



A PHARMACY CONTINUING EDUCATION PROGRAM

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May 2011 "New Drug Approvals: 2010 - 2011"



**THIS MONTH**  
**"New Drugs**  
**2010-2011"**

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**The FDA approved 29 new drugs in 2010.** Of these we will specifically discuss eight that seem like they will have the biggest immediate impact on therapy. This lesson provides 1.25 hours (0.125 CEUs) of credit, and is intended for pharmacists in all practice settings. **The program ID # for this lesson is 707-000-11-005-H01-P.** **Pharmacists completing this lesson by May 31, 2014 may receive full credit.**

**To obtain continuing education credit for this lesson,** you must answer the questions on the quiz (70% correct required), and return the quiz. Should you score less than 70%, you will be asked to repeat the quiz. Computerized records are maintained for each participant.

If you have any comments, suggestions or questions, contact us at the above address, or call toll free 1-800-323-4305. (In Alaska and Hawaii phone 1-847-945-8050). **Please write your ID Number (the number that is on the top of the mailing label) in the indicated space on the quiz page** (for continuous participants only).

**The objectives of this lesson are such that upon completion the participant will be able to:**

1. Describe new drugs approved by the FDA in 2010.
2. Discuss the role of these agents in therapy.
3. Summarize the adverse effects & potential drug interactions of these new agents.
4. Recommend specific counseling points that are essential when dispensing these agents to patients.

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Or, if you have questions, feel free to email me. We'll all survive this new procedure together.

Bill Feinberg (bill@wfprofessional.com)

**INTRODUCTION**

The Food and Drug Administration (FDA) approved 29 new chemical entities in 2010.<sup>1</sup> Of these, **we will specifically discuss: dabigatran, dalfampridine, fingolimod, liraglutide, lurasidone, tesamorelin, ulipristal and alcaftadine.**

Many of these agents are either orphan drugs or the first agent in a new class. Several agents approved this past year had a **risk evaluation and mitigation strategy (REMS)** included in the approval. These REMS are designed to decrease risks to patients and warn prescribers about potential adverse effects. Each REMS is designed to meet the unique needs of the product and population it serves. **Table 1** summarizes the REMS requirements for dabigatran, dalfampridine, fingolimod and liraglutide. Some of the agents approved this past year are injectable agents that may be available only through a closed distribution system.

**Table 1. REMS requirements<sup>2</sup>** (For discussed drugs)

Generic Name	Brand Name	REMS Description
Fingolimod	Gilenya	MedGuide; Dear Healthcare Professional letter
Liraglutide	Victoza	MedGuide; Dear Healthcare Professional letter
Dalfampridine	Ampyra	MedGuide; Dear Healthcare Professional letter
Dabigatran	Pradaxa	MedGuide only

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May 2011

## DABIGATRAN ETEXILATE (PRADAXA)

Dabigatran etexilate is a thrombin inhibitor and was approved by the FDA on October 19, 2010. This is the first new oral anticoagulant approved by the FDA since warfarin was approved nearly 50 years ago.<sup>3</sup> Dabigatran offers some benefits over warfarin in that it does not require monitoring of international normalized ratios (INRs), has minimal drug interactions, and has no dietary restrictions.

### Pharmacology/Pharmacokinetics

Dabigatran is a non-peptide direct thrombin inhibitor. It blocks both clot-bound and free thrombin. The inhibition of thrombin prevents the conversion of fibrinogen to fibrin and prevents the development of a thrombus or clot.<sup>4</sup>

Dabigatran etexilate is a pro-drug that is converted to the active form, dabigatran, by esterase-catalyzed hydrolysis in the plasma.<sup>4, 5</sup> It inhibits thrombin, thereby preventing the conversion of fibrinogen to fibrin in the coagulation cascade. Free thrombin, clot-bound thrombin and thrombin-induced platelet aggregation are inhibited by dabigatran. Only about 7% of a dose of dabigatran is absorbed following oral administration. When the capsule is chewed or crushed, the bioavailability increases to 75% of the dose, which may lead to toxicity.

Dabigatran is not metabolized by the liver so there are not drug-drug interactions involving the cytochrome P-450 system. Dabigatran has an elimination half-life of 12 to 17 hours.<sup>5</sup> The drug is eliminated primarily through the kidneys. The dose must be adjusted in patients with renal impairment; however, no adjustment is required in moderate hepatic impairment. The INR does not have to be monitored as with warfarin. Dabigatran can be removed through hemodialysis, but there is no specific antidote that can be given to reverse the effects of the drug if emergency reversal is required. In instances of life-threatening bleeding, where conventional measures have failed or are unavailable, agents such as recombinant activated factor VII and prothrombin complex concentrates can be considered.

### Indications

Dabigatran is indicated to reduce the risk of stroke and embolism in patients with non-valvular atrial fibrillation.<sup>4</sup>

### Dosing

The recommended dose of dabigatran is 150 mg twice a day.<sup>4</sup> In patients with a creatinine clearance (CrCl) of 15-30 mL/min, the dose should be reduced to 75 mg twice a day. Dabigatran can be given without regard to meals. The drug **should not** be crushed or chewed.

