New Drugs: Eliquis, Fulyzaq, Sirturo, and Xeljanz

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Dr. Thomas A. Gossel has no relevant financial relationships to disclose.

Goal. The goal of this lesson is to provide information on apixaban (Eliquis®), crofelemer (Fulyzaq™), bedaquiline (Sirturo™) and tofacitinib (Xeljanz®).

Objectives. At the completion of this activity, the participant will be able to:
1. identify the new drugs by generic name, trade name and chemical name when relevant;
2. select the indication(s), pharmacologic action(s) and clinical applications for each drug;
3. recognize important therapeutic uses for the drugs and their applications in specified pathologies; and
4. demonstrate an understanding of adverse effects and toxicity, significant drug-drug interactions, and patient counseling information for these drugs.

Drugs discussed within this lesson are new-molecular entity drugs for oral administration that are indicated to treat a variety of pathologies (Table 1). The lesson provides a brief introduction to the new drugs and is not intended to extend beyond an overview of the topic. The reader is, therefore, urged to consult the products’ full Prescribing Information leaflet (package insert), Medication Guide when available, and other published reference sources for detailed descriptions.

Apixaban (Eliquis)

Warfarin reduces the risk of stroke in patients with atrial fibrillation (AF) and is classified as a preferred therapy in practice guidelines. Its limitations, however, have contributed to its underuse in clinical practice. These limitations have led to development of several new oral anticoagulants, including direct thrombin inhibitors and blood clotting factor Xa inhibitors, for patients with AF. One of the new drugs is Eliquis.

Indications and Use. Eliquis is a factor Xa inhibitor anticoagulant indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF.

Stroke and systemic embolism in atrial fibrillation. AF is an abnormal, irregular, and rapid beating of the heart such that the atria do not contract in synchrony with the ventricles. This may lead to intra-atrial formation of thrombi that can break loose and circulate as emboli to the brain or elsewhere in the body. Anti-clotting drugs lower the risk of stroke by helping prevent thrombi from forming.

AF is the most common cardiac arrhythmia, currently estimated to be 1.5 to 2 percent of the general population worldwide. The average age of patients with AF is steadily rising, now averaging between 75 and 85 years. The arrhythmia is associated with a five-fold increase in risk of stroke, a three-fold increase in incidence of congestive heart failure, and higher mortality. Hospitalization of patients with AF is also very common. The arrhythmia is a major cardiovascular challenge in modern society and its medical, social and economic aspects are all predicted to intensify over the coming decades. Fortunately, a number of valuable treatments have been devised in recent years that may offer some solution to this problem.

Since its discovery in the early 1920s, warfarin has been the major therapeutic agent for reduction of thromboembolic events in patients with AF. Its benefits are well documented and include a 64 percent relative risk reduction in stroke compared with placebo and a 37 percent risk reduction compared with antiplatelet therapy. However, various drug and diet interactions can lead to an unpredictable dose response that can reduce its clinical effectiveness or increase its toxicity, sometimes with catastrophic results. Moreover, its need for regular laboratory monitoring, perhaps weekly, makes it an unattractive choice for many patients. As a result, use of warfarin in patients with AF is often not ideal, especially to those at highest risk for thromboembolic events. However, warfarin is safe when the patient’s international normalized ratio (INR) is maintained within the therapeutic range. Complications usually occur when it is not in range – i.e., bleeding can occur when the INR is high and the risk for ischemic stroke is increased when the INR is low.

Oral anticoagulants that pro-
vide stable, predictable anticoagulation without the need for monitoring have long been of interest. Agents such as apixaban and others have the potential to address some of the limitations of warfarin. In general, they have fewer drug and food interactions and a more predictable anticoagulant effect, thus allowing fixed dosing without the need for careful laboratory monitoring. Furthermore, their shorter half-life compared to warfarin may provide additional advantages, e.g., if temporary interruption is required for a surgical procedure in the case of a hemorrhagic complication.

**Mechanism of Action.** Apixaban is a reversible and selective inhibitor of coagulation factor Xa. It inhibits free and clot-bound factor Xa, and prothrombinase activity. Apixaban has no direct effect on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting factor Xa, apixaban decreases thrombin generation and thrombus development. As a result of factor Xa inhibition, the drug prolongs clotting tests such as prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT). Changes in these clotting tests with therapeutic drug doses, however, are small, subject to a high degree of variability, and not useful in monitoring the anticoagulation effect of apixaban.

