Drug Discovery

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FDA approved drugs – July 2015

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FDA APPROVED DRUGS – JULY 2015

1. Drug Name: Entresto (sacubitril and valsartan)
Company: Novartis
Approval Status: Approved by July 2015
Therapeutic Areas: Cardiology/Vascular Diseases

General Information
Entresto is specifically indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction. It is supplied as a tablet for oral administration. The recommended starting dose of Entresto is 49/51 mg (sacubitril/valsartan) twice-daily.

Mechanism of Action
Entresto is a combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin II receptor blocker. It inhibits neprilysin (neutral endopeptidase; NEP) via LBQ657, the active metabolite of the prodrug sacubitril, and blocks the angiotensin II type-1 (AT1) receptor via valsartan. The cardiovascular and renal effects of Entresto in heart failure patients are attributed to the increased levels of peptides that are degraded by neprilysin, such as natriuretic peptides, by LBQ657, and the simultaneous inhibition of the effects of angiotensin II by valsartan. Valsartan inhibits the effects of angiotensin II by selectively blocking the AT1 receptor, and also inhibits angiotensin II-dependent aldosterone release.

Side Effects
Adverse effects associated with the use of Entresto may include: hypotension, hyperkalemia, cough, dizziness, renal failure

2. Drug Name: Praluent (alirocumab)
Company: Sanofi Aventis
Approval Status: Approved by July 2015
Therapeutic Areas: Cardiology/Vascular Diseases

General Information
Praluent (alirocumab) is a PCSK9 (Proprotein Convertase Subtilisin Kexin Type 9) inhibitor antibody. It is specifically indicated as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-cholesterol (LDL-C). It is supplied as an injection for subcutaneous use. The recommended starting dose for Praluent is 75mg administered subcutaneously once every 2 weeks, since the majority of patients achieve sufficient LDL-C reduction with this dosage. If the LDL-C response is inadequate, the dosage may be increased to the maximum dosage of 150 mg administered every 2 weeks.

Mechanism of Action
Praluent (alirocumab) is a human monoclonal antibody that binds to proprotein convertase subtilisin kexin type 9 (PCSK9). PCSK9 binds to the low-density lipoprotein receptors (LDLR) on the surface of hepatocytes to promote LDLR degradation within the liver. LDLR is the primary receptor that clears circulating LDL, therefore the decrease in LDLR levels by PCSK9 results in higher blood levels of LDL-C. By inhibiting the binding of PCSK9 to LDLR, alirocumab increases the number of LDLRs available to clear LDL, thereby lowering LDL-C levels.

Side Effects
Adverse effects associated with the use of Praluent may include: nasopharyngitis, injection site reactions, influenza

3. Drug Name: Odomzo (sonidegib)
Company: Novartis
Approval Status: Approved by July 2015
Therapeutic Areas: Dermatology/Oncology

General Information
Odomzo is specifically indicated for the treatment of adult patients with locally advanced basal cell carcinoma (BCC) that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy. It is supplied as a capsule for oral administration. The recommended dose is 200 mg orally once daily taken on an empty stomach, at least 1 hour before or 2 hours after a meal.

Mechanism of Action
Odomzo (sonidegib) is a hedgehog pathway inhibitor. Sonidegib binds and inhibits Smoothened, a transmembrane protein involved in Hedgehog signal transduction.

Side Effects
Adverse effects associated with the use of Odomzo may include: muscle spasms, alopecia, dysgeusia, fatigue, nausea, musculoskeletal pain, diarrhea, decreased weight, decreased appetite, myalgia, abdominal pain, headache, pain, vomiting, pruritus

4. Drug Name: Daklinza (daclatasvir)
Company: Bristol-Myers Squibb
Approval Status: Approved by July 2015
Therapeutic Areas: Hepatology (Liver, Pancreatic, Gall Bladder)Infections and Infectious Diseases

General Information
Daklinza is specifically indicated for use with sofosbuvir for the treatment of patients with chronic hepatitis C virus (HCV) genotype 3 infection. It is supplied as tablets for oral administration. The recommended dose is 60 mg taken orally once daily with or without food in combination with sofosbuvir. The recommended treatment duration is 12 weeks. Dose modification: reduce dosage to 30 mg once daily with strong CYP3A inhibitors and increase dosage to 90 mg once daily with moderate CYP3A inducers.