Patients who are not well controlled on warfarin may be converted to dabigatran.<sup>4</sup> When converting a patient from warfarin, stop the warfarin therapy and initiate dabigatran when the INR is less than 2.0.

Patients taking dabigatran may need to be switched to warfarin therapy.<sup>4</sup> This conversion is based on the patient's CrCl.

### Contraindications

Dabigatran is contraindicated in any patient with active bleeding or those with a hypersensitivity to dabigatran.<sup>4</sup>

### Drug Interactions

Dabigatran should be used with caution in combination with P-glycoprotein (P-gp) inducers.<sup>4,5</sup> Concomitant administration of the P-gp inducer, rifampin, resulted in a 66% reduction in the area under the curve (AUC) and a 67% reduction in the maximum concentration ( $C_{max}$ ). These values returned to normal 7 days after discontinuation of rifampin.

Since dabigatran increases the risk of bleeding, it should be used with caution in combination with antiplatelet agents, heparin, and non-steroidal anti-inflammatory drugs (NSAIDs).<sup>4</sup>

### Warnings

Dabigatran increases the risk of bleeding and can cause severe, and possibly, fatal bleeding.<sup>4</sup> As mentioned above, patients receiving drugs that increase the risk of bleeding, such as antiplatelet drugs or NSAIDs, have a higher risk of bleeding.

### Adverse Effects

Dabigatran is associated with an increase risk of gastrointestinal (GI) side effects (33% vs 24% reported with warfarin).<sup>4</sup> The most common GI effects include dyspepsia and gastritis (esophagitis, gastric hemorrhage, and ulcer).

In the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial, dabigatran had a higher rate of major gastrointestinal bleeds compared to warfarin (1.6% vs 1.1%, respectively, with a hazard ratio vs warfarin of 1.5, [95% CI, 1.2 to 1.9], and a higher rate of any gastrointestinal bleeds (6.1% vs 4.0%, respectively).<sup>6</sup>

### **Pregnancy and Lactation**

Dabigatran is FDA Pregnancy Category C, which indicates that there are no well-controlled clinical trials in pregnant women.<sup>4</sup> The use of dabigatran in pregnancy should be reserved to those individuals where the benefit outweighs the risk. No information is available regarding the excretion of dabigatran in breast milk.

### **Role in therapy**

In 2011, the American College of Cardiology updated the guidelines for the management of patients with atrial fibrillation to include dabigatran as an alternative to warfarin in preventing systemic embolism or stroke.<sup>7</sup> This recommendation was based on the results of the RE-LY trial, which showed dabigatran was superior to warfarin in preventing embolism and stroke.<sup>6</sup>

### **Summary of Dabigatran**

Although dabigatran may offer some advantages over warfarin, its role in therapy is still evolving. It currently is only approved for use in patients with non-valvular atrial fibrillation. It does not have the drug or dietary interactions seen with warfarin and does not require laboratory monitoring. There appears to be a higher rate of gastrointestinal bleeding with dabigatran compared to warfarin. There is no antidote for dabigatran if emergency reversal is needed, and it cannot be used in patients with renal failure. There is a significant degree of dyspepsia reported with dabigatran. It may offer an advantage in patients who are intolerant or non-compliant with warfarin, but in patients who have a stable INR and are well controlled on warfarin, it may be prudent to continue that therapy. As with warfarin, patients taking dabigatran should be counseled about the importance of compliance with their regimen to prevent potentially life-threatening thrombus or stroke.

### **DALFAMPRIDINE (AMPYRA)**

Dalfampridine, or 4-aminopyridine, has been used in multiple sclerosis (MS) patients for several years to improve or maintain their ability to walk. A majority of patients with MS report a decrease in their ability to walk, which further limits their function and quality of life.<sup>8,9</sup> Dalfampridine has been shown to improve walking speed. It has been provided to patients through compounding pharmacies as a 5 mg immediate release capsule. On January 22, 2010 the FDA approved Ampyra, and it is available as a 10 mg extended release tablet.

### **Pharmacology/Pharmacokinetics**

Dalfampridine is a potassium channel blocker.<sup>8</sup> It appears to prolong action potential and improve conduction of the demyelinated pathways when the potassium channels are blocked. The drug is well absorbed following oral administration with a peak concentration seen 3 to 4 hours after dosing. Dalfampridine has an elimination half-life of 5 to 6.5 hours. It is excreted primarily in the urine.

### **Indications**

Dalfampridine is indicated to improve walking speed in patients with MS.<sup>8</sup> Walking speed is a clinical indicator of walking function.

