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June 2008 "New Drugs 2007-8: Impact on Ambulatory Care Pharmacy" 707-000-08-006-H01-P

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*NEW DRUGS*  
*2007-8*

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This lesson reviews new medication entities. Our goal is to identify current trends in drug approval. 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 707-000-08-006-H01-P. Pharmacists completing this lesson by June 31, 2011 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).

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

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1. Assess current trends in drug approval.
  2. Explain indications, pharmacology, adverse effects & dosing of the products discussed.
  3. Identify relevant patient information that should be provided by the pharmacist.
  4. Describe the role these products will play in ambulatory care practice.
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## TRENDS IN DRUG APPROVAL<sup>1</sup>

The Food and Drug Administration (FDA) approved only 16 new molecular entities (NME) in 2007, and as we move into 2008, the process continues to move slowly. This is a significant downward trend from previous years. In 2006 22 NME were approved, 20 in 2005 and 36 in 2004. Since the 2004 removal of Vioxx<sup>®</sup> from the market, the FDA has come under fire regarding prescription drug safety. Subsequently, there has been continued public concern with the safety of other drug classes such as erythropoiesis-stimulating agents (Procrit<sup>®</sup>, Aranesp<sup>®</sup>, Epogen<sup>®</sup>) and thiazolidinediones (Actos<sup>®</sup>, Avandia<sup>®</sup>). A transdermal drug rotigotine (Neupro<sup>®</sup>) was approved in 2007, but was withdrawn from the market in early 2008 due to a formulation problem resulting in crystals forming in the transdermal patch affecting drug delivery.

Although the FDA has not changed the criteria used to approve new drugs, they are looking at safety data in a new light. More safety data is being required than prior to 2004. It appears that the FDA has taken a conservative stance on drug approval, not wanting to have another serious safety issue arise after a drug has been approved. As a result, we are seeing a slow down in the number of NMEs approved.

This lesson will review the most clinically relevant NMEs approved in 2007 and early 2008 and the impact of those products on ambulatory pharmacy practice.

## NEW DRUGS RETAPAMULIN (ALTABAX<sup>®</sup>)<sup>2,3</sup>

Retapamulin is an antibacterial agent that is approved for use in the treatment of impetigo, which is a contagious superficial skin infection commonly seen in children. Most cases of impetigo are due to *Staphylococcus aureus* (methicillin resistant) or *Streptococcus pyogenes*. It is indicated for use in adults and children down to age 9 months.

### Pharmacology

Retapamulin is a pleuromutilins antibiotic. It binds to the L3 ribosomal protein and inhibits bacteria protein synthesis at the 50S subunit of the ribosome. Retapamulin is bacteriostatic against *Staphylococcus aureus* and *Streptococcus pyogenes*. Cross-resistance has not developed to retapamulin at this time.

### Pharmacokinetics

Retapamulin is poorly absorbed from both intact and abraded skin. The elimination of this agent from humans has not been studied.

### Black box warnings

There are no black box warnings with reptapamulin.

### Adverse effects

There are few clinically significant adverse effects with this agent. The most frequently reported adverse effects are application site irritation and pruritis.

### Drug Interactions

There are no clinically significant drug interactions with Altabax<sup>®</sup>. It should not be used concurrently at the same site with other topical agents. Use in this manner has not been studied.

### Dosage

Apply a thin film to the affected area twice a day for 5 days. The area may be covered with sterile bandage or gauze.

### Patient Information

- Altabax<sup>®</sup> should not be applied to the lips, mouth, inside of the nose or in the vagina.
- Patients may be encouraged to cover the treated area with sterile gauze or bandage. This may be important in small children or infants who may touch or rub the area and place fingers in or around the mouth or eyes.
- Patients or caregivers should be reminded to wash their hands thoroughly after application of the drug to the affected site.
- If there is no improvement in symptoms within 3-4 days of starting treatment, patients should be instructed to contact the prescribing physician.

