

Antidiabetic Agents

Charles Ruchalski, PharmD, BCPS

BIGUANIDES

Introduction

For newly diagnosed patients with type 2 diabetes, the biguanide metformin is the drug of choice for initial therapy, adjunctive to diet and exercise. Metformin is contraindicated in certain patients to prevent lactic acidosis, a rare but serious side effect (approximately 0.03 cases per 1,000 patient-years, with approximately 0.015 fatal cases per 1,000 patient-years). It is often used in combination with other oral antidiabetic agents and/or insulin in patients who do not reach glycemic goals on those therapies. HbA1c reductions with metformin are generally between 1.5% and 2%.

Mechanism of Action for the Drug Class

Biguanides improve glucose tolerance by lowering both basal and postprandial plasma glucose. They decrease hepatic glucose production and intestinal absorption of glucose and improve insulin sensitivity by increasing peripheral glucose uptake and utilization through the activation of adenosine monophosphate-activated protein kinase (AMPK).

Metformin

Brand Names

Fortamet, Glucophage, Glucophage XR, Glumetza, Riomet

Generic Names

Metformin, metformin extended-release

Rx Only

Dosage Forms

Tablet, extended-release tablet, oral solution

Usage

Type 2 diabetes mellitus,* polycystic ovary syndrome, antipsychotic-induced weight gain

Pregnancy Category B

Dosing

- Initial dose: 500 mg twice daily with morning and evening meals, 850 mg once daily with a meal, or 500 mg extended-release once daily with a meal
- Maintenance dose: 2,000–2,550 mg daily in divided doses or 2,000 mg extended-release once daily (2,500 mg daily with Fortamet)
- Renal dosage adjustment: Not recommended in patients with renal dysfunction (see Contraindications below)

Adverse Reactions: Most Common

Diarrhea, vomiting, dyspepsia, flatulence, metallic taste, weight loss

Adverse Reactions: Rare/Severe/Important

Lactic acidosis, megaloblastic anemia

Major Drug Interactions

Drugs Affecting Metformin

- Alcohol potentiates the effect on lactate metabolism
- Cimetidine increases plasma concentrations (use alternative H₂ blocker)
- Iodinated contrast media can lead to acute renal failure and metformin toxicity

Contraindications

Renal disease (males: SrCr \geq 1.5 mg/dL; females: SrCr \geq 1.4 mg/dL), decompensated heart failure, acute or chronic metabolic acidosis, active liver disease

Counseling Points

Discontinue immediately and promptly notify healthcare practitioner if unexplained myalgia, malaise, hyperventilation, or unusual somnolence occur because these are symptoms of lactic acidosis

Key Points

Temporarily withhold in patients undergoing radiologic procedures involving the parenteral administration of iodinated contrast media because it may result in acute alteration of renal function. Do not restart for at least 48 hours or until renal function appears adequate.

Throughout the text, an asterisk () is used to indicate the most common uses of a drug.

DI-PEPTIDYL PEPTIDASE-4 INHIBITORS

Introduction

Di-peptidyl peptidase-4 inhibitors inhibit the breakdown of active GLP-1 to inactive GLP-1 through the inhibition of the enzyme DPP-4. Active GLP-1 is released from the alpha cells of the pancreas in response to food intake. GLP-1 plays a role in regulating blood glucose by increasing the secretion of insulin from the pancreas in a glucose-dependent manner. GLP-1 also helps regulate glucagon secretion and decreases hepatic glucose production. These drugs are used as monotherapy as an adjunct to diet and exercise or in combination with other oral antidiabetic agents in patients who do not reach glycemic goals. Average HbA1c reductions are between 0.7% and 1%.

