New Drug Update 2017*

*Presentation by Daniel A. Hussar, Ph.D.
Remington Professor of Pharmacy
Philadelphia College of Pharmacy
University of the Sciences

Objectives:

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

1. Identify the indications and routes of administration of the new therapeutic agents.
2. Identify the important pharmacokinetic properties and the unique characteristics of the new drugs.
3. Identify the most important adverse events and precautions of the new drugs.
4. Compare the new drugs to the older therapeutic agents to which they are most similar in activity.
5. Identify information regarding the new drugs that should be communicated to patients.

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

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Lixisenatide (Adlyxin – Sanofi) Antidiabetic Agent

2016 New Drug Comparison Rating (NDCR) =

Indication: Administered subcutaneously as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Comparable drugs: Exenatide (Byetta), exenatide extended-release (Bydureon), liraglutide (Victoza), albiglutide (Tanzeum), dulaglutide (Trulicity)

Advantages:
--Labeling does not include boxed warning or contraindications regarding risk of thyroid C-cell tumors
--Less likely to cause injection site reactions (compared with albiglutide)

Disadvantages:
--Is less effective than liraglutide in reducing A1c concentrations
--Does not decrease (or increase) cardiovascular risks (compared with liraglutide that has been reported to reduce the risk of cardiac death and overall heart risks)
--Is administered more frequently (once a day compared with albiglutide, dulaglutide, and exenatide extended-release that are administered once a week)
--May be more likely to cause immunogenicity

Most important risks/adverse events: Pancreatitis (treatment should be discontinued if pancreatitis is suspected; other antidiabetic agents should be considered in patients with a history of pancreatitis); hypersensitivity reactions; hypoglycemia (when used concomitantly with insulin or an insulin secretagogue [e.g., a sulfonylurea]); acute kidney disease (renal function should be monitored in patients with renal impairment reporting severe adverse gastrointestinal reactions; not recommended in patients with end-stage renal disease); immunogenicity (development of antibodies may worsen glycemic control and increase risk of adverse events); slows gastric emptying (not recommended in patients with gastroparesis; may alter absorption and activity of concomitantly administered oral medications; medications such as antibiotics and acetaminophen should be administered 1 hour before lixisenatide; oral contraceptives should be administered at least 1 hour before or 11 hours after lixisenatide)

Most common adverse events: Nausea (25%), vomiting (10%), headache (9%), diarrhea (8%), dizziness (7%)

Usual dosage: Administered subcutaneously in the abdomen, thigh, or upper arm; initially, 10 mcg once a day within 1 hour before the first meal of the day for 14 days; on Day 15, the dosage should be increased to 20 mcg once a day; if a dose is missed, should be administered within 1 hour prior to the next meal

Products: Injection supplied in single-patient use pens containing 3 mL of solution; pens contain 50 mcg/mL and deliver 14 doses of 10 mcg, or 100 mcg/mL and deliver 14 doses of 20 mcg; (should be stored in a refrigerator prior to first use); (a combination product [Soliqua] that also includes insulin glargine has been subsequently approved)

Comments: Lixisenatide is the fifth glucagon-like peptide-1 (GLP-1) receptor agonist, joining exenatide (marketed initially in an immediate-release formulation [Byetta[and subsequently in an additional extended-release formulation [Bydureon]), liraglutide, albiglutide, and dulaglutide. Its effectiveness was demonstrated in 10 clinical trials that enrolled 5,400 patients with type 2 diabetes, in which it was used as monotherapy, and in combination with other antidiabetic agents including metformin, sulfonylureas, pioglitazone, and a basal insulin. Lixisenatide provided reductions in hemoglobin A1c and fasting plasma glucose concentrations. In an active-controlled study, it was noninferior to exenatide (twice a day) but provided less of an A1c reduction than exenatide. In a study in which lixisenatide (20 mcg once a day) was compared with liraglutide (1.8 mg once a day), the new drug was less effective in reducing A1c concentrations (-1.2% vs. -1.8%).

In a cardiovascular outcomes trial in patients with type 2 diabetes after a recent acute coronary syndrome event, the use of lixisenatide did not increase or decrease cardiovascular risks. The results of a recent study with liraglutide indicate a reduction in risk of cardiac death and overall heart risks. Unlike most other GLP-1 agonists, the labeling for lixisenatide does not include warnings or contraindications regarding a risk of thyroid C-cell tumors.

Patiromer sorbitex calcium (Veltassa – Relypsa) Agent for Hyperkalemia

2016 New Drug Comparison Rating (NDCR) =

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

Comparable drug: Sodium polystyrene sulfonate (e.g., SPS, Kayexalate)

Advantages:
--Less risk of serious gastrointestinal adverse events (e.g., intestinal necrosis)
--Less risk of sodium and fluid retention
--Is administered once a day (whereas sodium polystyrene sulfonate is administered multiple times a day in some patients)

Disadvantages:
--Rectal administration has not been evaluated (whereas sodium polystyrene sulfonate has been administered as an enema when oral administration is not feasible)
--Product should be refrigerated

Most important risks/adverse events: Worsening of gastrointestinal motility (should be avoided in patients with severe constipation or bowel obstruction or impaction, including abnormal post-operative bowel motility disorders); interactions with other oral medications (boxed warning; binds with many orally administered medications which may reduce their absorption and effectiveness; other oral medications should be administered at least 3 hours before or at least 3 hours after patiromer); hypomagnesemia (serum magnesium concentrations should be monitored)

Most common adverse events: Constipation (7%), diarrhea (5%), nausea (2%), abdominal discomfort (2%), flatulence (2%), hypomagnesemia (9%), hypokalemia (5%)

Usual dosage: Should be administered with food but should not be added to heated foods or liquids; recommended starting dosage – 8.4 grams once a day; dosage may be increased at 1-week or longer intervals, in increments of 8.4 grams, up to the maximum dosage of 25.2 grams once a day

Product: Powder for oral suspension; single-use packets – 8.4 grams, 16.8 grams, 25.2 grams (should be stored in a refrigerator; if it is stored at room temperature, must be used within 3 months of being taken out of the refrigerator); doses should be prepared immediately prior to administration; the contents of a packet should be emptied into a glass or cup containing about 1 ounce of water; the mixture should be stirred thoroughly and an additional 2 ounces of water should be added and thoroughly mixed; the powder does not dissolve and patients should be instructed to drink the mixture immediately

Comments: Hyperkalemia is characterized by a serum potassium concentration greater than 5.0 mEq/L. It is most often experienced by patients with kidney disease, heart failure, or diabetes, 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., valsartan), the direct renin inhibitor aliskiren (Tekturna), and aldosterone antagonists (spironolactone, eplerenone). The cation-exchange resin sodium polystyrene sulfonate has been used orally or as an enema in the treatment of hyperkalemia. However, it may cause serious gastrointestinal adverse events and sodium and fluid retention.

