Drug Discovery

FDA Approved Drugs

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FDA approved drugs – December 2014

Vidhya

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1. ZERBAXA (CEFTOLOZANE + TAZOBACTAM)

Company: Cubist Pharmaceuticals; Approved by December 2014

Treatment Area: complicated intra-abdominal and urinary tract infections

General Information
Zerbaxa is a combination of ceftolozan, a novel cephalosporin, and tazobactam, a beta-lactamase inhibitor. It is specifically indicated for the treatment of patients 18 years or older with the following infections caused by designated susceptible microorganisms:

Complicated intra-abdominal infections
Zerbaxa used in combination with metronidazole is indicated for the treatment of complicated intra-abdominal infections caused by the following Gram-negative and Gram-positive microorganisms: Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Bacteroides fragilis, Streptococcus anginosus, Streptococcus constellatus, and Streptococcus salivarius.

Complicated Urinary Tract Infections, including Pyelonephritis
Zerbaxa is indicated for the treatment of complicated urinary tract infections including pyelonephritis, caused by the following Gram-negative microorganisms: Escherichiacoli, Klebsiella pneumoniae, Proteus mirabilis, and Pseudomonas aeruginosa. Zerbaxa is supplied as a solution for intravenous infusion. The recommended dosage for Injection is 1.5 g (1 g/0.5 g) administered every 8 hours by intravenous infusion over 1 hour in patients 18 years or older and with normal renal function or mild renal impairment. The duration of therapy should be guided by the severity and site of infection and the patient's clinical and bacteriological progress.

Mechanism of Action
Zerbaxa is a combination of ceftolozane and tazobactam. Ceftolozane belongs to the cephalosporin class of antibacterial drugs. The bactericidal action of ceftolozane results from inhibition of cell wall biosynthesis, and is mediated through binding to penicillin-binding proteins (PBPs). Ceftolozane is an inhibitor of PBPs of P. aeruginosa (e.g. PBP1b, PBP1c, and PBP3) and E. coli (e.g., PBP3). Tazobactam sodium has little clinically relevant in vitro activity against bacteria due to its reduced affinity to penicillin-binding proteins. It is an irreversible inhibitor of some beta-

lactamases (e.g., certain penicillinases and cephalosporinases), and can bind covalently to some chromosomal and plasmid-mediated bacterial beta-lactamases.

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

2. XTORO (FINAFLOXACIN OTIC SUSPENSION) 0.3%

Company: Alcon; Approved by December 2014

Treatment Area: acute otitis externa

General Information
Xtoro (finafloxacin otic suspension) 0.3%) is a fluoroquinolone antimicrobial. It is specifically indicated for the treatment of acute otitis externa caused by susceptible strains of Pseudomonas aeruginosa and Staphylococcus aureus. It is supplied as a solution for topical administration. The recommended initial dose is as follows: Instill four drops in the affected ear(s) twice daily for seven days. For patients requiring use of an otowick, the initial dose can be doubled (to 8 drops), followed by 4 drops instilled into the affected ear twice daily for seven days.

Mechanism of Action
The fluoroquinolone class of antibacterials inhibit bacterial type II topoisomerase enzymes, DNA gyrase and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair and recombination.

Side Effects
Adverse effects associated with the use of Xtoro may include: ear pruritus, nausea

3. OPDIVO (NIVOLUMAB)

Company: Bristol-Myers Squibb; Approved by December 2014

Treatment Area: unresectable or metastatic melanoma

General Information
Opdivo (nivolumab) is a human monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. It is specifically indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. It is supplied as a solution for intravenous administration. The recommended dose is 3 mg/kg administered as an intravenous infusion over 60 minutes every two weeks until disease progression or unacceptable toxicity.

Mechanism of Action
Opdivo (nivolumab) is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Up regulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors.

Side Effects
The most common adverse reaction associated with the use of Opdivo was rash.

