

# New Drugs of 2007

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## Learning Objectives

### Pharmacists:

After completing this lesson, for each new drug described the pharmacist should be able to:

- List the generic and brand name, and manufacturer/distributor
- Explain the agent's major therapeutic use(s)
- Outline the drug's mechanism of action
- Describe the pharmacokinetic profile and common drug-interactions
- Discuss adverse effects and contraindications
- Describe the dosage schedule, route of administration, strengths, and any storage issues
- Outline monitoring parameters
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### Pharmacy Technicians:

After completing this lesson, for each new drug described the pharmacy technician should be able to:

- List the generic and brand name, and manufacturer/distributor
- Explain the agent's major therapeutic use(s)
- Describe the dosage schedule, route of administration, strengths, and any storage issues
- Outline monitoring parameters

In 2007, the Food and Drug Administration's (FDA) approval of new drugs slowed compared to the rate of approvals in prior years. The FDA approved 17 new molecular entities (NMEs) and 2 biologic license applications (BLAs) in 2007, the lowest number recorded since 1983. However, a number of new molecular entities were approved, including the first agent in a new class of antiretrovirals, a new agent for treatment of Parkinson's Disease, and the first in class agent for the treatment of pulmonary arterial hypertension. This CE program will provide pharmacists and pharmacy technicians with knowledge on the new molecular entities approved by the FDA in 2007.

### New Molecular Entities 2007

Generic Name	Brand Name	Sponsor	Indication	Date Approved
Aliskiren	Tekturna	Novartis	Hypertension	3/5/2007
Ambrisentan	Letairis	Gilead Sciences	Pulmonary arterial hypertension	6/15/2007 (P,O) *
Ammonia	Ammonia N13	Feinstein	PET scan agent	8/23/2007
Doripenem	Doribax	Ortho-McNeil	Broad-spectrum antibiotic	10/12/2007
Hydroxyethyl starch	Voluven	Fresenius Kabi	Blood volume loss	11/27/2007
Ixabepilone	Ixempra	Bristol Myers-Squibb	Breast cancer	10/16/2007 (P) *
Lanreotide	Somatuline Depot	Ipsen	Agromegaly	8/30/2007 (O) *
Lapatinib	Tykerb	GSK	Metastatic HER2-positive breast cancer	3/13/2007 (P) *
Lisdexamfetamine dimesylate	Vyvanse	Shire	ADHD	2/23/2007
Maraviroc	Selzentry	Pfizer	CCR5-tropic HIV-1	8/6/2007 (P) *
Nebivolol	Bystolic	Mylan Bertek	Hypertension	12/17/2007
Nilotinib	Tasigna	Novartis	Chronic myelogenous leukemia	10/29/2007 (O) *
Raltegravir	Isentress	Merck	HIV-1	10/12/2007 (P) *
Retapamulin ointment	Altabax	GSK	Impetigo	4/12/2007
Rotigotine	Neupro	Schwarz Biosciences	Parkinson's disease	5/9/2007
Sapropterin	Kuvan	BioMarin	Hyperphenylalaninemia	12/13/2007 (P,O) *
Temsirolimus	Torisel	Wyeth	Advanced renal cell cancer	5/30/2007 (P,O) *

### New Biologic Entities 2007

Eculizumab	Soliris	Alexion	Paroxysmal nocturnal hemoglobinuria	3/16/2007 (P,O) *
Methoxy polyethylene glycol-epoetin beta	Mircera	Hoffman La-Roche	Anemia associated with chronic kidney failure	11/14/2007 (P) *

*Adapted from the FDA ([www.fda.gov/cder/rdmt/InternetNDA07.htm](http://www.fda.gov/cder/rdmt/InternetNDA07.htm)) and Nature Reviews Drug Discovery 7, 107-109 (February 2008) doi:10.1038/nrd2514.*

*\* P is FDA Priority Review; O is FDA Orphan drug designation.*

#### **Aliskiren (Tekturna, Novartis)**

Tekturna is a renin inhibitor to treat hypertension through the renin-angiotensin-aldosterone system (RAAS.)

The drug provides maximum hypertensive effect within 2 weeks of administration. It has poor absorption, decreased by high-fat meals. It has a half-life of about 24 hours.

Tekturna is contraindicated in patients with a history of idiopathic or hereditary angioedema, bilateral renal artery stenosis, or in pregnancy. Adverse events include dizziness, rash, diarrhea, increased creatine clearance, increased BUN, and cough.