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### Place in therapy

The current mainstay of topical therapy for impetigo is mupirocin 2% (Bactroban<sup>®</sup>) ointment. The Infectious Disease Society of America guidelines for the treatment of skin and soft tissue infections recommends topical (mupirocin) rather than oral treatment for patients with limited impetigo lesions. Altanax<sup>®</sup> offers some advantage over mupirocin, since it is applied twice a day for only 5 days. Mupirocin is applied 3-4 times a day for 12 days. Resistance to mupirocin has been reported. Altanax<sup>®</sup> may offer an alternative in those patients who have failed Bactroban<sup>®</sup>.

## NEBIVOLOL (BYSTOLIC<sup>®</sup>)<sup>4,6</sup>

Nebivolol is the newest beta-1 selective adrenergic blocker to come to market in the United States. It is classified as a third generation beta blocker. Nebivolol is indicated for the treatment of hypertension as monotherapy or as combination therapy with other antihypertensive agents. The efficacy of nebivolol has also been evaluated for the management of heart failure.

### Pharmacology

Nebivolol has a greater degree of selectivity for beta-1 receptors compared to other agents in the class, and it also has a unique nitric oxide potentiating vasodilatory effect. Pharmacologic trials with nebivolol have shown that stimulation of this pathway leads to decreased oxidative stress and may have potential benefits on preserving endothelial function.

### Pharmacokinetics

Bystolic<sup>®</sup> is well absorbed following oral administration. Its absorption is not affected by the co-administration of food. It is metabolized primarily by the CYP2D6 enzyme system. Both of the stereospecific metabolites have pharmacologic activity. It is excreted approximately 40% in the urine and 40% in the feces.

### Black box warnings

There is no black box warning with Bystolic<sup>®</sup>.

### Adverse effects

The most common adverse events reported with nebivolol during clinical trials were headache, fatigue, dizziness, diarrhea, nausea, insomnia, chest pain, bradycardia, dyspnea, rash, and peripheral edema.

Nebivolol, like other beta blockers, is contraindicated in patients with severe bradycardia, second or third degree heart block, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome without a pacemaker, severe hepatic impairment, and in patients who are hypersensitive to nebivolol.

### Drug Interactions

Nebivolol is metabolized via CYP2D6; therefore, drugs that inhibit or induce CYP2D6 should be used cautiously with nebivolol. Concurrent use of nebivolol with agents that decrease heart rate or inhibit AV conduction, such as verapamil, diltiazem, or antiarrhythmics, should be done cautiously as the risk of bradycardia is increased.

No drug-drug interactions were seen when nebivolol was administered with digoxin, warfarin, diuretics (furosemide, hydrochlorothiazide, or spironolactone), ramipril, losartan, ranitidine, cimetidine, charcoal, or sildenafil.

### Dosage

The recommended starting dose of nebivolol is 5 mg once daily. It can be taken without regard to food. Doses can be increased at 2-week intervals up to a maximum dose of 40 mg once daily. In patients with severe renal impairment (creatinine clearance < 30 mL/min) or in patients with moderate hepatic impairment, the recommended starting dose is 2.5 mg once daily. When discontinuing nebivolol, the dose should be tapered over 1 to 2 weeks.

### Patient Information

- Counsel patient that they should NOT abruptly discontinue nebivolol. Severe exacerbations of angina or myocardial infarction can occur.
- Remind patients to inform their surgeon and anesthesiologist prior to any procedure that requires anesthesia that they are taking nebivolol.

### Place in therapy

Nebivolol has a unique mechanism of action (nitric oxide mediated vasodilatation); however, additional studies are needed to determine the clinical relevance of these effects. Clinical data with nebivolol show that it significantly reduces both diastolic and systolic blood pressure as compared to placebo, and those blood pressure reductions with nebivolol are similar to those seen with other antihypertensive therapies (beta-1 blockers, ACE inhibitors, calcium channel blockers, and an ARB). Although reductions in blood pressure with nebivolol are similar to other antihypertensive agents, additional studies are needed to address the long-term benefits of nebivolol for hypertension. Nebivolol should be reserved as a second- or third-line agent for the management of hypertension.

