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New Drugs 2017 PART 3

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THIS ARTICLE REVIEWS 11 drugs recently approved by the FDA, including:

> a drug for Duchenne muscular dystrophy that received accelerated FDA approval.

> an important advance in the treatment of spinal muscular atrophy.

> five new antineoplastic drugs.

Unless otherwise specified, the information in the following summaries applies to adults, not children. Consult a pharmacist or the package insert for information on drug safety during pregnancy and breastfeeding. Consult a pharmacist, the package insert, or a current and comprehensive drug reference for more details on precautions, drug interactions, and adverse reactions for all these drugs.

SELECTED REFERENCES

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DRUG FOR DUCHENNE MUSCULAR DYSTROPHY

Eteplirsen

Approved despite lack of evidence of efficacy

The muscular dystrophies are an inherited group of progressive myopathic disorders caused by mutations in a number of genes needed for normal muscle function. Duchenne muscular dystrophy (DMD) is caused by mutations in the dystrophin gene and is associated with the most severe signs and symptoms.[1]

Characterized by a progressive loss of muscle mass and strength, DMD almost always affects boys. Initial signs and symptoms are usually evident between ages 3 and 5 years and worsen over time. Most patients are nonambulatory by their early teens and face life-threatening cardiopulmonary complications as the disease worsens. Most patients with DMD die in their 20s or 30s.[2,3]

Some genetic mutations in DMD involve the deletion of certain exons, which are gene segments containing information needed for protein synthesis.[4] Eteplirsen (*Exondys 51*, Sarepta) is an antisense oligonucleotide designed to bind to exon 51 of dystrophin pre-messenger RNA (pre-mRNA), resulting in exclusion of this exon (exon skipping) during mRNA processing.[5] Exon skipping is designed to allow production of a partially functional dystrophin protein.

Eteplirsen is indicated for pediatric and adult patients who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping, which affects about 13% of patients with DMD.[2] Administered I.V., eteplirsen is the first drug to be approved to treat patients with DMD.

Eteplirsen was approved under the FDA's accelerated approval program, even though its clinical benefit hasn't been established. The primary study evaluating the new drug included a 6-minute walk test as a clinical outcome measure. No significant difference in the distance walked in 6 minutes was found between patients treated with eteplirsen and those receiving placebo. Continued approval may be contingent on verification of a clinical benefit in confirmatory trials.[5]

Precautions: Eteplirsen has no labeled contraindications. It hasn't been studied in pregnant or lactating women, or in patients with renal or hepatic impairment.

Adverse reactions: balance disorder, vomiting, contact dermatitis

Supplied as: single-dose vials containing 100 mg/2 mL (50 mg/mL) and 500 mg/10 mL (50 mg/mL) of the drug

Dosage: 30 mg/kg once a week via I.V. infusion over 35 to 60 minutes

Nursing considerations: (1) Before preparing doses, allow vials to warm to room temperature. (2) Invert, but don't shake, vials two or three times. Dilute the prescribed drug dose with 0.9% Sodium Chloride Injection to a total volume of 100 to 150 mL. See the prescribing information for complete instructions for preparation and administration. (3) Before eteplirsen administration, a topical anesthetic cream may be applied to the infusion site. (4) The infusion should be completed within 4 hours of dilution. If not used immediately, the diluted solution may be stored for up to 24 hours in a refrigerator. (5) Store vials in a refrigerator and protect from light. (6) Inform patients that they may experience transient erythema, facial flushing, and elevated temperature on the days they receive the drug.

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DRUG FOR SPINAL MUSCULAR ATROPHY

Nusinersen

An important treatment advance

Spinal muscular atrophy (SMA) is a group of inherited disorders characterized by motor neuron loss in the spinal cord and lower brainstem, muscle weakness, and atrophy.[1] It's the most common genetic cause of death in infants, but can affect people at any age. Age of onset, signs and symptoms, and rate of progression vary widely.[2] Patients with the most severe type of the disease (Type 1 SMA) can become paralyzed and experience difficulty breathing, swallowing, and performing 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 don't produce enough SMN protein. Disease severity correlates with the amount of SMN protein.[3]

Antisense oligonucleotides (ASOs) are short synthetic strings of nucleotides designed to bind to target RNA and regulate gene expression. Nusinersen (*Spinraza*, Biogen) is an SMN2-directed ASO designed to treat SMA caused by mutations in chromosome 5q that lead to SMN protein deficiency.[4]

Administered via intrathecal injection, nusinersen is indicated to treat SMA in pediatric and adult patients. Because it's the first drug to be approved to treat SMA, it's an important advance.

