HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EXENATIDE INJECTION safely and effectively. See full prescribing information for EXENATIDE INJECTION.

EXENATIDE injection, for subcutaneous use
Initial U.S. Approval: 2005

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

Warnings and Precautions, Pulmonary Aspiration During General Anesthesia or Deep Sedation. (5.10) 11/2024

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

Exenatide injection is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1, 14)

Limitations of Use

- Should not be used for the treatment of type 1 diabetes. (1)
- Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis. (1)

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

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

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

Exenatide injection is supplied as 250 mcg/mL exenatide in:

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

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

- History of severe hypersensitivity to exenatide or any of the excipients in exenatide injection. (4)
- History of drug-induced immune-mediated thrombocytopenia from exenatide products. (4)

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

- Never share an exenatide injection pen between patients, even if the needle is changed. (5.1)
- Acute Pancreatitis: Post-marketing reports with exenatide, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. Discontinue exenatide promptly. Exenatide should not be restarted. Consider other antidiabetic therapies in patients with a history of pancreatitis. (5.2)
- Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin: Patients taking an insulin secretagogue or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia. Reduction in the dose of insulin secretagogues or insulin may be necessary. (5.3)
- Acute Kidney Injury: Post-marketing reports with exenatide, sometimes requiring hemodialysis and kidney transplantation. Exenatide should *not* be used in patients with severe renal impairment or end-stage renal disease and should be used with caution in patients with renal transplantation. Caution should be applied when initiating exenatide or escalating the dose of exenatide in patients with moderate renal failure. (5.4, 8.6, 12.3)
- Severe Gastrointestinal Disease: Use of exenatide is not recommended in patients with severe gastrointestinal disease (e.g., gastroparesis). (5.5)
- Immunogenicity: Patients may develop antibodies to exenatide. If there is worsening glycemic control or failure to achieve target glycemic control, consider alternative antidiabetic therapy. (5.6)
- Hypersensitivity: Serious hypersensitivity reactions (e.g., anaphylaxis and angioedema) have been reported. Discontinue exenatide and promptly seek medical advice. (5.7)
- Drug-induced Immune-mediated Thrombocytopenia: Serious bleeding which may be fatal has been reported. Discontinue exenatide promptly and avoid re-exposure to exenatide. (5.8)
- Acute Gallbladder Disease: If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated. (5.9)
- Pulmonary Aspiration During General Anesthesia or Deep Sedation: Has been reported in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures. Instruct patients to inform healthcare providers of any planned surgeries or procedures. (5.10)

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

- Most common (≥ 5%) and occurring more frequently than placebo in clinical trials: nausea, hypoglycemia, vomiting, diarrhea, feeling jittery, dizziness, headache, dyspepsia, constipation, asthenia. Nausea usually decreases over time. (5.3, 6)
- Post-marketing reports with exenatide of increased international normalized ratio (INR) with concomitant use of warfarin, sometimes with bleeding. (6.2, 7.3)

To report SUSPECTED ADVERSE REACTIONS, contact Amneal Pharmaceuticals LLC at 1-877-835-5472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- May impact absorption of orally administered medications. (7.1, 12.3)
- Warfarin: Post-marketing reports of increased INR sometimes associated with bleeding. Monitor INR frequently until stable upon initiation or alteration of exenatide therapy. (6.2, 7.3)

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

- Pregnancy: Use during pregnancy only if the potential benefit justifies the risk to the fetus. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2024

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

Limitations of Use

- Exenatide injection is not indicated for use in patients with type 1 diabetes.
- Exenatide injection contains exenatide and should not be used with other products containing the active ingredient exenatide.
- Exenatide injection has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis *[see Warnings and Precautions (5.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

- Initiate exenatide injection at 5 mcg administered subcutaneously twice daily at any time within the 60-minute period before the morning and evening meals (or before the two main meals of the day, approximately 6 hours or more apart). Do not administer after a meal.
- Based on clinical response, the dose of exenatide injection can be increased to 10 mcg twice daily after 1 month of therapy.
- Administer as a subcutaneous injection in the thigh, abdomen, or upper arm.
- Inspect visually for particulate matter and discoloration. Only use exenatide injection if the solution appears clear, colorless and contains no particles.
- Do not mix exenatide injection with insulin. Do not transfer exenatide injection from the pen to a syringe or a vial.
- If a dose is missed, resume the treatment regimen as prescribed with the next scheduled dose.