4. LYNPARZA (OLAPARIB)

Company: AstraZeneca; Approved by December 2014

Treatment Area: previously treated BRCA mutated advanced ovarian cancer

General Information
Lynparza (olaparib) is a poly (ADP-ribose) polymerase (PARP) inhibitor. It selectively binds to and inhibits PARP, inhibiting PARP-mediated repair of single strand DNA breaks; PARP inhibition enhances the cytotoxicity of DNA-damaging agents and reverses tumor cell chemoresistance and radioresistance. It is specifically indicated as monotherapy in patients with deleterious or suspected deleterious germline BRCA mutated (as detected by an FDA-approved test) advanced ovarian cancer that have been treated with three or more prior lines of chemotherapy. It is

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supplied as capsules for oral administration. The recommended dose is 400 mg taken twice daily. Continue treatment until disease progression or unacceptable toxicity.

Mechanism of Action

Lynparza (olaparib) is a poly (ADP-ribose) polymerase (PARP) inhibitor. PARP enzymes are involved in normal cellular homeostasis, such as DNA transcription, cell cycle regulation, and DNA repair. It has been shown to inhibit growth of select tumor cell lines in vitro and decrease tumor growth in mouse xenograft models of human cancer both as monotherapy or following platinum-based chemotherapy. Increased cytotoxicity and anti-tumor activity following treatment with olaparib were noted in cell lines and mouse tumor models with deficiencies in BRCA. In vitro studies have shown that olaparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complex, resulting in disruption of cellular homeostasis and cell death.

Side Effects

Adverse effects associated with the use of Lynparza may include: anemia, nausea, fatigue (including asthenia), vomiting, diarrhea, dysgeusia, dyspepsia, headache, decreased appetite, nasopharyngitis/pharyngitis/URI, cough, arthralgia/musculoskeletal pain, myalgia, back pain, dermatitis/rash, abdominal pain/discomfort.

5. BLINCYTO (BLINATUMOMAB)

Company: Amgen; Approved by December 2014

Treatment Area: Philadelphia chromosome-negative relapsed /refractory B cell precursor acute lymphoblastic leukemia

General Information

Blincyto (blinatumomab) is an immunotherapy. It engages the body's T-cells, a type of white blood cell or lymphocyte, to destroy leukemia cells. The drug acts as a connector between a protein called CD19, which is found on the surface of most B-cell lymphoblasts, and CD3, a protein on T-cell lymphocytes. It is specifically indicated for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia. It is supplied as a solution for intravenous infusion. Hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle. For all subsequent cycle starts and reinitiation (eg, if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalization is recommended. Do not flush the Blincyto infusion line, especially when changing infusion bags. Flushing when changing bags or at completion of infusion can result in excess dosage and complications. The recommended dosing schedule is as follows:

A single cycle of treatment of Blincyto consists of 4 weeks of continuous intravenous infusion followed by a 2-week treatment-free interval.

• For patients at least 45 kg in weight:

- In Cycle 1, administer Blincyto at 9 mcg/day on Days 1–7 and at 28 mcg/day on Days 8–28.
- For subsequent cycles, administer Blincyto at 28 mcg/day on Days 1–28.

• Allow for at least 2 weeks treatment-free between cycles of Blincyto.

• A treatment course consists of up to 2 cycles of Blincyto for induction followed by 3 additional cycles for consolidation treatment (up to a total of 5 cycles).

Mechanism of Action

Blincyto (blinatumomab) is a bispecific CD19-directed CD3 T-cell engager that binds to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T cells. It activates endogenous T cells by connecting CD3 in the T-cell receptor (TCR) complex with CD19 on benign and malignant B cells. It mediates the formation of a synapse between the T cell and the tumor cell, upregulation of cell adhesion molecules, production of cytolytic proteins, release of inflammatory cytokines, and proliferation of T cells, which result in redirected lysis of CD19+ cells.

Side Effects

Adverse effects associated with the use of Blincyto may include: pyrexia, headache, peripheral edema, febrile neutropenia, nausea, hypokalemia, rash, constipation.

6. SAXENDA (LIRAGLUTIDE [RDNA ORIGIN] INJECTION)

Company: Novo Nordisk; Approved by December 2014

Treatment Area: chronic weight management

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General Information

Saxenda (liraglutide [rDNA origin] injection) is specifically indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of 30 kg/m2 or greater (obese), or 27 kg/m2 or greater (overweight) in the presence of at least one weight-related comorbid condition e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia). It is supplied as a solution for subcutaneous administration. The recommended dose is 3 mg daily. Administer at any time of day, without regard to the timing of meals. Dosing should be initiated at 0.6 mg per day for one week. Increase the dose in weekly intervals until a dose of 3 mg is reached. It should be injected subcutaneously in the abdomen, thigh or upper arm. The injection site and timing can be changed without dose adjustment.