**Safety.** Evidence for the safety of Eliquis was derived from the ARISTOTLE (Apixaban for Reduction In STroke and Other ThromboemboLic Events in atrial fibrillation) and AVERROES (Apixaban VErsus acetylsalicylic acid (ASA) to Reduce the Rate Of Embolic Stroke in atrial fibrillation) trials. These studies included 11,284 patients receiving Eliquis 5 mg twice daily and 602 patients taking doses of 2.5 mg twice daily. The duration of drug exposure in the two trials was ≥12 months for 9375 patients and ≥24 months for 3369 patients. In ARISTOTLE, the mean duration of exposure was 89 weeks (>15,000 patient-years). In AVERROES, the mean duration of exposure was approximately 59 weeks (>3000 patient-years).

The most common reason (Table 1) for discontinuation of treatment in both studies was bleeding-related events; in ARISTOTLE this occurred in 1.7 percent and 2.5 percent of patients treated with Eliquis and warfarin, respectively, and in AVERROES, in 1.5 percent and 1.3 percent on Eliquis and aspirin, respectively.

**Warnings, Precautions and Contraindications.** The following warnings and precautions are listed:

- **Serious and potentially fatal bleeding:** signs and symptoms of blood loss should be evaluated promptly.

- **Prosthetic heart valves:** because the use of Eliquis for patients with prosthetic heart valves has not been studied, its use in these patients is not recommended.

- A **Boxed Warning** advises that patients are at an increased

### Table 1

<table>
<thead>
<tr>
<th>Generic (Proprietary Name)</th>
<th>Applicant/Sponsor/ Distributor</th>
<th>Indication</th>
<th>Dose*</th>
<th>Dosage Form</th>
<th>Most Common Adverse Reactions</th>
<th>Medication Guide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban (Eliquis)</td>
<td>Bristol-Myers Squibb Company, &amp; Pfizer</td>
<td>Anticoagulant for patients with atrial fibrillation</td>
<td>5 mg twice daily</td>
<td>2.5, 5 mg tablets</td>
<td>Incidence &gt;1%: bleeding reactions</td>
<td>Yes</td>
</tr>
<tr>
<td>Bedaquiline (Sirturo)</td>
<td>Janssen Therapeutics</td>
<td>Pulmonary multi-drug resistant TB</td>
<td>400 mg/day for 2 weeks, then 200 mg 3 times a week for 22 weeks</td>
<td>100 mg tablets</td>
<td>Incidence ≥10%: nausea, arthralgia, headache</td>
<td>Yes</td>
</tr>
<tr>
<td>Crofelemer (Fulyzaq)</td>
<td>Salix Pharmaceuticals, Inc.</td>
<td>Antidiarrheal for patients with HIV/AIDS</td>
<td>125 mg twice daily</td>
<td>125 mg delayed-release tablets</td>
<td>Incidence ≥3%: URT§ infections bronchitis, cough, flatulence, increased bilirubin</td>
<td>No</td>
</tr>
<tr>
<td>Tofacitinib (Xeljanz)</td>
<td>Pfizer</td>
<td>Moderate to severe rheumatoid arthritis</td>
<td>5 mg twice daily</td>
<td>5 mg tablets</td>
<td>Incidence ≥2%: URT§ infections, headache, diarrhea, nasopharyngitis</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Recommended dose for most patients  §URT – Upper respiratory tract  †At the time of lesson publication
that regulates movement of sub-
P-glycoprotein (P-gp; a transporter associated with a low risk of bleeding
risk of thrombotic events following Eliquis discontinuation.
Contraindications for Eliquis include active pathological bleeding, and severe hypersensitivity to the drug.
Eliquis should be discontinued at least 24 hours prior to elective surgery or invasive procedures associated with a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled. Eliquis should be discontinued at least 48 hours prior to elective surgery or invasive procedures that have a moderate or high risk of unacceptable or clinically significant bleeding.
Drug Interactions. Apixaban is a substrate of both CYP3A4 and P-glycoprotein (P-gp; a transporter that regulates movement of sub-
stances across biological membranes). Strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, clarithromycin) increase blood levels of apixaban and increase the risk of bleeding. Eliquis dosage should be reduced to 2.5 mg with concomitant drug use. Simultaneous use of strong inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John’s wort) decrease exposure to apixaban and, thus, increase the risk of stroke. Concomitant use should be avoided.

