New drugs approved in 2007

Erin Sears, PharmD

This article briefly reviews the new drug entities approved by the Food and Drug Administration in 2007.

**ALISKIREN (TEKTURNA)**

*Therapeutic use:* Aliskiren (1–3) is a direct renin inhibitor that decreases plasma renin activity and inhibits the conversion of angiotensinogen to angiotensin I. It is indicated for the treatment of hypertension, either as monotherapy or in combination with other antihypertensive agents. Clinical trials have demonstrated that aliskiren provides antihypertensive efficacy similar to that of angiotensin receptor blockers. Doses of 300 mg daily have resulted in mean changes in systolic blood pressure of approximately 15 mm Hg and diastolic blood pressure of approximately 12 mm Hg.

*Recommended dosage:* The initial dosage is 150 mg once daily. In patients whose blood pressure is not adequately controlled, the dosage may be increased to 300 mg once daily. Aliskiren is supplied in 150- and 300-mg tablets.

*Drug interactions:* Aliskiren is metabolized by the cytochrome P450 isoenzyme 3A4 (CYP3A4). Thus, drug interactions can be of concern; caution should be used when administering aliskiren with medications that inhibit or induce CYP3A4. Pharmacokinetic studies have noted the following interactions: 1) irbesartan reduced the maximum concentration ($C_{\text{max}}$) of aliskiren up to 50% in patients, 2) atorvastatin increased the aliskiren $C_{\text{max}}$ and bioavailability (AUC) by 50%, 3) ketoconazole resulted in an 80% increase in aliskiren plasma levels, and 4) when coadministered with furosemide, the AUC and $C_{\text{max}}$ of furosemide were reduced by 30% and 50%, respectively. Furthermore, cyclosporine use resulted in a 2.5-fold increase in $C_{\text{max}}$ and a 5-fold increase in the AUC of aliskiren; the manufacturer states that concomitant use of the two medications is not recommended. Aliskiren does not inhibit any of the cytochrome P450 isoenzymes, nor does it induce CYP3A.

*Black box warning:* Aliskiren’s action on the renin-angiotensin system can negatively impact the developing fetus, and use should be discontinued when pregnancy is detected.

*Adverse reactions:* Treatment with aliskiren is generally well tolerated. Effects reported with therapy include edema (0.4%), gastrointestinal disturbances (2.3%), cough (1.1%), rash (1%), elevated uric acid (0.4%), gout (0.2%), and renal stones (0.2%).

**AMBRISENTAN (LETAIRIS)**

*Therapeutic use:* Ambrisentan (4, 5) is a high-affinity endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (World Health Organization [WHO] group I) in patients with WHO class II or III symptoms to improve exercise capacity and delay clinical worsening. Clinical trials have demonstrated that ambrisentan improves symptoms, exercise capacity, and hemodynamics in patients with pulmonary arterial hypertension.

*Recommended dosage:* Treatment should begin with 5 mg once daily and may be increased to 10 mg as tolerated. Ambrisentan is available in 5- and 10-mg tablets.

*Black box warning:* Elevations in liver transaminases and serious liver injury have been reported with ambrisentan and/or related drugs. Thus, liver function should be monitored and treatment should be discontinued if liver transaminases increase to >5 times the upper limit of normal or if elevations are accompanied by other signs and symptoms of liver dysfunction (e.g., bilirubin levels >2 times the upper limit of normal). Ambrisentan may cause harm to the fetus, and its use is contraindicated in pregnancy.

*Drug interactions:* Due to the large number of enzymes potentially involved in the metabolism of ambrisentan (e.g., CYP3A4, CYP2C19, uridine 5'-diphosphosphate glucuronosyltransferases [UGTs], organic anion transport protein, and P-glycoprotein) the potential for drug interactions is high. Unfortunately, in vivo drug studies have been limited. Caution should be used with concomitant administration of cyclosporine A and strong inhibitors of CYP3A and CYP2C19, which can cause increased exposure to ambrisentan. Caution should also be used with concomitant administration of P-glycoprotein, CYPs, and UGT inducers, which could potentially lower concentrations of ambrisentan. Of note, studies evaluating the dual use of ambrisentan with warfarin or sildenafil have indicated that dose adjustments are not needed.

From the Department of Pharmacy Services, Baylor University Medical Center, Dallas, Texas.