3 DOSAGE FORMS AND STRENGTHS

Exenatide Injection, USP is a clear, colorless sterile solution for subcutaneous injection containing 250 mcg/mL exenatide, USP supplied as follows:

- 5 mcg per dose in a 1.2 mL single-patient-use prefilled pen (60 doses)
- 10 mcg per dose in a 2.4 mL single-patient-use prefilled pen (60 doses)

4 CONTRAINDICATIONS

Exenatide injection is contraindicated in patients with:

- A prior severe hypersensitivity reaction to exenatide or to any of the excipients in exenatide injection. Serious hypersensitivity reactions including anaphylaxis and angioedema have been reported with exenatide injection *[see Warnings and Precautions (5.7)]*.
- A history of drug-induced immune-mediated thrombocytopenia from exenatide products. Serious bleeding, which may be fatal, from drug-induced immune-mediated thrombocytopenia has been reported with exenatide use *[see Warnings and Precautions (5.8)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Never Share an Exenatide Injection Pen Between Patients

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

5.2 Acute Pancreatitis

Based on post-marketing data, exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. After initiation of exenatide, 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, exenatide should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, exenatide should not be restarted. Consider antidiabetic therapies other than exenatide in patients with a history of pancreatitis.

5.3 Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin

Patients receiving exenatide in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia including severe hypoglycemia *[see Adverse Reactions (6)* and *Drug Interactions (7.2)]*.

The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogue) or insulin. Inform patients using these concomitant medications of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.

5.4 Acute Kidney Injury

There have been post-marketing reports of altered renal function with exenatide, 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 exenatide. Exenatide has not been found to be directly nephrotoxic in preclinical or clinical studies.

Exenatide is not recommended 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)]*. Because exenatide may induce nausea and vomiting with transient hypovolemia, treatment may worsen renal function. Caution should be applied when initiating or escalating doses of exenatide from 5 mcg to 10 mcg in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min).

5.5 Gastrointestinal Disease

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

5.6 Immunogenicity

Patients may develop antibodies to exenatide following treatment with exenatide. 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 exenatide. 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)]*.

5.7 Hypersensitivity

There have been post-marketing reports of serious hypersensitivity reactions (e.g., anaphylaxis and angioedema) in patients treated with exenatide. If a hypersensitivity reaction occurs, the patient should discontinue exenatide and other suspect medications and promptly seek medical advice. Inform and closely monitor patients with a history of anaphylaxis or angioedema with another GLP-1 receptor agonist for allergic reactions, because it is unknown whether such patients will be predisposed to anaphylaxis with exenatide *[see Adverse Reactions (6.2)]*.

5.8 Drug-Induced Thrombocytopenia

Serious bleeding, which may be fatal, from drug-induced immune-mediated thrombocytopenia has been reported in the post-marketing setting with exenatide use. Drug-induced thrombocytopenia is an immune-mediated reaction, with exenatide-dependent anti-platelet antibodies. In the presence of exenatide, these antibodies cause platelet destruction. If drug-induced thrombocytopenia is suspected, discontinue exenatide immediately and do not re-expose the patient to exenatide *[see Adverse Reactions (6.2)]*.

5.9 Acute Gallbladder Disease

Acute events of gallbladder disease such as cholelithiasis or cholecystitis have been reported in GLP-1 receptor agonist trials and post-marketing. In a clinical study with exenatide, 1.9% of exenatide-treated patients and 1.4% of placebo-treated patients reported an acute event of gallbladder disease, such as cholelithiasis or cholecystitis. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated.

5.10 Pulmonary Aspiration During General Anesthesia or Deep Sedation

Exenatide delays gastric emptying *[see Clinical Pharmacology (12.2)]*. There have been rare post-marketing reports of pulmonary aspiration in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures requiring general anesthesia or deep sedation who had residual gastric contents despite reported adherence to preoperative fasting recommendations.

