	• Injection is complete when the ▲ is in the center of the dose window. • The pen is now ready to reset.	

Note: If you see several drops of Byetta leaking from the needle after the injection, you may not have received a complete dose. See **Commonly Asked Questions,** number 4, in Section 4 of this user manual.

STEP 5 Reset the Pen

	• **Turn dose knob away from you until it stops** and the → is in the dose window.	**Note:** If you cannot turn the dose knob, or if your pen leaks, your full dose has not been delivered. See **Commonly Asked Questions,** numbers 4 and 7, in Section 4 of this user manual.

STEP 6 Remove and Dispose of the Needle

		
• Carefully put the outer needle shield back over the needle. • **Remove the needle after each injection.**	• Unscrew the needle.	• Throw away needles in a puncture-resistant container or as recommended by your healthcare provider.

STEP 7 Store Pen for Next Dose

- Replace Blue Pen Cap on pen before storage.
- Store your Byetta Pen at a temperature between 36°F to 77°F (2°C to 25°C). (See **Storing Your Byetta Pen** in Section 1 of this user manual for complete storage information.)
- When it is time for your next routine dose, go to **Section 3, Step 1,** and repeat Steps 1–7.

Section 4

COMMONLY ASKED QUESTIONS

1. Do I need to do the One-Time-Only New Pen Setup before every dose?

- No. **The One-Time-Only New Pen Setup is done only once, just before each new pen is used for the first time.**
- The purpose of the setup is to make sure that your Byetta Pen is ready to use for the next 30 days.
- **If you repeat the One-Time-Only New Pen Setup before each routine dose, you will not have enough Byetta for 30 days.** The small amount of Byetta used in the new pen setup will not affect the 30-day supply of Byetta.

2. Why are there air bubbles in the cartridge?

- A small air bubble is normal. It will not harm you or affect your dose.
- If the pen is stored with a needle attached, air bubbles may form in the cartridge. **Do not** store the pen with the needle attached.

3. What should I do if Byetta does not come out of the needle tip after four tries during One-Time-Only New Pen Setup?

- Carefully put the outer needle shield back over the needle. Remove the needle by unscrewing it. Throw away the needle properly.

- Attach a new needle and repeat **One-Time-Only New Pen Setup, Steps B–E,** in Section 2 of this user manual. Once you see several drops or a stream of liquid coming out of the tip of the needle, the setup is complete.

4. Why do I see Byetta leaking from my needle after I have finished my injection?
It is normal for a single drop to remain on the tip of your needle after your injection is complete. If you see more than one drop:

- You may not have received your full dose. **Do not inject another dose.** Talk with your healthcare provider about what to do about a partial dose.

- To make sure that you get your full dose, when you take your injections, **firmly push and hold** the injection button in and **slowly count to 5** (see **Section 3, Step 4: Inject the Dose**).

5. How can I tell when the injection is complete?
The injection is complete when:

- You have firmly pushed the injection button in all the way **until it stops**
and

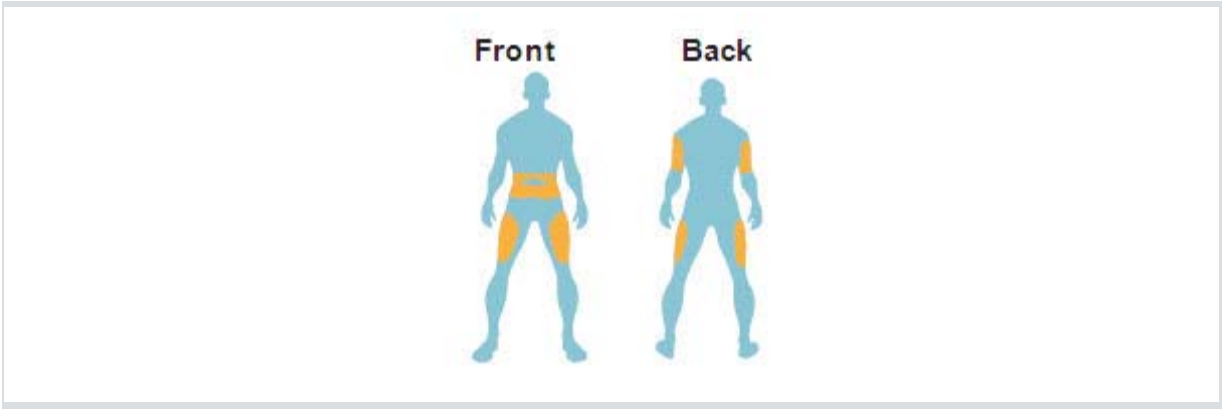
- **You have slowly counted to 5** while you are still holding the injection button in and the needle is still in your skin
and