**Corresponding author:** Erin Sears, PharmD, Department of Pharmacy Services, Baylor University Medical Center, 3500 Gaston Avenue, Dallas, Texas 75246 (e-mail: ErinSe@BaylorHealth.edu).
*Adverse reactions:* Peripheral edema, nasal congestion, sinusitis, flushing, palpitations, nasopharyngitis, abdominal pain, constipation, dyspnea, and headache all occurred more frequently in patients receiving ambrisentan than in those receiving placebo.

*Other comments:* Tablets should not be crushed, chewed, or broken. Ambrisentan may only be prescribed via the Letairis Education and Access Program.

**ARMODAFINIL (NUVIGIL)**

*Therapeutic use:* Armofin is the R-enantiomer of modafinil and acts as a central nervous system stimulant. It is indicated to improve wakefulness in obstructive sleep apnea/hypopnea syndrome, narcolepsy, and shift work sleep disorder. Clinical trials noted by the manufacturer have demonstrated that armodafinil significantly increases wakefulness in those individuals with the aforementioned conditions compared with placebo. These results were based on sleep latency assessed by the Maintenance of Wakefulness Test and the change in the patient’s overall disease status measured by the Clinical Global Impression of Change.

*Recommended dosage:* The treatment dose for obstructive sleep apnea/hypopnea syndrome and narcolepsy is 150 mg or 250 mg given as a single dose in the morning, and the treatment dose for shift work sleep disorder is 150 mg given daily administered approximately 1 hour before start of the work shift. Armofin should be administered at a reduced dose in patients with severe hepatic impairment and possibly in elderly patients as well. Armofin is available in 50-, 150-, and 250-mg tablets.

*Drug interactions:* Due to the partial involvement of CYP3A enzymes in the metabolic elimination of armofin and coadministration of potent inducers of CYP3A (e.g., rifampin, phenobarbital, and carbamazepine) or inhibitors of CYP3A (e.g., ketoconazole, erythromycin) could alter the plasma levels of armofin. Furthermore, armofin has demonstrated moderate inductive effects on CYP3A and moderate inhibitory effects on CYP2C19 activity. Specifically, dose adjustments should be considered in patients taking concomitant medications that are substrates for CYP3A4/5 (e.g., steroidal contraceptives, triazolam, and cyclosporine) and CYP2C19.

*Adverse reactions:* Therapy is generally well tolerated, with the most common effects including headache, nausea, dizziness, and insomnia.

*Other comments:* Armofin is classified as a schedule IV controlled substance, indicating the potential for limited physical or psychological dependence.

**DORIPENEM (DORIBAX)**

*Therapeutic use:* Doripenem is a carbapenem bactericidal antimicrobial that inactivates essential penicillin-binding proteins in the cell wall, inhibiting cell wall biosynthesis, thereby resulting in bacterial cell death. It is indicated for the treatment of complicated intra-abdominal infections and complicated urinary tract infections, including pyelonephritis caused by susceptible bacteria. Clinical trials demonstrated that doripenem is noninferior to meropenem in intra-abdominal infections and noninferior to levofloxacin in complicated urinary tract infections, including pyelonephritis.

*Recommended dosage:* The recommended treatment dose is 500 mg every 8 hours via intravenous infusion administered over 1 hour for patients at least 18 years of age. Dosage adjustments in patients with renal impairment may result in loss of seizure control. Probenecid is not recommended for patients taking doripenem since probenecid may result in loss of seizure control. Probenecid is not recommended for patients taking doripenem since probenecid increases doripenem concentrations by interfering with the active tubular secretion of doripenem.

*Adverse reactions:* Doripenem has been associated with headache, nausea, diarrhea, rash, and phlebitis. Postmarketing adverse events noted outside the United States include anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis, interstitial pneumonia, and seizures; causality has not been established.

**ECULIZUMAB (SOLIRIS)**

*Therapeutic use:* Eculizumab is a monoclonal antibody that inhibits terminal complex-mediated intravascular hemolysis. It is indicated in patients with paroxysmal nocturnal hemoglobinuria to reduce hemolysis. Clinical trials have demonstrated that eculizumab reduces the need for transfusion and improves patients’ quality of life, fatigue, and anemia.

*Recommended dosage:* Treatment should begin with 600 mg every 7 days for the first 4 weeks followed by 900 mg for the fifth dose 7 days later and 900 mg every 14 days thereafter. Eculizumab comes as a 300-mg single-use vial. The dose should be administered via a 35-minute intravenous infusion.

*Drug interactions:* No formal drug-drug, drug-food, or drug-herb interaction studies have been performed.

