Abstract

Objective: To provide information about the most important properties of new therapeutic agents approved by FDA and first marketed in 2015.

Data sources: Product labeling supplemented selectively with published studies and drug information reference sources.

Data synthesis: This review covers 11 new therapeutic agents approved by FDA and first marketed in the United States in 2015: selexipag, cobimetinib, osimertinib, necitumumab, alectinib, insulin degludec, lesinurad, mepolizumab, brexpiprazole, cariprazine, and flibanserin. Indications and information on dosage and administration for these agents are reviewed, as well as efficacy, safety, the most important pharmacokinetic properties, drug interactions, and other precautions. Practical considerations for use of these new agents also are discussed. Whenever possible, properties of the new drugs are compared with those of older agents marketed for the same indications.

Summary: Selexipag is the second oral prostacyclin agonist for the treatment of pulmonary arterial hypertension. Cobimetinib is a new agent indicated for unresectable or metastatic melanoma. Three new drugs (osimertinib, necitumumab, and alectinib) have been approved for the treatment of various types of non–small cell lung cancer. Insulin degludec is a new long-acting basal insulin for diabetes. Lesinurad is a novel agent approved for the treatment of hyperuricemia in gout. Mepolizumab is a monoclonal antibody for adolescents and adults with severe eosinophilic asthma. Brexpiprazole and cariprazine are two new atypical antipsychotics indicated for schizophrenia. Brexpiprazole is also approved as an adjunct to antidepressant therapy for major depressive disorder, and cariprazine is also approved for bipolar disorders. Flibanserin is the first drug approved for women with hypoactive sexual desire disorder.

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Learning objectives

■ List new therapeutic agents approved by FDA and first marketed in 2015.
■ Describe the mechanisms of action and indications for these new therapeutic agents.
■ Compare and contrast the new therapeutic agents with products available with similar indications.
■ Summarize adverse effects and patient safety considerations for the new therapeutic agents.
■ Discuss important patient education and therapeutic monitoring parameters for the new therapeutic agents.
New cardiology agent: Selexipag

Pulmonary arterial hypertension (PAH) is an uncommon disease. Patients with PAH have a dysregulation in the endothelin, nitric oxide, and/or prostacyclin metabolic pathways that leads to constriction of the pulmonary arteries and an enlarged right ventricle. Right heart failure and pulmonary edema are the principal consequences of PAH.1

Multiple classes of drugs are used in the treatment of PAH, such as endothelin receptor antagonists (ambrisentan, bosentan, and macitentan); drugs that work in the nitric oxide pathway, including phosphodiesterase-5 inhibitors (tadalafil and sildenafil) and guanylate cyclase stimulators (riociguat); and prostacyclin receptor agonists (epoprostenol, treprostinil, and iloprost). Until recently, use of a prostacyclin agonist was limited to IV and inhaled therapies. Treprostinil became available in an oral dosage form in 2013 with the approval of Orenitram (United Therapeutics). Prostacyclins became available in an oral dosage form in 2013 with the approval of Orenitram (United Therapeutics). Prostacyclins are typically not used as first-line treatment for PAH but instead became available in an oral dosage form in 2013 with the approval of Orenitram (United Therapeutics). Prostacyclins are typically not used as first-line treatment for PAH but instead are used later in the course of the disease in patients with a worsened functional classification.1

Selexipag (Uptravi—Actelion), approved for the treatment of PAH (World Health Organization [WHO] Group I), is the second oral agent that works in the prostacyclin pathway to delay disease progression and reduce the risk of hospitalization. Endogenously, prostacyclin is produced in endothelial cells, where it induces vasodilation and inhibits platelet aggregation. Though selexipag is similar to endogenously produced prostacyclin, it has its own distinct mechanism of action as a selective prostacyclin IP receptor agonist, which could theoretically decrease adverse gastrointestinal drug reactions (nausea and vomiting) in comparison with other prostacyclin agonists.2

Selexipag has rapid absorption and is highly protein bound (~99%) to albumin and alpha-1 acid glycoprotein. With hepatic metabolism, selexipag is converted to an active metabolite via the isoenzymes cytochrome P450 (CYP) 3A4, CYP2C8, uridine 5'-diphosphate-glucuronosyltransferase (UGT) 1A3, and UGT2B7. The active metabolite has a half-life of 6.2 to 13.5 hours, and absorption of the drug is delayed with food. Excretion is primarily in the feces (~93%).2

Selexipag is dosed 200 mcg orally twice daily, then increased by 200 mcg twice daily, typically at weekly intervals, to the highest tolerated dose. See additional dosing information in Table 2. A missed dose should be taken as soon as possible unless the next dose is within the next 6 hours. If 3 or more days of treatment are missed, restart at a lower dose and then titrate.3

No dose adjustments are necessary in renal impairment or mild hepatic impairment, although the label recommends once-daily instead of twice-daily dosing for moderate hepatic impairment (Child-Pugh Class B). Use should be avoided in severe hepatic impairment. Selexipag has not been studied in patients with a glomerular filtration rate (GFR) of less than 15 mL/min or in hemodialysis.

Efficacy of selexipag was evaluated in the GRIPHON study, a randomized, double-blind, placebo-controlled trial in 1,156 patients with symptomatic PAH (mostly WHO Group II or III) who were treatment naive or already on treatment. Patients were randomized to receive either selexipag 200 mcg orally twice daily or placebo and continue therapy until a prespecified number of primary endpoints was reached. The dose was increased weekly by increments of 200 mcg twice daily to the highest tolerated dose up to 1,600 mcg twice daily. The primary endpoint was time to a composite endpoint of death or a complication related to PAH, whichever occurred first. Disease progression was defined as a decrease from baseline of at least 15% in the 6-minute walk distance (6MWD).3

Results of the GRIPHON study showed a 40% reduction in the primary composite endpoint in the selexipag arm compared with the placebo arm. Of note, there was no significant difference in mortality between the selexipag and placebo groups. The secondary endpoint of 6MWD showed an increase of 4.0 m in the selexipag group and a decrease of 9.0 m in the placebo group from baseline to week 26. The median treatment duration was 70.7 weeks with selexipag and 63.7 weeks with placebo. The observed benefit of selexipag was similar regardless of the dose achieved.3

There are no adequate or well-controlled studies of selexipag in pregnant women. With regard to use while breastfeeding, either selexipag or breastfeeding should be discontinued. Selexipag has no reported contraindications. Patients with pulmonary veno-occlusive disease should be warned about the risk of pulmonary edema. If the disease is confirmed, selexipag should be discontinued.2

Objective

The fourth and final part of this four-part series on new therapeutic agents approved in the United States in 2015 covers 11 new drugs: selexipag, cobimetinib, osimertinib, necitumumab, alectinib, insulin degludec, lesinurad, mepolizumab, brexpiprazole, cariprazine, and flibanserin. Tables 1 through 11 provide additional information on these newly approved agents, including detailed dosing, pharmacology, pregnancy and lactation information, and related abbreviations.
Table 1. New therapeutic drugs approved in 2015: Part 4

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Manufacturer</th>
<th>Indication</th>
<th>Route</th>
<th>Pronunciation</th>
<th>FDA approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiology</td>
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</tr>
<tr>
<td>Selexipag</td>
<td>Uptravi</td>
<td>Actelion</td>
<td>Pulmonary arterial hypertension (PAH)</td>
<td>Oral</td>
<td>se LEX i pag</td>
<td>12/15</td>
</tr>
<tr>
<td>Hematology/oncology</td>
<td></td>
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<tr>
<td>Cobimetinib</td>
<td>Cotellie</td>
<td>Genentech</td>
<td>Unresectable or metastatic melanoma with a BRAFV600E or V600K mutation</td>
<td>Oral</td>
<td>koe bi ti nib</td>
<td>11/15</td>
</tr>
<tr>
<td>Osimertinib</td>
<td>Tagrisso</td>
<td>AstraZeneca</td>
<td>Metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non–small cell lung cancer (NSCLC)</td>
<td>Oral</td>
<td>oh si MER ti nib</td>
<td>11/15</td>
</tr>
<tr>
<td>Necitumumab</td>
<td>Portrazza</td>
<td>Eli Lilly</td>
<td>Metastatic squamous NSCLC</td>
<td>I.V.</td>
<td>ne siTOOM oo mab</td>
<td>11/15</td>
</tr>
<tr>
<td>Alectinib</td>
<td>Alecensa</td>
<td>Genentech</td>
<td>Metastatic ALK-positive NSCLC</td>
<td>Oral</td>
<td>al EK ti mab</td>
<td>12/15</td>
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<td>Endocrinology</td>
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<tr>
<td>Insulin</td>
<td>Degludec</td>
<td>Novo Nordisk</td>
<td>Diabetes</td>
<td>SubQ</td>
<td>IN su lin de GLOO dek</td>
<td>9/15</td>
</tr>
<tr>
<td>Lesinurad</td>
<td>Zurampic</td>
<td>AstraZeneca</td>
<td>Hyperuricemia associated with gout</td>
<td>Oral</td>
<td>le SIN ure ad</td>
<td>12/15</td>
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<tr>
<td>Pulmonology</td>
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<tr>
<td>Mepolizumab</td>
<td>Nucala</td>
<td>GlaxoSmithKline</td>
<td>Severe asthma with an eosinophilic phenotype</td>
<td>SubQ</td>
<td>me poe LIZ ue mab</td>
<td>11/15</td>
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<tr>
<td>Psychology/neurology</td>
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<tr>
<td>Brexpiprazole</td>
<td>Rexulti</td>
<td>Otsuka</td>
<td>Schizophrenia and adjunctive for major depressive disorder</td>
<td>Oral</td>
<td>breks PIP ray zole</td>
<td>7/15</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>Vraylar</td>
<td>Actavis</td>
<td>Schizophrenia and bipolar disorder</td>
<td>Oral</td>
<td>kar IP ra zeen</td>
<td>9/15</td>
</tr>
<tr>
<td>Flibanserin</td>
<td>Addyi</td>
<td>Sprout Pharmaceuticals</td>
<td>Hypoactive sexual desire disorder (HSDD)</td>
<td>Oral</td>
<td>flib AN ser in</td>
<td>8/15</td>
</tr>
</tbody>
</table>

Abbreviations used: ALK, anaplastic lymphoma kinase; SubQ, subcutaneous.
Sources: 2, 7, 10, 12, 14, 18, 23, 25, 28, 29, 45.