Its effectiveness was evaluated in a sham-procedure clinical trial in 121 patients with infantile-onset (most likely to develop Type 1) SMA. Two-thirds of patients received the drug and one-third underwent a sham procedure (a skin prick) without 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 with untreated patients (43%).[4]

Before administration of nusinersen, 5 mL of cerebrospinal fluid should be removed. The drug is administered as an intrathecal bolus injection over 1 to 3 minutes using a spinal anesthetic needle.

Adverse reactions: lower respiratory infection, upper respiratory infection, constipation

Precautions: (1) Thrombocytopenia and coagulation abnormalities have been reported, so platelet count, prothrombin time, and activated partial thromboplastin time should be determined at baseline, before each dose, and as clinically needed. (2) Nusinersen is excreted via the kidneys and a potential for renal toxicity exists. Quantitative spot urine protein testing (preferably using a first morning urine specimen) should be conducted at baseline and before each dose.

Supplied as: single-dose vials containing 12 mg/5 mL

Dosage: 12 mg (5 mL) per administration. 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.

Nursing considerations: (1) Store vials in their cartons in a refrigerator until the time of use. (2) Warm

New antineoplastic drugs[1-5]

Drug (*trade name*, manufacturer)	**Indications**	**Route**
Venetoclax (*Venclexta*, AbbVie)	chronic lymphocytic leukemia with 17p deletion, as detected by an FDA-approved test, in patients who have received at least one prior therapy	oral
Rucaparib camsylate (*Rubraca*, Clovis)	monotherapy for the treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who've been treated with two or more chemotherapies	oral
Alectinib (*Alecensa*, Genentech)	anaplastic lymphoma kinase-positive, metastatic non–small cell lung cancer in patients who've progressed on or are intolerant to crizotinib	oral
Atezolizumab (*Tecentriq*, Genentech)	• locally advanced or metastatic urothelial carcinoma in patients who have disease progression during or following platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy • metastatic non–small cell lung cancer in patients who have disease progression during or following platinum-containing chemotherapy	I.V. infusion
Olaratumab (*Lartruvo*, Lilly)	in combination with doxorubicin, soft tissue sarcoma in patients with a histologic subtype for which an anthracycline-containing regimen is appropriate and which isn't amenable to curative treatment with radiotherapy or surgery.	I.V. infusion

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2. Rubraca (rucaparib camsylate) tablets, for oral use. Prescribing information. http://clovisoncology.com/files/rubraca-prescribing-info.pdf.
3. Alecensa (alectinib) capsules, for oral use. Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/208434s000lbl.pdf.
4. Tecentriq (atezolizumab) injection, for intravenous use. Prescribing information. https://www.gene.com/download/pdf/tecentriq_prescribing.pdf.
5. Lartruvo (olaratumab) injection, for intravenous use. Prescribing information. http://pi.lilly.com/us/lartruvo-uspi.pdf.

vials to room temperature prior to administration without using external heat sources. (3) Inspect vial contents for particulate matter and discoloration before administration. Don't administer the drug if it's discolored or contains particulates.

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DRUG FOR PULMONARY HYPERTENSION

Selexipag

Indicated to delay disease progression and reduce the risk of hospitalization

Pulmonary arterial hypertension (PAH) is characterized by elevated pulmonary artery pressures and increased right ventricular workload, resulting in exertional dyspnea and fatigue. More serious and debilitating complications may lead to a need for lung transplantation or death.[1,2]

Selexipag (*Uptravi*, Actelion) is a selective nonprostanoid IP prostacyclin receptor agonist indicated to treat patients with PAH (WHO Group 1) to delay progression and reduce the risk of hospitalization for PAH.[3] Administered orally, the new drug is structurally distinct from prostacyclin. Unlike the other prostacyclin agonists used to treat PAH, selexipag and its active metabolite, which is 37-fold as potent as the parent drug, have selective activity for the IP receptor versus other prostanoid receptors.[2] Greater selectivity may permit use of lower dosages, reducing the incidence of adverse reactions.

