Abstract: Each year, the FDA approves many pharmaceuticals and products designed to treat or improve a patient’s condition. The following is a sampling of some of the most important drugs approved in 2012 that specifically apply to nurse practitioner practice.

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Erectile dysfunction

Avanafil (Stendra)

Erectile dysfunction (ED) is defined as the persistent or recurrent inability to achieve or maintain an erection sufficient for satisfactory sexual performance.1,2 ED is associated with both impaired psychological health and reduced self-esteem.3 The emotional distress that a man may experience can impact the patient’s social or marital life, which leads to the need for treatment of this condition.

ED affects 30 million men in the United States and 150 million worldwide. This number is expected to increase as the population ages.1 It was found that the prevalence of ED increases with age (40% at 40 years of age, 70% at 70 years of age).1 ED occurs more often in males with diabetes, heart disease, previous radical prostatectomy, and neurologic conditions. ED is also associated with cardiovascular risk factors, which include hypertension, diabetes, dyslipidemia, chronic kidney disease, and obesity.4,5

A series of interrelated mechanisms play a role in the changes in vascular pressure within the cavernosal sinuses that cause penile erection. The main mechanism is the nitric oxide/cyclic guanosine monophosphate (NO/cGMP) pathway. Nitric oxide is released during sexual arousal or nocturnal tumescence, which causes smooth muscle relaxation in the trabeculae and arterioles of the penis.3,6 Cyclic nucleotide phosphodiesterases (PDEs) are a family of hydrolyzing enzymes that cleave cAMP or cGMP. The PDE that is the major cGMP-hydrolyzing enzyme in the cavernosal tissue is

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phosphodiesterase type 5 (PDE5). PDE5 plays an important role in regulating nitric oxide-mediated smooth muscle relaxation. PDE5 inhibitors are similar in structure to cGMP and competitively bind to PDE5. This binding inhibits the hydrolysis of cGMP, allowing for accumulation of cGMP levels, leading to penile erection. With this effective mechanism of action in mind, the oral PDE5 inhibitor therapy is recommended as first-line treatment for ED. The PDE5 inhibitors have been shown to restore penile blood flow and erections in response to sexual stimulation.

Despite these options, many men suffering from ED fail to respond clinically. Most of these men are patients with severe ED involving diabetes mellitus, severe vascular insufficiency, or postprostatectomy complications. Newer medications in the PDE5-inhibitor class are being studied that have greater efficacy and lower the adverse reaction profile.

Avanafil is a novel PDE5 inhibitor that was approved by the FDA on April 27, 2012. This medication has been shown to have greater selectivity of PDE5 and a higher selectivity against PDE1 and PDE6. Vivus, Inc. will market the drug under the brand name Stendra.

**Indication**

Avanafil is a PDE5 inhibitor approved for the treatment of ED.

**Mechanism of action**

Avanafil works by inhibiting the effect of PDE5 on degradation of cGMP. This inhibition leads to penile erection due to the inflow of blood into the area.

**Dosing and administration**

The recommended dose of avanafil is 100 mg by mouth 30 minutes prior to sexual activity. This medication can be taken without regards to food. Avanafil should be taken on an as needed basis, but no more than once a day. Based upon efficacy and tolerability, the dose can be increased to a 200 mg maximum dose or decreased to 50 mg. Dosing adjustments are not needed in patients with either mild or moderate renal or hepatic impairment. The drug should not be used in patients with severe renal or hepatic impairment.

**Contraindications**

Avanafil should not be used in combination with any form of organic nitrates. If a nitrate is needed and is seen as medically necessary in a life-threatening situation, 12 hours must have lapsed since a dose of avanafil was taken.

**Warnings and precautions**

There are cardiovascular risks associated with the use of avanafil during sexual activity in patients with preexisting cardiovascular disease. Avanafil should not be used in men who have been advised by their healthcare provider to abstain from sexual activity because of their cardiac history. Avanafil should not be used in the following patient groups:

- individuals who have had a myocardial infarction, stroke, life-threatening dysrhythmia, or coronary revascularization within the last 6 months
- men with resting hypotension or hypertension

The recommended dose of avanafil is 100 mg by mouth 30 minutes prior to sexual activity.

- men with unstable angina or angina that occurs during sexual intercourse
- patients with a diagnosed New York Heart Association (NYHA) class 2 or greater congestive heart failure

Avanafil has systemic vasodilatory properties that can have an effect on antihypertensive medications and augment the BP-lowering effects. Erections lasting more than 4 hours and priapism have been documented with the use of the other PDE5-inhibitors. Due to this information, patients taking avanafil need to be educated about this adverse reaction. Caution needs to be taken if avanafil is prescribed in patients who have an anatomical deformity of the penis or in patients who have other medical conditions that predispose them to priapism.

Avanafil should be stopped immediately if the patient experiences vision loss in one or both eyes. This can be a sign of permanent vision loss called nonarteritic anterior ischemic optic neuropathy (NAION).

The other PDE5-inhibitors have been documented to have a sudden decrease or loss in hearing, which can occur with tinnitus or dizziness. Patients who experience any of these symptoms should stop taking avanafil immediately.

Avanafil should be used with caution in patients taking alpha-blockers due to the vasodilating effects of the PDE5-inhibitors. The following must be considered in the outlined patient populations:

- Men should be on stable alpha-blocker therapy prior to starting avanafil.
- Men who are on stable dosing of alpha-blocker therapy should be started on avanafil at the lowest dosage of 50 mg.
**Adverse reactions**
Throughout clinical trial experience, the most commonly documented adverse reactions included headache, flushing, nasal congestion, nasopharyngitis, and back pain. These adverse reactions were seen in 2% or more of the patients studied in clinical trials. Other adverse reactions that occurred in less than 2% of the patients included the following: upper respiratory infection (URI), bronchitis, sinusitis, sinus congestion, influenza, hypertension, nausea, dyspepsia, constipation, and rash.10 Back pain, dizziness, arthralgia, and diarrhea were also documented in open-label extension trials.

**Drug interactions**
The use of avanafil in combination with any organic nitrate is contraindicated. In a life-threatening situation, nitrate medication can only be administered at least 12 hours after the last dose of avanafil was administered.10 Caution must be taken when using avanafil concomitantly with alpha-blocker medications and antihypertensive medications.

The use of alcohol along with avanafil is not recommended due to the increased potentiation of BP-lowering effects leading to orthostatic hypotension, headache, and dizziness.10 Because avanafil is a substrate of CYP3A4, any medication that inhibits CYP3A4 can increase the concentration of avanafil.

**Pharmacokinetics**
Avanafil is administered orally and is rapidly absorbed. A patient can experience a peak concentration in 30 to 45 minutes. Avanafil is metabolized and cleared by the liver. Its metabolites are excreted in both the feces and urine. The half-life of avanafil is 5 hours.10

**Clinical pearls**
- Avanafil is a pregnancy category C drug.
- Avanafil is to be administered 30 minutes prior to sexual activity, and is to be used on an as-needed basis, but not more than once a day.
- Patients should be educated about the danger of an erection lasting longer than 4 hours or priapism. Patients should know to seek medical attention immediately.
- Avanafil should not be prescribed for patients with a documented cardiovascular disease.
- Patients should stop taking avanafil, and seek medical attention if they experience sudden loss of vision or a decrease or loss of hearing.
- A patient who experiences any suspected adverse reactions should contact Vivus at 1-866-330-1871 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.10