The most common adverse effects (>5% compared with placebo) of selexipag include headache, diarrhea, jaw pain and pain in extremities, nausea and vomiting, myalgia, and flushing.

Most of selexipag’s drug interactions are related to metabolism by CYP2C8. Consult the product labeling prior to giving concomitantly with abiraterone, CYP2C8 substrates, or the moderate to strong CYP2C8 inhibitors gemfibrozil, deferasirox, lumacaftor, and mifepristone.

Monitoring includes liver function tests (LFTs), signs of pulmonary edema, and improvements in pulmonary function, exercise tolerance, and quality of life.2

To date, selexipag has only been compared with placebo. Clinical trial results showed a delay in disease progression and a reduction in the risk of hospitalization related to PAH. Selexipag offers another option as the second available oral prostacyclin for the treatment of PAH.

New hematology/oncology agents
More drugs used to treat cancer were approved in 2015 than drugs for any other group of diseases. Of the 45 novel drugs approved, 14 (31%) were antineoplastics.4 Cancer is the second leading cause of death in the United States. The American Cancer Society (ACS) estimates that cancer claims 1,630 American lives every day.5

Skin cancer is the most common of all cancers. Melanoma accounts for about 1% of skin cancer cases and the majority of deaths. ACS has estimated that approximately 76,000 new
Table 2. Dosing of newly approved therapeutic agents

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Dosage forms</th>
<th>Dosing</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selexipag</td>
<td>Uptravi</td>
<td>Tablet, oral: 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1,200 mcg, 1,400 mcg, 1,600 mcg</td>
<td>Initial: 200 mcg twice/d; increase by 200 mcg twice/d, usually at weekly intervals (maximum dose: 1,600 mcg twice/d). If a dose is not tolerated, reduce dose to previously tolerated dose.</td>
<td>Administer with or without food. Swallow tablets whole; do not split, crush, or chew. Moderate hepatic impairment: initial dose of 200 mcg/d; may increase by 200 mcg/d at weekly intervals, as tolerated.</td>
</tr>
<tr>
<td>Cobimetinib</td>
<td>Cotellic</td>
<td>Tablet, oral: 20 mg</td>
<td>60 mg/d for first 21 d of each 28-d cycle until disease progression or unacceptable toxicity</td>
<td>Hazardous agent. Not indicated for treatment of patients with wild-type B-Raf melanoma.</td>
</tr>
<tr>
<td>Osimertinib</td>
<td>Tagrisso</td>
<td>Tablet, oral: 40 mg, 80 mg</td>
<td>80 mg/d</td>
<td>Hazardous agent. Must confirm the presence of T790M mutation in tumor specimens prior to initiation of treatment.</td>
</tr>
<tr>
<td>Necitumumab</td>
<td>Portrazza</td>
<td>Injectable solution in a single-dose vial: 800 mg/50 mL (16 mg/mL)</td>
<td>800 mg as an I.V. infusion over 60 min on days 1 and 8 of each 3-wk cycle</td>
<td>Not indicated for treatment of nonsquamous non–small cell lung cancer.</td>
</tr>
<tr>
<td>Alectinib</td>
<td>Alecensa</td>
<td>Capsule, oral: 150 mg</td>
<td>600 mg twice/d; continue until disease progression or unacceptable toxicity.</td>
<td>T1DM, insulin-naive: initial dose of one-third to one-half the TDD (~0.2–0.4 units/kg); remainder of TDD should be given as a short-acting insulin and divided between meals. Insulin-experienced: initiate with same unit dose as the total daily long- or intermediate-acting insulin unit dose. T2DM, insulin-naive: initial dose of 10 units/d. Insulin-experienced: initiate with the same unit dose as the total daily long- or intermediate-acting insulin unit dose.</td>
</tr>
<tr>
<td>Insulin degludec</td>
<td>Tresiba</td>
<td>100 units/mL (U-100): 3 mL FlexTouch 200 units/mL (U-200): 3 mL FlexTouch</td>
<td>Individualize dose based on type of diabetes, metabolic needs, blood glucose monitoring results, and glycemic control goal.</td>
<td>Not for treatment of other eosinophilic conditions; not for relief of acute bronchospasm or status asthmaticus.</td>
</tr>
<tr>
<td>Lesinurad</td>
<td>Zurampic</td>
<td>Film-coated tablet: 200 mg</td>
<td>200 mg/d</td>
<td>Given in combination with a xanthine oxidase inhibitor (allopurinol or febuxostat).</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>Nucala</td>
<td>Injectable, single-dose vials with 100 mg of lyophilized powder for reconstitution</td>
<td>100 mg given SubQ every 4 wk</td>
<td>Not for treatment of other eosinophilic conditions; not for relief of acute bronchospasm or status asthmaticus.</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>Rexulti</td>
<td>Tablet, oral: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg</td>
<td>Schizophrenia, initial dose: 1 mg/d; target dose: 2–4 mg/d; max dose: 4 mg/d</td>
<td>Hepatic impairment (Child-Pugh ≥ 7): MDD max dose = 3 mg/d; schizophrenia max dose = 4 mg/d</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>Vraylar</td>
<td>Capsule, oral: 1.5 mg, 3 mg, 4.5 mg, 6 mg</td>
<td>Initial dose: 1.5 mg (may increase to 3 mg on day 2); schizophrenia dosage range: 1.5–6 mg/d; bipolar mania dosage range: 3–6 mg/d</td>
<td>Administer with or without food. Maximum dose: 6 mg/d. Due to the long half-life of cariprazine and its active metabolites, changes in dose will not be fully reflected in plasma for several weeks.</td>
</tr>
<tr>
<td>Flibanserin</td>
<td>Addyi</td>
<td>Tablet, oral: 100 mg</td>
<td>100 mg/d at bedtime</td>
<td>Administration during waking hours increases risk of hypotension, syncope, accidental injury, and CNS depression.</td>
</tr>
</tbody>
</table>

Abbreviations used: T1DM, type 1 diabetes mellitus; TDD, total daily dose; T2DM, type 2 diabetes mellitus; SubQ, subcutaneous; MDD, major depressive disorder; CrCL, creatinine clearance; CNS, central nervous system. Sources: 2, 7, 10, 12, 14, 15, 23, 25, 28, 29, 45.
melanoma cases will be diagnosed in 2016, with about 10,000 deaths due to melanoma. More men than women will develop melanoma, and it is 20 times more common in whites than in African Americans, according to ACS. In addition, the risk increases as people age.6

**Cobimetinib**

Cobimetinib (Cotellic—Genentech) is a newly approved agent indicated for the treatment of unresectable or metastatic melanoma in patients with a BRAF V600E or V600K mutation. Cobimetinib is a kinase inhibitor that must be given in combination with vemurafenib, a BRAF (pronounced BEE-raf) inhibitor.7

Specifically, cobimetinib is a mitogen-activated protein kinase (MEK) enzyme inhibitor.7 MEK inhibitors target kinases in the signaling pathway for melanoma, increase apoptosis, and reduce growth of tumor cell lines in patients with BRAF mutations. BRAF mutations, present in about 40% of patients with melanoma, activate the BRAF pathway, including the MEK proteins.7

The drug is 95% bound to plasma proteins, undergoes hepatic metabolism, and is mostly excreted in feces (76%). It is dosed 60 mg orally once daily during days 1 to 21 of each 28-day treatment cycle, given in combination with vemurafenib, and continued until disease progression or unacceptable toxicity. No dosage adjustment is necessary in mild to moderate renal impairment or in mild hepatic impairment. If hepatic markers are significantly abnormal ALT, AST, or alkaline phosphatase [ALP] > 20 times the upper limit of normal (ULN) or total bilirubin > 10 times ULN, or if the patient is hepatotoxic, the drug should be withheld for up to 4 weeks. Check the product label for more details about dose adjustments in hepatic impairment.7

Approval of cobimetinib was based on a randomized, double-blind, placebo-controlled trial (coBRIM) conducted in previously untreated patients.8 All patients (n = 495) had unresectable or metastatic melanoma that was BRAF V600 mutation positive. The presence of the mutation was detected using an FDA-approved companion test.8

Patients were randomized (1:1) to receive cobimetinib 60 mg once daily plus vemurafenib or vemurafenib and placebo until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS). Secondary outcomes included objective response rate (ORR), overall survival, and duration of response.8

There was a statistically significant median PFS of 9.9 months in the cobimetinib arm and 6.2 months in the placebo arm. The combination cobimetinib group also showed a statistically significant rate of complete or partial response of (68%), compared with 43% in the control group.8

Adverse events were observed in animal studies, and based on the mechanism of action, cobimetinib would be expected to cause fetal harm. The manufacturer does not recommend breastfeeding during therapy or for 2 weeks after the final dose (Table 4).7

Cobimetinib has no contraindications. Warnings and precautions include cardiomyopathy, dermatologic toxicity, hemorrhage, hepatotoxicity, malignancy, ophthalmic effects, rhabdomyolysis, and embryo–fetal toxicity.