Although there are some clinical trials with nebivolol in the treatment of heart failure, its use in this condition cannot be recommended at this time.

## AMBRISENTAN (LETAIRIS<sup>®</sup>)<sup>7,8</sup>

Ambrisentan is the newest agent approved for treatment of pulmonary arterial hypertension (PAH). Current guidelines for the initial treatment of PAH recommend the use of anticoagulation, oxygen, digoxin and diuretics. In patients with more resistant disease, prostacyclins (epoprostenol [Flolan<sup>®</sup>] and treprostinil [Remodulin<sup>®</sup>]) are available as intravenous infusions. Iloprost (Ventavis<sup>®</sup>) is available as a multiple day inhalation. Oral alternatives are available and include the phosphodiesterase inhibitor sildenafil (Revatio<sup>®</sup>) or a non-selective endothelin type A receptor antagonist, bosentan (Tracleer<sup>®</sup>) which both require multiple daily dosing.

### Pharmacology

Ambrisentan is similar to bosentan which is a non-selective endothelin receptor antagonist. Ambrisentan, however, is a selective endothelin Type A receptor antagonist. When the endothelin type A receptor is activated, vasoconstriction occurs.

### Pharmacokinetics

Ambrisentan is rapidly absorbed and is not affected by food. It is highly bound (99%) to plasma proteins. The elimination of ambrisentan is predominantly by non-renal pathways. The elimination half-life of ambrisentan is 9 hours. Ambrisentan is metabolized via P glycoprotein, CYP3A4, and CYP2C19 pathways.

### Black box warnings

All endothelin receptor antagonists have been associated with elevated aminotransferase levels and liver damage. All of these agents, including ambrisentan, have a black box warning requiring aminotransferase level monitoring before treatment and each month during treatment.

### Adverse effects

The most frequently reported adverse reactions reported with ambrisentan are peripheral edema, flushing, sinusitis, and tachycardia. Patients may experience an initial drop in hemoglobin and hematocrit; however, there is usually stabilization after the patient has been taking the drug for a few months. Patients should still have their hemoglobin and hematocrit monitored quarterly.

Ambrisentan carries a Pregnancy Category X label. In women who are of childbearing potential taking ambrisentan, a negative pregnancy test should be obtained before treatment begins. In addition, women should use 2 effective forms of birth control while taking ambrisentan.

### Drug Interactions

Ambrisentan is metabolized through a variety of pathways including CYP 3A4, 2C19, and p-glycoprotein. As a result, there are clinically significant drug interactions with ambrisentan.

When used in combination with CYP3A inhibitors such as cyclosporine, azole antifungals, ritonavir or clarithromycin, use caution. It should also be used with caution when combined with CYP2C19 inhibitors such as proton pump inhibitors.

Ambrisentan has not been shown to interact with other agents used to treat PAH including warfarin and sildenafil.

### Dosage

The approved dose of ambrisentan is 5 mg once daily by mouth. If needed, the dose may be increased to 10mg daily.

### Patient Information

- Ensure all female patients are educated about the pregnancy risk associated with ambrisentan.
- All patients with PAH should be asked if they are taking this medication since it is distributed through a closed system in order to screen for interactions and monitor patient for adverse effects.
- Inform patients of potential drug interactions and potential adverse effects.
- Reinforce the need for liver and hematocrit level monitoring while on therapy.

### Place in therapy

Ambrisentan is the first selective endothelin receptor antagonist that is approved for use in the treatment of PAH. It is dosed once a day compared to Tracleer<sup>®</sup>, a non-selective endothelin receptor antagonist, which is administered twice a day. Based on the average wholesale price, ambrisentan is comparable in price to Tracleer<sup>®</sup>. Both agents cost approximately \$60,000 annually. Currently it has not been directly compared to the other oral agents used for PAH, so its role in treatment remains unclear.