Available data are insufficient to inform recommendations to mitigate the risk of pulmonary aspiration during general anesthesia or deep sedation in patients taking exenatide, including whether modifying preoperative fasting recommendations or temporarily discontinuing exenatide could reduce the incidence of retained gastric contents. Instruct patients to inform healthcare providers prior to any planned surgeries or procedures if they are taking exenatide.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below or elsewhere in the prescribing information:

- Never Share an Exenatide Pen Between Patients *[see Warnings and Precautions (5.1)]*

- Acute Pancreatitis *[see Warnings and Precautions (5.2)]*
- Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin *[see Warnings and Precautions (5.3)]*
- Acute Kidney Injury *[see Warnings and Precautions (5.4)]*
- Gastrointestinal Disease *[see Warnings and Precautions (5.5)]*
- Immunogenicity *[see Warnings and Precautions (5.6)]*
- Hypersensitivity *[see Warnings and Precautions (5.7)]*
- Drug-Induced Thrombocytopenia *[see Warnings and Precautions (5.8)]*
- Acute Gallbladder Disease *[see Warnings and Precautions (5.9)]*
- Pulmonary Aspiration During General Anesthesia or Deep Sedation *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trial Experience

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

Hypoglycemia

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

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

	Placebo BID	Exenatide 5 mcg BID	Exenatide 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

	Placebo BID	Exenatide 5 mcg BID	Exenatide 10 mcg BID
% 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 exenatide was initiated in combination with insulin glargine, the dose of insulin glargine was decreased by 20% in patients with an $HbA_{1c} \leq 8.0\%$ 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 exenatide. In the 30-week controlled trials of exenatide 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 exenatide; the remaining 27 (3% overall) had a glycemic response comparable to that of patients without antibodies.

In the 16-week trial of exenatide 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 exenatide; the remaining 6 (5% overall) had a glycemic response comparable to that of patients without antibodies.

In the 24-week trial of exenatide 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 exenatide; the remaining 2 (1% overall) had a glycemic response comparable to that of patients without antibodies.

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

In the 30-week comparator-controlled trial of exenatide 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 exenatide; the remaining 8 (3% overall) had a glycemic response comparable to that of patients without antibodies.

Two hundred and ten patients with antibodies to exenatide in the exenatide 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 exenatide used as a monotherapy, Table 2 summarizes adverse reactions (excluding hypoglycemia) occurring with an incidence ≥ 2% and occurring more frequently in exenatide-treated patients compared with placebo-treated patients.

Table 2: Treatment-Emergent Adverse Reactions ≥ 2% Incidence with Exenatide used as Monotherapy (excluding Hypoglycemia)[*]

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

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

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

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

Cholelithiasis and cholecystitis

In a clinical study with exenatide, 1.9% of exenatide-treated patients and 1.4% of placebo-treated patients reported an acute event of gallbladder disease, such as cholelithiasis or cholecystitis.

Combination Therapy

Add-On to Metformin and/or Sulfonylurea

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

Table 3: Treatment-Emergent Adverse Reactions ≥ 2% Incidence and Greater Incidence with Exenatide Treatment used with Metformin and/or a Sulfonylurea (excluding Hypoglycemia)[*]

	Placebo BID N=483 %	All Exenatide 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 exenatide 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 exenatide-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 exenatide 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 exenatide-treated patients compared with placebo-treated patients.

Table 4: Treatment-Emergent Adverse Reactions ≥ 2% Incidence with Exenatide used with a Thiazolidinedione (TZD), with or without Metformin (MET) (excluding Hypoglycemia)[*]

With a TZD or TZD/MET	Placebo N=112 %	All Exenatide 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 exenatide and reported more frequently than with placebo included decreased appetite. Chills (n=4) and injection-site reactions (n=2) occurred only in

exenatide-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 exenatide arm. No serious adverse events were reported in the placebo arm.

The most common adverse reactions leading to withdrawal for exenatide-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 exenatide 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 exenatide-treated patients compared with placebo-treated patients.

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

With Insulin Glargine	**Placebo N=122 %**	**All Exenatide BID N=137 %**
Nausea	8	41
Vomiting	4	18
Diarrhea	8	18
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 exenatide-treated patients were nausea (5.1%) and vomiting (2.9%). No placebo-treated patients withdrew due to nausea or vomiting.

6.2 Post-marketing Experience

The following additional adverse reactions have been reported during post-approval use of exenatide or other exenatide formulations. 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.

Blood and Lymphatic Systems: drug-induced thrombocytopenia.

Drug Interactions: International normalized ratio (INR) increased with concomitant warfarin use sometimes associated with bleeding *[see Drug Interactions (7.3)]*.