Mechanism of Action for the Drug Class

Inhibition of DPP-4 enhances the activity of active GLP-1, thus increasing glucose-dependent insulin secretion and decreasing levels of circulating glucagon and hepatic glucose production

Members of the Drug Class

In this section: Sitagliptin

Others: Linagliptin, saxagliptin

● Sitagliptin

Brand Name

Januvia

Generic Name

Sitagliptin

Rx Only

Dosage Form

Tablet

Usage

Type 2 diabetes mellitus

Pregnancy Category B

Dosing

- 100 mg once daily with or without food
- Renal dosage adjustment:
 - 50 mg once daily: CrCl \geq 30 to $<$ 50 mL/min
 - 25 mg once daily: CrCl $<$ 30 mL/min

Adverse Reactions: Most Common

Nasopharyngitis, nausea, diarrhea, vomiting, hypoglycemia, weight loss

Adverse Reactions: Rare/Severe/Important

Acute pancreatitis, rash (Stevens-Johnson syndrome)

Major Drug Interactions

Sitagliptin's Effect on Other Drugs

Digoxin: Increased levels

Counseling Points

Discontinue immediately and promptly notify healthcare practitioner if unexplained persistent nausea and vomiting occur (signs of acute pancreatitis)

INSULIN

Introduction

The hormone insulin is endogenously released from the beta cells of the pancreas. Patients with type 1 diabetes mellitus have an absolute deficiency of insulin; patients with type 2 diabetes mellitus may also have decreased production of endogenous insulin. Type 1 diabetics require insulin as a lifelong treatment. Insulin is commonly used in type 2 diabetic patients as either adjunct therapy to oral antidiabetic agents or as monotherapy as the disease progresses. Various substitutions on the insulin molecule and other modifications have led to multiple types of insulin. They are characterized and administered based on their pharmacodynamic and pharmacokinetic characteristics, such as onset, peak, and duration of action. The various

types of insulin are classified as rapid-acting, short-acting, intermediate-acting, or long-acting insulin.

Mechanism of Action for the Drug Class

Insulin lowers blood glucose by stimulating peripheral glucose uptake, especially in skeletal muscle and fat, and by inhibiting hepatic glucose production

Usage for the Drug Class

Type 1 diabetes mellitus,* type 2 diabetes mellitus,* hyperkalemia, diabetic ketoacidosis*/diabetic coma

Dosing for the Drug Class

- Initial dose: 0.5–1 unit/kg per day SUB-Q (high interpatient variability)

- Maintenance dose: Adjust doses to achieve premeal blood glucose levels of 70–130 mg/dL
- Renal dosage adjustment:
 - CrCl 10–50 mL/min: Administer 75% of normal dose
 - CrCl < 10 mL/min: Administer 25–50% of normal dose; monitor closely

Adverse Reactions for the Drug Class: Most Common

Hypoglycemia (anxiety, blurred vision, palpitations, shakiness, slurred speech, sweating), weight gain

Adverse Reactions for the Drug Class: Rare/Severe/Important

Severe hypoglycemia (seizure/coma), edema, lipatrophy or lipohypertrophy at injection site

Major Drug Interactions for the Drug Class

Drugs Affecting Insulin (Decreased Hypoglycemic Effect)

- Acetazolamide
- Diuretics
- Oral contraceptives
- Albuterol
- Epinephrine
- Phenothiazines
- Asparaginase
- Estrogens
- Terbutaline
- Corticosteroids
- HIV antivirals
- Thyroid hormones
- Diltiazem
- Lithium

Drugs Affecting Insulin (Increased Hypoglycemic Effect)

- Alcohol
- Fluoxetine
- Anabolic steroids
- Lithium
- Beta blockers
- Sulfonamides
- Clonidine

Contraindications for the Drug Class

Severe hypoglycemia; allergy or sensitivity to any ingredient of the product

Essential Monitoring Parameters for the Drug Class

Fasting blood sugar (70–130 mg/dL)

Counseling Points for the Drug Class

- Follow a prescribed diet and exercise regularly
- Rotate injection sites to prevent lipodystrophy
- Insulin requirements may change during times of illness, vomiting, fever, and emotional stress
- Wear diabetic identification

- Insulin stored at room temperature will be less painful to inject compared to refrigerator-stored insulin
- Mild episodes of hypoglycemia may be treated with oral glucose or carbohydrates

Members of the Drug Class

In this section: Insulin glulisine, insulin lispro, insulin NPH, insulin (R), insulin glargine, insulin detemir, insulin aspart
Various mixtures also are available

⦿ Insulin Glulisine

Brand Names

Apidra, Apidra SoloStar

Generic Name

Insulin glulisine (rapid-acting insulin)

Rx Only

Dosage Form

Injection 100 units/mL (10 mL vial and 3 mL cartridge for pen use)

