## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**BYDUREON™ (exenatide extended-release for injectable suspension).**
**Initial U.S. Approval: 2012**

**WARNING: RISK OF THYROID C-CELL TUMORS**
***See full prescribing information for complete boxed warning.***

- **Exenatide extended-release causes thyroid C-cell tumors at clinically relevant exposures in rats. It is unknown whether BYDUREON causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be determined by clinical or nonclinical studies (5.1).**
- **BYDUREON is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) (5.1).**

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

BYDUREON 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 in multiple clinical settings (1.1, 14).

BYDUREON is an extended-release formulation of exenatide. Do not co-administer with BYETTA.

**Important Limitations of Use**

- Not recommended as first-line therapy for patients inadequately controlled on diet and exercise (5.1).
- Should not be used to treat type 1 diabetes or diabetic ketoacidosis (1.2).
- Use with insulin has not been studied and is not recommended (1.2).
- Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis (1.2, 5.2).

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

- Administer 2 mg by subcutaneous injection once every seven days (weekly), at any time of day and with or without meals (2.1).
- Administer immediately after the powder is suspended (2.1).

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

BYDUREON is 2 mg exenatide for extended-release injectable suspension.

### ----------CONTRAINDICATIONS----------

- Do not use if personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (4.1).
- Do not use if history of serious hypersensitivity to exenatide or any product components (4.2).

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

- Thyroid C-cell tumors in animals: Human relevance unknown. Counsel patients regarding the risk of medullary thyroid carcinoma and the symptoms of thyroid tumors (5.1).
- Pancreatitis: Postmarketing reports with exenatide, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. Consider other antidiabetic therapies if history of pancreatitis (5.2).
- Hypoglycemia: Increased risk when BYDUREON is used in combination with a sulfonylurea. Consider reducing the sulfonylurea dose (5.3).
- Renal Impairment: Postmarketing reports with exenatide, sometimes requiring hemodialysis and kidney transplantation. Not recommended if severe renal impairment or end-stage renal disease. Use with caution in patients with renal transplantationor moderate renal impairment (5.4, 8.6, 12.3).
- Severe Gastrointestinal Disease: Not recommended if severe gastrointestinal disease (e.g., gastroparesis) (5.5).
- Hypersensitivity: Postmarketing reports with exenatide of serious hypersensitivity reactions (e.g. anaphylaxis and angioedema). In such cases, patients are to discontinue BYDUREON and other suspect medications and promptly seek medical advice (5.7).
- Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with BYDUREON or any other antidiabetic drug (5.8).

### ----------ADVERSE REACTIONS----------

- Most common (≥5%) and occurring more frequently than comparator in clinical trials: nausea, diarrhea, headache, vomiting, constipation, injection site pruritus, injection site nodule, and dyspepsia (5.3, 6.1).

**To report SUSPECTED ADVERSE REACTIONS contact Amylin Pharmaceuticals, Inc at 1-877-700-7365 and www.bydureon.com 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: Postmarketing reports with exenatide of increased INR sometimes associated with bleeding. Monitor INR frequently until stable upon initiation of BYDUREON therapy (7.2, 6.2).

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

- Pregnancy: Based on animal data, may cause fetal harm. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. To report drug exposure during pregnancy call 1-800-633-9081 (8.1).
- Nursing Mothers: Use caution when administering to a nursing woman (8.3).

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.**

**Revised: 01/2012**

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**FULL PRESCRIBING INFORMATION: CONTENTS***



* Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

**WARNING: RISK OF THYROID C-CELL TUMORS**

Exenatide extended-release causes an increased incidence in thyroid C-cell tumors at clinically relevant exposures in rats compared to controls. It is unknown whether BYDUREON causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be determined by clinical or nonclinical studies. BYDUREON is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value in patients treated with BYDUREON. Patients should be counseled regarding the risk and symptoms of thyroid tumors [see *Contraindications (4.1), Warnings and Precautions (5.1) and Nonclinical Toxicology (13.1)*].

## 1 INDICATIONS AND USAGE

BYDUREON is an extended-release formulation of exenatide, administered as an injection once every seven days (weekly).

### 1.1 Type 2 Diabetes Mellitus

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

### 1.2 Important Limitations of Use

Because of the uncertain relevance of the rat thyroid C-cell tumor findings to humans, prescribe BYDUREON only to patients for whom the potential benefits are considered to outweigh the potential risk.

BYDUREON is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.

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

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

BYDUREON and BYETTA® (exenatide) injection both contain the same active ingredient, exenatide, and therefore should not be used together.

Based on postmarketing data, exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. BYDUREON 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 BYDUREON. Other antidiabetic therapies should be considered in patients with a history of pancreatitis.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Recommended Dosing

BYDUREON (2 mg per dose) should be administered once every seven days (weekly). The dose can be administered at any time of day, with or without meals.

Missed Dose

If a dose is missed, it should be administered as soon as noticed, provided the next regularly scheduled dose is due at least three days later. Thereafter, patients can resume their usual dosing schedule of once every seven days (weekly).

If a dose is missed and the next regularly scheduled dose is due one or two days later, the patient should not administer the missed dose and instead resume BYDUREON with the next regularly scheduled dose.

Changing Weekly Dosing Schedule

The day of weekly administration can be changed if necessary as long as the last dose was administered 3 or more days before.

### 2.2 Administration

BYDUREON is intended for patient self-administration. BYDUREON is provided in a single-dose tray containing: one vial of 2 mg exenatide, one vial connector, one prefilled diluent syringe and two needles (one provided as a spare) [see *How Supplied/Storage and Handling (16.1)*]. **Do not substitute needles or any other components in the tray**.

BYDUREON must be injected immediately after the powder is suspended in the diluent and transferred to the syringe. BYDUREON is administered as a subcutaneous (SC) injection in the abdomen, thigh or upper arm region. Advise patients to use a different injection site each week when injecting in the same region. BYDUREON must not be administered intravenously or intramuscularly.

**See the BYDUREON Instructions for Use for complete administration instructions with illustrations**. The instructions can also be found at www.bydureon.com.

### 2.3 Changing from BYETTA to BYDUREON

Prior treatment with BYETTA is not required when initiating BYDUREON therapy. If the decision is made to start BYDUREON in an appropriate patient already taking BYETTA,

BYETTA should be discontinued. Patients changing from BYETTA to BYDUREON may experience transient (approximately two weeks) elevations in blood glucose concentrations.

