## Diabetes Drug List 2015

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### MEDICATIONS THAT INCREASE INSULIN SENSITIVITY

#### 1. BIGUANIDES

**METFORMIN SUMMARY**

**Brand name:** Glucophage, Glucophage XR  
**Image:** Metformin 500 mg (Mylan)
Action: Decreases hepatic glucose production through a reduction in hepatic insulin resistance. Insulin secretion is unchanged, but fasting and daytime insulin response may actually decrease due to improved insulin sensitivity.

Indications and combination usage: To improve glucose control in people with type 2 diabetes, used as monotherapy, and combination therapy with sulfonylureas, repaglinide, nateglinide, thiazolidinediones, exenatide, and insulin

Essential for efficacy: Insulin (exogenous or endogenous), insulin resistance

Effect on glucose patterns: Generalized improvement in glucose levels. Reduction in hepatic glucose production leads to reduced fasting glucose levels.

Optimal efficacy possible in: Type 2 diabetes with significant signs of insulin resistance syndrome, especially obesity, dyslipidemia

Pharmacology:

- The absolute bioavailability of a metformin hydrochloride 500mg tablet given under fasting conditions is approximately 50-60%. Studies using single oral doses of varying strengths of metformin indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent and slightly delays the absorption of metformin, as shown by approximately 40% lower mean peak concentration. The clinical relevance of these decreases is unknown. Approximately 90% of the drug is excreted renally.

Effect on A1C:

- A reduction of up to 1.8 % vs. placebo

Risk of hypoglycemia:

- Quite low in monotherapy. Increased in patients with marked reductions in caloric intake, undergoing strenuous exercise, using concomitant medications that increase insulin levels, and consuming excessive alcohol.

Dosing:

- 500 mg BID, taken with breakfast and supper (mealtime dosing helps reduce GI side effects. Start with 500 or 850 mg once daily if GI side effects are bothersome).

Titration pattern:

- Start with 500 mg BID; increase in 2 to 6 weeks as needed to 1000 mg every morning and 500 mg at suppertime, then in 2–6 weeks more, if needed, increase to 1000 mg BID. If extended release is used, full dose can be given once daily, usually at suppertime.

List updated October 16th, 2015

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Optimal daily dose:
- 1000 mg BID

Maximal daily dose:
- 2550 mg (850 mg TID)

Dosage forms:
- Glucophage (metformin) – 500 mg; 850 mg, 1000 mg – 500 mg/ml liquid
- Glucophage XR (metformin extended release) – 500 mg; 750 mg

* Note: extended release system requires intact tablet. DO NOT split or crush

- Combination Tablets (brand names in parentheses)
  - Metformin / glyburide (Glucovance)
    - metformin 250 mg and glyburide 1.25 mg
    - metformin 500 mg and glyburide 2.5 mg
    - metformin 500 mg and glyburide 5mg
  - Metformin / glipizide (Metaglip)
    - metformin 250 mg and glipizide 2.5 mg
    - metformin 500 mg and glipizide 2.5 mg
    - metformin 500 mg and glipizide 5mg
  - Metformin / rosiglitazone (Avandamet)
    - metformin 500 mg and rosiglitazone 1 mg
    - metformin 500 mg and rosiglitazone 2 mg
    - metformin 500 mg and rosiglitazone 4 mg
  - Metformin / pioglitazone (Actosplus Met)
    - metformin 500 mg and pioglitazone 15 mg
    - metformin 850 mg and pioglitazone 15mg
  - Metformin / sitagliptin (Janumet)
    - metformin 500 mg and sitagliptin 50 mg
    - metformin 1000 mg and sitagliptin 50 mg

The utility of combination tablets includes:
- Improved adherence to treatment regimen
- Addressing dual defects (for combinations with sulfonylureas, insulin resistance and insulin secretory deficiency, for combination with thiazolidinedione, hepatic and peripheral insulin resistance) that are likely present as early as the time of diagnosis of type 2 diabetes
- For the lowest dose of the metformin/glyburide combination, the ability to utilize low doses of both medications concurrently

*List updated October 16th, 2015*
Drug interactions with potential for clinical significance:

- Most clinically significant interaction is cimetidine/metformin, leading to increased metformin levels
- Nifedipine enhances metformin absorption. Metformin has minimal effects on metformin
- Metformin has minimal effect on nifedipine
- Cationic drugs that are eliminated by the kidneys (including amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, trimethoprim) have the potential for interaction with metformin by competing for common renal tubular transport systems. Theoretically, they may increase the metformin levels.

Adverse events/side effects:

- Diarrhea
- Flatulence
- Lactic acidosis
- Subclinical reductions in vitamin b12 levels
- Infrequent hypoglycemia in people not adequately nourished
- Weight: decreases
- Lipids: reduces: triglycerides, LDL, total cholesterol
- Coagulation: decreased plasminogen activator inhibitor

Contraindications and precautions:

- Known hypersensitivity to metformin
- To reduce risk of lactic acidosis, avoid use in contraindicated patients:
  - Renal disease: serum creatinine: ~1.5 mg/dl in males, ~1.4 mg/dl in females, or abnormal creatinine clearance
  - Hepatic dysfunction has been associated with some cases of lactic acidosis, so use of metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.
  - Congestive heart failure (CHF) requiring pharmacologic treatment
  - History of alcohol abuse/binge drinking
  - Acute or chronic metabolic acidosis, including diabetic ketoacidosis
- Metformin should be withheld in conditions predisposing to renal insufficiency and/or hypoxia, including:
  - Cardiovascular collapse
  - Acute myocardial infarction
  - Acute CHF
  - Severe infections
- Metformin should be temporarily discontinued in patients undergoing radiologic studies or surgical procedures involving intravascular administration of iodinated contrast materials at the time of the procedure. Metformin should be withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been reevaluated and found to be normal.
- May result in ovulation in anovulatory women
- Not indicated for use in pregnancy

List updated October 16th, 2015

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Patient Education:

- Contact healthcare professional if deterioration of glucose control occurs.
- Contact healthcare professional for symptoms of hepatic disease: jaundice, anorexia, unexplained abdominal pain, nausea, vomiting, fatigue, or dark urine.
- Contact healthcare professional if anyone tells you that your kidneys are not working properly.
- Discuss potential for GI symptoms early in treatment (in particular, diarrhea), and the possibility of slower dose titration to reduce symptoms.
- Discuss symptoms of lactic acidosis (weakness, muscle pain, trouble breathing, stomach discomfort, dizziness or lightheadedness, irregular heart beat).
- Avoid excessive alcohol.
- Potential for resumed ovulation in anovulatory women.

Manufacturer Phone: 724-514-1800  
Customer Care Phone: 1-800-796-9526

2. THIAZOLIDINEDIONES

CLASS SUMMARY:

Action: Improves glucose control by improving insulin sensitivity. Works primarily to reduce peripheral insulin resistance (primarily muscle, adipose) but also can have hepatic effects. Thiazolidinediones are agonists for the peroxisome proliferators-activated receptor-gamma (PPAR-γ), which regulate transcription of insulin-responsive genes involved in glucose production, transport, and utilization, as well as fatty acid metabolism.

Effect on A1C: 1%–2%

Titration: Because thiazolidinediones impact genes which are involved in glucose metabolism, their full clinical effect can take some time to be fully manifest. Upon treatment initiation or a change in dose, it may take as much as 2–4 months for the full clinical effect to be seen. Further, with this mode of action, if a patient has marked hyperglycemia requiring rapid reduction in glucose levels, thiazolidinediones should not be the primary mode of therapy, and a more rapid-acting treatment should be selected.

Adverse effects/side effects:

- Edema, anemia (probably dilutional), potential unmasking or exacerbation of congestive heart failure, weight gain.
- Based on meta-analyses, concerns have been raised about the relationship between rosiglitazone and coronary events. These fears seem to have been allayed by a subsequent double blind trial. Other trials still suggest concern with rosiglitazone, but not pioglitazone, and the literature should be monitored for further resolution of this issue.
- Concerns about increased fracture rate/increased risk of osteoporosis in post-menopausal women.

List updated October 16th, 2015
• Rare hepatotoxicity (see below)
• Weight: increases
• Lipids: variable among members of class, as studies have different inclusion parameters and results are not consistent. Ultimately, many of the patients who would be candidates for thiazolidinedione treatment would also benefit from a statin, and one of these medications should be used in addition, if indicated.
• Procoagulant state: probable decrease

Class contraindications and precautions:

• Hepatic disease
• Class tendency to produce edema and unmask/exacerbate congestive heart failure (CHF), use caution in the setting of current or potential CHF. Medications should be used with caution and careful monitoring in patients with mild to moderate heart failure (New York Heart Association (NYHA) Class 1 or 2) and not used in patients with more severe heart failure (NYHA Class 3 or 4).
• New onset or worsening macular edema has been noted very rarely with use of rosiglitazone. It is unclear if this is unique to rosiglitazone, or could be related to the class. Consider discontinuation of thiazolidinedione use, particularly rosiglitazone, if macular edema is diagnosed, and if a patient using a thiazolidinedione reports decreased visual acuity, consider the possibility of macular edema.

INDIVIDUAL MEDICATION SUMMARIES:

A. ROSIGLITAZONE

Brand name: Avandia

Image: Avandia 2 mg (GSK)

Indications:
• Use as monotherapy, or in combination with sulfonylureas, metformin, or insulin.

Pharmacology:
• Exclusively metabolized by cytochrome P450, CYP2C8 mostly, with CYP2C9 having a minor role. Excreted 64% in urine, 28% in feces.

Risk of hypoglycemia:

List updated October 16th, 2015
- Low when used as monotherapy. Increased when used in combination, particularly with an agent that increases insulin levels. Reduction of the dose of that other medication may be needed.

**Dosing:**
- 4 mg per day, given at breakfast or in divided doses, 2 mg each at breakfast and suppertime.

**Usual dose titration pattern:**
- Increase every 4 to 8 weeks or more, as needed, to either 8 mg every morning, or 4 mg BID.

**Maximum daily dose:**
- 8 mg daily, in single or divided dose; can be taken with or without food.
- While initial recommendations were that better control could be achieved with BID dosing, long-term studies now suggest that this difference may not be significant, and once-daily dosing is probably adequate.

**Tablet sizes:**
- 2 mg, 4mg, 8 mg

- Combination Tablets:
  - Rosiglitazone/metformin (Avandamet)
    - rosiglitazone 1 mg and metformin 500 mg
    - rosiglitazone 2 mg and metformin 500 mg
    - rosiglitazone 4 mg and metformin 500 mg
  - Rosiglitazone/glimepiride (Avandaryl)
    - rosiglitazone 4 mg and glimepiride 1 mg
    - rosiglitazone 4 mg and glimepiride 2 mg
    - rosiglitazone 4 mg and glimepiride 4 mg

**Drug Interactions with potential clinical significance:**
- As rosiglitazone is primarily metabolized by CYP2C8, which is an uncommon pathway for drug metabolism, there are no clinically significant interactions with drugs metabolized by CYP3A4 such as nifedipine or oral contraceptives. Nevertheless, if changes in glucose control are noted with initiation or discontinuation of certain drugs which are metabolized by CYP3A4 (gemfibrozil inhibits, and may thus increase rosiglitazone effect, rifampin induces, and may decrease rosiglitazone effect), dose adjustments of diabetes treatments may be needed.

**Adverse effects:**
- Based on meta-analyses, concerns have been raised about the relationship between rosiglitazone and coronary events. A subsequent double blind, controlled trial did not find any increased risk, but other data may still suggest an increased risk compared to pioglitazone. This concern remains under discussion, and it is recommended that the literature be monitored for the latest opinions. See class effects for other possible issues.

*List updated October 16th, 2015*
Contraindications and precautions:

- Can be used with renal impairment
- Contraindicated with hepatic dysfunction (ALT > 2.5 ULN)
- As a precaution, it is recommended that liver enzymes be checked prior to initiation of therapy, and then periodically thereafter per the clinical judgment of the healthcare professional
- Rosiglitazone should not be initiated in people with elevated baseline liver enzyme levels (ALT > 2.5 X the upper limit of normal)
- Patients with mild elevations (ALT levels ~ 2.5 X upper limit of normal) at baseline or during therapy should be evaluated to determine the cause of the liver enzyme elevation. Treatment can continue with caution and more frequent monitoring, per the judgment of the physician.
- If at any time, ALT levels increase to 3 X ULN, recheck enzyme levels as soon as possible. If ALT levels remain > 3 X ULN, therapy should be discontinued.
- Due to tendency for edema formation, rosiglitazone should not be used in people with New York Heart Association Class 3 or 4 cardiac status, unless the benefit is judged to outweigh the potential risk.
- Not indicated in pregnancy (Category C)
- May result in ovulation in an anovulatory female

Patient Education:

- Contact healthcare professional if deterioration of glucose control occurs.
- You need to have your liver function screened periodically when using rosiglitazone. Ask your healthcare provider about this screening.
- Contact healthcare professional for symptoms of liver disease: jaundice, anorexia, unexplained abdominal pain, nausea, vomiting, fatigue, or dark urine.
- Use of this medication with oral contraceptives could decrease the efficacy of these birth control medications.
- This medication is not indicated in pregnancy — contact healthcare professional if you become pregnant.
- This medication should not be used with severe heart failure, referred to as New York Heart Association Class 3 and 4 cardiac status, unless the benefit is judged to outweigh the potential risk. If heart failure develops, carefully consider the risks of continuing this medication vs. its benefits. Consult a healthcare professional to discuss this issue.
- Use of this medication may result in ovulation in anovulatory women.

