Continuing Education

New & Noteworthy Medication Approvals of 2015

Authors:

Kavita Patel
Pharm.D. Candidate 2016
Harrison School of Pharmacy, Auburn University

Keith Dasinger
Pharm.D. Candidate 2016
Harrison School of Pharmacy, Auburn University

Jeremy Burgess
Pharm.D. Candidate 2016
Harrison School of Pharmacy, Auburn University

Corresponding Author:
Bernie R. Olin, Pharm.D.
Associate Clinical Professor and Director
Drug Information Center
Harrison School of Pharmacy, Auburn University

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EDUCATIONAL OBJECTIVES

Name three new drugs approved in 2015.
Discuss the new class of drugs in the treatment of hyperlipidemia.
Explain the contraindications for secukinumab**.**
Describe the new treatment option for Hepatitis C (HCV).

INTRODUCTION

New drugs, defined here as new molecular entities (NME), are medications with an active substance that has never before been approved for the market in the United States.[1] As of September 28, 2015 there have been 27 new molecular entities approved this year.[2] During the calendar year of 2014 the Center for Drug Evaluation and Research (CDER) approved 41 new drugs.[3] From 2005 to 2013, an average of 25 new novel medications have been approved yearly.[3] With new medications coming to market almost weekly, keeping up with new information can be a daunting task.

A select group of noteworthy approvals are discussed here. Two new PCSK9 inhibitors, Praluent® (alirocumab) and Repatha® (evolocumab), are a new class of drugs in the treatment of hyperlipidemia. Kengreal® (cangrelor) is a new P2Y12 inhibitor which may be more efficacious than clopidogrel when used during percutaneous coronary intervention (PCI). Corlanor® (ivabradine) is in a new class of medications used for heart failure that may decrease morbidity. Cosentyx® (secukinumab) is new biologic agent that provides a new option for psoriasis patients who have failed other biologic agents. Natpara® (parathyroid hormone) is covered because hypoparathyroidism has not traditionally been treated by the hormone therapy. Addyi® (flibanserin) has been popularized in the media as the "female Viagra®" and was chosen because its novel mechanism of action. Two new anti-psychotics, Rexulti® (brexpiprazole) and Vraylar (cariprazine), are included because of the adverse events associated with this class of medications in general. Finally, Daklinza® (daclatasvir) is currently the newest addition in the treatment of hepatitis C, a disease state which has continually evolving treatments.

PRALUENT® (ALIROCUMAB) AND REPATHA® (EVOLOCUMAB)

Praluent® (alirocumab) and Repatha® (evolocumab) are monoclonal antibodies approved on July 24, 2015, and August 27, 2015, respectively. Both are in a new class of drugs known as the proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors.[2] Alirocumab and evolocumab are approved for certain patients with heterozygous familial hypercholesterolemia (HeFH) or patients with clinical atherosclerotic cardiovascular disease (ASCVD), who require additional low-density lipoprotein (LDL) lowering.[4] In addition evolocumab is also indicated for homozygous familial hypercholesterolemia (HoFH).[5] They are adjuncts to diet and statin therapy. ASCVD defined by the 2013 ACC/AHA Blood Cholesterol Guidelines includes acute coronary syndromes, or a history of myocardial infarction (MI), stable or unstable angina, revascularization, stroke, transient ischemic stroke (TIA), or peripheral arterial disease.[6] In HeFH and HoFH there is a reduction in the number of functional LDL receptors resulting in an increase in LDL usually ranging from 250 to 450 mg/dL for HeFH and higher for HoFH. It is diagnosed with very high LDL, a strong family history of premature heart disease, and the presence of tendon xanthomas (caused by cholesterol deposits in tendons). FH can be caused by "gain of function" mutations in the gene encoding for PCSK9.[7] PCSK9 in the plasma binds to LDL receptors causing endocytosis of the receptor, intracellular degradation, and an increase in LDL. Alirocumab and evolocumab bind to the PCSK9 enzyme, increasing the number of LDL receptors, thereby increasing LDL clearance.[4,5]

Alirocumab and evolocumab are injected subcutaneously (SC) into the thigh, abdomen, or upper arm every 2 weeks.[8,9] They should be stored in the refrigerator in the outer carton to protect it from light, and patients should be instructed to keep the prefilled pen or syringe at room temperature for 30 to 40 minutes prior to injection.[8,9] The prefilled pen or syringe should not be shaken or exposed to extreme heat. The usual dosage for alirocumab is 75 mg, SC, injected every 2 weeks. If adequate response is not achieved in 4 to 8 weeks the dose may be increased to 150 mg, SC, every 2 weeks.[8,9] For evolocumab, the dose is 140 mg SC every 2 weeks or 420 mg once monthly.[8,9] There are no dose adjustments for mild to moderate renal or hepatic impairment; neither have been studied in severe impairment and the manufacturers do not recommend adjustment.[8,9]