## 3 DOSAGE FORMS AND STRENGTHS

BYDUREON is 2 mg exenatide extended-release for injectable suspension for subcutaneous administration once every seven days (weekly).

## 4 CONTRAINDICATIONS

### 4.1 Medullary Thyroid Carcinoma

BYDUREON is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

### 4.2 Hypersensitivity

BYDUREON is contraindicated in patients with a prior serious hypersensitivity reaction to exenatide or to any of the product components.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Risk of Thyroid C-cell Tumors

In both genders of rats, exenatide extended-release caused a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures compared to controls [see *Nonclinical Toxicology (13.1)*]. A statistically significant increase in malignant thyroid C-cell carcinomas was observed in female rats receiving exenatide extended-release at 25-times clinical exposure compared to controls and higher incidences were noted in males above controls in all treated groups at ≥2-times clinical exposure. The potential of exenatide extended-release to induce C-cell tumors in mice has not been evaluated. Other GLP-1 receptor agonists have also induced thyroid C-cell adenomas and carcinomas in male and female mice and rats at clinically relevant exposures. It is unknown whether BYDUREON will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of exenatide extended-release-induced rodent thyroid C-cell tumors could not be determined by clinical or nonclinical studies. Serum calcitonin was not assessed in the clinical trials supporting the approval of BYDUREON [see *Boxed Warning, Contraindications (4.1)*].

Serum calcitonin is a biological marker of MTC. Patients with MTC usually have calcitonin values >50 ng/L. Patients with thyroid nodules noted on physical examination or neck imaging should be referred to an endocrinologist for further evaluation. Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with BYDUREON. Such monitoring may increase the risk of unnecessary

procedures, due to the low specificity of serum calcitonin testing for MTC and a high background incidence of thyroid disease. If serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation [see *Patient Counseling Information (17)*].

### 5.2 Acute Pancreatitis

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

### 5.3 Hypoglycemia

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

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

### 5.4 Renal Impairment

BYDUREON 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 BYDUREON may induce nausea and vomiting with transient hypovolemia, treatment may worsen renal function. Use BYDUREON with caution in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min) [see *Use in Specific Populations (8.6) Clinical Pharmacology (12.3)*]. BYDUREON has not been studied in patients with end-stage renal disease or severe renal impairment.

There have been postmarketing 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.

### 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 BYDUREON is not recommended in patients with severe gastrointestinal disease.

### 5.6 Immunogenicity

Patients may develop antibodies to exenatide following treatment with BYDUREON. Anti-exenatide antibodies were measured in all BYDUREON-treated patients in the five comparator-controlled 24-30 week studies of BYDUREON. In 6% of BYDUREON-treated patients, 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 postmarketing reports of serious hypersensitivity reactions (e.g. anaphylaxis and angioedema) in patients treated with exenatide. If a hypersensitivity reaction occurs, the patient should discontinue BYDUREON and other suspect medications and promptly seek medical advice [see *Adverse Reactions (6.2)*].

### 5.8 Macrovascular Outcomes

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

## 6 ADVERSE REACTIONS

### 6.1 Clinical Trial Experience

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

The safety of BYDUREON was assessed in five comparator-controlled trials, in patients who entered the studies not achieving adequate glycemic control on their current therapy. In a double-blind 26 week trial, patients on diet and exercise were treated with BYDUREON 2 mg once every seven days (weekly), sitagliptin 100 mg daily, pioglitazone 45 mg daily, or metformin 2000 mg daily. In a double-blind 26 week trial, patients on metformin were treated

with BYDUREON 2 mg once every seven days (weekly), sitagliptin 100 mg daily, or pioglitazone 45 mg daily. In an open-label 26 week trial, patients on metformin or metformin plus sulfonylurea were treated with BYDUREON 2 mg once every seven days (weekly) or optimized insulin glargine. In two open-label 24 to 30 week studies, patients on diet and exercise or metformin, a sulfonylurea, a thiazolidinedione or combination of oral agents were treated with BYDUREON 2 mg once every seven days (weekly) or BYETTA 10 mcg twice daily.

Withdrawals

The incidence of withdrawal due to adverse events was 4.9% (N=45) for BYDUREON-treated patients, 4.9% (N=13) for BYETTA-treated patients and 2.0% (N=23) for other comparator-treated patients in the five comparator-controlled 24-30 week trials. The most common adverse reactions leading to withdrawal for BYDUREON-treated patients were nausea 0.5% (N=5) versus 1.5% (N=4) for BYETTA and 0.3 % (N=3) for other comparators, injection site nodule 0.5% (N=5) versus 0.0% for BYETTA and 0.0% for other comparators, diarrhea 0.3% (N=3) versus 0.4% (N=1) for BYETTA and 0.3% (N=3) for other comparators, injection site reaction 0.2% (N=2) versus 0.0% for BYETTA and 0.0% for other comparators and headache 0.2% (N=2) versus 0.0% for BYETTA and 0.0% for other comparators.

Hypoglycemia

Table 1 summarizes the incidence and rate of minor hypoglycemia in the five comparator-controlled 24-30 week trials of BYDUREON used as monotherapy or as add-on to metformin, a sulfonylurea, a thiazolidinedione or combination of these oral antidiabetic agents. In these trials, an event was classified as minor hypoglycemia if there were symptoms of hypoglycemia with a concomitant glucose <54 mg/dL and the patient was able to self-treat.

