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DRUG DISCOVERY

FDA approved drugs – December 2012

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1. ICLUSIG (PONATINIB)

1.1. Company
Ariad Pharmaceuticals; Approved by December 2012

1.2. Treatment Area
Chronic myeloid leukemia and Philadelphia chromosome positive acute lymphoblastic leukemia

1.3. General Information
Iclusig (ponatinib) is a small-molecule dual Abl/Src protein inhibitor. It is specifically indicated for the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) that is resistant or intolerant to prior tyrosine kinase inhibitor therapy or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) that is resistant or intolerant to prior tyrosine kinase inhibitor therapy. It is supplied as a tablet for oral administration. The recommended initial dose is 45 mg administered orally once daily. Treatment should be continued until evidence of disease progression or unacceptable toxicity. Dose modifications should be considered for myelosuppression, non-hematologic adverse reactions, and use with strong CYP3A inhibitors. See drug label for appropriate dose modifications.

1.4. Mechanism of Action
Ponatinib is a kinase inhibitor. Ponatinib inhibited the in vitro viability of cells expressing native or mutant BCR-ABL, including T315I. In mice, treatment with ponatinib reduced the size of tumors expressing native or T315I mutant BCR-ABL when compared to controls.

1.5. Side Effects
Adverse events associated with the use of Iclusig may include: hypertension, rash, abdominal pain, fatigue, headache, dry skin, constipation, arthralgia, nausea, pyrexia, thrombocytopenia, anemia, neutropenia, lymphopenia, and leucopenia.

2. SIRTURO (BEDAQUILINE)

2.1. Company
Janssen Therapeutics; Approved by December 2012

2.2. Treatment Area
Multi-drug resistant tuberculosis

2.3. General Information
Sirturo (bedaquiline) is a diarylquinoline antimycobacterial. It specifically inhibits mycobacterial ATP-synthase, responsible for the cell's energy production. It is specifically indicated as part of combination therapy in adults with pulmonary multi-drug resistant tuberculosis. It is supplied as a tablet for oral administration. It should only be used in combination with at least 3 other drugs to which the patient's MDR-TB isolate has been shown to be susceptible in vitro. If in vitro testing results are unavailable, treatment may be initiated with Sirturo in combination with at least 4 other drugs to which the patient's MDR-TB isolate is likely to be susceptible. The recommended dosage of Sirturo is as follows: Weeks 1-2: 400 mg (4 tablets of 100 mg) once daily with food. Weeks 3-24: 200 mg (2 tablets of 100 mg) 3 times per week with food (with at least 48 hours between doses) for a total dose of 600 mg per week. The tablet should be swallowed whole with water.

2.4. Mechanism of Action
Bedaquiline is a diarylquinoline antimycobacterial drug that inhibits mycobacterial ATP (adenosine 5'-triphosphate) synthase, an enzyme that is essential for the generation of energy in Mycobacterium tuberculosis.

2.5. Side Effects
Adverse events associated with the use of Sirturo include: nausea, arthralgia, and headache

3. ELIQUIS (APIXABAN)

3.1. Company
Bristol-Myers Squibb; Approved by December 2012

3.2. Treatment Area
Stroke and systemic embolism resulting from nonvalvular atrial fibrillation

3.3. General Information
Eliquis (apixaban) is an orally available Factor Xa antagonist. By inhibiting FXa, apixaban decreases thrombin generation and thrombus development. It is specifically indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. It is supplied as a capsule for oral

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administration. The recommended dose for most patients is 5 mg taken orally twice daily. The recommended dose of Eliquis is 2.5 mg twice daily in patients with any two of the following characteristics: > age 80 years, body weight <60 kg, serum creatinine is >1.5 mg/dL. When Eliquis is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp, the recommended dose is 2.5 mg twice daily.

3.4. Mechanism of Action
Eliquis (apixaban) is an orally available Factor Xa antagonist. Apixaban inhibits free and clot-bound FXa, and prothrombinase activity. Apixaban has no direct effect on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting FXa, apixaban decreases thrombin generation and thrombus development.

3.5. Side Effects
The most common adverse events associated with the use of Eliquis are related to bleeding.

4. JUXTAPID (LOMITAPIDE)

4.1. Company
Aegerion Pharmaceuticals; Approved by December 2012

4.2. Treatment Area
Homozygous familial hypercholesterolemia

4.3. General Information
Juxtapid (lomitapide) is an oral inhibitor of the microsomal triglyceride transport protein (MTP). The inhibition of MTP blocks the hepatic secretion of very low density lipoproteins and the intestinal secretion of chylomicrons. It is specifically indicated as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apo B), and non-highdensity lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia. It is supplied as a capsule for oral administration. Before beginning treatment: Measure transaminases (ALT, AST), alkaline phosphatase, and total bilirubin, Obtain a negative pregnancy test in females of reproductive potential and Initiate a low-fat diet supplying <20% of energy from fat. The recommended starting dosage of Juxtapid is 5 mg once daily, and the dose should be escalated gradually based on acceptable safety and tolerability. The maintenance dosage of Juxtapid should be individualized, taking into account patient characteristics such as goal of therapy and response to treatment, to a maximum of 60 mg daily. See drug label for any dose modifications.