The recommended dosage in adults is 150 mg once daily which may be increased to a maximum of 300 mg. Tekturna is available as a 150-mg oral tablet.

### **Ambrisentan (Letairis, Gilead Sciences)**

Letairis is a new endothelin receptor antagonist used to treat pulmonary arterial hypertension classified by the World Health Organization (WHO) Groups II and III to improve exercise capacity and delay disease worsening.

Letairis is more selective than the other endothelin receptor on the market, Bosentan (Tracleer, Actelion Pharmaceuticals). It is rapidly absorbed with peak concentrations reached about 2 hours after administration, and is highly protein bound. It is a substrate of CYP3A4, CYP2C19, and UGT so should be used with caution with agents also metabolized by these pathways.

Ambrisentan should not be used in pregnant women or those who may become pregnant. The drug may also be toxic to the liver. The most common side effects are peripheral edema, headache, nasal congestion, palpitations, and flushing.

The recommended dosage in adults is 5 mg once daily, increased to 10 mg if treatment is well tolerated. Letairis is available as 5-mg and 10-mg tablets through restricted distribution.

### **Ammonia (Ammonia N13, Feinstein)**

Ammonia N13 is a positron emitting radiopharmaceutical used with positron emission tomography (PET) imaging of the myocardium.

After IV administration, the drug enters myocardial cells and is metabolized to glutamine N13 and retained in cells, allowing PET imaging. Its half-life is 1.67 minutes.

The recommended dosage of Ammonia N13 is 10-20mCi injected through a large vein catheter.

### **Doripenem (Doribax, Ortho-McNeil)**

Doribax is an intravenous carbapenem broad-spectrum antibiotic used to treat complicated intra-abdominal and urinary tract infections. It is the fourth drug in this class marketed in the US.

Doribax inhibits cell wall formation facilitating bacterial lysis. It is infused over one hour and is widely distributed in most body fluids, and its elimination half-life is about an hour through renal pathways.

Doribax is contraindicated in patients with known hypersensitivity to it, cephalosporins, carbapenems, penicillins or other beta-lactam antibiotics.

The most common adverse effects include nausea, diarrhea, anemia, phlebitis, rash, and headache.

The recommended dosage, infused over 1 hour, is 500 mg every 8 hours for 5-14 days for intraabdominal infections and for 10 days with urinary tract infections. It comes in 500-mg vials.

### **Hydroxyethyl (Voluven, Fresenius)**

Voluven is an intravenous solution to prevent and treat a dangerous loss of blood volume, a condition that sometimes occurs during and after surgery.

Voluven is manufactured from a water-insoluble starch modified to form hetastarch. Hetastarch-linked units (polymers) increase and maintain blood volume more effectively when used in combination with salt-and-water solutions.

The most common side effect from Voluven was itching. Voluven is not recommended for the following: patients with known abnormal sensitivity to the synthetic starch used in the product, with fluid overload, kidney failure not related to low blood volume, dialysis patients, head bleeding or very high sodium or chloride blood levels.

Voluven is available as a 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection.

### **Ixabepilone (Ixempra, BMS)**

Ixempra is an antineoplastic agent for the treatment of patients with advanced breast cancer who have failed other treatments.

Ixempra is primarily metabolized in the liver by the CYP3A4 system.

The most common adverse effects of the drug are peripheral neuropathy, fatigue, asthenia, myalgia, arthralgia, alopecia, nausea, vomiting, stomatitis, mucositis, diarrhea, and musculoskeletal pain.

The recommended dosage is 40 mg/m<sup>2</sup> infused over three hours every three weeks. It is available as 15 mg and 45 mg vials with diluent.

### **Lanreotide (Somatuline Depot, Ipsen)**

Somatuline Depot is an injection used to treat acromegaly. It is a sustained-release formulation that mimics the hormone somatostatin.

Somatuline Depot's effects last 28 days and it has a half-life of 23-30 days. The drug may reduce absorption of other drugs given concomitantly. It may reduce gallbladder motility and cause gallstones, cause hyperglycemia and hypoglycemia, and bradycardia. Dosage adjustments for patients on cyclosporine may be necessary as the drug reduces cyclosporine availability.

The most common side effects of Somatuline are diarrhea, abdominal pain, cholelithiasis, anemia, and injection site pain/inflammation.

The recommended dose of Somatuline is 90 mg subcutaneously or IV every four weeks for three months. Somatuline Depot is available as prefilled, non-reconstituted syringes in 60 mg, 90 mg and 120 mg dosages. It is stored in the refrigerator.

