New Drug Update 2019*

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Objectives:

After attending this program, the participant will be able to:

1. Identify the new therapeutic agents and explain their appropriate use.
2. Identify the indications and mechanisms of action of the new drugs.
3. Identify the most important adverse events and other risks of the new drugs.
4. State the route of administration for each new drug and the most important considerations regarding dosage and administration.
5. Compare the new therapeutic agents with older medications to which they are most similar in properties and/or use, and identify the most important advantages and disadvantages of the new drugs.

New Drug Comparison Rating (NDCR) system

5 = important advance
4 = significant advantage(s) (e.g., with respect to use/effectiveness, safety, administration)
3 = no or minor advantage(s)/disadvantage(s)
2 = significant disadvantage(s) (e.g., with respect to use/effectiveness, safety, administration)
1 = important disadvantage(s)

Additional information

The Pharmacist Activist monthly newsletter: www.pharmacistactivist.com

Erenumab-aooe (Aimovig – Amgen; Novartis) Agent for Migraine

2018 New Drug Comparison Rating (NDCR) =

Indication: Administered subcutaneously for the preventive treatment of migraine in adults

Comparable drugs: Beta-adrenergic blocking agents (e.g., propranolol); (fremanezumab [Ajovy] and galcanezumab [Emgality] have been subsequently marketed)

Advantages:
--Is more effective in some patients
--Has a unique mechanism of action (calcitonin gene-related peptide [CGRP] receptor antagonism)
--Is less likely to cause adverse events and interact with other drugs
--Is administered less frequently (once a month)

Disadvantages:
--Is administered subcutaneously (whereas beta-blockers are administered orally)
--Effectiveness and safety have not been established in pediatric patients
--Has not been directly compared with other medications in clinical studies
--Is much more expensive

Most important risks/adverse events: Clinical studies excluded patients with medication overuse headache, as well as patients with myocardial infarction, stroke, transient ischemic attacks, unstable angina, coronary artery bypass surgery, or other revascularization procedures within 12 months prior to screening; latex allergy

Most common adverse events: Injection site reactions (6%)

Usual dosage: Administered subcutaneously; 70 mg once a month; some patients may benefit from a dosage of 140 mg once a month, which is administered as two consecutive injections of 70 mg each

Products: Injection in single-dose prefilled syringes and prefilled autoinjectors containing 70 mg of the drug per mL (products should be stored in a refrigerator and, prior to administration, should be allowed to sit at room temperature for at least 30 minutes protected from direct sunlight)

Comments: Patients who experience migraine attacks frequently are often candidates for preventive management to reduce the frequency and severity of attacks. Those who experience 4 to 14 migraine days per month (i.e., monthly migraine days [MMD]) are classified as having episodic migraines, whereas those with 15 or more headache days per month with at least 8 migraine days per month are classified as having chronic migraines. Certain beta-adrenergic blocking agents (i.e., propranolol, timolol) and certain antiepileptic drugs (i.e., divalproex sodium, topiramate) have labeled indications for migraine prevention, as does onabotulinumtoxinA (Botox; for patients with chronic migraine). Calcitonin gene-related peptide (CGRP) is a neuropeptide that is primarily distributed in the central and peripheral nervous systems and acts as a vasodilator. It is involved in the transmission of pain impulses and elevated concentrations have been associated with migraine attacks. Erenumab is a human monoclonal antibody that exhibits high affinity binding to the CGRP receptor and is the first of a new class of CGRP antagonists.

The effectiveness of erenumab was demonstrated in three placebo-controlled clinical trials, two of which were conducted in patients with a history of episodic migraine. The largest of these studies was conducted over a 6-month period using erenumab in dosages of 70 mg once a month and 140 mg once a month. Patients treated with erenumab experienced, on average, one to two fewer MMD than those on placebo, and 43% and 50% of patients, respectively, experienced at least a 50% reduction from baseline in MMD, compared with 27% of those receiving placebo. The third study was conducted in patients with a history of chronic migraine and, over the course of 3 months, patients treated with erenumab experienced, on average, 2.5 fewer MMD, with dosages of 70 mg and 140 mg once a month, than those receiving placebo. Forty percent and 41%, respectively, experienced at least a 50% reduction from baseline in MMD, compared with 24% of those receiving placebo. Erenumab has not been directly compared with other agents that have been used in the prevention of migraine.

Fremanezumab-vfrm (Ajovy – Teva) Agent for Migraine

2018 New Drug Comparison Rating (NDCR) =

Indication: Administered subcutaneously for the preventive treatment of migraine in adults

Comparable drug: Erenumab (Aimovig); (galcanezumab [Emgality] has been subsequently marketed)

Advantages:
--May be administered less frequently (every month or every 3 months, whereas erenumab is administered every month)
--Product does not contain latex derivatives (to which some patients may be sensitive)

Disadvantages:
--May be more likely to cause injection site reactions (although incidence is similar to that with placebo, but may also be related to the larger volume of the dose [1.5 mL compared with 1 mL with erenumab])
--May be more likely to cause hypersensitivity reactions

Most important risks/adverse events: Hypersensitivity reactions; clinical studies excluded patients with a history of significant cardiovascular disease, vascular ischemia, or thrombotic events, such as cerebrovascular accidents, transient ischemic attacks, deep vein thrombosis, or pulmonary embolism

Most common adverse events: Injection site reactions (45%, compared with 38% with placebo)

Usual dosage: Administered subcutaneously; 225 mg once a month or 675 mg every 3 months (quarterly); the 675 mg dose is administered as 3 consecutive injections of 225 mg each

Product: Injection in single-dose prefilled syringes – 225 mg/1.5 mL (should be stored in a refrigerator and, prior to administration, should be allowed to sit at room temperature for 30 minutes protected from direct sunlight)

Comments: Calcitonin gene-related peptide (CGRP) is a neuropeptide that is involved in the transmission of pain impulses, and elevated concentrations have been associated with migraine attacks. Fremanezumab is a human monoclonal antibody that binds to CGRP ligand and blocks its binding to the receptor. It is the second CGRP antagonist approved for the preventive treatment of migraine, joining erenumab.

The effectiveness of fremanezumab was demonstrated in two placebo-controlled studies. One study was conducted in patients with episodic migraine (i.e., 4 to 14 migraine days per month [MMD]). Patients treated with fremanezumab experienced, on average, one to two fewer MMD than those on placebo with dosages of both 225 mg once a month and 675 mg once every 3 months, over a 3-month treatment period. Approximately 46% of patients experienced at least a 50% reduction from baseline in MMD, compared with 28% of those receiving placebo. The second study was conducted in patients with chronic migraine (i.e., 15 or more headache days per month with at least 8 migraine days per month). Patients treated with fremanezumab (in both dosage regimens) experienced, on average, two fewer MMD, than those receiving placebo. Approximately 39% of patients experienced at least a 50% reduction in monthly average number of headache days of at least moderate severity, compared with 18% of those receiving placebo.

Galcanezumab-gnlm (Emgality – Lilly) Agent for Migraine

2018 New Drug Comparison Rating (NDCR) =

Indication: Administered subcutaneously for the preventive treatment of migraine in adults

Comparable drugs: Erenumab (Aimovig), fremanezumab (Ajovy)

Advantages:
--Product does not contain latex derivatives (compared with erenumab)

Disadvantages:
--Is administered more frequently (compared with fremanezumab that may be administered once every 3 months)
--May be more likely to cause hypersensitivity reactions (compared with erenumab)

Most important risks/adverse events: Hypersensitivity reactions; clinical studies excluded patients with a history of stroke, myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass grafting, deep vein thrombosis, or pulmonary embolism within 6 months of screening

Most common adverse events: Injection site reactions (18%, compared with 13% with placebo)

Usual dosage: Administered subcutaneously; loading dose of 240 mg (administered as two consecutive injections of 120 mg each), followed by 120 mg once a month

Products: Injection in single-dose prefilled pens and prefilled syringes containing 120 mg of the drug per mL (products should be stored in a refrigerator and, prior to administration, should be allowed to sit at room temperature for 30 minutes protected from direct sunlight)

Comments: Calcitonin gene-related peptide (CGRP) is a neuropeptide that is involved in the transmission of pain impulses, and elevated concentrations have been associated with migraine attacks. Galcanezumab is a human monoclonal antibody that binds to CGRP ligand and blocks its binding to its receptor. It is the third CGRP antagonist approved for the preventive treatment of migraine, joining erenumab and fremanezumab.