Pregnancy Category C

Dosing

- Administer SUB-Q 15 minutes before or immediately after starting a meal
- May be administered by continuous subcutaneous infusion (insulin pump)

⦿ Insulin Lispro

Brand Names

Humalog, Humalog KwikPen

Generic Name

Insulin lispro (rapid-acting insulin)

Rx Only

Dosage Forms

Injection 100 units/mL (10 mL vial and 3 mL cartridge for pen use)

Pregnancy Category B

Dosing

- Administer SUB-Q 15 minutes before or immediately after starting a meal
- May be administered by continuous subcutaneous infusion (insulin pump)

⦿ Insulin NPH

Brand Names

Humulin N, Novolin N

Generic Name

Insulin NPH (intermediate-acting insulin)

OTC

Dosage Forms

Injection, suspension, 100 units/mL (10 mL vial and 3 mL cartridge for pen use)

Pregnancy Category B

Dosing

- NPH should only be mixed with regular insulin
- Draw regular insulin into the syringe first, then add the NPH insulin to the syringe

⦿ Insulin Regular

Brand Names

Humulin R, Novolin R

Generic Name

Insulin regular (short-acting insulin)

OTC

Dosage Forms

Injection 100 units/mL (10 mL vial and 3 mL cartridge for pen use)

Pregnancy Category B

Dosing

- Administer SUB-Q 30 minutes before a meal
- May be administered by continuous subcutaneous infusion (insulin pump)
- Caution: A concentrated 20 mL vial containing 500 units/mL is available

⦿ 70% NPH and 30% Regular Insulin Mixture

Brand Names

Humulin 70/30, Novolin 70/30

Generic Name

70% NPH and 30% regular insulin mixture

OTC

Dosage Forms

Injection, suspension, 100 units/mL (10 mL vial and 3 mL cartridge for pen use)

Pregnancy Category B

Brand Name

Humulin 50/50

⦿ 50% NPH and 50% Regular Insulin Mixture

Generic Name

50% NPH and 50% regular insulin mixture

OTC

Dosage Forms

Injection, suspension, 100 units/mL (10 mL vial and 3 mL cartridge for pen use)

Pregnancy Category B

⦿ 75% Intermediate-Acting Lispro Suspension and 25% Rapid-Acting Lispro Solution

Brand Name

Humalog Mix 75/25

Generic Name

75% intermediate-acting lispro suspension and 25% rapid-acting lispro solution

Rx Only

Dosage Forms

Injection 100 units/mL (10 mL vial and 3 mL cartridge for pen use)

Pregnancy Category B

⦿ Insulin Glargine

Brand Names

Lantus, Lantus SoloStar

Generic Name

Insulin glargine (long-acting insulin)

Rx Only

Dosage Forms

Injection 100 units/mL (10 mL vial and 3 mL cartridge for pen use)

Pregnancy Category C

Dosing

- When changing to insulin glargine from once-daily NPH, the initial dose of insulin glargine should be the same. When changing to insulin glargine from

twice-daily NPH, the initial dose of insulin glargine should be reduced by 20% and adjusted according to patient response.

- Administer once daily
- Starting dose in a type 2 diabetic patient is 10 units at bedtime and then titrate according to patient response

⦿ Insulin Detemir

Brand Names

Levemir, Levemir FlexPen

Generic Name

Insulin detemir (long-acting insulin)

Rx Only

Dosage Forms

Injection 100 units/mL (10 mL vial and 3 mL cartridge for pen use)

Pregnancy Category B

Dosing

- Indicated for once-daily or twice-daily dosing
- Once daily is dosed SUB-Q with the evening meal or at bedtime
- Twice daily is dosed every 12 hours

⦿ Insulin Aspart

Brand Names

NovoLog, NovoLog FlexPen

Generic Name

Insulin aspart (rapid-acting insulin)

Rx Only

Dosage Forms

Injection 100 units/mL (10 mL vial and 3 mL cartridge for pen use)

Pregnancy Category B

Dosing

- Administer SUB-Q 15 minutes before or immediately after starting a meal
- May be administered by continuous subcutaneous infusion (insulin pump)

⦿ 70% Intermediate-Acting Insulin Aspart Suspension and 30% Rapid-Acting Aspart Solution

Brand Name

NovoLog Mix 70/30

Generic Name

70% intermediate-acting insulin aspart suspension and 30% rapid-acting aspart solution

Rx Only

Dosage Forms

Injection 100 units/mL (10 mL vial and 3 mL cartridge for pen use)

Pregnancy Category B

Comparison of Insulin Products

Refer to **Table 2-1**.