Adverse effects (occurring in > 20% of patients) were diarrhea, photosensitivity reaction, nausea, pyrexia, and vomiting. The most common (> 5%) lab-related abnormalities are lymphopenia; LFTs, including increased gamma-glutamyl transpeptidase (GGT), creatinine phosphokinase (CPK), ALT, AST, and ALP; and decreased serum phosphate and sodium.7

Cobimetinib has several important drug interactions. Administration with strong and moderate CYP3A4 inhibitors, as well as with strong and moderate CYP3A4 inducers, should be avoided. Monitoring includes BRAF V600K or V600E mutation status (prior to treatment), LFTs, and CPK and serum creatinine levels (baseline and monthly during treatment; more frequently if clinically indicated). Left ventricular ejection fraction (LVEF) should be assessed by echocardiogram or multigated acquisition (MUGA) scan prior to therapy initiation, 1 month after initiation, and every 3 months thereafter until cobimetinib is discontinued, as well as at approximately 2, 4, 10, and 16 weeks and as clinically indicated after a dose reduction or treatment interruption.7

Monitoring of cobimetinib includes dermatologic and ophthalmic exams, including signs and symptoms of dermatologic toxicity, hemorrhage, noncutaneous malignancy, photosensitivity, and rhabdomyolysis.7

Cobimetinib provides another option in combination with vemurafenib for patients with a BRAF mutation and unresectable or metastatic melanoma. Cobimetinib is the second available oral MEK inhibitor for advanced skin cancer.

Three new drugs for various forms of non–small cell lung cancer (NSCLC) were approved in 2015: osimertinib, necitumumab, and alectinib (Table 6). Lung cancer (both small cell and non–small cell) is the second most common cancer in both men and women. About 221,000 new cases of lung cancer were diagnosed in 2015, with approximately 158,000 related deaths. Each year, more people die of lung cancer than of colon, breast, and prostate cancer combined. About 85% to 90% of lung cancers are NSCLCs.9

**Osimertinib**

Osimertinib (Tagrisso—AstraZeneca) is one of three new antineoplastic indicated for metastatic NSCLC. Specifically, osimertinib is indicated for metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive NSCLC, as detected by an approved test, in patients who have progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy.10 Osimertinib has a complex mechanism of action (Table 3). The most common mechanism of resistance to EGFR TKIs is via the T790M resistance mutation. Osimertinib binds selectively to these mutations to prevent tumor growth.10

Although osimertinib is expected to be highly protein bound, this is as yet unknown. The drug undergoes hepatic metabolism to two active metabolites. Concentrations are increased with a high-fat, high-calorie meal. Osimertinib has an estimated half-life of 48 hours, with primary excretion in the feces (68%).10

The drug is dosed orally as 80 mg once daily with or without food until disease progression or unacceptable toxicity. No dose adjustments are necessary in mild or moderate
Table 3. Mechanism of action of new therapeutic agents

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selexipag</td>
<td>Uptravi</td>
<td>Selective prostacyclin IP receptor agonist. Prostacyclin is produced in the endothelial cells and induces vasodilation, as well as inhibits platelet aggregation. Patients with pulmonary arterial hypertension appear to have a dysregulation in the prostacyclin metabolic pathways.</td>
</tr>
<tr>
<td>Cobimetinib</td>
<td>Cotellic</td>
<td>Reversible inhibitor of mitogen-activated protein kinase (MAPK)/extracellular signal regulated kinase (MEK) 1 and MEK2.</td>
</tr>
<tr>
<td>Osimertinib</td>
<td>Tagrisso</td>
<td>Kinase inhibitor of the epidermal growth factor receptor (EGFR), which binds irreversibly to certain mutant forms of EGFR (T790M, L858R, and exon 19 deletion) at approximately ninefold lower concentrations than wild-type EGFR.</td>
</tr>
<tr>
<td>Necitumumab</td>
<td>Portrazza</td>
<td>Recombinant human IgG1 monoclonal antibody that binds to the human EGFR and blocks the binding of EGFR to its ligands.</td>
</tr>
<tr>
<td>Alectinib</td>
<td>Alecensa</td>
<td>Tyrosine kinase receptor inhibitor that inhibits anaplastic lymphoma kinase (ALK) and rearranged during transfection (RET). ALK gene abnormalities due to mutations or translocations may result in expression of oncoprogenic fusion proteins (e.g., ALK fusion protein) and thus alter signaling and expression and result in increased cellular proliferation and survival in tumors that express these fusion proteins. Inhibition of ALK phosphorylation and ALK-mediated activation of downstream signaling results in decreased tumor cell viability. Alectinib is more potent than crizotinib against ALK and can inhibit most of the clinically observed acquired ALK resistance mutations to crizotinib.</td>
</tr>
<tr>
<td>Insulin degludec</td>
<td>Tresiba</td>
<td>Lowers blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Lipolysis and proteolysis are also inhibited, enhancing protein synthesis.</td>
</tr>
<tr>
<td>Lesinurad</td>
<td>Zurampic</td>
<td>Decreases serum uric acid levels by inhibiting the function of transporter proteins involved in uric acid reabsorption in the kidney and inhibits the function of URAT1 and OAT4.</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>Nucala</td>
<td>Monoclonal antibody interleukin-5 (IL-5) antagonist (IgG1 kappa) that binds to IL-5 and inhibits bioactivity by blocking its binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface. Inhibits IL-5 signaling, which reduces the production and survival of eosinophils; however, the drug's mechanism of action in asthma has not been definitively established.</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>Rexulti</td>
<td>Unknown, but efficacy may be mediated through a combination of partial agonist activity at serotonin 5-HT_{1A} and dopamine D_{2} receptors, and antagonist activity at serotonin 5-HT_{2A} receptors.</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>Vraylar</td>
<td>Unknown. It is a partial agonist of serotonin 5-HT_{1A} activity and dopamine D_{2} receptors and an antagonist of serotonin 5-HT_{2A} activity.</td>
</tr>
<tr>
<td>Flibanserin</td>
<td>Addyi</td>
<td>Unknown. It exhibits agonist activity at 5-HT_{1A} and antagonist activity at 5-HT_{2A}; moderate antagonist activity is seen at the 5-HT_{2B}, 5-HT_{2C}, and dopamine D_{4} receptors.</td>
</tr>
</tbody>
</table>

Abbreviations used: IgG1, immunoglobulin G1; URAT1, urate transporter 1; OAT4, organic anion transporter 4.
Sources: 2, 7, 10, 12, 14, 16, 23, 25, 28, 29, 45.

renal impairment or mild hepatic impairment. No data are available for use in severe renal impairment, end-stage renal disease, or moderate and severe hepatic impairment.10

Efficacy and safety of osimertinib were evaluated in two single-arm, open-label Phase II studies (AURA extension and AURA2).11 The AURA studies randomized metastatic EGFR T790M NSCLC patients who had disease progression on or after an EGFR TKI. ORR measuring tumor shrinkage was the primary efficacy endpoint.11

Results from both AURA trials showed the overall ORR was 59%. Patients with a partial response represented 59% of the study participants, and those with a complete response represented 0.5%. In a separate dose-finding analysis of the AURA studies, the ORR was 51%, and the median duration of response was 12.4 months.10,11

Use of osimertinib during pregnancy is expected to cause fetal harm. Women should use effective contraception during therapy and for 6 weeks after the last dose. Males with female partners of reproductive potential should also use effective contraception during therapy and for 4 months after the last dose. Because of the potential for serious adverse reactions in the nursing infant, breastfeeding is not recommended during therapy or for 2 weeks after the last dose.10

The most common adverse effects of osimertinib (occurring in ≥ 25% of patients) include rash, diarrhea, dry skin, and nail toxicity. No contraindications are listed in the manufacturer’s label; however, significant warnings and precautions exist.10 See Table 7 for more details.

Osimertinib has many drug interactions, and concomitant administration with CYP3A inhibitors and inducers should be avoided. Monitoring includes cytogenetic mutation status (prior to treatment), electrocardiogram, and elec-
tory of time was 11.5 months with necitumumab and 9.9 months with placebo. PFS was greater with necitumumab (5.7 mo) compared with placebo (5.5 mo). There was no difference in ORR between arms (31% vs. 29%). In a separate trial, necitumumab in nonsquamous NSCLC failed to demonstrate a benefit.