**REFERENCES**

**HIV-1 infection**

**Elvitegravir, cobicistat, emtricitabine, tenofovir disoprophil fumarate (Stribild)**
AIDS is a global pandemic.1 Antiretroviral medications have helped tremendously decrease the morbidity and mortality associated with HIV. Since the mid-1990s, international guidelines recommend initial treatment to consist of a combination of at least three active agents from two or more classes of antiretroviral drugs.2 The guidelines recommend that for patients who are treatment-naive to be initially started with two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) plus a nonnucleoside reverse transcriptase inhibitor (NNRTI), usually efavirenz (EFV), a ritonavir-boosted protease inhibitor (PI), or the integrase strand transfer inhibitor raltegravir. The guidelines also mention the use of a fixed-dose combination...
tablet of emtricitabine (FTC) plus tenofovir disoproxil fumarate (TDF) as a backbone to therapy.3

The current treatment regimens have successfully improved HIV morbidity and mortality, but the regimens are associated with heavy pill burdens, multiple dosing per day, and unwanted adverse reactions. The pill burden and dosing regimens affect patient adherence, can lead to treatment failure, and the need for regimen changes that can be more costly.4

Combination therapy for HIV has been more effective due to the constantly changing genetic material of HIV mutations. Resistance can occur to all current classes of antiretroviral therapy and can occur easily due to the rapid application of HIV and its turnover.1 Regimens that include the ritonavir-boosted PI have shown the ability to decrease the development of drug resistance in comparison to the alternative regimens with NNRTIs. Ritonavir-boosted regimens are well-tolerated but have documented metabolic complications, including dyslipidemia, lipodystrophy, insulin resistance, and multiple drug interactions. The major limitation of ritonavir is the need for an additional pill to the regimen, leading to tolerability issues and pill burdens.5

Elvitegravir (EVG) is a once-daily HIV integrase strand transfer inhibitor that demonstrates potent antiretroviral activity when given with pharmacokinetic boosting.2,3 EVG can be given in combination with either ritonavir or cobicistat (COBI). COBI has a better adverse-effect profile in comparison to ritonavir. COBI is a new chemical entity that is used as a pharma-enhancer (booster) to increase the systemic exposure levels of concomitant medications that are metabolized by CYP3A enzymes, including EVG and/or HIV PIs that require boosting.6 It also has a long elimination half-life, which allows once-a-day dosing. COBI does not have any antiviral activity, so there is no concern of the development of PI resistance that is usually seen with ritonavir combination therapy.7,8

A single tablet regimen has been developed and investigated that contains EVG, COBI, emtricitabine (FTC), and TDF. This combination product has been shown to have the same antiretroviral activity as EFV/FTC/TDF.2

On August 27, 2012, the FDA approved elvitegravir (EVG)/cobicistat (COBI)/emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF), under the brand name Stribild, which is a combination of two previously approved HIV medications FTC and TDF, in addition to two new medications EVG and COBI.9,10 This regimen is to be used in treatment-naïve adults. EVG/COBI/FTC/TDF will be made available through Gilead Sciences, Inc.9

**Indication**

EVG/COBI/FTC/TDF is FDA approved as a complete regimen for the treatment of HIV-1 infection in adults who are antiretroviral treatment naïve.11

**Mechanism of action**

EVG/COBI/FTC/TDF is a combination product comprised of antiviral medications and a pharmacokinetic enhancer. All four medications need to have a full explanation of their mechanisms of action to understand the combination.

COBI does not have any antiviral activity, so PI resistance is not a concern.

EVG works by inhibiting the strand transfer activity of HIV-1 integrase. HIV-1 integrase is an enzyme that is needed for viral replication. The inhibition achieved by EVG prevents the integration of HIV-1 DNA into host genomic DNA, blocking HIV-1 previous formation and propagation of the viral infection.11

COBI is a selective mechanism-based inhibitor of CYP3A. It works by enhancing the exposure of CYP3A substrates, leading to the enhancement of bioavailability, and increasing the half-life of medications such as EVG. Thus, COBI exhibits booster-like activity.

FTC works by inhibiting the activity of HIV-1 RT by a competitive fashion and becomes incorporated into the viral DNA, which causes chain termination.11

TDF inhibits the activity of HIV-1 RT by competing for incorporation into DNA leading to DNA chain termination.11

**Dosing and administration**

EVG/COBI/FTC/TDF is comprised of the following: elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg, and tenofovir disoproxil fumarate 300 mg. EVG/COBI/FTC/TDF is to be taken as one tablet once a day with food.11

Do not use EVG/COBI/FTC/TDF in patients with renal impairment as defined with a creatinine clearance below 70 mL/min. Discontinue the drug in patients who have a drop in their creatinine clearance to less than 50 mL/min.11

For patients with mild or moderate hepatic impairment, no dosing adjustments are needed when using EVG/COBI/FTC/TDF. If a patient develops severe hepatic impairment, EVG/COBI/FTC/TDF should be discontinued due to a lack of research in this patient population.11

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**Contraindications**

EVG/COBI/FTC/TDF should not be used in combination with medications that are dependent upon CYP3A for clearance. When used concomitantly, these medications can show an increase in plasma concentrations and, in turn, lead to resistance of EVG/COBI/FTC/TDF.\(^{11}\)

**Warnings and precautions**

A Boxed Warning is associated with the use of EVG/COBI/FTC/TDF. The Boxed Warning covers lactic acidosis/severe hepatomegaly with steatosis and posttreatment acute exacerbation of hepatitis B. Tenofovir is the main drug that causes lactic acidosis and severe hepatomegaly with steatosis. EVG/COBI/FTC/TDF is not to be used for the treatment of chronic hepatitis B virus infection. Two components of EVG/COBI/FTC/TDF, emtricitabine and tenofovir, have been associated with exacerbations of hepatitis B. It is important to continually monitor hepatic function in these patients.\(^{11}\)

Patients using EVG/COBI/FTC/TDF can develop new or worsening renal impairment. This impairment can include acute renal failure and Fanconi syndrome.\(^{11}\) It is important to obtain baseline renal function information prior to starting EVG/COBI/FTC/TDF in addition to periodic monitoring throughout treatment.

In patients who are at risk for experiencing osteoporosis, bone loss, or a fracture, monitoring of bone mineral density is needed.\(^{11}\) EVG/COBI/FTC/TDF has the potential of decreasing bone mineral density.\(^{11}\)

Do not coadminister EVG/COBI/FTC/TDF with any drugs that can contain any of the individual drug components of EVG/COBI/FTC/TDF. Do not use EVG/COBI/FTC/TDF in combination with drugs containing emtricitabine or tenofovir, or with drugs containing lamivudine or adefovir dipivoxil.

As with all antiretroviral medications, EVG/COBI/FTC/TDF can cause immune reconstitution syndrome.

**Adverse reactions**

Through clinical trial experience, in addition to the adverse reactions mentioned in the warnings and precautions section, the most commonly observed adverse reactions include nausea, diarrhea, headache, fatigue, and abnormal dreams. Other adverse reactions include depression, dyspepsia, back pain, insomnia, and rash.\(^{11}\)

**Drug interactions**

Since EVG/COBI/FTC/TDF is the complete regimen for the treatment of HIV, no other antiretroviral is needed to be administered. Do not give EVG/COBI/FTC/TDF in combination with other medications indicated for the treatment of HIV.\(^{11}\)

As mentioned previously, do not give EVG/COBI/FTC/TDF in conjunction with medications that are metabolized by CYP3A and CYP2D6. These drug interactions can lead to altered concentrations of EVG/COBI/FTC/TDF.\(^{11}\)

**Pharmacokinetics**

EVG/COBI/FTC/TDF is administered orally. Peak plasma concentrations for each of the drug components are EVG (4 hours), COBI (3 hours), FTC (3 hours), and TDF (2 hours).\(^{11}\) EVG is metabolized by the CYP3A pathway, and it also undergoes glucuronidation via UGT1A1/3 enzymes. COBI is metabolized by CYP3A, and to a lesser extent, by CYP2D6. Emtricitabine and tenofovir are not significantly metabolized.\(^{11}\) Drug elimination is via feces and urine for EVG and COBI, and via urine for FTC and TDF.\(^{11}\)

**Clinical pearls**

- EVG/COBI/FTC/TDF is a pregnancy category B drug.
- Both FTC and TDF can be detected in breast milk. Mothers taking EVG/COBI/FTC/TDF should not breastfeed while on this medication.
- Patients should understand the signs and symptoms associated with the development of lactic acidosis: weak or tired feeling, unusual muscle pain, difficulty breathing, and cold extremities.
- Patients should be instructed to contact their healthcare provider if they develop symptoms associated with the development of liver abnormalities: jaundice, icterus, dark urine, light-colored bowel movements, nausea, and/or loss of appetite.
- EVG/COBI/FTC/TDF is an all-in-one medication for the treatment of HIV and should be taken once daily with food.
- The most common adverse reactions with EVG/COBI/FTC/TDF are nausea and diarrhea. Patients who experience any other suspected adverse reactions should contact Gilead Sciences, Inc. at 1-800-GILEAD-5 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
• Gilead’s UC Advancing Access program provides assistance to patients who do not have insurance or who need financial assistance to pay for their medications. Have patients contact Advancing Access at 1-800-266-2056.