In a placebo-controlled trial, treatment with selexipag resulted in a 40% reduction of the occurrence of primary endpoint events such as time to disease progression resulting in death, hospitalization, or need for transplantation. The beneficial effect was primarily attributable to a reduction in hospitalization for PAH and a reduction in other disease-worsening events. Exercise capacity was evaluated as a secondary endpoint and, at week 26, a median treatment effect of 12 meters in the 6-minute walk distance was attributed to the use of selexipag. However, no significant difference in mortality was found between the test and placebo groups.

Precautions: (1) The possibility of pulmonary veno-occlusive disease (PVOD) should be considered if signs of pulmonary edema occur. If PVOD is confirmed, selexipag treatment should be discontinued. (2) Because of the risk of serious adverse events in nursing infants, a decision should be made to discontinue nursing or not use the drug in lactating women. (3) Reduce the dosage in patients with moderate hepatic impairment. Use of selexipag should be avoided in patients with severe hepatic impairment. (4) Avoid concurrent use with strong inhibitors of the CYP2C8 metabolic pathway such as gemfibrozil, which may increase the exposure and activity of selexipag and its active metabolite.

Adverse reactions: headache, diarrhea, nausea, jaw pain, vomiting, pain in extremity, myalgia, flushing, arthralgia, rash

Supplied as: 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1,000 mcg, 1,200 mcg, 1,400 mcg, and 1,600 mcg oral tablets

Dosage: initially, 200 mcg twice a day. The dosage should be increased in increments of 200 mcg twice a day, usually at weekly intervals, to the highest tolerated dosage up to 1,600 mcg twice a day. In patients with moderate hepatic impairment, the initial dosage is 200 mcg once a day, which may be increased in increments of 200 mcg once a day at weekly intervals, to the highest tolerated dose up to 1,600 mcg.

Nursing considerations: (1) Advise patients to take selexipag with food, which may minimize adverse reactions. (2) If the patient misses a dose, the next dose should be taken as soon as possible unless the next dose is within the next 6 hours. If the patient misses treatment for 3 days or more, he or she should contact the healthcare provider, who will restart the medication at a lower dosage and then titrate it upward. (3) Tell the patient not to split, crush, or chew the tablets.

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DRUG FOR PRIMARY BILIARY CHOLANGITIS

Obeticholic acid

Only the second drug to be approved for PBC

Primary biliary cholangitis (PBC) is a rare, chronic liver disease caused by autoimmune destruction of the bile ducts that eventually leads to cirrhosis and liver failure. When bile ducts become inflamed and damaged, bile accumulates in the liver and damages hepatocytes. Death can result unless the patient receives a liver transplant.[1]

Until now, ursodeoxycholic acid (UDCA) was the only drug approved for treating PBC. Although this medication is effective in about half of patients with PBC, up to 40% don't respond adequately, and up to 10% can't tolerate it.[1]

Obeticholic acid (*Ocaliva*, Intercept), the second drug to be approved to treat patients with PBC, acts as an agonist for farnesoid X

receptor (FXR) found in the nucleus of cells in the liver and intestine.[2] FXR is a key regulator of bile acid, inflammatory, fibrotic, and metabolic pathways. Obeticholic acid activates FXR, which 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. These actions limit the overall size of the circulating bile acid pool while promoting choleresis (bile secretion by the liver), thereby reducing hepatic exposure to bile acids.

Obeticholic acid is indicated in combination with UDCA to treat adults with an inadequate response to UDCA, or as monotherapy in adults who can't tolerate UDCA. A designated orphan drug, it 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 alkaline phosphatase [ALP]) that is reasonably likely to predict clinical benefit for patients. However, an improvement in disease-related symptoms or survival hasn't yet been established.[2]