**Table 1: Incidence (% of subjects) and Rate (episodes/subject year) of Minor[†] Hypoglycemia in the Monotherapy Trial and in the Combination Therapy Trials**

| **26-Week Monotherapy Trial** | |
|---|---|
| BYDUREON 2 mg (N = 248) | 2.0% (0.05) |
| Sitagliptin 100 mg (N = 163) | 0.0% (0.00) |
| Pioglitazone 45 mg (N = 163) | 0.0% (0.00) |
| Metformin 2000 mg QD (N = 246) | 0.0% (0.00) |
| **26-Week Add-on to Metformin Trial** | |
| BYDUREON 2 mg (N = 160) | 1.3% (0.03) |
| Sitagliptin 100 mg (N = 166) | 3.0% (0.12) |
| Pioglitazone 45 mg (N = 165) | 1.2% (0.03) |

| 26-Week Add-on to Metformin or Metformin + Sulfonylurea Trial | |
|---|---|
| **With Concomitant Sulfonylurea Use (N = 136)** | |
| BYDUREON 2 mg (N = 70) | 20.0% (1.11) |
| Titrated Insulin Glargine (N = 66) | 43.9% (2.87) |
| **Without Concomitant Sulfonylurea Use (N = 320)** | |
| BYDUREON 2 mg (N =163) | 3.7% (0.11) |
| Titrated Insulin Glargine‡ (N = 157) | 19.1% (0.64) |
| **24-Week Monotherapy or add-on to Metformin, a Sulfonylurea, a Thiazolidinedione or Combination of Oral Agents Trial** | |
| **With Concomitant Sulfonylurea Use (N = 74)** | |
| BYDUREON 2 mg (N = 40) | 12.5% (0.72) |
| BYETTA 10 mcg (N = 34) | 11.8% (0.31) |
| **Without Concomitant Sulfonylurea Use (N = 178)** | |
| BYDUREON 2 mg (N = 89) | 0.0% (0.00) |
| BYETTA 10 mcg (N = 89) | 0.0% (0.00) |
| **30-Week Monotherapy or add-on to Metformin, a Sulfonylurea, a Thiazolidinedione or Combination of Oral Agents Trial** | |
| **With Concomitant Sulfonylurea Use (N = 107)** | |
| BYDUREON 2 mg (N =55) | 14.5% (0.55) |
| BYETTA 10 mcg (N = 52) | 15.4% (0.37) |
| **Without Concomitant Sulfonylurea Use (N = 186)** | |
| BYDUREON 2 mg (N = 93) | 0.0% (0.00) |
| BYETTA 10 mcg (N = 93) | 1.1% (0.02) |

Abbreviations: N = The number of intent-to-treat patients
Note: Percentages are based on the number of intent-to-treat patients in each treatment group.
† Reported event that has symptoms consistent with hypoglycemia with a concomitant glucose <54 mg/dL and the patient was able to self-treat.
‡ Insulin glargine was dosed to a target fasting glucose concentration of 72 to 100 mg/dL. The mean dose of insulin glargine was 10 Units/day at baseline and 31 Units/day at endpoint.

There were no reported events of major hypoglycemia in these five comparator-controlled 24-30 week trials. Major hypoglycemia was defined as loss of consciousness, seizure or coma (or other

mental status change consistent with neuroglycopenia in the judgment of the investigator or physician) which resolved after administration of glucagon or glucose or required third party assistance to resolve because of severe impairment in consciousness or behavior. Patients were to have a concomitant glucose <54 mg/dL.

Immunogenicity

Anti-exenatide antibodies were measured at prespecified intervals (4-14 weeks) in all BYDUREON-treated patients (N=918) in the five comparator-controlled studies of BYDUREON. In these five trials, 452 BYDUREON-treated patients (49%) had low titer antibodies (≤125) to exenatide at any time during the trials and 405 BYDUREON-treated patients (45%) had low titer antibodies to exenatide at study endpoint (24-30 weeks). The level of glycemic control in these patients was generally comparable to that observed in the 379 BYDUREON-treated patients (43%) without antibody titers. An additional 107 BYDUREON-treated patients (12%) had higher titer antibodies at endpoint. Of these patients, 50 (6% overall) had an attenuated glycemic response to BYDUREON (<0.7% reduction in $HbA_{1c}$); the remaining 57 (6% overall) had a glycemic response comparable to that of patients without antibodies [see *Warnings and Precautions (5.6)*]. In the 30-week trial in which anti-exenatide antibody assessments were performed at baseline and at 4-week intervals from week 6 to week 30, the mean anti-exenatide antibody titer in the BYDUREON-treated patients peaked at week 6 then declined by 56% from this peak by week 30.

A total of 246 patients with antibodies to exenatide in the BYETTA and BYDUREON 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

BYDUREON

Tables 2 and 3 summarize adverse reactions with an incidence ≥5% reported in the five comparator controlled 24-30 week trials of BYDUREON used as monotherapy or as add-on to metformin, a sulfonylurea, a thiazolidinedione or combination of these oral antidiabetic agents.

**Table 2: Treatment-Emergent Adverse Reactions Reported in ≥5% of BYDUREON-Treated Patients in Monotherapy Trial**

| 26-Week Monotherapy Trial | | | | |
|---|---|---|---|---|
| | **BYDUREON 2 mg N = 248** % | **Sitagliptin 100 mg N = 163** % | **Pioglitazone 45 mg N = 163** % | **Metformin 2000 mg N = 246** % |
| Nausea | 11.3 | 3.7 | 4.3 | 6.9 |
| Diarrhea | 10.9 | 5.5 | 3.7 | 12.6 |
| Injection Site Nodule† | 10.5 | 6.7 | 3.7 | 10.2 |
| Constipation | 8.5 | 2.5 | 1.8 | 3.3 |
| Headache | 8.1 | 9.2 | 8.0 | 12.2 |
| Dyspepsia | 7.3 | 1.8 | 4.9 | 3.3 |

N = The number of intent-to-treat patients.
Note: Percentages are based on the number of intent-to-treat patients in each treatment group.
† Patients in the sitagliptin, pioglitazone and metformin treatment groups received weekly placebo injections.