*Black box warning:* Use of eculizumab places patients at higher risk of serious meningococcal infections. Patients should be vaccinated with the meningococcal vaccine a minimum of 2 weeks prior to receiving the first dose of eculizumab and should be monitored closely for signs and symptoms of infection.

*Adverse reactions:* Effects associated with therapy include headache, nasopharyngitis, back pain, nausea, fatigue, cough, herpes simplex infection, sinusitis, respiratory tract infection, constipation, myalgia, extremity pain, and influenza-like illness.

*Other comments:* The product must be stored in the refrigerator and protected from light.
in the inner aspect of the upper arm and provides continuous release of histrelin, delivering approximately 65 µg of drug daily.

**Drug interactions:** No formal drug-drug, drug-food, or drug-herb interaction studies have been performed.

**Adverse reactions:** The most common adverse event noted is implant site reaction, including complications related to the insertion or removal of the implant.

**Other comments:** Initial transient increases of estradiol and/or testosterone may cause a temporary worsening of symptoms.

**LANREOTIDE (SOMATULINE DEPOT)**

**Therapeutic use:** Lanreotide (12) is a somatostatin analog indicated for the long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy. Clinical trials have demonstrated that efficacy is achieved in the first 16 weeks.

**Recommended dosage:** Treatment should be initiated at 90 mg every 4 weeks for 3 months and adjusted thereafter based on growth hormone and/or insulin-like growth factor-1 levels. Patients with moderate to severe renal or hepatic impairment should be started at a reduced initial dose of 60 mg every 4 weeks for 3 months and adjusted based on levels thereafter. Lanreotide is available in single-use syringes of 60, 90, and 120 mg.

**Drug interactions:** Cyclosporine may need dosing adjustment since concomitant use with lanreotide may reduce the relative bioavailability of cyclosporine. Caution should be used with concomitant administration of bradykinin-inducing drugs due to the risk of an additive reduction in heart rate. Somatostatin analogs may decrease the clearance of compounds metabolized by CYP450 enzymes; thus, patients receiving such concomitant medications with a narrow therapeutic index (e.g., quinidine) should be more closely monitored.

**Adverse reactions:** Common effects associated with therapy include diarrhea, cholelithiasis, abdominal pain, nausea, and injection-site reactions. Other events noted in long-term trials include sinus bradycardia, hypertension, and anemia.

**Other comments:** Blood glucose levels should be monitored due to inhibition of secretion of glucagon and insulin by lanreotide. The medication should be injected in the superior external quadrant of the buttock, and the injection site should be alternated.

**LEVOCETIRIZINE (XYZAL)**

**Therapeutic use:** Levocetirizine (13), an H-1 receptor antagonist, is the active enantiomer of cetirizine and is indicated for relief of symptoms associated with seasonal and perennial allergic rhinitis and also the treatment of uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 6 years of age and older.

**Recommended dosage:** Adults and children 12 years of age and older should be initiated on 5 mg once daily in the evening. The dose should be halved (2.5 mg) in children 6 to 11 years of age. Dosage adjustments are also required in patients 12 years and older with decreased renal function (creatinine clearance of 10 to 80 mL/min). Levocetirizine should not be used in patients with a creatinine clearance below 10 mL/min or those who are undergoing hemodialysis. The drug is available in 5-mg tablets.

**Drug interactions:** No in vivo drug interaction studies have been performed with levocetirizine.

**Adverse reactions:** Nasopharyngitis, somnolence, fatigue, dry mouth, and pharyngitis are common side effects associated with the medication in patients 12 years and older; children 6 to 11 years more commonly experience pyrexia, cough, somnolence, and epistaxis.

**LISDEXAMFETAMINE (VYVANSE)**

**Therapeutic use:** Lisdexamfetamine (14, 15) is a prodrug of dextroamphetamine, a central nervous system stimulant, and is indicated for the treatment of attention-deficit/hyperactivity disorder. Clinical trials have demonstrated efficacy and tolerability similar to those of other drugs for attention-deficit/hyperactivity disorder.

**Recommended dosage:** The recommended initial treatment dose is 30 mg once daily in the morning for children 6 to 12 years of age who are starting treatment for the first time or switching therapies. Dosage may be adjusted in 20 mg/day increments weekly. The maximum daily recommended dose for children is 70 mg daily. Lisdexamfetamine is supplied in 30-, 50-, and 70-mg capsules.