4.4. Mechanism of Action
Juxtapid (lomitapide) directly binds and inhibits microsomal triglyceride transfer protein (MTP), which resides in the lumen of the endoplasmic reticulum, thereby preventing the assembly of apo B-containing lipoproteins in enterocytes and hepatocytes. This inhibits the synthesis of chylomicrons and VLDL. The inhibition of the synthesis of VLDL leads to reduced levels of plasma LDL-C.

4.5. Side Effects
Adverse events associated with the use of Juxtapid include: diarrhea, nausea, vomiting, dyspepsia, abdominal pain

5. SIGNIFOR (PASIREOTIDE DIASPARTATE)

5.1. Company
Novartis

5.2. Approval Status
Approved December of 2012

5.3. Treatment Area
Cushing's disease

5.4. General Information
Signifor (pasireotide diaspartate) is a somatostatin analog. Pasireotide exerts its pharmacological activity via binding to somatostatin receptor subtypes (ssts) 1, 2, 3, 4, and 5. These receptor subtypes are expressed in different tissues under normal physiological conditions. Corticotroph tumor cells from Cushing's disease patients frequently over-express ssts5 whereas the other receptor subtypes are often not expressed or are expressed at lower levels. Pasireotide binds and activates the hsst receptors resulting in inhibition of Adrenocorticotropic hormone secretion, which leads to decreased cortisol secretion. It is specifically indicated for the treatment of adults with Cushing's disease for whom pituitary surgery is not an option or has not been curative. It for is supplied as a solution for subcutaneous injection. The recommended initial dose is either 0.6 mg or 0.9 mg by subcutaneous injection twice a day. The recommended dosage range is 0.3 to 0.9 mg. Patients should be evaluated for a treatment response [clinically meaningful reduction in 24-hour urinary free cortisol levels and/or improvement in signs or symptoms of the disease] and should continue receiving therapy with Signifor as long as benefit is derived. See prescription label for any dose modifications.

5.5. Mechanism of Action
Signifor (pasireotide diaspartate) is a somatostatin-based cyclohexapeptide somatostatin receptor -1, -2, -3 and -5 agonist. Pasireotide exerts its pharmacological activity via binding to these somatostatin receptors (ssts). These receptor subtypes are expressed in different tissues under normal physiological conditions. Corticotroph tumor cells from Cushing's disease patients frequently over-express hsst5 whereas the other receptor subtypes are often not expressed or are expressed at lower levels. Pasireotide binds and activates the hsst receptors resulting in inhibition of ACTH secretion, which leads to decreased cortisol secretion.

5.6. Side Effects
Adverse events associated with the use of Signifor include: diarrhea, nausea, hyperglycemia, cholelithiasis, headache, abdominal pain, fatigue, and diabetes mellitus

6. FULYZAQ (CROFELEMER)

6.1. Company
Salix Pharmaceuticals; Approved by December 2012

6.2. Treatment Area
Non-infectious diarrhea in adults with HIV/AIDS

6.3. General Information
Fulyzaq (crofelemer) is extracted from the latex of the Croton lechleri tree. it reduces excess chloride ion secretion via the cystic fibrosis transmembrane conductance regulator (CFTR) channel. The chloride channel CFTR regulates water balance in the intestines through control of chloride ion secretion and sodium absorption. It is specifically indicated for symptomatic relief of non-infectious diarrhea in adult patients with HIV/AIDS on anti-retroviral therapy. It is

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supplied as a delayed-release tablet for oral administration. The recommended dose is one 125 mg delayed-release tablet taken orally two times a day, with or without food. Tablets should not be crushed or chewed. Tablets should be swallowed whole.

6.4. Mechanism of Action
Fulyzaq (crofelemer) is extracted from the latex of the Croton lechleri tree. It is an inhibitor of both the cyclic adenosine monophosphate (cAMP)-stimulated cystic fibrosis transmembrane conductance regulator (CFTR) chloride ion (Cl-) channel, and the calcium-activated Clc hannels (CaCC) at the luminal membrane of enterocytes. The CFTR Cl channel and CaCC regulate Cl-and fluid secretion by intestinal epithelial cells. Crofelemer acts by blocking Cl secretion and accompanying high volume water loss in diarrhea, normalizing the flow of Cl and water in the GI tract.