The only contraindication to either PCSK9 inhibitor is hypersensitivity to the drug or any components. Information for alirocumab and evolocumab in pregnancy is not available; however IgG molecules usually cross the placenta.[4,8] The most common adverse effects, in ≥5% of patients, for both are nasopharyngitis, injection site reactions, and influenza.[4,5] In alirocumab, other less common adverse events, are neurocognitive events (confusion or memory impairment), hepatic disorders (abnormal liver enzymes usually), bronchitis, sinusitis, cough, and muscle symptoms.[4] In evolocumab, less common adverse events include rash, eczema, myalgia, and urticaria.[5] In trials of alirocumab, the most common event leading to discontinuation was allergic reactions and elevated liver enzymes, while in evolocumab it was myalgia.[4,5] Since both are monoclonal antibodies immunogenicity may occur leading to greater incidence of allergic reaction and short or long term loss of efficacy.[8,9] Alirocumab costs about $672 for each SC injection; recently Express Scripts® announced the company would cover both alirocumab and evolocumab for patients needing an alternative to statin therapy.[10]

Of the five double blind, placebo controlled trials, which led to the FDA approval of alirocumab, 3 trials included only patients with HeFH.[11-14] All trials were at least 52 weeks long, and the primary endpoint was mean change in LDL from baseline. All patients received the maximal statin dose tolerated, with or without other lipid therapies. All 5 trials found a significant reduction in

mean percent change in LDL compared to placebo. It will be of interest to see where alirocumab falls in updated blood cholesterol guidelines. As of now, alirocumab seems of use in patients with HeFH or clinical ASCVD who do not achieve adequate lipid lowering with statin therapy (with or without other lipid lowering medications). The effect of alirocumab on cardiovascular morbidity or morality has not been established.[4]

In evolocumab, four randomized controlled trials were conducted for FDA approval.[1,15-18] Two of the trials were in patients with clinical ASCVD who were on statin therapy, which was continued for the study. The two trials had a total of 435 patients who were randomized to evolocumab or placebo. The first study was 12 weeks while the next one was 52 weeks, however, both trials showed a significant reduction in LDL compared to placebo. The third study was conducted in 329 HeFH patients who were on statin therapy.[17] Patients were randomized to placebo, 140 mg SC every 2 weeks, or 420 mg once monthly. The LDL lowering in both doses of evolocumab was significantly greater than in the placebo group. The 140 mg every 2 weeks showed a difference of -61% in LDL lowering compared to placebo, while the 420 mg once monthly showed a -60% difference in lowering. The fourth study of evolocumab was in 49 HoFH patients.[18] There were 33 patients randomized to evolocumab and 16 to placebo; all patients were on statin therapy. The evolocumab groups showed a significant decrease in LDL compared to placebo; the difference in LDL lowering between evolocumab and placebo was -31%.

Both alirocumab and evolocumab show potential in patients who require additional lipid lowering than what is offered by statin therapy alone.

KENGREAL® (CANGRELOR)

Kengreal® (cangrelor) is a direct P2Y12 platelet receptor inhibitor that blocks ADP-induced platelet activation and aggregation.[8] It was approved for use on June 22, 2015 as an adjunct to percutaneous coronary intervention (PCI) to reduce the risk of peri-procedural myocardial infarction, repeat coronary vascularization, and stent thrombosis in patients not previously treated with a P2Y12 inhibitor.[20] It binds selectively and reversibly to the P2Y12 receptor to prevent further signaling and platelet aggregation.[20] PCI is used in patients with early ST Elevated Myocardial Infarction (STEMI) and non ST Elevated Myocardial Infarction (NSTEMI) for reperfusion of coronary arteries. The 2011 ACCF/AHA/SCAI Guidelines for PCI recommend a P2Y12 inhibitor as first line therapy in conjunction with other medications for thrombosis prevention.[19] Cangrelor is not included in these guidelines since it was approved after their publication. However, it belongs to an approved drug class for PCI and is indicated for PCI use and most likely will be included in the next update of the PCI guidelines.

Cangrelor is available as a 50 mg intravenous injection.[8,9] The recommended dose is 30 mcg/kg IV bolus prior to PCI procedure followed by continuous 4 mcg/kg IV infusion for at least 2 hours or the duration of the PCI, whichever is longer.[20] There is no well-established maximum dose.[3] Platelet inhibition occurs within 2 minutes of administration.[8] To maintain platelet inhibition after discontinuation of cangrelor infusion, an oral P2Y12 platelet inhibitor, such as ticagrelor, prasugrel, or clopidogrel, should be administered.[1,20] Clopidogrel and prasugrel should not be administered until after cangrelor discontinuation due to a blocking effect of cangrelor.[1,20,21] No other drug interactions are reported at this time.[20] The price of cangrelor is about $90 for 5 mg.