Letairis<sup>®</sup> is distributed exclusively through 8 specialty pharmacies developed as the Letairis<sup>®</sup> Education and Access Program (LEAP) restricted distribution program. This system is designed to monitor and provide education about the risks of liver injury and birth defects

## LISDEXAMFETAMINE (VYVANSE<sup>®</sup>)<sup>9-11</sup>

Lisdexamfetamine is the newest agent to enter the field of attention deficit hyperactivity disorder (ADHD). Lisdexamfetamine is approved for the treatment of ADHD in both children and adults. The product has only been evaluated in children from 6 to 12 years of age. It is classified as a prodrug stimulant. It must be converted in the body to its active form. There is some thought that this will decrease its abuse potential. However, it is still classified as a schedule II drug.

### Pharmacology

Lisdexamfetamine is a prodrug of dextroamphetamine bound to L-lysine. Once ingested orally, it is rapidly absorbed from the gastrointestinal tract and hydrolyzed to its active form, dextroamphetamine. Although the exact mechanism of action in the treatment of attention deficit/hyperactivity disorder (ADHD) is unknown, amphetamines block the reuptake of the neurotransmitters norepinephrine and dopamine in the presynaptic neuron, thereby increasing the release of these monoamines into the extraneuronal space.

### Pharmacokinetics

Vyvanse<sup>®</sup> is rapidly absorbed from the gastrointestinal tract and hydrolyzed to its active form, dextroamphetamine. Dextroamphetamine absorption is not affected by food. Approximately 96% of the dose of lisdexamfetamine is excreted in the urine. Approximately 42% of the dose is recovered as amphetamine, with 25% as hippuric acid. Only 2% of the dose is recovered as lisdexamfetamine.

### Black box warnings

Lisdexamfetamine has 2 boxed warnings: a high potential for abuse which may lead to dependence with prolonged administration, and if misused may cause sudden death and serious cardiovascular adverse events. Stimulants have been associated with cases of sudden death in children and adolescents with structural cardiac abnormalities or other serious heart problems, and sudden death, stroke, and myocardial infarction have been reported in adults taking stimulants. Stimulants may also increase blood pressure/heart rate, exacerbate symptoms of behavior disturbance, induce mixed/manic episodes in patients with bipolar disease, result in the emergence of new psychotic or manic symptoms, and produce symptoms of aggression. Other warnings/precautions associated with the use of lisdexamfetamine include seizures, visual disturbances, tics, and a temporary slowing in the growth rate of children.

### Adverse Events

The adverse effect profile of lisdexamfetamine is similar to that of other amphetamines. In children 6 to 12 years of age, the most common adverse events (incidence  $\geq 5\%$ ) were decreased appetite, dizziness, dry mouth, irritability, insomnia, upper abdominal pain, nausea, vomiting, and decreased weight. In adults, the most common adverse events (incidence  $\geq 5\%$  and a rate at least twice placebo) were upper abdominal pain, diarrhea, nausea, fatigue, feeling jittery, irritability, anorexia, decreased appetite, headaches, anxiety, and insomnia.

Lisdexamfetamine is contraindicated in patients with advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncratic reaction to sympathomimetic amines, glaucoma, and a history of drug abuse, agitated states, and during or within 14 days following the administration of monoamine oxidase inhibitors.<sup>1</sup>

### Drug Interactions

There are numerous drug-drug interactions with lisdexamfetamine. These potential drug interactions are shown in table 1. Vyvanse<sup>®</sup> should not be used within 14 days of monoamine oxidase inhibitors.

**Table 1. Drug Interactions with Amphetamines**

Mechanism of Interaction	Interacting Agents
Agents that lower blood levels of amphetamines by increasing urinary excretion	Urinary acidifying agents such as ammonium chloride and sodium acid phosphate
Agents that lower blood levels of amphetamines by decreasing urinary excretion	Urinary alkalinizing agents such as acetazolamide and thiazide diuretics
Agents whose effects may be reduced by amphetamines Adrenergic blockers	Antihistamines Antihypertensives Ethosuximide
Agents whose effects may be potentiated by amphetamines	Tricyclic antidepressants Meperidine Phenobarbital Phenytoin
Agents that may reduce the effects of amphetamines	Chlorpromazine Haloperidol Lithium carbonate