Patiromer sorbitex calcium consists of the active moiety, patiromer, a non-absorbed potassium-binding polymer, and a calcium-sorbitol counterion. When administered orally, the calcium-sorbitol counterion is exchanged for potassium that binds with patiromer in the lumen of the gastrointestinal tract. This exchange results in increased fecal potassium excretion and reduced serum potassium concentrations. Its effectiveness was evaluated in hyperkalemic patients with chronic kidney disease and/or type 2 diabetes who were taking at least one RAAS inhibitor. Within 4 weeks of initiation of treatment, most patients experienced a reduction in serum potassium

Brivaracetam (Briviact – UCB) Antiepileptic Drug

2016 New Drug Comparison Rating (NDCR) =

Indication: Administered orally or intravenously as adjunctive therapy in the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy

Comparable drug: Levetiracetam (e.g., Keppra, Keppra XR)

Advantages:
--Reduced seizure frequency in some patients in whom previous treatment did not provide adequate control

Disadvantages:
--Has not been directly compared with other antiepileptic drugs in clinical studies
--Labeled indications are more limited (levetiracetam is also indicated for adjunctive treatment of patients with myoclonic seizures, and primary generalized tonic-clonic seizures)
--Has not been evaluated in patients younger than 16 years of age (whereas levetiracetam is indicated for younger patients, the age of which is based on the indication [one month of age or older for patients with partial-onset seizures])
--Is administered twice a day (whereas the extended-release formulation of levetiracetam is administered once a day for patients with partial-onset seizures)
--Is included in Schedule V (whereas levetiracetam is not a controlled substance)

Most important risks/adverse events: Hypersensitivity reactions (bronchospasm, angioedema; treatment should be discontinued if such events occur, and use is contraindicated in patients known to be hypersensitive to the drug); suicidal behavior and ideation; psychiatric adverse events (e.g., psychotic symptoms, irritability, depression); neurological adverse events (somnolence, fatigue; patients should be cautioned not to drive or operate machinery until they have gained sufficient experience with the medication); included in Schedule V under the provisions of the Controlled Substances Act; should only be used during pregnancy if the anticipated benefit justifies the risk to the unborn child; is metabolized, in part, via the CYP2C19 metabolic pathway, and action may be increased in patients who are poor CYP2C19 metabolizers, or who are taking a CYP2C19 inhibitor concurrently; action may be reduced by the concurrent use of rifampin; caution must be exercised when used concurrently with carbamazepine and/or phenytoin

Most common adverse events: Somnolence/sedation (16%), dizziness (12%), fatigue (9%), nausea/vomiting (5%)

Usual dosage: Starting dosage – 50 mg twice a day; based on individual patient therapeutic response and tolerability, dosage may be reduced to 25 mg twice a day, or increased to 100 mg twice a day; in patients with any stage of hepatic impairment, the recommended starting dosage is 25 mg twice a day and the recommended maximum dosage is 75 mg twice a day; when rifampin is used concurrently, the dosage of brivaracetam should be increased to up to double the usual dosage; when oral administration is not feasible, may be administered intravenously over 2 to 15 minutes at the same dosage and same frequency as with oral administration (the experience with the intravenous use of the drug is limited to 4 consecutive days of treatment); when treatment is to be discontinued, the drug should be withdrawn gradually

Products: Tablets – 10 mg, 25 mg, 50 mg, 75 mg, 100 mg; oral solution – 10 mg/mL (may also be administered using a nasogastric tube or gastrostomy tube); single-dose vials – 50 mg/5 mL

Comments: Brivaracetam is an analog of levetiracetam and their effectiveness in the treatment of seizure disorders is thought to be due to their affinity for synaptic vesicle protein 2A in the brain. The effectiveness of brivaracetam in reducing the frequency of seizures was demonstrated in three placebo-controlled studies in patients who were also taking other antiepileptic drugs concomitantly. Levetiracetam was a concomitant medication in approximately 20% of the patients in two of the studies, and brivaracetam provided no added benefit in these patients. Brivaracetam and levetiracetam have not been directly compared in clinical studies.

Ocrelizumab (Ocrevus – Genentech) Agent for Multiple Sclerosis

2017 New Drug Comparison Rating (NDCR) =

Indication: Administered intravenously for the treatment of adult patients with relapsing or primary progressive forms of multiple sclerosis (MS)

Comparable drug: Interferon beta-1a (e.g., Rebif)

Advantages:
--Is the first drug to be shown to be effective in the treatment of primary progressive multiple sclerosis (PPMS)
--Is more effective than interferon beta-1a in the treatment of relapsing MS
--Has a unique mechanism of action (is a CD20-directed cytolytic antibody)
--Is administered less frequently (every 6 months compared with 3 times a week with interferon beta-1a)

Disadvantages:
--Is administered by intravenous infusion under the supervision of a health professional (whereas interferon beta-1a is self-administered subcutaneously or intramuscularly)
--Often causes infusion reactions
--More likely to be associated with occurrence of infections
--May be associated with an increased risk of malignancy

Most important risks/adverse events: Contraindicated in patients with active hepatitis B virus infection; infusion reactions (e.g., dermatological events, dyspnea, bronchospasm, hypotension; contraindicated in patients with a history of a life-threatening infusion reaction to the drug; patients should be observed during the infusion and for at least one hour following the completion of the infusion); infections (e.g., respiratory infections, herpes infections; however, in the clinical trials there were no reports of progressive multifocal leukoencephalopathy [PML] or reactivation of hepatitis B virus infection); use of live or live-attenuated vaccines during treatment is not recommended; increased risk of malignancies including breast cancer

Most common adverse events (and incidence in patients with PPMS): Upper respiratory tract infections (49%), infusion reactions (40%), skin infections (14%), lower respiratory tract infections (10%), cough (7%)

Usual dosage: Administered by intravenous infusion; initial dose – 300 mg over at least 2.5 hours, followed two weeks later by a second 300 mg dose; subsequent doses – 600 mg as a single infusion over at least 3.5 hours every 6 months; patients should be pre-medicated with 100 mg of methylprednisolone (or an equivalent corticosteroid) intravenously approximately 30 minutes prior to each infusion and with an antihistamine (e.g., diphenyhdramine) approximately 30-60 minutes prior to each infusion

Product: Injection – single-dose vials containing 300 mg/10 mL (should be stored in a refrigerator); intended dose should be withdrawn and diluted into an infusion bag containing 0.9% Sodium Chloride Injection to a final drug concentration of approximately 1.2 mg/mL (i.e., 300 mg in 250 mL, 600 mg in 500 mL)

Comments: Multiple sclerosis affects approximately 400,000 people in the United States. Relapsing MS is the most common form of the disease in which patients experience relapses that are followed by remissions of varying duration. Approximately 15% of patients with MS have primary progressive disease (PPMS) that is characterized by steadily worsening function sometimes without early relapses and remissions. The disease-modifying drugs for MS (i.e, interferon beta [e.g., Rebif, Plegridy, Avonex], glatiramer acetate [e.g., Copaxone], natalizumab [Tysabri], alemtuzumab [Lemtrada], fingolimod [Gilenya], teriflunomide [Aubagio], dimethyl fumarate [Tecfidera]) are of value in reducing the frequency and severity of relapses, but are of limited benefit in more severe disease.

Ocrelizumab is a humanized monoclonal antibody that, like the chimeric monoclonal antibody rituximab (Rituxan), is directed against CD20-expressing B-cells. In two studies in patients with relapsing MS conducted over 96 weeks, it was more effective than interferon beta-1a (Rebif) in reducing annualized relapse rate and in increasing the number of patients who were relapse-free. In a placebo-controlled study in patients with PPMS for 120 weeks, it lengthened the time to worsening of disability and is the first drug to be demonstrated to be effective for PPMS.

