New Drugs of 2016*

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Objectives:

At the completion of this knowledge-based activity, participants will be able to:

1. List new therapeutic agents that were approved by the U.S. Food and Drug Administration and first marketed in 2016.
2. Describe the mechanism of action and indications for new therapeutic agents first marketed in 2016.
4. Compare and contrast the new therapeutic agents first marketed in 2016 with products available with similar indications.
5. Discuss important patient education and therapeutic monitoring parameters for the new therapeutic agents

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
**Insulin degludec** (Tresiba – Novo Nordisk)  

**Antidiabetic Agent**

**2016 New Drug Comparison Rating (NDCR) =**

**Indication:** Administered subcutaneously to improve glycemic control in adults with diabetes mellitus

**Comparable drugs:** Insulin detemir (Levemir), insulin glargine (Lantus)

**Advantages:**
- Has a longer duration of action and does not have to be administered at the same time each day
- May be less likely to cause nocturnal hypoglycemia

**Disadvantages:**
- Has not been evaluated in pediatric patients (whereas insulin detemir is indicated in children with type 1 diabetes as young as 2 years of age, and insulin glargine is indicated in children with type 1 diabetes as young as 6 years; (has subsequently been approved for use in children as young as 1 year of age)

Most important risks/adverse events: Not recommended for use in patients with diabetic ketoacidosis; contraindicated during episodes of hypoglycemia; hypoglycemia (monitoring should be increased when changes are made in insulin dosage, co-administered glucose-lowering medications, meal patterns, and/or physical activity, and in patients with hepatic or renal impairment); hypersensitivity reactions; hypokalemia (potassium concentrations should be monitored in patients at risk); fluid retention and heart failure with concurrent use of a thiazolidinedione (e.g., pioglitazone); risk of hypoglycemia may be increased by the concurrent use of other antidiabetic agents, and medications such as ACE inhibitors and angiotensin II receptor blocking agents; blood glucose lowering effect may be reduced by the concurrent use of medications such as corticosteroids, diuretics, antipsychotic agents, and oral contraceptives; activity may be altered by the concurrent use of alcohol or beta-blockers; signs and symptoms of hypoglycemia may be blunted by anti-adrenergic drugs (e.g., beta-blockers, clonidine, guanethidine, reserpine)

Most common adverse events: Hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, pruritus, rash, edema, weight gain, nasopharyngitis, upper respiratory tract infection, headache, sinusitis, gastroenteritis

**Usual dosage:** Administered subcutaneously once a day at any time of day; dosage must be individualized based on the patient’s metabolic needs, blood glucose monitoring results, and glycemic control goal; recommended starting dose in insulin-naïve patients with type 1 diabetes is approximately one-third to one-half of the total daily insulin dose (as a general rule, 0.2 to 0.4 units of insulin/kg can be used to calculate the initial total daily insulin dose); remainder of the total daily insulin dose should be administered as a short-acting insulin and divided between each daily meal; recommended starting dose in insulin-naïve patients with type 2 diabetes is 10 units once a day; recommended starting dose in patients already on insulin therapy is the same unit dose as the total daily long or intermediate-acting insulin unit dose

**Products:** Prefilled pens – 100 units/mL (U-100; 3 mL), 200 units/mL (U-200; 3 mL); should be stored in a refrigerator; “in-use” pens should not be refrigerated but should be kept at room temperature for up to 8 weeks; also approved in a combination formulation with the rapid acting analog insulin aspart (Ryzodeg 70/30); (a combination product [Xultophy 100/3.6] that also includes liraglutide has been subsequently approved)

**Comments:** Insulin degludec is the third long-acting human insulin analog, joining insulin glargine and insulin detemir. It is prepared using recombinant DNA technology and, following subcutaneous administration, forms multi-hexamers that result in a depot of the drug and delayed absorption from the subcutaneous tissues. Its duration of action is approximately 42 hours, compared with a duration of action of approximately 24 hours for insulin glargine and insulin detemir. A new formulation of insulin glargine (Toujeo) has a duration of action that continues slightly beyond 24 hours. The delayed absorption and elimination may provide a more consistent response. Insulin degludec may be administered at any time of the day, unlike the other long-acting insulin analogs.