### **Lapatinib (Tykerb, GSK)**

Tykerb is an EGFR/HER2 inhibitor for use in combination with capecitabine, for the treatment of advanced or metastatic HER2-positive breast cancer in women who have received prior therapy, including Herceptin (trastuzumab).

The drug is extensively metabolized by the liver through the CYP3A4 and 3A5 pathways, and to a lesser extent by CYP2C19 and 2C8. It has an elimination half-life of 24 hours. It will increase the effect/toxicity of other drugs that inhibit CYP3A4 such as azole antifungals, clarithromycin, diclofenac, doxycycline, erythromycin, and others.

Adverse reactions include fatigue, hand-and-foot syndrome, diarrhea, rash, nausea, vomiting, abdominal pain, mucosal inflammation, stomatitis, dyspepsia, anemia, neutropenia, thrombocytopenia, limb and back pain, dyspnea, and insomnia, among others.

Tykerb is formulated as a 250 mg oral tablet. Tykerb is available at specialty pharmacies through a restricted-access program.

### **Lisdexamfetamine dimesylate (Vyvanse, Shire)**

Vyvanse is a prodrug of dextroamphetamine for the treatment of attention deficit/hyperactivity disorder.

Vyvanse is rapidly absorbed and widely distributed in the plasma. It undergoes non-CYP liver metabolism with an elimination half-life of less than an hour prior to being converted to dextroamphetamine with a 10-13 hour half-life.

Vyvanse is contraindicated in individuals with cardiovascular disease, hypertension, hyperthyroidism, glaucoma, a history of drug abuse and within 2 weeks of using an MAO inhibitor. Adverse events include insomnia, headache, decreased appetite, irritability, dizziness, fever, vomiting, and rash.

Vyvanse is formulated as 30-mg, 50-mg and 70-mg oral capsules with a recommended dose of 30 mg daily with increases in increments of 20mg/day until optimal response is achieved.

### **Maraviroc (Selzentry, Pfizer)**

Selzentry is an anti-retroviral agent indicated for combination treatment of CCR5-tropic HIV. It is the first in a new class of agents called CCR5 co-receptor antagonists that block the HIV entry into human cells via the CCR5 co-receptor.

Selzentry is a CYP3A substrate and should be used in caution in patients with preexisting liver conditions.

The most common side effects of Selzentry include upper respiratory tract infections, cough, pyrexia, rash, musculoskeletal symptoms, abdominal pain, and dizziness.

The recommended dosage is 300 mg twice daily and the product is available as 150 mg and 300 mg tablets. A dose of 150 mg twice daily is used for patients on a CYP3A inhibitor.

### **Nebivolol (Bystolic, Mylan/Forest)**

Bystolic is a new, cardioselective beta-1 receptor blocker used to treat hypertension alone or in combination with other agents.

Bystolic is metabolized in the liver primarily through glucuronidation. Peak plasma concentrations are achieved 1-1/2 to 4 hours after administration.

The drug is contraindicated in patients with severe bradycardia, heart block greater than the first degree, cardiogenic shock, decompensated heart failure, sick sinus syndrome, or severe hepatic impairment. The most common adverse events are headache, nausea, and bradycardia.

The recommended dosage of Bystolic is 5 mg daily, which can be increased at two-week intervals up to 40 mg daily. The product comes as 2.5 mg, 5 mg, and 10 mg tablets.

### **Nilotinib (Tasigna, Novartis)**

Tasigna is a kinase inhibitor used to treat chronic myelogenous leukemia (CML) in the chronic phase and accelerated Philadelphia chromosome positive CML in adult patients resistant to or intolerant to prior therapy, including imatinib (Gleevec, Novartis.)

Tasigna reaches peak plasma concentrations in three hours. Its bioavailability increases if given with meals. Its half-life is 17 hours.

Tasigna must be used with caution in patients with hypokalemia, hypomagnesia, or long QT syndrome because the drug elongates the QT interval. Concurrent use with other drugs that do so as well should be avoided.

The most common adverse reactions associated with Tasigna are grade 3 or 4 thrombocytopenia, neutropenia, rash, pruritis, headache, nausea, fatigue, diarrhea, constipation and vomiting.

The recommended dosage is 400 mg twice daily, 12 hours apart, at least 2 hours before or one hour after food. The product is available as 200 mg capsules.

### **Raltegravir (Isentress, Merck)**

Isentress is a new antiretroviral agent indicated for HIV-treatment in patients who are treatment-experienced with HIV-1 strains resistant to other medications. It is the first in a new class of drugs called HIV integrase strand transfer inhibitors (ISTIs) that block viral replication.