Hypersensitivity and significant active bleeding are contraindications for cangrelor use.[8,9] Bleeding can be increased by cangrelor use as with other P2Y12 inhibitors, however, due to a short half life (t1/2) of 3-6 minutes no antiplatelet effect is observed an hour after discontinuation.[8,20] There is a greater incidence of bleeding with cangrelor than with clopidogrel, approximately 16% versus 11%, respectively.[8,20] No dosage adjustments appear necessary for the elderly or patients with hepatic impairment.[8,9,20] Adjustments are not required for renal impairment, however, further worsening was reported in patients who were already renally impaired with a CrCL <30 ml/min.[8]

There was a randomized, double-blind study performed in which subjects with coronary artery disease requiring PCI and receiving standard therapy including aspirin and heparin or bivalirudin were randomized to cangrelor or to clopidogrel.[22] Cangrelor was administered as 30 mcg/kg bolus followed by 4 mcg/kg/min infusion for 2 to 4 hours. Clopidogrel 600 mg was administered immediately at the end of the cangrelor infusion in subjects randomized to cangrelor. Clopidogrel 300 mg or 600 mg was administered shortly before PCI or shortly afterward, in subjects randomized to the clopidogrel group. The primary outcome was the first occurrence of any one of the composite endpoints of all-cause mortality, myocardial infarction (MI), ischemia-driven revascularization (IDR), and stent thrombosis (ST) within 48 hours after randomization. Cangrelor significantly reduced the occurrence of primary composite endpoint events compared to clopidogrel (relative risk reduction [RRR] 22%). Most of the effect was a reduction in post-procedural MIs detected solely by elevations in CK-MB (type 4a MI). Cangrelor did not reduce the risk of death.[22]

CORLANOR® (IVABRADINE)

Corlanor® (ivabradine) was approved on April 15, 2015 in a new class of drugs known as the hyperpolarization-activated cyclic nucleotide-gated channel blockers.[23] It is approved for certain patients with stable, symptomatic chronic heart failure (HF) with left ventricular ejection fraction (EF) ≤35%, who are in sinus rhythm with a resting heart rate ≥70, and either on the maximally tolerated dose of beta- blocker or have a contraindication to beta-blocker use.[23] Ivabradine works by disrupting ion current flow in the sinoatrial node, which lengthens diastolic depolarization and slows heart rate. HF as defined by the ACCF/AHA Guidelines for the Management of Heart Failure include HF with reduced ejection fraction (HFrEF) and HF with preserved EF (HFpEF).[18] Clinical diagnosis of HFrEF is defined as HF and EF of ≤40%.[24] In half of patients with HFrEF, variable degrees of left ventricular (LV) enlargement are present.[24] It is diagnosed mainly by signs and symptoms based on the ACC/AHA HF staging system and the NYHA (New York Heart Association) Functional Classification.[24] The ACC/AHA staging system focuses on recognizing the progression of the disease, emphasizes risk factor modification, and preventative treatment strategies.[24] It consists of stages A: patients at high risk of structural heart disease, B: development of structural heart disease, C: HF symptoms develop, D: treatment-resistant symptoms.[24,25] NYHA Functional Classification is intended to classify symptoms according to the health-care-providers

evaluation.[24,25] HF can be exacerbated by the following cardiovascular (CV) risk factors: hypertension, diabetes, atrial fibrillation, and hyperlipidemia.[25]

The starting dose of ivabradine is 5 mg twice daily by mouth. After 2 weeks of treatment, the dose is adjusted based on heart rate. The maximum dose is 7.5 mg twice daily. However, if the patient is hemodynamically compromised or experiencing bradycardia defined as heart rate (HR) <60 beats per minute (bpm) then a dose of 2.5 mg twice daily is recommended.[23] There are no dose adjustments for mild or moderate hepatic impairment, but it is contraindicated in patients with severe hepatic impairment (Child-Pugh C).[23] Also, there are no dose adjustments for renal impairment in which the creatinine clearance (CrCL) is 15 to 60 mL/min; it has not been studied in CrCL <15 mL/min; 60 tablets of ivabradine costs $450.

Contraindications to ivabradine include: acute decompensated heart failure, blood pressure <90/50 mm Hg, sick sinus syndrome, sinoatrial block, resting heart rate <60 bpm prior to treatment, severe hepatic impairment, pacemaker dependence, and concomitant use with strong CYP3A4 inhibitors.[8,23] Ivabradine is likely to cause fetal harm based on animal data.[23] It is recommended that women of child bearing age use effective contraception. The most common adverse effects, in ≥5% of patients are bradycardia, hypertension, and atrial fibrillation.[23] Other, less common, adverse events include syncope, hypotension, angioedema, erythema, rash, pruritus, urticaria, vertigo, diplopia, and visual impairment.[23] In clinical trials, the most common event leading to discontinuation was visual symptoms.[9,23,26]