Manufacturer Phone: 1-888-825-5249
Patient Assistance Programs
Bridges to Access (for those without prescription insurance) 1-866-728-4368
GSK Access (for those with Medicare) 1-866-518-4357
RRC (for those that do not meet above qualifications) 1-800-745-2967

B. PIOGLITAZONE

List updated October 16th, 2015

Copyright © 2015 DiabetesinControl.com  info@diabetesincontrol.com
Brand name: Actos

Image: Actos 15 mg (Takeda Pharmaceutical U.S.A Inc.)

Indications:
- Used as monotherapy, or in combination with sulfonylureas, metformin, or insulin.

Pharmacology:
- Hepatic metabolism via cytochrome P450 (CYP2C8, CYP3A4). Most goes to bile and is excreted. A remaining 15 to 30% is eliminated in the urine.

Risk of hypoglycemia:
- Low when used as monotherapy. Increased when used in combination, particularly with an agent that increases insulin levels. Reduction of the dose of that other medication may be needed.

Dosing:
- 15 mg/day, given once daily before breakfast, for monotherapy or combination therapy. Can be given with or without food.

Titration pattern:
- Increase every 4 to 8 weeks or more, as needed, to 30 mg, and then 45 mg daily. Full doses can be given at once before breakfast.

Maximum daily dose:
- 45mg

Tablet sizes:
- 15 mg, 30mg, 45 mg

Combination Tablets:
- Rosiglitazone/metformin (Actoplus Met)
  - pioglitazone 15 mg and metformin 500 mg
  - pioglitazone 15 mg and metformin 850 mg
- Pioglitazone/glimepiride (Duetact)
  - pioglitazone 30 mg and glimepiride 2 mg
  - pioglitazone 30 mg and glimepiride 4 mg

List updated October 16th, 2015
Drug Interactions with potential clinical significance:

- Pioglitazone may decrease concentrations of oral estrogens.
- Three active metabolites via CYP3A4 and CYP2C8. In vitro, ketoconazole inhibits the metabolism of pioglitazone by 85%; with unknown clinical significance, but more frequent evaluation of glycemic control is recommended. Further drug interaction studies with drugs metabolized by the CYP3A4 pathway are not available at this writing.

Adverse effects:

- Fracture risk is increased
- Weight gain can be significant
- Edema

Contraindications and precautions:

- Known hypersensitivity to thiazolidinediones
- Contraindicated in patients with impaired hepatic function as reflected by ALT > 2.5 X the upper limit of normal (ULN)
- Measurement of liver enzymes:
  - Determine baseline ALT, and then periodically thereafter, per the judgment of the physician.
  - People with mildly elevated liver enzymes (ALT 1 to 2.5 X ULN) at baseline or at any time during therapy should be evaluated to determine the cause.
  - Initiation of, or continuation of, therapy with pioglitazone should proceed with caution and should include appropriate follow-up and more frequent liver monitoring.
  - If ALT > 2.5 X ULN liver function tests should be evaluated more frequently until the levels return to normal or pretreatment values.
  - If ALT > 3 X ULN during pioglitazone therapy, retest promptly and discontinue if ALT remains >3 X ULN or if patient shows signs of liver disease such as jaundice.
- Can be used to treat patients with renal insufficiency. No dose adjustment is usually needed.
- Not indicated in pregnancy (Category C)
- Due to tendency for edema formation, rosiglitazone should not be used in people with New York Heart Association Class 3 or 4 cardiac status, unless the benefit is judged to outweigh the potential risk.
- May result in ovulation in anovulatory women

Patient education:

- Contact healthcare professional if deterioration of glucose control occurs.
- You need to have your liver function screened with a blood test every 2 months for the first month of the use of this medication and periodically thereafter. Be sure you have made these arrangements with your healthcare provider.
- Contact healthcare professional for symptoms of hepatic disease: jaundice, anorexia, unexplained abdominal pain, nausea, vomiting, fatigue, or dark urine.
- Use of this medication with oral contraceptives could decrease the efficacy of these birth control medications.

List updated October 16th, 2015
• This medication is not indicated in pregnancy — contact healthcare professional if you become pregnant.
• This medication should not be used with severe heart failure, referred to as New York Heart Association Class 3 and 4 cardiac status, unless the benefit is judged to outweigh the potential risk. If heart failure develops, carefully consider the risks of continuing this medication vs. its benefits. Consult a healthcare professional to discuss this issue.
• Use of this medication may result in ovulation in anovulatory women.

Manufacturer Phone: 224-554-6500
Patient Assistance Phone: 1-800-830-9159

MEDICATIONS THAT BLOCK GLUCOSE ABSORPTION

3. α-GLUCOSIDASE INHIBITORS

CLASS SUMMARY

Action: Competitive, reversible inhibitors of intestinal brush border α-glycosidase enzymes, which leads to delayed glucose absorption from the gastrointestinal tract and a lowering of postprandial hyperglycemia. Reduces elevations of postprandial glucose levels. Optimal efficacy in early type 2 diabetes with significant postprandial hyperglycemia

Effect on A1C: 0.5%–1%

Significant side effects: flatulence, which is usually mild and self-limited, or diarrhea, minimal increase in weight.

Additional side effects of note: rare elevations of liver transaminases, need liver function test every 3 months for the first year and periodically thereafter.

Contraindications: inflammatory bowel disease, colon ulceration, intestinal obstruction, significant renal disease (creatinine > 2.0 mg/dl)

INDIVIDUAL MEDICATION SUMMARIES

A. ACARBOSE

Brand Name: Precose

List updated October 16th, 2015
Indications:
- Monotherapy or in combination with a sulfonylurea, metformin, or insulin

Pharmacology:
- Less than 2% absorbed
- Most excreted in the feces. A few metabolites are absorbed and are excreted in the urine.
- Metabolized in the GI tract by intestinal bacteria

Dosing:
- 25 mg orally given TID with the first bite of each meal
- Can titrate more slowly based on clinical need or side effects, starting with 25 mg once daily, and then increasing to 25 mg TID

Titration pattern:
- 25 mg TID, adjusted upward every 4 to 8 weeks to a maximum of 100 mg TID
- Can start with lower dose and/or frequency for milder effect or to reduce likelihood of adverse symptoms

Optimal dose:
- Depends on clinical effect and side effects, but usually 50–100 mg TID

Maximum dose:
- Weight ~ 60 kg: 50 mg TID
- Weight > 60 kg: 100 mg TID

Tablet size:
- 25 mg, 50 mg, 100 mg

Drug interactions:
- May affect bioavailability of digoxin and require a dose adjustment of digoxin

List updated October 16th, 2015
• Intestinal adsorbents (charcoal) and digestive preparations may reduce the effect
• Drugs that potentiate hyperglycemia: thiazides, other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid

Contraindications and precautions:
• Contraindications with known hypersensitivity to the drug and in the treatment of diabetic ketoacidosis
• Contraindicated in patients with inflammatory bowel disease or other significant bowel, intestinal, or digestive conditions
• Doesn’t usually cause hypoglycemia
• Can cause transient elevations of serum transaminase levels
• Pregnancy: category B — use only if clearly needed

Patient education:
• Take only 3 times daily.
• Discuss side effects and the possibility of adjusting titration schedule if side effects are excessive.
• Hypoglycemia treatment: Hypoglycemia may occur with use of these medications, particularly in combination with a medication that increases insulin levels. Keep in mind that these medications will delay the absorption of glucose that is consumed in the form of complex carbohydrates. Hypoglycemia must therefore be treated with a form of glucose (e.g., glucose tablets) rather than a complex form of carbohydrate.

Manufacturer Phone: 412-777-2000
Diabetes care: 862-404-3000

B. MIGLITOL
Brand name: Glyset
Image: Glycet 50 mg (Pfizer)

Indications:
• Monotherapy or in combination with a sulfonylurea

List updated October 16th, 2015

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Pharmacology:
- Absorption depends on dose: 25-mg dose: 100% absorbed; 100-mg dose: 50%–75% absorbed. Absorption is not involved in therapeutic effect
- Metabolism: not metabolized
- Excretion: mostly renal as unchanged drug

Dosing:
- 25 mg orally given TID with the first bite of each meal
- Can titrate more slowly based on clinical need or side effects, starting with 25 mg once daily, and then increasing to 25 mg TID

Titration pattern:
- 25 mg TID, adjusted upward every 4 to 8 weeks to a maximum of 100 mg TID
- Can start with lower dose and/or frequency for milder effect or to reduce the likelihood of adverse symptoms

Optimal dose:
- Depends on clinical effect and side effects, but usually 50–100 mg TID
- Maximum dose: 100 mg TID

Tablet size:
- Tablet size: 25 mg, 50 mg, 100 mg

Drug interactions:
- Drugs that potentiate hyperglycemia: thiazides, other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid
- Intestinal adsorbents (charcoal) and digestive preparations may reduce the effect

Contraindications and precautions:
- Contraindications with known hypersensitivity to the drug
- Treatment of diabetic ketoacidosis
- Contraindicated in patients with inflammatory bowel disease or other significant bowel, intestinal, or digestive conditions
- Doesn’t usually cause hypoglycemia
- Can cause transient elevations of serum transaminase levels

List updated October 16th, 2015
• Do not use in patients with a creatinine level > 2.0 mg/dl
• Pregnancy: category B — use only if clearly needed

Patient education:
• Take only TID.
• Discuss side effects and the possibility of adjusting titration schedule if side effects are excessive.
• Hypoglycemia Treatment: Hypoglycemia may occur with use of these medications, particularly in combination with a medication that increases insulin levels. Keep in mind that these medications will delay the absorption of glucose that is consumed in the form of complex carbohydrates. Hypoglycemia must therefore be treated with a form of glucose (e.g., glucose tablets), rather than a complex form of carbohydrate.

Customer Care Phone: 1-800-879-3477
Patient Assistance Phone: 1-866-706-2400

MEDICATIONS THAT INCREASE INSULIN SECRETION

4. SULFONYLUREAS

CLASS SUMMARY:

Action: Insulin secretagogues. Initial effects are to increase insulin secretory capacity. With establishment of long-term glucose control, this increase may not persist and other extrapancreatic effects, either direct or indirect, may also occur.

Required for efficacy: Some remaining endogenous pancreatic insulin secretory capacity

Effect on glucose patterns: General reductions in elevated glucose levels throughout the day

Effect on A1C: 1%–2%

Significant adverse effects/side effects:
• Weight gain
• Hypoglycemia (particularly in older individuals who may under eat or miss meals)

List updated October 16th, 2015
Additional adverse effects of note: Past concerns about increased risk of coronary events (stemming from the University Group Diabetes Project study) seem to have diminished with the findings of the United Kingdom Prospective Diabetes Study (UKPDS) showing no increased cardiac risk with sulfonylurea use. However, some suggestion that use of these medications in the acute post-infarct period worsens outcomes has led many to avoid their use in these situations, often switching to insulin therapy.

Optimal efficacy possible in: Type 2 diabetes with insufficient insulin secretory capacity (relative or absolute), yet enough beta-cell function remaining for some stimulation of further insulin secretion to be possible.

INDIVIDUAL MEDICATION SUMMARIES:

Capsule Information on First-Generation Agents Still in Occasional Use:

Tolbutamide (Orinase)
- Short-acting sulfonylurea
- Half-life 4.5–6.5 hours
- Duration of action 6–10 hours
- Metabolized in the liver to inactive metabolites, which are excreted via the kidney. This medication may be used in mild renal impairment.
- Dose range 500–3000 mg daily, usually given 2–3 times daily – Comment: short duration and frequent dosing requirement make compliance an issue

Image: Tolbutamide 500 mg (Mylan)

Manufacturer Phone: 724-514-1800
Customer Care Phone: 1-800-796-9526

Tolazamide (Tolinase)

Image: Tolazamide 250 mg (Mylan)

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Summary:
- Intermediate duration of action
- Half-life 7 hours
- Duration 16–24 hours
- Metabolized in the liver to mildly active metabolites, which are excreted via the kidney
- Dosing range 100–1000 mg daily, taken 1–2 times daily

Manufacture Phone: 724-514-1800
Customer Care Phone: 1-800-796-9526

Chlorpropamide (Diabinese)

Image: Chlorpropamide 100 mg (Mylan)

Summary:
- Very long duration of action
- Half-life 36 hours
- Duration can extend for 2–3 days
- Metabolized incompletely in the liver to metabolites with hypoglycemic activity, excreted via the kidney. Contraindicated with renal impairment.
- Dosing range 100–500 mg/day, usually in a single dose
- Adverse effect is the chlorpropamide-alcohol flush (Antabuse-like reaction)
- Long duration of action makes it potent but hypoglycemia can persist for a long time

Manufacture Phone: 724-514-1800
Customer Care Phone: 1-800-796-9526

Second-Generation Agents:

**A. GLYBURIDE (GENERIC)**

**ALTERNATE GENERIC NAME: GLYBENCLAMIDE**

List updated October 16th, 2015
Brand Names: Diabeta, Micronase

Image: Glyburide 5 mg (Teva Pharmaceuticals)

Pharmacology:
- Half-life biphasic: 4 and 10 hours
- Duration of action 16–24 hours
- Metabolized in the liver to weakly active and inactive metabolites, which are excreted in liver (50%) and bile (50%). This is different from other sulfonylureas, which have primarily a renal excretion.