**Patient Information**

- Discuss the signs and symptoms of depression with the patient. Be sure to educate patient that if they (or their child) develop any of these symptoms while taking Vyvanse<sup>®</sup> to contact the physician.
- Take Vyvanse<sup>®</sup> once a day in the morning. It can be taken with or without food.
- If a child cannot swallow the capsule, the capsule can be opened and the contents dissolved in a glass of water and taken immediately. Do not store for later use.
- It is important to monitor heart rate and blood pressure when starting this medication. Offer to check patient's blood pressure and heart rate if available in your practice.
- Since Vyvanse<sup>®</sup> is a schedule II drug, explain refill procedures to the patient. Be sure to have them initiate prescription refills before all of the medication is used.
- Vyvanse<sup>®</sup>, like other drugs used for ADHD may lead to misuse and abuse of amphetamines.
- If you (or your child) develop blurred vision while taking Vyvanse<sup>®</sup>, contact your physician.

**Place in Therapy**

Lisdexamfetamine was developed as a prodrug to have less potential for abuse than amphetamine itself. No clinical data has been published to date to suggest that this product has less abuse potential. Lisdexamfetamine is a Schedule II controlled substance which is in the same category as all the other stimulants approved for the treatment of ADHD.

Currently, there are no published clinical trials that suggest any benefit of lisdexamfetamine over other available ADHD preparations. All of the current data are placebo-controlled, short-term trials (4 weeks). Stimulants are considered first-line therapy for the management of ADHD in both children and adults; however, agents such as methylphenidate and mixed amphetamine salts have substantially more efficacy and safety data published.

Lisdexamfetamine should be reserved as a second- or third-line agent for the management of ADHD in children and adults due to the lack of controlled trials.

**ALISKIREN (TEKTURNA<sup>®</sup>)<sup>12,13</sup>**

Aliskiren is the first drug available that is classified as a direct renin inhibitor. It is approved for the treatment of hypertension in adults, either alone or in combination with other agents.

**Pharmacology**

Aliskiren is a direct renin inhibitor. It decreased plasma renin activity through inhibiting the conversion of angiotensinogen to angiotensin I.

**Pharmacokinetics**

Tekturna<sup>®</sup> is poorly absorbed after oral administration. It has a bioavailability of around 2.5%. The elimination half life of the drug is long (24 hours), and it requires approximately 1 week to reach steady states. Approximately one quarter of the dose is excreted in the urine as the active drug aliskiren. No dose adjustment is required in elderly patients or those with renal or liver disease.

**Black box warnings**

Aliskiren should be stopped as soon as possible if the patient becomes pregnant. Aliskiren is pregnancy category C in the 1<sup>st</sup> trimester and Category D in the 2<sup>nd</sup> and 3<sup>rd</sup> trimesters. Reports of fetal death have been noted in patients who were taking drugs that act on the renin-angiotensin system.

**Adverse effects**

The most frequently reported side effects are gastrointestinal and include diarrhea, dyspepsia and abdominal pain. Although cough has been reported with Tekturna<sup>®</sup>, it is less frequent than what is reported with angiotensin converting enzyme inhibitors. Angioedema of the head and neck has been reported. Patients who are salt or volume depleted, or those taking other antihypertensive agents may be at risk for hypotension when Tekturna<sup>®</sup> is administered. Other side effects reported less frequently include increased uric acid, rash, and hyperkalemia.

**Drug Interactions**

Aliskiren is metabolized in part via the p-glycoprotein (PgP) system and, therefore, can interact with certain drugs. Ketoconazole, atorvastatin and cyclosporine are potent inhibitors of PgP and increase aliskiren plasma levels. Cyclosporine should not be used with aliskiren. Aliskiren reduces the effect of furosemide when given concomitantly.

Interactions are not reported with lovastatin, warfarin, digoxin, valsartan, and metformin. Irbesartan reduced aliskiren plasma levels by 50%.

**Dosage**

The starting dose of Tekturna<sup>®</sup> is 150 mg once a day. The dose may be increased to 300 mg daily. Doses greater than 300 mg daily have not been shown to increase effectiveness. Dosage adjustments are generally not required in patients with liver or renal dysfunction or in the elderly.