Precautions: (1) Contraindicated in patients with complete biliary obstruction. If this complication develops during treatment, discontinue treatment. (2) In clinical trials, 19% of patients experienced severe pruritus, which is also a common symptom of PBC. Management strategies include the use of a bile acid binding resin such as cholestyramine, colestipol, or colesevelam, an antihistamine, dosage reduction, and/or temporary interruption of therapy with obeticholic acid. Because bile acid binding resins may reduce the effectiveness of obeticholic acid, concurrent use of the two medications should be separated by as long an interval as possible, 4 hours at minimum. (3) Liver-related adverse reactions have been reported including jaundice, worsening ascites, and PBC flare. Monitor patients for these events and for elevations in liver biochemical tests. The dosage of obeticholic acid should be reduced in patients with moderate or severe hepatic impairment. (4) Monitor patients for changes in serum lipid concentrations during treatment, especially reduction in HDL cholesterol. (5) Obeticholic acid may inhibit CYP1A2, and it has been reported to increase the exposure to caffeine, a CYP1A2 substrate. Monitor concentrations of CYP1A2 substrates with a narrow therapeutic index (such as theophylline and tizanidine) when the new drug is administered concurrently. (6) The concurrent use of obeticholic acid and warfarin may reduce the international normalized ratio (INR). Monitor INR and adjust the warfarin dosage as necessary.

Adverse reactions: pruritus, fatigue, abdominal pain and discomfort, rash, oropharyngeal pain, dizziness, constipation, arthralgia, thyroid function abnormality, eczema

Supplied as: 5 mg and 10 mg oral tablets

Dosage: initially, 5 mg orally once a day; this lower starting dosage is recommended to reduce pruritus. If an adequate reduction in ALP and/or total bilirubin isn't achieved after 3 months of treatment with this dosage and the patient is tolerating the drug, the dosage should be increased to 10 mg orally once a day; this is also the maximum recommended dosage. Consult the prescribing information for specific dosage reduction recommendations in patients with moderate or severe hepatic impairment and in patients who experience intolerable pruritus.

Nursing considerations: (1) Inform patients they can take the drug without regard to food. (2) Tell patients to report new or worsening pruritus to the healthcare provider. (3) Teach patients to recognize and report signs and symptoms of liver dysfunction. Inform patients that they may need to undergo periodic blood tests to monitor liver function and/or lipid levels.

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PROFIBRINOLYTIC DRUG

Defibrotide sodium

Therapy for severe hepatic veno-occlusive disease following HSCT

Hematopoietic stem cell transplantation (HSCT), a procedure performed in some patients with certain blood or bone marrow cancers such as leukemias, lymphomas, and multiple myeloma, is immediately preceded with chemotherapy. Some patients who receive these stem cell transplants experience hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome. In hepatic VOD, occlusion of terminal hepatic venules and intercalated veins ultimately leads to widespread zonal liver disruption and centrilobular hemorrhagic necrosis. Patients develop hepatomegaly, right upper quadrant pain, jaundice, and ascites, and may experience renal and pulmonary dysfunction. Fewer than 2% of patients develop severe hepatic VOD following HSCT, but as many as 80% of those who experience VOD don't survive.[1]

Defibrotide sodium (*Defitelio*, Jazz) is an oligonucleotide mixture with profibrinolytic properties.[2] It's thought to enhance the enzymatic activity of plasmin to hydrolyze fibrin clots, and may also protect hepatic cells from damage caused by chemotherapy and other factors. Administered by I.V. infusion, it's

indicated to treat adult and pediatric patients with hepatic VOD with renal or pulmonary dysfunction following HSCT. The first drug to be approved for this disease, it represents an important advance in the management of complications resulting from the treatment of patients with blood and bone marrow cancers.

The effectiveness of defibrotide 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 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.

Precautions: (1) Contraindicated in patients with active bleeding. Because defibrotide is thought to increase the action of fibrinolytic enzymes, it may increase bleeding risks. Monitor patients treated with the new drug for signs and symptoms of bleeding. (2) Concurrent use with a systemic anticoagulant or fibrinolytic therapy is contraindicated because of the increased risk of bleeding. Treatment with an anticoagulant or a fibrinolytic agent such as alteplase should be discontinued before initiating therapy with defibrotide. Clinicians should consider delaying the start of therapy until the anticoagulant's effects have abated. (3) No reversal agent for defibrotide's profibrinolytic action is available. Infusion of the drug should be stopped at least 2 hours before an invasive procedure and resumed after the procedure as soon as any procedure-related risk of bleeding is resolved. (4) Hypersensitivity reactions including rash, urticaria, and angioedema have occurred in less than 2% of patients. One patient who'd been previously treated with defibrotide experienced an anaphylactic reaction.