Dosing:
- 2.5 to 5 mg daily, in single dose. Can start with 1.25 mg if there is concern about possible hypoglycemia or decreased drug clearance.

Titration pattern:
- Range 1.25–20 mg daily

Optimal dose:
- 10 mg/daily. commonly given once or twice daily

Tablet size:
- Glyburide: 1.25 mg, 2.5 mg, 5 mg, 10 mg
- Combination Tablets:
  - Metformin / glyburide (Glucovance)
    - glyburide 1.25 mg and metformin 250 mg
    - glyburide 2.5 mg and metformin 500 mg
    - glyburide 5 mg and metformin 500 mg

Utility of this combination tablet includes:
- The ability to utilize low doses of both medications concurrently (some not otherwise available)
- Improved adherence to treatment regimen and ease of use
- Ability to “dual defect” of insulin resistance and insulin secretory deficiency, particularly early in the natural history in a conveniently dosed single tablet

List updated October 16th, 2015

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Potential drug interactions:

- **Hypoglycemic** effects may be potentiated by the following medications: NSAIDS, salicylates, sulfonamides, alcohol, fibrates, chloramphenicol, probenecid, allopurinol, Coumadin, trimethoprim, mono-amine oxidase inhibitors, J-blockers. Interactions with ciprofloxacin causing a potentiation of hypoglycemic effect have been described.

- **Hyperglycemia** may potentiated by the following medications: corticosteroids, thiazides, other diuretics, barbiturates, rifampin, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. Interactions with miconazole and gluconazole causing hypoglycemia have been described.

Contraindications and precautions:

- Known sensitivity to glyburide and in the treatment of diabetic ketoacidosis, with or without coma
- Hypoglycemia
- Pregnancy: category B — use only if clearly needed

Patients Education:

Discuss risks of hypoglycemia.

**Customer Service Phone:** 1-800-545-8800

**ALTERNATE FORMULATION OF GLYBURIDE: MICRONIZED**

**Brand name:** Glynase PresTab

**Image:** Glynase 3 mg (Pfizer)

Differences in action/pharmacology from glyburide:

- The micronized glyburide provides somewhat greater bioavailability per milligram than standard glyburide, with peak drug levels occurring at 2–3 hours (4 hours for glyburide)

Differences in dosing:

*List updated October 16th, 2015*
Dosing: while 3 mg of micronized glyburide has a somewhat similar efficacy to 5 mg of glyburide, the actual peak drug availability curves differ slightly and some retitration is often necessary when a switch is made.

Dosing:
- Usual starting dose 1.5 to 3 mg daily, in a single dose

Titration pattern:
- Dosing range 1.5 to 12 mg daily

Optimal dose:
- Optimal dose 6 mg daily, in single or divided dose

Tablet size:
- 1.5 mg, 3 mg, 6 mg

Customer Care Phone: 1-800-879-3477
Patient Assistance Phone: 1-866-706-2400

B. Glipizide

Brand name: Glucotrol

Image: Glipizide 10 mg (Mylan)

Pharmacology:
- Half-life of 2–4 hours
- Duration of action 12–24 hours
- Metabolized in liver to inactive metabolites with excretion primarily via kidney and small amounts in bile

Dosing:
- 5 mg daily, in single dose. Can start with 2.5 if there is concern about possible hypoglycemia or
decreased drug clearance.

Titration pattern:
- Dosing range 2.5–40 mg daily

Optimal dose:
- 20 mg/daily. Usually given once or twice daily.

Tablet size:
- 5 mg, 10 mg
- Combination Tablets (brand name in parentheses):
  - Metformin/glipizide (Metaglip)
    - glipizide 2.5 mg and metformin 250 mg
    - glipizide 2.5 mg and metformin 500 mg
    - glipizide 5 mg and metformin 500 mg

The utility of this combination tablet includes:
- Improved adherence to treatment regimen and ease of use
- Ability to “dual defect” of insulin resistance and insulin secretory deficiency.

Potential drug interactions:
- **Hypoglycemic** effects may be potentiated by the following medications: NSAIDS, salicylates, sulfonamides, alcohol, fibrates, chloramphenicol, probenecid, allopurinol, coumadin, trimethoprim, mono-amine oxidase inhibitors, β-blockers. Interactions with ciprofloxacin causing a potentiation of hypoglycemic effect have been described.
- **Hyperglycemia** may potentiated by the following medications: corticosteroids, thiazides, other diuretics, barbiturates, rifampin, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. Interactions with miconazole and gluconazole causing hypoglycemia have been described.

Contraindications and precautions:
- Contraindications with known hypersensitivity to the drug and in the treatment of diabetic ketoacidosis, with or without coma
- Precautions: metabolism and excretion slowed with renal or hepatic disease; can cause hypoglycemia
- Pregnancy: category C — not indicated for use

Patient education:
- Discuss risks of hypoglycemia.

Manufacturer Phone: 724-514-1800
Customer Care Phone: 1-800-796-9526

List updated October 16th, 2015
**ALTERNATE FORMULATION OF GLIPIZIDE: THE GLIPIZIDE “GITS” (GASTROINTESTINAL THERAPEUTIC SYSTEM), OR GLIPIZIDE XL**

Brand name: Glucotrol XL

Image: Glucotrol 10 mg (Pfizer)

Differences in action/pharmacology from glipizide:

- These tablets consist of an osmotically active drug core surrounded by a semipermeable membrane. Drug is released into the gastro-intestinal tract through an orifice in the membrane at a controlled rate during the transit of the tablet. This formulation produces a constant drug release, resulting in even drug availability over the 24-hour duration of action period.

Dosing:

- Usual starting dose 5 mg daily, in a single dose

**Usual dose titration pattern:**

- Dosing range 5 to 20 mg daily, usually in single dose
- Start with 5 mg daily, and titrate up to 10 mg daily
- As the added advantage of going to 20 mg daily is not great, once the 10 mg dose is reached, usually another medication is added rather than increasing to glipizide XL 20 mg daily as the next step

**Optimal dose:**

- Optimal dose 10 mg daily, in single dose

**Maximum dose**

- 20 mg daily in a single dose

**Tablet size:**

- 2.5 mg, 5 mg, 10 mg

**Patient education:**

- Discuss risks of hypoglycemia.

*List updated October 16th, 2015*
Tell patients that they must swallow this pill whole. They might see pill casing pass out in the stool — this is normal.

Do not cut pill in half or crush.

Customer Care Phone: 1-800-879-3477
Patient Assistance Phone: 1-866-706-2400

C. GLIMEPIRIDE

Brand names: Amaryl

Image:

Pharmacology:

- Half-life: 3–7 hours
- Duration of action 24 hours
- Metabolized in liver to weakly active metabolites. Excreted by kidney (60%) and bile (40%).

Dosing:

- 1–2 mg daily, in single dose at breakfast or the main meal. People who are potentially sensitive to these medications should start with 1 mg.

Usual dose titration pattern:

- Dosing range 1–4 mg given once daily

Optimal dose:

- 2 mg/daily. Usually given as a single dose.
- Maximum dose 4 mg/daily, given as a single dose.

Tablet size:

List updated October 16th, 2015
• 1 mg, 2 mg, 4 mg

• Combination Tablets (brand names in parentheses):
  • pioglitazone/glimepiride (Duetact)
    • pioglitazone 30 mg and glimepiride 2 mg
    • pioglitazone 30 mg and glimepiride 4 mg
  • rosiglitazone / glimepiride (Avandaryl)
    • rosiglitazone 4 mg and glimepiride 1 mg
    • rosiglitazone 4 mg and glimepiride 2 mg
    • rosiglitazone 4 mg and glimepiride 4 mg

Potential drug interactions:

• Hypoglycemic effects may be potentiated by the following medications: NSAIDS, salicylates, sulfonamides, alcohol, fibrates, chloramphenicol, probenecid, allopurinol, coumadin, trimethoprim, mono-amine oxidase inhibitors, J-blockers. Interactions with ciprofloxacin causing a potentiation of hypoglycemic effect have been described.

• Hyperglycemia may potentiated by the following medications: corticosteroids, thiazides, other diuretics, barbiturates, rifampin, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. Interactions with miconazole and gluconazole causing hypoglycemia have been described.

Contraindications and precautions:

• Known sensitivity to glimepiride, and in the treatment of diabetic ketoacidosis, with or without coma
• Hypoglycemia
• Pregnancy: category C — not indicated

Patient education:

• Discuss risks of hypoglycemia.

Manufacturer Phone: 724-514-1800
Customer Care Phone: 1-800-796-9526

D. GLICLAZIDE (GENERIC) — NOT AVAILABLE IN THE UNITED STATES

Brand name: Diamicron

Summary:

• Half-life 6–12 hours

List updated October 16th, 2015
- Duration of action 16–24 hours
- Metabolized in liver to metabolites that are probably inactive, and excreted by kidney (70%) and bile (30%)
- Dosage 80–160 mg given 1–2 times daily

5. MEGLITINIDES

REPAGLINIDE

Brand name: Prandin

Image: Repaglinide 0.5 mg Tablet (Mylan)

Action: stimulates the glucose-dependent postprandial insulin release from functioning β-cells

Pharmacology:
- Completely absorbed from GI tract
- Peak serum level at about 1 hour, dissipation in 3–4 hours
- Peak insulin response is seen 10 minutes after administration
- Metabolism: Cytochrome P-450 system, specifically 3A4. Metabolites are not active. Most elimination is through feces, which may be advantageous for patients in renal insufficiency.

Essential for efficacy: Functioning β-cells

Effect on glucose patterns:
- Primarily reduces postprandial glucose excursions. However, impact on overall control can also lead to reductions in fasting and preprandial glucose levels as well.

Effect on A1C:
- 1.6%–1.9% vs. placebo; somewhat greater in drug naïve patients

Optimal efficacy possible:
- Type 2 diabetes with loss of postprandial, particularly first-phase, insulin release, manifest by significant elevations in glucose levels between the pre- and postprandial period. Useful for patients with erratic meal schedules or who skip meals, particularly if they have been having difficulty with hypoglycemia using sulfonylureas.

Tablet Sizes:
- 0.5 mg, 1 mg, 2 mg

List updated October 16th, 2015
Dosing:
- Drug-naïve (no prior antidiabetes medication): 0.5 mg, 0–30 minutes before each meal (15 minutes is ideal)
- Prior antidiabetes therapy: 1–2 mg 0–30 minutes before each meal (15 minutes is ideal)

Titration pattern:
- Maximum efficacy at each dosing level seen in 1–2 weeks
- Titrate upward to maximum of 4 mg before each meal
- Can be given for up to 4 meals per day. Doses may vary before specific meals, adjusted for food quantity and differing response. If meal is omitted, medication is omitted.
- Indicated also for use with metformin

Optimal dose:
- Most of the therapeutic efficacy is seen in the first half of the dosing range, i.e., up through 2 mg preprandially

Other suggested clinical effects:
- Weight: decrease
- Lipids: reduces: triglycerides, LDL, total cholesterol
- Coagulation: decreased plasminogen activator inhibitor

Drug interactions:
- Increases repaglinide metabolism: rifampin, barbiturates, carbamazepine
- Decreases repaglinide metabolism: antifungals, erythromycin
- Increases repaglinide effect: NSAIDs, J-blockers, sulfonamides, salicylates, chloramphenicol, Coumadin, MAOIs, probenecid
- Decreases repaglinide action: corticosteroids, calcium channel blockers, oral contraceptives, thiazide diuretics, thyroid preparations, estrogens, phenothiazines, phynoptyrin, rifampin, isoniazid, phenobarbital, sympathomimetics

Significant adverse effects/side effects:
- Hypoglycemia

Contraindications and precautions:
- Known hypersensitivity to repaglinide
- Type 1 diabetes and ketoacidosis
- Hepatic insufficiency can cause elevated repaglinide blood levels as well as decrease gluconeogenesis, leading to hypoglycemia. Use cautiously, and have longer intervals between dose adjustments to allow full assessment of response.
- Renal insufficiency: initial doses do not need to be adjusted, but subsequent increases should be made with caution. Repaglinide not tested in people with creatinine clearance < 20 mg/ml or on hemodialysis.

List updated October 16th, 2015

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• Pregnancy category C

Patient education:
• Contact healthcare professional if deterioration of glucose control occurs.
• Explain risk of hypoglycemia.
• Explain pre-meal dosing instructions (0–30 minutes pre-meal, 15 minutes being ideal), adjustments for missed meals (skip dose) or meals of various sizes (may adjust per individualized needs).

Manufacturer Phone: 724-514-1800
Customer Care Phone: 1-800-796-9526

6. D-PHENYLALANINE DERIVATIVES

NATEGLINIDE SUMMARY

Brand name: Starlix

Image: Nateglinide 60 mg (Dr. Reddy labs)

Indications:
• Monotherapy or in combination with metformin.