- The

is in the center of the dose window.

If you hear a click sound from your Byetta Pen, ignore it. You must follow all the steps listed above to make sure your injection is complete.

6. Where should I inject Byetta?
Inject Byetta into your abdomen, thigh, or upper arm using the injection method explained to you by your healthcare provider.



7. What if I cannot pull, turn, or push the dose knob?
Check the symbol in the dose window. Follow the steps next to the matching symbol.

If is in the dose window:

- Pull the dose knob out until

appears.

If is in the dose window and the dose knob will not turn:

- The cartridge in your Byetta Pen may not have enough medicine to deliver a full dose. A small amount of Byetta will always stay in the cartridge. If the cartridge contains a small amount and the dose knob will not turn, your pen does not have enough Byetta and will not deliver any more doses. Obtain a new Byetta Pen.

If and part of are in the dose window and the dose knob cannot be pushed in:

- The dose knob was not turned all the way. Continue turning the dose knob away from you until

is in the center of the dose window.

If part of and part of are in the dose window and the dose knob cannot be pushed in:

- The needle may be clogged, bent, or incorrectly attached.
-

Attach a new needle. Make sure needle is on straight and screwed on all the way.

- Firmly push the injection button in all the way. Byetta should come from needle tip.

If  is in the dose window and the dose knob will not turn:

- The injection button was not pushed in all the way and a complete dose was not delivered. **Talk with your healthcare provider about what to do about a partial dose.**
- Follow these steps to reset your pen for your next injection:
- Firmly push the injection button in all the way **until it stops**. Keep holding the injection button in and **slowly count to 5**. Then release the injection button and turn the dose knob away from you until

appears in the dose window.

- If you cannot turn the dose knob, the needle may be clogged. Replace the needle and repeat the step above.
- For your next dose, be sure to **firmly push and hold** the injection button in and **slowly count to 5** before removing needle from skin.

See the complete Byetta *Medication Guide* that comes with Byetta. For more information, call toll free 1-800-236-9933 or visit www.Byetta.com

Distributed by:
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Wilmington, DE 19850

Byetta is a registered trademark of the AstraZeneca group of companies.

Revised: December 2014

PEN USER MANUAL
Byetta® exenatide injection
250 mcg/mL, 2.4 mL
10 mcg

10 mcg PEN USER MANUAL

Section 1
Read this section completely before you begin. Then, move on to Section 2−Getting Started.

WHAT YOU NEED TO KNOW ABOUT YOUR Byetta PEN

PEN USER MANUAL

Read these instructions carefully BEFORE using your Byetta Pen. For complete dosing and safety information, also read the Byetta *Medication Guide* that comes with the Byetta Pen carton.

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- **Do not** mix Byetta and insulin in the same syringe or vial even if you take them at the same time.
- If any part of your pen appears broken or damaged, do not use the pen.
- This Byetta Pen is not recommended for use by people who are blind or have vision problems without the help of a person trained in the proper use of the pen.
- **Follow the injection method explained to you by your healthcare provider.**
- Follow Section 2 only to set up a new pen before first use.
- Section 3 of this manual should be used for every injection.

ABOUT PEN NEEDLES

What kinds of needles can be used with my Byetta Pen?

- **Pen needles are not included with your pen.** You may need a prescription to get them from your pharmacist.