**Patient Information**

- Describe the symptoms of angioedema. If it occurs, patients should immediately discontinue aliskiren and contact their physician.
- Establish a routine pattern of taking this medication with regards to meals. High fat meals can decrease its absorption.
- Review patient medication profile for any potential drug interactions.
- Warn patients that there can be an increase in uric acid and for those at risk for kidney stones, may want to consult physician.

**Place in therapy**

There are currently a number of agents available for the treatment of hypertension. Although aliskiren is the first direct renin inhibitor available in the U.S., its role in therapy is still unclear. There is currently a lack of outcomes data with this agent. Until more data becomes available, this agent should be reserved for patients who have not been controlled on conventional agents.

**METHOXY POLYETHYLENE GLYCOL-EPOETIN BETA (MIRCERA<sup>®</sup>)<sup>14-17</sup>**

Anemia of chronic kidney disease has been treated for many years with erythropoiesis stimulating agents (ESA). The first generation ESA was epoetin which has a relatively short half life requiring dosing 3 times a week. The second generation ESA, Aranesp<sup>®</sup> has a much longer half life due to changes in the epoetin molecule. This longer half life allows for extended dosing every 2 weeks. The newest ESA is methoxy polyethylene glycol-epoetin beta (Mircera<sup>®</sup>) which is classified as a continuous ESA due to its much longer half life. Mircera was approved for treatment of anemia associated with chronic kidney disease in November, 2007; however, it has still not been released for sale in the United States. Amgen (maker of Epogen<sup>®</sup>, Aranesp<sup>®</sup>) has successfully obtained a temporary injunction against Roche so that the drug cannot be released in the United States, even though it is available in several European countries. This product is beta epoetin covalently bound to polyethylene glycol. Roche has appealed the injunction and intends to have the product available in the U.S. soon.

**Pharmacology**

Mircera<sup>®</sup> is a continuous erythropoiesis stimulating agent (CESA). It combines a methoxy polyethylene glycol polymer chain to epoetin beta which allows it to bind differently to the receptor.

**Pharmacokinetics**

Mircera<sup>®</sup> has a much longer elimination half life than other generation ESAs allowing for once monthly dosing. The

t ½ life of Mircera<sup>®</sup> is 134 hours, compared to darbepoetin (21 hours) and epoetin (5 hours).

**Black box warnings**

Although the final product labeling has not been released, it is expected that Mircera<sup>®</sup> will contain the same black box warnings as other erythropoiesis stimulating agents.

**Adverse effects**

The most frequently reported adverse effects seen in clinical trials with Mircera<sup>®</sup> include hypertension, diarrhea, headache, muscle spasms, fluid overload, and back pain. Other side effects include peripheral edema, urinary tract infections, constipation, vomiting, extremity pain and arteriovenous fistula thrombosis.

**Drug Interactions**

There are no clinically significant drug interactions that have been identified for Mircera<sup>®</sup>.

**Dosage**

In patients not taking an erythropoiesis stimulating agent, start Mircera<sup>®</sup> at 0.6 mcg/kg body weight once every 2 weeks IV or SC. In patients currently taking an erythropoiesis stimulating agent, convert to Mircera<sup>®</sup> using the chart below:

Weekly Darbepoetin IV or SC Dose (mcg/week)	Weekly epoetin IV or SC dose(IU/week)	Monthly starting dose of Mircera IV or SC(mcg/once month)
< 40	<8000	120
40-80	8000-16,000	200
>80	>16,000	360

As with other erythropoiesis stimulating agents, it is important to maintain the patient's hemoglobin (Hb) below 12 gm/dL. If the Hb is increasing >2 G/dL in 1 month, the dose should be decreased by 25%.

**Patient Information**

- Inform patient that they may need to take supplemental iron.
- Explain to patient that it is important to monitor blood pressure before treatment is started and regularly during treatment.
- Patients may administer Mircera<sup>®</sup> subcutaneously in the arm, thigh or abdomen. All of these sites are appropriate.