Pharmacology:
• Action: Stimulates the rapid, glucose-dependent postprandial insulin release from functioning β-cells. Primarily reduces postprandial glucose excursions. Significantly lesser effect of fasting glucose levels
• Pharmacokinetics: Stimulates pancreatic insulin secretion within 20 minutes of oral administration. Peak levels at 1 hour after dosing, and return to baseline at 4 hours after dosing.
• Metabolism: In the liver, primarily by CYP2C9 (70%) with some contribution by CYP3A4 (30%), to 3 major and several minor metabolites, none active. There is no significant interaction with other medications metabolized through similar mechanisms.
• Elimination: 83% urinary excretion, of which 84% is metabolized drug, 16% is intact drug.

Essential for efficacy:
• Functioning β-cells

List updated October 16th, 2015

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Effect on A1C:

- 0.45% vs. baseline in non-drug naïve patients, with initial study A1C level 8.3%. Additional efficacy when used in combination with metformin.

Optimal efficacy possible in:

- Type 2 diabetes with a predominant defect of loss of first-phase insulin release, as manifest by significant elevations in glucose levels between the pre-and postprandial period. This might be the thinner patient with type 2 diabetes, with fasting glucose levels above 125 mg/dl, but not close to 200 mg/dl or above. Also, for patients on biguanide or thiazolidinedione with suboptimal control, but who need insulin stimulatory effect to be meal-targeted to avoid hypoglycemia.

Dosing:

- 120 mg 1–30 minutes before meals. If no meal is eaten, no dose is taken. This is the usual dose for most patients, and no titration needed. Response is glucose dependent, not dose dependent.
- Taking medication after meals results in reduced drug levels
- For patients with A1C values close to target and for whom only minimal additional drug effect is desired, the 60-mg tablet is available
- Indicated also for use with metformin
- Same doses for patients with renal impairment and mild hepatic dysfunction

Adverse effects:

- Mild hypoglycemia
- Slight increase in weight.
- Can decrease postprandial triglycerides

Precautions and Contraindications:

- Response to drug is dependent on glucose load. Therefore, if inadvertent overdose is taken without food, minimal hypoglycemia is likely to occur. However, if one attempts to “treat” such an overdose with glucose, the glucose load will stimulate a brisk insulin secretory response and the resultant hypoglycemia is likely to be worse!

Manufacturer Phone: 1-800-425-0014
Customerservices@drreddys.com
7. GLP-1 AGONISTS

CLASS SUMMARY

Action: Enhances glucose-dependent insulin secretion by the 13-cell, suppresses inappropriately elevated glucagon secretion, and slows gastric emptying. 13-cells with some functional capacity remaining needed for efficacy.

Action on glucose patterns: Generalized improvement in glucose levels, particularly postprandially. Reduction in hepatic glucose production leads to reduced fasting glucose levels.

Optimal efficacy possible in: Type 2 diabetes, overweight, with postprandial hyperglycemia

Side Effects: possible increased risk of pancreatitis

INDIVIDUAL MEDICATION SUMMARIES

EXENATIDE

Brand name: Byetta

Image: Byetta 10 mcg/dose (Astrazeneca Pharmaceuticals)

Indications:
- Monotherapy or in combination with a sulfonylurea and/or metformin

Pharmacology:
- Injected drug reaches peak plasma concentration in 2.1 hours. Elimination by glomerular filtration with subsequent proteolytic degradation. Concentrations measurably present for 10 hours post-administration.

Metabolism and elimination:
- Excreted unchanged in the urine

Effect on A1C:
- 0.4–0.9%, depending on starting A1C and use of combination therapeutic agents

List updated October 16th, 2015

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Risk of hypoglycemia:

- Hypoglycemia: primarily when used in combination with a sulfonylurea. Not increased over placebo in combination with metformin alone.

Significant adverse events/side effects:

- Nausea: usually moderate and dose dependent. Decreased over time with continued therapy. Lead to withdrawal of therapy in 3% of patients.
- Pancreatitis: The use of exenatide has been very rarely associated with the development of pancreatitis. As a more common side effect of exenatide use is nausea unassociated with pancreatitis, clinicians should be cognizant of the need to differentiate GI symptoms that are and are not caused by pancreatitis. Clinicians are encouraged to discuss possible GI symptoms with their patients, and tell them to watch in particular for any persistent, unexplained abdominal pain, which could be quite severe and possibly accompanied by vomiting. The discomfort may or may not be accompanied by vomiting. In instances of such severe pain, the use of exenatide should be stopped if pancreatitis is suspected and the diagnosis of pancreatitis should be confirmed, including by the performance of enzyme testing. If pancreatitis is confirmed, exenatide should not be restarted unless an alternate cause of the pancreatitis is identified.

Dosing:

- 5 mcg per dose administered twice daily at any time within the 60-minute period before the morning and evening meals. Do not administer after a meal. Injection by prefilled pen SC into the thigh, abdomen, or upper arm.

Titration and optimal daily dose:

- After 1 month of therapy at 5 mcg/dose level, if patient is without significant problems with nausea or hypoglycemia, increase to 10 mcg/dose with is the usual maintenance dose. When given with metformin, the dose of metformin usually does not need to be reduced. When given with sulfonylurea, a reduction in dose is often warranted initially to reduce the risk of hypoglycemia.

Maximal daily dose:

- 10 mcg/dose, given BID

Prefilled pen dosage sizes:

- 5 mcg per dose, 60 doses, 1.2 ml
- 10 mcg per dose, 60 doses 2.4 ml

Drug interactions with potential for clinical significance:

- The effect of exenatide to slow gastric emptying may reduce the absorption of other orally administered medications. Use with caution in combination with medications which require rapid gastrointestinal absorption. Medications that are dependent on threshold concentrations for efficacy such as contraceptives and antibiotics should be taken at least 1 hour before an injection of exenatide. If such

List updated October 16th, 2015

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medications are to be taken with food, have the person take them with a snack at which exenatide is not administered.

Contraindications and precautions:

- Persons with hypersensitivity to exenatide or one of its components
- In patients with mild to moderate renal impairment (creatinine clearance 30–80 ml/min) clearance was only mildly reduced, and no dose reduction is needed. However, exenatide is not recommended in people with end-stage renal disease/dialysis (creatinine clearance < 30 ml/min).
- Not recommended for use in people with severe gastrointestinal disease
- Pregnancy Category C
- Reduces appetite
- Slows gastric emptying

Patient education:

- Explain use of prefilled pen devices, injection technique, and titration plan.
- Explain use of detachable needles and equipment disposal techniques.
- Explain potential for adverse events, including nausea and hypoglycemia.
- Advice regarding potential reduction in appetite.
- Advice that they should inform their physician if they become pregnant or plan pregnancy.

Manufacturer Phone: 1-800-236-9933.

EXENATIDE ER
Brand name: Bydureon
Image: Bydureon (AstraZeneca)

Pharmacology:

- Following a single SC injection, exenatide is released from the microspheres over approximately 10 weeks. Initially, surface-bound exenatide is released, resulting in a peak around week 2. This is followed by a gradual release of exenatide from the microspheres and a second peak around week 6-7. The two peaks represent the hydration and erosion of the microspheres. After 6 to 7 weeks, mean exenatide concentrations were maintained.

List updated October 16th, 2015
Effect on A1C:

- Decrease of ~1.6%

Risk of hypoglycemia:

- The risk of hypoglycemia is increased when exenatide ER is used in combination with an agent that induces hypoglycemia, such as a sulfonylurea.

Dosing:

- Administer 2mg by subcutaneous injection once every seven days, at any time of day, with or without meals.

Dosage forms:

- Single dose tray containing 2mg vial
- Single dose 2mg pen

Other suggested clinical effects:

Drug interactions with potential for clinical significance:

- Warfarin: Reports of increased INR sometimes associated with bleeding. Monitor INR until stable.
- May impact absorption of orally administered medications.

Adverse Effects:

- Exenatide ER causes thyroid C-cell tumors at clinically relevant exposures in rats. It is unknown whether exenatide-ER causes thyroid C-cell tumors, including medullary thyroid carcinoma, in humans, as human relevance could not be determined by clinical or non-clinical studies.
- Most common and occurring more frequently than comparator in clinical trials: nausea, diarrhea, headache, vomiting, constipation, injection-site reactions and dyspepsia.
- Weight loss
- Decreases gastric emptying

Precautions and Contraindications:

- Do not use for patients with personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2.
- Postmarketing reports of pancreatitis.
- Not recommended for patients with severe renal impairment or end-stage renal disease. Use caution in patients with renal transplantation or moderate renal impairment.
- Not recommended in patients with severe gastrointestinal disease (i.e. gastroparesis).

List updated October 16th, 2015
Patient education:

- Explain use of prefilled pen devices, injection technique, and titration plan.
- Explain use of detachable needles and equipment disposal techniques.
- Explain potential for adverse events, including nausea and hypoglycemia.
- Advice regarding potential reduction in appetite.
- Advise that they should inform their physician if they become pregnant or plan pregnancy.

Manufacturer Phone: 1-800-236-9933.

LIRAGlutide

Brand name: Victoza

Image: Victoza (Novo Nordisk)

Pharmacology:

- Following SC administration, maximum concentrations of liraglutide are achieved 8-12 hours post dose. Absolute bioavailability is approximately 55%. Liraglutide is endogenously metabolized in a similar manner to large proteins without a specific organ as a major route of elimination. Only a minor amount of the drug is excreted as related metabolites in urine or feces (6% and 5% respectively).

Other suggested clinical effects:

- Liraglutide causes a delay of gastric emptying, thereby reducing the rate at which postprandial glucose appears in circulation.

Effect on A1C:

- Decreases ~1.0% at a dose of 1.8mg/day

Risk of hypoglycemia:

- Serious hypoglycemia can occur when liraglutide is used with a sulfonylurea or insulin.

Adverse events/side effects:

- Risk of thyroid c-cell tumors and pancreatitis.
- Most common and occurring more frequently than comparator in clinical trials: nausea, diarrhea, headache, vomiting, constipation, injection-site reactions and dyspepsia.

List updated October 16th, 2015
Immunogenicity-related events, including urticaria, were more common among patients treated with liraglutide (0.8%) than among comparator-treated patients (0.4%) in clinical trials.

Dosing:
- 0.6mg/day for one week
- Increase of 0.6mg per week to a maximum of 1.8mg/day
- No dosage adjustment for renal impairment

Drug interactions with potential for clinical significance:
- None of significance

Precautions and Contraindications:
- Do not use for patients with personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2.
- Postmarketing reports of pancreatitis, sometimes fatal.
- Use caution in patients with hepatic or renal impairment.

Patient education:
- Explain use of prefilled pen devices, injection technique, and titration plan.
- Explain use of detachable needles and equipment disposal techniques.
- Explain potential for adverse events, including nausea and hypoglycemia.
- Advice regarding potential reduction in appetite.
- Advise that they should inform their physician if they become pregnant or plan pregnancy.
- Advice patient that if more than 3 days have elapsed since the last dose, they should reinitiate liraglutide at 0.6mg to lessen any gastrointestinal side effects associated with reinitiating treatment.

Manufacturer Phone: 1-800-727-5800
Patient Assistance Phone: 1-866-310-7549

ALBIGLUTIDE
Brand name: Tanzeum
Image: Tanzeum (GSK)
Boxed Warning:

- Thyroid C-cell tumors have been observed in animal studies with glucagon-like peptide-1 (GLP-1) receptor agonists at clinically relevant exposures. It is unknown if albiglutide causes thyroid C-cell tumors in humans, including medullary thyroid carcinoma (MTC).
- Albiglutide is contraindicated in patients with a personal or family history of MTC or in patients with multiple endocrine neoplasia syndrome type 2. Patients should be counselled about the risk and symptoms of thyroid tumors prior to initiating treatment.

Indications:

- As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Pharmacology:

- Following SC administration of a single 30-mg dose to subjects with type 2 diabetes mellitus, maximum concentrations of albiglutide were reached at 3 to 5 days post-dosing. Steady-state exposures are achieved following 4 to 5 weeks of once-weekly administration.
- Metabolism: Degradation to small peptides and individual amino acids by proteolytic enzymes.
- Half-life elimination: ~5 days.
- Time to peak, plasma: 3 to 5 days.

Effect on A1C:

- ↓ 0.8–1%, depending on starting A1C and use of dose of albiglutide.

Dosing: Adult

- Subcutaneous: 30 mg once weekly; may increase to 50 mg once weekly if inadequate glycemic response.

Dosing adjustment:

- Renal Impairment: No dosage adjustment necessary; use caution when initiating or escalating doses.
- Hepatic Impairment: There are no dosage adjustments provided in the manufacturer’s labeling.

Dosage Forms:

List updated October 16th, 2015
• Subcutaneous powder for solution: 30mg, 50mg.

**Contraindication:**

• Hypersensitivity to albiglutide or any component of the product.
• Medullary thyroid carcinoma, personal or family history.
• Multiple endocrine neoplasia syndrome type 2.

**Precautions:**

• Could possibly increase risk of thyroid c-cell tumors. Patients with thyroid nodules and/or elevated calcitonin levels should be referred to an endocrinologist.
• Gastrointestinal disease, preexisting and severe: use not recommended.
• Hypersensitivity reactions, severe, with pruritus, rash and dyspnea have been reported; discontinue use immediately.
• Hypoglycemia: increased risk with concomitant use of insulin or insulin secretagogues (eg, sulfonylureas); consider reducing dose of insulin or insulin secretagogue when initiating albiglutide.
• Pancreatitis, acute, has been reported; consider alternative therapy in patients with history of pancreatitis; monitoring is recommended; if pancreatitis suspected, suspend therapy immediately; if confirmed, permanently discontinue therapy.
• Acute or worsening of chronic renal failure has been reported – even in patients without underlying renal disease.
• Renal impairment: use caution when initiating therapy and also when increasing dosage.