• For patients with private insurance, Gilead’s copay coupon program provides assistance with out-of-pocket expenses for Gilead’s HIV medications starting at the first dollar.9,11

REFERENCES
9. Anon. US FDA approved Gilead’s Stribild, a complete once-daily single tablet regimen for treatment-naive adults with HIV-1 infection. www.gilead.com/pr_/1728981.0

Lorcaserin is an agonist of the 5-HT2C receptor that has been designed and studied for weight loss.

Serotonin shows its effects through 14 different receptors. The serotonin 5-HT1 receptor contains three receptor subtypes: 5-HT1A, 5-HT1B, and 5-HT1D.8 The 5-HT2C receptors are found primarily in the central nervous system and are important in controlling mood, cognition, and appetite. Activation of the 5-HT2C receptor can increase satiety and decrease hunger, leading to decreased food intake.9 Through the history of trying to develop 5-HT2C agonists, there has been a lack of selectivity over 5-HT1A and 5-HT2B receptors. When activated, 5-HT2B can cause hallucinations. Activation of 5-HT2B can lead to the development of cardiac valvular insufficiency and pulmonary hypertension.10 With research, better selectivity of 5-HT2C and the development of 5-HT2C receptor agonists, more efficacious weight loss medications can be developed without the historical adverse reactions experienced by the older, nonselective serotonin agonists. Additionally, 5-HT2C selective agents can potentially have a role in glucose tolerance regulation and sensitivity of hepatic insulin.4,9

Lorcaserin is an agonist of the 5-HT2C receptor that has been designed and studied for weight loss.10 Lorcaserin is the first selective 5-HT2C agonist. This medication

Obesity

Lorcaserin (Belviq)

In 2008, it was estimated that 33.9% of adults were obese, and 34.4% were overweight.1,2 Obesity is defined as an individual having a body mass index (BMI) of 30 or greater; overweight is a BMI of 25 to 29.9. Excess body weight increases the risk of developing type 2 diabetes, hypertension, hyperlipidemia, stroke, heart disease, respiratory problems, sleep apnea, osteoarthritis, depression, and several types of cancer.3-5

Sustained weight loss of 5% to 10% in obese individuals can have a positive impact on several cardiovascular risk factors, decrease the incidence of type 2 diabetes, and reduce pain that is associated with osteoarthritis.5 Weight loss should start with healthy eating, physical activity, and behavior modifications. The use of medications in the fight against obesity can augment the initial weight loss options and can also provide additional benefit for some patients who did not attain adequate weight loss by lifestyle modifications alone. Dexfenfluramine was the first medication approved for the long-term treatment of obesity. Fenfluramine is the racemic mixture of dexfenfluramine and was used as both monotherapy and in combination with phentermine for weight loss. Both of these medications were removed from the market due to documentation that showed these drugs increased the risk of cardiac valvulopathy and pulmonary hypertension.6,7 Both dexfenfluramine and fenfluramine worked to suppress the appetite by inhibiting serotonin (5-HT) reuptake and increasing 5-HT release.5 After the removal of these agents from the market, more research was completed in improving the understanding of the actions of the 5-HT receptor subtypes that are involved in appetite suppression.
was approved by the FDA on June 27, 2012. Lorcaserin will be marketed under the brand name Belviq and will be distributed by Eisai, Inc.11

■ Indication
Lorcaserin is approved as an adjunct therapy to lifestyle modifications, a reduced-calorie diet, and increased physical activity for weight management in patients with either a BMI of 30 or greater, a BMI of 27 to 29.9, and a weight-related, comorbid condition such as type 2 diabetes, hypertension, or dyslipidemia.12

■ Mechanism of action
Lorcaserin’s exact mechanism of action is unknown. The proposed mechanism is that it decreases food consumption and promotes satiety through selective activation of 5-HT2C receptors. These receptors are located within the hypothalamus on the anorexigenic proopiomelanocortin (POMC) neurons. POMC is a precursor for alpha-melanocortin-4 receptors to decrease food intake.12

■ Dosing and administration
Lorcaserin is dosed 10 mg by mouth twice daily. The doses can be administered without regard to food, and dosing adjustments are not needed based upon tolerability.12

No dosing adjustments are needed in patients with mild renal impairment. Caution should be taken in patients with moderate renal impairment. Lorcaserin should not be used in patients with severe renal impairment or end-stage renal disease.12

For patients with mild-to-moderate hepatic impairment, lorcaserin dosing does not need to be modified. The drug should not be used in patients with severe hepatic impairment.12

Therapy should be evaluated at week 12. If a patient has not lost at least 5% of baseline body weight, lorcaserin should be stopped, since the patient is not responding and will not be able to sustain appropriate weight loss.12

■ Contraindications
Lorcaserin is contraindicated in women who are pregnant. Therefore, this medication is a pregnancy category X drug.12

■ Warnings and precautions
There are a number of warnings and precautions that the provider should know when prescribing Lorcaserin.

Since Lorcaserin is a serotonergic medication, patients taking this drug can be at risk for developing serotonin syndrome or neuroleptic malignant syndrome (NMS)-like symptoms. Serotonin syndrome is associated with chills, tremors, confusional state, disorientation, hyperhidrosis, nausea, vomiting, and diarrhea. When serotonin syndrome is at its most severe state, it can resemble NMS in which the patient will experience hyperthermia, muscle rigidity, autonomic instability, and mental status changes.12 If, for some reason, lorcaserin must be used in patients taking a serotonergic medication, extreme caution and close monitoring are needed.

As seen with the other 5-HT, agonists, dexfenfluramine and fenfluramine, there is a risk of developing valvular heart disease. Symptoms associated with valvular heart disease include dyspnea, edema, heart failure, or a cardiac murmur that is newly diagnosed. Lorcaserin should not be prescribed to patients with heart failure.12

It has been documented that there is an increase in risk of developing attention and memory impairments, confusion, fatigue, and somnolence while taking lorcaserin. All patients starting treatment with this medication should be cautioned about the operation of machinery and automobiles until they gain a better understanding of the effects of the medication on their functioning.12

Patients should be monitored for signs and symptoms of euphoria, hallucinations, and dissociation, in addition to new development or worsening of depression, suicidal thoughts or behavior, or changes in mood or behavior.12

In patients with diabetes that are currently receiving treatment, the use of lorcaserin can increase the risk of developing hypoglycemia; therefore, adjustments should be made to the treatment regimens of the antidiabetic medications.