Valbenazine tosylate (Ingrezza – Neuroscience) Agent for Tardive Dyskinesia

2017 New Drug Comparison Rating (NDCR) =

Indication: Treatment of adults with tardive dyskinesia

Comparable drug: None (although valbenazine is the first drug to be approved for the treatment of tardive dyskinesia, its properties and actions are similar to those of tetrabenazine [Xenazine])

Advantages:
--Is the first drug to be demonstrated to be effective for the treatment of tardive dyskinesia

Limitations:
--May prolong the QT interval and increase the risk of arrhythmias
--May interact with numerous other medications

Most important risks/adverse events: QT prolongation (increased risk of arrhythmias; should be avoided in patients with congenital long QT syndrome or arrhythmias associated with a long QT interval; risk is increased in patients who are CYP2D6 poor metabolizers, and in patients who are also taking a strong CYP3A4 inhibitor [e.g., clarithromycin] or strong CYP2D6 inhibitor [e.g., paroxetine, quinidine], and a reduction in dosage will usually be necessary); somnolence (patients should be advised to not perform activities requiring mental alertness until they know how the drug affects them); may cause harm to the unborn child if used during pregnancy; women should not breastfeed during treatment and for 5 days after the final dose; use is not recommended in patients with severe renal impairment; in patients with moderate or severe hepatic impairment, should be used in a reduced dosage; should not be used concurrently in patients treated with a monoamine oxidase inhibitor [risk of serotonin syndrome may be increased] or a strong CYP3A4 inducer (e.g., carbamazepine, St. John's wort); may increase digoxin concentrations

Most common adverse events: Somnolence (11%), anticholinergic effects (5%; e.g., dry mouth, blurred vision)

Usual dosage: Initial dosage – 40 mg once a day; after one week, the dosage should be increased to the recommended dosage of 80 mg once a day; the 40 mg once daily dosage should be continued in patients with moderate or severe hepatic impairment, and in patients treated concurrently with a strong CYP3A4 inhibitor; a reduction in dosage (i.e., 40 mg once daily) should be considered in patients who are known to be CYP2D6 poor metabolizers and in patients treated concurrently with a strong CYP2D6 inhibitor

Product: Capsules – 40 mg (valbenazine free base provided in 73 mg of valbenazine tosylate)

Comments: Tardive dyskinesia is a neurological disorder that is characterized by repetitive voluntary movements including rapid eye blinking, grimacing, smacking the lips, and rapid movement of the arms and legs. Some individuals may experience difficulty in speaking, swallowing, and breathing, and the problem can be disabling and further stigmatizing for patients with mental illness. Tardive dyskinesia occurs most often in patients treated for long periods with antipsychotic medications, and may develop during the period of treatment or even after the treatment is discontinued. The long-term use of metoclopramide for gastrointestinal conditions, as well as certain other medications, has also been associated with the occurrence of tardive dyskinesia.

Valbenazine is the first drug to be approved for the treatment of tardive dyskinesia, and represents an important advance in the treatment of this disorder. Its therapeutic effect is thought to be mediated through the reversible inhibition of vesicular monoamine transporter 2, a transporter that regulates monoamine (e.g., dopamine) uptake from the cytoplasm to the synaptic vesicle for storage and release. The actions of valbenazine are similar to those of tetrabenazine, a drug that was initially marketed in 2008 as the first drug for the treatment of chorea associated with Huntington's disease, a rare inherited neurological disorder. Both valbenazine and tetrabenazine are converted to the active metabolite, alpha-dihydrotetrabenazine. The effectiveness of valbenazine was demonstrated in a placebo-controlled study in 234 patients, of whom approximately 85% were being treated with antipsychotic agents. At the end of Week 6 the patients treated with valbenazine experienced improvement in the severity of abnormal involuntary movements. The benefit continued for patients who participated in the study through Week 48. When treatment was discontinued, dyskinesias appeared to return toward baseline.

Eteplirsen (Exondys 51 – Sarepta) Agent for Muscular Dystrophy

2016 New Drug Comparison Rating (NDCR) =

Indication: Administered intravenously for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping

Comparable drug: None

Advantages:
--Is the first drug to be approved for the treatment of DMD
--Has been reported to increase dystrophin concentrations

Disadvantages:
--A clinical benefit has not been established

Most important risks/adverse events: None

Most common adverse events: Balance disorder (38%), vomiting (38%), contact dermatitis (25%)

Usual dosage: Administered by intravenous infusion over a period of 35 to 60 minutes; 30 mg/kg once a week; application of a topical anesthetic cream to the infusion site prior to administration may be considered; if a dose is missed, it may be administered as soon as possible after the scheduled time

Product: Single-dose vials (50 mg/mL) – 100 mg/2 mL, 500 mg/10 mL (should be protected from light and stored in a refrigerator); vial should be gently inverted 2 or 3 times but should not be shaken; volume of injection needed to provide the calculated dose should be diluted in 0.9% Sodium Chloride Injection to a total volume of 100 – 150 mL

Comments: Muscular dystrophy is a group of disorders that is caused by mutations on the X chromosome. It is a rare genetic degenerative neuromuscular disorder that is associated with a deficiency or defect of dystrophin, a protein that is essential for building and repairing muscle. Duchenne muscular dystrophy (DMD) is the most common variant in which dystrophin is almost totally absent. It almost always affects boys and is characterized by a progressive loss of muscle mass and strength. Initial symptoms are usually evident between three and five years of age, and worsen over time. Patients often require use of a wheelchair by their early teens, and life-threatening respiratory and heart conditions occur as the disease worsens. Death often occurs before the age of 30.

Certain genetic mutations in DMD involve the deletion of exons, which interrupt proper translation of the genetic code into protein. Eteplirsen is an antisense oligonucleotide that is designed to bind to exon 51 of dystrophin pre-messenger ribonucleic acid (pre-mRNA), resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 51 skipping. Exon skipping is intended to allow for production of an internally truncated dystrophin protein. Approximately 13% of patients with DMD have the gene mutation that is amenable to exon 51 skipping. The approval of eteplirsen was based on the surrogate endpoint of an increase in dystrophin in skeletal muscle that was observed in some patients. The increased dystrophin production is considered to be a reasonably likely predictor of clinical benefit in patients with DMD with a gene mutation amenable to exon 51 skipping. The primary study in which eteplirsen was evaluated included a 6-minute walk test as a clinical outcome measure, However, there was not a significant difference in the distance walked in 6 minutes between patients treated with eteplirsen and those receiving placebo, and the drug was approved under the accelerated approval pathway that requires additional study to confirm clinical benefit.

Nusinersen (Spinraza – Biogen) Agent for Spinal Muscular Atrophy

2016 New Drug Comparison Rating (NDCR) =

Indication: Administered intrathecally for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients

Comparable drug: None

Advantages:
--Is the first drug to be demonstrated to be effective for the treatment of patients with spinal muscular atrophy

Limitations:
--Must be administered by intrathecal injection

Most important risks/adverse events: Thrombocytopenia and coagulation abnormalities (platelet count, prothrombin time, and activated partial thromboplastin time should be determined at baseline, prior to each dose, and as clinically needed); renal toxicity (quantitative spot urine protein testing [preferably using a first morning urine specimen] should be conducted at baseline and prior to each dose)

Most common adverse events: Lower respiratory infection (43%), upper respiratory infection (39%), constipation (30%)

Usual dosage: Prior to administration, 5 mL of cerebrospinal fluid should be removed; administered as an intrathecal bolus injection over 1 to 3 minutes using a spinal anesthesia needle; 12 mg (5 mL) per administration, and treatment is initiated with four loading doses; the first three loading doses should be administered at 14-day intervals, and the fourth loading dose should be administered 30 days after the third dose; a maintenance dose should be administered every 4 months thereafter

Product: Single-dose vials – 12 mg/5 mL (should be stored in their cartons in a refrigerator); should be warmed to room temperature prior to administration

Comments: Spinal muscular atrophy (SMA) is a rare but often fatal genetic disease that affects muscle strength and movement. It is the most common genetic cause of death in infants, but can affect people at any age. SMA is characterized by a loss of motor neurons in the spinal cord and lower brain stem, resulting in progressive and debilitating muscular atrophy and weakness. Individuals with the most severe type of disease (Type 1 SMA) can become paralyzed and experience difficulty in breathing, swallowing, and other basic functions. Survival motor neuron (SMN) protein is essential for the maintenance of motor neurons. Patients with SMA have a defect in, or loss of, the SMN1 gene and do not produce enough SMN protein. The severity of the disease correlates with the amount of SMN protein.