Necitumumab is expected to cross the placenta and cause fetal harm if administered during pregnancy. Because of the potential for serious adverse reactions in the nursing infant, breastfeeding is not recommended. No contraindications are listed in the product label; however, many warnings and precautions exist (Table 7).

The most common adverse effects in a combination regimen with gemcitabine and cisplatin (occurring in >10% of patients) include headache, skin toxicity, electrolyte abnormalities (particularly hypomagnesemia), weight loss, vomiting, diarrhea, and stomatitis.

There are no significant drug interactions. Monitoring of necitumumab therapy includes serum electrolytes, specifically magnesium, potassium, and calcium (prior to each dose during treatment and for at least 8 wk following completion). Signs and symptoms of infusion-related reactions, dermatologic toxicity, and thromboembolism should also be monitored.

Necitumumab is the first EGFR inhibitor for squamous cell NSCLC.

**Alectinib**

Alectinib (Alecensa—Genentech) is the third of three drugs approved in 2015 for metastatic NSCLC. To summarize, osimertinib is approved for patients with a T790M resistance mutation whose treatment failed with previous EGFR TKI therapy, while necitumumab can be used as a first-line treatment for metastatic squamous cell NSCLC along with gemcitabine and cisplatin. Alectinib is indicated for patients with anaplastic lymphoma kinase (ALK)–positive, metastatic NSCLC who have progressed on or are intolerant to crizotinib.

Alectinib, a second-generation TKI, inhibits ALK and rearranged during transfection (RET). About 3% to 7% of patients with NSCLC have ALK rearrangements (ALK positivity) that lead to expression of oncogenic fusion proteins (e.g., ALK fusion protein). These rates vary widely depending on geographic region. Increased cellular proliferation is the result, with inhibition of ALK leading to decreased tumor cell viability. Currently, most patients with ALK-positive disease are started on crizotinib first-line. Unfortunately, crizotinib–treated patients usually relapse and have progression of their disease within 12 months. The central nervous system (CNS) is a common site for metastasis. Approximately 26% of ALK-positive patients with newly diagnosed, metastatic disease have CNS metastases.

When taken with a high-fat, high-calorie meal, alectinib concentrations were increased. About one-third of the drug is bioavailable when taken with food. Alectinib is highly protein bound and crosses the blood–brain barrier. It undergoes hepatic metabolism via CYP3A4 to a major active metabolite with a half-life of 33 hours. Alectinib is primarily eliminated...
Table 4. Use of new therapeutic agents during pregnancy and lactation

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Pregnancy category</th>
<th>Comments</th>
<th>Lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selexipag</td>
<td>–</td>
<td>Adverse events have not been observed in animal reproduction studies</td>
<td>Not recommended; unknown if excreted in human milk</td>
</tr>
<tr>
<td>Cobimetinib</td>
<td>–</td>
<td>May cause fetal harm; women should use effective contraception during therapy and for 2 wk after final dose.</td>
<td>No data</td>
</tr>
<tr>
<td>Osimertinib</td>
<td>–</td>
<td>May cause fetal harm</td>
<td>No data</td>
</tr>
<tr>
<td>Necitumumab</td>
<td>–</td>
<td>May cause fetal harm; women should use effective contraception during therapy and for 3 mo after final dose.</td>
<td>Not recommended during therapy or for 3 mo after last dose</td>
</tr>
<tr>
<td>Alectinib</td>
<td>–</td>
<td>May cause fetal harm: Women should use effective contraception during therapy and for 1 wk after final dose, and men with a female partner should use effective contraception during therapy and for 3 mo after final dose</td>
<td>Not recommended during therapy and for 1 wk after final dose because of potential for serious adverse reactions</td>
</tr>
<tr>
<td>Insulin degludec</td>
<td>C</td>
<td>No adequate or well-controlled studies in pregnant women</td>
<td>Caution; both exogenous and endogenous insulin are excreted into breast milk</td>
</tr>
<tr>
<td>Lesinurad</td>
<td>–</td>
<td>Adverse events were not observed in animal studies</td>
<td>Caution; unknown if excreted in breast milk</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>–</td>
<td>No adequate or well-controlled studies in pregnant women</td>
<td>Not studied</td>
</tr>
<tr>
<td>Brexipiprazole</td>
<td>–</td>
<td>No adequate or well-controlled studies in pregnant women; third-trimester use may cause extrapyramidal and/or withdrawal symptoms in a neonate</td>
<td>Not studied</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>–</td>
<td>Fetal risk cannot be ruled out; a pregnancy exposure registry monitors pregnancy outcomes in women exposed to cariprazine during pregnancy</td>
<td>Excreted in rat milk</td>
</tr>
<tr>
<td>Filbanserin</td>
<td>–</td>
<td>Adverse effects have been observed in animal studies (decreased fetal weight, structural anomalies, and increased fetal loss)</td>
<td>Not recommended; unknown if excreted in human milk; potential of sedation/serious adverse reactions</td>
</tr>
</tbody>
</table>

Sources: 2, 7, 10, 12, 14, 18, 23, 25, 28, 29, 45.

in feces. Alectinib is dosed orally, 600 mg twice daily with food, until there is evidence of disease progression or unacceptable toxicity (Table 2). No dosing adjustments for renal or hepatic impairment are provided in the product label. Should hepatotoxicity occur while on alectinib, the drug should be withheld until liver function (ALT, AST, and bilirubin) returns to normal or an acceptable range. See the label for more details about dosing in liver impairment.

Approval of alectinib was based on two single-arm, multicenter trials of patients (n = 225) with metastatic, ALK-positive NSCLC whose disease was no longer controlled with crizotinib. Patients were randomized in both studies to receive oral alectinib 600 mg twice daily or placebo. The primary endpoint of the trials was ORR. The majority of patients (60%-61%) had CNS metastasis upon entry to the studies.

Between the two trials, patients achieved an ORR of 38% to 44%, with a duration of response of 7.5 months to 11.2 months, according to an assessment from an independent review committee. The trials also examined the effect on CNS metastases. Of those with measurable CNS disease, the ORR was 61%, with a duration of response of 9.1 months. Based on data from animal studies and its pharmacology, alectinib may be expected to cause fetal harm. The manufacturer does not recommend breastfeeding while taking the drug. No contraindications are listed in the manufacturer’s labeling; however, key warnings and precautions should be noted (Table 7).

The most common adverse effects of alectinib (occurring in ≥20% of patients) are fatigue, constipation, edema, and myalgia. Drug interactions for alectinib include those agents that may cause bradycardia because of an enhanced bradycardic effect. Monitoring of patients on alectinib involves testing for ALK positivity (prior to treatment); LFTs (ALT, AST, total bilirubin); CPK levels; vitals; and signs and symptoms of interstitial lung disease/pneumonitis and myalgia.

Because alectinib is a hazardous agent, special handling is required. Use is approved only in patients with metastatic
NSCLC and a confirmed positive test for the abnormal ALK gene. Alectinib is the third available oral oncologic agent that targets the ALK gene. FDA is requiring confirmatory efficacy studies because of the drug’s accelerated approval.

**New endocrinology agents**

According to CDC’s National Diabetes Statistics Report, formerly known as the National Diabetes Fact Sheet, approximately 29 million Americans (9.3%) have diabetes. In adults, type 1 diabetes mellitus (T1DM) accounts for 5% to 10% of all patients diagnosed with diabetes, while type 2 diabetes mellitus (T2DM) accounts for 90% to 95%. About 6% of those diagnosed use insulin to help manage their disease.17

**Insulin degludec**

Insulin degludec (Tresiba—Novo Nordisk) is the third long-acting basal insulin approved to treat glycemic control in adults with diabetes. Exogenous insulin is necessary in T1DM to replace insulin that the body is not producing from the pancreatic beta cells. In T2DM, basal insulin is typically added to therapy after a trial of one or more oral agents, depending on the patient’s glycemic control, as evidenced by their glycosylated hemoglobin (A1C) levels. Patients with higher A1C levels (>10%) will likely require insulin to achieve glycemic control.

Insulin degludec works like other insulins via specific receptors on target tissues to regulate metabolism of carbohydrates, proteins, and fats. Its onset of action is about 1 hour, and it has a half-life of approximately 25 hours, giving it a slightly longer duration of action than insulin glargine. Insulin degludec reaches its peak concentration in 9 hours.

Dosing of insulin degludec is similar to that of the other basal insulins (i.e., glargine and detemir) depending on whether patients are insulin naive or experienced (Table 2). In T2DM patients who are insulin naive, 10 units should be administered subcutaneously once daily at the same time every day. No dosing adjustments are required for renal or hepatic impairment; however, insulin requirements may be reduced if changes in insulin clearance or metabolism occur.

Insulin degludec has been compared head to head with both insulin glargine and insulin detemir. Six studies evaluated insulin degludec in T2DM patients, and three studies evaluated the drug in T1DM patients. All T2DM patients had background therapy with at least one or more oral agents, and none of the T1DM patients were on oral medications. The primary efficacy measure was change in A1C from baseline. A1C provides an estimate of a patient’s average blood glucose levels over the last 3 months. According to the American Diabetes Association, the goal A1C level is less than 7%.