**Adverse Effects (Serious and common):**

• Gastrointestinal: Diarrhea, nausea
• Respiratory: Upper respiratory infection, pneumonia.
• Endocrine, metabolic: Hypoglycemia with concomitant use of insulin secretagogues or insulin, medullary thyroid carcinoma
• Dermatologic: Injection site reactions.
• Gastrointestinal: Appendicitis, acute pancreatitis.
• Hepatic: ALT/SGPT levels increased.
• Immunologic: Hypersensitivity reactions reported.
• Renal: Renal failure

**Drug interactions:** Albiglutide delays gastric emptying. May impact absorption of concomitantly administered oral medications.

**Patient education:**

• Counsel patients to discontinue drug use at least one month before a planned pregnancy.
• Side effects include diarrhea, nausea, upper respiratory tract infections, cough, sinusitis, influenza, injection site reactions, back/joint pain, etc.
• Advise patients to report symptoms of thyroid tumors (eg, lump in the neck, hoarseness, dysphagia, or dyspnea).

*List updated October 16th, 2015*
- Counsel patients to discontinue drug and contact a physician if symptoms of hypersensitivity or severe abdominal pain occurs.
- Instruct patients to report signs/symptoms of pancreatitis (ie, severe abdominal pain that may radiate to the back and may [or may not] be accompanied by vomiting).
- Counsel patients to report signs/symptoms of hypoglycemia.
- Advise patients on proper use, storage, and disposal of pen.
- Instruct patients to administer once a week on the same day each week.
- Advise patients to administer at any time of the day, independent of meals.
- Instruct patients to administer a missed dose as soon as possible (if within 3 days) and resume weekly dosing on usual day. If more than 3 days have elapsed, advise patient to wait until next scheduled dose.

Manufacturer Phone: 1-888-825-5249
Patient Assistance Phone: 1-866-518-4357

DULAGLUTIDE

Brand Names: Trulicity

Image: Trulicity (Eli Lilly)

Boxed warning:
- Dulaglutide caused thyroid C-cell tumors in rats that was related to dose and duration of treatment. However, it is unknown if dulaglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans.
- Dulaglutide is contraindicated in patients who have a personal or family history of MTC and in patients with multiple endocrine neoplasia syndrome type 2. The value of monitoring calcitonin levels or thyroid ultrasound routinely is uncertain.

Indications:
- As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (noninsulin dependent, NIDDM).

List updated October 16th, 2015
Pharmacology: Dulaglutide is an agonist of the human glucagon-like peptide-1 (GLP-1) receptor and augments glucose dependent insulin secretion and slows gastric emptying.

Bioavailability: 47% to 65%.

Metabolism: Degradation to amino acids by protein catabolism pathways.

Half-life elimination: ~ 5 days.

Time to peak, plasma: 24 to 72 hours.

Effect on A1C:

- ↓ ~0.87–1.10 %, depending on dose of dulaglutide.

Dosing: Adult

- SC: 0.75mg once weekly; may increase to 1.5 mg once weekly if inadequate glycemic response; maximum: 1.5mg once weekly.

Dosing:

- Renal Impairment: No dosage adjustment necessary; use caution when initiating or escalating doses.
- Hepatic Impairment: There are no dosage adjustments provided in the manufacturer’s labeling; use with caution

Dosage Forms:

Solution Pen-injector, subcutaneous:

- 0.75 mg/0.5 mL (0.5 mL); 1.5 mg/0.5 mL (0.5 mL) [contains polysorbate 80]

Administration

- Do not inject intravenously or intramuscularly.
- Inject subcutaneously into the upper arm, thigh, or abdomen; when administering within the same body region, use a different injection site each week.
- Administer once weekly on the same day each week, without regard to meals or time of day.
- The day of weekly administration may be changed, as long as the last dose was administered ≥ 3 days before.
- If using concomitantly with insulin, administer as separate injections (do not mix); may inject in the same body region as insulin, but not adjacent to one another.

Contraindications:

- Serious hypersensitivity to dulaglutide or any component of the formulation.
- Personal or family history of medullary thyroid carcinoma.
- Patients with multiple endocrine neoplasia syndrome type 2.

List updated October 16th, 2015
Warnings/Precautions:

- Pancreatitis has been reported; monitor for signs and symptoms, and permanently discontinue if confirmed.
- Severe gastrointestinal adverse reactions may occur; not recommended in patients with severe gastrointestinal disease, including severe gastroparesis.
- Acute renal failure and worsening of chronic renal failure have been reported, particularly with nausea, vomiting, diarrhea or dehydration; in patients with renal impairment, use caution when starting or adjusting dosage and monitor renal function in those with severe adverse gastrointestinal reactions.

Adverse effects (Serious and common):

- Gastrointestinal: Abdominal pain, decreased appetite, diarrhea, nausea, vomiting.
- Cardiovascular: Atrioventricular block, first degree.
- Endocrine metabolic: Hypoglycemia with concomitant use of insulin secretagogues or insulin, malignant tumor of thyroid gland.
- Gastrointestinal: Pancreatitis.
- Immunologic: Hypersensitivity reactions.
- Renal: Acute renal failure, chronic renal failure exacerbation

Patient education:

- Counsel patients to report symptoms of pancreatitis or renal failure.
- Advise patients to report hypoglycemia if used with insulin or a sulfonylurea.
- Side effects may include decreased appetite, nausea, abdominal pain, diarrhea, or vomiting.
- Instruct patients to report symptoms of a thyroid tumor.
- Teach patients proper technique and placement of injections.
- Tell patients to maintain adequate hydration.
- Instruct patients to take a missed dose as soon as possible if there are at least 3 days (72 hours) before the next scheduled dose, but if less than 3 days remain they should skip the missed dose.

Manufacturer Phone: 1-317-279-2000
Patient Assistance Phone: 1-844-878-4636

8. DPP-IV INHIBITORS CLASS SUMMARY

Mechanism of action: These medications are competitive inhibitors of DPP-IV, an enzyme that normally inactivates the incretin hormones (GLP-1). As a result of their action, there are increased concentrations of these incretin hormones released into the bloodstream from the small intestine in response to meals. These hormones enhance glucose-dependent insulin secretion by the β-cell. They also suppress inappropriately elevated glucagon secretion seen with type 2 diabetes which reduces hepatic glucose production.

Essential for efficacy: β.cells with some functional capacity remaining

List updated October 16th, 2015

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**Effect on glucose patterns:** Improvement in glucose levels, fasting and, in particular, postprandially.

**Optimal efficacy possible in:** Type 2 diabetes, particularly those with postprandial hyperglycemia

**INDIVIDUAL MEDICATION SUMMARIES:**

**A. SITAGLIPTIN**

**Brand name:** Januvia

**Image:** Januvia 100 mg (Merck)

**Indications:**
- Monotherapy or in combination with a metformin or a thiazolidinedione

**Pharmacology:**
- Sitagliptin reaches its peak plasma concentration in 1–4 hours post administration. The absolute bioavailability is 87%. It may be administered with or without food. Approximately 79% of the drug is excreted unchanged in the urine, with metabolism being a minor pathway of elimination.

**Effect on A1C:**
- ↓ 0.5–1.0%, depending on starting A1C and use of combination therapeutic agents

**Risk of hypoglycemia:**
- Hypoglycemia is not a significant problem with normal usage

**Significant adverse events/side effects:**
- Not significantly different from placebo. Details in package insert.

**Additional clinical effects:**
- May reduce appetite and promote weight loss
- Slows gastric emptying

**Usual dose:**
- 100 mg once daily for people with creatinine clearance > 50

*List updated October 16th, 2015*
50 mg daily for patients with moderate renal insufficiency as defined as creatinine clearance ≤ 50 but > 30
25 mg daily for patients with severe renal insufficiency as defined as creatinine clearance < 30 or end stage renal disease.
No dose titration.

Also available as a combination tablet with metformin:

- Sitagliptin/metformin (Janumet)
  - sitagliptin 50 mg and metformin 500
  - sitagliptin 50 mg and metformin 1000 mg

Contraindications and precautions:
- No contraindications
- Precaution, with dose adjustment, in patients with mild to moderate renal impairment

Manufacturer Phone: 908-423-1000
Patient Assistance Phone: 1-800-727-5400

B. SAXAGLIPTIN

Brand name: Onglyza

Image: Onglyza 2.5 mg (AstraZeneca)

Indications:
- Monotherapy

Pharmacology:
- Saxagliptin reaches its peak plasma concentration in 2 hours post administration, and 4 hours for its active metabolite. Administration with a high fat meal increased this by about 20 minutes. It may be administered with or without food. Metabolism is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5). The major metabolite is also a DPP-IV inhibitor which is 1/2 as potent as saxagliptin. It

List updated October 16th, 2015

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is eliminated by both active renal and hepatic pathways as drug and active metabolite.

**Effect on A1C:**
- ↓ 0.5–1.0%, depending on starting A1C

**Risk of hypoglycemia:**
- Hypoglycemia is not a significant problem with normal usage as monotherapy

**Significant adverse events/side effects:**
- Not significantly different from placebo. Details in package insert.

**Additional clinical effects:**
- May reduce appetite and promote weight loss
- Slows gastric emptying

**Dosing:**
- 5 mg once daily for people with creatinine clearance > 50
- 2.5 mg daily for people with moderate to severe renal insufficiency as defined by a creatinine clearance < 50 or who are also using strong cytochrome P450 3A4/5 (CYP3A4/5) inhibitors (ex: ketoconazole, atazanavir, clarithromycin – see package insert for full list).
- No dose titration at either dose level

**Drug interactions with potential for clinical significance:**
- Strong CYP3A4/5 inhibitors (see above and package insert)

**Contraindications and precautions:**
- Not studied in pregnant women
- Dose adjustment in patients with mild to moderate renal impairment

**Manufacturer Phone:** 1-800-236-9933.

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**C. LINAGLIPTIN**

**Brand name:** Tradjenta

**Image:** Tradjenta 5 mg (Boehringer Ingelheim)

*List updated October 16th, 2015*
Indications:
- Monotherapy or in combination for the treatment of type 2 diabetes

Pharmacology:
- Linagliptin reaches its peak plasma concentration 1.5 hours post administration. It may be administered with or without food. Linagliptin is a weak to moderate inhibitor of CYP3A4 but does not inhibit other CYP isoenzymes and is not an inducer of CYP isoenzymes. Metabolism is a minor pathway of elimination; a small fraction of absorbed Linagliptin is metabolized to an inactive metabolite and over 90% of the drug is excreted unchanged. Approximately 80% is excreted via the enterohepatic system and only 5% is renally eliminated.

Effect on A1C:
- ↓0.5–0.7%, depending on starting A1C

Risk of hypoglycemia:
- Risk of hypoglycemia is increased when administered in combination with metformin and a sulfonylurea.

Significant adverse events/side effects:
- Adverse reactions reported in >5% of patients treated with Linagliptin and more commonly than in patients treated with placebo included nasopharyngitis.

Additional clinical effects:
- May reduce appetite and promote weight loss
- Slows gastric emptying

Usual dose:
- 5 mg once daily
- No dose adjustment is recommended for patients with renal or hepatic impairment.

List updated October 16th, 2015
Drug interactions with potential for clinical significance:

- Efficacy of linagliptin may be reduced when administered in combination with CYP3A4 inducers (i.e. rifampin).

Contraindications and precautions:

- Not studied in pregnant women
- Caution should be used when administered to nursing women
- Safety and effectiveness has not been established in patients below the age of 18.
- There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis. If pancreatitis is suspected, promptly discontinue linagliptin.

Manufacturer Phone: 1-800-243-0127

D. ALOGLIPTIN

Brand name: Nesina

Image: Nesina 25 mg (Takeda)

Indications:

- Monotherapy or in combination for the treatment of type 2 diabetes

Pharmacology:

- Alogliptin reaches its peak plasma concentration 1-2 hours post administration. It may be administered with or without food. The absolute bioavailability of alogliptin is 100%. It does not undergo extensive metabolism and 60% to 71% of the dose is excreted unchanged in the urine. Elimination is primarily renal.

Effect on A1C:

- 25mg daily ↓ A1C by 0.4% to 0.6%

Risk of hypoglycemia:

List updated October 16th, 2015
• Hypoglycemia is not a significant problem with normal usage as monotherapy.

Significant adverse events/side effects:
• Adverse reactions reported in >4% of patients treated with alogliptin 25mg and more commonly than in patients treated with placebo included nasopharyngitis, headache and upper respiratory tract infection.

Additional clinical effects:
• May reduce appetite and promote weight loss
• Slows gastric emptying

Dosing:
• 25 mg once daily
• Decrease dose to 12.5mg once daily for CrCl 30-59mL/min and 6.25mg once daily for CrCl < 30. The recommended dose for patients undergoing intermittent hemodialysis is 6.25mg once daily.