### **Dosing**

The dose of dalfampridine is 10 mg given orally every 12 hours. It may be given with or without food.<sup>9</sup>

### **Contraindications**

Dalfampridine is contraindicated in patients with a history of seizure disorder or renal impairment (CrCl < 50 mL/min).<sup>8</sup> Administering this medication to patients with moderate or severe renal impairment may increase the risk for seizure.

### **Warnings**

Patients with mild renal impairment (CrCl between 51 to 80 mL/min) may also be at risk for seizure.<sup>8</sup> Plasma levels in these individuals may be similar to those seen when dosing dalfampridine at 15 mg twice a day, which may increase the seizure risk.

### **Drug Interactions**

No specific drug-drug interactions have been reported.<sup>8</sup>

### **Adverse Effects**

The most common adverse effects reported with dalfampridine include urinary tract infection, dizziness, insomnia, headache, balance disorders and asthenia.<sup>8,9</sup>

### **Pregnancy and Lactation**

Dalfampridine is FDA Pregnancy Category C.<sup>8</sup> Clinical trials in pregnant women have not been conducted. It is unknown if dalfampridine is excreted into breast milk. Mothers should avoid breastfeeding while taking this drug.

### Role in therapy

Dalfampridine was studied in MS patients to determine its benefit in improving walking function.<sup>10</sup> Patients were randomized to dalfampridine 10 mg twice a day or placebo for 14 weeks. Patients were assessed using a timed 25 foot walk (T25FW). A 20% improvement in T25FW is considered significant. The number of patients who had an improved T25FW was 78/224 (35%) in the dalfampridine group and 6/72 (8%) in the placebo group (p<0.0001).

When counseling patients who are prescribed dalfampridine, it is important to point out the following:

- It is important that dalfampridine not be taken in addition to a compounded formulation of the drug (4-aminopyridine, 4-AP, fampridine).
- It is important that a pharmacy-compounded formulation of the drug (4-aminopyridine, 4-AP, and fampridine) should not be substituted for dalfampridine due to the differences in absorption of compounded formulations and the potential for overdose and increased risk of seizures.
- Tablets should not be scored, divided, crushed, chewed or dissolved in fluids.
- Be sure to verify patient's CrCl before initiating dalfampridine. Contact prescriber if there is a significant change in renal function during treatment.

### FINGOLIMOD (GILENYA)

On September 22, 2010 the FDA approved the first oral agent for the treatment of multiple sclerosis. Unlike dalfampridine, which targets walking ability, fingolimod reduces the occurrence of exacerbations in patients with relapsing multiple sclerosis.<sup>11</sup>

#### Pharmacology/Pharmacokinetics

Fingolimod is a sphingosine-1-phosphate-receptor modulator. It blocks the movement of lymphocytes from lymph nodes and reduces the total number of lymphocytes in the peripheral blood stream.<sup>11,12</sup> The exact mechanism of action is not clear, but fingolimod may also prevent lymphocytes from entering the central nervous system.<sup>12</sup>

Fingolimod is well absorbed following oral administration.<sup>11</sup> It is a prodrug that is metabolized to the active fingolimod phosphate in the body. The elimination half-life is 6 to 9 days. The drug reaches steady states following 1 to 2 months of administration. Fingolimod is metabolized in the liver primarily via the CYP 4F2 pathway, with some additional metabolism via CYP 2D6, 2E1 and 4F12. It is excreted primarily through the urine as an inactive metabolite.

#### Indications

Fingolimod is indicated in patients with relapsing MS to reduce the frequency of clinical exacerbations and to delay physical disability.<sup>11</sup>

#### Dosing

The recommended dose is 0.5 mg once a day.<sup>11</sup> This medication can be taken with or without food. There is no data to suggest higher doses will provide any additional benefit, but they can increase the risk of adverse events.

#### Contraindications

There are no known contraindications to the administration of fingolimod.<sup>11</sup>

#### Warnings

Although there are no specific contraindications, there are a number of warnings associated with the use of fingolimod.<sup>11,12</sup> It can cause bradycardia and atrio-ventricular block. Patients should be monitored for 6 hours following the first dose. In patients with risk factors for these conditions, an electrocardiogram should be completed prior to therapy. Patients who may be at risk for bradycardia include individuals with a low resting heart rate (55 beats per minute), those on antiarrhythmic therapy including beta blockers and calcium channel blockers, patients with heart failure, sick sinus or ischemic heart disease and those with second degree or higher heart block.

Because fingolimod reduces the number of lymphocytes in the peripheral blood stream, patients are at risk for infection.<sup>11,12</sup> If a patient develops signs and symptoms of infection, fingolimod should be discontinued. Since it remains in the system for up to 2 months, careful monitoring of patients should continue. There are 2 reports of death due to herpes infections in patients receiving high dose (1.25mg) fingolimod in combination with corticosteroids.

Macular edema has been reported with fingolimod in about 0.4% of patients in clinical trials.<sup>11,12</sup> It appears to occur in the first 3 to 4 months of treatment. It is important to conduct ophthalmic examination before and during treatment with the drug.