The effectiveness of galcanezumab was demonstrated in three placebo-controlled clinical studies, two of which were conducted in patients with episodic migraine (i.e., 4 to 14 migraine days per month [MMD]) for a period of 6 months. Patients treated with galcanezumab experienced, on average, two fewer MMD than those on placebo, and 62% and 59% of patients, respectively, experienced at least a 50% reduction from baseline in MMD, compared with 39% and 26% of those receiving placebo. The third study was conducted in patients with chronic migraine (i.e., 15 or more headache days per month with at least 8 MMD) for a period of 3 months. Patients treated with galcanezumab experienced, on average, two fewer MMD, than those receiving placebo. Twenty-eight percent experienced at least a 50% reduction from baseline in MMD, compared with 15% of those receiving placebo.

Cannabidiol (Epidiolex – Greenwich) Antiepileptic Drug

2018 New Drug Comparison Rating (NDCR) =

Indications: Treatment of seizures associated with Dravet syndrome or Lennox-Gastaut syndrome in patients 2 years of age and older

Comparable drugs: None

Advantages:
--Is the first drug to be approved for the treatment of patients with Dravet syndrome
--Is the first natural product to be derived from marijuana to be approved
--Is not likely to be associated with dependence and addiction (is classified in Schedule V)

Limitations:
--Causes central nervous system depressant effects in many patients
--May interact with numerous other medications

Most important risks/adverse events: Central nervous system depressant effects (e.g., sedation); suicidal behavior and ideation; hypersensitivity reactions; hepatic adverse events (may cause elevations of liver transaminases [ALT, AST]; serum transaminases and total bilirubin concentrations should be determined prior to starting treatment, at 1, 3, and 6 months after initiation of treatment, and periodically thereafter); pregnancy (studies in animals suggest a risk of adverse developmental effects; patients who are pregnant should be encouraged to enroll in the North American Antiepileptic Drug Pregnancy Registry); dosage should be reduced in patients with moderate or severe hepatic impairment; activity may be increased by the concurrent use of moderate or strong CYP3A4 and/or CYP2C19 inhibitors, and decreased by strong CYP3A4 and/or CYP2C19 inducers (adjustment of dosage should be considered); concurrent use with clobazam (Onfi) may increase activity of both drugs; may increase the activity of phenytoin and diazepam; product labeling should be consulted for additional information regarding interactions

Most common adverse events: Somnolence (25%), fatigue/asthenia (12%), lethargy (8%), sedation (6%), decreased appetite (22%), diarrhea (20%), rash (13%), infections (40%), liver transaminase elevations (16%)

Usual dosage: Exposure is increased 4-fold when it is administered with a high fat/high calorie meal; initially, 2.5 mg/kg twice a day; after one week, dosage can be increased to a maintenance dosage of 5 mg/kg twice a day; may be further increased to a maximum maintenance dosage of 10 mg/kg twice a day, in weekly increments of 2.5 mg/kg twice a day; dosage should be decreased in patients with moderate or severe hepatic impairment; when treatment is to be discontinued, dosage should be reduced gradually to reduce risk of increased seizure frequency

Product: Oral solution – 100 mg/mL in bottles containing 100 mL; inactive ingredients include sesame seed oil; any solution remaining 12 weeks after first opening the bottle should be discarded

Comments: Dravet syndrome is a rare genetic epileptic disease that appears during the first year of life and is associated with frequent seizures. Lennox-Gastaut syndrome is a rare epileptic disease in which children usually begin having frequent seizures between ages 3 and 5. Cannabidiol (CBD) is a natural component of the *Cannabis sativa* plant (marijuana) that exhibits anticonvulsant activity. However, unlike tetrahydrocannabinol (THC), the major psychoactive component of marijuana, CBD does not cause euphoria or intoxication. CBD is the first drug to be approved for the treatment of patients with Dravet syndrome, and joins 6 other antiepileptic drugs (clobazam, valproate, lamotrigine, rufinamide, topiramate, felbamate) that have been approved for the treatment of Lennox-Gastaut syndrome. The mechanism through which CBD exerts its anticonvulsant action is not known, but it does not appear to be related to interaction with cannabinoid receptors. Its effectiveness was demonstrated in 14-week placebo-controlled trials in which either CBD or placebo was added to existing treatment (most often clobazam). In patients with Dravet syndrome, the median percent reduction in the frequency of convulsive seizures (39%) was significantly greater than in those receiving placebo (13%). In patients with Lennox-Gastaut syndrome, the median percent reduction in the frequency of drop seizures (43%) was significantly greater than in those receiving placebo (20%). CBD was reclassified by the Drug Enforcement Administration from Schedule I to Schedule V.

Lofexidine hydrochloride (Lucemyra – US WorldMeds; Salix) Agent for Opioid Withdrawal

2018 New Drug Comparison Rating (NDCR) =

Indication: Mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults

Comparable drugs: Buprenorphine, methadone (although the properties of lofexidine are most similar to those of clonidine, the latter agent does not have a labeled indication for the management of opioid withdrawal symptoms)

Advantages:
--Is the first non-opioid treatment for the management of opioid withdrawal symptoms
--Increases the likelihood of successful opioid discontinuation
--May reduce the need for continued use of opioid agonist substitutes (i.e., buprenorphine, methadone)
--Is not a controlled substance

Disadvantages:
--Greater risk of cardiovascular adverse events (e.g., hypotension)
--Is administered frequently (4 times a day)

Most important risks/adverse events: Hypotension/orthostatic hypotension, bradycardia, syncope (should be avoided in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, chronic renal failure, those with marked bradycardia, and those taking other medications that decrease pulse or blood pressure); prolongation of QT interval (should be avoided in patients with congenital long QT syndrome, and should be closely monitored in patients with other risk factors including concurrent use of other medications that may cause QT prolongation [e.g., methadone, moxifloxacin]; hypokalemia or hypomagnesemia should be corrected prior to initiating treatment); may increase the CNS depressive effect of benzodiazepines, barbiturates, alcohol, and other sedating agents (patients should be cautioned about activities such as driving or operating machinery); action may be increased by the concurrent use of a CYP2D6 inhibitor (e.g., paroxetine); efficacy of orally-administered naltrexone may be reduced if it is administered within 2 hours of lofexidine

Most common adverse events: Hypotension (30%), orthostatic hypotension (29%), bradycardia (24%), dizziness (19%), sedation (13%), somnolence (11%), dry mouth (10%)

Usual dosage: Recommended starting dosage – 0.54 mg (3 tablets) 4 times daily during the period of peak withdrawal symptoms (e.g., the first 5 to 7 days following the last dose of the opioid); a period of 5 to 6 hours should separate doses; no single dose should exceed 0.72 mg (4 tablets) and the total daily dosage should not exceed 2.88 mg (16 tablets); dosage adjustments should be guided by the symptoms, and treatment may be continued for up to 14 days; when treatment is to be discontinued, the dosage should be reduced gradually over a 2- to 4-day period to mitigate withdrawal symptoms of the drug (e.g., reducing by 1 tablet per dose every 1 to 2 days); product labeling should be consulted for dosage recommendations for patients with impaired hepatic or renal function

Product: Film-coated tablets – 0.18 mg lofexidine

Comments: Opioids (e.g., morphine) reduce norepinephrine concentrations and, with continued use, the brain establishes a new equilibrium by increasing norepinephrine production in order to maintain normal functioning. When the use of an opioid is discontinued or its dosage is significantly reduced, the brain's increased norepinephrine concentrations are no longer offset by the presence of the opioid. This results in a norepinephrine surge that produces the acute symptoms of withdrawal (e.g., pain, muscle spasms, stomach cramps, nausea, agitation, drug craving). For patients with opioid use disorder, addiction and withdrawal are often managed with the partial opioid agonist buprenorphine (e.g., Suboxone) or the opioid agonist methadone. The central alpha-2 adrenergic agonist clonidine has also been used in the management of withdrawal symptoms but this is not a labeled indication.