The FDA approval of ivabradine was based on the SHIFT trial.[26] The SHIFT trial was 23 months long, and the primary endpoint was the composite of first occurrence of hospital admission for worsening heart failure or cardiovascular death.[9] The majority of patients received beta blockers, ACE inhibitors, and diuretic drugs.[8] The SHIFT trial found a significant reduction in mean heart rate compared to placebo. Ivabradine reduced morbidity associated with hospitalization for worsening heart failure or cardiovascular death, but there was no statistically significant benefit in cardiovascular death. Current 2012 European Society of Cardiology (ESC) Guidelines for Heart failure states that ivabradine may be considered in patients with NYHA class II-IV, LVEF ≤35%, and HR ≥70 beats/min once other medications have failed.[27] Patients must try an ACEI, beta-blocker, and mineralocorticoid therapy before consideration for ivabradine. As of now, ivabradine seems of use in patients in HFrEF who meet the specific criteria.

COSENTYX® (SECUKINUMAB)

Cosentyx® (secukinumab) is a human interleukin-17A antagonist approved on January 21, 2015.[28] It is approved for adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Psoriasis is a common, chronic inflammatory, multisystem disease with predominantly skin and joint manifestations.[29] In psoriasis there is a progressive T-lymphocyte-mediated systemic inflammatory response that results from a complex interplay between genetic factors and environmental influences.[30] Genetic predisposition and precipitating "trigger" factors play a role in the "march of psoriasis," which is referring to the march of innate and adaptive immune response.[30] Diagnosis of psoriasis is usually based on recognition of psoriatic lesions and is not based on laboratory tests.[30] The extent of psoriasis is defined by the extent of body surface area (BSA), hands, feet, facial, or genital regions involvement.[29] Secukinumab selectively binds to the interleukin-17 A and inhibits its interaction with the IL-17 receptor, thus inhibiting the release of pro-inflammatory cytokines and chemokines.[8,31]

Secukinumab is available as a *sensoready* pen, prefilled syringe, and lyophilized powder for reconstitution.[8,28,31] The lyophilized powder is only handled by a health care professional since it involves reconstitution of the powder, but the pen and the prefilled syringe may be self-injected by the patient.[28] The recommended dose of the human interleukin is 300 mg (two doses of 150 mg) injected subcutaneously (SC) into the thigh, abdomen, or upper arm every week for the first 4 weeks, then 300 mg once every 4 weeks.[8,28,31] Secukinumab is only available in 150 mg/ml because some patients may only require 150 mg per dose. It should be stored in the refrigerator in the outer carton to protect it from light, and patients should be instructed to keep the prefilled pen or syringe at room temperature for 15 to 30 minutes prior to injection.[8,31] The prefilled pen or syringe should not be shaken or exposed to extreme heat.[8,28,31] No dose adjustments for renal or liver impairment since it has not been studied in that population.[8,31] Secukinumab 150 mg/ml is about $2194.

The only contraindications are hypersensitivity to secukinumab and concomitant use of live vaccines.[8,9] Secukinumab is pregnancy category B, although there are insufficient controlled trials in pregnant women.[8,28] The most common adverse effects, in ≥5% of patients, are infection, nasopharyngitis, exacerbations of Crohn's Disease, and hypersensitivity.[28,31] Others appearing less often include urticaria, diarrhea, mucocutaneous candidiasis, oral herpes, pharyngitis, rhinitis, and upper respiratory tract infection.[28] Since secukinumab is a monoclonal antibody, the possibility of an increased incidence of an allergic reaction may occur over time.[7,23,26] Thus, leading to decreased long-term safety and efficacy.[8,28,31]

There were four multicenter, randomized, double blind, placebo controlled trials conducted in 2,403 total patients, which led to the FDA approval of secukinumab.[32-35] All trials were at least 12 weeks long, and the primary endpoint was the proportion of subjects who achieved a reduction in Psoriasis Area and Severity Index (PASI) score of at least 75% (PASI 75) from baseline to week 12 and treatment success (clear or almost clear or a score of 0-1) on the Investigator Global Assessment modified 2011 (IGA). In all four trials, the secukinumab group had significantly more patients meet PASI 75 and more patients with an IGA of 0 or 1 compared to placebo.[32-35] Further studies comparing secukinumab to other therapies for plaque psoriasis would provide more insight into efficacy.