Gastrointestinal: nausea, vomiting and/or diarrhea resulting in dehydration; abdominal distension, abdominal pain, eructation, constipation, flatulence, ileus, acute pancreatitis, hemorrhagic and necrotizing pancreatitis sometimes resulting in death *[see Indications and Usage (1)]*.

Hepatobiliary: cholecystitis, cholelithiasis requiring cholecystectomy.

Metabolic: Severe hypoglycemia with concomitant use of sulfonylurea or insulin.

Neurologic: dysgeusia; somnolence.

Pulmonary: Pulmonary aspiration has occurred in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures requiring general anesthesia or deep sedation.

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.

Skin and Subcutaneous Tissue Disorders: alopecia.

7 DRUG INTERACTIONS

7.1 Orally Administered Drugs

The effect of exenatide to slow gastric emptying can reduce the extent and rate of absorption of orally administered drugs. Exenatide 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 exenatide injection. If such drugs are to be administered with food, patients should be advised to take them with a meal or snack when exenatide is not administered *[see Clinical Pharmacology (12.3)]*.

7.2 Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin

When initiating exenatide, consider reducing the dose of concomitantly administered insulin secretagogues (such as sulfonylureas) or insulin to reduce the risk of hypoglycemia *[see Warnings and Precautions (5.3)* and *Adverse Reactions (6)]*.

7.3 Warfarin

There are post-marketing reports of increased INR sometimes associated with bleeding, with concomitant use of warfarin and exenatide *[see Adverse Reactions (6.2)]*. In a drug interaction study, exenatide 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 exenatide therapy. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on warfarin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited data with exenatide in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *(see Clinical Considerations)*. Based on animal reproduction studies, there may be risks to the fetus from exposure to exenatide during pregnancy. Exenatide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal reproduction studies identified increased adverse fetal and neonatal outcomes from exposure to exenatide during pregnancy and lactation in association with maternal effects. In mice, exenatide administered during gestation and lactation caused increased neonatal deaths at systemic exposure 3-times the human exposure resulting from the maximum recommended human dose (MRHD) of 20 mcg/day for exenatide *(see Data)*.

The estimated background risk of major birth defects is 6% to 10% in women with pre-gestational diabetes with an $HbA_{1c} > 7$ and has been reported to be as high as 20% to 25% in women with $HbA_{1c} > 10$. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryofetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Animal Data

In studies evaluating reproduction and development in pregnant mice and rabbits, maternal animals were administered exenatide, the active ingredient in exenatide injection, by subcutaneous injection twice a day.

In pregnant mice given 6, 68, 460, or 760 mcg/kg/day exenatide during fetal organogenesis, skeletal variations associated with slowed fetal growth, including changes in number of rib pairs or vertebral ossifications sites, and wavy ribs were observed at 760 mcg/kg/day, a dose that produced maternal toxicity and yielded systemic exposure 390-times the human exposure resulting from the MRHD of exenatide based on AUC comparison.

In pregnant rabbits given 0.2, 2, 22, 156, or 260 mcg/kg/day exenatide during fetal organogenesis, irregular fetal skeletal ossifications were observed at 2 mcg/kg/day, a dose yielding systemic exposure up to 12-times the human exposure from the MRHD of exenatide based on AUC comparison.

In maternal mice given 6, 68, or 760 mcg/kg/day exenatide from gestation day 6 through lactation day 20 (weaning), an increased number of neonatal deaths was observed on postpartum days 2 to 4 in dams given 6 mcg/kg/day, a dose yielding a systemic exposure 3-times the human exposure from the MRHD of exenatide based on AUC comparison.

8.2 Lactation

Risk Summary

There is no information regarding the presence of exenatide, in human milk, the effects of exenatide on the breastfed infant, or the effects of exenatide on milk production. Exenatide was present in the milk of lactating mice. However, due to species-specific differences in lactation physiology, the clinical relevance of these data is not clear *(see Data)*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for exenatide and any potential adverse effects on the breastfed child from exenatide or from the underlying maternal condition.

Data

In lactating mice subcutaneously injected twice a day with exenatide, the concentration of exenatide in milk was up to 2.5% of the concentration in maternal plasma.

8.4 Pediatric Use

The safety and effectiveness of exenatide have not been established in pediatric patients.