Tablet sizes:
• 6.25mg, 12.5mg, 25mg
• Combination Tablets
  o Alogliptin / Metformin (Kazano)
    • Alogliptin 12.5mg and metformin 500mg
    • Alogliptin 12.5mg and metformin 1000mg
  o Alogliptin / Pioglitazone (Oseni)
    • Alogliptin 12.5mg and pioglitazone 15mg
    • Alogliptin 12.5mg and pioglitazone 30mg
    • Alogliptin 12.5mg and pioglitazone 45mg
    • Alogliptin 25mg and pioglitazone 15mg
    • Alogliptin 25mg and pioglitazone 30mg
    • Alogliptin 25mg and pioglitazone 45mg

Contraindications and precautions:
• There have been postmarketing reports of hepatic failure, sometimes fatal. Causality cannot be excluded.
• There have been postmarketing reports of serious hypersensitivity including anaphylaxis, angioedema and severe cutaneous reactions.
• Safety and effectiveness has not been established in patients below the age of 18.
• There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis. If pancreatitis is suspected, promptly discontinue linagliptin.

Manufacturer Phone: 224-554-6500
Patient assistance Phone: 1-800-830-9159

List updated October 16th, 2015

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E. VILDAGLIPTIN

Brand name: Galvus

- Under FDA review at the time of this writing

9. BILE ACID SEQUESTRANTS (BINDING MOLECULE)

A. COLESEVELAM SUMMARY

Brand name: Welchol

Image: Welchol 625 mg (Daiichi Sankyo)

Action: Binds bile acids in the intestine without being absorbed. Reduced reabsorption of the bile acids leads to depletion of cholesterol. Postulated mechanisms of glucose-lowering include: alteration of bile acid composition which affects intestinal glucose absorption, increased cholecystokinin release which stimulates insulin release, decreased enterhepatic bile acid pool decreases FXR enzymatic activity which reduces inhibition of enzyme LXR which leads to a reduction in hepatic insulin resistance, suppresses hepatic gluconeogenesis, and improves hepatic glucose utilization and uptake, and/or other mechanisms to stimulate increased insulin secretion.

Metabolism and elimination: Non absorbed, eliminated in the stool

Indications and combination usage:

- As an adjunct to diet and exercise to improve glucose control in adults with type 2 diabetes, particularly in combination therapy

Essential for efficacy: Insulin (exogenous or endogenous)

Effect on A1C:

- A reduction of about 0.5 % vs. placebo

Risk of hypoglycemia:

List updated October 16th, 2015
MEDICATIONS THAT INCREASE GLUCOSE EXCRETION

10. SODIUM-GLUCOSE CO-TRANSPORTER 2 INHIBITORS (SGLT2)

CLASS SUMMARY

Action:
- SGLT2 is a low-affinity, high capacity transporter that is exclusive to the kidneys and accounts for 90% of the reabsorbed filtered glucose. These medications work by blocking the reabsorption of glucose by the kidney, which results in increased glucose excretion and lower blood glucose concentrations.

Essential for efficacy:
- β-cells with some functional capacity remaining

Manifestation on glucose patterns:
- Improvement in glucose levels, fasting and, in particular, postprandially.

Usual patient with optimal efficacy:
- Type 2 diabetes, particularly those with postprandial hyperglycemia

INDIVIDUAL MEDICATION SUMMARIES:

A. CANAGLIFLOZIN

Brand name: Invokana

Image: Invokana 100 mg (Janssen)
Indications:
- Monotherapy or in combination

Pharmacology:
- Canagliflozin reaches its peak plasma concentration in 1–2 hours post administration. The mean absolute bioavailability is 65%. It may be administered with or without food; however based on the potential to reduce postprandial plasma glucose excursions due to delayed intestinal glucose absorption, it is recommended that to take before the first meal of the day. O-glucuronidation is the major metabolic elimination pathway to two inactive metabolites. 41.5%, 7% and 3.2% of the dose was recovered in the feces as canagliflozin, a hydroxylated metabolite, and an O-glucuronide metabolite. 33% of the drug is renally excreted. Enterohepatic circulation was negligible.

Additional clinical effects:
- May promote weight loss
- Positive effects on blood pressure
- Increases LDL by 4-8%

Effect on A1C:
- ↓ 0.6–1.1%, depending on starting A1C and use as monotherapy or add-on therapy

Risk of hypoglycemia:
- Hypoglycemia is not a significant problem with normal usage

Dosing:
- 100 mg once daily taken before the first meal of the day. The dose can be increased to 300mg QD in those who require additional glycemic control and whose eGFR > 60mL/min.
- Do not use when eGFR < 45mL/min

Dosage form and Strength:
- 100mg, 300mg tablet

Adverse events/side effects:
- Female genital mycotic infections (~10-11%)
- UTIs (~5%)
- Polyuria (~5%)

Drug Interactions with potential for clinical significance:
- UGT inducers (rifampin, phenytoin, phenobarbital, ritonavir) – consider increasing dose from 100mg to 300mg

List updated October 16th, 2015
Digoxin

Contraindications and precautions:
- Do not use in patients with severe renal impairment, ESRD, or on dialysis
- Not studied in pregnant women
- Nursing mothers: discontinue drug or nursing
- Not recommended with severe hepatic impairment

Patient education:
- Inform patients that symptomatic hypotension may occur and that dehydration may increase the risk
- Inform male patients that yeast infections of the penis may occur, especially in patients with prior history.
- Inform patients of the potential for urinary tract infections.
- Due to its mechanism of action, patients will test positive for glucose in their urine

Manufacturer Phone: 1-800-526-7736
Patient Assistance Phone: 1-800-652-6227

B. CANAGLIFLOZIN-METFORMIN

Brand name: Invokamet

Image: Canagliflozin/Metformin 50mg/500mg (Janssen)

List updated October 16th, 2015
Indications:

- Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing metformin or canagliflozin, or in patients who are already treated with both canagliflozin and metformin.

Pharmacology:

- Administration of INVOKAMET 150 mg/1,000 mg fixed-dose combination with food resulted in no change in overall exposure of canagliflozin. There was no change in metformin AUC; however, the mean peak plasma concentration of metformin was decreased by 16% when administered with food. A delayed time to peak plasma concentration was observed for both components (a delay of 2 hours for canagliflozin and 1 hour for metformin) under fed conditions.

Additional clinical effects:

- Positive effects on blood pressure
- Increases LDL
- Decreases B12 levels due to metformin therefore these levels should be monitored

Effect on A1C:

- Greater reductions in A1C compared to monotherapies; however there are smaller reductions in patients aged 65 and older.

Risk of hypoglycemia:

- Consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia when used in combination with Invokamet

Dosing:

- Take twice daily with meals, with gradual dose escalation to reduce the gastrointestinal side effects due to metformin
- Do not exceed a daily dose of metformin 2,000 mg and canagliflozin 300 mg; INVOKAMET is limited to canagliflozin 50 mg twice daily in patients with an eGFR of 45 to < 60 mL/min/1.73 m²
- Assess renal function before initiating INVOKAMET. Do not initiate or continue INVOKAMET if

*List updated October 16th, 2015*
creatinine levels are greater than or equal to 1.5 mg/dL for males or 1.4 mg/dL for females, or if eGFR is persistently < 45 mL/min/1.73 m²

**Dosage forms and Strength:**

- Film-coated tablets:
  - Canagliflozin 50 mg and metformin hydrochloride 500 mg
  - Canagliflozin 50 mg and metformin hydrochloride 1,000 mg
  - Canagliflozin 150 mg and metformin hydrochloride 500 mg
  - Canagliflozin 150 mg and metformin hydrochloride 1,000 mg

**Adverse events/side effects:**

- The most common (≥5%) adverse reactions with canagliflozin were female genital mycotic infections, urinary tract infections, and increased urination.
- The most common adverse reactions due to initiation of metformin are diarrhea, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache.

**Drug Interactions with potential for clinical significance:**

- UGT inducers (rifampin, phenytoin, phenobarbital, ritonavir): consider increasing dose from 50 mg to 150 mg twice daily
- Digoxin: monitor levels
- Cationic drugs: may reduce metformin elimination

**Contraindications and precautions:**

- Do not use in patients with severe renal impairment, ESRD, or on dialysis
- Not studied in pregnant women
- Metabolic acidosis, including diabetic ketoacidosis
- History of serious hypersensitivity reaction to canagliflozin or metformin
- Nursing mothers: discontinue drug or nursing
- Not recommended with severe hepatic impairment
- Lactic Acidosis: Warn against excessive alcohol use. Invokamet is not recommended in hepatic impairment or hypoxic states. Ensure normal renal function before initiating and at least annually thereafter

**Patient education:**

- Inform patients that symptomatic hypotension may occur and that dehydration may increase the risk
- Inform patients to avoid drinking alcohol due to the risk of lactic acidosis
- Inform male patients that yeast infections of the penis may occur, especially in patients with prior history.
- Inform patients of the potential for urinary tract infections.
- Due to its mechanism of action, patients will test positive for glucose in their urine

*List updated October 16th, 2015*
C. DAPAGLIFLOZIN

Brand name: Farxiga

Image: Farxiga 5 mg (AstraZeneca)

Indications:
- Used to improve glycemic control, along with diet and exercise, in adults with type 2 diabetes. Used as monotherapy and in combination with other type 2 diabetes therapies including metformin, pioglitazone, glimepiride, sitagliptin and insulin.

Pharmacology:
- Dapagliflozin reaches its peak plasma concentration within 2 hours post-dose under fasting state. The absolute oral bioavailability is 78% following a 10 mg PO dose. Dapagliflozin can be administered with or without food. The metabolism of the drug is primarily mediated by UGT1A9; CYP-mediated metabolism is a minor clearance pathway. Dapagliflozin and its related inactive metabolites are eliminated via the renal pathway. The efficacy of Dapagliflozin is compromised in patients with higher degrees of renal impairment and should not be used. No adjustments needed in patients with hepatic impairment.

Additional clinical effects:
- May promote weight loss
- Lowers blood pressure
- Increases LDL cholesterol

Effect on A1C:
- ↓0.6–1.1%, depending on starting A1C and use as monotherapy or add-on therapy

Risk of hypoglycemia:
- Hypoglycemia is not a significant problem with normal usage.

Dosing:
- The recommended starting dose is 5 mg tablet once daily, taken in the morning, with or without food.

List updated October 16th, 2015
Dose can be increased to 10mg once daily in patients tolerating Dapagliflozin who require additional glycemic control.

**Dosage forms and Strength:**

- 5mg, 10mg

**Adverse events/side effects:**

- Female genital mycotic infections
- UTIs
- Nasopharyngitis

**Contraindications and precautions:**

- Do not use in patients with severe renal impairment, ESRD, or on dialysis
- Not studied in pregnant women
- Nursing mothers: discontinue drug or nursing
- Not recommended with severe hepatic impairment
- An imbalance in bladder cancers was observed in clinical trials; Dapagliflozin should not be used in patients with active bladder cancer and should be used with caution in patients with a prior history of bladder cancer.

**Patient education:**

- Inform patients that symptomatic hypotension may occur and that dehydration may increase the risk
- Inform male patients that yeast infections of the penis may occur, especially in patients with prior history.
- Inform patients of the potential for urinary tract infections.
- Due to its mechanism of action, patients will test positive for glucose in their urine

Manufacturer Phone: 1-800-236-9933.
Patient Assistance Phone: 1-800-292-6363

**D. DAPAGLIFLOZIN-METFORMIN**

**Brand name:** Xigduo XR

**Image:** Dapagliflozin/Metformin 5mg/1000mg (AstraZeneca)

*List updated October 16th, 2015*
Indication:

- As an adjunct to diet and exercise to improve glycemic control in adults with Type 2 Diabetes when treatment with both Dapagliflozin-Metformin is appropriate.
- Limitations for use not indicated in patients with Type 1 Diabetes or for the treatment of diabetic ketoacidosis.

Boxed Warning:

- Lactic acidosis is rare, but serious, complication that can occur due to metformin accumulation. The risk increases with condition such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment and congestive heart failure.

Pharmacology: Xigduo XR combines two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: dapagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and metformin hydrochloride, a biguanide.

Effect on A1C: There have been no clinical studies conducted with Xigduo XR combination tablets to characterize its effect on HbA1c.

Dosing:

- Individualize the starting dose based on the patient’s current treatment.
- Administer once daily in the morning with food.
- Do not exceed a daily dose of 10 mg dapagliflozin/2000 mg metformin HCl ER
- XIGDUO XR should not be used in patients with moderate to severe renal impairment (defined as eGFR < 60 mL/min/1.73 m² or CrCl < 60 mL/min) or end-stage renal disease.

Dosage forms and Strength:

- 5 mg of dapagliflozin/ 500 mg of metformin ER
- 5 mg of dapagliflozin/ 1000 mg of metformin ER
- 10 mg of dapagliflozin/ 500 mg of metformin ER
- 10 mg of dapagliflozin/ 1000 mg of metformin ER

Contraindications and Precautions:

List updated October 16th, 2015

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• Serious hypersensitivity to Dapagliflozin, Metformin or any component of the formulation.
• Moderate to Severe renal impairment (Serum Creatinine ≥1.5mg/dL in males or ≥1.4mg/dL in females which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction and septicemia.
• Acute or chronic metabolic acidosis (including diabetic ketoacidosis with or without coma).
• Lactic acidosis: Warn patients against excessive alcohol intake.
• Hypotension: Before initiating XIGDUO XR, assess volume status and correct hypovolemia in the elderly, in patients with renal impairment or low systolic blood pressure, and in patients on diuretics.
• Hypoglycemia: In patients taking insulin or an insulin secretagogue with XIGDUO XR.
• Vitamin B12 deficiency: Metformin may lower vitamin B12 levels.
• Genital mycotic infections.
• Increased LDL-C.
• Bladder Cancer: Dapagliflozin should not be used in patients with active bladder cancer and should be used with caution in patients with a prior history of bladder cancer.