The effectiveness of insulin degludec was demonstrated in multiple clinical studies in which it was determined to be noninferior to insulin glargine and insulin detemir in lowering HbA1c concentrations. It was more effective than sitagliptin in lowering HbA1c concentrations, but also caused more episodes of hypoglycemia.
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:
--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); 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)

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 a placebo-controlled study, patients treated with lixisenatide experienced a reduction in A1c concentrations of 0.83% compared with a reduction of 0.18% in patients receiving placebo, representing a difference from placebo of -0.65%. In an active-controlled study, it was noninferior to exenatide (twice a day) but provided less of an A1c reduction than exenatide.

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. Lixisenatide may be more likely than other GLP-1 agonists to be associated with the development of antibodies.
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 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., 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 concentrations to the target range of 3.8 mEq/L to less than 5.1 mEq/L.
Cariprazine hydrochloride (Vraylar – Allergan) Antipsychotic Agent

2016 New Drug Comparison Rating (NDCR) =

Indications: Treatment of patients with schizophrenia, and in the acute treatment of manic or mixed episodes associated with bipolar I disorder

Comparable drugs: Aripiprazole (e.g., Abilify)

Advantages:
--May be effective in some patients who have not experienced an adequate response with other agents
--Is less likely to be implicated in drug interactions involving the CYP2D6 metabolic pathway
--Labeling does not include warning regarding a risk of suicidal thoughts and behaviors

Disadvantages:
--Has not been directly compared with comparable drugs in clinical studies
--Labeled indications are more limited (aripiprazole also has labeled indications for adjunctive treatment of patients with major depressive disorder, the treatment of patients with Tourette’s disorder, and the treatment of irritability associated with autistic disorder)
--Has not been evaluated in pediatric patients (whereas aripiprazole is indicated for use in patients as young as 6 years for certain conditions)
--May be more likely to cause extrapyramidal reactions
--May accumulate with continued use and increase the possibility of late-occurring adverse events
--Dosage forms are more limited (aripiprazole is also available in an oral solution formulation, and in a parenteral formulation for intramuscular injection)

Most important risks/adverse events: Increased risk of death in elderly patients with dementia-related psychosis (boxed warning), and a higher incidence of cerebrovascular events (e.g., stroke) in these patients; neuroleptic malignant syndrome; tardive dyskinesia; seizures; orthostatic hypotension and syncope; body temperature dysregulation; dysphagia; metabolic changes (e.g., hyperglycemia/diabetes, dyslipidemia, weight gain); leukopenia, neutropenia, and agranulocytosis; potential for cognitive and motor impairment (patients should be cautioned about operating hazardous machinery); late-occurring adverse events (cariprazine and its major metabolites may accumulate over time, and adverse events may not be evident, or worsen, over a period of several weeks after initiating treatment and dosage increases); is a substrate of the CYP3A4 metabolic pathway and activity is increased by the concurrent use of a strong CYP3A4 inhibitor (e.g., clarithromycin; dosage of cariprazine should be reduced); action is reduced by the concurrent use of a strong CYP3A4 inducer (e.g., carbamazepine; concurrent use is not recommended); may cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure;

Most common adverse events: In patients with schizophrenia – extrapyramidal symptoms (19%), akathisia (13%); in patients with bipolar mania – extrapyramidal symptoms (26%), akathisia (20%), nausea (13%), vomiting (10%),

Usual dosage: Recommended starting dosage is 1.5 mg once a day on Day 1; in patients with schizophrenia, the dosage can be increased to 3 mg once a day on Day 2, and the recommended dosage range is 1.5 mg to 6 mg once a day; in patients with manic or mixed episodes associated with bipolar I disorder, the dosage should be increased to 3 mg once a day on Day 2, and the recommended dosage is 3 to 6 mg once a day; in patients being treated concurrently with a strong CYP3A4 inhibitor, the dosage should be reduced and the product labeling should be consulted for the specific recommendations.

Products: Capsules – 1.5 mg, 3 mg, 4.5 mg, 6 mg

Comments: Cariprazine is an atypical antipsychotic agent with activity that is most similar to that of aripiprazole and brexpiprazole (Rexulti). It exhibits partial agonist activity at dopamine D2 and serotonin 5-HT1A receptors, and antagonist activity at serotonin 5-HT2A receptors. It has been demonstrated to be more effective than placebo in reducing the occurrence of symptoms of schizophrenia and bipolar disorder. It is converted to two major active metabolites, one of which has a long half-life.
Pimavanserin tartrate (Nuplazid – Acadia)  Antipsychotic Agent