Lorcaserin, like all 5-HT2C receptor agonists, can increase the risk of developing priapism. Lorcaserin should not be used in men with diagnosed conditions that can cause priapism such as sickle-cell anemia, multiple myeloma, leukemia, or in men with an anatomical deformity of the penis.12

Lorcaserin can cause a decrease in heart rate. Patients with bradycardia or a history of heart block should be monitored.12

Routine lab monitoring is needed while a patient is taking lorcaserin. Nurse practitioners (NPs) should consider monitoring a complete blood count with a focus on white blood cell count and prolactin levels. Lorcaserin
can decrease white blood cell count and increase prolactin levels.12

Due to the incidence of developing pulmonary hypertension associated with other serotonin-acting weight-loss medications (fenfluramine and dexfenfluramine), patients should be monitored for signs and symptoms of developing pulmonary hypertension.12

Although clinical trials did not show this development, caution is warranted based on history of other medications that work by similar mechanism of action.

### Adverse reactions

In addition to the adverse reactions outlined in the “Warnings and Precautions” section, clinical trial experience shows that the most common documented adverse reactions include nausea, vomiting, headache, and dizziness. Other common adverse reactions that can occur include nasopharyngitis, URI, constipation, and dizziness. Other common adverse reactions that work by similar mechanism of action.

### Drug interactions

Lorcaserin can increase exposure of CYP2D6 substrates, so monitoring is necessary. Due to the potential for developing serotonin syndrome, the use of lorcaserin with other medications that can affect the serotonergic neurotransmitter system should be monitored.12 Refer to the manufacturer’s prescribing information for a complete list of medications that can affect the serotonergic neurotransmitter system.

### Pharmacokinetics

After oral administration, lorcaserin is absorbed from the gastrointestinal tract. It reaches a peak plasma concentration within 1.5 to 2 hours. Steady state is reached within 3 days and has a half-life of 11 hours. Lorcaserin is 70% bound to plasma proteins, and is distributed into the cerebrospinal fluid and central nervous system. This medication is extensively metabolized in the liver by multiple enzymatic pathways. The major route of elimination for the metabolites is the urine with minor elimination in the feces.12

### Clinical pearls

- Lorcaserin is a pregnancy category X drug.
- The safety and efficacy of combination therapy including lorcaserin and any other weight loss prescription medication have not been studied. Weight loss medications should not be combined with lorcaserin.
  - It is important to evaluate patients’ weight loss progress by week 12. If the patient did not lose at least 5% of baseline body weight at that point, the patient is considered a nonresponder, and lorcaserin should be stopped.
  - Lorcaserin is approved for chronic weight management in combination with a reduced-calorie diet and exercise.
  - Patients should know the signs and symptoms associated with valvular heart disease such as dyspnea, edema, dizziness, fatigue, or weakness, and fast or irregular heartbeat.
  - Patients should understand the importance of seeking medical attention in the event of new or worsening depression, suicidal thoughts, or changes in mood or behavior.
  - NPs should obtain a full medication list from any patient taking lorcaserin, including over-the-counter medications, vitamins, and herbal supplements.
  - Patients should report any adverse events to Eisai, Inc. at 1-888-274-2378 or the FDA at 1-800-FDA-1088 or www.fda.gov/memwatch.12

### REFERENCES

Respiratory distress syndrome

Lucinactant (Surfaxin)

Respiratory distress syndrome (RDS) is the leading cause of morbidity and mortality in preterm infants. The incidence of RDA is inversely related to gestational age and results from morphologic and biochemical immaturity of the lungs. Developmental and biochemical abnormalities are associated with preterm delivery. Morphologically, the lung parenchyma has decreased alveoli, leading to a decrease in surface area, which causes a reduction in gas exchange. Absent or inadequate production of pulmonary surfactant results in high alveolar surface tension and a tendency toward progressive atelectasis, with alterations in pulmonary gas exchange and lung mechanics. In addition to a decrease in surfactant levels, these patients experience deficiencies in antioxidants and anti-inflammatory modulators that can worsen RDS and lead to the development of chronic lung disease and bronchopulmonary dysplasia (BPD).

Surfactant replacement therapy with either animal-derived or synthetic surfactants can reduce mortality.

Pulmonary surfactant is composed of lipids and proteins that work together to form a layer at the air-water interface of the alveoli in addition to lowering surface tension to prevent alveolar collapse.

Surfactant replacement therapy with either animal-derived or synthetic surfactants can improve oxygenation and reduce mortality. Animal-derived surfactants are obtained by lung lavage or from lung minces from cows or pigs that are purified and extracted with organic solvents. The problems with animal-derived products include the following: the amount of surfactant protein (SP)-B differs among the formulations; the compositions can have varying protein amounts; carry the risk of transmission of infectious agents; evoke immunogenicity to foreign proteins; and the introduction of proinflammatory mediators. Synthetic surfactants have compositions that can be easily reproduced, are free from the risk of developing immune reactions or infections, have an identified improvement outcome, and can be produced in large quantities.

Although surfactant replacement therapy has dramatically improved the survival of preterm infants, it has not shown to reduce the incidence of BPD. Currently, antenatal corticosteroid treatment, surfactant replacement therapy, and mechanical ventilation are the main treatments for preterm infants with RDS.

Lucinactant is a bioengineered synthetic compound that contains a mixture of phospholipids and a unique peptide that functions as human SP-B. Lucinactant (Surfaxin) was approved by the FDA on March 6, 2012, and is manufactured and distributed by Discovery Laboratories, Inc., a specialty biotechnology company that is dedicated to respiratory critical care treatments.

Indication

Lucinactant is indicated for the prevention of RDS that occurs in premature infants at high risk for developing RDS. Lucinactant has been shown to reduce the incidence of RDS at 24 hours and mortality due to RDS.

Mechanism of action

Lucinactant, with the help of the presence of SP-B, works by lowering the surface tension of the alveolar air-water interface. This stabilizes the alveoli against collapse at resting pulmonary pressures. Lucinactant helps improve lung compliance and gas exchange in the lungs by being the compensatory agent for the deficiency of surfactant these patients experience; it also helps restore surface activity to the infant’s lungs.

Dosing and administration

Only healthcare providers experienced in intubation, ventilator management, and general care of premature infants should use lucinactant. The recommended starting dose is 5.8 mL/kg birth weight. Within the first 48 hours of life, up to four doses can be given, and this medication should not be used more than every 6 hours. Refer to the manufacturer’s prescribing information for dosing recommendations and directions for use.

Before administering a dose, the vial should be removed from the refrigerator and warmed for 15 minutes in a dry block heater set at 111.2° F (44° C). After warming is completed, the vial must be shaken vigorously until the liquid is in a uniform and free-flowing suspension. Sterile technique must be used to draw up the suspension into a syringe. After ensuring proper placement of the endotracheal tube, the infant should be placed in the right lateral decubitus position with the head and thorax inclined upward 30 degrees. Each dose of lucinactant must be given in four aliquots. The first aliquot is one-fourth of the total volume instilled as a bolus while the infant is turned in the right lateral decubitus position. The procedure should be repeated while the infant is in the left decubitus position, followed by the right, then the left to administer all four aliquots. Between each aliquot, the infant’s respiratory status should be assessed. The infant should be ventilated until stable (oxygen saturation 90% or greater and a heart rate...
rate 120 beats/minute or greater). After the lucinactant is instilled completely, the head of the bed is elevated at least 10 degrees for 1 to 2 hours.6

■ Contraindications
There are no documented contraindications associated with lucinactant.