Coadministration of aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombotic agents, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the risk of bleeding.

Patient Counseling Information. An FDA-approved Medication Guide must be dispensed with Eliquis. Specific points for counseling are summarized in Table 2.

Bedaquiline (Sirturo)
The number of multi-drug resistant tuberculosis (MDR-TB) cases reported to the World Health Organization (WHO) increased from 29,000 to 53,000 between 2008 and 2010. According to the U.S. Centers for Disease Control and Prevention (CDC), nearly nine million people around the world and 10,528 people in this country became sick with TB in 2011. Sirturo is the first FDA-approved agent to treat MDR-TB.

Indications and Use. Sirturo is an antimycobacterial drug indicated as part of combination therapy in adults ≥18 years of age with pulmonary MDR-TB. The drug should be reserved for use when an effective treatment regimen cannot otherwise be provided. The drug is not indicated for treatment of latent, extra-pulmonary or drug-sensitive tuberculosis. Safety and efficacy of Sirturo for treatment of latent infection due to Mycobacterium tuberculosis or drug-sensitive TB has yet to be established. Likewise, there are no data to support treatment with Sirturo for extra-pulmonary TB (e.g., central nervous system); therefore, use of the drug in these conditions is not recommended.

Sirturo should only be used in combination with at least three other drugs to which the patient’s MDR-TB isolate has been shown to be susceptible in vitro. If in vitro testing results are unavailable, treatment may be initiated with Sirturo in combination with at least four other drugs to which the patient’s MDR-TB isolate is likely to be susceptible.

Tuberculosis. TB, a term that describes a broad range of clinical illnesses caused primarily by M. tuberculosis, was identified as far back as ancient Egyptian times. It is one of the world’s deadliest diseases. TB did not emerge as a major health problem until the advent of the industrialized revolution, which led to crowded living and working conditions that favored its spread. It is spread through the air when an infected person coughs, sneezes, speaks or sings. The pathogen can remain airborne for several hours. TB usually affects the lungs but can also affect other parts of the body such as the brain, spine and kidneys. Humans are the only known reservoir for M. tuberculosis, an aerobic, non-spore-forming, nonmotile bacillus. The emerging threat is development of extensively drug-resistant TB, first reported in 2005. A WHO Emergency Global Task Force defines MDR-TB as TB that is resistant to at least isoniazid and rifampin (among the first-line antimycobacterial agents), to any fluoroquinolone antibiotic, and to at least one second-line injectable drug (amikacin, capreomycin or kanamycin).

Mechanism of Action. Bedaquiline inhibits mycobacterial ATP (adenosine 5’-triphosphate) synthase, an enzyme essential for cellular generation of energy in M. tuberculosis. The drug is primarily subjected to oxidative metabolism
Table 3  
**Patient counseling information for Sirturo**

Patients should be advised:
- Tuberculosis is a serious disease that can be fatal; some patients with resistant TB may have limited treatment options.
- Serious side effects can occur: death, heart rhythm abnormalities, and/or hepatitis.
- Patients should also be advised about other potential side effects with Sirturo: nausea, joint pain, headache, hemoptysis (coughing up of blood or blood-stained sputum), chest pain, anorexia, and/or rash. Additional testing may be needed to monitor or reduce the likelihood of adverse effects.
- Take Sirturo in combination with other antmycobacterial drugs as prescribed. Stay fully compliant with the full course of therapy. Skipping doses or not completing the full course of therapy may decrease the effectiveness of the treatment and increase the likelihood that the infection may develop resistance and the disease will not be treatable by Sirturo or other antibacterial drugs in the future.
- If a dose is missed during the first two weeks of treatment, patients should not make up the missed dose but should continue the usual dosing schedule. From Week 3 onward, if a 200 mg dose is missed, patients should take the missed dose as soon as possible, and then resume the three times a week regimen.
- Take the drug with food. Swallow the tablets whole with water.
- Abstain from alcohol, hepatotoxic medications or herbal products.
- Discuss with their physician the other medications they are taking and other medical conditions before starting treatment with Sirturo.
- Consult with their physician if they have a personal or family history of congenital QT prolongation or heart failure.

leading to formation of the metabolite N-monodesmethyl (M2). M2 is not believed to contribute significantly to clinical efficacy given its low average exposure (23 to 31 percent) and four- to six-fold lower antimycobacterial activity compared to the parent compound. M2 concentrations appear to correlate with QT prolongation.