**Drug interactions:** Lisdexamfetamine may alter the therapeutic effects of adrenergic blockers, tricyclic antidepressants, antihistamines, antihypertensives, ethosuximide, meperidine, norepinephrine, phenobarbital, phenytoin, and Veratrum alkaloids. Furthermore, the effects of lisdexamfetamine may be increased by tricyclic antidepressants, monoamine oxidase inhibitors, and propoxyphene and may be decreased by chlorpromazine, haloperidol, lithium carbonate, methenamine therapy, and urinary acidifying agents (e.g., ammonium chloride, sodium acid phosphate).

**Black box warning:** Amphetamines are associated with a high potential for abuse. Prolonged periods of administration may result in dependence, and misuse of the medication can result in sudden death and serious cardiovascular adverse events.

**Adverse reactions:** As with other central nervous system stimulants, a large number of adverse events are associated with the use of lisdexamfetamine. Some of the more common side effects include decreased appetite, insomnia, upper abdominal pain, headache, irritability, vomiting, decreased weight, and nausea. Serious cardiovascular and psychiatric adverse events have been associated with the medication as well.

**Other comments:** Lisdexamfetamine is classified as a schedule II controlled substance, indicating that the medication has a high potential for abuse and its use can result in psychological or physical dependence.

**METHOXY POLYETHYLENE GLYCOL-EPOETIN BETA (MIRCERA)**

**Therapeutic uses:** Methoxy polyethylene glycol-eopoetin beta (Mircera) (16), an erythropoiesis-stimulating agent (ESA), is indicated for the treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not
on dialysis. Open-label clinical trials randomizing patients to Mircera or a comparator ESA have demonstrated comparable efficacy in hemoglobin effect.

**Recommended dosage:** Mircera should be administered subcutaneously or intravenously at 0.6 µg/kg body weight once every 2 weeks. To convert from another ESA, the total weekly dose should be used. It is important that when Mircera is initiated or the dose is adjusted, hemoglobin is monitored every 2 weeks until stabilized. Follow-up monitoring should occur thereafter at 2- to 4-week intervals. Dose reductions are recommended if the rate of rise in hemoglobin is >1 g/dL in 2 weeks or if the hemoglobin is increasing and approaching 12 g/dL. Mircera is available in single-use vials containing 50, 100, 200, 300, 400, 600, or 1000 µg, and it is available in single-use prefilled syringes containing 50, 75, 100, 150, 200, 250, 400, 600, or 800 µg.

**Drug interactions:** No formal drug-drug interaction studies have been performed.

**Black box warning:** Mircera has a black box warning to inform health care professionals of the increased mortality, serious cardiovascular and thromboembolic events, and tumor progression associated with ESA treatment. Patients with renal failure are at greater risk of death and serious cardiovascular events when ESA therapy targets higher versus lower hemoglobin levels; thus, treatment should be individualized to achieve and maintain a target of 10 to 12 g/dL. In patients with cancer, Mircera is not indicated for the treatment of anemia due to cancer chemotherapy. A clinical study performed in this population was terminated early because of the occurrence of significantly more deaths among patients receiving Mircera compared with another ESA.

**Adverse reactions:** Effects most commonly associated with therapy include hypertension, diarrhea, nasopharyngitis, headache, and upper respiratory tract infections.

**NEBIVOLOL (BYSTOLIC)**

**Therapeutic use:** Nebivolol (17, 18) is a third-generation beta-blocker with preferential β1 selection in extensive metabolizers and at doses ≤10 mg. Nebivolol loses its selectivity as plasma concentrations increase. It is indicated for the treatment of hypertension and can be used as monotherapy or in combination with other antihypertensive agents. Clinical studies have demonstrated similar effectiveness between nebivolol and other antihypertensives (e.g., atenolol, bisoprolol, lisinopril, nifedipine extended release).

**Recommended dosage:** Initial treatment should commence at a dose of 5 mg once daily as monotherapy or in combination with other agents. The dose can be increased at 2-week intervals up to 40 mg. For patients with severe renal impairment (creatinine clearance ≤30 mL/min) and moderate hepatic impairment, the recommended initial dose is 2.5 mg once daily. Nebivolol is available as 2.5-, 5-, and 10-mg tablets.

**Drug interactions:** When nebivolol is coadministered with an inhibitor of CYP2D6 (e.g., quinidine, propafenone, fluoxetine, paroxetine), the bioavailability of nebivolol could be affected. Thus, patients receiving such drugs should be closely monitored and the nebivolol dose adjusted according to blood pressure response. Caution should be used in combining nebivolol with myocardial depressants, inhibitors of atrioventricular conduction, or antiarrhythmics due to an increased risk of bradycardia. Nebivolol should not be used in combination with other beta-blockers. Due to the risk of a severe reduction in sympathetic activity, it is important to closely monitor patients receiving nebivolol concurrently with catecholamine-depleting drugs (e.g., reserpine, guanethidine). Finally, in patients concomitantly receiving nebivolol and clonidine, nebivolol should be discontinued several days prior to tapering clonidine.