■ Warnings and precautions
Exogenous surfactants including lucinactant can rapidly change lung compliance and oxygenation. Throughout administration of lucinactant, the infant should be monitored for respiratory changes and have oxygen and ventilator support interventions as needed.6

There are a number of administration-related adverse reactions associated with lucinactant. These can include bradycardia, oxygen desaturation, reflux of the drug into the endotracheal tube, and airway obstruction.6 If any of these occur, the dosing of lucinactant should be stopped, and the patient stabilized. Once the infant is suctioned and stabilized, dosing can be restarted with increased monitoring.6

■ Adverse reactions
In clinical trials, the most common administration-related adverse reactions associated with lucinactant included pallor, endotracheal tube reflux, dose interruption, and endotracheal tube obstruction.6 In the continuation of the trials, the following adverse reactions were documented in infants 36 weeks postconceptual age: anemia, jaundice, metabolic acidosis, oxygen desaturation, hyperglycemia, pneumonia, hyponatremia, hypotension, respiratory acidosis, and bradycardia.6

■ Drug interactions
There are no documented drug interactions associated with lucinactant.

■ Pharmacokinetics
The absorption, distribution, metabolism, or elimination of lucinactant has not been studied because it is administered directly to the lungs, and the effects occur at the terminal airways and alveolar surface.6

■ Clinical pearls
• Lucinactant should only be used by healthcare professionals experienced in intubation, ventilator management, and general care of premature infants.
• Lucinactant should not be returned to the refrigerator after warming. The vial should be discarded if not used within 2 hours of warming.
• Each vial is intended for single use only.
• Providers should not suction the infant during the first hour after dosing unless the infant exhibits signs of significant airway obstruction.
• Lucinactant needs to be stored in the refrigerator at 36° F (2° C) to 46° F (8° C) and protected from light until ready for administration.
• If a patient experiences any suspected adverse reactions, providers should contact Discovery laboratories, Inc. at 1-877-DURFAXN or the FDA at 1-880-FDA-1088 or www.fda.gov/medwatch.*

REFERENCES

Endogenous Cushing syndrome

Mifepristone (Korlym)
Cushing syndrome results from chronic exposure to excessive, endogenous, or exogenous glucocorticoids. If there is an excess, endogenous glucocorticoids are primarily a consequence of excess production and not inadequate destruction of glucocorticoids. This elevation of glucocorticoid secretion can be caused by two sources: (1) an autonomously functioning adrenal cortex or (2) from an excessive production of adrenocorticotropic hormone (ACTH).1,3 Chronic exposure to excessive corticosteroids can lead to the development of multiple metabolic abnormalities, including glucose intolerance, dyslipidemia, hypertension, osteoporosis, and weight gain.4

The first-line treatment for malignant Cushing syndrome is surgery—especially in cases of adrenocortical carcinoma and ectopic ACTH secretion—and chemotherapy and/or radiotherapy for advanced disease.5 Medications that control excessive glucocorticoid secretion include aminoglutethimide, ketoconazole, metyrapone, and mitotane.6 These drugs are associated with significant adverse reactions. They all work by decreasing adrenal
steroid secretion. Another option that works as a glucocorticoid antagonist is mifepristone.

Mifepristone was originally developed in the early 1980s as an antiprogestin but was considered an antiglucocorticoid compound. Since it had such strong antiprogestin activity, investigators started to research this medication for use in progesterone-dependent conditions such as pregnancy. \(^6\) Complete abortion is achieved with the combination of mifepristone and a prostaglandin.

Mifepristone was shown to act as an antiglucocorticoid by antagonizing the negative feedback on the pituitary of endogenous and exogenous glucocorticoids. With this information, the use of mifepristone in patients with glucocorticoid excess was closely studied.

On February 17, 2012, mifepristone was approved for the treatment of hyperglycemia in adults with endogenous Cushing syndrome. Mifepristone is marketed under the brand name Korlym by Corcept Therapeutics. \(^7\)

**Indication**

Mifepristone is recommended for use in patients with endogenous Cushing syndrome to control hyperglycemia. It should only be used in patients with type 2 diabetes or glucose intolerance who have either failed surgery or are not candidates for surgery. \(^8\)

**Mechanism of action**

At higher doses, mifepristone is able to overcome the progesterone receptor antagonism and block the glucocorticoid receptor. It has a greater affinity for the glucocorticoid type II (GR-II) receptor over the GR-I receptor. Mifepristone does not have an effect on estrogen, muscarinic, histaminic, or monoamine receptors. \(^5\) Mifepristone blocks the binding of cortisol to its receptors, which decreases the levels of cortisol, including high blood glucose.

**Dosing and administration**

Mifepristone must be started with a dose of 300 mg once daily taken with food. This medication should be given in a single dose; do not split, crush, or chew the tablet. \(^8\) Every 2 to 4 weeks, the dose may be titrated in 300 mg increments to a maximum dose of 1200 mg, without exceeding 20 mg/kg/day. \(^8\) Each dose adjustment should be based upon tolerability and improvement of symptoms. Early changes in symptom response can include changes in glucose control, antidiabetic medication requirements, changes in insulin levels, and improvements in psychiatric symptoms. Symptoms that change later include changes in cushingoid appearance, hirsutism, acne, and body weight. \(^8\) Each of these changes will help properly complete the dosing titrations.

Mifepristone can be used in both renal impairment and mild-to-moderate hepatic impairment at a maximum dose of 600 mg daily. Mifepristone is not recommended to be used in patients with severe hepatic impairment. \(^8\)

**Contraindications**

Mifepristone is not to be used in pregnant women or in women who have a history of unexplained vaginal bleeding, endometrial hyperplasia, or carcinoma. \(^8\)

Mifepristone is not to be used in combination with any medication that is metabolized via the CYP3A, which includes simvastatin, lovastatin, cyclosporine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus. This combination will increase the risk of adverse events. \(^8\)

Since mifepristone antagonizes glucocorticoids, it should not be used in combination in patients who require systemic corticosteroids for other conditions. \(^8\)

**Warnings and precautions**

There are a number of warnings and precautions associated with mifepristone. Patients taking mifepristone should be monitored for the development of adrenal insufficiency. Signs and symptoms that can occur include nausea, weakness, fatigue, hypotension, and hypoglycemia. Once adrenal insufficiency is suspected and diagnosed, mifepristone should be stopped, and the patient should be started on glucocorticoids to reverse symptoms. \(^8\)

Mifepristone may cause hypokalemia. Potassium levels should be monitored prior to starting therapy and then again 1 to 2 weeks after starting therapy or with any dose change. For patients who need replacement, oral or I.V. potassium can be used. \(^8\)

Mifepristone should be used with caution in patients who have hemorrhagic disorders, since this medication has the potential to increase vaginal bleeding and cause endometrial changes. \(^8\)

Mifepristone produces a dose-dependent change in the QT interval. Patients may experience QT prolongation. \(^4\) Periodic monitoring is required.

Patients with endogenous Cushing syndrome who are taking mifepristone are also at risk for opportunistic infections, such as *Pneumocystis jiroveci* pneumonia, and should be monitored for signs of infection.
Mifepristone should be taken with food to ensure...

**Drug interactions**

Mifepristone has a significant effect on the CYP450 isoclass system. Mifepristone is a CYP3A inhibitor, and concomitant use with a medication that relies on CYP3A to be metabolized will cause the medication to have higher plasma concentrations. For drugs that inhibit CYP3A, mifepristone concentrations can be increased, requiring a dose reduction. Avoid coadministration of mifepristone and drugs that are CYP3A inducers, in which a dose reduction of the inducers medication many be needed. Mifepristone is also an inhibitor of CYP2C8/2C9 and CYP2B6. Concurrent administration of mifepristone with medications that rely on these isoenzymes to be metabolized will cause an increase in their plasma levels. Mifepristone is a progesterone-receptor antagonist and will interfere with hormonal contraceptives. Concurrent use is not recommended.

**Pharmacokinetics**

After oral absorption, the peak plasma concentration of mifepristone is reached within 1 to 2 hours. Steady state is reached in 2 weeks, and it has a half-life of 85 hours. Mifepristone and its metabolites bind to albumin and are distributed to the central nervous system and other tissues. Mifepristone is metabolized by CYP3A4 and is excreted via the fecal route.