Effectiveness of exenatide was not demonstrated in a randomized, double-blind, placebo-controlled study conducted in 120 pediatric patients (78 received exenatide and 42 received placebo) aged 10 to 17 years with type 2 diabetes mellitus.

8.5 Geriatric Use

Population pharmacokinetic analysis of patients ranging from 22 to 73 years of age suggests that age does not influence the pharmacokinetic properties of exenatide *[see Clinical Pharmacology (12.3)]*. Exenatide 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.

8.6 Renal Impairment

Exenatide 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. In patients with end-stage renal disease receiving dialysis, single doses of exenatide 5 mcg were not well-tolerated due to gastrointestinal side effects. No dosage adjustment of exenatide is required in patients with mild renal impairment (creatinine clearance 50 to 80 mL/min). Caution should be applied when initiating or escalating doses of exenatide from 5 mcg to 10 mcg in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min) *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

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

10 OVERDOSAGE

In a clinical study of exenatide, three patients with type 2 diabetes each experienced a single overdose of 100 mcg SC (10-times the maximum recommended dose). Effects of the overdoses included severe nausea, severe vomiting and rapidly declining blood glucose concentrations. One of the three patients experienced severe hypoglycemia requiring parenteral glucose administration. The three patients recovered without complication.

In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

11 DESCRIPTION

Exenatide is a synthetic peptide, glucagon-like peptide-1 (GLP-1) receptor agonist, that was originally identified in the lizard *Heloderma suspectum*.

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

Exenatide injection, USP is supplied for subcutaneous administration 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, USP, 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).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

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

12.2 Pharmacodynamics

Glucose-Dependent Insulin Secretion

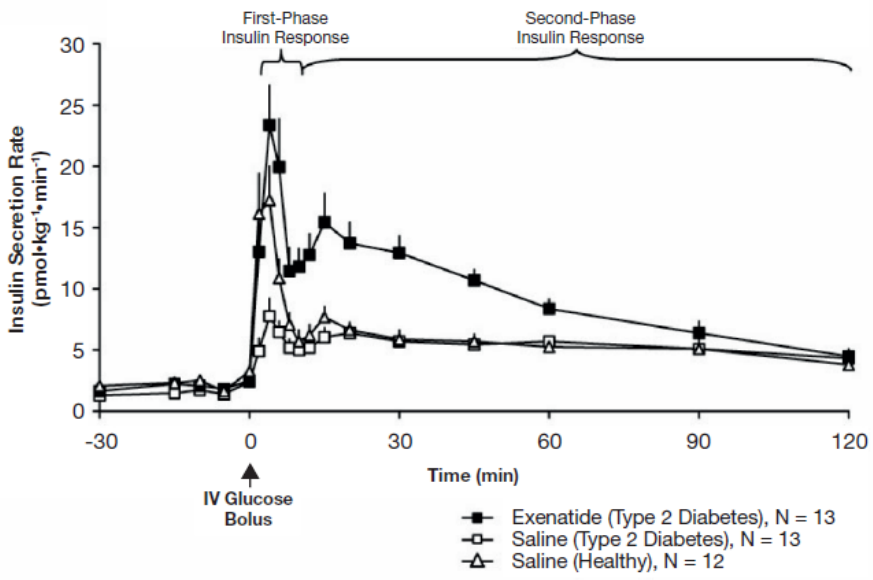
Exenatide has acute effects on pancreatic beta-cell responsiveness to glucose leading to insulin release predominantly in the presence of elevated glucose concentrations. This insulin secretion subsides as blood glucose concentrations decrease and approach euglycemia. However, exenatide does not impair 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 exenatide 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 exenatide compared with saline ($p < 0.001$ for both).