NATPARA® (PARATHYROID HORMONE)

Natpara® (recombinant parathyroid hormone) was FDA approved on January 8, 2015 as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism.[2] Hypoparathyroidism can be caused by autoimmune disorders, congenital defects, by inadvertent removal of the parathyroid gland, or by damage with radiation therapy.[37] Hypocalcemia and low or absent parathyroid hormone are typical signs of hypoparathyroidism.[37] Other lab abnormalities are

hyperphosphatemia, hypercalciuria, and decreased 1,25-dihydroxyvitamin D.[37,38] Symptoms of hypoparathyroidism usually manifest as a result of hypocalcemia and include: perioral numbness, paresthesia, and carpal/pedal muscle spasms.[37,38] Formal guidelines for hypoparathyroidism treatment do not exist, however usual therapy consists of active vitamin D and calcium supplementation.[38] Parathyroid hormone increases renal tubular calcium absorption, increases intestinal calcium absorption, and increases calcium release from bone.[8] Hypoparathyroidism is the only hormonal deficiency left that is not primarily treated with the missing hormone.[39]

Natpara® is self administered by the patient subcutaneously into alternate thighs each day.[36] A *Q-Cliq* pen, dual chambered medication cartridges, and a mixing device are provided for injection.[36] The *Q-Cliq* pen may be reused for up to 2 years and the reconstituted medication cartridge should be changed every 2 weeks.[36] The unused medication cartridges and reconstituted medication cartridges in the *Q-Cliq* pen should be stored in the refrigerator.[36] It is available in 25 mcg, 50 mcg, 75 mcg, and 100 mcg. The initial dose is 50 mcg daily; it can be increased in 25 mcg increments every 4 weeks to a maximum dose of 100 mcg.[8,9,36] There are no dose adjustments in mild to moderate hepatic or renal impairment, and it has not been studied in severe impairments (hepatic or renal). It is primarily metabolized hepatically and excreted renally.[8,9] One SC injection of Natpara® is about $4750.

Natpara® should only be used in patients who cannot be controlled on calcium and vitamin D alone because of the risk of osteosarcoma, which is a black box warning.[8,9] Parathyroid hormone should also be avoided in those at an increased risk for osteosarcoma, for example those with Paget's disease.[36] There are no contraindications with this medication. Natpara® is only available through a REMS (risk evaluation and mitigation strategy) program. Severe hypercalcemia can occur during initiation or dose adjustment and severe hypocalcemia can occur when discontinuing. The serum calcium and vitamin D levels should be monitored in patients.[36] Adverse events occurring most commonly include paresthesia, hypocalcemia, headache, hypercalcemia, nausea, diarrhea, vomiting, arthralgia, hypercalciuria, and pain in the extremities.[36] Drug interactions include alendronate and digoxin.[8,9] Alendronate should be avoided because it may diminish the effects of parathyroid hormone by interfering with calcium normalization.[8,9] Digoxin should be monitored with parathyroid hormone because hypercalcemia can predispose patients to digoxin toxicity.[8,9,36]

The main trial conducted with Natpara® for FDA approval was the REPLACE trial.[39] It was a randomized, double blind, placebo-controlled study conducted for 24 weeks. Patients with hypoparathyroidism on calcium and active vitamin D were randomized to either placebo or Natpara®. Patients were considered "responders" if they met all 3 of the following criteria:

1. At least a 50% reduction in the dose of active vitamin D
2. At least a 50% reduction in calcium supplementation
3. An albumin corrected calcium level between 7.5 and 10.6 mg/mL

There were significantly more responders in the Natpara® group compared to placebo with 54.8% responding in the Natpara® group versus 2.5% in the placebo group. Natpara® may be an efficacious option in patients with hypoparathyroidism who cannot be controlled on calcium and vitamin D alone.

ADDYI® (FLIBANSERIN)

Addyi® (flibanserin) was approved in August 18, 2015.[41] It is approved for treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD) which is characterized by low sexual desire caused by distress, interpersonal difficulty, and is not due to co-existing medical or psychiatric conditions, problems within the relationship, or the effects of medications.[9,41] Flibanserin is the first FDA approved treatment for HSDD. Perimenopause is defined by the American Association of Clinical Endocrinologists (AACE) guidelines as the time period before menopause occurs in a woman.[44] The most common symptom seen with perimenopause is hot flashes.[8,44] Flibanserin is a serotonin 1A receptor agonist and a serotonin 2A receptor antagonist, but the exact mechanism by which it improves sexual desire and related distress is unknown.[41,42] The recommended dosage is 100 mg administered orally once daily at bedtime.[41] It is important to instruct patients to take flibanserin at night due to the increased risks of hypotension, syncope, or accidental injury.[41]

Contraindications reported are the combination of flibanserin with alcohol due to the increased central nervous system depression, any degree of hepatic impairment and concomitant use with CYP3A4 inhibitors.[8,41] Additionally, flibanserin has a black box warning for the combination with alcohol and a REMS program because of the increased risk of hypotension/syncope with alcohol.[41] Flibanserin's FDA approval, involved some controversy involving the alcohol interaction.[42] It is reported that at least three FDA reviewers objected to the approval stating the risks outweigh the benefits; they wanted additional alcohol interaction tests due to a previous test that was almost exclusively conducted in men.[43] However, the FDA deemed it satisfactory to approve flibanserin on the condition that three post market studies are conducted in women. The most common adverse effects, in $\geq$5% of patients, are dizziness, drowsiness, and fatigue.[8] Other less common ADRs are sedation, vertigo, and anxiety.[41]