The actions of lofexidine are most similar to those of clonidine. It binds to receptors on adrenergic neurons and reduces the release of norepinephrine. It is used as part of a broad, long-range treatment plan. Its effectiveness was evaluated in two placebo-controlled studies and patients treated with lofexidine experienced less severe withdrawal symptoms, and a higher proportion of patients completed the period of treatment.

Revefenacin (Yupelri – Theravance; Mylan) Bronchodilator

2018 New Drug Comparison Rating (NDCR) =

Indication: For oral inhalation via nebulization for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD)

Comparable drug: Glycopyrrolate (Lonhala Magnair inhalation solution for nebulization)

Advantages:
--Is administered once a day (whereas glycopyrrolate is administered twice a day)
--May be used with any standard jet nebulizer (whereas glycopyrrolate should only be used with the Magnair system)

Disadvantages:
--Has not been directly compared with glycopyrrolate or other long-acting muscarinic antagonists (LAMAs) in clinical studies
--Administration of a dose requires a longer period of time (approximately 8 minutes; compared with 2 to 3 minutes with glycopyrrolate via nebulization)
--Use should be avoided in patients with hepatic impairment
--Concurrent use with certain organic anion-transporting polypeptide (OATP) inhibitors (e.g., cyclosporine, rifampin) is not recommended

Most important risks/adverse events: Must not be used for the treatment of acute symptoms or in patients with acutely deteriorating COPD; hypersensitivity reactions; paradoxical bronchospasm (treatment should be discontinued); worsening of urinary retention; worsening of narrow-angle glaucoma; action may be increased by other agents with anticholinergic activity (e.g., tiotropium, tolterodine, diphenhydramine), and concurrent use should be avoided; should not be used in patients with hepatic impairment because exposure of active metabolite may be increased; active metabolite is a substrate of OATP1B1 and OATP1B3 and action may be increased by inhibitors of these transporters (e.g., cyclosporine, rifampin; concurrent use should be avoided)

Most common adverse events: Cough (4%), nasopharyngitis (4%), headache (4%), upper respiratory tract infection (3%), back pain (2%)

Usual dosage: 175 mcg once a day using a mouthpiece and a standard jet nebulizer connected to an air compressor

Product: Inhalation solution for oral inhalation: polyethylene unit-dose vials – 175 mcg in 3 mL of sterile, aqueous solution; vials are wrapped in a foil pouch and should only be removed from the pouch and opened immediately before use

Comments: Revefenacin is the fifth long-acting muscarinic antagonist (LAMA) to be approved for use via oral inhalation as bronchodilators in the treatment of patients with COPD, joining tiotropium (Spiriva Respimat), aclidinium (Tudorza Pressair), umeclidinium (Incruze Ellipta), and glycopyrrolate (Seebri Neohaler). The LAMAs are most often administered via oral inhalation using metered-dose delivery devices. However, the effective use of these devices requires manual dexterity and coordination of actuation of the device and inhalation that deviates from regular breathing, which present a challenge for some patients. Approximately 10% of the patients treated for COPD in the United States administer bronchodilators by oral inhalation using a nebulizer. Glycopyrrolate was the first nebulized LAMA to be approved for the treatment of COPD, and it is administered over a period of 2 to 3 minutes twice a day. Revefenacin is the second LAMA to be approved for oral inhalation using nebulization, and the first to be administered once a day. The effectiveness of revefenacin was evaluated in two 12-week, placebo-controlled studies in patients with moderate to very severe COPD. The primary endpoint was the change from baseline in trough (predose) forced expiratory volume in one second (FEV_1). In both studies, revefenacin demonstrated significant improvement in lung function compared to placebo.

Following oral inhalation, revefenacin is rapidly hydrolyzed to a major active metabolite that can

Baricitinib (Olumiant – Lilly) Antiarthritic Agent

2018 New Drug Comparison Rating (NDCR) =

Indication: Treatment of adult patients with moderately or severely active rheumatoid arthritis who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies

Comparable drugs: Tofacitinib (Xeljanz, Xeljanz XR)

Advantages:
--Is less likely to interact with other medications

Disadvantages:
--Is associated with a risk of thrombosis (identified as a boxed warning in labeling)
--Labeled indication for rheumatoid arthritis is more limited (tofacitinib is indicated in patients who have had an inadequate response or intolerance to methotrexate)
--Labeled indications are more limited (tofacitinib is also indicated for patients with psoriatic arthritis or ulcerative colitis)
--Use is not recommended in patients with moderate or severe renal impairment (whereas tofacitinib is used in a reduced dosage)

Most important risks/adverse events: Serious infections (boxed warning; treatment should not be initiated in patients with an active serious infection, including localized infections; patients should be evaluated for active or latent tuberculosis infection; should not be used concurrently with another Janus kinase inhibitor, a biologic disease-modifying antirheumatic drug [DMARDs; e.g., TNF inhibitors], or a potent immunosuppressant [e.g., azathioprine, cyclosporine]; live vaccines should not be used concurrently); lymphoma and other malignancies (boxed warning; risk should be evaluated in patients with a known malignancy other than a successfully treated non-melanoma skin cancer); thrombosis, including deep venous thrombosis, pulmonary embolism, arterial thrombosis (boxed warning); gastrointestinal perforation (caution should be exercised in patients at increased risk such as those with a history of diverticulitis); hematologic laboratory abnormalities (neutropenia, lymphopenia, anemia; treatment should not be initiated, or should be interrupted, in patients with an absolute neutrophil count less than 1000 cells/mm^3, an absolute lymphocyte count less than 500 cells/mm^3, or hemoglobin less than 8g/dL); elevated liver enzymes; elevated lipid concentrations (should be evaluated 12 weeks following initiation of treatment); women with infants should be advised not to breastfeed; action may be increased by strong organic anion transporter 3 (OAT3) inhibitors (e.g., probenecid) and concurrent use is not recommended; use in patients with moderate or severe renal impairment or severe hepatic impairment is not recommended

Most common adverse events: Upper respiratory tract infections (16%), nausea (3%), herpes simplex (1%), herpes zoster (1%), multiple laboratory abnormalities

Usual dosage: 2 mg once a day, with or without food

Product: Film-coated tablets – 2 mg

Comments: Janus kinase (JAK) enzymes are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Inhibition of these enzymes blocks the activation of mediators of inflammation. Baricitinib is the second JAK inhibitor to be approved for the treatment of patients with rheumatoid arthritis, joining tofacitinib. It may be used as monotherapy or with methotrexate or another nonbiologic DMARD.

The effectiveness of baricitinib was evaluated in placebo-controlled studies in which the primary endpoint was the proportion of patients who achieved an ACR20 response (i.e., a 20% improvement in criteria established by the American College of Rheumatology) at 12 weeks. One of the studies was conducted in patients who had an inadequate response or intolerance to nonbiologic DMARDs (e.g., methotrexate), and another study was conducted in patients who had been treated with one or more TNF inhibitors. Patients treated with baricitinib achieved ACR20 responses of 66% and 49%, respectively, at Week 12, compared with 39% and 27% in those receiving placebo.