2016    New Drug Comparison Rating (NDCR) =

Indication: Treatment of hallucinations and delusions associated with Parkinson’s disease psychosis

Comparable drugs: Atypical antipsychotic drugs (e.g., risperidone)

Advantages:
--Is the first drug to be demonstrated to be effective in the treatment of hallucinations and delusions associated with Parkinson’s disease psychosis
--Has a unique mechanism of action (a combination of inverse agonist and antagonist activity at serotonin 5-HT₂A receptors)
--Does not act at dopamine receptors and is not likely to cause extrapyramidal effects
--May be less likely to cause serious adverse events (e.g., tardive dyskinesia, neuroleptic malignant syndrome)

Disadvantages:
--Is more likely to cause QT interval prolongation and increase the risk of arrhythmias (the atypical antipsychotic drug ziprasidone is also associated with this risk)

Most important risks/adverse events: Increased risk of death in elderly patients with dementia-related psychosis (boxed warning; is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson’s disease psychosis); prolongs the QT interval (use should be avoided in patients with QT prolongation, congenital prolongation of the QT interval, a history of cardiac arrhythmias, symptomatic bradycardia, hypokalemia, and/or hypomagnesemia, or in combination with other drugs known to prolong the QT interval including Class 1A antiarrhythmics [e.g., quinidine, procainamide, disopyramide], Class 3 antiarrhythmics [e.g., amiodarone, sotalol], certain antipsychotic medications [e.g., ziprasidone, chlorpromazine, thioridazine], and certain antibacterial agents [e.g., moxifloxacin]); is a substrate of the CYP3A4 metabolic pathway and action may be increased by the concurrent use of a strong CYP3A4 inhibitor (e.g., clarithromycin, itraconazole; dosage should be reduced); action may be reduced by the concurrent use of a strong CYP3A4 inducer (e.g., carbamazepine, rifampin, St. John’s wort), and it may be necessary to increase the dosage; use is not recommended in patients with hepatic impairment or in patients with severe renal impairment

Most common adverse events: Nausea (7%), peripheral edema (7%), confusional state (6%)

Usual dosage: 34 mg (two 17 mg tablets) once a day; in patients treated concurrently with a strong CYP3A4 inhibitor, the recommended dosage is 17 mg once a day

Product: Tablets – 17 mg (pimavanserin base provided by 20 mg pimavanserin tartrate)

Comments: An estimated 40% of patients with Parkinson’s disease experience psychosis characterized by hallucinations and delusions. Serotonin 5-HT₂A receptors are thought to play an important role in Parkinson’s disease psychosis. Pimavanserin has a unique mechanism of action that preferentially targets 5-HT₂A receptors and is mediated through a combination of inverse agonist and antagonist activity at these receptors. Unlike other antipsychotic drugs, it does not act at dopamine receptors. Therefore, it does not interfere with patients’ dopaminergic therapy (e.g., levodopa) and does not impair motor function. The FDA granted pimavanserin a breakthrough therapy designation that is designed to expedite the development and review of drugs that are intended to treat a serious condition and where preliminary evidence indicates that the drug may demonstrate substantial improvement over available therapy.

Pimavanserin is metabolized primarily via the CYP3A4 pathway to a major active metabolite. Its effectiveness was evaluated in a 6-week placebo-controlled study that included 199 patients. A Parkinson’s disease (PD)-adapted Scale for the Assessment of Positive Symptoms (SAPS-PD) was used to evaluate efficacy. This is a 9-item scale adapted for PD from the Hallucinations and Delusions domains of the SAPS. The new drug was demonstrated to be superior to placebo in decreasing the frequency and/or severity of both hallucinations and delusions, without worsening the primary motor symptoms of Parkinson’s disease.
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.
**Eteplirsen (Exondys 51 – Sarepta)**

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**Agent for Muscular Dystrophy**

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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 adverse events

Disadvantages:
--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 pediatric patients including 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.
Lesinurad (Zurampic – AstraZeneca; Ironwood)  
Agent for Gout  

2016 New Drug Comparison Rating (NDCR) =

Indication: In combination with a xanthine oxidase inhibitor for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid concentrations with a xanthine oxidase inhibitor alone

Comparable drugs: Xanthine oxidase inhibitors: allopurinol, febuxostat (Uloric)

Advantages:
--Has a unique mechanism of action (inhibits uric acid transporter 1 [URAT1] and organic anion transporter 4 [OAT4])
--Provides additional reduction in serum uric acid concentrations