Results showed no difference between treatment groups in reduction of A1C from baseline. Insulin degludec was noninferior to glargine in improvement of glycemic control. A meta-analysis of insulin degludec studies showed a greater reduction in fasting plasma glucose (FPG) from baseline in T1DM patients and in insulin-naive T2DM patients compared with insulin glargine, but not in T2DM patients previously treated with oral agents. The total daily dose of insulin was lower to a statistically significant degree for insulin degludec compared with insulin glargine in two of three patient groups.

For pregnancy and lactation concerns, refer to Table 4. Risk of hypersensitivity is the only noted contraindication. Some warnings and precautions for insulin degludec are listed below:

1. Do not share pens or syringes between patients, even if needles are changed.
2. When changing the insulin regimen, monitor for hyperglycemia or hypoglycemia, and carry out under close medical supervision. Increase the frequency of blood glucose monitoring.
3. Hypoglycemia may be life threatening. Patients may need to increase monitoring frequency.
4. The agent may cause hypokalemia that is life threatening. Monitor potassium levels closely at risk, and treat as needed.
5. Hypersensitivity reactions may be life threatening. Discontinue, monitor, and treat if indicated.
6. Fluid retention and heart failure (HF) may occur with concomitant use of thiazolidinediones. Patients should monitor for signs and symptoms of HF and consider a dosage reduction or discontinuation if HF occurs.

The most common adverse effects of insulin degludec include hypoglycemia, lipodystrophy, injection site reactions, rash, edema, pruritus, allergic reactions, and weight gain. Important drug interactions for insulin degludec include drugs that may increase risk of hypoglycemia (e.g., other antidiabetic agents, ACE inhibitors, angiotensin receptor blockers (ARBs), disopyramide, fribates, fluoxetine, MAOI, etc.). Drugs that may decrease the blood glucose-lowering effect of insulins include atypical antipsychotics, corticosteroids, diuretics, estrogen, oral contraceptives, protease inhibitors, sympathomimetic agents, and thyroid hormones. Consult the product label for additional interactions.

Patients using insulin degludec should have their glucose, electrolytes, A1C levels, lipid profile, renal function, and hepatic function monitored closely. Insulin degludec is the first available ultra–long acting insulin. Until its place in therapy becomes clearer, its approval provides another basal insulin option in addition to insulin glargine and insulin detemir.

**Lesinurad**

Gout, a common form of inflammatory arthritis that affects about 8.3 million people in the United States, leads to increased serum uric acid followed by deposition of monosodium urate crystal in tissue and joints. Lesinurad (Zurampic—AstraZeneca) is FDA approved for hyperuricemia in patients with gout who have not achieved target uric acid levels with a xanthine oxidase inhibitor (XOI) alone. Lesinurad lowers serum uric acid levels by inhibiting the function of the transporter proteins urate transporter (URAT) 1 and organic anion transporter (OAT) 4, which are involved in uric acid reabsorption in the kidney (Table 5).

Lesinurad is dosed 200 mg orally once daily and taken with food and water. Based on results from clinical trials, it should be coadministered with an XOI such as allopurinol
CPE NEW THERAPEUTIC AGENTS MARKETED IN 2015: PART 4

Table 5. Relevant abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>LFT</td>
<td>Liver function test</td>
<td>Measure of liver function</td>
</tr>
<tr>
<td>GGT</td>
<td>Gamma-glutamyl transpeptidase</td>
<td>Measure of liver function</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
<td>Measure of liver function</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
<td>Measure of liver function</td>
</tr>
<tr>
<td>ALP</td>
<td>Alkaline phosphatase</td>
<td>Useful but nonspecific indicator of liver or bone disease</td>
</tr>
<tr>
<td>CPK</td>
<td>Creatinine phosphokinase</td>
<td>Useful in diagnosis and monitoring of skeletal muscle disease and injury</td>
</tr>
<tr>
<td>FEV1</td>
<td>Forced expiratory volume in 1 s</td>
<td>Measure of lung function</td>
</tr>
<tr>
<td>MUGA</td>
<td>Multigated acquisition scan</td>
<td>Evaluates the function of right and left ventricles of the heart</td>
</tr>
<tr>
<td>URAT</td>
<td>Urate transporter</td>
<td>Mediates reabsorption of uric acid in the kidney and regulates blood uric acid concentration; target for gout therapy</td>
</tr>
<tr>
<td>OAT</td>
<td>Organic anion transporter</td>
<td>Responsible for renal organic anion transport; target for gout therapy</td>
</tr>
<tr>
<td>NSCLC</td>
<td>Non–small cell lung cancer</td>
<td>Squamous and nonsquamous</td>
</tr>
<tr>
<td>EGFR</td>
<td>Epidermal growth factor receptor</td>
<td>Binding to a ligand induces cell proliferation; target in oncologic therapy</td>
</tr>
<tr>
<td>TKI</td>
<td>Tyrosine kinase inhibitor</td>
<td>Inhibits activation of proteins; target in oncologic therapy</td>
</tr>
<tr>
<td>ALK</td>
<td>Anaplastic lymphoma kinase</td>
<td>Regulates signaling pathway, which is important in cell growth and proliferation; target in oncologic therapy</td>
</tr>
<tr>
<td>BRAF</td>
<td>B-Raf proto-oncogene, serine/threonine protein kinase</td>
<td>Instructs production of protein that helps transmit chemical signals; target in melanoma therapy</td>
</tr>
<tr>
<td>MAPK</td>
<td>Mitogen-activated protein kinase</td>
<td>Regulates cell functions, including proliferation, gene expression, differentiation, mitosis, cell survival, and apoptosis; target in melanoma therapy</td>
</tr>
<tr>
<td>MEK</td>
<td>Mitogen-activated protein kinase (MAPK)/MAP extracellular signal regulated kinase (MEK) 1 and MEK2</td>
<td>When inhibited, cell proliferation is blocked and apoptosis is induced; target in melanoma therapy</td>
</tr>
</tbody>
</table>

When lesinurad was added to febuxostat 80 mg and compared with febuxostat alone, there was no difference between groups. Fifty percent of patients did not reach a target uric acid level of less than 5.0 mg/dL. In addition, there was no significant difference between mean gout flare rates and patients with complete tophus resolution. More than one-half of patients in all three studies (61%–66%) had renal impairment.

No teratogenicity or effects on fetal development were observed in animal studies (see Table 4 for additional information). Contraindications for lesinurad are patients with severe renal impairment (CrCL < 30 mL/min), end-stage renal disease, or kidney transplant or patients on dialysis. In addition, lesinurad is contraindicated in tumor lysis syndrome or Lesch-Nyhan syndrome.

Labeling for lesinurad includes a boxed warning for the risk of acute renal failure, which is more common when the drug is used without an XOI. For this reason, lesinurad should be taken along with allopurinol or febuxostat.

The most common adverse effects of lesinurad include headache, influenza, elevations in serum creatinine, and gastroesophageal reflux disease (GERD). Several drug interactions exist, including CYP2C9 inhibitors, poor metabolizers, and inducers; CYP3A substrates; epoxide hydrolase inhibitors; hormonal contraceptives; and aspirin. Monitoring of le-
Table 6. Treatment options for metastatic NSCLC

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Manufacturer</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osimertinib</td>
<td>Tagrisso</td>
<td>AstraZeneca</td>
<td>Oral agent for metastatic, epidermal growth factor receptor (EGFR) T790M mutation-positive NSCLC, as detected by an FDA-approved test, for patients who have progressed on or after EGFR TKI therapy</td>
</tr>
<tr>
<td>Necitumumab</td>
<td>Portrazza</td>
<td>Eli Lilly</td>
<td>Given intravenously, in combination with gemcitabine and cisplatin, for first-line treatment of patients with metastatic, squamous NSCLC</td>
</tr>
<tr>
<td>Alectinib</td>
<td>Alecensa</td>
<td>Genentech</td>
<td>Oral agent for metastatic, ALK-positive NSCLC after failure with crizotinib; used in combination with crizotinib</td>
</tr>
</tbody>
</table>

Abbreviations used: NSCLC, non–small cell lung cancer; TKI, tyrosine kinase inhibitor; ALK, anaplastic lymphoma kinase. Sources: 10, 12, 14.