**Place in therapy**

Mircera<sup>®</sup> has been shown to be equally effective in maintaining hemoglobin levels in patients with chronic kidney disease with far fewer doses of drug. The risk of medication errors with ESAs is significant with the numerous doses, and dose adjustments that are seen. Use of Mircera<sup>®</sup> would result in 12-13 injections per year to manage anemia, while shorter acting ESAs require 52-150 doses per year. The use of this CESA provides good hemoglobin management with a far lower risk of medication error since the number of doses needed is reduced so dramatically compared to shorter acting ESAs. Although Mircera<sup>®</sup> is not available in the U.S. at this time, it should be considered for maintenance of patients requiring ESAs for chronic kidney disease.

**MARAVIROC (SELZENTRY<sup>®</sup>)<sup>18,19</sup>**

Maraviroc is a non-competitive antagonist of the chemokine receptor CCR5. CCR5 plays an important role in allowing HIV-1 to enter the host cell. Both CCR5 and CXCR4 are co-receptors that are needed for HIV-1 entry into the host cell. The HIV-1 virus strains that are generally seen early in the disease utilize the CCR5 co-receptor, while the strains that are detected later in the disease use the CXCR4 co-receptor. The viruses which use the CXCR4 receptor are usually present later in the disease process, often when patients develop AIDS. There has been a great deal of interest in HIV research to develop drugs that work at these co-receptors in an effort to prevent progression of HIV to AIDS. Researchers have now determined that tropism testing can allow physicians to target therapy based on CCR5 or CXCR4 tropism. Maraviroc is approved for use in combination with other antiretroviral therapy in patients who are treatment experienced with evidence of CCR5 tropic HIV-1 disease, resistant to other therapies.

**Pharmacology**

Maraviroc is a non-competitive antagonist of CCR5. By binding to CCR5, maraviroc prevents the HIV-1 virus from entering the host cell.

**Pharmacokinetics**

Maraviroc is not well absorbed following oral administration. The bioavailability of the 100mg dose is 23% and 33% for the 300mg dose. Maraviroc can be taken without regard for meals.

**Black box warnings**

Liver toxicity has been reported with maraviroc. Patients may present with hepatitis or an allergic type reaction prior to developing liver toxicity. Monitor patients for rash, eosinophilia, or elevations of IgE. If these symptoms occur, the patient should be assessed by their physician.

**Adverse effects**

The most common adverse effects reported with maraviroc include dizziness and postural hypotension, fever, rash, upper respiratory tract infection, cough, muscle pain, and abdominal pain. Other side effects include diarrhea, edema, sleep disorders, and urinary abnormalities.

**Drug Interactions**

There are potential drug interactions when maraviroc is administered with CYP3A inhibitors and/or inducers. The dose of maraviroc needs to be adjusted when these agents are given concomitantly. The dose adjustments are shown below in the dosage section.

**Dosage**

Other additional therapies	Maraviroc dose
CYP3A inhibitors (with or without a CYP3A inducer) <i>Protease inhibitors (except tipranavir/ritonavir)</i> <i>Delavirdine</i> <i>Ketoconazole, itraconazole, clarithromycin</i> <i>Other CYP3A inducers (nefazodone, telithromycin)</i>	150 mg twice a day
All NRTIs and enfuvirtide, nevirapine, tipranavir/ritonavir	300 mg twice a day
CYP3A inducers (without CYP3A inhibitor) <i>Efavirenz</i> <i>Rifampin</i> <i>Carbamazepine, phenobarbital, and phenytoin</i>	600 mg twice a day

The recommended starting dose of maraviroc is dependant on other antiretroviral therapy prescribed.

**Patient Information**

- Explain signs and symptoms of hepatitis (abdominal pain, dark urine, yellow eyes or skin) or allergic reaction (rash, itching skin) and inform patients that they should contact their physician immediately if they develop these symptoms.
- Maraviroc can be taken without regard for meals.
- Patients who are taking medication for high blood pressure should get up from a seated or lying position slowly, as maraviroc may cause postural hypotension.
- Maraviroc is taken in combination with other antiretroviral therapies. Do not stop taking other HIV drugs unless instructed to do so by physician.