Figure 1: Mean (+SEM) Insulin Secretion Rate during Infusion of Exenatide or Saline in Patients with Type 2 Diabetes and during Infusion of Saline in Healthy Subjects



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

Glucagon Secretion

In patients with type 2 diabetes, exenatide 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

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

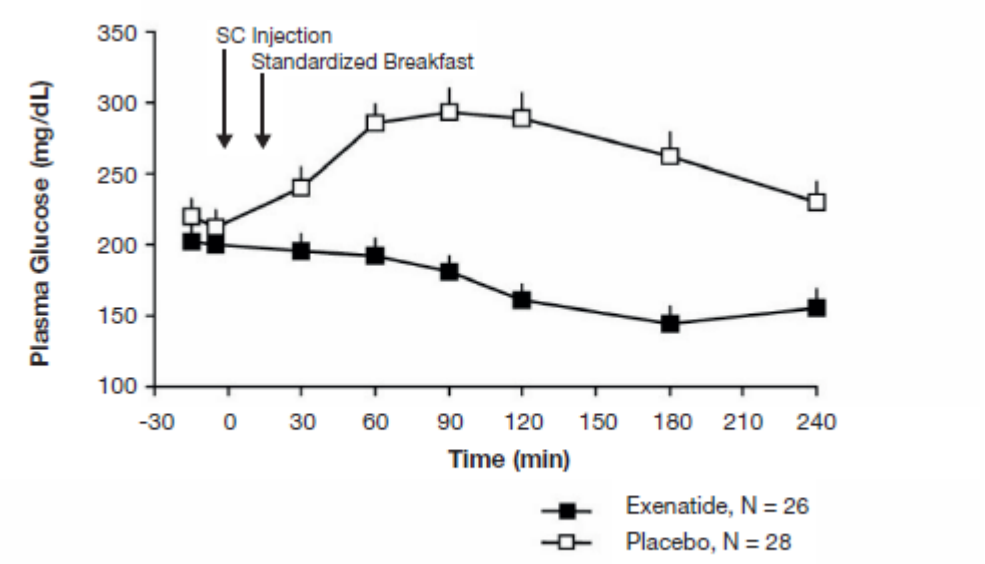
Food Intake

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

Postprandial Glucose

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

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

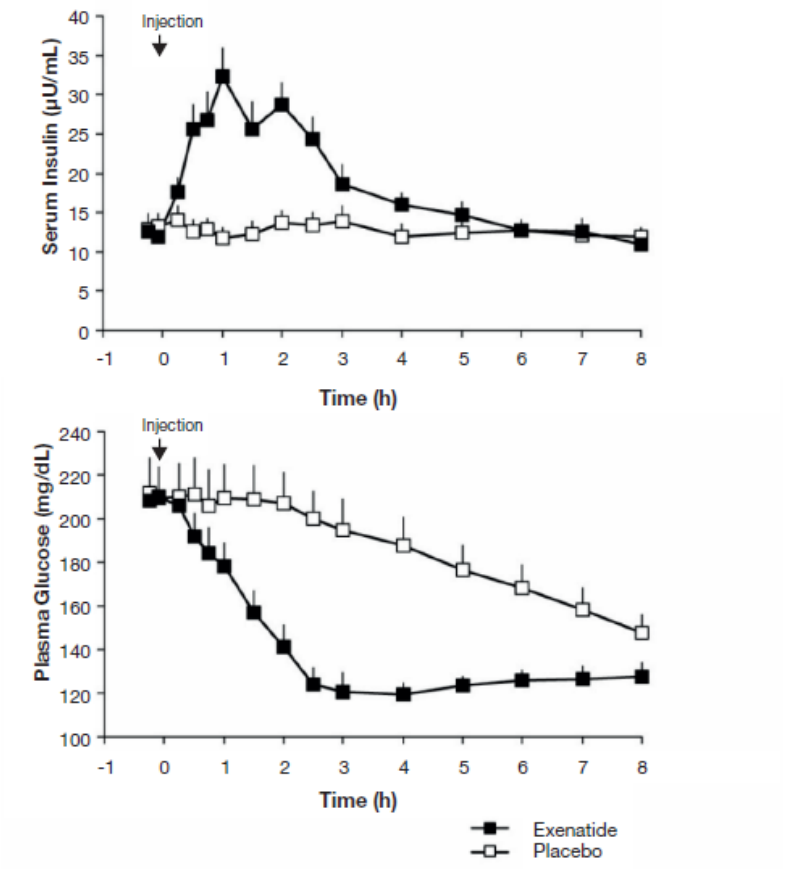


[a]Mean dose (7.8 mcg based on body weight) was administered by subcutaneous (SC) injection.

Fasting Glucose

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

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



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

Cardiac Electrophysiology

The effect of exenatide 10 mcg 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, exenatide (10 mcg single-dose) was not associated with clinically meaningful prolongation of the QTc interval.