**Table 3: Treatment-Emergent Adverse Reactions Reported in ≥5% of BYDUREON-Treated Patients in 24-30 week Add-on Combination Therapy Trials**

| 26-Week Add-On to Metformin Trial | | | |
|---|---|---|---|
| | **BYDUREON 2 mg N = 160** % | **Sitagliptin 100 mg N = 166** % | **Pioglitazone 45 mg N = 165** % |
| Nausea | 24.4 | 9.6 | 4.8 |
| Diarrhea | 20.0 | 9.6 | 7.3 |
| Vomiting | 11.3 | 2.4 | 3.0 |
| Headache | 9.4 | 9.0 | 5.5 |
| Constipation | 6.3 | 3.6 | 1.2 |
| Fatigue | 5.6 | 0.6 | 3.0 |
| Dyspepsia | 5.0 | 3.6 | 2.4 |
| Decreased appetite | 5.0 | 1.2 | 0.0 |
| Injection Site Pruritus† | 5.0 | 4.8 | 1.2 |

| 26-Week Add-on to Metformin or Metformin + Sulfonylurea Trial | | |
|---|---|---|
| | **BYDUREON 2 mg N = 233** % | **Insulin glargine Titrated N = 223** % |
| Nausea | 12.9 | 1.3 |
| Headache | 9.9 | 7.6 |
| Diarrhea | 9.4 | 4.0 |
| Injection Site Nodule | 6.0 | 0.0 |

| 30-Week Monotherapy or as Add-on to Metformin, a Sulfonylurea, a Thiazolidinedione or Combination of Oral Agents Trial | | |
|---|---|---|
| | **BYDUREON 2 mg N = 148** % | **BYETTA 10 mcg N = 145** % |
| Nausea | 27.0 | 33.8 |
| Diarrhea | 16.2 | 12.4 |
| Vomiting | 10.8 | 18.6 |
| Injection Site Pruritus | 18.2 | 1.4 |
| Constipation | 10.1 | 6.2 |
| Gastroenteritis viral | 8.8 | 5.5 |
| Gastroesophageal reflux disease | 7.4 | 4.1 |
| Dyspepsia | 7.4 | 2.1 |
| Injection site erythema | 7.4 | 0.0 |
| Fatigue | 6.1 | 3.4 |
| Headache | 6.1 | 4.8 |
| Injection site hematoma | 5.4 | 11.0 |
| **24-Week Monotherapy or as Add-on to Metformin, a Sulfonylurea, a Thiazolidinedione or Combination of Oral Agents Trial** | | |
| | **BYDUREON 2 mg N = 129** % | **BYETTA 10 mcg N = 123** |
| Nausea | 14.0 | 35.0 |
| Diarrhea | 9.3 | 4.1 |
| Injection site erythema | 5.4 | 2.4 |

N = The number of intent-to-treat patients.
Note: Percentages are based on the number of intent-to-treat patients in each treatment group.
† Patients in the sitagliptin, pioglitazone and metformin treatment groups received weekly placebo injections.

Nausea was the most common adverse reaction associated with initiation of treatment with BYDUREON, and usually decreased over time.

Injection Site Reactions

In the five comparator-controlled 24-30 week trials, injection site reactions were observed more frequently in patients treated with BYDUREON (17.1%) than in patients treated with BYETTA (12.7%), titrated insulin glargine (1.8%) or those patients who received placebo injections (sitagliptin (10.6%), pioglitazone (6.4%), and metformin (13.0%) treatment groups). These reactions for patients treated with BYDUREON were more commonly observed in antibody-positive patients (14.2%) compared with antibody-negative patients (3.1%), with a greater incidence in those with higher titer antibodies [see *Warnings and Precautions (5.6)*]. Incidence of injection site reactions for patients treated with BYETTA was similar for antibody positive patients (5.8%) and antibody negative patients (7.0%). One percent of patients treated with BYDUREON withdrew due to injection site adverse reactions (injection site mass, injection site nodule, injection site pruritus, and injection site reaction).

Small, asymptomatic subcutaneous injection site nodules are seen with the use of BYDUREON. In a separate 15-week study in which information on nodules were collected and analyzed, 24 out of 31 subjects (77%) experienced at least one injection site nodule during treatment; 2 subjects (6.5%) reported accompanying localized symptoms. The mean duration of events was 27 days. The formation of nodules is consistent with the known properties of the microspheres used in BYDUREON.

BYETTA

In three 30-week controlled trials of BYETTA (N=963) add-on to metformin and/or sulfonylurea, adverse reactions (excluding hypoglycemia) with an incidence of ≥1% and reported more frequently than with placebo included nausea (44% BYETTA, 18% placebo), vomiting (13% BYETTA, 4% placebo), diarrhea (13% BYETTA, 6% placebo), feeling jittery (9% BYETTA, 4% placebo), dizziness (9% BYETTA, 6% placebo), headache (9% BYETTA, 6% placebo), dyspepsia (6% BYETTA, 3% placebo), asthenia (4% BYETTA, 2% placebo), gastroesophageal reflux (3% BYETTA, 1% placebo), hyperhidrosis (3% BYETTA, 1% placebo) and decreased appetite (1% BYETTA, <1% placebo). Similar types of adverse reactions were observed in 24-week and 16-week controlled trials of BYETTA used as monotherapy or as add-on to a thiazolidinedione, with or without metformin, respectively.

### 6.2 Post-Marketing Experience

BYETTA

The following additional adverse reactions have been reported during post-approval use of BYETTA. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Allergy/Hypersensitivity: injection-site reactions, generalized pruritus and/or urticaria, macular or papular rash, angioedema; anaphylactic reaction [see *Warnings and Precautions (5.7)*].

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

Gastrointestinal: nausea, vomiting, and/or diarrhea resulting in dehydration; abdominal distension, abdominal pain, eructation, constipation, flatulence, acute pancreatitis, hemorrhagic and necrotizing pancreatitis sometimes resulting in death [see *Limitations of Use (1.2) and Warnings and Precautions (5.2)*].

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

## 7 DRUG INTERACTIONS

### 7.1 Orally Administered Drugs

Exenatide slows gastric emptying. Therefore, BYDUREON has the potential to reduce the rate of absorption of orally administered drugs. Use caution when administering oral medications with BYDUREON [see *Clinical Pharmacology (12.3)*].

In patients with type 2 diabetes, BYDUREON did not affect the absorption of orally administered acetaminophen to any clinically relevant degree.

### 7.2 Warfarin

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

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of BYDUREON use in pregnant women. In rats, exenatide extended-release administered during the major period of organogenesis reduced fetal growth and produced skeletal ossification deficits in association with maternal effects; exenatide extended-release was not teratogenic in rats. In animal developmental studies, exenatide, the active ingredient of BYDUREON, caused cleft palate, irregular skeletal ossification and an increased number of neonatal deaths. BYDUREON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Fetuses from pregnant rats given subcutaneous doses of exenatide extended-release at 0.3, 1 or 3 mg/kg on gestation days 6, 9, 12 and 15 demonstrated reduced fetal growth at all doses and produced skeletal ossification deficits at 1 and 3 mg/kg in association with maternal effects (decreased food intake and decreased body weight gain). There was no evidence of malformations. Doses of 0.3, 1 and 3 mg/kg correspond to systemic exposures of 3, 7 and 17-

times, respectively, the human exposure resulting from the recommended dose of 2 mg/week, based on area under the time-concentration curve (AUC) [see *Nonclinical Toxicology (13.3)*].