Mechanism of Action

Saxenda is an acylated human glucagon-like peptide-1 (GLP-1) receptor agonist. GLP-1 is a physiological regulator of appetite and calorie intake, and the GLP-1 receptor is present in several areas of the brain involved in appetite regulation. In animal studies, peripheral administration of liraglutide resulted in the presence of liraglutide in specific brain regions regulating appetite, including the hypothalamus. Although liraglutide activated neurons in brain regions known to regulate appetite, specific brain regions mediating the effects of liraglutide on appetite were not identified in rats.

Side Effects

Adverse effects associated with the use of Saxenda may include: nausea, hypoglycemia, diarrhea, constipation, vomiting, headache, decreased appetite, dyspepsia, fatigue, dizziness, abdominal pain

7. NAMZARIC (MEMANTINE HYDROCHLORIDE EXTENDED-RELEASE + DONEPEZIL HYDROCHLORIDE)

Company: Forest Laboratories; Approved by December 2014

Treatment Area: moderate to severe dementia of the Alzheimer's type

General Information

Namzaric is specifically indicated for the treatment of moderate to severe dementia of the Alzheimer's type in patients stabilized on memantine hydrochloride and donepezil hydrochloride. It is supplied as a capsule for once daily oral administration. The capsules can also be opened to allow the contents to be sprinkled on food to facilitate dosing for patients who may have difficulty swallowing.

Mechanism of Action

Namzaric is a fixed-dose combination of memantine hydrochloride extended-release, a NMDA receptor antagonist, and donepezil hydrochloride, an acetylcholinesterase inhibitor.

Side Effects

Adverse effects associated with the use of Namzaric may include: headache, diarrhea, dizziness

8. DYLOJECT (DICLOFENAC SODIUM) INJECTION

Company: Hospira; Approved by December 2014

Treatment Area: mild, moderate or severe pain

General Information

Dyloject is specifically indicated for the management of mild to moderate pain and management of moderate to severe pain alone or in combination with opioid analgesics. It is supplied as a solution for intravenous administration. The recommended dose of Dyloject is 37.5 mg administered by intravenous bolus injection over 15 seconds every 6 hours as needed, not to exceed 150 mg/day.

Mechanism of Action

Dyloject (diclofenac sodium) Injection is a non-steroidal anti-inflammatory drug. It exhibits anti-inflammatory analgesic and antipyretic activities in animal models. The mechanism of action of Dyloject, like that of other NSAIDs, is not completely understood but may involve inhibition of the cyclooxygenase (COX-1 and COX-2) pathways. Dyloject's mechanism may also be related to inhibition of prostaglandin synthetase.

Side Effects

Adverse effects associated with the use of Dyloject may include: nausea, constipation, headache, infusion site pain, dizziness, flatulence, vomiting, insomnia.

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9. VIEKIRA PAK (OMBITASVIR, PARITAPREVIR, RITONAVIR AND DASABUVIR) TABLETS

Company: Abbvie; Approved by December 2014

Treatment Area: genotype 1 chronic hepatitis C virus

General Information

Viekira Pak is specifically indicated for the treatment of patients with genotype 1 chronic hepatitis C virus (HCV) infection including those with compensated cirrhosis. It is supplied as a tablet for oral administration. The recommended dosage is two ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg tablets once daily (in the morning) and one dasabuvir 250 mg tablet twice daily (morning and evening) with a meal without regard to fat or calorie content.

Mechanism of Action

Viekira Pak includes ombitasvir, a hepatitis C virus NS5A inhibitor, paritaprevir, a hepatitis C virus NS3/4A protease inhibitor, ritonavir, a CYP3A inhibitor and dasabuvir, a hepatitis C virus non-nucleoside NS5B palm polymerase inhibitor.

Side Effects

Adverse effects associated with the use of Viekira Pak may include: fatigue, nausea, pruritus, other skin reactions, insomnia, asthenia.