Disadvantages:
--Is not a first-line treatment
--Labeled indications are more limited (compared with allopurinol that is also indicated for patients receiving cancer treatments that cause increased uric acid concentrations, and for the management of patients with recurrent calcium oxalate calculi)
--Is more likely to cause acute renal failure and other renal adverse events
--May reduce the reliability of hormonal contraceptives

Most important risks/adverse events: Acute renal failure (boxed warning; risk is greater when lesinurad is used alone, and should be used in combination with a xanthine oxidase inhibitor; renal function should be monitored when initiating and during therapy, and particularly in patients with an estimated creatinine clearance below 60 mL/minute; treatment should not be initiated in patients with an estimated creatinine clearance below 45 mL/minute; patients should be evaluated for symptoms of acute uric acid nephropathy); contraindicated in patients with severe renal impairment, end-stage renal disease, in recipients of kidney transplants, patients on dialysis, or patients with tumor lysis syndrome or Lesch-Nyhan syndrome); major cardiovascular adverse events (a causal relationship has not been established); not recommended in patients with severe hepatic impairment; is a CYP2C9 substrate and activity may be increased in patients who are poor CYP2C9 metabolizers and in those also being treated with a CYP2C9 inhibitor (e.g., fluconazole, amiodarone); activity may be reduced in patients treated with a CYP2C9 inducer (e.g., carbamazepine); concurrent use with inhibitors of epoxide hydrolase (e.g., valproic acid) should be avoided; effectiveness may be reduced by aspirin in doses higher than 325 mg a day; may reduce the concentrations of CYP3A substrates (e.g., sildenafil, amlodipine); may reduce the reliability of hormonal contraceptives and women should be advised to use additional methods of contraception

Most common adverse events: Headache (5%), influenza (5%), gastroesophageal reflux disease (3%), increased serum creatinine concentrations (4%)

Usual dosage: 200 mg once a day in the morning with food and water; if treatment with the xanthine oxidase inhibitor is interrupted, the use of lesinurad should also be interrupted; patients should be instructed to stay well hydrated (e.g., 2 liters [68 ounces] of liquid each day); gout flare prophylaxis (e.g., colchicine, nonsteroidal anti-inflammatory drugs) is recommended when starting treatment; treatment should be discontinued if estimated creatinine clearance is reduced and is persistently less than 45 mL/minute

Product: Tablets - 200 mg

Comments: Lesinurad inhibits uric acid transporter 1 (URAT1) and organic anion transporter 4 (OAT4). URAT1 is responsible for the majority of the reabsorption of filtered uric acid from the renal tubular lumen, and OAT4 is a uric acid transporter associated with diuretic-induced hyperuricemia. By inhibiting the action of these transporters, lesinurad increases renal clearance and excretion of uric acid, and reduces serum uric acid concentrations. Its effectiveness was demonstrated in studies in which lesinurad or placebo was used with allopurinol or febuxostat. The combination of lesinurad with the xanthine oxidase inhibitor reduced serum uric acid concentrations to the target in approximately twice as many patients (55%) as in patients receiving placebo.
**Ixekizumab** (Taltz – Lilly) 

**Agent for Psoriasis**

2016  

2016 New Drug Comparison Rating (NDCR) =

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

**Comparable drug:** Secukinumab (Cosentyx)

**Advantages:**

--Following the initial dose (two injections), the dose is administered as a single injection (whereas the recommended dosage of secukinumab for patients with plaque psoriasis requires two injections for each dose)

--Products may be less likely to cause reactions in latex-sensitive individuals

**Disadvantages:**

--Labeled indications are more limited (labeled indications for secukinumab also include patients with psoriatic arthritis and ankylosing spondylitis)

--May be more likely to cause injection site reactions

**Most important risks/adverse events:** Risk of infection (if a serious infection develops during treatment the drug should be discontinued until the infection resolves); exacerbation of tuberculosis (patients should be evaluated for tuberculosis infection prior to initiating treatment); exacerbation of inflammatory bowel disease (i.e., Crohn’s disease, ulcerative colitis); hypersensitivity reactions; live vaccines should not be administered during treatment

**Most common adverse events:** Injection site reactions (17%), upper respiratory tract infections (14%), nausea (2%), tinea infections (2%)

**Usual dosage:** Administered subcutaneously – 160 mg (two 80 mg injections) at Week 0, followed by 80 mg at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks

**Products:** Single-dose prefilled syringes and single-dose prefilled autoinjectors - 80 mg/mL; should be stored in a refrigerator

**Comments:** Interleukin-17A (IL-17A) is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. It is present in elevated concentrations in psoriatic plaques. Ixekizumab is the second monoclonal antibody that selectively binds to IL-17A, joining secukinumab. By inhibiting the interaction of IL-17A with its receptors, these agents inhibit the release of proinflammatory cytokines and chemokines.