Female mice given subcutaneous doses of exenatide, the active ingredient of BYDUREON, at 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 148 times the human exposure resulting from the recommended dose of 2 mg/week, based on AUC [see *Nonclinical Toxicology (13.3)*].

In developmental toxicity studies, pregnant animals received exenatide, the active ingredient of BYDUREON, subcutaneously during organogenesis. Specifically, fetuses from pregnant rabbits given subcutaneous doses of exenatide at 0.2, 2, 22, 156, or 260 mcg/kg/day from gestation day 6 through 18 experienced irregular skeletal ossifications from exposures 4 times the human exposure resulting from the recommended dose of 2 mg/week, based on AUC. Fetuses from pregnant mice given subcutaneous doses of exenatide at 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 that is equivalent to the human exposure resulting from the recommended dose of 2 mg/week, based on AUC [see *Nonclinical Toxicology (13.3)*].

Lactating mice given subcutaneous doses of exenatide, the active ingredient of BYDUREON, at 6, 68, or 760 mcg/kg/day from gestation day 6 through lactation day 20 (weaning), experienced an increased number of neonatal deaths. Deaths were observed on postpartum days 2-4 in dams given 6 mcg/kg/day, a systemic exposure that is equivalent to the human exposure resulting from the recommended dose of 2 mg/week, based on AUC [see *Nonclinical Toxicology (13.3)*].

Pregnancy Registry

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

### 8.3 Nursing Mothers

Exenatide is present in the milk of lactating mice at concentrations less than or equal to 2.5% of the concentration in maternal plasma following subcutaneous dosing. It is not known whether exenatide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for exenatide extended-release in animal studies, a decision should be made whether to discontinue nursing or to discontinue BYDUREON, taking into account the importance of the drug to the mother.

### 8.4 Pediatric Use

Safety and effectiveness of BYDUREON have not been established in pediatric patients. BYDUREON is not recommended for use in pediatric patients.

### 8.5 Geriatric Use

In the five comparator-controlled 24-30 week trials, BYDUREON was studied in 132 patients (16.6%) who were at least 65 years old and 20 patients who were at least 75 years old. No differences in safety (N = 152) and efficacy (N = 52) were observed between these patients and younger patients, but the small sample size for patients ≥75 years old limits conclusions.

In separate trials, BYETTA was studied in 282 patients at least 65 years old and in 16 patients at least 75 years old. No differences in safety and efficacy were observed between these patients and younger patients, but the small sample size for patients ≥75 years old limits conclusions.

Because elderly patients are more likely to have decreased renal function, use caution when initiating BYDUREON in the elderly.

### 8.6 Renal Impairment

BYDUREON 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. Use BYDUREON with caution in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min) [see *Warnings and Precautions (5.4) and 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 impairment is not expected to affect blood concentrations of exenatide [see *Clinical Pharmacology (12.3)*].

## 10 OVERDOSAGE

There were no reports of overdose in the five comparator-controlled 24-30 week trials of BYDUREON. Effects of overdoses with BYETTA in clinical studies included severe nausea, severe vomiting, and rapidly declining blood glucose concentrations, including severe hypoglycemia requiring parenteral glucose administration. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

## 11 DESCRIPTION

BYDUREON (exenatide extended-release for injectable suspension) is supplied as a sterile powder to be suspended in the diluent included in the single-dose tray and administered by subcutaneous injection. Exenatide is a 39-amino acid synthetic peptide amide with an empirical formula of $C_{184}H_{282}N_{50}O_{60}S$ and a 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-$NH_2$

BYDUREON is a white to off-white powder that is available in a dosage strength of 2 mg exenatide per vial. Exenatide is incorporated in an extended release microsphere formulation containing the 50:50 poly(D,L-lactide-co-glycolide) polymer (37.2 mg per vial) along with sucrose (0.8 mg per vial). The powder must be suspended in the diluent prior to injection. The diluent is provided in a prefilled syringe. Each prefilled syringe delivers 0.65 mL of the diluent as a clear, colorless to pale yellow solution composed of carboxymethylcellulose sodium (23 mg), polysorbate 20 (0.77 mg), sodium phosphate monobasic monohydrate (0.74 mg), sodium phosphate dibasic heptahydrate (0.62 mg), sodium chloride (5.0 mg), and water for injection.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

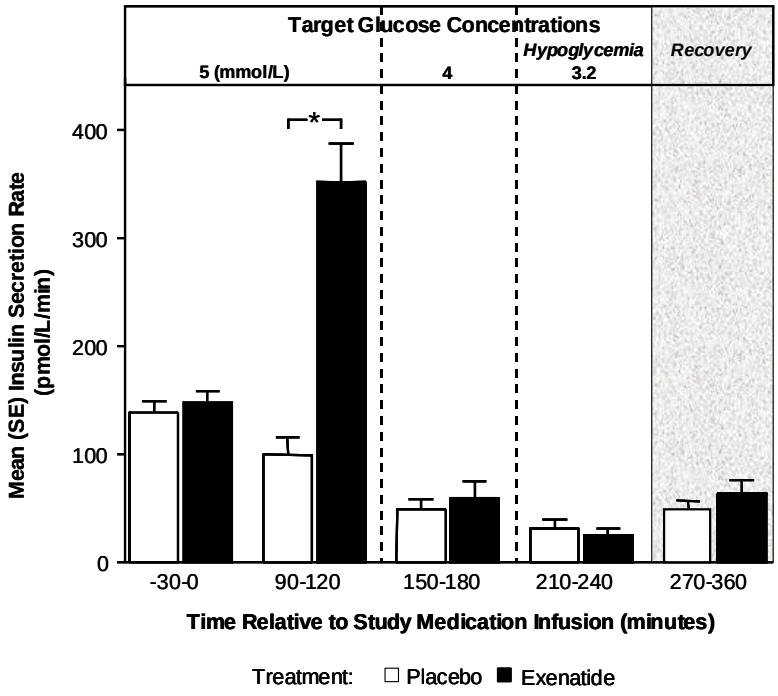
Incretins, such as glucagon-like peptide-1 (GLP-1), enhance glucose-dependent insulin secretion and exhibit other antihyperglycemic actions following their release into the circulation from the gut. BYDUREON is a GLP-1 receptor agonist that enhances glucose-dependent insulin secretion by the pancreatic 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 is a GLP-1 receptor agonist that has been shown to bind and activate the human GLP-1 receptor *in vitro*. This leads to an increase in both glucose-dependent synthesis of insulin and *in vivo* secretion of insulin from pancreatic beta cells, by mechanisms involving cyclic AMP and/or other intracellular signaling pathways. Exenatide promotes insulin release from pancreatic beta cells in the presence of elevated glucose concentrations.