10. RAPIVAB (PERAMIVIR INJECTION)

Company: Biocryst; Approved by December 2014

Treatment Area: treatment of acute uncomplicated influenza in adults

General Information

Rapivab is specifically indicated for the treatment of acute uncomplicated influenza in patients 18 years and older who have been symptomatic for no more than 2 days. It is supplied as a solution for intravenous administration. It should be administered within 2 days of onset of symptoms of influenza. The recommended dose in adult patients 18 years of age or older with acute uncomplicated influenza is a single 600 mg dose, administered via intravenous infusion for 15 to 30 minutes.

Mechanism of Action

Rapivab (peramivir injection) is an influenza virus neuraminidase inhibitor. Neuraminidase is an enzyme that releases viral particles from the plasma membrane of infected cells.

Side Effects

The most common adverse reaction associated with the use of Rapivab was diarrhea.

11. DYLOJECT (DICLOFENAC SODIUM) INJECTION

Company: Hospira; Approved by December 2014

Treatment Area: mild, moderate or severe pain

General Information

Dyloject is specifically indicated for the management of mild to moderate pain and management of moderate to severe pain alone or in combination with opioid analgesics. It is supplied as a solution for intravenous administration. The recommended dose is 37.5 mg administered by intravenous bolus injection over 15 seconds every 6 hours as needed, not to exceed 150 mg/day.

Mechanism of Action

Dyloject (diclofenac sodium) Injection is a non-steroidal anti-inflammatory drug. It exhibits anti-inflammatory analgesic and antipyretic activities in animal models. The mechanism of action is not completely understood but may involve inhibition of the cyclooxygenase (COX-1 and COX-2) pathways. The mechanism may also be related to inhibition of prostaglandin synthetase.

Side Effects

Adverse effects associated with the use of Dyloject may include: nausea, constipation, headache, infusion site pain, dizziness, flatulence, vomiting, insomnia

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12. SIGNIFOR LAR (PASIREOTIDE)

Company: Novartis; Approved by December 2014

Treatment Area: acromegaly

General Information

Signifor LAR is specifically indicated for the treatment of patients with acromegaly who have had an inadequate response to surgery and/or for whom surgery is not an option. It is supplied as an injectable suspension for intramuscular injection. The recommended initial dose is 40 mg administered by intramuscular injection once every 4 weeks (every 28 days). For dose modifications please see drug label.

Mechanism of Action

Signifor LAR is an injectable cyclohexapeptide somatostatin analog. Pasireotide exerts its pharmacological activity via binding to somatostatin receptors (SSTR). There are five known human somatostatin receptor subtypes: SSTR 1, 2, 3, 4, and 5. These receptor subtypes are expressed in different tissues under normal physiological conditions. Somatostatin analogs bind to SSTRs with different potencies. Pasireotide binds with high affinity to four of the five SSTRs. Somatostatin receptors are expressed in many tissues including neuroendocrine tumors (e.g., growth hormone secreting pituitary adenomas). Pasireotide binds to SSTR2 and SSTR5 subtype receptors which may be relevant for inhibition of GH secretion. In vivo studies show that Signifor LAR lowers GH and IGF-1 levels in patients with acromegaly.

Side Effects

Adverse effects associated with the use of Signifor LAR may include: diarrhea, cholelithiasis, hyperglycemia, and diabetes mellitus.

13. SOOLANTRA (IVERMECTIN) CREAM, 1%

Company: Galderma Labs; Approved by December 2014
Treatment Area: inflammatory lesions of rosacea

General Information

Soolantra (ivermectin) cream is a broad-spectrum antiparasitic agent. It is specifically indicated for the treatment of inflammatory lesions of rosacea. It is supplied as a cream for topical administration. It should be applied to the affected areas of the face once daily. Use a pea-size amount for each area of the face (forehead, chin, nose, each cheek) that is affected. Spread as a thin layer, avoiding the eyes and lips.

Mechanism of Action

Soolantra (ivermectin) cream is a semi-synthetic derivative isolated from the fermentation of Streptomyces avermitilis that belongs to the avermectin family of macrocyclic lactones. The exact mechanism of action by which it works against rosacea is not clear.

Side Effects

Adverse effects associated with the use of Soolantra may include: skin burning sensation, skin irritation.

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