Tildrakizumab-asmn (Ilumya – Sun) Agent for Psoriasis

2018 New Drug Comparison Rating (NDCR) =

Indication: Administered subcutaneously for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy

Comparable drugs: Guselkumab (Tremfya), Ustekinumab (Stelara)

Advantages:
--Is administered less frequently (every 12 weeks for maintenance treatment compared with guselkumab that is administered every 8 weeks)
--One dosage regimen is appropriate for all adult patients (compared with ustekinumab that is used in two dosage regimens based on patient weight)

Disadvantages:
--May be less effective (compared with guselkumab based on results of noncomparative studies of the individual agents)
--Labeled indications are more limited (compared with ustekinumab that is also indicated for patients with active psoriatic arthritis and patients with moderately to severely active Crohn's disease)
--Labeled indications do not include pediatric patients (compared with ustekinumab that is indicated for the treatment of patients 12 years of age and older with plaque psoriasis)
--Is administered by a healthcare provider (compared with guselkumab that may also be self-administered by patients)

Most important risks/adverse events: Infections (treatment should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated; if a serious infection occurs during treatment or an infection is not responding to standard therapy, discontinuation of tildrakizumab should be considered); tuberculosis (patients should be evaluated for tuberculosis prior to initiating treatment); live vaccines should not be administered during treatment

Most common adverse events: Upper respiratory tract infections (14%), injection site reactions (3%), diarrhea (2%)

Usual dosage: Administered subcutaneously – 100 mg at Weeks 0 and 4, and every 12 weeks thereafter

Product: Single-dose prefilled syringes – 100 mg (should be stored in a refrigerator); may be stored in original carton at room temperature for up to 30 days but, once stored at room temperature, should not be placed back in the refrigerator

Comments: Certain interleukins (ILs) have been identified as having a role in the occurrence and worsening of psoriasis, and six monoclonal antibodies that inhibit specific ILs have been developed for the treatment of patients with psoriasis. Ustekinumab inhibits IL-12 and IL-23 and was the first IL inhibitor to be marketed (2009). Guselkumab also inhibits IL-23, and has also been reported to reduce serum concentrations of several other interleukins, including IL-17A. Tildrakizumab is the third IL-23 inhibitor and acts by binding to the p19 subunit of IL-23. The three other IL inhibitors indicated for the treatment of patients with psoriasis inhibit IL-17A and include secukinumab (Cosentyx), ixekizumab (Taltz), and brodalumab (Siliq).

The effectiveness of tildrakizumab was evaluated in two placebo-controlled studies. The primary endpoints were a reduction in the Psoriasis Area and Severity Index (PASI) score of at least 75% (PASI 75) from baseline to Week 12 and an improvement in the Physician Global Assessment (PGA) to clear or minimal. Of the patients treated with tildrakizumab, 64% and 61% attained a PASI 75 response, compared with 6% in each study of those receiving placebo, and 14% and 12% of those treated with the new drug attained a PASI 100 response, compared with 1% and 0% of those receiving placebo. Of the patients treated with tildrakizumab, 58% and 55% received a PGA of clear or minimal, compared with 7% and 4% of those receiving placebo. In one of the studies some patients were treated with etanercept (Enbrel), and 48% of these patients attained a PASI 75 response and a PGA of clear or minimal.

Tezacaftor/ivacaftor (Symdeko – Vertex) Agents for Cystic Fibrosis

2018 New Drug Comparison Rating (NDCR) =

Indication: Treatment of patients with cystic fibrosis aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence

Comparable drugs: Lumacaftor/ivacaftor (Orkambi)

Advantages:
--Labeled indication includes a larger patient population (indication for lumacaftor/ivacaftor is limited to patients who are homozygous for F508del mutation in the CFTR gene)
--May be less likely to cause adverse events (labeling for lumacaftor/ivacaftor also includes precautions regarding respiratory events and hypertension)
--Interacts with fewer medications

Disadvantages:
--Has not been studied in patients less than 12 years (whereas lumacaftor/ivacaftor is indicated for children as young as 6 years)

Most important risks/adverse events: Elevated transaminases (ALT and AST should be assessed prior to initiating treatment, every 3 months during the first year, and annually thereafter); non-congenital lens opacities/cataracts (baseline and follow-up ophthalmological examinations are recommended in pediatric patients); action is reduced by CYP3A inducers (e.g., carbamazepine, rifampin), and concurrent use should be avoided; action is increased by CYP3A inhibitors (e.g., fluconazole, clarithromycin) and dosage of tezacaftor/ivacaftor should be reduced when used concurrently (consumption of grapefruit products and Seville oranges should be avoided); dosage should be reduced in patients with moderate or severe hepatic impairment

Most common adverse events: Headache (15%), nausea (9%), sinus congestion (4%), dizziness (4%)

Usual dosage: Should be administered with fat-containing food (e.g., eggs, cheeses, nuts, whole milk, meats); 100 mg tezacaftor/150 mg ivacaftor in the morning and 150 mg ivacaftor in the evening, approximately 12 hours apart; product labeling should be consulted for the recommendations for dosage adjustment in patients with hepatic impairment or who are also being treated with a CYP3A inhibitor

Products: Combination tablets containing 100 mg of tezacaftor and 150 mg of ivacaftor that are co-packaged with tablets containing 150 mg of ivacaftor

Comments: Cystic fibrosis (CF) is caused by a mutation in a gene that encodes for the protein cystic fibrosis transmembrane conductance regulator (CFTR) that regulates chloride and water transport in the body. Children must inherit two defective CFTR genes, one from each parent, to have CF. The F508del mutation is the most common cause of CF and people who have two copies of the F508del mutation account for approximately one-half of the CF population in the US. Defective functioning of the CFTR protein results in the formation of thick mucus in the affected areas, and manifestations include chronic cough and persistent lung and sinus infections, pancreatic insufficiency and other severe digestive problems, and other complications.

Tezacaftor facilitates the cellular processing and trafficking of normal and mutant forms of CFTR to increase the amount of mature CFTR delivered to the cell surface. Ivacaftor is a CFTR potentiator that facilitates increased chloride transport by potentiating the gating of the CFTR protein at the cell surface. The use of tezacaftor and ivacaftor in combination results in a further enhancement of chloride transport than that provided with either agent given alone. The effectiveness of the tezacaftor/ivacaftor regimen was demonstrated in two placebo-controlled trials in which patients treated with the combination therapy experienced statistically significant and clinically meaningful improvements in lung function and other measures of disease that were sustained for up to 48 weeks of treatment.

Sodium zirconium cyclosilicate (Lokelma – AstraZeneca) Agent for Hyperkalemia

2018 New Drug Comparison Rating (NDCR) =

Indication: Treatment of hyperkalemia in adults;
should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action

Comparable drug: Patiromer sorbitex calcium (Veltassa)

Advantages:
--Is not likely to cause hypomagnesemia
--Product does not require refrigeration

Disadvantages:
--Is more likely to cause edema

Most important risks/adverse events: Gastrointestinal adverse events in patients with motility disorders (should be avoided in patients with severe constipation or bowel obstruction or impaction, including abnormal post-operative bowel motility disorders); edema (patients should be monitored for signs of edema, particularly those who should restrict their sodium intake or are vulnerable to fluid overload [e.g., heart failure, kidney disease]; as appropriate, dietary sodium should be adjusted and the dosage of diuretics increased); interactions with other oral medications (in general, other oral medications should be administered at least 2 hours before or 2 hours after the new drug; may transiently increase gastric pH and change the absorption of co-administered drugs that exhibit pH-dependent solubility [systemic exposure of weak acids such as furosemide and atorvastatin is increased and that of weak bases such as dabigatran {Pradaxa} is decreased])

Most common adverse events: Edema (6% -11%), hypokalemia (4%)

Usual dosage: Initial treatment – 10 grams three times a day for up to 48 hours; maintenance treatment – 10 grams once a day; during maintenance treatment the dosage may be increased based on serum potassium concentrations at intervals of 1 week or longer and in increments of 5 grams; dosage may be decreased or discontinued if the serum potassium is below the desired target range; recommended maintenance dosage range is 5 grams every other day to 15 grams daily

Product: Powder for oral suspension – packets containing 5 grams and 10 grams; contents of a packet should be emptied into a drinking glass containing 3 tablespoonfuls or more of water; mixture should be stirred well and patient should drink immediately; procedure should be repeated as needed so that the patient drinks the entire dose

Comments: Hyperkalemia is characterized by elevated serum potassium concentrations (generally above 5 mEq/L). It is most often experienced by patients with kidney disease or heart failure, particularly in those who are taking medications that inhibit the renin-angiotensin-aldosterone system (RAAS) such as angiotensin-converting enzyme inhibitors (ACEIs; e.g., lisinopril), angiotensin receptor blockers (ARBs; e.g., losartan), the direct renin inhibitor aliskiren (Tekturna), and aldosterone antagonists (e.g., spironolactone, eplerenone). The cation-exchange resin sodium polystyrene sulfonate (e.g., Kayexalate) has been available for more than 50 years and has been used orally or as an enema in the treatment of hyperkalemia. Patiromer sorbitex calcium was marketed in 2016 and consists of the active moiety, patiromer, a non-absorbed potassium-binding polymer, and a calcium-sorbitol counterion. When administered orally, the counterion is exchanged for potassium that binds with patiromer, resulting in increased fecal potassium excretion and reduced serum potassium concentrations.