TABLE 2-1 Comparison of Insulin Products

Product	Onset (hours)	Peak (hours)	Duration (hours)	Appearance
<i>Rapid-Acting Insulin</i>				
Insulin aspart (NovoLog)	0.25	1-2	3-5	Clear
Insulin glulisine (Apidra)	0.25	1	3-4	Clear
Insulin lispro (Humalog)	0.25	0.5-1.5	3-4	Clear
<i>Short-Acting Insulin</i>				
Regular insulin (Humulin R, Novolin R)	0.5-1	2-3	3-6	Clear
<i>Intermediate-Acting Insulin</i>				
NPH insulin (Humulin N, Novolin N)	2-4	6-10	10-16	Cloudy
<i>Long-Acting Insulin</i>				
Insulin detemir (Levemir)	4	N/A	12-24	Clear
Insulin glargine (Lantus)	4	N/A	24	Clear

SULFONYLUREAS

Introduction

The sulfonylureas are used as adjunctive therapy to diet and exercise in patients with type 2 diabetes mellitus. Although periodically used as monotherapy, sulfonylureas are more commonly used in combination with other oral antidiabetic agents, sometimes in the same formulation, in patients who do not reach glycemic goals. General dosing guidelines are to start with a low dose and titrate upward according to patient response while monitoring for signs and symptoms of hypoglycemia, which is a common adverse effect of the drug class. Use cautiously in patients with renal or hepatic impairment. HbA1c reductions are between 1% and 2%.

Mechanism of Action for the Drug Class

Lowers blood glucose by stimulating insulin release from the beta cells of the pancreatic islets

Usage for the Drug Class

Type 2 diabetes mellitus*

Pregnancy Category C for the Drug Class

Except for glyburide (pregnancy category B)

Adverse Reactions for the Drug Class: Most Common

Hypoglycemia, GI distress, dizziness

Adverse Reactions for the Drug Class:

Rare/Severe/Important

SIADH (most commonly with chlorpropamide); disulfiram-like reactions

Major Drug Interactions for the Drug Class

Drugs Affecting Sulfonylureas

- Anticoagulants, azole antifungals, gemfibrozil-enhanced hypoglycemic effects
- Beta blockers cause decreased hypoglycemic effects; also may mask signs and symptoms of hypoglycemia

Sulfonylureas' Effects on Other Drugs

Digoxin: Increased levels

Contraindications for the Drug Class

Diabetes complicated by ketoacidosis, with or without coma; Type 1 diabetes mellitus; diabetes complicated by pregnancy

Counseling Points for the Drug Class

Monitor glucose as directed and be aware of the signs and symptoms of hypoglycemia

Members of the Drug Class

In this section: Glimepiride, glipizide, glyburide
Others: Chlorpropamide, tolazamide, tolbutamide

Glimepiride

Brand Name

Amaryl

Generic Name

Glimepiride

Rx Only

Dosage Form

Tablet

Dosing

- Initial dose: 1–2 mg once daily at breakfast
- Maintenance dose: 1–8 mg once daily

Glipizide

Brand Names

Glucotrol, Glucotrol XL

Generic Names

Glipizide, glipizide extended-release

Rx Only

Dosage Forms

Tablet, extended-release tablet

Dosing

- Initial dose:
 - Glucotrol: 2.5–5 mg once daily 30 minutes before breakfast
 - Glucotrol XL: 5 mg extended-release once daily with breakfast
- Maintenance dose:
 - Glucotrol: 10–40 mg daily (> 15 mg/day should be divided)
 - Glucotrol XL: 5–20 mg extended-release once daily

Glyburide

Brand Names

DiaBeta, Micronase, Glynase PresTab

Generic Name

Glyburide

Rx Only

Dosage Form

Tablet

Dosing

DiaBeta and Micronase

- Initial dose: 1.25–5 mg once daily with breakfast
- Maintenance dose: 1.25–20 mg once daily; may give as single or divided doses