Nusinersen is an antisense oligonucleotide that is designed to treat SMA caused by mutations in chromosome 5q that leads to SMN protein deficiency. It is thought to increase exon 7 inclusion in SMN2 messenger ribonucleic acid (mRNA) transcripts and increase the production of full-length SMN protein. It is the first drug to be approved for the treatment of patients with SMA, and represents an important advance. The effectiveness of nusinersen was evaluated in a sham-procedure clinical trial in 121 patients with infantile-onset (most likely to develop Type 1) SMA, in which two-thirds of the patients received the drug and one-third underwent a sham procedure (a pin prick) without the injection of a drug. The trial assessed the extent of improvement in motor milestones such as head control, sitting, ability to kick in the supine position, rolling, crawling, standing, and walking. In a group of 82 of these patients who were eligible for inclusion in an interim analysis, 40% of those treated with nusinersen achieved improvement in motor milestones, whereas none of the control patients did. Additionally, a smaller number of patients treated with the new drug died (23%) compared to untreated patients (43%).

Sugammadex sodium (Bridion – Merck) Muscle Relaxant Reversal Agent

2016 New Drug Comparison Rating (NDCR) =

Indication: For intravenous administration for the treatment of neuromuscular blockade induced by rocuronium bromide and vecuronium bromide in adults undergoing surgery

Comparable drug: Neostigmine (e.g., Bloxiverz)

Advantages:
--Has a faster onset of action and provides a faster recovery from neuromuscular blockade
--Is effective in reversing deep neuromuscular blockade (whereas neostigmine is less likely to be effective)
--Has a unique mechanism of action (forms a complex with rocuronium and vecuronium and reduces their binding to cholinergic receptors)
--May be less likely to cause certain adverse events (e.g., gastrointestinal effects)

Disadvantages:
--May be more likely to cause hypersensitivity reactions
--Labeled indications are more limited (whereas the indications for neostigmine include reversal of the effects of any of the nondepolarizing neuromuscular blocking agents)
--Has not been evaluated in pediatric patients (whereas neostigmine is indicated in patients as young as neonates)

Most important risks/adverse events: Hypersensitivity reactions including anaphylaxis; bradycardia (an anticholinergic agent should be administered if clinically significant bradycardia is observed); is eliminated in unchanged form in the urine and use is not recommended in patients with severe renal impairment; exhibits a high binding affinity for steroidal agents (if an oral contraceptive is taken on the same day, an additional nonhormonal contraceptive method should be used for the next 7 days; if a non-oral hormonal contraceptive is being used, an additional contraceptive method should be used for the next 7 days); toremifene (Fareston) may bind with sugammadex and delay the reversal of neuromuscular blockade; may increase coagulation parameters (e.g., INR)

Most common adverse events: Pain (52%), nausea (26%), vomiting (12%), headache (5%), hypotension (5%) – incidence of these effects is generally similar in patients who received placebo

Usual dosage: Administered intravenously as a single bolus injection over 10 seconds into the IV line of a running infusion with a compatible solution (e.g., 0.9% Sodium chloride); 2 mg/kg in patients with moderate neuromuscular blockade induced by rocuronium or vecuronium, or 4 mg/kg in patients with deep blockade; a dosage of 16 mg/kg may be used if there is a clinical need to reverse rocuronium-induced neuromuscular blockade soon (approximately 3 minutes) after administration of a single dose of 1.2 mg/kg of rocuronium

Products: Single-use vials – 200 mg/2 mL, 500 mg/5 mL

Comments: Sugammadex is a modified gamma cyclodextrin that forms a complex with rocuronium and vecuronium, and reduces the binding of these agents to the nicotinic cholinergic receptors in the neuromuscular junction. It has a rapid onset of action and provides greater flexibility than neostigmine in reversing the effect of rocuronium and vecuronium when needed. Its effectiveness was evaluated in two studies in which it was compared with neostigmine. In patients with moderate neuromuscular blockade, the median recovery times with sugammadex (2 mg/kg) in patients treated with rocuronium and vecuronium were 1.4 minutes and 2.1 minutes, respectively, compared with median recovery times with neostigmine (50 mcg/kg) of 21.5 and 29 minutes, respectively. In patients with deep neuromuscular blockade, the median recovery times with sugammadex (4 mg/kg) with rocuronium and vecuronium were 2.7 and 3.3 minutes, respectively. Although neostigmine was not expected to reverse this greater depth of blockade, it was used in some patients and the recovery time was much longer. In another study, a higher dosage of sugammadex (16 mg/kg) was demonstrated to reverse the neuromuscular blockade induced by a dose of 1.2 mg/kg of rocuronium that was administered 3 minutes earlier. The median recovery time was 4.2 minutes, compared with the median spontaneous (i.e., without a reversal agent) recovery time of 7.1 minutes with the depolarizing neuromuscular blocking agent succinylcholine.

Plecanatide (Trulance – Synergy) Agent for Constipation

2017 New Drug Comparison Rating (NDCR) =

Indication: Treatment of chronic idiopathic constipation (CIC) in adults

Comparable drug: Linaclotide (Linzess)

Advantages:
--May be administered without regard to food (whereas linaclotide should be administered on an empty stomach at least 30 minutes prior to the first meal of the day)

Disadvantages:
--Labeled indications are more limited (linaclotide is also indicated for the treatment of irritable bowel syndrome with constipation)

Most important risks/adverse events: Risk of serious dehydration in pediatric patients (boxed warning; contraindicated in patients less than 6 years of age, and use should be avoided in patients 6 years to less than 18 years of age); contraindicated in patients with known or suspected mechanical gastrointestinal obstruction; severe diarrhea (if experienced, treatment should be suspended and the patient rehydrated)

Most common adverse events: Diarrhea (5%)

Usual dosage: 3 mg once a day; tablets should be swallowed whole; for patients with swallowing difficulties, the tablets may be crushed and administered orally either in applesauce or with water, or administered with water via a nasogastric or gastric feeding tube; product labeling should be consulted for the specific preparation and administration instructions

Products: Tablets – 3 mg; should be dispensed in the original bottle and not repackaged or subdivided; should be protected from moisture and the desiccant should not be removed from the bottle; also supplied in unit dose blister packs

Comments: Individuals who experience persistent constipation (i.e., for more than 6 months) for which there is no apparent explanation (e.g., obstruction, use of medications such as opioids) are diagnosed as having chronic idiopathic constipation (CIC). CIC does not typically respond to standard treatment such as laxatives. Medications with a labeled indication for CIC include linaclotide and lubiprostone (Amitiza).

Plecanatide is a 16-amino acid peptide with properties that are most similar to those of linaclotide. Both agents act as guanylate cyclase-C (GC-C) agonists, and they and their active metabolites bind to GC-C and act locally on the luminal surface of the intestinal epithelium. Activation of GC-C results in an increase in both intracellular and extracellular concentrations of cyclic guanosine monophosphate (cGMP). Elevation of intracellular cGMP stimulates secretion of chloride and bicarbonate into the intestinal lumen, resulting in increased intestinal fluid and accelerated transit. A change in stool consistency occurs, and intestinal pain may be reduced.

The effectiveness of plecanatide was demonstrated in two 12-week placebo-controlled studies. The primary endpoint was defined as a patient who had at least 3 complete spontaneous bowel movements (CSBMs) in a given week and an increase of at least 1 CSBM from baseline in the same week for at least 9 weeks out of the 12-week treatment period and at least 3 of the last 4 weeks of the study. There was a 21% responder rate in both studies in patients treated with plecanatide, compared with 10% and 13% of the patients receiving placebo. Improvements in the frequency of CSBMs/week were seen as early as week 1, and improvements in stool frequency and consistency and straining were also experienced. Plecanatide is minimally absorbed and systemic availability is negligible.