New pulmonology agent: Mepolizumab

Approximately 50% of severe asthma is associated with a persistent elevation in inflammatory markers, which is likely due to the inflammatory cytokines interleukin (IL)-4, -5, and -13.24

Mepolizumab (Nucala—GlaxoSmithKline) is a monoclonal antibody approved for add-on maintenance treatment of severe asthma in adults and children aged 12 years and older with an eosinophilic phenotype. Mepolizumab is a novel, first-in-class IL-5 receptor antagonist. Note that the drug is not indicated for the relief of acute bronchospasm or status asthmaticus.25

IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. By inhibiting IL-5 signaling, mepolizumab reduces the production and survival of eosinophils; however, the exact mechanism in asthma is uncertain.25

Mepolizumab is degraded by proteolytic enzymes that are distributed throughout the body and not restricted to the liver. The half-life of the drug ranges from 16 to 22 days, which allows for extended dosing. Mepolizumab is given 100 mg subcutaneously once every 4 weeks. Children aged 12 years or older are dosed the same as adults; the drug has not been studied in children younger than 12 years. No dosing adjustments are necessary for renal or hepatic impairment.25

The mepolizumab studies used for approval included one dose-ranging study and two confirmatory trials. The confirmatory studies are reviewed here.25–27 These randomized, double-blind, placebo-controlled studies included 711 patients with asthma. Patients were included if their serum eosinophils were greater than or equal to 150 cells/mcL at screening or greater than or equal to 300 cells/mcL within 12 months of enrollment. Mepolizumab was administered every 4 weeks in both trials as add-on to background treatment, and all participants continued their background asthma therapy for the duration of the trials.25–26

One study of 32 weeks included an active control arm. Study participants had asthma with a history of two or more exacerbations in the previous year despite regular use of high-dose inhaled corticosteroids plus additional controller(s) with or without oral steroids. Patients were randomized to mepolizumab 75 mg IV, mepolizumab 100 mg subcutaneously, or placebo. The primary endpoint was frequency of exacerbations.27

Results showed that patients treated with mepolizumab experienced fewer exacerbations compared with those on placebo. In addition, patients receiving mepolizumab had sinusurad includes renal function and serum uric acid.23

Lesinurad is a novel, first-in-class URAT1 inhibitor approved for the treatment of hyperuricemia in gout. While it offers another option to help lower uric acid levels, limitations to use include the drug’s contraindications and the requirement to use it in combination with an XOI.

Table 7. Warnings and precautions of agents for metastatic NSCLC

<table>
<thead>
<tr>
<th>Agent</th>
<th>Warnings, precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osimertinib</td>
<td>Interstitial lung disease/ pneumonitis</td>
</tr>
<tr>
<td></td>
<td>QTc interval prolongation</td>
</tr>
<tr>
<td></td>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td></td>
<td>Embryo–fetal toxicity</td>
</tr>
<tr>
<td>Necitumumab</td>
<td>Cardiopulmonary arrest  (boxed warning)</td>
</tr>
<tr>
<td></td>
<td>Hypomagnesemia (boxed warning)</td>
</tr>
<tr>
<td></td>
<td>Venous and arterial thromboembolic events</td>
</tr>
<tr>
<td></td>
<td>Dermatologic toxicities</td>
</tr>
<tr>
<td></td>
<td>Infusion-related reactions</td>
</tr>
<tr>
<td></td>
<td>Increased toxicity</td>
</tr>
<tr>
<td></td>
<td>Embryo–fetal toxicity</td>
</tr>
<tr>
<td>Alectinib</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td>Interstitial lung disease/ pneumonitis</td>
</tr>
<tr>
<td></td>
<td>Bradycardia</td>
</tr>
<tr>
<td></td>
<td>Severe myalgia and creatine phosphokinase elevation</td>
</tr>
<tr>
<td></td>
<td>Embryo–fetal toxicity</td>
</tr>
</tbody>
</table>

Abbreviations used: NSCLC, non–small cell lung cancer; QTc, heart rate–corrected QT. Sources: 10, 12, 14.
fewer exacerbations requiring hospitalization and/or emergency department visits and fewer exacerbations requiring only inpatient hospitalization.27

The second study was an oral corticosteroid-reduction trial that continued for 24 weeks. Study participants had asthma and required daily oral corticosteroids in addition to regular use of high-dose inhaled corticosteroids plus additional controller(s) to maintain asthma control. They were not required to have a history of exacerbations in the prior year. Patients were randomized to mepolizumab 100 mg subcutaneously or placebo. The primary endpoint in this study was the percentage of reduction of oral corticosteroid dose during weeks 20 to 24 compared with the baseline dose. Results showed a greater reduction in daily dose of maintenance oral corticosteroids for mepolizumab versus placebo. In the mepolizumab group, 23% of patients achieved a 90% to 100% reduction in their oral corticosteroid dose compared with 11% in the placebo group.26

Adverse events were not observed in animal studies; however, mepolizumab is expected to cross the placenta, and potential effects to the fetus may be greater in the second and third trimesters. In addition, uncontrolled asthma is associated with adverse events in pregnancy. Asthma should be closely monitored in pregnant women. The manufacturer recommends that the decision to breastfeed during therapy should take into account benefits and risks.25

Mepolizumab is contraindicated in patients with hypersensitivity, which can occur within hours or days. Warnings and precautions include hypersensitivity reactions and infection.24 The drug’s most common adverse effects are headache, fatigue, eczema, pruritus, upper abdominal pain, urinary tract infection, hypersensitivity reaction, immunogenicity, injection site reactions, back pain, and muscle spasm.25

No significant drug interactions should be noted with mepolizumab. Monitoring of patients taking this drug includes forced expiratory volume in 1 second (FEV1), peak flow, and other pulmonary function tests as clinically appropriate. Providers should monitor for an increased use of short-acting beta-2-agonist inhalers, as this may be a marker of worsening asthma.

Mepolizumab is the second available monoclonal antibody for treatment of severe asthma. Patients with a baseline serum eosinophil count of greater than or equal to 150 cells/μL may potentially see the most benefit with mepolizumab.23 Omalizumab (Xolair—Genentech/Novartis) is the other subcutaneous agent; however, it is approved for moderate to severe asthma, has a different mechanism of action, and has weight-based dosing determined by pretreatment immunoglobulin E (IgE) levels.

New psychology/neurology agents

Two new agents were approved in 2015 for the treatment of schizophrenia: brexpiprazole (Rexulti—Otsuka) and cariprazine (Vraylar—Actavis). Brexpiprazole is also approved as an adjunct to antidepressants for the treatment of major depressive disorder (MDD).26 Cariprazine has an additional indication for acute treatment of manic or mixed episodes associated with bipolar I disorder.29

Mental illnesses refer to disorders generally characterized by dysregulation of mood, thought, and/or behavior, as recognized by the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM–IV). Schizophrenia, a brain disorder that affects the way a person thinks, is characterized by a range of cognitive, behavioral, and emotional experiences. The Substance Abuse and Mental Health Services Administration describes the lifetime prevalence of schizophrenia as approximately 1% of the U.S. population.30

Patients with bipolar disorders experience atypical, dramatic swings in mood that may include manic, hypomanic, and major depressive episodes or mixed states. It is estimated that the combined prevalence of bipolar disorders is 2.6% of the U.S. adult population and 11.2% of individuals aged 13 to 18 years.30

Depressive disorders, defined as mood and cognitive changes that significantly interfere with daily life, are one of the most common mental health disorders in the United States. On the basis of a survey conducted in 2014, researchers have estimated that 6.6% of adults aged 18 or older have had a major depressive episode.29

Brexpiprazole

Brexpiprazole (Rexulti—Otsuka) is a second-generation antipsychotic indicated for schizophrenia and as adjunctive therapy to antidepressants for the treatment of MDD.28

Brexpiprazole's mechanism of action is unknown, but researchers hypothesize that it is mediated through a combination of partial agonist activity at serotonin 5-HT1A and dopamine D2 receptors, as well as antagonist activity at serotonin 5-HT2A receptors. Brexpiprazole is bound primarily to albumin and alpha-1-acid glycoprotein and is metabolized predominantly by the liver via CYP3A4 and CYP2D6.28

Brexpiprazole is initially dosed 1 mg once daily for both MDD and schizophrenia. Refer to Table 2 for detailed dosing instructions. In general, no dosage adjustments are necessary for brexpiprazole. In patients with CrCl less than 60 mL/min or with a Child-Pugh Class B or C score, the maximum dose of brexpiprazole is 2 mg/d for MDD and 3 mg/d for schizophrenia.28

Brexpiprazole in the setting of MDD was studied in two 6-week, double-blind, placebo-controlled trials that enrolled patients who met DSM–IV–Text Revision (TR) criteria for MDD. The primary endpoint was change from baseline to week 6 in the Montgomery–Asberg Depression Rating Scale (MADRS), a 10-item clinical rating scale used to assess the degree of depressive symptomatology.31, 32

Results showed that brexpiprazole 2 mg and 3 mg were superior to placebo in treating depressive symptoms in MDD, with a greater decrease in MADRS from baseline. Brexpiprazole 1 mg failed to show a statistically significant difference in efficacy compared with placebo.31, 32

Efficacy of brexpiprazole in schizophrenia was also studied in two separate 6-week, randomized, double-blind, placebo-controlled trials. Both studies enrolled patients who met DSM–IV–TR criteria for schizophrenia. The primary endpoint was change from baseline to week 6 in the Positive
and Negative Syndrome Scale (PANSS), a 30-item scale (total score range, 30–210) used to measure the severity of schizophrenia. PANSS consists of separate scores in nine domains, including positive and negative symptoms, depression, and a composite index. A higher score indicates a greater severity of schizophrenia.25,33–36

In both trials, brexpiprazole showed a statistically significant improvement in PANSS total score compared with placebo, proving its efficacy in improving the symptoms of patients with schizophrenia.29,34

Brexiprazole should be used with caution in women who are pregnant or breastfeeding, and therapy should be individualized on the basis of risks and benefits. A key boxed warning includes increased mortality in older adult patients with dementia-related psychosis treated with antipsychotic drugs and an increased risk of suicidal thoughts and behaviors in patients aged 24 years and younger. Monitoring for worsening of symptoms is recommended. Warning and precautions for the drug include blood dyscrasias, cerebrovascular effects, CNS depression, dyslipidemia, esophageal dysmotility, extrapyramidal symptoms (EPS), hyperglycemia, neuroleptic malignant syndrome, orthostasis, suicidal thinking, temperature dysregulation, and weight gain.29

The most common adverse effects are weight gain and akathisia. Monitoring of patients taking brexpiprazole includes vitals, complete blood count (CBC), mental status, LFTs, lipids, and glucose. There are numerous drug interactions with brexpiprazole. Concomitant use of brexpiprazole with strong CYP3A4 inhibitors and inducers as well as with strong CYP2D6 inhibitors or poor metabolizers requires dosing adjustment. For detailed instructions, refer to the package insert.28

Although approval of brexpiprazole provides another option for patients with schizophrenia or those who require augmentation of antidepressant therapy for MDD, brexpiprazole’s place in therapy remains unclear. Patients and providers have a plethora of options to choose from in this class.