### 12.2 Pharmacodynamics

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

Glucose-dependent insulin secretion: The effect of exenatide infusion on glucose-dependent insulin secretion rates (ISR) was investigated in 11 healthy subjects. In these healthy subjects, on average, the ISR response was glucose-dependent (Figure 1). Exenatide did not impair the normal glucagon response to hypoglycemia.




SE = standard error.
Notes: 5 mmol = 90mg/dL, 4 mmol/L = 72 mg/dL, 3.2 mmol/L = 58 mg/dL; Study medication infusion was started at time = 0 min.
Statistical assessments were for the last 30 min of each glycemic step, during which the target glucose concentrations were maintained.
*p <0.05, exenatide treatment relative to placebo.

**Figure 1: Mean (SE) Insulin Secretion Rates During Infusion of Exenatide or Placebo by Treatment, Time, and Glycemic Condition in Healthy Subjects**

Glucagon secretion: In patients with type 2 diabetes, exenatide moderates glucagon secretion and lowers serum glucagon concentrations during periods of hyperglycemia.

Gastric emptying: Exenatide slows gastric emptying, thereby reducing the rate at which postprandial glucose appears in the circulation.

Food intake: Infusion of exenatide in eight healthy subjects resulted in a 19% decrease in caloric intake following an ad libitum meal.

Fasting and Postprandial Glucose

In a separate 15-week controlled study, where fasting glucose was assessed on a weekly basis, BYDUREON treatment resulted in a mean reduction in fasting glucose of 17 mg/dL following two weeks of therapy with full effect on fasting glucose not observed until approximately 9 weeks.

In a 30-week controlled study of exenatide extended-release compared to BYETTA, postprandial glucose levels were measured during a mixed meal tolerance test in a subset of patients with type

2 diabetes mellitus. Following treatment for 14 weeks, when steady-state concentrations had been achieved (approximately 280 to 310 pg/mL), the LS mean change from baseline was significantly greater with BYETTA (-126 mg/dL) than exenatide extended-release (-96 mg/dL).

Cardiac Electrophysiology

The effect of exenatide at therapeutic (253 pg/mL) and supratherapeutic (627 pg/mL) concentrations, following an intravenous infusion on QTc interval was evaluated in a randomized, placebo- and active-controlled (moxifloxacin 400 mg) three-period crossover thorough QT study in 74 healthy subjects. The upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on population correction method (QTcP) was below 10 ms. Therefore, exenatide was not associated with prolongation of the QTc interval at therapeutic and supratherapeutic concentrations.

### 12.3 Pharmacokinetics

Absorption

Following a single dose of BYDUREON, exenatide is released from the microspheres over approximately 10 weeks. There is an initial period of release of surface-bound exenatide followed by a gradual release of exenatide from the microspheres, which results in two subsequent peaks of exenatide in plasma at around week 2 and week 6-7, respectively, representing the hydration and erosion of the microspheres.

Following initiation of once every seven days (weekly) administration of 2 mg BYDUREON, gradual increase in the plasma exenatide concentration is observed over 6 to 7 weeks. After 6 to 7 weeks, mean exenatide concentrations of approximately 300 pg/mL were maintained over once every seven days (weekly) dosing intervals indicating that steady-state was achieved.

Distribution

The mean apparent volume of distribution of exenatide following subcutaneous administration of a single dose of BYETTA is 28.3 L and is expected to remain unchanged for BYDUREON.

Metabolism and Elimination

Nonclinical studies have shown that exenatide is predominantly eliminated by glomerular filtration with subsequent proteolytic degradation. The mean apparent clearance of exenatide in humans is 9.1 L/h and is independent of the dose. Approximately 10 weeks after discontinuation of BYDUREON therapy, plasma exenatide concentrations generally fall below the minimal detectable concentration of 10 pg/mL.

Drug Interactions

*Acetaminophen*

When 1000 mg acetaminophen tablets were administered, either with or without a meal, following 14 weeks of BYDUREON therapy (2 mg weekly), no significant changes in acetaminophen AUC were observed compared to the control period. Acetaminophen $C_{max}$ decreased by 16% (fasting) and 5% (fed) and $T_{max}$ was increased from approximately 1 hour in the control period to 1.4 hours (fasting) and 1.3 hours (fed).

The following drug interactions have been studied using BYETTA. The potential for drug-drug interaction with BYDUREON is expected to be similar to that of BYETTA.

*Digoxin*

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

*Lisinopril*

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

*Oral Contraceptives*

The effect of BYETTA (10 mcg twice-daily) 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 [see *Drug Interactions (7.1)*].

*Warfarin*

Administration of warfarin (25 mg) 35 minutes after repeated doses of BYETTA (5 mcg twice-daily on days 1-2 and 10 mcg twice-daily 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*

BYDUREON has not been studied in patients with severe renal impairment (creatinine clearance <30 mL/min) or end-stage renal disease receiving dialysis. Population pharmacokinetic analysis of renally-impaired patients receiving 2 mg BYDUREON indicate that there is a 62% and 33% increase in exposure in moderate (N=10) and mild (N=56) renally-impaired patients, respectively as compared to patients with normal renal function (N=84).

In a study of BYETTA in subjects with end-stage renal disease receiving dialysis, mean exenatide exposure increased by 3.4-fold compared to that of subjects with normal renal function [see *Use in Specific Populations (8.6)*].

*Hepatic Impairment*

BYDUREON has not been studied in patients with 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 suggests that gender does not influence the steady-state concentrations of exenatide following BYDUREON administration.