The FDA approved flibanserin based on the results of three double blind, placebo controlled trials which together included 1,188 patients on flibanserin and 1,198 patients on placebo.[45-47] The participants were premenopausal women with acquired, generalized HSDD of at least 6 months duration. All trials were at least 24-weeks long, and the primary efficacy endpoints were satisfying sexual events (SSEs) and sexual desire. The first two studies conducted had different sexual desire endpoints than the third study. In two trials, they observed the change in sexual desire from baseline to week 24. In comparison, the third study observed desire with the female sexual function index (FSFI) score. The FSFI involved two questions asking for the satisfaction of the sexual experience with response ranging from 1 (almost never or never) to 5 (almost always or always). All three trials resulted in statistically significant improvement in the change from baseline in monthly SSEs at week 24 compared to placebo.[45-47] Currently, flibanserin seems of use in adult women with HDSS who do not achieve adequate sexual desire.

REXULTI® (BREXPIPRAZOLE) AND VRAYLAR® (CARIPRAZINE)

Rexulti® (brexpiprazole) and Vraylar® (cariprazine) are atypical antipsychotics (second generation antipsychotics) approved on July 10, 2015 and September 17, 2015, respectively.[2] Brexpiprazole is a partial agonist at serotonin, 5-HT_{1A}, receptor and dopamine, D_2, receptor and it is an antagonist at the serotonin, 5-HT_{2A}, receptor.[49] It is approved for schizophrenia as well as for adjunctive therapy in major depressive disorder (MDD).[49] Cariprazine is a partial agonist at the D_3, D_2, and 5-HT_{1A} receptors and an antagonist at the 5-HT_{2B} and 5-HT_{2A} receptors.[50] It is indicated for schizophrenia like brexpiprazole, but also for acute treatment of the manic or mixed episodes in bipolar disorder.[50] In schizophrenia, decreasing the activity of dopamine helps treat positive symptoms.[51] The efficacy of an antipsychotic to treat positive symptoms is somewhat proportional to its affinity to D_2 receptors in particular.[51] Positive symptoms include hallucinations, delusions, disorganized speech, unusual behavior, and combativeness. Agonism of serotonin receptors in the mesocortical area of the brain may have an inhibitory effect on dopamine receptors or dopamine release, and this possibly aids in treating negative symptoms. Negative symptoms include psychomotor retardation, affective flattening, avolition, alogia, lack of socialization, and loss of emotional connectedness.[51] The American Psychiatric Association guidelines for schizophrenia states both first and second-generation anti-psychotics are first line depending on specific symptoms of the patients, ADRs of concern, and past treatments.[52] There are many neurotransmitter theories in depression; however, the actual cause of depression remains partially unknown.[53] In depression, brexpiprazole is used as add on therapy if existing therapies are not sufficient. Similar to depression and even more unclear with regards to pathophysiology, bipolar depression is thought to be caused by genetics and altered synaptic and circuit functioning of neurons.[58]

Brexpiprazole is available in 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg tablets.[8,49] In schizophrenia, the starting dose is 1 mg daily, which then should be titrated to the recommended dose of 2 to 4 mg daily. Titrate to 2 mg daily on days 5-7, then to 4 mg on day 8 based on clinical response and tolerability.[49] The maximum daily dose recommended in schizophrenia is 4 mg. As adjunctive therapy in depression, the starting dose is 0.5 mg to 1 mg daily. The starting dose should be titrated by doubling the dose no more than weekly until the recommended dose of 2 mg daily for MDD is reached.[49] The maximum daily dose for MDD is 3 mg.

For brexpiprazole in schizophrenia, there have been two randomized, double blind, placebo controlled clinical trials.[54,55] Both trials were six weeks in duration and the primary outcome was Positive and Negative Syndrome Scale (PANSS) total score. One study (636 randomized patients) showed significant improvement in the PANSS score at week 6 with both the 4 mg and 2 mg doses, while the other study (674 randomized patients) only showed a significant improvement with the 4 mg dose. For adjunctive therapy in MDD, there are two randomized, double blind, placebo controlled studies in patients who had inadequate response to prior therapy.[56,57] These two studies were also 6 weeks in duration and the primary outcome was the change in Montgomery-Asberg Depression Rating Scale (MADRS). A lower score in the MADRS represents fewer symptoms. In one study (379 randomized patients), only the 2 mg dose was tested and there was a significant lowering of the MADRS score. In the other study (677 randomized patients), the 3 mg dose showed a significant lowering while the 1 mg did not.

Cariprazine is dosed from 1.5 mg to 6 mg orally.[1,50] In schizophrenia the starting dose is 1.5 mg, which is increased to 3 mg on day 2; depending on response and tolerability the dose can be adjusted in increments of 1.5 or 3 mg to a max dose of 6 mg. For bipolar disorder, 3 mg or 6 mg daily is recommended, however it is started at 1.5 mg and increased to 3 mg on day 2.