**Clinical pearls**

- Mifepristone is a pregnancy category X drug.
- Patients requiring contraception should only use nonhormonal contraceptives. Mifepristone should not be used in the treatment of patients with type 2 diabetes unrelated to Cushing syndrome.
- Mifepristone should be taken with food to ensure appropriate plasma levels.
- Mifepristone is not to be used in patients who are pregnant because the medication can terminate the pregnancy.
- A patient who suspects she is pregnant must inform a healthcare provider immediately.
- Adverse events should be reported to Corcept Therapeutics at 1-855-844-3270 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**REFERENCES**


**Overactive bladder**

**Mirabegron (Myrbetriq)**

About 33 million people in the United States suffer from overactive bladder. Overactive bladder has symptoms that include urinary frequency, urinary urgency, and urge urinary incontinence. Researchers have recently discovered that beta-1, -2, and -3 adrenoreceptors are in the human urothelium and detrusor muscle. The urothelium has three layers: an apical cell layer, an intermediate layer, and a basal cell layer. When the beta-2 and -3 adrenoreceptors are stimulated, relaxation of the detrusor muscles occur, which is due to the activation of G proteins and adenylyl cyclase. This subsequently leads to increased levels of cyclic adenosine monophosphate. Beta-3 adrenoreceptors relax the detrusor muscle during the storing phase of the micturition cycle, thus, improving the bladder’s storage capacity without leading to unwanted voiding.

Mirabegron is a new, selective beta-3 adrenoreceptor agonist that decreases the frequency of bladder contractions that occur during the filling phase but does not suppress bladder during micturition.

On June 28, 2012, mirabegron, an extended-release tablet, was approved for the treatment of overactive bladder in adult patients. Mirabegron, the first beta-3 adrenoreceptor agonist, is marketed under the brand name Myrbetriq by Astellas Pharma US, Inc.

**Indication**

Mirabegron has been approved for the treatment of overactive bladder, encompassing the symptoms of urge urinary incontinence, urgency, and urinary frequency.

**Mechanism of action**

Mirabegron works by relaxing the detrusor smooth muscle during the storage phase due to the increase in

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**REFERENCES**


bladder capacity. This occurs in the urinary bladder fill-void cycle.  

- **Dosing and administration**
  Mirabegron should be started at a daily dose of 25 mg taken with or without food. The patient should experience the full effect of mirabegron within 8 weeks of starting therapy. Based upon the patient’s tolerability and overall effect of the medication, the dose can be increased to 50 mg once daily. Patients with either severe renal impairment or moderate hepatic impairment should take only 25 mg daily. Do not prescribe mirabegron for patients who have end-stage renal disease or severe hepatic impairment.  

- **Contraindications**
  Mirabegron has no documented contraindications.  

- **Warnings and precautions**
  Mirabegron may increase BP. Periodic BP monitoring is recommended, especially for patients with hypertension. The drug is not recommended for use in patients with severe uncontrolled hypertension (systolic BP of 180 mm Hg or greater and/or a diastolic BP of 110 mm Hg or greater).  

- **Adverse reactions**
  During clinical trials, the most commonly documented adverse reactions included hypertension, nasopharyngitis, nausea, diarrhea, constipation, headache, dizziness, and tachycardia. Other adverse reactions that occurred in less than 5% of patients included urinary tract infection, abdominal pain, and arthralgia.  

- **Drug interactions**
  The major drug interactions associated with the use of mirabegron that require monitoring are digoxin, warfarin, and drugs metabolized by CYP2D6. For all patients starting a combination of mirabegron and digoxin, the lowest dose of digoxin should be used and increased as needed based on serum digoxin levels. Mirabegron increases serum digoxin levels. As for warfarin, it has been shown that Mirabegron will increase the S- and R-warfarin maximum concentration and area under the curve. Prothrombin time and the international normalized ratio need to be monitored. Mirabegron is a CYP2D6 inhibitor. Caution must be taken when using mirabegron in combination with agents that are metabolized by the CYP2D6 enzyme. When these two medications are used in combination, mirabegron can cause an increase in exposure of the interacting medication.  

- **Pharmacokinetics**
  Mirabegron is orally absorbed and will reach a maximum concentration within 3.5 hours. A patient will reach steady-state concentration within 7 days. Mirabegron has a large volume of distribution and is plasma protein bound. It is metabolized by a number of pathways including dealkylation, oxidation, glucuronidation, and amide hydrolysis. It is renally eliminated and also has a half-life of 50 hours.  

- **Clinical pearls**
  - Mirabegron is a pregnancy category C drug.
  - Mirabegron should not be used in patients who have severe, uncontrolled hypertension, as this medication can increase BP.
  - Patients should be advised to take mirabegron with water and not to chew, divide, or crush the extended-release tablet.
  - Patients should be educated about the importance of informing all of their healthcare providers about all medications they are taking, including over-the-counter medications, vitamins, and herbal supplements.
  - Be sure to inform patients about missed doses of mirabegron. Instruct the patient to take the dose as soon as it is remembered, but do not double up doses, and do not take two doses of the drug in the same day.
  - Providers should give patients a list of the most common adverse reactions associated with mirabegron, including increased BP, common cold symptoms, urinary tract infections, and headache.
  - Adverse reactions that may be related to mirabegron should be reported to Astellas Pharma US, Inc. at 1-800-727-7003 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.  

- **REFERENCES**
chronology is being studied.2

the risks of adverse reactions. In order to help reduce the

either high doses or for prolonged periods of time increases

the following indications:

Prednisone delayed-release is a corticosteroid approved for

Indications

■ Immunosuppressive therapy

Prednisone delayed-release

(Rayos)

Glucocorticoids are a major player in the treatment of many inflammatory conditions including rheumatic disorders, allergic airway disease, dermatologic diseases, and other local and systemic disorders.1 The use of these medications in either high doses or for prolonged periods of time increases the risks of adverse reactions. In order to help reduce the risks of adverse reactions, chronotherapy is being studied.1

Chronotherapy coordinates drug administration with the body’s circadian rhythm to help increase the therapeutic effects of the drug and decrease adverse reactions.2

Chronotherapy has been studied in the treatment of rheumatoid arthritis (RA) by coordinating glucocorticoid administration with the circadian rhythm. In other conditions, such as hypertension, allergic rhinitis, and bronchial asthma, chronotherapy has shown benefits.2 Chronotherapy can be beneficial in the treatment of RA because the symptoms of this disease follow circadian rhythms. These overnight symptoms are due to proinflammatory cytokine levels.3

RA is a chronic, inflammatory disease characterized by joint swelling and tenderness that causes progressive and irreversible damage to the synovial-lined joints.4

A new, modified-release prednisone tablet has been developed to optimize chronotherapy. If taken at bedtime (22:00), prednisone release will occur 4 hours later (02:00).3 This medication formulation and timing matches up to the circadian rhythm.

On July 26, 2012, prednisone delayed-release (Rayos) was approved by the FDA. Rayos is the first delayed-release formulation of prednisone available on the market. The drug is marketed and distributed by Horizon Pharma, Inc. The drug approval was based on data from the Circadian Administration of Prednisone in RA (CAPRA 1 and 2) trials.3 The information provided from these two trials and the pharmacokinetics presented helped this medication gain approval for a long list of diseases and treatments.