12.3 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 1,036 pg•h/mL following SC administration of a 10-mcg dose of exenatide. Exenatide exposure (AUC) increased proportionally over the therapeutic dose range of 5 mcg to 10 mcg. The C_{max} values increased less than proportionally over the same range. Similar exposure is achieved with SC administration of exenatide in the abdomen, thigh, or upper arm.

Distribution

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

Metabolism and Elimination

Nonclinical studies have shown that exenatide is predominantly eliminated by glomerular filtration with subsequent proteolytic degradation. The mean apparent clearance of exenatide in humans is 9.1 L/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 1,000 mg acetaminophen elixir was given with 10 mcg exenatide (0 hour) and 1 hour, 2 hours and 4 hours after exenatide 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 exenatide injection.

Digoxin

Administration of repeated doses of exenatide (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 exenatide (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 exenatide, the use of exenatide 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 mg/day to 20 mg/day), exenatide (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 exenatide (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 exenatide 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 exenatide 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. Exenatide 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 exenatide administration injection as compared to when the OC was given alone. The effect of exenatide 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 exenatide injection.

Warfarin

Administration of warfarin (25 mg) 35 minutes after repeated doses of exenatide (5 mcg BID on Days 1 to 2 and 10 mcg BID on Days 3 to 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. Exenatide did not significantly alter the pharmacodynamic properties (e.g., international normalized ratio) of warfarin *[see Drug Interactions (7.3)]*.

Specific Populations

Renal Impairment

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

Hepatic Impairment

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

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) $\geq$ 30 kg/m^2 and $<$ 30 kg/m^2 suggests that BMI has no significant effect on the pharmacokinetics of exenatide.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

14 CLINICAL STUDIES

Exenatide 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.

14.1 Monotherapy

In a randomized, double-blind, placebo-controlled trial of 24 weeks duration, exenatide 5 mcg BID (n=77), exenatide 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 exenatide initially received 5 mcg BID for 4 weeks. After 4 weeks, those patients either continued to receive exenatide 5 mcg BID or had their dose increased to 10 mcg BID. Patients assigned to placebo received placebo BID throughout the trial. Exenatide 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, exenatide 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 Exenatide used as Monotherapy

	Placebo BID	Exenatide 5 mcg BID	Exenatide 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]

* Exenatide 5 mcg twice daily (BID) for 1 month followed by 10 mcg BID for 5 months before the morning and evening meals.
† Least squares means are adjusted for screening HbA_{1c} strata and baseline value of the dependent variable.
‡ $p < 0.01$, treatment vs. placebo.
§ Measured using the hexokinase-based glucose method.
BID = twice daily.

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

14.2 Combination Therapy with Oral Antihyperglycemic Medicines

Three 30-week, double-blind, placebo-controlled trials were conducted to evaluate the safety and efficacy of exenatide 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 exenatide 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 exenatide 5 mcg BID, exenatide 10 mcg BID, or placebo BID before the morning and evening meals, in addition to their existing oral antidiabetic agent. All patients assigned to exenatide initially received 5 mcg BID for 4 weeks. After 4 weeks, those patients either continued to receive exenatide 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 1,446 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, exenatide (n=121) or placebo (n=112) was added to existing thiazolidinedione (pioglitazone or rosiglitazone) treatment, with or without metformin. Randomization to exenatide or placebo was stratified based on whether the patients were receiving metformin. Exenatide 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. Exenatide 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 exenatide 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 Exenatide used in Combination with Oral Antidiabetic Agents

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

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

* Exenatide 5 mcg twice daily for 1 month followed by 10 mcg BID for 6 months for the 30-week trials or 10 mcg BID for 3 months in the 16-week trial before the morning and evening meals.
† Least squares means are adjusted for baseline HbA_{1c} strata or value, investigator site, baseline value of the dependent variable (if applicable) and background antihyperglycemic therapy (if applicable).
‡ $p < 0.01$, treatment vs. placebo.
§ Measured using the hexokinase-based glucose method.
BID = twice daily.

HbA_{1c}

The addition of exenatide 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 exenatide add-on to thiazolidinediones, with or without metformin, exenatide 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, exenatide reduced postprandial plasma glucose concentrations in a dose-dependent manner. The mean (SD) change in 2-hour postprandial glucose concentration following administration of exenatide 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).