Glyrase PresTab

- Initial dose: 1.5–3 mg once daily with breakfast
- Maintenance dose: 1.5–12 mg once daily; may give as single or divided doses

THIAZOLIDINEDIONES

Introduction

The thiazolidinediones decrease insulin resistance by enhancing insulin-receptor sensitivity. They are used as adjuncts to diet and exercise in patients with type 2 diabetes mellitus. Although periodically used as monotherapy, thiazolidinediones are more frequently used in combination with other oral antidiabetic agents in patients who do not reach glycemic goals. Recent clinical data suggest that patients taking thiazolidinediones may be at an increased risk of myocardial infarction and death; thus, they should be used with caution in patients with a history of previous cardiac disease. They are contraindicated in patients with NYHA class III or IV heart failure. A structurally similar thiazolidinedione, troglitazone, was removed from the market due to cases of liver failure and death. It is recommended to avoid use in patients with hepatic dysfunction. HbA1c reductions are between 1% and 1.5%.

Mechanism of Action for the Drug Class

Thiazolidinediones increase insulin sensitivity by affecting the peroxisome proliferator-activated receptor gamma (PPAR- γ). Acting as an agonist to this receptor, thiazolidinediones decrease insulin resistance in adipose tissue, skeletal muscle, and the liver.

Usage for the Drug Class

Type 2 diabetes mellitus*

Adverse Reactions for the Drug Class: Most Common

Weight gain, edema, hypoglycemia (when used with other oral antidiabetic drugs that may cause hypoglycemia)

Adverse Reactions for the Drug Class:

Rare/Severe/Important

Hepatic failure, heart failure, anemia, ovulation in anovulatory premenopausal women, bone loss, bladder cancer, macular edema

Major Drug Interactions for the Drug Class

Drugs Affecting Thiazolidinediones

- Gemfibrozil: Increased levels
- Rifampin: Decreased levels

Thiazolidinediones' Effects on Other Drugs

Oral contraceptives: Decreased efficacy

Contraindications for the Drug Class

Patients with NYHA class III and IV heart failure; active liver disease (alanine aminotransferase [ALT] > 2.5 times the upper limit of normal)

Counseling Points for the Drug Class

Report signs and symptoms of liver dysfunction and/or shortness of breath immediately

Members of the Drug Class

In this section: Pioglitazone

Others: Rosiglitazone

● Pioglitazone

Brand Name

Actos

Generic Name

Pioglitazone

Rx Only

Dosage Form

Tablet

Pregnancy Category C

Dosing

- Initial dose:
 - 15–30 mg once daily without regard to meals
 - Limit initial dose to 15 mg once daily in patients with NYHA class I and II heart failure
- Maintenance dose:
 - 15–45 mg once daily
 - Maximum recommended dose is 15 mg once daily in patients taking strong CYP2C8 inhibitors (e.g., gemfibrozil)

REVIEW QUESTIONS

- Which of the following is the drug of choice for initial treatment of a patient with newly diagnosed type 2 diabetes and no contraindications?
 - Lantus
 - Glucophage
 - Actos
 - Amaryl
- Which of the following is *not* a brand name of metformin?
 - Glumetza
 - Fortamet
 - DiaBeta
 - Riomet
- Which of the following is the correct initial starting dose for metformin?
 - 500 mg PO BID
 - 1,000 mg PO BID
 - 1,500 mg PO BID
 - 2,000 mg PO BID
- Which of the following is the average HbA1c reduction with metformin?
 - 0.7–1%
 - 1–1.5%
 - 1–2%
 - 1.5–2%
- Which of the following works primarily by decreasing hepatic glucose production?
 - Micronase
 - Januvia
 - Glucophage
 - Actos
- Which of the following is the mechanism of action of sitagliptin?
 - Decreases hepatic glucose production
 - Inhibits di-peptidyl peptidase-4
 - Stimulates peripheral glucose uptake
 - Acts as a direct GLP-1 agonist
- Which class of drugs may cause SIADH in rare instances?
 - Biguanides
 - Sulfonylureas
 - Insulin
 - DPP-4 inhibitors
- Which of the following medications does *not* cause weight gain?
 - Metformin
 - Glyburide
 - Insulin detemir
 - Pioglitazone
- Which of the following medications is indicated for the treatment of diabetic ketoacidosis?
 - Glucophage
 - Actos
 - Insulin
 - Januvia
- Which insulin product comes in a highly concentrated 500 units/mL, 20 mL vial and should be used with caution?
 - NPH
 - Glargine
 - Regular
 - Detemir
- Humulin 70/30 contains which of the following?
 - 70% NPH and 30% regular insulin
 - 30% NPH and 70% regular insulin
 - 70% glargine and 30% regular insulin
 - 30% glargine and 70% regular insulin
- Which of the following should be discontinued immediately and a healthcare provider notified if unexplained myalgia, malaise, or hyperventilation occurs?
 - Pioglitazone
 - Glipizide
 - Sitagliptin
 - Metformin
- Which of the following is *not* a member of the sulfonylurea drug class?
 - Glipizide
 - Sitagliptin
 - Glyburide
 - Glimepiride
- Which of the following is an example of a biguanide?
 - Amaryl
 - Actos
 - Glucophage
 - Januvia
- Insulin is released from which of the following?
 - Beta cells of the liver
 - Alpha cells of the pancreas
 - Beta cells of the pancreas
 - Alpha cells of the liver