*Race*

There were no apparent differences in steady-state concentrations of exenatide among Caucasian, Hispanic, and Black patients following BYDUREON administration.

*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.

*Pediatric*

BYDUREON has not been studied in pediatric patients [see *Use in Specific Populations (8.4)*]

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 104-week carcinogenicity study was conducted with exenatide extended-release in male and female rats at doses of 0.3, 1.0 and 3.0 mg/kg (2, 9, and 26-times human systemic exposure based on AUC, respectively) administered by subcutaneous injection every other week. A statistically significant increase in thyroid C-cell tumor incidence was observed in both males and females. The incidence of C-cell adenomas was statistically significantly increased at all doses (27% to 31%) in females and at 1.0 and 3.0 mg/kg (46% and 47%, respectively) in males compared with the control group (13% for males and 7% for females). A statistically significantly higher incidence of C-cell carcinomas occurred in the high dose group females (6%), while numerically higher incidences of 3%, 7%, and 4% (non-statistically significant versus controls) were noted in the low, mid, and high dose group males compared with the control group (0% for both males and females). An increase in benign fibromas was seen in the skin subcutis at injection sites of males given 3 mg/kg. No treatment-related injection site fibrosarcomas were observed at any dose. The human relevance of these findings is currently unknown.

A 104-week carcinogenicity study was conducted with exenatide, the active ingredient in BYDUREON, in male and female rats at doses of 18, 70, or 250 mcg/kg/day (3, 6, and 27 times human systemic exposure based on AUC, respectively) administered by once daily bolus subcutaneous 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.

In a 104-week carcinogenicity study with exenatide, the active ingredient in BYDUREON, in male and female mice at doses of 18, 70, or 250 mcg/kg/day administered by once daily bolus subcutaneous injection, no evidence of tumors was observed at doses up to 250 mcg/kg/day, a systemic exposure up to 16 times the human exposure resulting from the recommended dose of 2 mg/week, based on AUC. The carcinogenicity of exenatide extended-release has not been evaluated in mice.

BYDUREON and exenatide, the active ingredient in BYDUREON, were 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 exenatide, the active ingredient in BYDUREON, at twice-daily subcutaneous 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 148 times the human exposure resulting from the recommended dose of 2 mg/week, based on AUC.

### 13.3 Reproductive and Developmental Toxicology

A rat embryo-fetal developmental toxicity study was conducted with exenatide extended-release. A complete reproductive and developmental toxicity program was conducted with exenatide, the active ingredient in BYDUREON.

Fetuses from pregnant rats given subcutaneous doses of exenatide extended-release at 0.3, 1 or 3 mg/kg on gestation days 6, 9, 12 and 15 demonstrated reduced fetal growth at all doses and produced skeletal ossification deficits at 1 and 3 mg/kg in association with maternal effects (decreased food intake and decreased body weight gain). There was no evidence of malformations. Doses of 0.3, 1 and 3 mg/kg correspond to systemic exposures of 3, 7 and 17-times, respectively, the human exposure resulting from the recommended dose of 2 mg/week, based on AUC.

In female mice given twice-daily subcutaneous doses of 6, 68, or 760 mcg/kg/day exenatide, the active ingredient in BYDUREON, 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 148 times the human exposure resulting from the maximum recommended dose of 2 mg/day, based on AUC.

In pregnant mice given twice-daily subcutaneous doses of 6, 68, 460, or 760 mcg/kg/day exenatide, the active ingredient in BYDUREON, 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 equal to the human exposure resulting from the maximum recommended dose of 2 mg/day, based on AUC.

In pregnant rabbits given twice-daily subcutaneous doses of 0.2, 2, 22, 156, or 260 mcg/kg/day exenatide, the active ingredient in BYDUREON, from gestation day 6 through 18 (organogenesis), irregular fetal skeletal ossifications were observed at 2 mcg/kg/day, a systemic exposure 4 times the human exposure resulting from the maximum recommended dose of 2 mg/day, based on AUC.

In pregnant mice given twice-daily subcutaneous doses of 6, 68, or 760 mcg/kg/day exenatide, the active ingredient in BYDUREON, 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 equal to the human exposure resulting from the maximum recommended dose of 2 mg/day, based on AUC.

## 14 CLINICAL STUDIES

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

### 14.1 24-Week Comparator-Controlled Study

A 24-week, randomized, open-label trial was conducted to compare the safety and efficacy of BYDUREON to BYETTA in patients with type 2 diabetes and inadequate glycemic control with diet and exercise alone or with oral antidiabetic therapy, including metformin, a sulfonylurea, a thiazolidinedione, or combination of two of those therapies.

A total of 252 patients were studied: 149 (59%) were Caucasian, 78 (31%) were Hispanic, 15 (6%) were Black and 10 (4%) were Asian. Patients were treated with diet and exercise alone (19%), a single oral antidiabetic agent (47%), or combination therapy of oral antidiabetic agents (35%). The mean baseline $HbA_{1c}$ was 8.4%. Patients were randomly assigned to receive BYDUREON 2 mg once every seven days (weekly) or BYETTA (10 mcg twice-daily), in addition to existing oral antidiabetic agents. Patients assigned to BYETTA initiated treatment with 5 mcg twice-daily then increased the dose to 10 mcg twice-daily after 4 weeks.

The primary endpoint was change in $HbA_{1c}$ from baseline to Week 24 (or the last value at time of early discontinuation). Change in body weight was a secondary endpoint. Twenty-four week study results are summarized in Table 4.

**Table 4: Results of 24-week Trial of BYDUREON**

| | BYDUREON 2 mg | BYETTA 10 mcg |
|---|---|---|
| Intent-to-Treat Population (N) | 129 | 123 |
| $HbA_{1c}$ (%) | | |
| Mean Baseline | 8.5 | 8.4 |
| Mean Change at Week 24† | -1.6 | -0.9 |
| Difference from BYETTA† [95% CI] | -0.7 [-0.9, -0.4]¶ | |
| Percentage Achieving $HbA_{1c}$ <7% at Week 24 (%) | 58¶ | 30 |
| Fasting Plasma Glucose (mg/dL) | | |
| Mean Baseline | 173 | 168 |
| Mean Change at Week 24 | -25 | -5 |
| Difference from BYETTA† [95% CI] | -20 [-31, -10]¶ | |

N = The number of patients in each treatment group.
Note: Mean Change is Least Squares Mean Change
* BYETTA 5 mcg twice daily before the morning and evening meals for 4 weeks followed by 10 mcg twice daily for 20 weeks.
† Least squares means are adjusted for baseline $HbA_{1c}$ strata, background antihyperglycemic therapy, and baseline value of the dependent variable (if applicable).
¶ p <0.001, treatment vs. comparator.