Patient Education:

• Counsel patient to report symptoms of hypoglycemia or lactic acidosis
• Side effects may include urinary tract infection, genital infection, nausea, vomiting, diarrhea, abdominal pain, anorexia, and back pain
• Tell patient to report symptoms of dehydration or hypotension
• Instruct patient to take drug with food
• Advise patient to avoid ingestion of alcohol and alcohol-containing products due to increased risk of lactic acidosis

Manufacturer Phone: 1-800-236-9933
Patient Assistance Phone: 1-800-292-6363

E. EMPAGLIFLOZIN

Brand name: Jardiance

Image: Jardiance 10 mg (Boehringer Ingelheim)
Indications:
- Treatment of type 2 diabetes mellitus (noninsulin dependent, NIDDM) as an adjunct to diet and exercise to improve glycemic control.

Pharmacology:
- Empagliflozin reaches its peak plasma concentration in about 1.5 hours post dose. Food decreases AUC by 16% and Cmax is decreased by 37%. Its metabolism is mediated primarily by glucuronidation via UGT2B7, UTG1A3, UGT1A8, and UGT1A9. 54.4% is eliminated renally and 41.2% via the fecal route. Elimination half-life is about 12.4 hours.

Effect on A1C:
- ↓ 0.48% – 0.74% for empagliflozin 10 mg and ↓ 0.59% – 0.85% for empagliflozin 25 mg after 24 weeks of treatment.

Risk of hypoglycemia:
- Hypoglycemia, severe, is present (monotherapy or combined with metformin alone, metformin plus sulfonylurea, or pioglitazone [with/without metformin] and in combination with insulin).

Dosing:
- Starting dose is 10 mg orally once daily in the morning.
- May increase to 25 mg orally once daily.
- Max 25 mg orally once daily.
- eGFR less than 45 mL/min/1.73 m²: Do not initiate therapy; discontinue use if eGFR drops and remains below 45 mL/min/1.73 m².

Dosage form and Strength:
- Oral Tablet: 10mg, 25mg.

Adverse events/side effects:

List updated October 16th, 2015
• Hypoglycemia, overall (monotherapy, 0.4%; combination therapy
• Increased frequency of urination, urinary tract infectious disease; increased percentage in 75 years and older
• Female genital infection.
• Hypoglycemia, severe (monotherapy or combined with metformin alone, metformin plus sulfonylurea, or pioglitazone [with/without metformin]; combined with insulin).

Contraindications and Precautions:
• Do not use in patients on dialysis or with end stage renal disease.
• Do not initiate treatment in patients with estimated GFR of less than 45 mL/min/1.73 m².
• Do not use in patients with hypersensitivity to empagliflozin.
• Increased risk of volume depletion in patients aged 75 years and older.
• Symptomatic hypotension may occur.
• Increased risk of hypotension in patients with renal impairment, the elderly, concomitant diuretic use, and patients with low systolic blood pressure.
• Not recommended in patients with type 1 diabetes
• Do not use for treatment of diabetic ketoacidosis
• Increases in LDL-C may occur.
• Decreases in estimated GFR (eGFR) have been reported; discontinue use if eGFR is persistently less than 45 mL/min/1.73 m²
• Increased serum creatinine and reduced GFR have been reported; monitoring recommended
• Increased risk of renal impairment in elderly patients and those with moderate renal impairment; more frequent monitoring recommended.
• Increased risk or urinary tract infection; monitoring recommended.
• Patients will test positive for glucose in urine due to the mechanism of action of empagliflozin.
• Increased risk of genital mycotic infection, particularly in patients with a history of chronic or recurrent genital mycotic infections.
• Increased risk of hypoglycemia with insulin secretagogues or insulin; may require dose reduction in other therapies

Patient Education:
• Warn female patients of childbearing potential that the drug may cause fetal harm, particularly during the second and third trimesters. If pregnancy occurs, they should report it to a healthcare professional as quickly as possible.
• Recommend that female patients not breastfeed nor provide breast milk to their infants.
• Side effects may include increased urination, genital infections, upper respiratory tract infections, arthralgia, or nausea.
• Tell patients to report symptoms of urinary tract infection.
• Counsel patients to report symptoms of hypotension.
• Instruct patients to report periods of stress (ie, fever, trauma, infection, or surgery).
• Advise patients that urine glucose tests will be positive based on action of drug
• Encourage patients to maintain adequate hydration during treatment.

Manufacturer Phone: 1-800-243-0127

List updated October 16th, 2015
F. EMPAGLIFLOZIN-LINAGLIPTIN

Brand name: Glyxambi

Image: Empagliflozin/Linagliptin 25mg/5mg (Boehringer Ingelheim)

Indications:
- Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and linagliptin is appropriate.

Pharmacology:
- Glyxambi combines 2 antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: empagliflozin, a sodium-glucose co-transporter (SGLT2) inhibitor, and linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor.

Additional Clinical Effects:
- Increase in LDL-C
- Reductions in blood pressure

Effect on A1C: Reductions in A1C by > 1%
Risk of Hypoglycemia: There were no severe hypoglycemic events in clinical trials.

Dosing:
- The recommended dose of Glyxambi is 10 mg empagliflozin/5 mg linagliptin once daily in the morning, taken with or without food.
- In patients tolerating Glyxambi, the dose may be increased to 25 mg empagliflozin/5 mg linagliptin once daily.
- Glyxambi should not be initiated in patients with an eGFR < 45 mL/min/1.73 m².

Dosage forms and Strength:

List updated October 16th, 2015
- 10 mg empagliflozin/5 mg linagliptin tablets
- 25 mg empagliflozin/5 mg linagliptin tablets

**Adverse events/side effects:**

- The most common adverse reactions associated with Glyxambi (a 5% or greater incidence) were urinary tract infections, nasopharyngitis, and upper respiratory tract infections.

**Drug Interactions with potential for clinical significance:**

- Digoxin
- Strong inducers of CYP3A4 or P-gp (e.g., rifampin) decrease exposure to linagliptin to subtherapeutic and likely ineffective concentrations

**Contraindications and Precautions:**

- Contraindicated in patients with severe renal impairment, end-stage renal disease, or dialysis
- There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis, in patients taking linagliptin.
- History of hypersensitivity reactions.
- Empagliflozin increases the risk for genital mycotic infections and urinary tract infections.

**Patient Education:**

- Inform patients that persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis.
- Hypoglycemia risk is increased when Glyxambi is added on to a sulfonylurea or insulin.
- Yeast infections may occur in the penis.
- There is a potential for urinary tract infections.
- Inform patients that it is necessary to assess renal function prior to initiating Glyxambi and renal function should be monitored periodically thereafter.
- Glucose in urine is expected while on Glyxambi.

**Manufacturer Phone:** 1-800-542-6257
**Patient Assistance Phone:** 1-800-556-8317

**G. EMPAGLIFLOZIN-METFORMIN**

**Brand name:** Synjardy

**Image:** Empagliflozin/Metformin 12.5mg/500mg (Boehringer Ingelheim)
Indication:

- As an adjunct to diet and exercise to improve glycemic control in adults with Type 2 Diabetes when treatment with both Empagliflozin-Metformin is appropriate.

Boxed Warning:

- Lactic acidosis is rare, but serious, complication that can occur due to metformin accumulation. The risk increases with condition such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment and congestive heart failure.

Pharmacology: See Metformin on page 3 and Empagliflozin on page 52.

Effect on A1C: See Metformin on page 3 and Empagliflozin on page 52.

Dosing:

- Individualize the starting dose based on the patient’s current treatment.
- Administer daily doses in 2 divided doses.
- Gradually increase daily dose up to 25 mg empagliflozin/2000 mg metformin HCl
- Should not be used in patients with eGFR < 45 mL/min/1.73 m² or serum creatinine ≥ 1.5 mg/dL (males); ≥ 1.4 mg/dL (females), end-stage renal disease, or on dialysis.

Dosage forms and Strength:

- 12.5 mg of empagliflozin/ 500 mg of metformin tablets
- 5 mg of empagliflozin/ 500 mg of metformin tablets
- 5 mg of empagliflozin/ 1000 mg of metformin tablets
- 12.5 mg of empagliflozin/ 1000 mg of metformin tablets

Contraindications and Precautions: See Metformin on page 5 and Empagliflozin on page 53.

Patient Education: See Metformin on page 5 and Empagliflozin on page 54.

Manufacturer Phone: 1-800-243-0127
Patient Assistance Phone: 1-800-556-8317

List updated October 16th, 2015

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MEDICATIONS THAT WORK WITH INSULIN

SYNTHETIC AMYLIN ANALOGS

PRAMlintide SUMMARY

Brand name: Symlin

Image: Symlin (AstraZeneca)

Indications:

- Used in adjunct to insulin therapy in patients with type 1 and type 2 diabetes mellitus.

Pharmacology:

Pramlintide is a synthetic analog of human amylin, a naturally occurring neuroendocrine hormone synthesized by pancreatic beta cells that contributes to glucose control during the postprandial period. Amylin is secreted along with insulin in response to food intake. Amylin slows gastric emptying and suppresses glucagon secretion which leads to suppression of endogenous glucose output from the liver. The absolute bioavailability of a single SC dose of pramlintide is approximately 30 to 40%. Pramlintide is metabolized primarily by the kidneys. No dosage adjustments are needed for patients with renal or hepatic impairment.

Effect on A1C:

- In Type 1 diabetes: 0.1 to 0.67%
- In Type 2 diabetes: 0.3 to 0.62%

Additional clinical effects:

- Satiety leading to decrease caloric intake and increased weight loss

Risk of hypoglycemia:

- Pramlintide alone does not cause hypoglycemia. However, it is indicated for adjunct treatment with meal-time insulin and co-administration can increase the risk of insulin-induced hypoglycemia, particularly in patients with type 1 diabetes (BOXED WARNING).

Usual dose:

- Administer SC in the abdomen or thigh before meals containing 250 kcal or 30 grams of carbohydrates or more

List updated October 16th, 2015
- Type 2: Initiate at 60 mcg before major meals; May increase to 120 mcg in 3 to 7 days (nausea is the limiting factor)
- Type 1: Initiate at a dose of 15 mcg and titrate at 15 mcg increments to a maintenance dose of 30 mcg or 60 mcg as tolerated.

**Adverse events/side effects:**
- Severe hypoglycemia (Black Box Warning) especially in type 1 diabetes
- Gastrointestinal upset, nausea

**Drug Interactions with potential for clinical significance:**
- Do not administer with α-glucosidase inhibitors
- Due to its effects on gastric emptying, pramlintide should not be taken with drugs that alter gastrointestinal motility (i.e. anticholinergic agents such as atropine) and agents that slow the intestinal absorption of nutrients.

**Contraindications and precautions:**
- Do not give to patients with confirmed diagnosis of gastroparesis
- Hypoglycemia unawareness
- Hypersensitivity

**Patient education:**
- Patients may experience redness, swelling or itching at the site of injection
- Pramlintide and Insulin must be administered separately
- Pregnancy category C – Do not use
- Inform patients about self-management practices including glucose monitoring, proper injection technique, timing of dosing, and proper storage of pramlintide.
- Reinforce management of hypoglycemia

Manufacturer Phone: 1-800-236-9933.
Patient Assistance Phone: 1-800-292-6363

**MEDICATIONS THAT IMPROVE GLYCEMIC CONTROL**

**BROMOCRIPTINE SUMMARY**

Brand name: CYCLOSET

Image: Bromocriptine (Mylan)
Indications:

- Used in adjunct to diet and exercise to improve glycemic control in type 2 diabetes; can be combined with metformin and/or sulfonylureas

Pharmacology:

- Bromocriptine is a dopamine receptor antagonist. Its exact mechanism of action in diabetes is unknown but studies have shown that it improves glucose control without affecting serum insulin levels. It may also reverse some of the metabolic changes that are associated with insulin resistance and obesity. When administered orally, approximately 65-95% of the drug is absorbed. Due to extensive hepatic extraction and first-pass metabolism, only about 7% of the dose reaches systemic circulation. Taking with a standard high-fat meal increases maximum plasma concentration and the relative bioavailability. Metabolism by CYP3A4 is the major metabolic pathway. The major route of elimination is via the bile with only 2-6% eliminated via urine. When evaluated for safety, a 52-week, 74-center, randomized placebo-controlled trial found that bromocriptine demonstrated no increased risk of adverse cardiovascular events. The Cycloset Safety Trial assessed the effect of Cycloset on the time to first occurrence of major adverse cardiovascular events (MACE) which includes MI, stroke and CVD death. This is significant because cardiovascular disease and associated events occur at least 2 times more often in patients with type 2 diabetes compared to those who do not have diabetes. What the study showed is that cycloset had a statistically significant (55% risk reduction) beneficial effect on the risk of cardiovascular events occurring.
- Hypoglycemia is not a significant problem with normal usage

Effect on A1C:

- Reduction by 0.4-0.5%

Dosing:

- Initial dose is 0.8 mg daily; can be increased weekly by one 0.8mg tablet until maximal tolerated daily dose of 1.6 to 4.8mg is achieved.
- Take within 2 hours of waking in the morning with food
- If missed, do not take later in the day

Adverse events/side effects:

- Postmarketing reports with higher doses of bromocriptine used for other indications include psychotic disorders, hallucinations and fibrotic complications
- Nausea

List updated October 16th, 2015

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- Fatigue
- Dizziness
- Vomiting
- Headache

**Drug Interactions with potential for clinical significance:**

- May increase the unbound fraction of highly protein-bound therapies, altering their effectiveness and safety
- May increase ergot-related side effects or reduce ergot effectiveness for migraines if administered within 6 hours of ergot related drugs
- Extensively metabolized by CYP3A4. Use caution when administering strong inhibitors, induces of substrates of CYP3A4.