**Safety.** Adverse drug reactions for Sirturo (Table 1) were identified from the pooled safety data from 335 bedaquiline-exposed patients who received the drug for eight weeks (Study 2) and 24 weeks (Studies 1 and 3) at the proposed dose. In both treatment groups, patients received Sirturo or placebo in combination with other drugs used to treat MDR-TB. Study 3 is an ongoing, open-label, noncomparative study with Sirturo administered as part of an individualized pulmonary MDR-TB treatment regimen to previously treated patients.

Patients in Study 1 had a statistically significant increased mortality risk by Week 120 in the Sirturo treatment group compared to the placebo group. Five of the Sirturo-group deaths and the two placebo-group deaths were TB-related. One death occurred during the 24-week Sirturo treatment period. The median time to death for the remaining eight subjects in the Sirturo treatment group was 329 days after their last intake of Sirturo. This imbalance in deaths is unexplained; no discernible pattern between death and sputum conversion, relapse, sensitivity to other drugs used to treat TB, HIV status, and severity of disease was observed.

**Warnings, Precautions and Contraindications.** The following warnings and precautions include:
- **QT prolongation:** patients’ ECGs should be monitored frequently. Sirturo should be discontinued if significant ventricular arrhythmias or QT prolongation develops. Use with other QT-prolonging drugs (e.g., fluoroquinolones, macrolide antibacterials, clofazimine) or in persons with a history of **Torsade de Pointes**, congenital long QT syndrome, hypothyroidism and bradycardhythmias, uncompensated heart failure, or serum calcium, magnesium or potassium levels below the lower limits of normal may cause additional QT prolongation.
- **Hepatic-related adverse drug reactions:** liver-related laboratory tests should be monitored carefully.
- **Non-adherence to the prescribed treatment regimen:** this can result in drug failure or M. tuberculosis resistance.
- **A Boxed Warning alerts health care professionals and patients that QT prolongation can occur with Sirturo, and that increased risk of death can occur with the drug.**

There are no contraindications listed.

**Drug Interactions.** Use of systemic potent CYP3A4 inducers should be avoided. Sirturo should not be used for more than 14 consecutive days along with strong CYP3A4 inhibitors unless benefit outweighs risk. Appropriate clinical monitoring for Sirturo-related adverse reactions is recommended.

**Patient Counseling Information.** An FDA-approved Medication Guide must be dispensed with Sirturo. Specific points for counseling are summarized in Table 3.

**Crofelemer (Fulyzaq)**

Diarrhea is a common and often inadequately treated complication in patients with HIV infection. It is also a common reason why patients discontinue or switch their antiretroviral therapies. It is estimated that 50 to 60 percent of patients with AIDS experience diarrhea at some point during their illness. Although the CDC defines chronic diarrhea as an average of ≥2 loose or watery stools per day for one month or longer, various other definitions are used in the literature. Before Fulyzaq was approved, there were no FDA-approved therapies for HIV-associated diarrhea.

The new drug is a proanthocyanidin oligomer that has been isolated and purified from the latex of Croton lechleri (family Euphorbiaceae). This plant is widely distributed throughout Western Amazonian South America. The red, viscous latex from this plant is widely known for its medicinal properties.
including relief of diarrhea. According to ethnobotanists who have interviewed indigenous populations using this plant product, adverse effects are minimal after routine oral use.

**Indications and Use.** Fulyzaq is an antidiarrheal indicated for symptomatic relief of non-infectious diarrhea in adult patients with HIV/AIDS who are taking antiretroviral therapy.