Sodium zirconium cyclosilicate is a non-absorbed zirconium silicate that preferentially captures potassium in exchange for hydrogen and sodium. It has a high affinity for potassium even in the presence of other cations. It was evaluated in placebo-controlled studies in multiple phases. In the acute phase (the first 48 hours), patients treated with a dosage of 10 grams three times daily had a mean serum potassium reduction of -0.7mEq/L, compared with -0.2 mEq/L in those receiving placebo. Patients with higher starting concentrations of potassium (>5.5 mEq/L) had a greater response. Continued efficacy was demonstrated in longer studies (e.g., 29 days, 12 months).

Angiotensin II acetate (Giapreza – La Jolla) Vasopressor

2018 New Drug Comparison Rating (NDCR) =

Indication: Administered intravenously to increase blood pressure in adults with septic or other distributive shock

Comparable drugs: Other vasopressors (e.g., norepinephrine, phenylephrine, vasopressin)

Advantages:
--May further increase blood pressure and reduce mortality in patients in shock
--Increases blood pressure by a different mechanism of action

Disadvantages:
--May be more likely to cause thrombotic and thromboembolic events

Most important risks/adverse events: Risk for thrombosis (patients should receive concurrent venous thromboembolism prophylaxis); response may be increased by the concurrent use of an angiotensin-converting enzyme inhibitor, and decreased by the concurrent use of an angiotensin receptor blocker

Most common adverse events: Thromboembolic events (13%), thrombocytopenia (10%), tachycardia (9%), fungal infection (6%), delirium (6%), acidosis (6%)

Usual dosage: Administered by continuous intravenous infusion, preferably through a central venous line; starting dosage – 20 nanograms (ng)/kg/min; blood pressure response should be monitored and the dosage of the drug titrated every 5 minutes by increments of up to 15 ng/kg/min as needed to achieve or maintain target blood pressure; a dosage of 80 ng/kg/min should not be exceeded in the first 3 hours of treatment; maintenance doses should not exceed 40 ng/kg/min; once the underlying shock has sufficiently improved, the dosage should be down-titrated every 5 to 15 minutes by increments of up to 15 ng/kg/min based on blood pressure

Product: Vials – 2.5 mg, 5 mg (should be stored in a refrigerator); contents of a vial must be diluted in 0.9% Sodium Chloride Injection to achieve a final concentration of 5,000 ng/mL or 10,000 ng/mL

Comments: The treatment of patients in shock usually includes the administration of intravenous fluids and vasopressors (e.g., norepinephrine, vasopressin, phenylephrine, epinephrine, dopamine). However, in some patients, these measures are insufficient to prevent irreversible organ damage and/or death. Angiotensin II is a naturally occurring peptide hormone of the renin-angiotensin-aldosterone system (RAAS) that causes vasoconstriction and an increase in blood pressure. The plasma half-life of angiotensin II is less than one minute which necessitates administration via continuous intravenous infusion.

The effectiveness of angiotensin II was evaluated in a study of 321 adults with shock who remained hypotensive despite fluid and vasopressor therapy. More than 90% of the patients had septic shock, and 83% had received two or more vasopressors and 47% three or more vasopressors prior to the administration of angiotensin II. Doses of angiotensin II or placebo were titrated to a target mean arterial pressure (MAP) of at least 75 mmHg during the first 3 hours of treatment while doses of other vasopressors were maintained. From Hour 3 to Hour 48, angiotensin II or placebo was titrated to maintain MAP between 65 and 70 mmHg while reducing doses of other vasopressors. The primary endpoint was the percentage of patients who achieved either a MAP of at least 75 mmHg or at least a 10 mmHg increase in MAP without an increase in baseline vasopressor therapy at 3 hours. The primary endpoint was achieved by 70% of patients treated with angiotensin II, compared with 23% of those receiving placebo. Mortality through Day 28 was 46% of the patients on angiotensin II and 54% of those on placebo.

Elagolix sodium (Orilissa – AbbVie) Agent for Endometriosis

2018 New Drug Comparison Rating (NDCR) =

Indication: Management of moderate to severe pain associated with endometriosis

Comparable drugs: Gonadotropin-releasing hormone (GnRH) receptor agonists (leuprolide [e.g., Lupron], nafarelin [Synarel])

Advantages:
--Is administered orally (whereas leuprolide is administered intramuscularly and nafarelin is administered intranasally)
--Does not cause initial flare of symptoms
--Labeled dosage recommendations permit use (150 mg once a day) for up to 24 months (whereas, when used for treating endometriosis, leuprolide should not be used for longer than 12 months and nafarelin should not be used for more than 6 months)

Disadvantages:
--Interacts with more medications
--Has not been directly compared with other therapies in clinical studies
--Labeled indications are more limited (leuprolide and nafarelin are indicated for use in children with central precocious puberty, and leuprolide is also indicated for the treatment of uterine fibroids and prostate cancer)
--Is administered once a day (compared with leuprolide depot 11.25 mg that is administered every 3 months)

Most important risks/adverse events: Bone loss (causes dose- and duration-dependent decreases in bone mineral density [BMD]; contraindicated in women with osteoporosis; BMD should be assessed in women with additional risk factors for bone loss); contraindicated in pregnant women (risk of pregnancy loss may be increased; change in menstrual bleeding may reduce the ability to recognize the occurrence of pregnancy in a timely manner; women who are sexually active should use non-hormonal contraception during treatment and for one week following discontinuation of treatment; estrogen-containing contraceptives should not be used); suicidal ideation and mood disorders (patients with depressive symptoms should be promptly evaluated and appropriate actions taken); action may be increased in patients with hepatic impairment and is contraindicated in patients with severe hepatic impairment); may cause elevations of hepatic enzymes and blood lipids; action may be increased by organic anion transporting polypeptide (OATP) 1B1 inhibitors (concurrent use of strong OATP1B1 inhibitors such as cyclosporine and gemfibrozil is contraindicated), as well as by strong CYP3A inhibitors; action may be reduced by CYP3A inducers; may reduce the action of CYP3A substrates such as oral midazolam, and increase the action of digoxin and rosuvastatin

Most common adverse events (and incidence with a dosage of 150 mg once a day): hot flushes/night sweats (24%), headache (17%), nausea (11%), insomnia (6%), mood alteration/swings (6%), amenorrhea (4%), depression (3%)

Usual dosage: 150 mg once a day for up to 24 months; in patients with dyspareunia, treatment with a dosage of 200 mg twice a day for up to 6 months should be considered; product labeling should be consulted for recommended dosage adjustments in patients with moderate hepatic impairment or who are taking interacting drugs

Products: Tablets – 150 mg, 200 mg

Comments: Elagolix is a gonadotropin-releasing hormone (GnRH) receptor antagonist that binds to GnRH receptors in the pituitary gland. It causes a dose-dependent suppression of luteinizing hormone and follicle-stimulating hormone, leading to decreased blood concentrations of the ovarian sex hormones, estradiol and progestin. The GnRH *agonists* also reduce estrogen concentrations with continued use, but only following an initial increase in estrogen concentrations that may be poorly tolerated. The effectiveness of elagolix was demonstrated in two placebo-controlled studies in which the new drug was significantly more effective than placebo in reducing dysmenorrhea and nonmenstrual pelvic pain. Patients with dyspareunia experienced improvement with a dosage of 200 mg twice a day but statistical significance was not achieved with a dosage of 150 mg once a day.