- Use 29 (thin), 30, or 31 (thinner) gauge disposable pen needles with your Byetta Pen. Ask your healthcare provider which needle gauge and length is best for you.

Do I use a new needle for each injection?

- Yes. Do not reuse or share needles with another person.
- Remove the needle from the pen immediately after you complete each injection. This will help prevent leakage of Byetta, keep out air bubbles, reduce needle clogs, and decrease the risk of infection.
- Do not push the injection button on your pen unless a needle is attached to the pen.

How do I throw away my needles?

- Do not throw away the pen with a needle attached.
- Place used needles in a closeable, puncture-resistant container. You may use a sharps container (such as a red biohazard container), a hard plastic container (such as a detergent bottle), or a metal container (such as an empty coffee can). Ask your healthcare provider for instructions on the right way to throw away (dispose of) your used pens and the container. There may be state and local laws about how you should throw away used pens and needles.
- Do not throw the disposal container in the household trash. Do not recycle.
- Always keep the puncture-proof container out of reach of children.

Do not share your Byetta pen with another person, even if the needle is changed. You may give another person an infection, or get an infection from them.

STORING YOUR Byetta PEN

How do I store my Byetta Pen?

- Prior to first use, store your unused Byetta Pen in the original carton in a refrigerator at 36°F to 46°F (2°C to 8°C).
- After first use, your Byetta Pen can be kept at a temperature not to exceed 77°F (25°C).
- Do not freeze. Do not use Byetta if it has been frozen. Byetta should be protected from light.
- When carrying the pen away from home, store the pen at a temperature between 36°F to 77°F (2°C to 25°C) and keep dry.
- Do not store the pen with the needle attached. If the needle is left on the pen, Byetta may leak from the pen and air bubbles may form in the cartridge.

Keep your pen and needles out of the reach of children.

How long can I use a Byetta Pen?

- You can use your Byetta Pen for up to 30 days after setting up a new pen for first use. **After 30 days, throw away the Byetta Pen, even if it is not completely empty.**
- Mark the date when you first used your pen and the date 30 days later in the spaces below:

Date of First Use _____ Date to Throw Away Pen _____

- Byetta should not be used after the expiration date printed on the pen label.

How do I clean my Byetta Pen?

- Wipe the outside of the pen with a clean, damp cloth.
- White particles may appear on the outside tip of the cartridge during normal use. You may remove them with an alcohol wipe or alcohol swab.

See the complete Byetta *Medication Guide* that comes with Byetta. For more information, call toll free 1-800-236-9933 or visit www.Byetta.com

Section 2
Read and follow the directions in this section only after you've read Section 1—What You Need To Know About Your Byetta Pen.

GETTING STARTED

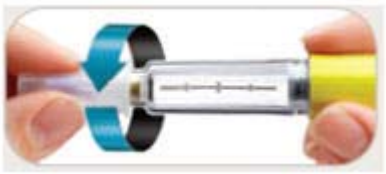
Set up your new pen just before you use it the first time. For routine use, do not repeat this one-time-only new pen setup. If you do, you will run out of Byetta before 30 days of use.

ONE-TIME-ONLY NEW PEN SETUP

STEP A Check the Pen

		**Note:** A small air bubble in the cartridge is normal.
• Wash hands prior to use. • Check pen label to make sure it is your 10 mcg pen. • Pull off the blue pen cap.	• Check Byetta in the cartridge. The liquid should be clear, colorless, and free of particles. If not, do not use.	

STEP B Attach the Needle

		
• Remove paper tab from outer needle shield. • **Push** outer needle shield containing the needle **straight** onto the pen, then **screw** needle on until secure.	• Pull off outer needle shield. **Do not** throw away.	• Pull off inner needle shield and throw away. A small drop of liquid may appear. This is normal.

STEP C Dial the Dose

		
• Check that the is in the dose window. If not, turn dose knob away from you (clockwise) **until it stops** and the is in the dose window.	• **Pull dose knob out until it stops** and the is in the dose window.	• **Turn dose knob away from you until it stops** at . Make sure that the 10 with the line under it is in the center of the dose window.

