Drug Discovery

FDA Approved Drugs

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FDA approved drugs – February 2015

Vidhya

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1. AVYCAZ (CEFTAZIDIME-AVIBACTAM)

Company: Actavis; Approved by February 2015

Treatment Area: complicated intra-abdominal and urinary tract infections

General Information

Avycaz (ceftazidime-avibactam) is a combination of a cephalosporin and a beta-lactamase inhibitor. In combination with metronidazole, it is used for the treatment of complicated intra-abdominal infections (cIAI) caused by the following susceptible microorganisms: Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii, Enterobacter cloacae, Klebsiella oxytoca, and Pseudomonas aeruginosa in patients 18 years or older. It is also indicated for the treatment of complicated urinary tract infections (cUTI) including pyelonephritis caused by the following susceptible microorganisms: Escherichia coli, Klebsiella pneumoniae, Citrobacter koseri, Enterobacter aerogenes, Enterobacter cloacae, Citrobacter freundii, Proteus spp., and Pseudomonas aeruginosa in patients 18 years or older. It is supplied as a solution for intravenous infusion. The recommended dosage is 2.5 grams (2 grams ceftazidime and 0.5 grams avibactam) administered every 8 hours by intravenous (IV) infusion over 2 hours. For treatment of cIAI, metronidazole should be given concurrently.

Mechanism of Action

The ceftazidime component of Avycaz is a cephalosporin antibacterial drug with in vitro activity against certain gram-negative and gram-positive bacteria. The bactericidal action of ceftazidime is mediated through binding to essential penicillin-binding proteins (PBPs). The avibactam component of Avycaz is a non-betalactam beta-lactamase inhibitor that inactivates some beta-lactamases and protects ceftazidime from degradation by certain beta-lactamases. Avibactam does not decrease the activity of ceftazidime against ceftazidime susceptible organisms.

Side Effects

Adverse effects associated with the use of Avycaz may include: vomiting, nausea, constipation, anxiety.

2. FARYDAK (PANOBINOSTAT)

Company: Novartis; Approved by February 2015

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Treatment Area: Multiple myeloma

General Information

Farydak is specifically indicated for use in combination with bortezomib and dexamethasone for the treatment of patients with multiple myeloma who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent. This indication is approved under accelerated approval based on progression free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. It is supplied as a capsule for oral administration. The recommended dose is 20 mg, taken orally once every other day for three doses per week (on Days 1, 3, 5, 8, 10, and 12) of Weeks 1 and 2 of each 21-day cycle for 8 cycles.

Mechanism of Action

Farydak (panobinostat) is a histone deacetylase (HDAC) inhibitor that inhibits the enzymatic activity of HDACs at nanomolar concentrations. HDACs catalyze the removal of acetyl groups from the lysine residues of histones and some non-histone proteins. Inhibition of HDAC activity results in increased acetylation of histone proteins, an epigenetic alteration that results in a relaxing of chromatin, leading to transcriptional activation. In vitro, panobinostat caused the accumulation of acetylated histones and other proteins, inducing cell cycle arrest and/or apoptosis of some transformed cells. Increased levels of acetylated histones were observed in xenografts from mice that were treated with panobinostat. Panobinostat shows more cytotoxicity towards tumor cells compared to normal cells.

Side Effects

Adverse effects associated with the use of Farydak may include: diarrhea, fatigue, nausea, peripheral edema, decreased appetite, pyrexia, vomiting.

3. IBRANCE (PALBOCICLIB)

Company: Pfizer; Approved by February 2015

Treatment Area: ER-positive, HER2-negative breast cancer

General Information

Ibrance (palbociclib) is an orally available pyridopyrimidine-derived cyclin-dependent kinase (CDK) inhibitor with antineoplastic activity. It is specifically indicated for use in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease. This indication is approved under accelerated approval based on progression-free survival (PFS). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. It is supplied as a capsule for oral administration. The recommended dose of Ibrance is a 125 mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. It should be taken with food in combination with letrozole 2.5 mg once daily given continuously throughout the 28-day cycle. The dose should be taken at approximately the same time each day. If the patient vomits or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time. Ibrance capsules should be swallowed whole (do not chew, crush or open them prior to swallowing). No capsule should be ingested if it is broken, cracked, or otherwise not intact.

Mechanism of Action

Ibrance (palbociclib) is an inhibitor of cyclin-dependent kinase (CDK) 4 and 6. Cyclin D1 and CDK4/6 are downstream of signaling pathways which lead to cellular proliferation. In vitro, palbociclib reduced cellular proliferation of estrogen receptor (ER)-positive breast cancer cell lines by blocking progression of the cell from G1 into S phase of the cell cycle. Treatment of breast cancer cell lines with the combination of palbociclib and antiestrogens leads to decreased retinoblastoma protein (Rb) phosphorylation resulting in reduced E2F expression and signaling and increased growth arrest compared to treatment with each drug alone. In vitro treatment of ER-positive breast cancer cell lines with the combination of palbociclib and antiestrogens leads to increased cell senescence, which was sustained for up to 6 days following drug removal. In vivo studies using a patient-derived ER-positive breast cancer xenograft model demonstrated that the combination of palbociclib and letrozole increased the inhibition of Rb phosphorylation, downstream signaling and tumor growth compared to each drug alone.

Side Effects

Adverse effects associated with the use of Ibrance may include: neutropenia, leucopenia, fatigue, anemia, upper respiratory infection, nausea, stomatitis, alopecia, diarrhea, thrombocytopenia, decreased appetite, vomiting, asthenia, peripheral neuropathy, epistaxis.

4. LENVIMA (LENVATINIB)

Company: Eisai; Approved by February 2015

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Treatment Area: thyroid cancer

General Information

Lenvima is specifically indicated for the treatment of locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer. It is supplied as a capsule for oral administration. The recommended daily dosage is 24 mg (two 10 mg capsules and one 4 mg capsule) orally taken once daily with or without food. It should be taken at the same time each day. If a dose is missed and cannot be taken within 12 hours, skip that dose and take the next dose at the usual time of administration. It should be administered until disease progression or until unacceptable toxicity occurs.

Mechanism of Action

Lenvima (lenvatinib) is a receptor tyrosine kinase (RTK) inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). Lenvatinib also inhibits other RTKs that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4; the platelet derived growth factor receptor alpha (PDGFRα), KIT, and RET.

Side Effects

Adverse effects associated with the use of Lenvima may include: hypertension, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, weight decreased, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysesthesia syndrome, abdominal pain, dysphonia.

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