Crisaborole (Eucrisa – Pfizer) Agent for Atopic Dermatitis

2017 New Drug Comparison Rating (NDCR) =

Indication: Applied topically for the treatment of mild to moderate atopic dermatitis in patients 2 years of age and older

Comparable drugs: Topical corticosteroids (e.g., hydrocortisone, triamcinolone)

Advantages:
--May be more effective in some patients
--Has a unique mechanism of action (phosphodiesterase type 4 inhibition)
--May be less likely to cause systemic adverse events

Disadvantages:
--Has not been directly compared with other drugs in clinical studies
--Labeled indications are more limited (topical corticosteroids have numerous other dermatologic indications)

Most important risks/adverse events: Hypersensitivity reactions (should be discontinued if such events occur)

Most common adverse events: Application site pain (4%)

Usual dosage: Applied topically twice a day to the affected areas

Product: Ointment – 2%

Comments: Atopic dermatitis is the most common type of eczema and is a chronic inflammatory skin disease that typically begins in childhood and can last through adulthood. It is caused by a combination of genetic, immune, and environmental factors, and may be characterized by red, scaly lesions, pruritus, inflammation, cracking, exudation, and, eventually, coarsening and thickening of the skin. Approximately 90% of patients have the mild to moderate form of the condition. The use of moisturizers (e.g., Aquaphor) and emollients may relieve the symptoms. For patients who do not experience adequate benefit from these nonpharmacologic products, a low-potency topical corticosteroid (e.g., hydrocortisone) is often effective in the treatment of mild atopic dermatitis, and a medium-potency (e.g., triamcinolone) or high potency (e.g., fluocinonide) topical corticosteroid is typically used in the treatment of patients with moderate to severe disease. The topical calcineurin inhibitors tacrolimus (Prograf) and pimecrolimus (Elidel) are indicated as second-line therapy for the treatment of atopic dermatitis in non-immunocompromised patients who have not responded adequately to other topical prescription treatments, or when those treatments are not advisable.

Crisaborole is a PDE4 inhibitor that, by increasing concentrations of cyclic adenosine monophosphate (cAMP), may suppress the production of proinflammatory cytokines. Its effectiveness was evaluated in two vehicle-controlled studies in which Investigator's Static Global Assessment (ISGA), based on erythema, induration/population, and oozing/crusting on a severity scale of 0 to 4, was determined at baseline and on the day following completion of the 28-day course of twice-daily treatment. Success was defined as an ISGA grade of Clear (score of 0) or Almost Clear (score of 1) with a 2-grade or greater improvement from baseline. Patients treated with crisaborole achieved a greater response with successful results experienced in 33% and 31% of the patients in the two studies, compared with 25% and 18% of the patients treated with the vehicle.

Dupilumab (Dupixent – Regeneron; Sanofi) Agent for Atopic Dermatitis

2017 New Drug Comparison Rating (NDCR) =

Indication: Administered subcutaneously for the treatment of adult patients with moderate to severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable; may be used with or without topical corticosteroids; topical calcineurin inhibitors (i.e., tacrolimus, pimecrolimus) may be used but should be reserved for problem areas only, such as the face, neck, intertriginous and genital areas

Comparable drugs: Topical corticosteroids (e.g., triamcinolone, fluocinonide)

Advantages:
--Is more effective in many patients
--Has a unique mechanism of action (is an interleukin-4 [IL-4] receptor alpha antagonist)
--Is less likely to cause adverse events
--Is administered less frequently (once every two weeks)

Disadvantages:
--Has not been directly compared with topical corticosteroids in clinical studies
--Has not yet been evaluated in pediatric patients
--Is administered subcutaneously (whereas corticosteroids are applied topically)

Most important risks/adverse events: Hypersensitivity reactions (should be discontinued if clinically important events occur); conjunctivitis and keratitis; comorbid asthma (patients with asthma should be advised not to stop or adjust their asthma treatment without consultation with their physician); use of live vaccines should be avoided during period of treatment

Most common adverse events: Injection site reactions (10%), conjunctivitis (10%), oral herpes (4%; e.g., cold sores in the mouth or on the lips), other herpes simplex virus infections (2%)

Usual dosage: Administered subcutaneously; 600 mg in an initial dose administered as two 300 mg injections at different injection sites, followed by 300 mg every other week; if a dose is missed, the patient should administer the injection within 7 days of the missed dose and then resume the original schedule

Product: Injection in single-dose prefilled syringes – 300 mg/2 mL (should be stored in a refrigerator)

Comments: Atopic dermatitis is the most common type of eczema and is a chronic inflammatory skin disease that typically begins in childhood and can last through adulthood. Approximately 90% of patients have the mild to moderate form of the condition. Moderate to severe disease is often treated with a medium-potency (e.g., triamcinolone) or high-potency (e.g., fluocinonide) topical corticosteroid. The topical calcineurin inhibitors tacrolimus (Prograf) and pimecrolimus (Elidel) are indicated as second-line therapy for the treatment of atopic dermatitis in non-immunocompromised patients who have not responded adequately to other topical prescription therapies, or when those treatments are not advisable.

Dupilumab is a human monoclonal antibody that is designated as an interleukin-4 (IL-4) receptor alpha antagonist. It inhibits IL-4 and IL-13 signaling by specifically binding to the IL-4R alpha subunit that is shared by the IL-4 and IL-13 receptor complexes, and inhibits IL-4 and IL-13 cytokine-induced responses, including the release of proinflammatory cytokines, chemokines, and IgE. The effectiveness of dupilumab was established in three placebo-controlled clinical trials in patients with moderate to severe atopic dermatitis that was not adequately controlled with topical medications. The primary endpoint was the change from baseline to Week 16 in the Investigator's Global Assessment score, with success defined as a grade of Clear (score of 0) or Almost Clear (score of 1) with a 2-grade or greater improvement from baseline. Patients treated with the new drug achieved a greater response, with successful results experienced in 38%, 36%, and 39% of the patients in the three studies, compared with 10%, 9%, and 12% of the patients treated with placebo. Other endpoints in which dupilumab provided a greater response were the Eczema Area and Severity Index and a reduction in itch.

Reslizumab (Cinqair – Teva) Antiasthmatic Agent

2016 New Drug Comparison Rating (NDCR) =

Indication: Administered intravenously for the add-on maintenance treatment of patients with severe asthma aged 18 years and older, and with an eosinophilic phenotype;
Is not indicated for the treatment of other eosinophilic conditions, or for the relief of acute bronchospasm or status asthmaticus

Comparable drug: Mepolizumab (Nucala)

Advantages:
--Less likely to cause headache, injection site reactions, and back pain

Disadvantages:
--May be more likely to cause anaphylaxis (boxed warning)
--Malignant neoplasms were infrequently reported in clinical studies
--Is administered intravenously (whereas mepolizumab is administered subcutaneously)
--Less convenient administration for patients (doses must be prepared and administered by a healthcare professional)

Most important risks/adverse events: Anaphylaxis (boxed warning; contraindicated in patients with known hypersensitivity; should be administered in a healthcare setting by a healthcare professional who is prepared to manage anaphylaxis; patients should be observed for an appropriate period of time following administration; if severe systemic reactions, including anaphylaxis, occur, administration of the drug should be stopped immediately); malignant neoplasms were experienced by some patients (0.6% compared with 0.3% of those receiving placebo); reduction in dosage or discontinuation of systemic or inhaled corticosteroids (to avoid systemic withdrawal symptoms and/or unmasking of conditions previously suppressed by systemic corticosteroid therapy, if appropriate, dosage should be reduced gradually under the supervision of a physician); parasitic (helminth) infections (should be treated prior to starting reslizumab; if a helminth infection develops during treatment and does not respond to anti-helminth treatment, reslizumab should be discontinued until the infection resolves)