Note: If you cannot turn the dose knob away from you to the , see **Commonly Asked Questions,** number 7, in Section 4 of this user manual.

STEP D Prepare the Pen

		
• Point the needle of the pen up and away from you.	**PUSH & HOLD** • **Use thumb to firmly push injection button in until it stops,** then continue holding the injection button in while **slowly counting to 5.** • **If you do not see a stream or several drops come from the needle tip, repeat Steps C & D.**	• Pen preparation is complete when the is in the center of the dose window AND you have seen a stream or several drops come from the needle tip.

Note: If you do not see liquid after 4 times, see **Commonly Asked Questions,** number 3, in Section 4 of this user manual.

STEP E Complete New Pen Setup

	• **For routine use,** do not repeat this one-time-only new pen setup. If you do, you will run out of Byetta before 30 days of use.	• You are now ready for your first dose of Byetta. • **Go to Section 3, Step 3, for**

• **Turn dose knob away from you until it stops** and the  is in the dose window.		**instructions on how to inject your first routine dose.**

Note: If you cannot turn the dose knob, see **Commonly Asked Questions,** number 7, in Section 4 of user manual.

Section 3

Now that you have done the one-time-only new pen setup, follow Section 3 for all of your injections.

ROUTINE USE

STEP 1 Check the Pen

		**Note:** A small air bubble will not harm you or affect your dose.
• Wash hands prior to use. • Check pen label to make sure it is your 10 mcg pen. • Pull off the blue pen cap.	• Check Byetta in the cartridge. • The liquid should be clear, colorless, and free of particles. If it is not, do not use.	

STEP 2 Attach the Needle

		
• Remove paper tab from outer needle shield. • **Push** outer needle shield containing the needle **straight** onto pen, then **screw** needle on until secure.	• Pull off outer needle shield. **Do not** throw away.	• Pull off inner needle shield and throw away. A small drop of liquid may appear. This is normal.

STEP 3 Dial the Dose

		
• Check that the ➔ is in the dose window. If not, turn dose knob away from you (clockwise) **until it stops** and the ➔ is in the dose window.	• **Pull dose knob out until it stops** and the ➔ is in the dose window.	• **Turn dose knob away from you until it stops** at ◉. Make sure that the 10 with the line under it is in the center of the dose window.

Note: If you cannot turn the dose knob away from you to the ◉, see **Commonly Asked Questions,** number 7, in Section 4 of this user manual.

STEP 4 Inject the Dose

		
• Grip pen firmly. • Insert needle into skin using the under-the-skin (subcutaneous) injection method explained by your healthcare provider.	**PUSH & HOLD** • **Use thumb to firmly push injection button in until it stops.** Continue holding in the injection button while **slowly counting to 5** to get a full dose. • Remove needle from skin.	• Injection is complete when the ◆ is in the center of the dose window. • The pen is now ready to reset.

Note: If you see several drops of Byetta leaking from the needle after the injection, you may not have received a complete dose. See **Commonly Asked Questions,** number 4, in Section 4 of this user manual.

STEP 5 Reset the Pen

	• **Turn dose knob away from you until it stops** and the ➔ is in the dose window.	**Note:** If you cannot turn the dose knob, or if your pen leaks, your full dose has not been delivered. See **Commonly Asked Questions,** numbers 4 and 7, in Section 4 of this user manual.

STEP 6 Remove and Dispose of the Needle

		
• Carefully put the outer needle shield back over the needle. • **Remove the needle after each injection.**	• Unscrew the needle.	• Throw away needles in a puncture-resistant container or as recommended by your healthcare provider.

STEP 7 Store Pen for Next Dose

- Replace Blue Pen Cap on pen before storage.
- Store your Byetta Pen at a temperature between 36°F to 77°F (2°C to 25°C). (See **Storing Your Byetta Pen** in Section 1 of this user manual for complete storage information.)
- When it is time for your next routine dose, go to **Section 3, Step 1,** and repeat Steps 1–7.