The effectiveness of ixekizumab was demonstrated in three placebo-controlled studies that included almost 4,000 participants. 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. Between 87% and 90% of the patients treated with ixekizumab attained a PASI 75, compared with 7% or fewer of the patients who received placebo. Approximately 70% of those treated with the new drug attained a PASI 90, compared with less than 3% of those receiving placebo. Approximately 40% of the patients treated with ixekizumab received a PGA of clear, compared with 0% of those receiving placebo. In two studies, ixekizumab was compared with etanercept (Enbrel; 50 mg twice a week). The PASI 75 and PASI 90 scores for patients treated with ixekizumab for 12 weeks were 87% and 64%, respectively, compared with 41% and 18%, respectively, for those treated with etanercept.
**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%)

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 (FEV₁) 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 titrated; 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 (Addcirca), 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, Velreti 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.
**Elbasvir/grazoprevir (Zepatier – Merck)**

Antiviral Agents

2016 New Drug Comparison Rating (NDCR) =

**Indication:** With or without ribavirin for the treatment of adult patients with chronic hepatitis C virus (HCV) genotypes 1 or 4 infection

**Comparable drugs:** Ledipasvir/sofosbuvir (Harvoni)

**Advantages:**
--May be safer in patients with impaired renal function
--Is less likely to interact with amiodarone and cause bradycardia

**Disadvantages:**
--Labeled indications are more limited (ledipasvir/sofosbuvir is also indicated for HCV genotypes 5 and 6 infection)
--Patients with genotype 1a infection should be tested for NS5A resistance-associated polymorphisms
--Is more likely to cause hepatic adverse events and liver function tests should be monitored
--Is contraindicated in patients with moderate or severe hepatic impairment
--Is contraindicated in patients treated with a strong CYP3A inducer (e.g., carbamazepine, efavirenz, or an organic anion transporting polypeptide (OATP) 1B1/3 inhibitor (e.g., cyclosporine, atazanavir, darunavir)

**Most important risks/adverse events:** Contraindicated in patients with moderate or severe hepatic impairment; alanine aminotransferase (ALT) elevations (liver function tests should be performed prior to therapy, at treatment week 8, and as clinically indicated; for patients receiving 16 weeks of therapy testing should also be performed at treatment week 12); are substrates of CYP3A and concurrent use with a strong CYP3A inducer (e.g., carbamazepine, rifampin, St. John’s wort) or efavirenz is contraindicated, and concurrent use with a moderate CYP3A inducer is not recommended; concurrent use with a strong CYP3A inhibitor (e.g., clarithromycin) is not recommended; concurrent use with an OATP1B1/3 inhibitor (e.g., cyclosporine) is contraindicated

**Most common adverse events:** Fatigue (11%), headache (10%), nausea

**Usual dosage:** 50 mg of elbasvir and 100 mg of grazoprevir in a single tablet once a day with or without food; patients with genotype 1a infection should be tested for the presence of NS5A resistance-associated polymorphisms; treatment is continued for 12 weeks in most patients; is used in combination with ribavirin in a 16-week regimen in patients with genotype 1a infection who are treatment-naive or peginterferon alfa/ribavirin-experienced and have baseline NS5A polymorphisms, or in patients with genotype 4 infection who are peginterferon alfa/ribavirin-experienced; is used in combination with ribavirin in a 12-week regimen in patients with genotype 1a or 1b infection who are peginterferon alfa/ribavirin/HCV NS3/4A protease inhibitor (e.g., simeprevir, telaprevir)-experienced