Eravacycline dihydrochloride (Xerava – Tetraphase) Antibacterial Agent

2018 New Drug Comparison Rating (NDCR) =

Indication: Administered intravenously for the treatment of complicated intra-abdominal infections caused by susceptible microorganisms: *Escherichia coli, Klebsiella pneumoniae, Citrobacter freundii, Enterobacter cloacae, Klebsiella oxytoca, Enterococcus faecalis, Enterococcus faecium, Staphylococcus aureus, Streptococcus anginosus* group, *Clostridium perfringens, Bacteroides* species, and *Parabacteroides distasonis* in patients 18 years or older

Comparable drugs: Other tetracyclines (e.g., doxycycline, minocycline)

Advantages:
--Is active against strains of certain bacteria that are resistant to other tetracyclines
--Is more effective in some patients with complicated intra-abdominal infections (cIAI)

Disadvantages:
--Labeled indications are much more limited (doxycycline and minocycline have labeled indications for numerous types of infections)
--Is not available in an oral formulation (whereas doxycycline and minocycline are administered orally and parenterally)
--Effectiveness and safety have not been evaluated in patients less than 18 years of age (whereas doxycycline and minocycline are used in patients 8 years and older)

Most important risks/adverse events: Hypersensitivity reactions including anaphylaxis (use is contraindicated in patients with known hypersensitivity to any of the tetracyclines); tooth discoloration and enamel hypoplasia (use in infants and children younger than 8 years, nursing mothers, or during the second or third trimester of pregnancy is not recommended); inhibition of bone growth; *Clostridium difficile*-associated diarrhea (should be considered in any patient who develops diarrhea); potential for tetracycline class adverse events (e.g., photosensitivity, anti-anabolic effects); action may be reduced by concurrent use of a strong CYP3A inducer (e.g., rifampin; dosage of eravacycline should be increased); may increase action of anticoagulants that may require reduction of anticoagulant dosage; dosage should be reduced in patients with severe hepatic impairment

Most common adverse events: Infusion site reactions (8%), nausea (7%), vomiting (4%), diarrhea (2%)

Usual dosage: Administered by intravenous infusion over approximately 60 minutes: 1 mg/kg every 12 hours for 4 to 14 days; if a strong CYP3A inducer is being used concurrently, the dosage should be increased to 1.5 mg/kg every 12 hours; in patients with severe hepatic impairment the dosage should be 1 mg/kg every 12 hours on Day 1 and then decreased to 1 mg/kg every 24 hours

Product: For injection: lyophilized powder (50 mg) in single-dose vials (should be stored in a refrigerator); contents of a vial should be reconstituted with 5 mL of Sterile Water for Injection and swirled gently, but not shaken; reconstituted solution is then diluted to a target concentration of 0.3 mg/mL in a 0.9% Sodium Chloride Injection infusion bag

Comments: cIAI include infections such as appendicitis, diverticulitis, peritonitis, intra-abdominal abscess, and perforations of the gastrointestinal tract. Infections are usually polymicrobial and caused by gram-negative, gram-positive, and/or anaerobic bacteria, and are associated with systemic symptoms. Empiric treatment with a broad-spectrum antibacterial regimen often includes a beta-lactam antibiotic (carbapenems, cephalosporins, penicillins [sometimes with a beta-lactamase inhibitor]) but some patients are hypersensitive to these agents or experience infections caused by strains of bacteria that are resistant. Eravacycline is a tetracycline class antibacterial agent that is also designated as a fluorocycline because its structure includes a fluorine substituent. It exhibits activity against strains of bacteria that are resistant to other tetracyclines. The effectiveness of eravacycline was demonstrated in two studies in which it was compared with ertapenem or meropenem. Clinical cures were achieved in 87% of the patients treated with eravacycline or ertapenem, and 91% of patients treated with eravacycline or meropenem. However, it did not meet non-inferiority endpoints in a study in patients with complicated urinary tract infections.

Plazomicin sulfate (Zemdri – Achaogen) Antibacterial Agent

2018 New Drug Comparison Rating (NDCR) =

Indication: Administered intravenously in patients 18 years of age or older for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis caused by the following susceptible organisms: *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis,* and *Enterobacter cloacae*

Comparable drugs: Other aminoglycoside antibacterial agents (e.g., amikacin, gentamicin, tobramycin)

Advantages:
--Is more effective in some patients with a cUTI caused by bacteria that are resistant to first-line treatment
--Cross-resistance with other aminoglycosides is not likely
--Is administered once a day (whereas other aminoglycosides are sometimes administered more frequently)

Disadvantages:
--Labeled indication does not include infections caused by *Pseudomonas aeruginosa*
--Labeled indications are more limited (e.g., other aminoglycosides are also indicated for the treatment of infections such as septicemia, respiratory, central nervous system, skin and soft tissue, and intra-abdominal infections)
--Has not been evaluated in pediatric patients

Most important risks/adverse events: Nephrotoxicity (boxed warning; risk is greater in patients with impaired renal function, the elderly, and those receiving concomitant nephrotoxic medications); ototoxicity (boxed warning); neuromuscular blockade (boxed warning); pregnancy (boxed warning; may cause harm to the unborn child); contraindicated in patients with known hypersensitivity to any aminoglycoside; hypersensitivity reactions; *Clostridium difficile*-associated diarrhea

Most common adverse events: Decreased renal function (4%), diarrhea (2%), hypertension (2%)

Usual dosage: Administered by intravenous infusion over 30 minutes; in patients with a creatinine clearance of at least 90 mL/min, the recommended dosage is 15 mg/kg every 24 hours for 4 to 7 days; in patients with a creatinine clearance of at least 15 to less than 90 mL/min, therapeutic drug monitoring is recommended to maintain plasma trough concentrations below 3 mcg/mL; product labeling should be consulted for recommended dosage adjustments based on creatinine clearance and trough concentrations

Product: Injection - single-dose vials – 500 mg/10 mL (should be stored in a refrigerator); appropriate volume to provide the required dose should be diluted in 0.9% Sodium Chloride Injection or Lactated Ringer's Injection to achieve a final volume of 50 mL

Comments: Although a beta-lactam antibiotic or fluoroquinolone would usually be used in the treatment of complicated urinary tract infections caused by Enterobacteriaceae, the emergence of carbapenem-resistant and other resistant strains of these bacteria has resulted in additional challenges in treating these infections. Plazomicin is a semi-synthetic aminoglycoside antibacterial agent that, like the other aminoglycosides, binds to bacterial 30S ribosomal subunits, thereby inhibiting protein synthesis and exhibiting a bactericidal action. It is primarily active against gram-negative aerobic bacteria. Its action is not inhibited by most of the aminoglycoside modifying enzymes that may result in resistance to other aminoglycosides, and cross-resistance is unlikely. Activity of plazomicin has also been demonstrated *in vitro* in the presence of certain carbapenemases.

The effectiveness of plazomicin was evaluated in a study of hospitalized adults with cUTI, in which it was compared with meropenem (administered IV every 8 hours). At Day 5 of treatment the rates of resolution or improvement of symptoms and microbiological eradication were 88% and 91%, respectively. A Test of Cure (resolution of symptoms [i.e., cure] and microbiological eradication) visit was scheduled for at least 2 weeks following the first dose of treatment. These results for plazomicin and meropenem were 82% and 70%, respectively. Some of the patients who were effectively treated with plazomicin had cUTI that were caused by isolates of bacteria that were resistant to gentamicin and tobramycin.

Baloxavir marboxil (Xofluza – Genentech; Shionogi) Antiviral Agent

2018 New Drug Comparison Rating (NDCR) =

Indication: Treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours

Comparable drug: Oseltamivir (e.g., Tamiflu)

Advantages:
--Is a single-dose treatment (whereas oseltamivir is usually administered twice a day for 5 days)
--Has a unique mechanism of action (is a polymerase acidic endonuclease inhibitor)
--May be effective in some patients with influenza that is resistant to oseltamivir
--Use has not been associated with neuropsychiatric adverse events
--Dosage adjustment is not necessary in patients with renal impairment

Disadvantages:
--Effectiveness and safety have not been evaluated in patients less than 12 years of age or over 65 years of age (whereas oseltamivir is indicated for the treatment of patients 2 weeks of age and older)
--Has not been evaluated for the prophylaxis of influenza (whereas oseltamivir is indicated for the treatment and prophylaxis of influenza)
--Absorption and activity may be reduced by coadministration with polyvalent cation-containing products

Most important risks/adverse events: Bacterial infection (may coexist with or occur as a complication of influenza); absorption and activity may be reduced by polyvalent cation-containing products (e.g., antacids), and coadministration should be avoided; may decrease the effectiveness of intranasal live attenuated influenza vaccine

Most common adverse events: Diarrhea (3%), bronchitis (2%)

Usual dosage: For patients weighing 40 kg to less than 80 kg – single dose of 40 mg; for patients weighing at least 80 kg – single dose of 80 mg

Products: Film-coated tablets – 20 mg, 40 mg; supplied in blister card packaging

Comments: Baloxavir marboxil is a prodrug that is almost completely converted by hydrolysis to its active metabolite, baloxavir, that exerts activity against influenza A and influenza B viruses. Baloxavir inhibits the endonuclease activity of the polymerase acidic protein, an influenza virus-specific enzyme in the viral RNA polymerase complex required for viral gene transcription, resulting in inhibition of influenza virus replication. Oseltamivir and related agents act by inhibiting influenza neuraminidase.