Indications

Prednisone delayed-release is a corticosteroid approved for the following indications:

- As an anti-inflammatory or immunosuppressive agent that encompasses allergic, dermatologic, gastrointestinal, ophthalmologic, respiratory, rheumatologic, renal, nervous system, and hematologic conditions
- As an immunosuppressive medication in organ transplantation
- In the treatment of endocrine conditions
- As a palliative agent in neoplastic conditions.6

Mechanism of action

Prednisone delayed-release causes a number of metabolic effects in addition to modifying the body’s immune response to many stimuli.6 Prednisone delayed-release possesses all of the properties of corticosteroids. The pharmacologic effects include the following6:

- Promotion of gluconeogenesis
- Increased deposition of glycogen in the liver
- Inhibition of the utilization of glucose
- Anti-insulin activity
- Increased catabolism of protein
- Increased lipolysis
- Stimulation of fat synthesis and storage
- Increased glomerular filtration rate
- Increased calcium excretion
- Decreased production of eosinophils and lymphocytes
- Stimulation of leukocytes and erythropoiesis
- Inhibition of wound healing.

Dosing and administration

Like all corticosteroids, dosing should be based upon the severity of the disease and the response achieved.

The recommended starting dose is 5 to 60 mg daily, depending on the specific disease that is being treated. Dosing should be monitored and changed according to response. The drug should be taken with food.6 Patients who are currently taking immediate-release prednisone, prednisolone, or methylprednisolone can be switched to prednisone delayed-release at an equivalent dose based upon potency.5 Prescribers should refer to the manufacturer’s prescribing information for a corticosteroid comparison chart.6

Contraindications

Prednisone delayed-release is contraindicated for use in patients with a documented allergy to prednisone or any of the medication’s ingredients.6


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Warnings and precautions

Patients taking prednisone delayed-release who have hypothalamic-pituitary-adrenal axis suppression, Cushing syndrome, and/or hyperglycemia should be monitored. Patients with hypothyroid disorders may experience decreased clearance of prednisone delayed-release, while those with hyperthyroidism may demonstrate increased clearance.

Prednisone delayed-release may exacerbate infections, increase the risk of disseminated infections, and increase the risk of reactivation or exacerbation of latent infections. Prednisone delayed-release can also mask signs of infection, or reduce a patient’s ability to fight new infections.

Corticosteroids can increase BP and cause sodium and water retention as well as increased excretion of potassium and calcium. Practitioners should monitor BP, serum electrolytes, and calcium levels in patients receiving prednisone delayed-release. Prednisone delayed-release should be used with caution in patients with certain gastrointestinal (GI) disorders, including abscess, perforation, diverticulitis, or peptic ulcer disease. The use of corticosteroids in these patients may increase the risk of GI perforation.

Chronic corticosteroid use has been associated with decreases in bone density. If prednisone delayed-release is to be used long term, the patient’s bone density levels must be monitored throughout therapy.

Chronic corticosteroid use has also been associated with ophthalmic effects, including cataracts and glaucoma. Monitor the intraocular pressure in patients receiving prednisone delayed-release for more than 6 weeks.

Adverse reactions

The most common adverse reactions associated with prednisone delayed-release include fluid retention, altered glucose tolerance, an increase in BP, changes in behavior and mood, and increased appetite/weight gain. The list is extensive, so please refer to the prescribing information for a more detailed list.

Drug interactions

There are many drug interactions associated with the use of prednisone delayed-release. Therapeutic effects of anticoagulant medications can be either increased or decreased. Prednisone delayed-release may increase blood glucose concentrations while a patient takes any antidiabetic medication. Dosing adjustments of prednisone delayed-release must be made for patients taking CYP3A4 inhibitors or inducers. There is also a reported increase in the activity of both prednisone delayed-release and cyclosporine when they are used together. The combination of these two medications can increase the risk of seizures. Using prednisone delayed-release with nonsteroidal anti-inflammatory drugs, aspirin, or salicylates can increase the risk of GI adverse reactions. There is also the risk of hypokalemia in patients taking prednisone delayed-release and a potassium-depleting drug. Patients taking digoxin are at increased for dysrhythmias due to the risk of hypokalemia.

Pharmacokinetics

Prednisone delayed-release has a unique formulation that allows for modified release of prednisone 4 hours after ingestion. Peak plasma concentrations are reached later in time compared to conventional immediate-release prednisone formulations. It will reach a peak plasma concentration at 6 to 6.5 hours compared to 2 hours achieved by immediate release.

Prednisone delayed-release is converted to the active metabolite prednisolone. It is metabolized by the liver and excreted in the urine. The half-life of the drug is 2 to 3 hours.

Clinical pearls

- Prednisone delayed-release is a pregnancy category D drug.
- Live, attenuated vaccines must not be used in patients who are taking prednisone delayed-release in doses used for immunosuppression.
- For patients taking prednisone delayed-release, the following should be monitored on a routine basis: BP, body weight, lab values of blood glucose and serum potassium, and chest X-ray.
- Patients should be educated about the need to take prednisone delayed-release with food. Patients should be taught that the tablets cannot be broken, divided, or chewed because doing this will interfere with the delayed release properties of the drug.
- Educate patients about the importance of not discontinuing prednisone delayed-release abruptly or without supervision by a healthcare professional.
- Provide patients with the list of most common adverse reactions associated with prednisone delayed-release: fluid retention, changes in glucose levels, increase in BP, changes in mood and behavior, and weight gain/increased appetite.
- Instruct patients to not double up on doses if one dose of prednisone delayed-release is missed. Patients should take the missed dose as soon as possible unless it is time for the next dose; in that case, patients should take the regular dose at the scheduled time.
If the patient experiences a suspected adverse reaction while taking prednisone delayed-release, contact Horizon Pharma USA, Inc. at 1-866-479-6742 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. If the patient experiences a suspected adverse reaction while taking prednisone-delayed release, contact Horizon Pharma USA, Inc. at 1-866-479-6742 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

REFERENCES

▼ Diabetic macular edema

**Ranibizumab (Lucentis)**

Diabetic macular edema (DME) is the leading cause of blindness in patients with diabetic retinopathy. The Diabetes Control and Compliance Trail (DCCT) indicated that 27% of patients with type 1 diabetes will develop macular edema within 9 years of diabetes onset. It is estimated by the International Diabetes Foundation that 285 million individuals worldwide have diabetes, and 14% of this group has DME.

DME is a disease that causes swelling of the central retina that leads to vision loss. The common pathway that leads to DME is disruption of the blood-retinal barrier (BRB). Disruption of the BRB is multifactorial and causes abnormal inflow of fluid in the sensory retina that exceeds the outflow, resulting in residual fluid accumulation in the intraretinal layers of the macula.

DME pathogenesis includes chronic hyperglycemia and the accumulation of free radicals and proteins that lead to the activation of vascular endothelial growth factors (VEGFs), primarily VEGF-A, along with the increase in vascular permeability. VEGF level increase has brought to the forefront the potential for anti-VEGF treatment for the management of DME. Anti-VEGF has been hypothesized to restore normal retinal anatomy, and reverse the vision loss from DME.

Ranibizumab is an antibody that is targeted against VEGF-A and has been approved for the treatment of neovascular age-related macular degeneration. Ranibizumab is an anti-VEGF Fab fragment that is used intravitreally and has the ability to reduce macular edema, and improve visual acuity in DME.

**Ranibizumab works by binding to the receptor binding site of VEGF-A.**

With that in mind, ranibizumab, under the brand name Lucentis, was approved by the FDA on August 10, 2012, for the treatment of DME and will be marketed by Genetech.

**Indication**

Ranibizumab was originally approved in 2006, and over the years, obtained approval for the following conditions: neovascular (wet) age-related macular degeneration and macular edema following retinal vein occlusion. The most recent approval was for the treatment of DME.

**Mechanism of action**

Ranibizumab works by binding to the receptor binding site of VEGF-A. This binding prevents the interaction of VEGF-A with its receptors on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation.

**Dosing and administration**

For the treatment of DME, ranibizumab 0.3 mg is given as an ophthalmic intravitreal injection once a month. The injection must be completed in a controlled aseptic environment. The healthcare professional administering the medication must use sterile gloves, a sterile drape, and a sterile eyelid speculum. Prior to the injection, a proper anesthetic should be utilized. One vial should be used for the treatment of one eye. Do not use one vial for both eyes. No dosing adjustments are needed for special populations.