Most common adverse events: Oropharyngeal pain (3%), myalgia (1%), creatine phosphokinase elevations (14%)

Usual dosage: Administered as an intravenous infusion, and should not be used as an intravenous push or bolus; 3 mg/kg once every 4 weeks, infused over a period of 20-50 minutes

Product: Single-use vials – 100 mg/10 mL (should be stored in a refrigerator); doses of the drug should be prepared and administered by a healthcare professional; volume of solution needed to provide the dose should be withdrawn from the vial and slowly added to an infusion bag containing 50 mL of 0.9% Sodium Chloride Injection

Comments: Multiple cell types, including eosinophils, and mediators (e.g., cytokines) are involved in the inflammatory process that occurs in the airways of the lungs. Interleukin-5 (IL-5) is the major cytokine that is responsible for the growth and differentiation, recruitment, activation, and survival of neutrophils. Reslizumab is the second IL-5 antagonist to be approved, joining mepolizumab, for the add-on treatment of patients with severe asthma and with an eosinophilic phenotype. The effectiveness of reslizumab was demonstrated in four placebo-controlled studies in patients with severe asthma who were being treated with other antiasthmatic medications. Two of the studies continued for 52 weeks and reslizumab provided a significant reduction in the rate of asthma exacerbations, including those that required the use of a systemic corticosteroid as well as those that required hospitalization or an emergency room visit. The use of reslizumab resulted in a significant improvement in lung function as reflected by increases in forced expiratory volume in 1 second (FEV_1) determinations.

The labeling for reslizumab notes that its effectiveness and safety in patients less than 18 years of age have not been established. Although 39 patients in the clinical studies were in the 12-17 years age range, the asthma exacerbation rate was actually higher in these patients than in those receiving placebo. The indications for mepolizumab include patients as young as 12 years of age.

Selexipag (Uptravi – Actelion) Agent for Pulmonary Arterial Hypertension

2016 New Drug Comparison Rating (NDCR) =

Indication: Treatment of pulmonary arterial hypertension (PAH, WHO Group 1) to delay disease progression and reduce the risk of hospitalization for PAH

Comparable drug: Treprostinil (Orenitram)

Advantages:
--Has a selective action for prostacyclin IP receptors that may reduce the possibility of certain adverse events
--May be used (in reduced dosage) in patients with moderate hepatic impairment, but use should be avoided in patients with severe hepatic impairment (whereas oral treprostinil should be avoided in patients with moderate hepatic impairment and is contraindicated in patients with severe hepatic impairment)
--May be less likely to cause hypotension in patients taking antihypertensive drugs, or to increase the risk of bleeding in patients treated with an anticoagulant

Disadvantages:
--Is available for use by just one route of administration (oral; whereas treprostinil is also available in formulations that may be administered intravenously, subcutaneously, or by inhalation)

Most important risks/adverse events: Pulmonary veno-occlusive disease (use should be discontinued); use should be avoided in patients with severe hepatic impairment; action may be increased by a strong CYP2C8 inhibitor (e.g., gemfibrozil) and concurrent use should be avoided; should not be used by a nursing mother

Most common adverse events: Headache (65%), diarrhea (42%), nausea (33%), jaw pain (26%), vomiting (18%), pain in extremity (17%), myalgia (16%), flushing (12%), arthralgia (11%), rash (11%)

Usual dosage: Tolerability may be improved when administered with food; initially – 200 mcg twice a day; dosage should be increased in increments of 200 mcg twice a day, usually at weekly intervals, to the highest tolerated dose up to 1600 mcg twice a day; if a dose is missed, patients should take the missed dose as soon as possible unless the next dose is within the next 6 hours; if treatment is missed for 3 days or more, the medication should be restarted at a lower dosage and then retitrated; in patients with moderate hepatic impairment the initial dosage is 200 mcg once a day that may be increased in increments of 200 mcg once a day at weekly intervals, as tolerated

Products: Tablets – 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1000 mcg, 1200 mcg, 1400 mcg, 1600 mcg; tablets should not be split, crushed, or chewed

Comments: Pulmonary arterial hypertension (PAH) is a chronic disease that is associated with abnormally high blood pressure in the arteries that connect the heart to the lungs. It makes the right side of the heart work harder than normal, resulting in shortness of breath and limitations on exercise ability, and more serious and debilitating complications that may result in death or a need for lung transplantation. The medications that have been demonstrated to be effective in the treatment of patients with PAH include the phosphodiesterase-5 (PDE5) inhibitors sildenafil (Revatio) and tadalafil (Adcirca), the endothelin receptor antagonists bosentan (Tracleer), ambrisentan (Letairis), and macitentan (Opsumit), and the soluble guanylate cyclase stimulator riociguat (Adempas), all of which are administered orally. In addition, the prostacyclin agonists epoprostenol (e.g., Flolan, Veletri for intravenous use), iloprost (Ventavis for inhalation), and treprostinil (Remodulin for subcutaneous or intravenous use; Tyvaso for inhalation; Orenitram for oral use) have been approved for the treatment of patients with PAH. Treatment is usually initiated with an orally-administered agent.

Selexipag is a selective non-prostanoid IP prostacyclin receptor agonist that is structurally distinct from prostacyclin. Unlike the other prostacyclin agonists, selexipag and its active metabolite, that is 37-fold as potent as the parent drug, have selective activity for the IP receptor versus other prostanoid receptors. The effectiveness of selexipag was evaluated in a placebo-controlled trial in which treatment with the new drug resulted in a 40% reduction of the occurrence of primary endpoint events compared to placebo. The beneficial effect was primarily attributable to a reduction in hospitalization for PAH and a reduction in other disease worsening events.

Obeticholic acid (Ocaliva – Intercept) Agent for Primary Biliary Cholangitis

2016 New Drug Comparison Rating (NDCR) =

Indication: Treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adult patients with an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA

Comparable drug: Ursodeoxycholic acid (e.g., URSO)

Advantages:
--May increase the effectiveness of treatment of PBC
--Has a unique mechanism of action (is a farnesoid X receptor [FXR] agonist)
--Is administered once a day (whereas UDCA is administered two to four times a day)

Disadvantages:
--An improvement in disease-related symptoms and survival has not yet been demonstrated

Most important risks/adverse events: Contraindicated in patients with biliary obstruction; liver-related adverse events (patients should be monitored for elevations in liver biochemical tests and liver-related adverse events[e.g., jaundice, worsening ascites]; dosage should be reduced in patients with moderate or severe hepatic impairment); severe pruritus (management strategies include the use of a bile acid binding resin [cholestyramine, colestipol, colesevelam], an antihistamine, dosage reduction, and/or temporary interruption of treatment); reduction of high density lipoprotein-cholesterol (serum lipid concentrations should be monitored); concurrent use with a bile acid binding resin should be separated by an interval of at least 4 hours; may increase the action of CYP1A2 substrates with a narrow therapeutic index (e.g., theophylline, tizanidine); may reduce the action of warfarin (INR should be monitored)

Most common adverse events: Pruritus (56%), fatigue (19%), abdominal pain and discomfort (19%), rash (7%), oropharyngeal pain (7%), dizziness (7%), constipation (7%), arthralgia (6%), thyroid function abnormality (6%), eczema (6%)

Usual dosage: Initially, 5 mg once a day in patients who have not achieved an adequate biochemical response to an appropriate dosage of UDCA for at least one year or are intolerant of UDCA; if an adequate reduction in alkaline phosphatase (ALP) and/or total bilirubin has not been achieved after 3 months of treatment, and the patient is tolerating the drug, the dosage should be increased to 10 mg once a day, which is also the maximum dosage; the product labeling should be consulted for the recommendations for dosage reduction in patients with moderate or severe hepatic impairment, and in patients who experience intolerable pruritus