The effectiveness of baloxavir was evaluated in two clinical studies in which the primary endpoint was the time to alleviation of symptoms, defined as the time when all seven symptoms (cough, sore throat, nasal congestion, headache, feverishness, myalgia, and fatigue) had been assessed by the patient as none or mild for a duration of at least 21.5 hours. The first study was conducted in 400 adult patients and was placebo-controlled. The median time to alleviation of symptoms in patients treated with a single dose of 40 mg of baloxavir was 50 hours, compared with a median time of 78 hours in those receiving placebo. The second study was an active- and placebo-controlled trial in 1,436 adult and adolescent patients. The median time to alleviation of symptoms in patients treated with a single dose of 40 mg or 80 mg of baloxavir was 54 hours, compared with a median time of 80 hours in those receiving placebo. The second study included a group of patients who were treated with oseltamivir (twice a day for 5 days). There was no difference in the median time to alleviation of symptoms (i.e., 54 hours) between patients who received a single dose of baloxavir and those who received oseltamivir. The infections of most patients in the clinical studies were caused by influenza A viruses. The subset of patients with influenza B infections in the first study had a shorter median time to alleviation of symptoms than those in the placebo group, but in the subset of patients in the second study with influenza B infections, the median time to alleviation of symptoms was longer in those receiving baloxavir than in those receiving placebo.

Doravirine (Pifeltro – Merck) Antiviral Agent

2018 New Drug Comparison Rating (NDCR) =

Indication: In combination with other antiretroviral agents for the treatment of HIV-1 infection in adult patients with no prior antiretroviral treatment history

Comparable drugs: Other non-nucleoside reverse transcriptase inhibitors (NNRTI; rilpirivine [Edurant] is the NNRTI used for the basis of the following comparisons)

Advantages:
--Labeled indication is less restrictive (rilpivirine is indicated in patients with HIV-1 RNA less than or equal to 100,000 copies/mL)
--Is less likely to cause depressive disorders, hepatotoxicity, or prolongation of the QT interval
--Is not likely to interact with drugs that increase gastric pH (whereas these agents may reduce plasma concentrations of rilpivirine)

Disadvantages:
--Has not been evaluated in patients less than 18 years of age (whereas rilpivirine is indicated in patients 12 years of age and older)

Most important risks/adverse events: Action may be significantly reduced by strong CYP3A inducers (e.g., carbamazepine, enzalutamide, rifampin, St. John's wort) and concurrent use is contraindicated, and at least a 4-week cessation period is recommended prior to initiation of treatment with doravirine; action may be reduced by efavirenz, etravirine, and nevirapine, and concurrent use is not recommended; dosage should be increased if rifabutin is used concurrently; immune reconstitution syndrome

Most common adverse events: Nausea (7%), headache (6%), fatigue (6%), diarrhea (5%), abdominal pain (5%)

Usual dosage: 100 mg once a day; in patients also treated with rifabutin, the recommended dosage is 100 mg twice a day (approximately 12 hours apart)

Products: Film-coated tablets – 100 mg; a combination product, Delstrigo tablets, contains doravirine (100 mg), lamivudine (300 mg), and tenofovir disoproxil fumarate (300 mg), and is administered once a day as a complete regimen in patients with no antiretroviral treatment history

Comments: Doravirine is the sixth non-nucleoside reverse transcriptase inhibitor (NNRTI) to be marketed for the treatment of HIV infection, joining delavirdine (Rescriptor), efavirenz (Sustiva), etravirine (Intelence), nevirapine (Viramune), and rilpivirine. The effectiveness of doravirine was evaluated in two 48-week active controlled clinical studies. In the first study either doravirine or darunavir plus ritonavir was administered once daily in combination with emtricitabine/tenofovir disoproxil fumarate or abacavir/lamivudine. At Week 48 the percentages of patients with virologic outcomes of HIV-1 RNA of less than 50 copies/mL were 84% for the doravirine regimen and 80% for the darunavir/ritonavir regimen. In the second study the combination product (Delstrigo) with doravirine/lamivudine/tenofovir disoproxil fumarate was compared with a combination of efavirenz, emtricitabine, and tenofovir disoproxil fumarate. At Week 48, the percentages of patients with less than 50 copies/mL were 84% and 81%, respectively.

Although the new regimens are highly effective, they may not be as effective as regimens that include an HIV-1 integrase strand transfer inhibitor (INSTI; i.e., bictegravir, dolutegravir, elvitegravir, raltegravir). Biktarvy and Genvoya are INSTI-containing complete regimen combination formulations that include tenofovir alafenamide instead of tenofovir disoproxil fumarate as the prodrug for tenofovir. Tenofovir alafenamide is less likely than tenofovir disoproxil fumarate to cause renal toxicity and affect bone mineral density, although it may be more likely to increase blood lipid concentrations.

Bictegravir sodium/emtricitabine/tenofovir alafenamide fumarate (Biktarvy – Gilead)
Antiviral Agents

2018 New Drug Comparison Rating (NDCR) =

Indications: A complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 3 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Biktarvy

Comparable drugs: Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (Genvoya)

Advantages:
--Formulation does not include cobicistat that may interact with numerous other medications
--Indicated as a replacement regimen in patients with no history of treatment failure for at least 3 months (compared with at least 6 months with Genvoya)

Disadvantages:
--Is not indicated for pediatric patients (whereas Genvoya is indicated in pediatric patients weighing at least 25 kg)

Most important risks/adverse events: Severe acute exacerbations of hepatitis B virus (HBV) in patients who are coinfected with HIV-1 and HBV upon discontinuation of products containing emtricitabine and tenofovir disoproxil fumarate (boxed warning; hepatic function should be closely monitored for at least several months in patients who discontinue treatment); immune reconstitution syndrome; lactic acidosis/severe hepatomegaly with steatosis; new onset or worsening renal impairment (use is not recommended in patients with estimated creatinine clearance less than 30 mL per minute); women should not breastfeed due to the potential for HIV transmission; may increase the action of dofetilide and concurrent use is contraindicated; may increase the action of metformin; bictegravir is a substrate for the CYP3A and UGT1A1 pathways and action may be reduced by inducers of these pathways (concurrent use with rifampin is contraindicated, and use with rifampin, rifabutin, or St. John's wort is not recommended; in patients treated with carbamazepine, oxcarbazepine, phenobarbital, or phenytoin, alternative anticonvulsants should be considered); action of bictegravir may be reduced by polyvalent cations (may be administered under fasting conditions 2 hours before an antacid containing aluminum, magnesium, and/or calcium; may be administered together with supplements containing calcium or iron with food); because it is a complete regimen, concurrent use of other antiretroviral medications for HIV-1 infection is not recommended

Most common adverse events: Headache (5%), diarrhea (5%), nausea (4%)

Usual dosage: One tablet once a day with or without food

Product: Film-coated tablets – bictegravir 50 mg, emtricitabine 200 mg, tenofovir alafenamide 25 mg

Comments: Bictegravir is the fourth HIV-1 integrase strand transfer inhibitor to be approved, joining raltegravir (Isentress), elvitegravir (e.g., in the combination formulation Genvoya), and dolutegravir (Tivicay). Bictegravir is not available as a single agent but in a combination formulation with the HIV-1 nucleoside analog reverse transcriptase inhibitors emtricitabine and tenofovir alafenamide. Tenofovir alafenamide is a prodrug that is metabolized much more efficiently than the prodrug tenofovir disoproxil fumarate to the active tenofovir diphosphate. Tenofovir alafenamide may be used in a much lower dosage and its lower systemic exposure is less likely to be associated with renal toxicity and a reduction in bone mineral density.