**Contraindications**

Ranibizumab is contraindicated in two patient groups: those who have hypersensitivity to reactions to ranibizumab or patients who are diagnosed with ocular or periocular infections.
**Warnings and precautions**

As with any intravitreal injection, ranibizumab can cause endophthalmitis and retinal detachments. Proper sterile technique must be used during administration of the medication, and the patient must be monitored following the injection for infection.9

Monitor intraocular pressure prior to injection and then again postinjection. Ranibizumab has the potential to cause an increase in intraocular pressure.9

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There are no documented drug interactions associated with the use of ranibizumab.9

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**Adverse reactions**

Through clinical trial documentation, the most common adverse reactions reported included bleeding of the conjunctiva, eye pain, floaters, and increased intraocular pressure. Other adverse reactions include intraocular inflammation, cataract formation, increased lacrimation, and visual disturbance.9

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**Drug interactions**

There are no documented drug interactions associated with the use of ranibizumab.

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**Pharmacokinetics**

Pharmacokinetic studies were completed on patients with neovascular, age-related, macular degeneration, and that information can be related to the patients diagnosed with DME. The maximum serum concentration of ranibizumab is reached in 1 day. The maximum concentration has been determined to be 1.5 ng/mL. The estimated half-life of this medication is 9 days.9

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**Clinical pearls**

- Ranibizumab is a pregnancy category C drug.
- Sterile technique is used for medication administration, and only one vial per dose per eye.
- Patients need to be monitored prior to and 30 minutes following the intravitreal injection of ranibizumab for an increase in intraocular pressure using tonometry.
- Educate patients about the possibility of developing endophthalmitis. Inform them to contact their ophthalmologist if they experience reddening of the eye, increased sensitivity to light, pain, or changes in vision.
- Provide patients with a list of the most common adverse reactions: conjunctival hemorrhage, eye pain, floaters, and increase in intraocular pressure.
- If the patient develops a suspected adverse reaction, contact Genetech at 1-888-835-2555 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.9

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**REFERENCES**


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**Acne vulgaris**

Tazarotene (Fabior Foam)

Affecting 40 to 50 million Americans, the most common skin problem is acne. Acne affects most commonly adolescents and young adults, but it can occur at any age. Breakouts occur due to many different reasons, but they are mainly due to hormones. Hormones affect the skin’s sebaceous glands and hair follicles causing changes in the skin’s oil, clogging pores, and leading to the development of pimples. Other causes of acne can be due to genetics and heredity, greasy cosmetics, and adverse reactions of some medications.3

The four primary factors in the development of acne are as follows: abnormal desquamation of the follicular epithelial; hyperactivity of the sebaceous glands; Propionibacterium acnes proliferation; and perifolicular inflammation.4 Acne can appear as two different lesion types: inflammatory lesions and noninflammatory lesions. Inflammatory lesions consist of papules, pustules, and nodular cystic lesions.
Noninflammatory lesions include open and closed comedones.² Tretinoin was the first retinoid to be approved for the treatment of acne. As a metabolite of vitamin A, it plays a role as a mediator of cell differentiation and proliferation. Topical retinoids work by normalizing the desquamation pattern in sebaceous follicles and decreasing the coherence of follicular keratinocytes, causing a breakdown of existing comedones in addition to preventing new ones.³ Retinoids also play a role in reducing the proliferation of Propionibacterium acnes.⁴

Tazarotene was first approved in the treatment of psoriasis. It is now approved in a foam formulation for the treatment of acne. Having a topical formulation helps prevent systemic exposure, thus, leading to a better safety profile.³ On May 11, 2012, the FDA approved Fabior Foam, topical tazarotene foam for the treatment of acne. It will be marketed and distributed by Stiefel, a GSK company.²

■ Indication
Tazarotene foam is approved for the treatment of acne vulgaris in a topical form. It is to be used in patients over the age of 12.²,⁵,⁶

■ Mechanism of action
Tazarotene is a retinoid prodrug. Through deesterization, this drug is then converted to its active form—tazarotenic acid. Tazarotenic acid binds to all of the receptors in the retinoic acid receptor family with more selectivity for RAR-beta and RAR-gamma over RAR-alpha; the exact mechanism by which tazarotene works in acne is unknown, but it is speculated to be due to its antiproliferative, normalizing-of-differentiation, and anti-inflammatory effects.⁵

■ Dosing and administration
Tazarotene foam is to be applied topically once a day in the evening. After washing the face with a mild cleaner, the patient should apply a small amount of foam to cover the entire affected area. The foam should be massaged in until it completely disappears. Patients should be educated not to get the foam into the eyes, lips, or mucous membranes.⁵

■ Contraindications
Tazarotene foam is contraindicated in patients who are pregnant.⁶

■ Warnings and precautions
Tazarotene foam has an associated fetal risk. This medication is teratogenic and must not be used in pregnant women. Women of child-bearing age should have a negative pregnancy test within two weeks of starting the drug and must use adequate birth control measures while using this medication.⁵

Caution should be taken when using tazarotene foam in patients with a history of local hypersensitivity reactions or those with eczema or abraded skin. Some patients can develop redness, burning sensation, or excessive pruritus while using this medication. Also, extreme weather conditions can increase irritability.³

Tazarotene foam is to be applied topically once a day in the evening.

The use of multiple topical medications can cause an increase in irritation. If the patient develops skin irritation, the frequency of application might need to be changed or treatment stopped.³

Patients using tazarotene foam have an increased risk of developing sunburn, both due to natural sunlight or artificial tanning beds. Advise patients to use sunscreens and protective clothing while using tazarotene foam. Use tazarotene foam cautiously in patients with a personal or family history of skin cancer.³

Keep in mind that the propellant in tazarotene foam is flammable. Avoid fire, flames, and smoking during and after application of the medication.³

■ Adverse reactions
The most commonly experienced adverse reactions associated with the use of tazarotene foam are irritation, dryness, erythema, and exfoliation at the application site. Other adverse reactions include skin discoloration, rash, swelling, dermatitis, and pruritus.³

■ Drug interactions
There are no documented drug interactions associated with the use of tazarotene foam. To prevent excessive irritation, avoid the use of other dermatologic medications and cosmetics that have a strong drying effect.³

■ Pharmacokinetics
After topical administration of tazarotene foam, the majority of the medication stays on or in the skin. A small portion of the medication is absorbed. As mentioned previously, tazarotene is a prodrug that is metabolized in the skin to the active form—tazarotenic acid. These are both then metabolized to sulfoxides, sulfones, and other polar metabolites that are eliminated via urinary and fecal
• Tazarotene foam is not to be used orally, ophthalmically, or intravaginally.
• Educate the patients about the importance of avoiding exposure to natural or artificial sunlight. Sunscreens should be used during treatment.
• Instruct patients not to get tazarotene foam in the eyes. If this occurs, tell patients to rinse the eyes thoroughly with water.
• Tazarotene foam is not to be used orally, ophthalmically, or intravaginally.
• Advise patients that tazarotene foam is flammable, and tell patients to avoid fire, an open flame, and smoking during and immediately after application of the foam. Also instruct patients not to puncture the tazarotene foam can and to keep the can away from fire and heat.

Clinical pearls
• Tazarotene foam is a pregnancy category X drug.
• If the patient experiences irritation, consider reducing the application frequency or stopping therapy completely. Once irritation is resolved, treatment can be restarted.
• Advise patients to use moisturizers as needed.
• Advise female patients about the importance of proper contraception during treatment to avoid pregnancy.
• Educate the patients about the importance of avoiding exposure to natural or artificial sunlight. Sunscreens should be used during treatment.

Drug updates and approvals: 2012 in review


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