Respiratory effects and hepatic abnormalities have also been reported.<sup>11</sup> Patients should undergo baseline pulmonary function tests and liver function tests prior to therapy. Additional monitoring should occur while on therapy and the drug discontinued if adverse effects are seen.

### Drug Interactions

Since fingolimod may cause bradycardia, patients receiving Class Ia antiarrhythmic agents (quinidine, procainamide) or class III agents (sotalol, amiodarone) are at risk for torsades de pointes.<sup>11</sup> Beta blockers may result in additive bradycardia when combined with fingolimod.

Do not combine fingolimod with ketoconazole, an inhibitor of CYP 4F and 3A4.<sup>11</sup> It increases fingolimod concentrations up to 70% and can result in adverse effects.

Patients who are taking fingolimod should not receive live virus vaccines.<sup>11</sup> It can decrease the effectiveness of these vaccines. If a live virus vaccine must be given, fingolimod should be stopped for 2 months before the vaccine is given, and not resumed for 1 month following the vaccine administration.

### Adverse Effects

The most common adverse effects include headache, mild hypertension, cough, diarrhea and back pain. As described in the warnings above, there are serious adverse effects reported with fingolimod including bradycardia, AV-block, serious infection, macular edema and pulmonary dysfunction. Patients should be closely monitored while taking fingolimod.

### Pregnancy and Lactation

Fingolimod is FDA Pregnancy Category C.<sup>11</sup> Although no data is available in pregnant women, fingolimod has been reported to cause fetal death and vascular defects in animals. Because of the long half-life of this drug, it may remain in the system for up to 2 months after discontinuation. Women of childbearing potential should be counseled about using an effective form of birth control during treatment with fingolimod and for 2 months after the drug is stopped. Novartis has established a pregnancy registry in order to gather data on the use of fingolimod during pregnancy. The registry number is 1-877-598-7237.

It is unclear if fingolimod is excreted in human breastmilk.<sup>11</sup> Women who are lactating should consider the risks and benefits before breastfeeding while taking fingolimod.

### Role in therapy

This is the first oral agent available for the treatment of MS. Fingolimod appears to be beneficial in reducing relapse in MS; however, it is associated with significant toxicity. There are currently other agents available with a better safety profile than fingolimod. Its role in therapy is still being determined. At this time it may be prudent to reserve its use to patients who are unable to use injections or who have had break through with conventional treatment.

## LIRAGLUTIDE (VICTOZA)

Liraglutide (Victoza) is in the same class of agents as exenatide (Byetta).<sup>13</sup> It is administered once a day as a subcutaneous injection.

### Pharmacology/Pharmacokinetics

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor antagonist that is similar to exenatide (Byetta).<sup>13,14</sup> Liraglutide has an amino acid sequence that is similar to that of the human incretin hormone GLP-1 and in the presence of glucose acts to stimulate insulin secretion. It also slows gastric emptying time and decreases glucagon secretion.

After subcutaneous injection, the maximum peak concentration is achieved 8-12 hours after dosing.<sup>13,14</sup> The volume of distribution is 13L. It is metabolized endogenously like other large proteins with no specific organ responsible for metabolism. The parent compound, liraglutide, is not excreted in the urine or feces and only a small portion of inactive metabolites (5-6%) are excreted via these pathways. The elimination half-life is 13 hours.

### Indications

Liraglutide is approved as adjunctive therapy in the treatment of Type 2 Diabetes.<sup>13</sup> It is not indicated as first line treatment in patients who have failed diet and exercise. It has not been studied in combination with insulin.

### Dosing

The initial dose of liraglutide is 0.6 mg subcutaneously once a day for 7 days.<sup>13</sup> The dose is then increased to 1.2 mg subcutaneously once a day thereafter. For patients who do not have an adequate reduction in blood glucose, the dose can be increased to 1.8 mg once a day. The dose may be administered in the thigh, abdomen or upper arm.

### Contraindications

Liraglutide is contraindicated in patients with medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2.<sup>13</sup>

### Warnings

Pancreatitis has been reported in clinical trials with liraglutide.<sup>13-15</sup> If a patient develops pancreatitis while taking liraglutide, the drug should be stopped until the disease can be confirmed. Liraglutide should not be started in patients with a history of pancreatitis. The dose of a sulfonylurea should be decreased when adding liraglutide to decrease the risk of severe hypoglycemia. Liraglutide should be used with caution in patients with renal or liver disease.

### Drug Interactions

Hypoglycemia has been reported when liraglutide is used in combination with sulfonylureas.<sup>13,16</sup> When initiating liraglutide in patients currently receiving sulfonylureas, the dose of the sulfonylurea should be reduced.

No other drug interactions have been identified, however, because the drug decreases gastric emptying time, it may reduce the absorption of oral medications.<sup>13</sup>

### Adverse Effects

As described earlier, pancreatitis has been reported in patients treated with liraglutide.<sup>13,15,16</sup> The most common side effects seen are headache and gastrointestinal effects (diarrhea, nausea, vomiting and dyspepsia). Injection site reactions including rash and erythema have been reported in 2% of patients.