The effectiveness of Biktarvy was evaluated in two studies in adults with no antiretroviral treatment history, in which it was compared with a regimen of dolutegravir, abacavir, and lamivudine, as well as a regimen of dolutegravir, emtricitabine, and tenofovir alafenamide. The new combination formulation was similarly effective and the percentages of patients with HIV-1 RNA less than 50 copies/mL at Week 48 exceeded 90% for all regimens. Biktarvy was also studied in two studies in virologically-suppressed patients who were switched to Biktarvy, and compared with other HIV-1 antiretroviral regimens. The new combination formulation was similarly effective in maintaining virologic suppression at Week 48 in more than 90% of patients.

Ibalizumab-uiyk (Trogarzo – TaiMed; Thera) Antiviral Agent

2018 New Drug Comparison Rating (NDCR) =

Indication: In combination with other antiretroviral(s), administered intravenously for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their antiretroviral regimen

Comparable drugs: Other HIV-1 antiretroviral agents

Advantages:
--Is effective in some patients who have failed other treatments
--Has a unique mechanism of action (is a CD4-directed post-attachment HIV-1 inhibitor)
--Causes fewer adverse events and is less likely to interact with other medications
--Is administered less frequently (once every two weeks)

Disadvantages:
--Is administered intravenously (whereas most comparable agents are administered orally)
--Is not indicated for use in pediatric patients

Most important risks/adverse events: Immune reconstitution inflammatory syndrome; infusion-associated adverse events; women should not breastfeed because of the potential for HIV transmission

Most common adverse events: Diarrhea (8%), dizziness (8%), nausea (5%), rash (5%), elevated creatinine concentrations (10%)

Usual dosage: Administered by a trained medical professional as an intravenous infusion in the cephalic vein of the patient's right or left arm; initial loading dose of 2,000 mg (10 vials) followed by maintenance doses of 800 mg (4 vials) every 2 weeks; duration of the loading dose infusion should be no less than 30 minutes, and patients should be observed for one hour following administration for at least the first dose

Product: Single-dose vials that deliver approximately 1.33 mL containing 200 mg of the drug; (vials should be stored in a refrigerator); contents of the appropriate number of vials needed to provide the recommended dose should be diluted in 250 mL of 0.9% Sodium Chloride Injection

Comments: Most patients with HIV-1 infection can be successfully treated with a combination of two or more antiretroviral drugs such as integrase strand transfer inhibitors (INSTIs), nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTI), and HIV-1 protease inhibitors (PIs). However, as many as 25,000 patients in the United States have multidrug resistant (MDR) HIV-1 infection that is associated with a high risk of complications and death. Ibalizumab is a humanized monoclonal antibody and the first biologic drug to be approved for the treatment of HIV-1 infection. It is designated as a CD4-directed post-attachment HIV-1 inhibitor, and blocks HIV-1 from infecting $CD4^+$ T cells by binding to domain 2 of CD4 and interfering with post-attachment steps required for the entry of HIV-1 virus particles into host cells and preventing the viral transmission that occurs via cell-cell fusion. The binding specificity of ibalizumab to domain 2 of CD4 allows it to block viral entry into host cells without causing immunosuppression and, therefore, it does not interfere with CD4–mediated immune functions. It is active against HIV-1 resistant to all approved antiretroviral agents, and studies have not revealed cross-resistance with other agents.

Ibalizumab was evaluated in a clinical trial of 40 patients with MDR HIV-1 infection who had a viral load greater than 1,000 copies/mL and documented resistance to at least one drug in each of the NRTI, NNRTI, and PI classes. Fifty-three percent of the patients had been treated with 10 or more antiretroviral drugs. The primary efficacy endpoint was a significant decrease in the viral load (HIV-RNA), and 83% of the patients experienced this endpoint one week after the loading dose of ibalizumab was added to their failing antiretroviral regimen. At week 25 of treatment with ibalizumab in combination with other antiretroviral drugs, 43% of patients achieved virologic suppression (HIV-1 RNA less than 50 copies/mL). Treatment was discontinued in 13% of patients as a consequence of adverse events or death.

Tafenoquine succinate (Krintafel – GlaxoSmithKline) Antiparasitic Agent

2018 New Drug Comparison Rating (NDCR) =

Indication: For the radical cure (prevention of relapse) of *Plasmodium vivax* malaria in patients aged 16 years and older who are receiving appropriate antimalarial therapy for acute *P. vivax* infection; is NOT indicated for the treatment of acute *P. vivax* malaria

Comparable drug: Primaquine

Advantages:
--Is effective as a single-dose treatment (whereas primaquine is used in a 14-day course of treatment)

Disadvantages:
--May be more likely to cause psychiatric adverse events

Most important risks/adverse events: Hemolytic anemia (patients with glucose-6-phosphate dehydrogenase [G6PD] deficiency are at particular risk; is contraindicated in patients with G6PD deficiency or unknown G6PD status); pregnancy (is not recommended during pregnancy; women of reproductive potential should be advised to avoid pregnancy or use effective contraception for 3 months after the dose of tafenoquine; a woman with normal concentrations of G6PD could give birth to a G6PD-deficient infant); lactation (a G6PD-deficient infant could be at risk of hemolytic anemia from exposure through breast milk; is contraindicated in breastfeeding women when the infant is found to be G6PD-deficient or the G6PD status is unknown; women should be advised to not breastfeed for 3 months after the dose of tafenoquine); methemoglobinemia; hypersensitivity reactions (is contraindicated in patients with known hypersensitivity to any 8-aminoquinoline derivative); psychiatric effects (e.g., anxiety, insomnia; in patients with a psychiatric illness, anticipated benefit must be weighed against the risk of psychiatric adverse events); has a long half-life (approximately 15 days) and adverse events may be delayed in onset and/or duration; inhibits the activity of organic cation transporter-2 (OCT2) and multidrug and toxic extrusion (MATE) transporters (concentration and activity of substrates of these transporters [e.g., dofetilide, metformin] may be increased and concurrent use should be avoided)

Most common adverse events: Dizziness (8%), nausea (6%), vomiting (6%), headache (5%), decreased hemoglobin (5%)

Usual dosage: Single dose of 300 mg administered as two tablets taken together with food; should be coadministered on the first or second day of appropriate antimalarial therapy (e.g., chloroquine) for acute *P. vivax* malaria; tablets should be swallowed whole; if vomiting occurs within 1 hour of administration, a repeat dose should be given

Product: Film-coated tablets – 150 mg

Comments: Following a bite of an infected mosquito, *P. vivax* infects the blood and causes an acute malaria episode. It also has the ability to lie dormant in the liver from where it periodically reactivates to cause relapses of malaria. Most antimalarial drugs are active against the blood-stage of the parasite but are not very effective against the dormant forms in the liver. The 8-aminoquinoline derivative, primaquine, is the only previous antiparasitic agent to be approved to target the dormant liver stage to prevent relapse. Like primaquine, tafenoquine is an 8-aminoquinoline antimalarial agent. Its effectiveness was demonstrated in two clinical trials in patients positive for *P. vivax* who received a 3-day regimen of chloroquine to treat the acute infection in addition to a single dose of tafenoquine, an active control, or placebo. Patients were considered recurrence-free at 6 months if they demonstrated initial parasite clearance, took no subsequent antimalarial medication, and were confirmed parasite-free at the 6-month final assessment. In the largest study, recurrence-free efficacy occurred in 60% of the patients treated with chloroquine and tafenoquine, and in 26% of the patients treated with chloroquine and placebo. In patients in whom chloroquine/tafenoquine and chloroquine/primaquine regimens were compared, the efficacy rates at 6 months were generally similar (approximately 70%). The FDA has subsequently approved another tafenoquine product (Arakoda 100-mg tablets) that is indicated for the prophylaxis of malaria in a different dosage regimen.