6.5. Side Effects
Adverse events associated with the use of Fulyzaq include: upper respiratory tract infection, bronchitis, cough, flatulence, increased bilirubin.

7. GATTEX (TEDUGLUTIDE)

7.1. Company
NPS Pharmaceuticals; Approved by December 2012

7.2. Treatment Area
Short bowel syndrome

7.3. General Information
Gattex (teduglutide) is an analog of naturally occurring human glucagon-like peptide 2 (GLP-2), a peptide secreted primarily in the distal intestine and involved in the regeneration and repair of the intestinal epithelium. GLP-2 is known to increase intestinal and portal blood flow, and inhibit gastric acid secretion. It is specifically indicated for the treatment of adults with Short Bowel Syndrome who are dependent on parenteral support. It is supplied as a powder for reconstitution into a solution designed for subcutaneous injection. The recommended daily dose is 0.05 mg/kg body weight administered by subcutaneous injection once daily. Alternation of sites for subcutaneous injection is recommended.

7.4. Mechanism of Action
Gattex (teduglutide) is an analog of naturally occurring human glucagon-like peptide 2 (GLP-2), a peptide secreted primarily in the distal intestine and involved in the regeneration and repair of the intestinal epithelium. GLP-2 is known to increase intestinal and portal blood flow, and inhibit gastric acid secretion.Teduglutide binds to the GLP-2 receptors located in intestinal subpopulations of enteroendocrine cells, subepithelial myofibroblasts and enteric neurons of the submucosal and myenteric plexus. Activation of these receptors results in the local release of multiple mediators including insulin-like growth factor (IGF)-1, nitric oxide and keratinocyte growth factor (KGF).

7.5. Side Effects
Adverse events associated with the use of Gattex include: abdominal pain, injection site reactions, nausea, headaches, abdominal distension, upper respiratory tract infection, and vomiting, fluid overload.

8. JUXTAPID (LOMITAPIDE)

8.1. Company
Aegerion Pharmaceuticals; Approved by December of 2012

8.2. Treatment Area
Homozygous familial hypercholesterolemia

8.3. General Information
Juxtapid (lomitapide) is an oral inhibitor of the microsomal triglyceride transport protein (MTP). The inhibition of MTP blocks the hepatic secretion of very low density lipoproteins and the intestinal secretion of chylomicrons. It is specifically indicated as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apo B), and non-highdensity lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia. It is supplied as a capsule for oral administration. Before beginning treatment: Measure transaminases (ALT, AST), alkaline phosphatase, and total bilirubin, Obtain a negative pregnancy test in females of reproductive potential and Initiate a low-fat diet supplying <20% of energy from fat. The recommended starting dosage of Juxtapid is 5 mg once daily, and the dose should be escalated gradually based on acceptable safety and tolerability. The maintenance dosage of Juxtapid should be individualized, taking into account patient characteristics such as goal of therapy and response to treatment, to a maximum of 60 mg daily. See drug label for any dose modifications.

8.4. Mechanism of Action
Juxtapid (lomitapide) directly binds and inhibits microsomal triglyceride transfer protein (MTP), which resides in the lumen of the endoplasmic reticulum, thereby preventing the assembly of apo B-containing lipoproteins in enterocytes and hepatocytes. This inhibits the synthesis of chylomicrons and VLDL. The inhibition of the synthesis of VLDL leads to reduced levels of plasma LDL-C.

8.5. Side Effects
Adverse events associated with the use of Juxtapid include: diarrhea, nausea, vomiting, dyspepsia, abdominal pain

9. ABTHRAX (RAXIBACUMAB)

9.1. Company
GlaxoSmithKline; Approved by December 2012

9.2. Treatment Area
Anthrax

9.3. General Information
Abthrax (raxibacumab) is a monoclonal antibody that neutralizes toxins produced by B. anthracis that can cause massive and irreversible tissue injury and death. It is specifically approved for the treatment inhalational anthrax and the prevention of inhalational anthrax when alternative therapies are not available or not appropriate. It is supplied as a solution for injection.

9.4. Mechanism of Action
Raxibacumab is a monoclonal antibody that neutralizes toxins produced by B. anthracis that can cause massive and irreversible tissue injury and death. A monoclonal antibody is a protein that closely resembles a human antibody that identifies and neutralizes foreign material like bacteria and viruses.

9.5. Side Effects
Adverse effects associated with the use of raxibacumab include: rash, extremity pain, itching, drowsiness.

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