Section 4

COMMONLY ASKED QUESTIONS

1. Do I need to do the One-Time-Only New Pen Setup before every dose?

- No. **The One-Time-Only New Pen Setup is done only once, just before each new pen is used for the first time.**
- The purpose of the setup is to make sure that your Byetta Pen is ready to use for the next 30 days.
- **If you repeat the One-Time-Only New Pen Setup before each routine dose, you will not have enough Byetta for 30 days.** The small amount of Byetta used in the new pen setup will not affect the 30-day supply of Byetta.

2. Why are there air bubbles in the cartridge?

- A small air bubble is normal. It will not harm you or affect your dose.
- If the pen is stored with a needle attached, air bubbles may form in the cartridge. **Do not** store the pen with the needle attached.

3. What should I do if Byetta does not come out of the needle tip after four tries during One-Time-Only New Pen Setup?

- Carefully put the outer needle shield back over the needle. Remove the needle by unscrewing it. Throw away the needle properly.

- Attach a new needle and repeat **One-Time-Only New Pen Setup, Steps B–E,** in Section 2 of this user manual. Once you see several drops or a stream of liquid coming out of the tip of the needle, the setup is complete.

4. Why do I see Byetta leaking from my needle after I have finished my injection?
It is normal for a single drop to remain on the tip of your needle after your injection is complete. If you see more than one drop:

- You may not have received your full dose. **Do not inject another dose.** Talk with your healthcare provider about what to do about a partial dose.

- To make sure that you get your full dose, when you take your injections, **firmly push and hold** the injection button in and **slowly count to 5** (see **Section 3, Step 4: Inject the Dose**).

5. How can I tell when the injection is complete?
The injection is complete when:

- You have firmly pushed the injection button in all the way **until it stops**
and

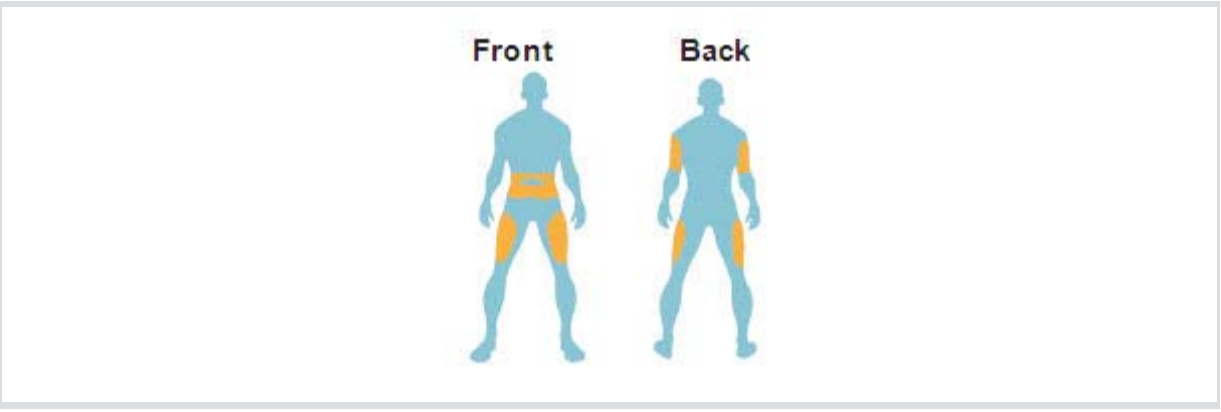
- **You have slowly counted to 5** while you are still holding the injection button in and the needle is still in your skin
and

- The

is in the center of the dose window.

If you hear a click sound from your Byetta Pen, ignore it. You must follow all the steps listed above to make sure your injection is complete.

6. Where should I inject Byetta?
Inject Byetta into your abdomen, thigh, or upper arm using the injection method explained to you by your healthcare provider.



7. What if I cannot pull, turn, or push the dose knob?
Check the symbol in the dose window. Follow the steps next to the matching symbol.

If is in the dose window:

- Pull the dose knob out until

appears.