Products: Tablets – 5 mg, 10 mg

Comments: Primary biliary cholangitis (PBC), formerly known as primary biliary cirrhosis, is a rare and chronic disease that is caused by autoimmune destruction of the bile ducts. The bile ducts transport bile acids out of the liver and, when they become inflamed and damaged, bile accumulates and causes damage to liver cells, As the condition worsens, fibrosis, cirrhosis, and liver failure may occur, and death can result unless the patient receives a liver transplant. Obeticholic acid is the second drug to be approved for the treatment of PBC, joining UDCA, and it acts as an agonist for farnesoid X receptor (FXR) that is found in the nucleus of cells in the liver and intestine. FXR is a key regulator of bile acid, inflammatory, fibrotic, and metabolic pathways. By activating FXR, obeticholic acid decreases the intracellular hepatocyte concentrations of bile acids by suppressing synthesis from cholesterol, as well as by increasing transport of bile acids out of the hepatocytes.

Obeticholic acid was approved under the provisions of the FDA's accelerated approval program based on data that it demonstrated an effect on a surrogate endpoint (reduction of ALP) that is reasonably likely to predict clinical benefit. The primary endpoint of the clinical study was a composite of three criteria: ALP less than 1.67 times the upper limit of normal (ULN); total bilirubin less than or equal to ULN; and an ALP decrease of at least 15%. At month 12, 47% of the patients treated with obeticholic acid, with or without UDCA, achieved the primary composite endpoint, compared with 10% of those receiving placebo.

Defibrotide sodium (Defitelio – Jazz) Profibrinolytic Agent

2016 New Drug Comparison Rating (NDCR) =

Indication: Administered intravenously for the treatment of adult and pediatric patients with hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), with renal or pulmonary dysfunction following hematopoietic stem cell transplantation (HSCT)

Comparable drugs: None

Advantages:
--Is the first drug to be approved for the treatment of hepatic VOD with renal or pulmonary dysfunction following HSCT
--May prolong survival of some patients with certain blood or bone marrow cancers

Limitations:
--No reversal agent available if its profibrinolytic action is excessive

Most important risks/adverse events: Hemorrhage (use should not be initiated in patients with active bleeding, and all patients should be monitored for signs of bleeding; concurrent use with a systemic anticoagulant or fibrinolytic therapy [e.g., alteplase] is contraindicated; treatment with an anticoagulant or a fibrinolytic agent should be discontinued prior to initiating therapy); hypersensitivity reactions

Most common adverse events: Hypotension (37%), diarrhea (24%), vomiting (18%), nausea (16%), epistaxis (14%), pulmonary alveolar hemorrhage (9%), gastrointestinal hemorrhage (9%), sepsis (7%), graft versus host disease (6%), lung infiltration (6%), pneumonia (5%)

Usual dosage: Administered as a 2-hour intravenous infusion; 6.25 mg/kg every 6 hours for a minimum of 21 days; dose should be based on a patient's baseline body weight, defined as the patient's weight prior to the preparative regimen for HSCT; product labeling should be consulted for the recommendations for treatment modifications when toxicity occurs, there is a need for an invasive procedure, or when signs and symptoms have not resolved after 21 days of treatment

Product: Single-use vials – 200 mg/5 mL (80 mg/mL); calculated dose should be diluted by adding it to an infusion bag containing 0.9% Sodium Injection or 5% Dextrose Injection to make a final concentration of 4 mg/mL to 20 mg/mL; diluted solution should be administered using an infusion set equipped with a 0.2 micron in-line filter

Comments: HSCT is a procedure performed in some patients with certain blood or bone marrow cancers (e.g., leukemias, multiple myeloma), and is immediately preceded by chemotherapy. Some patients who receive these stem cell transplants experience hepatic veno-occlusive disease (VOD). This situation may result in liver damage and, in the most severe forms, also damage of the kidneys and lungs.

Defibrotide is an oligonucleotide mixture with profibrinolytic properties that is thought to enhance the enzymatic activity of plasmin to hydrolyze fibrin clots. It is the first drug to be approved for the treatment of this disease and represents an important advance. Its effectiveness was evaluated in three studies that included a total of 528 patients. The percentage of patients who were still alive 100 days after HSCT was the parameter used to determine efficacy of the treatment. In the patients treated with defibrotide, 38% to 45% of the patients in the three studies were alive 100 days after HSCT, compared with expected survival rates 100 days after HSCT of 21% to 31% in patients who received only supportive care or interventions other than defibrotide, based on published reports and evaluation of patient data.

Velpatasvir/sofosbuvir (Epclusa – Gilead) Antiviral Agents

2016 New Drug Comparison Rating (NDCR) =

Indication: Treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5. or 6 infection without cirrhosis or with compensated cirrhosis, and with ribavirin in patients with decompensated cirrhosis

Comparable drugs: Ledipasvir/sofosbuvir (Harvoni), elbasvir/grazoprevir (Zepatier)

Advantages:
--Is the first product approved for the treatment of HCV infection of all 6 major genotypes (genotype testing may not be necessary in situations in which resources are not readily available)
--Labeled indications include chronic HCV genotypes 2 and 3 infection (whereas ledipasvir/sofosbuvir is indicated for genotypes 1, 4, 5, or 6 infections and elbasvir/grazoprevir is indicated for genotypes 1 or 4 infections
--Ribavirin is not needed in the treatment regimen in as many types of infections/situations (compared with elbasvir/grazoprevir that is used in combination with ribavirin in treatment-experienced patients)
--Patients with genotype 1a infection do not have to be tested for NS5A resistance-associated polymorphisms (compared with elbasvir/grazoprevir)
--Is safer in patients with impaired hepatic function (compared with elbasvir/grazoprevir that is contraindicated in patients with moderate or severe hepatic impairment and with which hepatic function tests should be monitored)
--Duration of treatment is 12 weeks in all patients (whereas ledipasvir/sofosbuvir treatment is continued for 24 weeks in some patients and elbasvir/grazoprevir treatment is continued for 16 weeks in some patients)

Disadvantages:
--Indications do not include patients who have received liver transplants (compared with ledipasvir/sofosbuvir)
--Experience is more limited in patients with HIV-1 co-infection
--Safety has not been established in patients with severe renal impairment (compared with elbasvir/grazoprevir that may be used without dosage adjustment)
--May cause bradycardia in patients treated with amiodarone (compared with elbasvir/grazoprevir)
--Shortest period of treatment is 12 weeks (compared with ledipasvir/sofosbuvir that may be used for an 8-week period in some treatment-naïve patients with genotype 1 infection without cirrhosis)

Most important risks/adverse events: Bradycardia in patients also being treated with amiodarone (concurrent use is not recommended; risk is greater in patients also receiving beta-blockers, or those with underlying cardiac comorbidities and/or advanced liver disease); action may be reduced by P-gp inducers and/or moderate to potent CYP inducers (e.g., carbamazepine, rifampin, St. John's wort), and concurrent use is not recommended; action may also be decreased by tipranavir/ritonavir (concurrent use is not recommended) and by acid-reducing agents (e.g., antacids, proton pump inhibitors [PPI]; concurrent use with a PPI is best avoided); may increase the action of topotecan, digoxin, tenofovir (e.g., Viread), atorvastatin, and rosuvastatin (daily dose should not exceed 10 mg)

Most common adverse events: Headache (22%), fatigue (15%), nausea (9%)

Usual dosage: One tablet (100 mg of velpatasvir and 400 mg of sofosbuvir) once a day for 12 weeks; patients with decompensated cirrhosis should also receive ribavirin

Product: Tablets – 100 mg velpatasvir and 400 mg sofosbuvir (should be dispensed in the original container)

Comments: Velpatasvir/sofosbuvir is a fixed-dose combination product that includes the new HCV NS5A inhibitor velpatasvir in combination with sofosbuvir that was already available as a single agent (Sovaldi) and in a combination product with ledipasvir. Velpatasvir has properties that are most similar to those of ledipasvir, elbasvir, ombitasvir (in Viekira Pak and Technivie), and daclatasvir (Daklinza). Velpatasvir/sofosbuvir is the first product to be approved for the treatment of patients with HCV infection of all 6 major genotypes. In clinical studies of patients with HCV infection of all 6 genotypes without cirrhosis or compensated cirrhosis, the sustained virologic response (SVR) rates were 95-99% at 12 weeks following the completion of a 12-week course of treatment. The SVR rate was 94% in a study in patients with decompensated cirrhosis who also received ribavirin.