### Pregnancy and Lactation

Liraglutide is Pregnancy Category C.<sup>13</sup> Fetal abnormalities have been reported in animal studies. When considering the use of liraglutide, the benefits should be weighed against the risks. It is not known if liraglutide is excreted in human breast milk, although it is excreted in the milk of lactating rats. Caution should be used if administering liraglutide to breastfeeding women. Alternative agents may need to be considered.

### Role in therapy

Liraglutide is approved as an adjunct to diet and exercise to improve glycemic control in type 2 diabetes. Liraglutide is not considered first line therapy in these patients. and has not been studied in conjunction with insulin. In addition, this drug is not appropriate for use in patients with a history of pancreatitis.

It is important for the pharmacist to be sure the patient understands how to prime the liraglutide pen when first starting treatment. Review appropriate administration techniques with the patient to ensure they are able to administer a subcutaneous injection. Patients need to understand that this is not an insulin injection and liraglutide is not approved for use in combination with insulin. The pharmacist should be sure that the patient has needles for the liraglutide pen device as it does not come supplied with needles.

## LURASIDONE (LATUDA)

Lurasidone is the 9<sup>th</sup> atypical antipsychotic agent approved by the FDA. There are very limited clinical trials published to evaluate its effectiveness. It appears to be effective in the treatment of schizophrenia.

### Pharmacology/Pharmacokinetics

Lurasidone is an atypical antipsychotic agent that is a central dopamine Type 2 and serotonin Type 2 antagonist.<sup>17</sup> The exact mechanism of action is unclear. Lurasidone is well absorbed and reaches peak serum levels 1 to 3 hours after administration. The elimination half-life is 18 hours. The drug is metabolized in the liver via CYP 3A4 and is excreted primarily in the feces.

### Indications

Lurasidone is approved for the treatment of schizophrenia.<sup>17</sup>

### Dosing

The initial dose of lurasidone is 40 mg once a day.<sup>17</sup> Although doses up to 120 mg have been studied, the maximum recommended dose is 80 mg a day. Dose should not exceed 40 mg per day in patients with CrCl  $\geq$  10 mL/min or  $<$  50 mL/min or in patients with moderate to severe liver disease.

### Contraindications

Lurasidone contains the same box warning regarding avoiding use in elderly patients with dementia-related psychosis. As with other atypical antipsychotics, there is an increased risk of mortality when these agents are used in elderly dementia patients.

Lurasidone is contraindicated in patients with hypersensitivity to the drug.<sup>17</sup> Lurasidone is also contraindicated in patients taking strong CYP3A4 inhibitors (ketoconazole) or strong CYP 3A4 inducers (rifampin).

### Warnings

In addition to the box warning regarding use in dementia, lurasidone carries the same warnings as other atypical agents including risk of stroke in dementia patients, neuroleptic malignant syndrome, tardive dyskinesias and metabolic syndrome.<sup>17,18</sup>

### Drug Interactions

As mentioned earlier, lurasidone is contraindicated in patients taking strong CYP3A4 inhibitors (ketoconazole) or strong CYP 3A4 inducers (rifampin).<sup>17</sup> In addition, lurasidone dose may need adjustment when used in combination with moderate CYP3A4 inhibitors like Diltiazem. (Do not use lurasidone doses above 40mg/day).

### Adverse Effects

Lurasidone demonstrates many of the same adverse effects reported with other drugs in this class. The most common adverse effects reported with lurasidone include somnolence (22%), akathisia (15%), nausea (12%), Parkinsonism (11%) and agitation (9%). Lurasidone has a low propensity for weight gain and minimal metabolic effects.

### Pregnancy and Lactation

Lurasidone is FDA Pregnancy Class B.<sup>17</sup> No well-controlled trials have been completed in pregnant women. As with other atypical antipsychotics, infants exposed to these agents during the third trimester may develop extrapyramidal reactions or withdrawal symptoms. Use in pregnancy should be limited to those cases where the benefits outweigh the risks. It is not known if lurasidone is excreted in breast milk.

### Role in therapy

Lurasidone is a new atypical antipsychotic agent that has entered an already crowded market. Clinical trials with this agent are limited. It appears to be effective in schizophrenia and has a low incidence of weight gain. Although this agent is effective, there is no data to suggest that it offers significant benefit over other available agents.

### TESAMORELIN (EGRIFTA)

The FDA approved tesamorelin on November 10, 2010.<sup>1</sup> It is the first FDA-approved treatment for HIV-lipodystrophy. Tesamorelin reduces deep belly fat or visceral adipose tissue (VAT) that accumulates in the abdomen and around the liver and other organs. This lipodystrophy is an adverse effect of antiretroviral therapy.