Reductions from mean baseline (97/94 kg) in body weight were observed in both BYDUREON (-2.3 kg) and BYETTA (-1.4 kg) treatment groups.

BYDUREON did not have adverse effects on blood pressure. An LS mean increase from baseline (74 beats per minute) in heart rate of 4 beats per minute was observed with BYDUREON treatment and 2 beats per minute with BYETTA treatment. The long term effects of the increase in pulse rate have not been established [see *Warnings and Precautions (5.8)*].

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

BYDUREON (exenatide extended-release for injectable suspension) for once every seven days (weekly) subcutaneous administration is supplied in cartons of 4 single-dose trays for use (NDC 66780-219-04).

Each single-dose tray contains:

- One vial containing 2 mg exenatide (as a white to off-white powder)
- One prefilled syringe delivering 0.65 mL diluent
- One vial connector
- Two custom needles (23G, 5/16") specific to this delivery system (one is a spare needle)

Do **not** substitute needles or any other components in the tray.

### 16.2 Storage and Handling

- BYDUREON should be stored in the refrigerator at 36℉to 46℉ (2℃ to 8℃), up to the expiration date or until preparing for use. BYDUREON should not be used past the expiration date. The expiration date can be found on the carton and the cover of the single-dose tray.
- Do not freeze the BYDUREON tray. Do not use BYDUREON if it has been frozen. Protect from light.
- Each single-dose tray can be kept at room temperature not to exceed 77°F (25℃) [see USP Controlled Room Temperature] for no more than a total of 4 weeks, if needed.
- Use the diluent only if it is clear and free of particulate matter.
- After suspension, the mixture should be white to off-white and cloudy.
- BYDUREON must be administered immediately after the exenatide powder is suspended in the diluent and transferred to the syringe.
- Use a puncture-resistant container to discard the syringe with the needle still attached. Do not reuse or share needles or syringes.
- Keep out of the reach of children.

## 17 PATIENT COUNSELING INFORMATION

Inform patients about the potential risks and benefits of BYDUREON and of alternative modes of therapy. Also inform patients about the importance of diabetes self-management practices, such as regular physical activity, adhering to meal planning, periodic blood glucose monitoring and $HbA_{1c}$ testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications.

### 17.1 Risk of Thyroid C-cell Tumors

Inform patients that exenatide extended-release causes benign and malignant thyroid C-cell tumors in rats and that the human relevance of this finding is unknown. Counsel patients to report symptoms of thyroid tumors (e.g., a lump in the neck, hoarseness, dysphagia or dyspnea) [see *Warnings and Precautions (5.1)*].

### 17.2 Risk of Pancreatitis

Inform patients treated with BYDUREON of the potential risk for pancreatitis. Explain 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 BYDUREON and contact their healthcare provider if persistent severe abdominal pain occurs [see *Warnings and Precautions (5.2)*].

### 17.3 Risk of Hypoglycemia

The risk of hypoglycemia is increased when BYDUREON is used in combination with an agent that induces hypoglycemia, such as a sulfonylurea [see *Warnings and Precautions (5.3)*]. Explain the symptoms, treatment, and conditions that predispose to the development of hypoglycemia. While the patient's usual instructions for hypoglycemia management do not need to be changed, these instructions should be reviewed and reinforced when initiating BYDUREON therapy, particularly when concomitantly administered with a sulfonylurea [see *Warnings and Precautions (5.3)*].

### 17.4 Risk of Renal Impairment

Inform patients treated with BYDUREON of the potential risk for worsening renal function and explain the associated signs and symptoms of renal impairment, as well as the possibility of dialysis as a medical intervention if renal failure occurs [see *Warnings and Precautions (5.4)*].

### 17.5 Risk of Hypersensitivity Reactions

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

### 17.6 Use in Pregnancy

Advise patients to inform their healthcare provider if they are pregnant or intend to become pregnant [see *Use in Specific Populations (8.1)*].

### 17.7 Instructions

Each dose of BYDUREON should be administered as a subcutaneous injection at any time on the dosing day, with or without meals. Patients should be informed that the day of once every seven days (weekly) administration can be changed if necessary as long as the last dose was administered 3 or more days before. If a dose is missed, it should be administered as soon as noticed, provided the next regularly scheduled dose is due at least three days later. Thereafter, patients can resume their usual once every seven days (weekly) dosing schedule. If a dose is missed and the next regularly scheduled dose is due in one or two days, the patient should not administer the missed dose and instead resume BYDUREON with the next regularly scheduled dose. [see *Dosage and Administration (2.1)*].

Counsel patients that they should never share a BYDUREON single-dose tray with another person, even if the needle is changed. Sharing of the single-dose trays or needles between patients may pose a risk of transmission of infection.

If a patient is currently taking BYETTA, it should be discontinued upon starting BYDUREON. Patients formerly on BYETTA who start BYDUREON may experience transient elevations in

blood glucose concentrations, which generally improve within the first two weeks after initiation of therapy [see *Dosage and Administration (2.3)* and *Clinical Studies (14.2)*].

Treatment with BYDUREON may also result in nausea, particularly upon initiation of therapy [see *Adverse Reactions (6)*].

Inform patients about the importance of proper storage of BYDUREON, injection technique, and dosing [see *Dosage and Administration (2)* and *How Supplied/Storage and Handling (16)*].

The patient should read the BYDUREON Medication Guide and the Instructions for Use before starting BYDUREON therapy and review them each time the prescription is refilled.

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Literature Revised January 2012

BYDUREON is a trademark of Amylin Pharmaceuticals, Inc.

U.S. Patent Nos. 5,424,286, 6,858,576, 6,872,700, 6,956,026, 7,456,254, 6,479,065, 6,495,164, 6,667,061, 6,824,822, 7,223,440, 7,563,871 and 7,612,176.

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