14.3 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 exenatide (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 exenatide initially received 5 mcg BID for 4 weeks. After 4 weeks, those patients assigned to exenatide had their dose increased to 10 mcg BID. Patients assigned to placebo received placebo BID throughout the trial. Exenatide or placebo was injected subcutaneously before the morning and evening meals. Patients with an $HbA_{1c} \leq 8.0\%$ decreased their pre-study dose of insulin glargine by 20% and patients with an $HbA_{1c} \geq 8.1\%$ 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, exenatide 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 Exenatide Used in Combination with Insulin Glargine with or without Metformin and/or Thiazolidinediones

	Placebo BID + Titrated Insulin Glargine	**Exenatide 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 $HbA_{1c} < 7\%$	29%	56%
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]

* Exenatide 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 HbA_{1c} 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 HbA_{1c} 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 exenatide (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 exenatide 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 exenatide initially received 5 mcg BID for four weeks. After four weeks, their dose was increased to 10 mcg BID. Patients in the exenatide-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 exenatide 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 Exenatide used in Combination with Insulin Glargine and Metformin

	Titrated Insulin Lispro TID + Titrated Insulin Glargine	Exenatide 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	130
Change at Week 30† #	5	−7
Difference from Insulin Lispro† # (95% CI)		−12 [−19, −4]

* Exenatide 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 Exenatide 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Exenatide Injection, USP is supplied as a clear, colorless sterile solution for subcutaneous injection containing **250 mcg/mL** exenatide, USP.
The following packages are available:

5 mcg per dose, 60 doses, 1.2 mL prefilled pen: NDC 70121-1685-1
10 mcg per dose, 60 doses, 2.4 mL prefilled pen: NDC 70121-1686-1

16.2 Storage and Handling

- Store exenatide injection in the refrigerator at 36° to 46°F (2° to 8°C).
- After first use, exenatide injection can be kept at a temperature not to exceed 77°F (25°C).
- Do not freeze. Do not use exenatide injection if it has been frozen.
- Protect exenatide injection from light.
- Discard the pen 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.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Never Share an Exenatide Injection Pen Between Patients

Advise patients that they must never share an exenatide injection pen with another person, even if the needle is changed, because doing so carries a risk for transmission of blood-borne pathogens *[see Warnings and Precautions (5.1)]*.

Acute Pancreatitis

Inform patients 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. Instruct patients to promptly discontinue exenatide and contact their physician if persistent severe abdominal pain occurs *[see Warnings and Precautions (5.2)]*.

Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin

Inform patients that the risk of hypoglycemia is increased when exenatide is used in combination with an agent that induces hypoglycemia, such as a sulfonylurea or insulin. Educate patients on the signs and symptoms of hypoglycemia *[see Warnings and Precautions (5.3)]*.

Acute Kidney Injury

Inform patients treated with exenatide of the potential risk for worsening renal function and 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)]*.

Drug-Induced Thrombocytopenia

Inform patients that drug-induced immune-mediated thrombocytopenia has been reported during use of exenatide. Inform patients that if symptoms of thrombocytopenia occur, stop taking exenatide and seek medical advice promptly *[see Warnings and Precautions (5.8)]*.

Hypersensitivity Reactions

Inform patients that serious hypersensitivity reactions have been reported during post-marketing use of exenatide. If symptoms of hypersensitivity reactions occur, instruct patients to stop taking exenatide and seek medical advice promptly *[see Warnings and Precautions (5.7)]*.

Acute Gallbladder Disease

Inform patients of the potential risk for cholelithiasis or cholecystitis. Instruct patients to contact their physician if cholelithiasis or cholecystitis is suspected for appropriate clinical follow-up *[see Warnings and Precautions (5.9)]*.

Pulmonary Aspiration During General Anesthesia or Deep Sedation

Inform patients that exenatide may cause their stomach to empty more slowly which may lead to complications with anesthesia or deep sedation during planned surgeries or procedures. Instruct patients to inform healthcare

providers prior to any planned surgeries or procedures if they are taking exenatide *[see Warnings and Precautions (5.10)]*.

Pregnancy

Advise patients to inform their physicians if they are pregnant or intend to become pregnant.

Instructions

Instruct patients to administer exenatide as a subcutaneous 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). Do not administer exenatide injection after a meal. If a dose is missed, resume the treatment regimen as prescribed with the next scheduled dose.

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