Mechanism of Action
Daklinza (daclatasvir) is an inhibitor of NS5A, a nonstructural protein encoded by HCV. It binds to the N-terminus of NS5A and inhibits both viral RNA replication and virion assembly. Characterization of daclatasvir-resistant viruses, biochemical studies, and computer modeling data indicate that daclatasvir interacts with the N-terminus within Domain 1 of the protein, which may cause structural distortions that interfere with NS5A functions.

Side Effects
Adverse effects associated with the use of Daklinza may include: headache, fatigue, nausea, diarrhea

5. Drug Name: Technivie, (ombitasvir, paritaprevir and ritonavir)
Company: Abbvie
Approval Status: Approved by July 2015
Therapeutic Areas: Hepatology (Liver, Pancreatic, Gall Bladder) Infections and Infectious Diseases

General Information
Technivie is specifically for use in combination with ribavirin for the treatment of patients with genotype 4 chronic hepatitis C virus (HCV) infection without cirrhosis. It is supplied as a tablet for oral administration. The recommended dose is two tablets taken orally once daily (in the morning) with a meal without regard to fat or calorie content, for 12 weeks. It is recommended to be used in combination with ribavirin.

Mechanism of Action
Technivie is a fixed-dose combination of ombitasvir, a hepatitis C virus NS5A inhibitor, paritaprevir, a hepatitis C virus NS3/4A protease inhibitor, and ritonavir, a CYP3A inhibitor.

Side Effects
Adverse effects associated with the use of Technivie may include: asthenia, fatigue, nausea, insomnia

6. Drug Name: Envarsus XR (tacrolimus extended-release)
Company: Veloxis
Approval Status: Approved by July 2015
Therapeutic Areas: Immunology / Nephrology

General Information
Envarsus XR is specifically indicated for the prophylaxis of organ rejection in kidney transplant patients converted from tacrolimus immediate-release formulations, in combination with other immunosuppressants. It is supplied as a tablet for oral administration. It should be taken on an empty stomach at the same time of the day, preferably in the morning (to ensure consistent and maximum possible drug exposure). The tablets should be swallowed whole with fluid (preferably water). Do not chew, divide, or crush the tablets. If a dose is missed, take it as soon as possible within 15 hours after missing the dose; beyond the 15-hour time frame, wait until the usual scheduled time to take the next regular daily dose. Do not double the next dose. Avoid eating grapefruit or drinking grapefruit juice or alcoholic beverage while taking Envarsus XR.

Mechanism of Action
Envarsus XR is an extended release formulation of tacrolimus, a calcineurin-inhibitor immunosuppressant. Tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin (an ubiquitous mammalian intracellular enzyme) is then formed and the phosphatase activity of calcineurin inhibited. Such inhibition prevents the dephosphorylation and translocation of various factors such as the nuclear factor of activated T-cells (NF-AT) and nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB). Tacrolimus inhibits the expression and/or production of several cytokines that include interleukin (IL)-1 beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, gamma interferon, tumor necrosis factor-alpha, and granulocyte macrophage colony stimulating factor. Tacrolimus also inhibits IL-2 receptor expression and nitric oxide release, induces apoptosis and production of transforming growth factor-beta that can lead to immunosuppressive activity. The net result is the inhibition of T-lymphocyte activation and proliferation as well as T-helper-cell-dependent B-cell response (i.e., immunosuppression).