### Pharmacology/Pharmacokinetics

Tesamorelin is a growth hormone releasing factor (GHRF) drug that is administered as a once-daily injection.<sup>19</sup> GHRF acts to release growth hormone, which has anabolic and lipolytic effects. Tesamorelin is injected subcutaneously with approximately 4% of the dose absorbed. No specific studies have been conducted to evaluate the metabolic fate of the drug. The elimination half-life is 26 to 38 minutes.

### Indications

Tesamorelin is indicated for treatment of excess abdominal fat in HIV-infected patients with lipodystrophy.<sup>19</sup>

### Dosing

The recommended dose of tesamorelin is 2 mg subcutaneously once a day.<sup>19</sup>

### Contraindications

Tesamorelin is contraindicated in individuals who are pregnant, those with active cancer or a disruption of the hypothalamic pituitary axis including pituitary tumors, head trauma or radiation to the head, or hypopituitarism. It is also contraindicated in individuals with hypersensitivity to tesamorelin.<sup>19</sup>

### Warnings

Since tesamorelin results in the release of growth hormone, it should be avoided in patients with cancer or who are at increased risk for cancer.<sup>19</sup> Tesamorelin can cause fluid retention. Pharmacists should explain to patients that they might experience edema, carpal tunnel syndrome and arthralgia, which is reversible when the drug is stopped.

### Drug Interactions

Many patients with HIV associated lipodystrophy may be taking concomitant statin medications.<sup>19</sup> Studies with simvastatin indicate there is no drug interaction with tesamorelin. Studies indicate that in patients receiving corticosteroids for hypoadrenalism, an additional dose or dose adjustment may be required when tesamorelin is prescribed.

### Adverse Effects

The most common adverse events are arthralgia, erythema and pruritis at injection site, stomach pain, swelling, and myalgia.<sup>19,20</sup> The mean levels of fasting glucose were unchanged in the tesamorelin group compared to placebo. There was an increased risk of diabetes in the tesamorelin group (4.5%) compared to placebo (1.3%) with a hazard ratio of 3.3 [95% CI 1.4, 9.6].

### Pregnancy and Lactation

Tesamorelin is FDA Pregnancy Category X.<sup>19</sup> It is contraindicated in pregnancy. It is not known if tesamorelin is excreted into human breast milk. However, the Center for Disease Control recommends that HIV-positive women not feed their infants breast milk to avoid transmission of HIV.

### Role in therapy

In clinical trials compared to placebo, the patients receiving tesamorelin had greater reductions in abdominal fat as shown with CT scan.<sup>20</sup> Specifically VAT decreased by 10.9% in the tesamorelin group compared to 0.6% in the placebo group (p<0.0001). There was no significant change on glucose levels in the tesamorelin patients. Although these results are impressive, the primary endpoint of decreased cardiovascular risk has not been evaluated. It will be important to continue to evaluate the effects of tesamorelin in reducing the cardiovascular mortality in this patient population.

When counseling patients using tesamorelin, pharmacists should educate patients about how to store and reconstitute the product. Tesamorelin should be stored in the refrigerator. The drug is reconstituted with sterile water and should be administered immediately. Do not store mixed tesamorelin. Patients should be educated on proper reconstitution procedures to decrease the risk of contamination of the product.

### ULIPRISTAL ACETATE (ELLA)

Ulipristal was approved by the FDA as an emergency contraception that can be used up to 5 days after unprotected sex. The other FDA-approved emergency contraceptive, levonorgestrel (Plan B), is only indicated for use within 72 hours of unprotected sex. Neither ulipristal nor levonorgestrel are abortifacients.

### Pharmacology/Pharmacokinetics

Ulipristal is a progesterone receptor modulator (PRM).<sup>21,22</sup> It delays or inhibits ovulation and interferes with the implantation of a fertilized ovum. This drug is well absorbed and highly plasma protein bound (>94%). It is metabolized in the liver via CYP 3A4. Both the parent compound and the metabolite have activity. Ulipristal has an elimination half-life of 26 to 38 hours.

### Indications

Ulipristal is approved for use as emergency contraception to prevent pregnancy after unprotected intercourse or contraceptive failure.<sup>21</sup> It is not intended for use as a routine contraceptive.

### Dosing

Ulipristal is given as a single 30 mg dose as soon as possible for up to 5 days.<sup>21</sup>

### Contraindications

The only contraindication to ulipristal is suspected or known pregnancy.<sup>21</sup>

### Warnings

Ectopic pregnancies have been reported in up to 10% of studies with progestin only contraceptives. An ectopic pregnancy requires immediate medical attention. Women who complain of lower abdominal pain or who become pregnant after taking ulipristal should be evaluated for ectopic pregnancy.<sup>21</sup> Ulipristal is not intended for use as a routine contraceptive. It should not be used multiple times during one cycle.

### Drug Interactions

There are no drug interaction trials that have been conducted with ulipristal.<sup>21,22</sup> Drugs that induce or inhibit CYP3A4 may impact the effectiveness of ulipristal.