FDA approval of cariprazine in schizophrenia was based on three randomized, double blind, controlled trials that were all six weeks long.[1,59] Two of the trials contained active controlled arms. The primary endpoint in all trials was the change in Positive and Negative Syndrome Scale (PANSS) score. In the first study, 711 patients were randomized to cariprazine 1.5 mg, cariprazine 3 mg, cariprazine 4.5 mg, risperidone, or placebo. The active control and all cariprazine doses were superior to placebo in the change in total PANSS. The second study was in 604 patients randomized to cariprazine 3 mg, cariprazine 6 mg, aripiprazole, or placebo. Again both doses of cariprazine and the active control showed significant change in the PANSS score from baseline compared to placebo. The third study used flexible dosing; 439 patients were randomized to cariprazine 3 mg to 6 mg, cariprazine 6 mg to 9 mg, or placebo. Both cariprazine arms were superior to placebo in the change in PANSS score.

Cariprazine was approved for bipolar disorder based on three more studies conducted in a total of 1,037 patients.[1,60,61] The primary outcomes were decrease in the Young Mania Rating Scale (YMRS) at the end of week 3. All three trials looked at flexible dosing ranges. Cariprazine 3 mg to 6 mg, cariprazine 6 mg to 12 mg, and cariprazine 3 mg to 12 mg were all shown to be superior to placebo. The maximum dose is 6 mg because higher doses did not show an additional benefit.

Hypersensitivity is the only contraindication for both brexpiprazole and cariprazine.[49,50] There are precautions for dementia, suicidal thinking/behavior, cerebrovascular event, neuromalignant syndrome, extrapyramidal symptoms, hyperglycemia, dyslipidemia, weight gain, blood dyscrasias, orthostatic hypotension, seizures, temperature regulation, dysphagia, and cognitive and motor impairment for both antipsychotics.[49,50] In addition, brexpiprazole has a precaution with alcohol. The most common adverse events are akathisia and weight gain for brexpiprazole, while for cariprazine they are extrapyramidal symptoms and akathisia.[49,50] In moderate to severe hepatic and renal impairment the maximum dose for brexpiprazole in schizophrenia is 3 mg daily and the max dose for MDD is 2 mg daily. Brexpiprazole is metabolized hepatically by CYP3A4 and CYP2D6, so there are many potential drug-drug interactions.[8,9] Cariprazine is not recommended with CYP3A4 inducers and a dose reduction is recommended with CYP3A4 inhibitors.[50] The pregnancy category of brexpiprazole has not been established however exposure during the third trimester of pregnancy may cause neonates to experience extrapyramidal or withdrawal symptoms after birth.[8,9] It is unknown if brexpiprazole is excreted in breast milk.[8,9] These two new antipsychotics will provide additional options for patients who have failed other second generation antipsychotics.

DAKLINZA® (DACLATASVIR)

Daklinza® (daclatasvir) was approved on July 24, 2015 for treatment of Hepatitis C (HCV) genotype 3 as an adjunct in combination with sofosbuvir (Solvaldi®).[1] Daclatasvir binds to nonstructural protein 5A (NS5A) and inhibits viral RNA replication and virion assembly.[8,64] HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C recommends daclatasvir for initial therapy in treatment naïve patients with or without cirrhosis and treatment experienced patients with or without cirrhosis not eligible to receive interferon.[65] Hepatitis C Virus (HCV) is an infection in the liver that leads to inflammation and eventually, cirrhosis.[63] However, most patients are unaware of the infection and are asymptomatic until years later when liver damage appears during routine medical tests.[63] Daclatasvir is indicated for genotype 3 of HCV, but is also mentioned in the guidelines for treatment in genotypes 1a, 1b, and 2.[64,65] Genotypes 1 and 2 are the most common, followed by genotype 3; other genotypes are more rare.

Daclatasvir is available in 30 mg and 60 mg formulations.[8,64] The recommended dose is 60 mg taken orally once daily with or without food in combination with sofosbuvir for a total of 12 weeks.[8,64] No dose adjustments are required for the elderly or those with renal or hepatic impairment.[8,9] It is contraindicated when used with drugs that are strong CYP3A4 inducers.[8,9] Monitor liver enzymes and serum creatinine at baseline and periodically for the duration of therapy.[8,9] Drug interactions include strong CYP3A4 inducers such as amiodarone, clarithromycin, ketoconazole, and St. John's Wort.[8,9,64] Adverse effects seen with daclatasvir include headache, fatigue, nausea, vomiting, and increased serum lipases.[8,9,64] Daclatasvir is extremely costly at $25,200 for 28 tablets.