Side Effects
Adverse effects associated with the use of Envarsus XR may include: diarrhea, blood creatinine increased

7. Drug Name: Orkambi (lumacaftor and ivacaftor)
Company: Vertex Pharmaceuticals
Approval Status: Approved by July 2015
Therapeutic Areas: Pediatrics/Neonatology/Pulmonary/Respiratory Diseases

General Information
Orkambi is specifically indicated for the treatment of cystic fibrosis (CF) in patients age 12 years and older who are homozygous for the F508del mutation in the CFTR gene. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the F508del mutation on both alleles of the CFTR gene. It is supplied as a tablet (lumacaftor 200 mg and ivacaftor 125 mg) for oral administration. The recommended dose for adults and pediatric patients age 12 years and older is two tablets taken orally every 12 hours. Reduce the dose in patients with moderate or severe hepatic impairment. When initiating Orkambi in patients taking strong CYP3A inhibitors, the reduce Orkambi dose for the first week of treatment.

Mechanism of Action
Orkambi is a combination of lumacaftor and ivacaftor, both of which are oral cystic fibrosis transmembrane conductance regulator (CFTR) modulators. The CFTR protein is a chloride channel present at the surface of epithelial cells in multiple organs. The F508del mutation results in protein misfolding, causing a defect in cellular processing and trafficking that targets the protein for degradation and therefore reduces the quantity of CFTR at the cell surface. The small amount of F508del-CFTR that reaches the cell surface is less stable and has low channel-open probability (defective gating activity) compared to wild-type CFTR protein. Lumacaftor improves the conformational stability of F508del-CFTR, resulting in increased processing and trafficking of mature protein to the cell surface. Ivacaftor is a CFTR potentiator that facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the CFTR protein at the cell surface. In vitro studies have demonstrated that both lumacaftor and ivacaftor act directly on the CFTR protein in primary human bronchial epithelial cultures and other cell lines harboring the F508del-CFTR mutation to increase the quantity, stability, and function of F508del-CFTR at the cell surface, resulting in increased chloride ion transport. In vitro responses do not necessarily correspond to in vivo pharmacodynamic response or clinical benefit.

Side Effects
Adverse effects associated with the use of Orkambi may include: dyspnea, nasopharyngitis, nausea, diarrhea, upper respiratory tract infection, fatigue, respiration abnormal, blood creatine phosphokinase increased, rash, flatulence, rhinorrhea, influenza

8. Drug Name: Rexulti (brexpiprazole)
Company: Otsuka
Approval Status: Approved by July 2015
Therapeutic Areas: Psychiatry/Psychology

General Information
Rexulti is specifically indicated for the adjunctive treatment of major depressive disorder and the treatment of schizophrenia. It is supplied as a tablet for oral administration. The recommended dose is as follows:
Major depressive disorder: the recommended starting dose is 0.5 mg or 1 mg once daily, taken orally with or without food. Titrate to 1 mg once daily, then up to the target dosage of 2 mg once daily. Dosage increases should occur at weekly intervals based on the patient's clinical response and tolerability. The maximum recommended daily dosage is 3 mg.
Schizophrenia: the recommended starting dose is is 1 mg once daily on Days 1 to 4, taken orally with or without food. The recommended target dosage is 2 mg to 4 mg once daily. Titrate to 2 mg once daily on Day 5 through Day 7, then to 4 mg on Day 8 based on the patient's clinical response and tolerability. The maximum recommended daily dosage is 4 mg.

Mechanism of Action
Rexulti (brexpiprazole) is an atypical antipsychotic. The mechanism of action of brexpiprazole in the treatment of major depressive disorder or schizophrenia is unknown. However, the efficacy of brexpiprazole may be mediated through a combination of partial agonist activity at serotonin 5-HT1A and dopamine D2 receptors, and antagonist activity at serotonin 5-HT2A receptors.

Side Effects
Adverse effects associated with the use of Rexulti may include: akathisia, weight gain