**Product:** Fixed-dose combination tablets – 50 mg of elbasvir and 100 mg of grazoprevir

**Comments:** Elbasvir and grazoprevir are direct-acting antiviral agents with activity against HCV. Elbasvir is an HCV NS5A inhibitor with properties that are most similar to those of ledipasvir (included in Harvoni), daclatasvir (Daklinza), and ombitasvir (included in Viekira Pak and Technivie). Grazoprevir is an HCV NS3/4A protease inhibitor with properties that are most similar to those of simeprevir (Olysio), paritaprevir (included in Viekira Pak and Technivie), boceprevir, and telaprevir. Other antiviral agents that are highly active against HCV include sofosbuvir (Sofvaldi), a nucleotide analog inhibitor of HCV NS5B polymerase, and dasabuvir (included in Viekira Pak), an HCV non-nucleoside NS5B palm polymerase inhibitor. The combination product (Harvoni) containing ledipasvir and sofosbuvir has become the standard of treatment for many patients with HCV infection. It is highly effective and is administered in a convenient one tablet once a day regimen. Viekira Pak is a combination formulation that includes ombitasvir, paritaprevir, and ritonavir, and is copackaged with dasabuvir. It is also highly effective but dasabuvir is administered twice a day and the regimen is more likely to interact with other medications.

The use of elbasvir/grazoprevir is most similar to that of ledipasvir/sofosbuvir. In clinical trials the overall sustained virologic response (SVR) rates ranged from 94-97% in patients with genotype 1 infection and from 97-100% in patients with genotype 4 infection.
**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)
-- Patients with genotype 1a infection do not have to be tested for NS5A resistance-associated polymorphisms (compared with elbasvir/grazoprevir)
-- 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 tizanidine (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 Technvie), 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.
**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:**
--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 1,000 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.
**Obiltoxaximab (Anthim – Elusys)**  
Agent for Inhalational Anthrax

2016 New Drug Comparison Rating (NDCR) =

Indication: Administered intravenously in adult and pediatric patients for the treatment of inhalational anthrax caused by *Bacillus anthracis* in combination with appropriate antibacterial drugs; also indicated for prophylaxis of inhalational anthrax due to *B. anthracis* when alternative therapies are not available or not appropriate.

Comparable drug: Raxibacumab

Advantages:
--Intravenous infusion time is shorter (one hour and 30 minutes, compared with 2 hours and 15 minutes)

Disadvantages:
--May be more likely to cause hypersensitivity reactions including anaphylaxis

Most important risks/adverse events: Hypersensitivity reactions, including anaphylaxis (boxed warning; diphenhydramine should be used as premedication)

Most common adverse events: Headache (8%), upper respiratory tract infection (5%), pruritus (4%), cough (3%), vessel puncture site bruise (3%), infusion site swelling (3%), infusion site pain (2%), pain in extremity (2%), urticaria (2%), nasal congestion (2%)

Usual dosage: Administered as an intravenous infusion over 1 hour and 30 minutes; 16 mg/kg after dilution in 0.9% Sodium Chloride Injection; infusion solution should be administered using a 0.22 micron inline filter; product labeling should be consulted for the dosage recommendations for adult patients weighing less than 40 kg and pediatric patients.

Product: Single-dose vials – 600 mg/6 mL (100 mg/mL); (vials should be stored in a refrigerator and should not be shaken)

Comments: Anthrax is a potential bioterrorism threat because the spores of the bacterium *Bacillus anthracis* resist destruction and can be easily spread by release in the air. The toxins released by the bacterium can cause irreversible tissue damage and death. Obiltoxaximab is a monoclonal antibody that has properties that are most similar to those of raxibacumab. Both agents neutralize toxins produced by *B. anthracis* by inhibiting the binding of the protective antigen (PA) of the bacterium to its cellular receptors. By inhibiting the binding of PA, these agents prevent the intracellular entry of the anthrax lethal factor and edema factor, the enzymatic toxin components responsible for the pathogenic effects of anthrax toxin. Obiltoxaximab and raxibacumab do not have direct antibacterial activity and are used in combination with an appropriate antibacterial agent (ciprofloxacin, levofloxacin, doxycycline).

Obiltoxaximab was approved using FDA’s Animal Rule, which permits efficacy findings from adequate and well-controlled animal studies to support FDA approval when it is not feasible or ethical to conduct efficacy trials in humans. In studies in rabbits and monkeys, 78% and 38% of the animals, respectively, treated with obiltoxaximab had survived at Day 28 after the spore challenge, compared with only one monkey in the 55 animals in the placebo groups. When obiltoxaximab was administered in combination with antibacterial drugs, there were higher survival outcomes than with antibacterial therapy alone. Obiltoxaximab is not expected to cross the blood-brain barrier and does not treat or prevent meningitis.