**Adverse reactions:** Common adverse events associated with therapy include headache, fatigue, paresthesia, dizziness, hypotension, and bradycardia.

**RETAPAMULIN (ALTABAX)**

**Therapeutic use:** Retapamulin (19) is a pleuromutilin antibacterial agent indicated for topical treatment of impetigo due to methicillin-susceptible Staphylococcus aureus or Streptococcus pyogenes in adults and pediatric patients 9 months or older.

**Recommended dosage:** A thin layer of ointment should be applied to the affected area twice daily for 5 days. Retapamulin is supplied as a 10 mg per 1 g ointment.

**Drug interactions:** Due to limited systemic exposure, drug interactions are not of clinical concern with retapamulin.

**Adverse reactions:** Application-site pruritus is the most common side effect noted with therapy.

**ROTIGOTINE (NEURPO)**

**Therapeutic use:** Rotigotine (20–23) is a nonergolinic dopamine agonist that is indicated for the management of signs and symptoms of early stage idiopathic Parkinson’s disease. Clinical trials have demonstrated that rotigotine significantly improves patients’ symptoms of early disease over a 6-month period. Clinical trials in advanced disease have demonstrated benefit over placebo; however, when compared with pramipexole, rotigotine has shown noninferiority for only a portion of endpoints. More studies will be required to determine its role in advanced disease.

**Recommended dosage:** Treatment should start at 2 mg/24 h and may be increased by 2 mg/24 h weekly to a maximum of 6 mg/24 h. Rotigotine is supplied as a 2-, 4-, and 6-mg transdermal patch.

**Drug interactions:** A potential decrease in rotigotine effectiveness could occur when administered concomitantly with dopamine antagonists.

**Adverse reactions:** Common adverse effects associated with rotigotine include application site reactions, nausea, vomiting, headache, somnolence, and insomnia. Other dose-related effects include abnormal dreaming, hallucinations, rash, weight decrease, and myalgia. Caution should be used in patients with cardiovascular disease due to the risk of syncope and elevations in heart rate and blood pressure.

**Other comments:** Other warnings and precautions noted by the manufacturer address the prevalence of sulfite allergy; reports of extreme somnolence and hallucinations resulting in discontinuation of therapy; the occurrence of symptomatic hypotension, weight gain, and fluid retention; and the increased incidence of melanoma in patients with Parkinson’s disease.
Patients undergoing magnetic resonance imaging or cardioversion should have the patch removed prior to the procedure.

**SAPROPTERIN (KUVAN)**

*Therapeutic use:* Sapropterin (24) is a biologically active synthetic form of tetrahydrobiopterin (BH4) indicated to reduce blood phenylalanine levels in patients with hyperphenylalaninemia due to BH4-responsive phenylketonuria. Sapropterin is to be used in conjunction with a phenylalanine-restricted diet.

*Recommended dosage:* The starting dose of sapropterin is 10 mg/kg once daily. Doses of sapropterin may be adjusted within the range of 5 to 20 mg/kg once daily based on phenylalanine levels in the blood. Sapropterin is supplied as 100-mg tablets.

*Drug interactions:* No formal drug-drug interaction studies have been performed.

*Adverse reactions:* The most common side effects associated with therapy include headache, diarrhea, abdominal pain, upper respiratory tract infection, pharyngolaryngeal pain, vomiting, and nausea. Postmarketing experience has additionally indicated the occurrence of convulsions and increased gamma-glutamyltransferase.

**OTHER**

Antiretroviral therapy added two new products to its repertoire in 2007: maraviroc (Selzentry) and raltegravir (Isentress). Both medications are the first in a new class of drugs. Maraviroc is a CCR5 co-receptor antagonist, and raltegravir is a human immunodeficiency virus integrase strand transfer inhibitor (25, 26).

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The Table provides information regarding new chemotherapeutic agents and their approved indications.

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<tr>
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<th>Generic name</th>
<th>Indication</th>
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<tr>
<td>Torisel</td>
<td>Temsirolimus</td>
<td>Treatment of advanced renal cell carcinoma</td>
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<tr>
<td>Tykerb</td>
<td>Lapatinib</td>
<td>Combination treatment with capcetibane for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab</td>
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*From references 27–30.*