Agents that **induce** CYP3A4<sup>21,22</sup> enzymes and may **decrease** effectiveness of ulipristal include: barbiturates, oxcarbazepine, bosentan, phenytoin, carbamazepine, rifampin, felbamate, St. John's Wort, griseofulvin and topiramate.

Agents that **inhibit** enzymes and may **increase** plasma levels of ulipristal include: itraconazole and ketoconazole.

### Adverse Effects

The most common adverse effects reported with ulipristal are nausea, abdominal pain, dizziness and dysmenorrhea.<sup>21,22</sup>

### **Pregnancy and Lactation**

Ulipristal is FDA Pregnancy Category X. It is contraindicated in known or suspected pregnancy. It is not recommended in breastfeeding women.<sup>21</sup>

### **Role in therapy**

Ulipristal is an emergency contraceptive that is as effective as levonorgestrel.<sup>23</sup> Ulipristal is indicated for emergency contraception for up to 5 days. Levonorgestrel is only indicated for up to 3 days after unprotected sex.

It is important for the pharmacist to be aware of the two emergency contraceptive agents approved for use by the FDA. Levonorgestrel is available as a dual label product. It is available without a prescription to women age 17 and older. Women under age 17 must present a valid prescription for levonorgestrel. Below we explain some of the differences between levonorgestrel and ulipristal.<sup>21,22,24</sup>

Levonorgestrel (Plan B, Plan B-One Step, various generics):

- Sold from behind the counter in pharmacy
- Single dose, or 2 doses (12 hours apart)
- Not intended for routine use
- Contraindicated in suspected or known pregnancy
- Not an abortifacient
- Individuals must be  $\geq 17$  years for OTC purchase
- May dispense if  $<17$  with a prescription
- Require valid proof of identification
- No limit to number of packages sold
- Customer not required to sign a register

Ulipristal (Ella)

- Prescription only
- Single dose
- Not intended for routine use
- Contraindicated in suspected or known pregnancy
- Not an abortifacient
- No limit to number of doses prescribed

### **ALCAFTADINE (LASTACFT)**

Alcaftadine is the 10<sup>th</sup> ophthalmic agent approved for the treatment of itching related to allergic conjunctivitis. Ophthalmic antihistamines offer an advantage over oral antihistamines in that they have a more rapid onset of action and are devoid of systemic adverse effects.

### **Pharmacology/Pharmacokinetics**

Alcaftadine is a histamine-1 receptor antagonist.<sup>25,26</sup> It blocks the release of histamine from mast cells. It also inhibits eosinophil activation. After application to affected eyes, effects are seen within 15 minutes. The plasma concentrations of alcaftadine are minimal by 3 hours following a dose. There does not appear to be any systemic accumulation of alcaftadine or its active metabolite with daily use.

### **Indications**

Alcaftadine is approved for use in the treatment of itching associated with allergic conjunctivitis.<sup>25</sup> It should not be used in children under the age of 2.

### **Dosing**

The drug is administered once a day.<sup>25</sup>

### **Contraindications**

There are no known contraindications to the use of alcaftadine.<sup>25</sup>

### **Warnings**

As with all ocular preparations, it is important for the pharmacist to demonstrate the proper use of eye drops to prevent contamination of the dropper tip.<sup>25</sup> Alcaftadine contains benzalkonium chloride as a preservative. This preservative can be absorbed by soft contact lenses. The pharmacist should educate the patient to remove their contact lenses prior to instilling alcaftadine into the eyes. Lenses can be reinserted 10 minutes after the drug has been administered.

### **Adverse Effects**

Alcaftadine is generally well-tolerated.<sup>25,26</sup> The most frequent adverse effects reported include: irritation, itching, erythema and burning of the eye. The pharmacist may counsel the patient to keep the product refrigerated to lessen burning upon application.

### Pregnancy and Lactation

Alcaftadine is FDA Pregnancy Category B.<sup>25</sup> There are no well controlled clinical trials with pregnant women. It is not known if alcaftadine is excreted in human breast milk. Caution is advised when breastfeeding while taking alcaftadine.

### Role in therapy

Alcaftadine is the newest ocular antihistamine approved for use in allergic conjunctivitis. Clinical trials have shown it to be as effective as olopatadine in controlling the itching. It may offer some advantage to patients since it is dosed once a day.