Bezlotoxumab (Zinplava – Merck) Agent for *Clostridium difficile* Infection

2017 New Drug Comparison Rating (NDCR) =

Indication: Administered intravenously to reduce recurrence of *Clostridium difficile* infection (CDI) in patients 18 years of age and older who are receiving antibacterial drug treatment of CDI and are at a high risk for CDI recurrence

Comparable drugs: Metronidazole, vancomycin, fidaxomicin (Dificid)

Advantages:
--May reduce the recurrence of CDI
--Has a unique mechanism of action (binds to *C. difficile* toxin B and neutralizes its effects)
--Is a single-dose treatment

Disadvantages:
--Does not exhibit an antibacterial action and is not indicated for the treatment of CDI
--Increased risk in patients with a history of congestive heart failure
--Is administered intravenously (whereas comparable drugs are administered orally)

Most important risks/adverse events: Risk of heart failure (in patients with a history of congestive heart failure, use should be reserved for situations in which the anticipated benefit outweighs the risk)

Most common adverse events: Nausea (7%), pyrexia (5%), headache (4%)

Usual dosage: Administered during antibacterial treatment for CDI; a single dose of 10 mg/kg administered as an intravenous infusion over 60 minutes

Product: Injection in single-dose vials – 1,000 mg/40 mL (25 mg/mL); should be stored in a refrigerator; must be diluted prior to intravenous infusion, and the volume of injection needed to provide the dose that has been determined should be transferred into an intravenous bag containing either 0.9% Sodium Chloride Injection or 5% Dextrose Injection; diluted solution should contain the medication in a final concentration ranging from 1 mg/mL to 10 mg/mL

Comments: *Clostridium difficile* is an anaerobic Gram-positive bacillus that produces two exotoxins (toxins A and B) and spores. Patients colonized with *C. difficile* may develop symptoms and active infection that may be characterized by watery diarrhea, fever, leukocytosis, abdominal pain, cramps, dehydration, and pseudomembranous colitis. The use of antibiotics is frequently associated with the occurrence of CDI because these agents disrupt normal colonic microbiota, that may enable *C. difficile* colony expansion. Other risk factors for CDI include age (i.e., 65 years and older), prior episodes of CDI, and being immunocompromised. Metronidazole is typically used for the treatment of mild to moderate CDI, with vancomycin being preferred for the treatment of patients with severe infection and in patients who are not candidates for metronidazole therapy. Fidaxomicin is an alternative that is also effective in the treatment of CDI. A significant challenge in the management of CDI is that the infection may recur in up to 40% of patients who were successfully treated for a prior CDI.

Bezlotoxumab is a human monoclonal antibody that binds to *C. difficile* toxin B (but not to toxin A) and neutralizes its effects. It is not an antibacterial drug and is not indicated for the treatment of CDI. Its effectiveness was evaluated in two placebo-controlled clinical trials in which a single intravenous infusion of bezlotoxumab or placebo was given to patients with CDI in addition to the standard of care 10-14 day course of treatment with metronidazole, vancomycin, or fidaxomicin. A sustained clinical response was defined as clinical cure of the presenting CDI episode and no CDI recurrence through 12 weeks after infusion. In Trial 1, the sustained clinical response rates in the patients receiving bezlotoxumab or placebo were 60% and 55%, respectively, a difference that was not statistically significant. However, a statistically significant difference in the results was observed in Trial 2, in which the sustained clinical response rates were 67% and 52%, respectively.

Lifitegrast (Xiidra – Shire) Agent for Dry Eye Disease

2016 New Drug Comparison Rating (NDCR) =

Indication: For ophthalmic use for the treatment of the signs and symptoms of dry eye disease

Comparable drugs: Cyclosporine ophthalmic emulsion (Restasis)

Advantages:
--Is the first agent to be approved for the treatment of both the signs and symptoms of dry eye disease (whereas cyclosporine is indicated to increase tear production)
--Has a unique mechanism of action (is a lymphocyte function-associated antigen-1[LFA-1] antagonist)
--May have a faster onset of action (improvement may be experienced within several weeks of initiation of treatment whereas the full benefit of cyclosporine may not be experienced for several months)

Disadvantages:
--Has not been directly compared with cyclosporine in clinical studies
--May cause dysgeusia

Most important risks/adverse events: None

Most common adverse events: (at an incidence of 5% to 25%) Instillation site irritation, decreased visual acuity, dysgeusia

Usual dosage: One drop in each eye twice a day, approximately 12 hours apart, using a single-use container that should be discarded after using in each eye

Product: Ophthalmic solution – 5% (50 mg/mL) in single-use containers; patients who wear contact lenses should remove them prior to administration, and they may reinsert them 15 minutes following administration

Comments: Dry eye disease is associated with inflammation of the ocular surface and, in addition to eye dryness, symptoms may include eye stinging, burning, or other discomfort, a gritty feeling, and blurred vision. It is usually a chronic disease and, if it becomes severe and is left untreated, pain, corneal ulceration, and scars may result. It is often treated with artificial tears products but many individuals do not experience an adequate response. Other agents that have been used in ophthalmic formulations include corticosteroids, hydroxypropyl cellulose (e.g., Lacrisert ophthalmic insert), and cyclosporine. Lifitegrast is the first medication to be approved for the treatment of both the signs and symptoms of dry eye disease. In contrast, cyclosporine ophthalmic emulsion is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.

The inflammation associated with dry eye disease is thought to be primarily mediated by T-cells and associated cytokines. This process may be initiated by the increased expression of intercellular adhesion molecule-1 (ICAM-1) in corneal and conjunctival tissues. ICAM-1 interacts with integrin lymphocyte function-associated antigen-1 (LFA-1), a cell surface protein. The LFA-1/ICAM-1 interaction can contribute to the occurrence of an immunological response that stimulates T-cell activation that leads to inflammation of the ocular surface. Lifitegrast is an integrin antagonist that binds to integrin LFA-1 and blocks its interaction with ICAM-1. It is classified as a LFA-1 antagonist and it is thought to reduce the secretion of inflammatory cytokines.

The effectiveness of lifitegrast was evaluated in four 12-week vehicle-controlled studies that involved more than 2,000 patients. The assessment of symptoms was based on a change from baseline in patient-reported eye dryness score (EDS) and, in all four studies, a larger reduction in EDS was observed with lifitegrast. In two of the four studies, an improvement in EDS was observed in two weeks following initiation of treatment, an onset of action that appears faster than that experienced with cyclosporine ophthalmic emulsion, although the two agents have not been directly compared in clinical studies. The assessment of signs was based on inferior corneal staining score (ICSS) using fluorescein. At week 12, a larger reduction in ICSS favoring lifitegrast was reported in three of the four studies.