**Place in therapy**

Maraviroc should be used in patients who are infected with CCR5-tropic HIV-1 only. These patients should exhibit resistance to multiple other antiretrovirals to be considered for maraviroc. Therefore, a patient's history of medication use and tropism status is required when determining if the patient is a candidate for this agent. In addition, maraviroc should not be used alone for treatment of HIV-1 infection.

**SUMMARY**

A number of new molecular entities have been approved in the past 18 months. It is important for pharmacists to become educated on these new agents and understand the potential adverse effects and interactions associated with these agents. The pharmacist can serve as a resource for patients when new medications are prescribed. It is the responsibility of the pharmacist to counsel patients when new medications are started to reduce the risk of harm to the patient.

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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?

- |   |     |    |
|---|-----|----|
| Assess current trends in drug approval  | Yes | No |
| Explain indications, pharmacology, adverse effects & dosing of products discussed | Yes | No |
| Identify relevant patient information that should be provided by the pharmacist   | Yes | No |
| Describe the role these products will play in ambulatory care practice            | Yes | No |

2. Was the program independent & non-commercial

- |  |           |         |
|--|-----------|---------|
|  | Yes       | No      |
|  | Excellent |         |
|  | Poor      | Average |
|  | 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 following test should be done monthly when taking ambrisentan.</p> <p>A. Pregnancy test<br/>                 B. Aminotransferase test<br/>                 C. Creatinine clearance<br/>                 D. None of these</p> <p>2. How does lisdexamfetamine differ from other stimulants?</p> <p>A. It's a transdermal patch used daily<br/>                 B. It's a prodrug &amp; requires activation in the body to its active form<br/>                 C. Does not carry a black box abuse warning<br/>                 D. Approved for children down to age 2</p> <p>3. The FDA has drastically changed the criteria for approving new drugs; this accounts for the reduction in new drugs this past year.</p> <p>A. True      B. False</p> <p>4. When initiating nebivolol therapy, the starting dose is:</p> <p>A. 5mg once daily<br/>                 B. 10mg once daily<br/>                 C. 2.5mg once daily<br/>                 D. 2.5 mg bid</p> <p>5. One benefit that retapamulin has compared to mupirocin is:</p> <p>A. Can be dosed twice a day for only 5 days<br/>                 B. No reported resistance to retapamulin<br/>                 C. There is no advantage over mupirocin<br/>                 D. Both A &amp; B are correct</p> | <p>6. Tekturna® should not be used during pregnancy.</p> <p>A. True<br/>                 B. False</p> <p>7. When counseling a patient who has a new prescription for Tekturna®, the pharmacist should:</p> <p>A. Warn the patient about angioedema<br/>                 B. Warn against eating fatty meals<br/>                 C. Discuss risk of kidney stones<br/>                 D. Both A &amp; C are correct</p> <p>8. A patient is taking epoetin SC 10,000 iu weekly. What dose of Mircera® should be taken?</p> <p>A. 120mcg once a month<br/>                 B. 200mcg once a month<br/>                 C. 300mcg once a month<br/>                 D. 360mcg once a month</p> <p>9. A patient taking Efavirenz® is switched to what dose of Selzentry®?</p> <p>A. 300mg bid<br/>                 B. 150mg bid<br/>                 C. 600mg bid<br/>                 D. None of these</p> <p>10. Maraviroc is approved for use in patients with the following type of HIV infection:</p> <p>A. XR4-tropic HIV-1 disease<br/>                 B. CCR5-tropic HIV-1 disease<br/>                 C. CCR5 HIV-3 disease<br/>                 D. None of these</p> |
|---|--|

**Contributing Author**

Mary Lynn Moody, BS Pharm  
Clinical Assistant Professor  
Director, Business Development  
Drug Information Group  
University of Illinois at Chicago  
College of Pharmacy

**Executive Editor**

William J. Feinberg,  
BS Pharm, MBA



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