If is in the dose window and the dose knob will not turn:

- The cartridge in your Byetta Pen may not have enough medicine to deliver a full dose. A small amount of Byetta will always stay in the cartridge. If the cartridge contains a small amount and the dose knob will not turn, your pen does not have enough Byetta and will not deliver any more doses. Obtain a new Byetta Pen.

If and part of are in the dose window and the dose knob cannot be pushed in:

- The dose knob was not turned all the way. Continue turning the dose knob away from you until

is in the center of the dose window.

If part of and part of are in the dose window and the dose knob cannot be pushed in:

- The needle may be clogged, bent, or incorrectly attached.
- Attach a new needle. Make sure needle is on straight and screwed on all the way.

- Firmly push the injection button in all the way. Byetta should come from needle tip.

If  is in the dose window and the dose knob will not turn:

- The injection button was not pushed in all the way and a complete dose was not delivered. **Talk with your healthcare provider about what to do about a partial dose.**
- Follow these steps to reset your pen for your next injection:
- Firmly push the injection button in all the way **until it stops**. Keep holding the injection button in and **slowly count to 5**. Then release the injection button and turn the dose knob away from you until

appears in the dose window.

- If you cannot turn the dose knob, the needle may be clogged. Replace the needle and repeat the step above.
- For your next dose, be sure to **firmly push and hold** the injection button in and **slowly count to 5** before removing needle from skin.

See the complete Byetta *Medication Guide* that comes with Byetta. For more information, call toll free 1-800-236-9933 or visit www.Byetta.com

Distributed by:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

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Revised: December 2014

Byetta 5 mcg Representative Packaging

See **How Supplied** section for a complete list of available packages of Byetta.