One open-label trial, ALLY-3, included 152 subjects with chronic HCV genotype 3 infection and compensated liver disease who were treatment-naïve or treatment-experienced.[66] Subjects received daclatasvir 60 mg plus sofosbuvir 400 mg once daily for 12 weeks and were monitored for 24 weeks post treatment. Sustained virologic response (SVR) was the primary endpoint and was defined as HCV RNA below the lower limit of quantification at post-treatment week 12 (SVR12). The daclatasvir plus sofosbuvir regimen demonstrated SVR12 in 90% of treatment-naïve and 86% of treatment-experienced chronic HCV genotype 3 patients. SVR12 rates were higher (96%) in genotype 3 patients without cirrhosis, regardless of treatment history. In the more difficult-to-treat patients with cirrhosis, SVR12 rates were reduced (63%). These SVR12 rates were achieved with 12 weeks of therapy without the use of ribavirin.[66]

CONCLUSION

New molecular entities provide advancement in disease management and hope for patients for whom current therapy is inadequate. To ensure the success of these new medications it is vital that pharmacists are knowledgeable about their uses. In this article, we discussed Praluent® (alirocumab), Kengreal® (cangrelor), Corlanor® (ivabradine), Cosentyx® (secukinumab), Natpara® (parathyroid hormone), Addyi® (flibanserin), Rexulti® (brexpiprazole), and Daklinza® (daclatasvir). All new molecular entities approved this year as of September 28, 2015 are listed in the table on the next page.

Table 1: New Drugs Approved in 2015 (through September 28, 2015		
New Molecular Entity[2]	Date approved	Indication
Savaysa® (edoxaban)	Jan. 8, 2015	• Anticoagulation for atrial fibrillation not caused by a heart valve problem
Cosentyx® (secukinumab)	Jan. 21, 2015	• Moderate to severe plaque psoriasis
Natpara® (parathyroid hormone)	Jan. 23, 2015	• Hypocalcemia due to hypothyroidism
Ibrance® (palbociclib)	Feb. 3, 2015	• Metastatic breast cancer
Lenvima® (lenvatinib)	Feb. 13, 2015	• Progressive, differentiated thyroid cancer (specifically radioactive iodine refractory disease)
Farydak® (panobinostat)	Feb. 23, 2015	• Multiple myeloma
Avycaz® (ceftazidime-avibactam)	Feb. 25, 2015	• Complicated intra-abdominal infections with metronidazole • Complicated urinary tract infections
Cresemba® (isavuconazonium sulfate)	Mar. 6, 2015	• Invasive aspergillosis • Invasive mucomycosis
Unituxin® (dinutuximab)	Mar. 10, 2015	• Pediatric patients with high risk neuroblastoma
Cholbam® (cholic acid)	Mar. 17, 2015	• Bile acid synthesis disorders due to single enzyme defects • Peroxisomal disorders
Corlanor® (ivabradine)	Apr. 15, 2015	• Worsening heart failure (to reduce hospitalizations)
Kybella® (deoxycholic acid)	Apr. 29, 2015	• Submental fat, cytolytic agent
Viberzi® (eluxadoline)	May 27, 2015	• Irritable bowel syndrome with diarrhea
Kengreal® (cangrelor)	June 22, 2015	• To prevent blood clots during percutaneous coronary intervention (PCI)
Orkambi® (lumacaftor 200 mg/ivacaftor 125 mg)	July 2, 2015	• Cystic fibrosis
Entresto® (sacubitril/valsartan)	July 7, 2015	• Heart failure
Rexulti® (brexpiprazole)	July 10, 2015	• Schizophrenia • Adjunctive therapy in major depressive disorder (MDD)
Praluent® (alirocumab)	July 24, 2015	• Heterozygous familial hypercholesterolemia • Adjunct to statin therapy in patients with ASCVD
Odomzo® (sonidegib)	July 24, 2015	• Locally advanced basal cell carcinoma recurring after surgery or radiation therapy
Daklinza® (daclatasvir)	July 24, 2015	• Genotype 3 chronic hepatitis C
Addyi® (flibanserin)	Aug. 18, 2015	• Hypoactive sexual desire disorder in premenopausal women
Repatha® (evolocumab)	Aug. 27, 2015	• Adjunct to statin therapy in primary hyperlipidemia • Heterozygous familial hypercholesterolemia • Homozygous familial hypercholesterolemia
Varubi® (rolapitant)	Sept. 2, 2015	• Delayed phase chemotherapy induced emesis
Xuriden® (uridine triacetate)	Sept. 4, 2015	• Hereditary orotic aciduria
Vraylar® (cariprazine)	Sept. 17, 2015	• Schizophrenia • Bipolar disorder
Lonsurf® (trifluridine and tipiracil)	Sept. 22, 2015	• Advanced colorectal cancer patients no longer responding to therapy
Tresiba® (insulin degludec injection)	Sept. 25, 2015	• Long acting human insulin analog for diabetes mellitus

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