## CASE SCENARIOS

### Case 1

**A physician calls your pharmacy to ask about prescribing dabigatran to a patient who has not been well controlled on warfarin. The physician is concerned because he is not sure how to convert the patient from warfarin to dabigatran. What do you tell him in order to assist in the conversion?**

*You explain to the physician that the warfarin dose is stopped and dabigatran is started when the INR is less than 2. You explain that the initial starting dose of dabigatran is 150 mg twice a day. If the patient has a CrCl of < 30 mL/minute the dose should be reduced to 75 mg twice a day.*

**The doctor states that the patient's INR is currently 1.8 and he has no renal impairment. The patient leaves the physician's office and stops at your pharmacy to have the prescription filled. What specific information do you provide to the patient when counseling him?**

You explain dabigatran is a new medication that the doctor is prescribing to replace the warfarin (Coumadin) prescription. You explain that the patient should not take the warfarin any longer. You explain that the dabigatran is taken once a day. You ask the patient if they understand why they are taking the medication. The patient states that this medication is supposed to thin the blood and prevent a blood clot or a stroke. You reinforce the importance of taking this medication each day at the same time. You also tell the patient that the medication can be taken with or without meals. Some patients have dyspepsia with dabigatran, so you explain that taking it with food may lessen the effect. You reinforce that the INR blood test required with warfarin is not needed with the new medication. You counsel the patient to avoid NSAIDs and other drugs that may increase the risk of bleeding.

### Case 2

**A woman comes to the pharmacy with a prescription for ulipristal (Ella). She is very anxious and shares with you that she experienced a contraceptive failure, the condom she was using during intercourse broke. This occurred yesterday and she is worried about getting pregnant. What important facts do you need to review when filling this prescription?**

In your conversation with the patient, you have verified that the unprotected sex occurred within the last 5 days. The patient stated that it occurred yesterday. It is important to review her medication history to determine if she is taking anything that may decrease the effectiveness of ulipristal. Medications that may decrease the effectiveness of ulipristal include agents that induce CYP3A4. You also should counsel the patient about the possibility of ectopic pregnancy. Convey that if she experiences severe lower abdominal pain she needs to contact her physician.

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**FUTURE TOPICS FOR THIS YEAR**  
 Healthcare Reform & Impact on Pharmacy;  
 Restless Leg Syndrome;  
 Vaccine Update

Fill in the information below, answer questions and return **Quiz Only** for certification of participation to:  
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**LESSON EVALUATION**

Please fill out this section as a means of evaluating this lesson. The information will aid us in improving future efforts. Either circle the appropriate evaluation answer, or rate the item from 1 to 7 (1 is the lowest rating; 7 is the highest).

1. Does the program meet the learning objectives?

- |  |     |    |
|--|-----|----|
| Describe new drugs approved by FDA in 2010                         | Yes | No |
| Discuss the role of these agents in therapy                        | Yes | No |
| Summarize adverse effects & drug interactions with these new drugs | Yes | No |
| Recommend specific counseling points related to these new drugs    | Yes | No |

2. Was the program independent & non-commercial

Yes No

Poor			Average		Excellent
1	2	3	4	5	6 7

3. Relevance of topic

4. What did you like most about this lesson? \_\_\_\_\_

5. What did you like least about this lesson? \_\_\_\_\_

**Please Select the Most Correct Answer**

- |   |   |
|---|---|
| <p>1. The FDA REMS program is designed to:</p> <p>A. Decrease medication risks to the patient</p> <p>B. Warn prescribers about potential side effects</p> <p>C. A &amp; B</p> <p>D. None of these</p> <p>2. When adding liraglutide to a sulfonylurea:</p> <p>A. The dose of sulfonylurea should be decreased</p> <p>B. The dose of sulfonylurea should remain the same</p> <p>C. Dose of liraglutide should be lowered</p> <p>D. None of these</p> <p>3. Dabigatran is associated with an increased risk of:</p> <p>A. Alopecia</p> <p>B. Hepatic injury</p> <p>C. Gastritis</p> <p>D. Bradycardia</p> <p>4. Dalfampridine should not be used in patients:</p> <p>A. With a CrCl &lt; 40mL/min</p> <p>B. History of seizure disorder</p> <p>C. Taking 4-aminopyridine</p> <p>D. All of these</p> <p>5. The following drugs should not be combined with fingolimod:</p> <p>A. Class 1a antiarrhythmics</p> <p>B. Live virus vaccines</p> <p>C. Dabigatran</p> <p>D. A &amp; B</p> | <p>6. When converting a patient from warfarin, before starting dabigatran, the INR should be below:</p> <p>A. 2.5</p> <p>B. 2.0</p> <p>C. 1.5</p> <p>D. 1.0</p> <p>7. A doctor calls you &amp; wants assistance in dosing lurasidone in a patient with CrCl of 37mL/min. What dose of you recommend?</p> <p>A. 80mg per day</p> <p>B. 40mg per day</p> <p>C. 120 mg per day</p> <p>D. 60mg per day</p> <p>8. The recommended dose of tesamorelin is:</p> <p>A. 2mg once daily</p> <p>B. 4mg once daily</p> <p>C. 1mg twice daily</p> <p>D. None of these</p> <p>9. Ulipristal is effective in preventing pregnancy:</p> <p>A. For up to 7 days</p> <p>B. For 2 days</p> <p>C. For 3 days</p> <p>D. For up to 5 days</p> <p>10. Patients remain at risk for infection for 2 months following discontinuation of fingolimod.</p> <p>A. True</p> <p>B. False</p> |
|---|---|

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