1.2 mL Cartridge Carton

5 mcg

NDC 0310-6512-01

Byetta® exenatide injection

250 mcg/mL, 1.2 mL

Dispense the enclosed Medication Guide to each patient

Each prefilled pen will deliver 60 subcutaneous doses, 5 mcg per dose

SUBCUTANEOUS USE ONLY
REFRIGERATE – DO NOT FREEZE

DO NOT TRANSFER THIS MEDICATION TO A SYRINGE

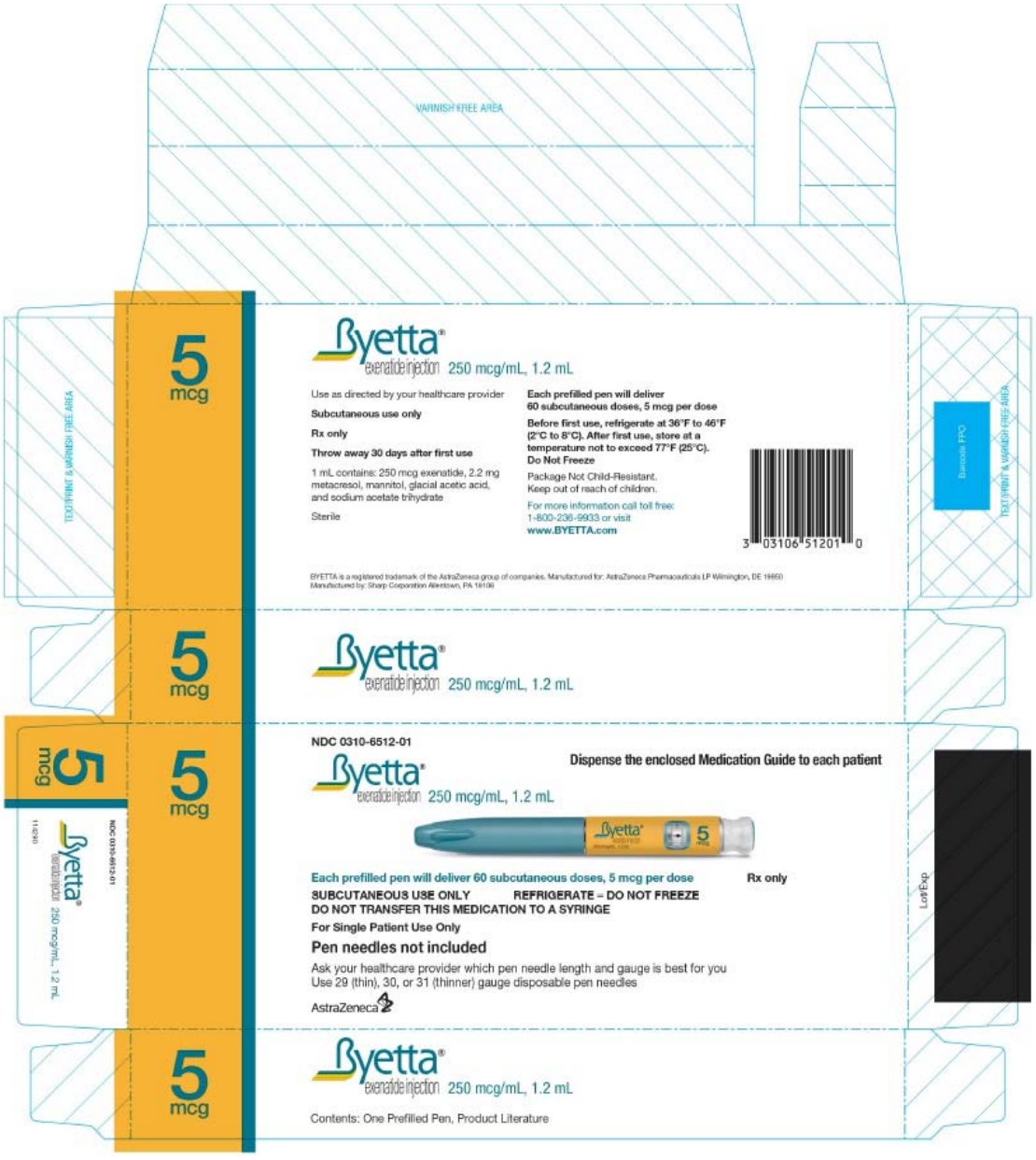
For Single Patient Use Only

Pen needles not included

Ask your healthcare provider which pen needle length and gauge is best for you
Use 29 (thin), 30, or 31 (thinner) gauge disposable pen needles

Rx Only

AstraZeneca



Byetta 10 mcg Representative Packaging

10 mcg

NDC 1310-6524-01

Byetta® exenatide injection

250 mcg/mL, 2.4 mL

Dispense the enclosed Medication Guide to each patient

Each prefilled pen will deliver 60 subcutaneous doses, 10 mcg per dose

SUBCUTANEOUS USE ONLY
REFRIGERATE – DO NOT FREEZE

DO NOT TRANSFER THIS MEDICATION TO A SYRINGE

For Single Patient Use Only

Pen needles not included

Ask your healthcare provider which pen needle length and gauge is best for you
Use 29 (thin), 30, or 31 (thinner) gauge disposable pen needles

Rx Only

AstraZeneca

Byetta

exenatide injection

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:0310-6512
Route of Administration	SUBCUTANEOUS	**DEA Schedule**	

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
exenatide (exenatide)	exenatide	250 ug in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**

metacresol	2.2 mg in 1 mL
mannitol	
acetic acid	
sodium acetate	
water	

Packaging		
#	**Item Code**	**Package Description**
1	NDC:0310-6512-01	1 CARTRIDGE in 1 CARTON
1		1.2 mL in 1 CARTRIDGE

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021773	12/10/2014	

Byetta
exenatide injection

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:0310-6524
Route of Administration	SUBCUTANEOUS	**DEA Schedule**	

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
exenatide (exenatide)	exenatide	250 ug in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
metacresol	2.2 mg in 1 mL
mannitol	
acetic acid	
sodium acetate	
water	

Packaging		
#	**Item Code**	**Package Description**
1	NDC:0310-6524-01	1 CARTRIDGE in 1 CARTON
1		2.4 mL in 1 CARTRIDGE

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021773	12/12/2014	

Labeler - AstraZeneca Pharmaceuticals LP (054743190)

Registrant - AstraZeneca PLC (230790719)

Revised: 12/2014

AstraZeneca Pharmaceuticals LP