The drug is absorbed in about three hours, reaching steady state concentrations in two days. It is metabolized by the liver and must be used in caution in patients with liver disease or abnormalities.

The most common adverse events associated with Isentress are nausea, headache, diarrhea, and pyrexia. Myopathy has been reported.

The recommended dosage is 400 mg twice daily and the product is available in 400 mg tablets.

### **Retapamulin ointment (Altabax, GSK)**

Altabax is a topical pleuromutilin antibiotic for the treatment of impetigo.

The drug is extensively metabolized by the liver through the CYP3A4 system and is 94% protein bound. When using topically, however, absorption is low.

Adverse events include headache, itching, eczema, diarrhea, nausea, and local site irritation.

The recommended dosage is to apply to the affected area twice daily for 5 days for adults and children over 9 months.

Altabax is a topical ointment in a 1% formulation in 5 g, 10 g, and 15 g tubes.

### **Rotigotine (Neupro, Schwarz)**

Neupro is a dopamine agonist delivered through a continuous transdermal system for the treatment of Parkinson's disease.

The drug stimulates dopamine D<sub>2</sub> receptors. Maximum concentration is achieved within 15-18 hours of patch application and steady state plasma levels occur in two to three days. The drug is highly plasma bound and excreted renally as inactive metabolites.

The most common side effects include application site reactions, nausea, somnolence, dizziness, headache, vomiting, and insomnia.

The recommended dosage is 2 mg daily, increased by 2mg/24 hours if well tolerated to a maximum of 6 mg/24 hours. The product is available as a transdermal patch in 2 mg, 4 mg, and 6 mg strengths.

### **Sapropteran (Kuvan, Biomarin)**

Kuvan is a novel agent used to reduce blood phenylalanine (Phe) concentrations in patients with phenylketonuria, in conjunction with a phenylalanine-restricted diet.

The drug is a synthetic form of the BH<sub>4</sub> cofactor for the phenylalanine hydroxylase enzyme. Kuvan's elimination half-life is 6.7 hours. High-fat, high-calorie meals increase drug absorption.

Blood phenylalanine concentrations should be monitored during treatment. Pregnant women are encouraged to enroll in a registry.

The most common side effects are headache, upper respiratory track infections, rhinorrhea, throat pain, diarrhea, vomiting, and cough.

The recommended dosage is 10 mg/kg/day once daily, which may be increased to 20 mg/kg/day if the Phe levels have not decreased one month after baseline. The drug comes as 100 mg tablets that are dissolved in 120-240 ml of water or apple juice and taken within 15 minutes of mixing.

### **Temsirolimus (Torisel, Wyeth)**

Torisel is a new agent for the treatment of advanced renal cell carcinoma. It suppresses progression of the cancer cell cycle.

Torisel is metabolized in the liver by the CYP3A4 system and eliminated in the feces. Drug adjustments should be considered when using the drug with other CYP3A4 inducers such as rifampin or inhibitors such as ketoconazole.

The most common adverse events include rash, asthenia, mucositis, nausea, edema, and anorexia. Blood effects include anemia, lymphopenia, and thrombocytopenia. Other lab effects include hyperlipemia, hypertriglyceridemia, hypophosphatemia, elevated alkaline phosphatase and serum creatinine.

The usual dose is 25 mg infused over 30-60 minutes once a week. Treatment continues until the cancer worsens or there is unacceptable toxicity. Product is available in 25 mg/ml vials that include the diluent.

**Eculizumab (Soliris, Alexion)**

Soliris is used to reduce hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH.) It is the sole agent approved for this condition.

The risk of meningococcal infection is very high and patient must be vaccinated for the disease at least 2 weeks before starting treatment.

The most common side effects of Soliris are headache, nasopharyngitis, back pain, nausea and fatigue.

The recommended dosage is 600 mg every week for the first 4 weeks, followed by 900 mg for the fifth dose one week later, then 900 mg every 2 weeks. The drug is administered via infusion.

**Methoxy polyethylene glycol-epoetin (Mircera, Roche)**

Mircera is the first once-monthly dosed erythropoiesis-stimulating agent used to treat anemia associated with chronic renal failure, including patients on dialysis.

Blood pressure should be adequately controlled prior to administration. The most common adverse events are hypertension, diarrhea, nasopharyngitis, headache, and upper respiratory tract infection.

The initial dosage is 0.6 mcg/kg body weight once every two weeks. It is available as single use vials and prefilled syringes for SC or IV injection.