Cariprazine
Cariprazine (Vraylar—Actavis) is a second-generation atypical antipsychotic indicated for the treatment of schizophrenia and for the acute treatment of manic or mixed episodes associated with bipolar I disorder. Cariprazine works as a partial agonist at dopamine D2 receptors and serotonin 5-HT1A receptors and as an antagonist at serotonin 5-HT2A receptors.29

Initially, cariprazine is dosed 1.5 mg once daily for both schizophrenia and bipolar I disorder. The dose for both disorders can be increased to 3 mg on day 2 of therapy. The recommended dosing range is 3 mg to 6 mg once daily (Table 2). Because cariprazine and its active metabolites have a long half-life, it is important to remember that changes in dose may not be fully reflected in plasma for several weeks.29

Efficacy of cariprazine in schizophrenia has been evaluated in three 6-week, randomized, double-blind, placebo-controlled trials that enrolled patients who met DSM–IV–TR criteria for schizophrenia. The primary endpoint was a change from baseline in PANSS.

All three studies showed a statistically significant improvement in the PANSS score for the cariprazine groups compared with those receiving placebo. A dose-related increase in certain adverse effects was present (seen more commonly at doses greater than 6 mg/d).28,35,36

For the treatment of bipolar I disorder, cariprazine was evaluated in three separate 3-week studies, each of which enrolled patients who met diagnostic criteria for bipolar disorder. The primary endpoint was a change in Young Mania Rating Scale (YMRS) score from baseline. The YMRS is an 11-item (total score, 0–60), clinician-administered scale used to assess the severity of manic symptomatology.27–29

Cariprazine was associated with a statistically significant decrease in YMRS score at week 3 compared with placebo. Doses greater than 6 mg/d failed to show additional benefits over lower doses.37–39

Use of cariprazine in patients with CrCl less than 30 mL/min or severe hepatic impairment (Child-Pugh Class C) is not recommended. In addition, antipsychotic use during the third trimester of pregnancy carries a risk of abnormal muscle movements and/or withdrawal symptoms in newborns after delivery. Use of antipsychotics during pregnancy and lactation should be individualized on the basis of benefits and risks.40

One warning for the drug is that increased mortality and cerebrovascular adverse effects were seen more often in older adults with dementia-related psychosis in clinical trials. Other warnings and precautions include neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes, blood dyscrasias related to leukocytes, orthostasis, seizures, cognitive/motor impairment, body temperature dysregulation, and dysphagia.29

The most common adverse effects associated with cariprazine (incidence ≥ 5% and at least twice the rate of placebo) are EPS and akathisia in patients with schizophrenia and EPS, akathisia, dyspepsia, vomiting, somnolence, and restlessness in patients with bipolar mania.29

Cariprazine is known to interact with strong CYP3A4 inhibitors. If concomitant use is unavoidable, refer to the package insert for detailed dosing information. Concomitant use of cariprazine and CYP3A4 inducers is not recommended. While patients are on cariprazine, monitoring of mental status, blood pressure, weight, height, body mass index, waist circumference, and complete blood count is recommended.29

Many options exist for the treatment of schizophrenia and bipolar mania. Currently, cariprazine’s place in therapy is unclear.

Flibanserin
Hypoactive sexual desire disorder (HSDD) is defined by the American Psychiatric Association as a persistent or recurrent deficiency or absence of sexual fantasies and desire for sexual activity that causes marked distress or interpersonal difficulty.41 According to a 2006 U.S. population–based survey, about 10% of premenopausal women experience low sexual desire with associated distress.42 The prevalence rate of HSDD varies between 5.4% and 13.6%.43 The cause of HSDD
### Table 8. Additional approvals of therapeutic agents

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Manufacturer</th>
<th>Indication</th>
<th>What’s new?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esomeprazole magnesium</td>
<td>Nexium 24HR</td>
<td>AstraZeneca</td>
<td>GERD</td>
<td>New dosage form</td>
</tr>
<tr>
<td>Methylphenidate HCl</td>
<td>QuilliChew ER</td>
<td>Pfizer</td>
<td>ADHD</td>
<td>New dosage form</td>
</tr>
<tr>
<td>Bendamustine HCl</td>
<td>Bendeka</td>
<td>Teva and Eagle</td>
<td>Chronic lymphocytic leukemia; indolent B-cell non-Hodgkin lymphoma</td>
<td>New formulation</td>
</tr>
<tr>
<td>Ethinyl estradiol; levonorgestrel</td>
<td>Elifemme</td>
<td>Sandoz</td>
<td>Oral contraceptive</td>
<td>New branded generic</td>
</tr>
<tr>
<td>IncobotulinumtoxinA</td>
<td>Xeomin</td>
<td>Merz Pharmaceuticals</td>
<td>Multiple myeloma; erythema nodosum leprosum</td>
<td>New efficacy data</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Thalomid</td>
<td>Celgene</td>
<td>Multiple myeloma; transfusion-dependent anemia due to myelodysplastic syndrome; mantle cell lymphoma</td>
<td>New efficacy data</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Revlimid</td>
<td>Celgene</td>
<td>Multiple myeloma; erythema nodosum leprosum</td>
<td>New efficacy data</td>
</tr>
<tr>
<td>Calcipotriene; betamethasone</td>
<td>Enstilar</td>
<td>Leo Pharma</td>
<td>Plaque psoriasis</td>
<td>New branded generic</td>
</tr>
<tr>
<td>Empagliflozin; metformin</td>
<td>Synjardy</td>
<td>Boehringer Ingelheim</td>
<td>Type 2 diabetes</td>
<td>New combination</td>
</tr>
<tr>
<td>Insulin degludec; insulin aspart</td>
<td>Ryzodeg 70/30</td>
<td>Novo Nordisk</td>
<td>Types 1 and 2 diabetes</td>
<td>New combination</td>
</tr>
<tr>
<td>Irinotecan liposome injection</td>
<td>Onivyde</td>
<td>Merrimack Pharmaceuticals</td>
<td>Metastatic adenocarcinoma of the pancreas</td>
<td>New formulation</td>
</tr>
<tr>
<td>Recombinant factor VIII</td>
<td>Nuwiq</td>
<td>Octapharma</td>
<td>Prophylaxis and treatment of hemophilia A</td>
<td>New formulation</td>
</tr>
<tr>
<td>Ombitasvir, paritaprevir, and ritonavir</td>
<td>Technivie</td>
<td>AbbVie</td>
<td>Genotype 4 chronic HCV infection without cirrhosis</td>
<td>New combination</td>
</tr>
<tr>
<td>Idarucizumab</td>
<td>Praxbind</td>
<td>Boehringer Ingelheim</td>
<td>Reversal of the anticoagulant effects of dabigatran</td>
<td>New molecular entity</td>
</tr>
<tr>
<td>Trabectedin</td>
<td>Yondelis</td>
<td>Janssen</td>
<td>Unresectable or metastatic liposarcoma or leiomyosarcoma</td>
<td>New molecular entity</td>
</tr>
<tr>
<td>Asfotase alfa</td>
<td>Strensiq</td>
<td>Alexion</td>
<td>Perinatal/infantile- and juvenile-onset hypophosphatasia</td>
<td>New molecular entity</td>
</tr>
<tr>
<td>Sebelipase alfa</td>
<td>Kanuma</td>
<td>Alexion</td>
<td>Lysosomal acid lipase deficiency</td>
<td>New molecular entity</td>
</tr>
<tr>
<td>Sugammadex</td>
<td>Bridion</td>
<td>Merck</td>
<td>Reversal of neuromuscular blockade induced by rocuronium bromide and vecuronium bromide</td>
<td>New molecular entity</td>
</tr>
</tbody>
</table>

Abbreviations used: GERD, gastroesophageal reflux disease; HCl, hydrochloride; ADHD, attention deficit hyperactivity disorder; HCV, hepatitis C virus.

is uncertain, but it is hypothesized to result from a deficiency in dopaminergic and noradrenergic activity and an excess in serotonergic activity. Flibanserin (Addyi—Sprout Pharmaceuticals) is the first agent approved for the treatment of premenopausal women with acquired, generalized HSDD, characterized by low sexual desire that causes marked distress or interpersonal difficulty and is not due to a coexisting condition, problems with one’s relationship, or effects of a medication or other drug substance. Flibanserin is not indicated for the treatment of HSDD in postmenopausal women, for men, or to enhance sexual performance.