Adverse reactions: hypotension, diarrhea, vomiting, nausea, epistaxis, pulmonary alveolar hemorrhage, gastrointestinal hemorrhage, sepsis, graft versus host disease, lung infiltration, pneumonia

Supplied as: single-patient-use vials containing 200 mg/2.5 mL (80 mg/mL) of the drug

Dosage: 6.25 mg/kg every 6 hours, administered as a 2-hour I.V. infusion. The dose is based on a patient's baseline body weight, defined as the patient's weight prior to the preparative regimen for HSCT. Treatment lasts for at least 21 days and then continues until VOD resolution or up to 60 days of treatment.

Nursing considerations: (1) The volume of the injection needed to provide the prescribed dose should be diluted by adding it to an infusion bag containing 0.9% Sodium Chloride Injection or 5% Dextrose Injection to make a final concentration of 4 mg/mL to 20 mg/mL. The diluted solution should be administered by constant I.V. infusion over 2 hours using an infusion set equipped with a 0.2 micron in-line filter. (2) The diluted solution should be used within 4 hours if stored at room temperature or within 24 hours if stored under refrigeration. Up to four doses of the solution may be prepared at one time if they're kept refrigerated.

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DRUG FOR INHALATIONAL ANTHRAX

Obiltoxaximab

New defense against bioterrorism

Anthrax is a potential bioterrorism threat because 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.[1] People who work in slaughterhouses, tanneries, and wool mills are also at risk if they inhale spores from infected animals. Inhalational anthrax is considered the most deadly form of anthrax; even with aggressive treatment, only about 55% of patients survive.[2]

Treatments for inhalational anthrax have included anthrax vaccine adsorbed, anthrax immune globulin, raxibacumab (a monoclonal antibody available from the CDC that neutralizes toxins produced by *B. anthracis*), and antibacterial drugs such as ciprofloxacin, levofloxacin, or doxycycline.

Obiltoxaximab (*Anthim*, Elusys) is a chimeric monoclonal antibody with properties similar to those of raxibacumab. Like raxibacumab, it neutralizes toxins produced by *B. anthracis*. Neither drug has direct antibacterial activity; rather, both act by binding to the bacterium's protective antigen, preventing intracellular entry of key enzymatic toxin components.[3]

Administered via I.V. infusion, obiltoxaximab is indicated in combination with appropriate antibacterial drugs for adult and pediatric patients with inhalational anthrax due to *B. anthracis*. It's also indicated for prophylaxis of inhalational anthrax when alternative therapies aren't available or aren't appropriate.

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 isn't 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, survival outcomes were higher than with antibacterial therapy alone.

The safety of obiltoxaximab has been evaluated in 320 healthy adult volunteers, but the safety and pharmacokinetics of the drug in pediatric patients hasn't been studied. Dosage recommendations for use in children were derived using pharmacokinetic data obtained from the safety study in volunteers.

Precautions: (1) Hypersensitivity reactions such as urticaria and pruritus were reported in 11% of the volunteers and three individuals experienced anaphylaxis. Administer diphenhydramine as premedication and closely observe patients in a monitored setting throughout the infusion period and for a period of time following administration. (2) Obiltoxaximab should be used for prophylaxis only when its benefit for prevention of inhalational anthrax outweighs the risk of hypersensitivity reactions and anaphylaxis.

Adverse reactions: headache, upper respiratory tract infection, pruritus, cough, vessel puncture site ecchymosis, infusion site edema, infusion site pain, pain in extremity, urticaria, nasal congestion

Supplied as: a sterile solution in single-dose vials containing 600 mg of the drug in 6 mL (100 mg/mL)

Dosage: 16 mg/kg for adults. Consult the prescribing information for weight-based pediatric dosage guidelines.

Nursing considerations: (1) Store vials in a refrigerator and protect from light. (2) Discard vials if the solution is discolored or contains particulate matter. Don't shake the vials. (3) Premedicate patients with diphenhydramine as prescribed. (4) Dilute the drug in 0.9% Sodium Chloride Injection and administer as an I.V. infusion over 90 minutes. See the prescribing information for full instructions on preparation, dilution, and administration. (5) Closely monitor patients for hypersensitivity reactions throughout the infusion and afterward. Inform them of the hypersensitivity risk and instruct them to seek immediate medical care if they experience signs and symptoms of hypersensitivity or anaphylaxis during or after the infusion. ■

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