16. Which of the following is the typical initial starting dose of insulin?
- 0.1–0.5 unit/kg per day
 - 0.5–1 unit/kg per day
 - 1–5 units/kg per day
 - 5–10 units/kg per day
17. A patient's CrCl is 10–50 mL/min. What is the appropriate dosing of insulin for this patient?
- Administer 100% normal dose
 - Administer 75% normal dose
 - Administer 50% normal dose
 - Administer 10% normal dose
18. When switching a patient from twice-daily insulin NPH to glargine, which of the following is the appropriate initial dose of glargine?
- Increase by 20% and adjusted accordingly
 - Increase by 10% and adjusted accordingly
 - Decrease by 20% and adjusted accordingly
 - Decrease by 10% and adjusted accordingly
19. Humulin R insulin should be dosed:
- 15 minutes prior to a meal.
 - 30 minutes prior to a meal.
 - 30 minutes after a meal.
 - at bedtime.
20. Which of the following is the maintenance dose of glyburide?
- 1–8 mg once daily
 - 2.5–5 mg once daily
 - 1.25–20 mg once daily
 - 10–40 mg once daily
21. Which class of antidiabetic drugs works primarily by activation of adenosine monophosphate-activated protein kinase (AMPK)?
- Biguanides
 - Sulfonylureas
 - Thiazolidinediones
 - Di-peptidyl peptidase-4 inhibitors
22. What is the average HbA1c reduction expected with sitagliptin?
- 0.7–1%
 - 1–1.5%
 - 1–2%
 - 1.5–2%
23. When initiating insulin glargine in a patient with type 2 diabetes not well controlled on metformin therapy, the most common starting dose is:
- 5 units before each meal.
 - 10 units before breakfast and 10 units before dinner.
 - 10 units before each meal.
 - 10 units at bedtime.
24. Which of the following is the maximum dose of Glipizide-XL?
- 5 mg once daily
 - 10 mg once daily
 - 20 mg once daily
 - 40 mg once daily
25. Recent clinical data suggest patients taking which of the following classes of antidiabetic drugs are at an increased risk for myocardial infarction and death?
- Di-peptidyl peptidase inhibitors
 - Biguanides
 - Thiazolidinediones
 - Insulin
26. Which of the following increases plasma concentrations of metformin and should not be used concomitantly with metformin?
- Cimetidine
 - Ranitidine
 - Omeprazole
 - Lansoprazole
27. Which of the following insulin products cannot be administered by continuous subcutaneous infusion (insulin pump)?
- Regular
 - Glulisine
 - NPH
 - Lispro
28. Pioglitazone can cause which of the following rare adverse reactions?
- Metallic taste
 - Weight loss
 - Bone loss
 - Lactic acidosis
29. Which of the following antidiabetic drugs can be used for antipsychotic-induced weight gain?
- Glyburide
 - Sitagliptin
 - Insulin
 - Metformin
30. The enzyme di-peptidyl peptidase is responsible for which of the following?
- Active absorption of glucose into the bloodstream
 - Passive reabsorption of glucose from kidney
 - Breakdown of active GLP-1 to inactive GLP-1
 - Active absorption of carbohydrates from gastrointestinal tracts