The mechanism of action of flibanserin is unknown; however, it has shown agonist activity at 5-HT and an-
tagonist activity at 5-HT_2A_. The drug also has moderate antagonist activities at the 5-HT_2B, 5-HT_3, and dopamine D3 receptors. Flibanserin corrects an imbalance of the levels of the neurotransmitters that affect sexual desire by increasing dopamine and norepinephrine, which are responsible for sexual excitement, and by decreasing serotonin, which is responsible for sexual inhibition.45

About 98% of flibanserin is bound to albumin, and its half-life is approximately 11 hours. Flibanserin is dosed 100 mg orally once daily at bedtime. Timing of the dose is important; it is not recommended that the drug be taken during waking hours because of an increased risk of hypotension, syncope, accidental injury, and CNS depression. Instruct patients who miss a dose to wait until bedtime to take the next dose and not to double the dose. No dose adjustments are necessary in patients with renal impairment; however, flibanserin is contraindicated for patients with any degree of hepatic impairment.45

Approval of flibanserin was based on three 24-week, randomized, double-blind, placebo-controlled trials. The studies enrolled premenopausal females with acquired, generalized HSDD of at least 6 months. Acquired HSDD was defined as patients who had no previous issues with sexual desire. Generalized HSDD was defined as HSDD that was not due to stimulations, situations, or partners.

The primary efficacy endpoints were satisfying sexual events (SSEs) and sexual desire measured by patient responses, the Female Sexual Function Index, and daily electronic diary entries. In all studies, flibanserin showed a statistically significant improvement from baseline in sexual desire and SSEs compared with placebo.46

Use of flibanserin during pregnancy and lactation is not recommended (Table 4). Because syncope has been observed with increased flibanserin exposure in CYP2C19 poor metabolizers, more frequent monitoring is advised with these patients. Flibanserin is contraindicated in patients who drink alcohol and in those with moderate and strong CYP3A4 inhibitors because concomitant use increases the risk of severe hypotension and syncope. Use of the drug is also contraindicated in patients with hepatic impairment because of the increased risk of syncope and hypotension.45

Flibanserin is available only through a Risk Evaluation and Mitigation Strategy (REMS) program because of the high risk of hypotension and syncope. Flibanserin may also cause CNS depression, such as somnolence or sedation. It most common adverse effects are dizziness, somnolence, nausea, fatigue, insomnia, and dry mouth.45

There are several drug interactions to note. As previously mentioned, because of the increased risk of syncope, hypotension, and CNS depression, concomitant use of alcohol, other CNS depressants, and CYP3A4 inhibitors should be avoided. Because flibanserin is metabolized primarily by CYP3A4 and CYP2C19, oral contraceptives, strong CYP2C19 inhibitors, and CYP3A4 inducers should be avoided. Increased digoxin concentrations are expected when used with digoxin. Increased monitoring of digoxin levels is advised.45

Flibanserin provides the first treatment option to improve sexual function in premenopausal women with HSDD. However, clinical utility remains unclear because of adverse effects and contraindications.

In addition to new molecular entities and new therapeutic biologies, FDA has approved many new combinations of previously approved drugs, new formulations, and new indications for currently marketed drugs. Although not an exhaustive list, Table 8 provides an overview of some of these products.

**References**

20. American Association of Clinical Endocrinologists, American Col-


45. Flibanserin [prescribing information]. Raleigh, NC: Sprout Pharmaceuticals; August 2015.
CPE assessment
This assessment must be taken online; please see "CPE information" for further instructions. The online system will present these questions in random order to help reinforce the learning opportunity. There is only one correct answer to each question.

1. Which medication is a tyrosine kinase receptor inhibitor?
   a. Cobimetinib
   b. Alectinib
   c. Osimertinib
   d. Necitumumab

2. How does brexpiprazole differ from cariprazine?
   a. Cariprazine is safe to use in breastfeeding and brexpiprazole is not.
   b. Brexpiprazole has an indication for major depressive disorder and cariprazine does not.
   c. The maximum brexpiprazole dose is 6 mg/d and the maximum cariprazine dose is 4 mg/d.
   d. Cariprazine needs no dose adjustment; however, brexpiprazole should be dose adjusted in severe hepatic impairment.

3. Which of the following drug : indication pairings is correct?
   a. Mepolizumab : non–small cell lung cancer
   b. Flibanserin : hypoactive sexual desire disorder
   c. Selexipag : hyperuricemia with gout
   d. Lesinurad : pulmonary arterial hypertension

4. Which of the following drugs is administered subcutaneously?
   a. Lesinurad
   b. Necitumumab
   c. Alectinib
   d. Mepolizumab

5. Which of the following statements is correct?
   a. Lesinurad is dosed 200 mg three times a day.
   b. Osimertinib is safe to use in pregnant woman.
   c. Insulin degludec is available as U-100.
   d. Necitumumab needs to be used in combination with crizotinib.

6. With the use of which of the following agents does bradycardia have the greatest risk?
   a. Alectinib
   b. Osimertinib
   c. Mepolizumab
   d. Necitumumab

7. Which of the following statements is correct about cobimetinib?
   a. It needs to be adjusted based on creatinine clearance.
   b. It must be given in combination with crizotinib.
   c. It is approved for patients with a BRAF V600E or V600K mutation.
   d. It has many drug interactions.

8. Which of the following statements is correct about insulin degludec?
   a. It is a long-acting basal insulin.
   b. It is only indicated for type 1 diabetes.
   c. It was superior when compared with insulin glargine.
   d. It does not have the risk of hypoglycemia.

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9. Which of the following statements is correct about brexpiprazole?
   a. Its most common adverse effect is weight loss.
   b. It is safe to use in pregnant women.
   c. Its warnings include blood dyscrasias, central nervous system effects, and dyslipidemia.
   d. It is safe to use in elderly patients.

10. Which of the following statements is correct about cariprazine?
   a. It is indicated for the treatment of schizophrenia and bipolar II disorder.
   b. Dose changes may not be fully reflected in plasma for several weeks due to the drug’s long half-life.
   c. Its recommended dosing range is 1.5 mg to 3 mg once daily.
   d. It failed to show superiority when compared with placebo.

11. Which of the following statements is correct about osimertinib?
   a. When on osimertinib, monitoring of cytogenetic mutation status, electrocardiogram, and electrolytes is recommended.
   b. It is dosed orally as 160 mg once daily until disease progression.
   c. It is contraindicated in renal impairment.
   d. It is safe to use in pregnancy.

12. Which of the following statements is correct about necitumumab?
   a. It is dosed 800 mg subcutaneously on days 1 and 8 of each 3-week treatment cycle.
   b. Dose adjustments are necessary in renal and hepatic impairment.
   c. It is indicated for treatment of nonsquamous non–small cell lung cancer.
   d. It needs to be given in combination with gemcitabine and cisplatin.

13. Which of the following statements is correct about lesinurad?
   a. It is dosed 200 mg orally once daily.
   b. It is approved as first-line treatment for hyperuricemia.
   c. It should not be given to geriatric patients.
   d. It should not be used in patients with a creatinine clearance level of less than 60 mL/min.

14. Which of the following statements is correct about lesinurad?
   a. Teratogenic effects on fetal development were observed in animal studies.
   b. The risk of acute renal failure is increased when lesinurad is used with a xanthine oxidase inhibitor.
   c. It is safe to use with aspirin.
   d. Its adverse effects include acute uric acid nephropathy including flank pain, nausea, and vomiting.

15. Which of the following statements is correct about flibanserin?
   a. It is indicated for treatment of men with hypoactive sexual desire disorder.
   b. It should not be taken during waking hours.
   c. It improves sexual performance.
   d. It is dosed 200 mg orally once daily at bedtime.

16. Which of the following statements is correct about flibanserin?
   a. It is only available through a Risk Evaluation and Mitigation Strategy program.
   b. Dose adjustment is necessary in patients with renal impairment.
   c. It is safe to use in patients with hepatic impairment.
   d. It is safe to consume alcoholic beverages while on flibanserin.

17. Which of the following statements is correct about brexpiprazole?
   a. In patients with a creatinine clearance level of less than 80 mL/min, the maximum dose is 2 mg/d for major depressive disorder.
   b. It is a 5-HT1A and D2 receptor partial antagonist and a 5-HT2A receptor agonist.
   c. Brexpiprazole 1 mg was superior when compared with placebo.
   d. It is indicated for adjunctive therapy to antidepressants for the treatment of major depressive disorder.

18. Which of the following statements is correct about mepolizumab?
   a. It is indicated for acute bronchospasm or status asthmaticus.
   b. It is not expected to cause fetal harm.
   c. Its warnings and precautions include hypersensitivity reactions and infection.
   d. It was approved as a monotherapy for severe asthma in adults and children aged 12 years and older.

19. Which of the following statements is correct regarding selexipag?
   a. It works the same as endogenous prostacyclin.
   b. It can help delay disease progression and reduce the risk of hospitalization.
   c. It is dosed 200 mg orally twice daily.
   d. It is safe to use while breastfeeding.

20. Which of the following is administered intravenously?
   a. Selexipag
   b. Flibanserin
   c. Necitumumab
   d. Mepolizumab