**Contraindications and precautions:**

- Can cause orthostatic hypotension and syncope, particularly upon initiation or dose increase. Use caution in patients taking anti-hypertensive medications.
- May exacerbate psychotic disorders or reduce effectiveness of antipsychotics. Use in patients with severe psychiatric disorders is not recommended.
- May cause drowsiness.
- Concomitant use with dopamine receptor antagonists is not recommended due to possibility for diminished effectiveness for both drugs.
- Do not use in lactating women

**Manufacturer Phone:** 724-514-1800
**Customer Care Phone:** 1-800-796-9526

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**MEDICATIONS FOR CHRONIC WEIGHT MANAGEMENT**

**QSYMIA (Phentermine and Topiramate)**

Manufacturer: Vivus

Image: QSYMIA (Phentermine and Topiramate 3.75 mg/23 mg)

_List updated October 16th, 2015_
Action:

- Phentermine, a sympathomimetic amine, shows activity similar to prototype amphetamines. Although the exact mechanism in weight loss is not known, phentermine increases hypothalamic release of catecholamines leading to reduced appetite and decreased food consumption. Other metabolic effects may also contribute.

- The mechanism of action of topiramate in chronic weight management is unknown, although it appears to suppress appetite and enhance satiety. Potential mechanisms include augmentation of gamma-aminobutyrate, modulation of voltage-gated ion channels, inhibition of AMPA/kainite excitatory glutamate receptors, or inhibition of carbonic anhydrase.

Indications:

As an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of

- 30 kg/m² or greater (Obese)
- 27 kg/m² or greater (Overweight) in the presence of at least one weight-related comorbidity such as hypertension, type 2 diabetes mellitus or dyslipidemia.

Effect on A1C:

- A reduction of up to 0.4% vs 0.1% with placebo.

Risk of hypoglycemia:

- Weight loss increases the risk of hypoglycemia in patients with type 2 diabetes on anti-diabetic therapy.

Dosing

- Take once daily in morning. Avoid evening dose to prevent insomnia.
- Recommended dose: Qsymia 3.75 mg/23 mg (phentermine 3.75 mg/topiramate 23 mg extended-release) daily for 14 days; then increase to 7.5 mg/46 mg daily.
- Discontinue or escalate dose (as described) if 3% weight loss is not achieved after 12 weeks on 7.5 mg/46 mg dose.
- Discontinue Qsymia if 5% weight loss is not achieved after 12 weeks on maximum daily dose of 15 mg/92 mg (2.1).

List updated October 16th, 2015
• Discontinue 15 mg/92 mg dose gradually to prevent possible seizure.
• Do not exceed 7.5mg/46mg dose for patients with moderate or severe renal impairment or patients with moderate hepatic impairment.

Dosage forms:
• Oral Capsule, Extended Release: (Phentermine Hydrochloride - Topiramate) 3.75 MG-23 MG, 7.5 MG-46 MG, 11.25 MG-69 MG, 15 MG-92 MG.

Drug interactions:
• Oral contraceptives: Altered exposure can cause irregular bleeding, but increased risk of bleeding. Advise patients not to discontinue oral contraceptives if spotting occurs.
• CNS Depressants including alcohol: Potentiate CNS depressant effects. Avoid concomitant use of alcohol.
• Non-potassium sparing Diuretics: May potentiate hypokalemia. Measure potassium before and during treatment.

Most common adverse reactions (Incidence greater than or equal to 5% and at 1.5 times placebo)
• Paresthesia
• Dizziness
• Dysgeusia
• Insomnia
• Constipation
• Dry mouth

Contraindications
• Concomitant use with MAOI therapy or within 14 days of discontinuation of MAOI.
• Glaucoma.
• Hypersensitivity or idiosyncrasies to sympathomimetic amines
• Hyperthyroidism
• Pregnancy

Precautions:
• Abrupt withdrawal may increase seizure frequency in patients with or without history of seizures/epilepsy; gradual taper recommended; if immediate discontinuation is required, monitoring is recommended.
• Cardiac or cerebrovascular disease, stable; increased risk of elevated resting heart rate; monitoring recommended, particularly when initiating therapy or with dose increases.
• Cardiac or cerebrovascular disease, resent or unstable; use not recommended.
• Cognitive dysfunction may occur; consider dose reduction or discontinuation.
• Concomitant use with alcohol should be avoided.
• Concomitant use of carbonic anhydrase inhibitors (eg, zonisamide, acetazolamide, or dichlorphenamide) should be avoided.

List updated October 16th, 2015
- Depression, history; increased risk of mood disorders; dose reduction or discontinuation may be required.
- Diabetes mellitus, type 2 treated with insulin or insulin secretagogues; increased risk of hypoglycemia; monitoring recommended before and during therapy; if occurs, modification of antidiabetic regimen recommended.
- Esrd, on dialysis; avoid use
- Hepatic impairment, moderate (child-pugh, 7 to 9); dose adjustment recommended
- Hepatic impairment, severe (child-pugh, 10 to 15); avoid use.
- High initial doses; increased risk of cognitive dysfunction.
- Hypertension, currently treated with antihypertensive agents; increased risk of hypotension; monitoring recommended prior to and during therapy; if suspected, adjustment of antihypertensive regimen recommended
- Hypokalemia may occur; monitoring recommended
- Ketogenic diet; increased risk of kidney stone formation
- Metabolic acidosis has been reported; increased risk in patients with conditions or therapies that predispose to acidosis (eg, renal disease, severe respiratory disorders, status epilepticus, diarrhea, surgery, ketogenic diet, or drugs); monitoring recommended; dose reduction may be necessary
- Myopia, acute and associated with secondary angle closure glaucoma, has been reported; drug discontinuation recommended
- Oligohidrosis and hyperthermia, possibly resulting in hospitalization, has been reported; monitoring recommended
- Pregnancy; may cause fetal harm, avoid pregnancy during therapy; pregnancy testing prior to initiation and monthly thereafter recommended; if pregnancy occurs, discontinue drug immediately
- Rapid titration; increased risk of cognitive dysfunction
- Renal impairment, moderate (crcl 30 to less than 50 ml/min) or severe (crcl less than 30 ml/min); dose adjustments recommended
- Resting heart rate increased; monitoring recommended; dose reduction or discontinuation recommended with a sustained increase
- Serum creatinine elevation; monitoring recommended prior to and during therapy; dose reduction or discontinuation may be necessary.
- Suicidal ideation, active, or suicide attempts; avoid use.
- Suicidal thoughts or behavior; increased risk of new onset or exacerbation; monitoring recommended; discontinue use if suicidal thoughts or behavior emerge.

**Patient Education:**

- Drug may cause decreased visual acuity and/or cognitive impairment. Patient should avoid driving or other activities requiring clear vision, mental alertness, or coordination until drug effects are realized.
- Drug may impair heat regulation. Advise patient to use caution with activities leading to an increased core temperature, such as strenuous exercise, exposure to extreme heat, or dehydration.
- This drug may cause paresthesia, dizziness, dysgeusia, insomnia, constipation, dry mouth, or an increase in resting heart rate.

*List updated October 16th, 2015*
• Instruct patient to notify their healthcare provider if they are breastfeeding or intend to breastfeed during therapy; formula feedings are recommended.
• Instruct patient to report depression or worsening depression, suicidal ideation, or unusual changes in behavior.
• Advise diabetic patients to monitor for signs/symptoms of hypoglycemia and to report difficulties with glycemic control.
• Advise patient against sudden discontinuation of drug.
• Tell patient to maintain adequate hydration to prevent kidney stone formation.
• Advise patient there are multiple significant drug-drug interactions for this drug. Consult healthcare professional prior to new drug use (including over-the-counter, nutritional supplements, vitamins, and herbal drugs).
• Patient should not drink alcohol while taking this drug.

Manufacturer Phone: 724-514-1800

Belviq (Lorcaserin)
Manufacturer: Eisai Inc
Image: Belviq 10 mg

Action:
Lorcaserin is a selective serotonin 2C (5-HT(2C)) receptor agonist. The exact mechanism of action is not known, but lorcaserin is believed to promote satiety and decrease food intake by activating 5-HT(2C) receptors on anorexigenic pro-opiomelanocortin neurons in the hypothalamus.

Indications:
As an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of
• 30 kg/m² or greater (Obese)
• 27 kg/m² or greater (Overweight) in the presence of at least one weight-related comorbidity such as hypertension, type 2 diabetes mellitus or dyslipidemia.

List updated October 16th, 2015
Effect on A1C:
- A reduction of up to 0.9 % Belviq vs 0.4% with placebo.

Risk of hypoglycemia:
- Weight loss may increase the risk of hypoglycemia in patients with type 2 diabetes mellitus treated with insulin and/or insulin secretagogues (e.g., sulfonylureas); hypoglycemia was observed in clinical trials with BELVIQ.

Dosing
- Obesity: 10 mg ORALLY twice daily; discontinue at week 12 if 5% weight loss has not been achieved; MAX 20 mg/day.

Dosing adjustment
- Renal impairment, mild: no adjustment necessary
- Renal impairment, severe or esrd: use not recommended
- Hepatic impairment, mild to moderate: no adjustment necessary

Dosage forms:
Belviq Oral Tablet: 10 MG

Drug interactions:
Serotonergic drugs (selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), triptans, bupropion, dextromethorphan, St. John’s Wort): use with extreme caution due to the risk of serotonin syndrome.

Most common adverse reactions (Incidence greater than 5%)
Non-diabetic patient
- Headache
- Dizziness
- Fatigue
- Nausea
- Dry mouth
- Constipation

Diabetic patients
- Hypoglycemia
- Headache
- Back pain
- Cough

List updated October 16th, 2015
Fatigue

Contraindications

- Pregnancy; weight loss may cause fetal harm

Precautions:

- Bradycardia; decreased heart rate has been reported.
- Concomitant use with serotonergic and dopaminergic drugs that are potent 5-HT(2b) receptor agonists and that are known to increase the risk for cardiac valvulopathy (eg, cabergoline) is not recommended.
- Congestive heart failure; potentially increased risk of regurgitant cardiac valvular disease.
- Diabetes mellitus treated with insulin or insulin secretagogues (eg, sulfonylureas); risk of hypoglycemia; dose adjustment of antidiabetic medications may be necessary.
- Heart block greater than first degree; decreased heart rate has been reported.
- Hematologic changes, including decreased wbc (eg, leukopenia, lymphopenia, neutropenia, and decreased white cell count) and decreased rbc (eg, anemia and decreases in hemoglobin and hematocrit), have been reported; monitoring recommended.
- Hepatic impairment, severe; use with caution.
- Priapism may occur; increased risk with predisposing conditions (eg, sickle cell anemia, multiple myeloma, or leukemia) or anatomical deformation of the penis; immediate discontinuation required.
- Prolactin level elevations have been reported.
- Pulmonary hypertension may occur.
- Renal impairment, moderate; use with caution.
- Renal impairment, severe, or end-stage renal disease; use not recommended.
- Serotonin syndrome, including cases that are life-threatening or that resemble neuroleptic malignant syndrome, may occur; increased risk with concomitant serotonergic or antidopaminergic medications or drugs that impair serotonin metabolism; discontinue use if symptoms occur.
- Suicidal ideation and behavior, new-onset or worsening of depression and unusual changes in mood or behavior may occur; monitoring recommended; discontinue therapy if suicidal thoughts or behaviors develop.
- Valvular heart disease, regurgitant, may occur; drug discontinuation may be required.

Limitations of Use:

- The safety and efficacy of coadministration with other products for weight loss have not been established.
- The effect of BELVIQ on cardiovascular morbidity and mortality has not been established.

Patient Education:

- Advise patient to avoid activities requiring mental alertness or coordination until drug effects are realized, as drug may cause dizziness, confusion, and somnolence.
- Drug may cause headache, back pain, nausea, dry mouth, constipation, hypoglycemia, cough, and fatigue.

List updated October 16th, 2015
• Counsel patient to report signs/symptoms of serotonin syndrome (agitation, confusion, diaphoresis, hallucinations, hyperreflexia). Concurrent use of serotonergic agents (triptans, tryptophan) may increase risk for serotonin syndrome.

• Advise patient to report the emergence or worsening of depression, suicidal thoughts or behavior, and/or unusual changes in mood or behavior, especially at initiation of therapy or with dose changes.

• Advise patient to report signs/symptoms of valvular heart disease (eg, dyspnea or dependent edema).

• Advise patient to discontinue the drug and immediately report an erection that persists longer than 4 hours.

• Instruct patient to discontinue use if weight loss of at least 5% of baseline weight has not been achieved after 12 weeks of use.

Manufacturer Phone: 201-692-1100

List updated October 16th, 2015