**Diarrhea in patients with HIV/AIDS.** Although the incidence of pathogen-associated diarrhea may be decreasing since introduction of highly active antiretroviral therapy (HAART), many patients with HIV continue to have chronic diarrhea with no identifiable pathogen despite an extensive evaluation. Regardless of the cause, diarrhea can result in decreased quality of life and significantly greater economic costs for affected patients with HIV infection when compared to those without diarrhea. Patients with adverse GI symptoms are likely to be less adherent to their mediation regimen, especially if they attribute the symptoms directly to their medications. Medication nonadherence can potentially lead to treatment failures and increased rates of resistant strains of virus. Therefore, evaluation of effective treatments for diarrhea in patients with AIDS is important for quality of life issues as well as other concerns.

Diarrhea can also cause a number of other important clinical ramifications. Chronic diarrhea contributes to malnutrition and weight loss. Along with thrush, weight loss, fever and night sweats, chronic diarrhea has emerged as a clinical indicator of progression of immunodeficiency. Patients with AIDS and chronic diarrhea are more likely to have increased weight loss and immunosuppression than patients without diarrhea, regardless of etiology. Survival is also known to be impacted by acute or chronic diarrhea. Determining the cause of diarrhea is important for therapeutic reasons: diarrhea can be attributed to infectious agents, gastrointestinal malignancies, HIV enteropathy, idiopathic etiology or medications.

**Mechanism of Action.** Although its mechanism of action remains to be fully elucidated, it is generally believed that crofelemer acts by blocking chloride secretion into the bowel and accompanying high volume water loss in diarrhea, thus normalizing the flow of chloride and water in the GI tract.

**Safety.** The safety profile of Fulyzaq was similar in patients with baseline CD4 cell count less than 404 cells/µL (lower limit of normal range) (N=388) and patients with baseline CD4 cell count greater than or equal to 404 cells/µL (N=289). The drug’s safety profile was also similar in patients with baseline HIV viral loads less than 400 copies/mL (N=142) and patients with baseline HIV viral loads greater than or equal to 400 copies/mL (N=278). Therefore, no dose modifications are recommended with respect to CD4 cell count and HIV viral load, based on the findings in subgroups of patients defined by CD4 cell count and HIV viral load.

**Warnings, Precautions and Contraindications.** The following warning is listed:

- **Infectious etiologies of diarrhea:** These should be ruled out before starting Fulyzaq. If infectious etiologies are not considered and treatment is initiated based on a presumptive diagnosis, there is a risk that patients with such etiologies will not receive the appropriate therapy and their disease may worsen.

There are no contraindications listed.

**Drug Interactions.** In vitro studies have shown that crofelemer has the potential to inhibit CYP3A4 at drug concentrations expected in the gut. Due to the minimal absorption of crofelemer, it is unlikely to inhibit CYP450 isoenzymes 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 and CYP3A4 systemically.

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**Table 4: Patient counseling information for Fulyzaq**

Patients should be advised:
- Tablets should not be crushed or chewed; they must be swallowed whole.
- Tablets may be taken with or without food.

**Patient Counseling Information.** Specific points for counseling are summarized in Table 4.

**Tofacitinib (Xeljanz)**

The natural history of rheumatoid arthritis (RA) has changed dramatically since the 1980s with introduction of methotrexate into its therapy. Methotrexate changed the course of the disease, slowing or even preventing development of bone erosions, thus becoming the first-line choice disease modifying antirheumatic drug (DMARD). In the 1990s, significant work on the pathophysiology of RA led to development of specific DMARDs using monoclonal antibodies and receptor decoys, which made them a mainstay of treatment with or without methotrexate. However, these biologic treatments need to be injected parenterally, are expensive, and have significant adverse effects. Moreover, a significant proportion of patients treated with biologics and/or methotrexate fail to respond or lose their response to the treatment. Therefore, oral, relatively inexpensive, small molecules that target specific pathways could represent a valuable addition to the current DMARD armamentarium. Xeljanz provides a new treatment option for adults suffering from debilitating RA.

**Indications and Uses.** Xeljanz is indicated for treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to methotrexate. It may be used as monotherapy or in combination with methotrexate or other nonbiologic DMARDs. The drug...
should not be used in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine.

**Rheumatoid Arthritis.** RA, a chronic autoimmune disease of the musculoskeletal system estimated to affect 1.5 million people in the United States, is characterized by infiltration of inflammatory cells into the synovium, a structure that lines the joints. The thickened synovium forms an abnormal layer of fibrovascular or granulation tissue called pannus that slowly destroys cartilage and bone adjacent to the joint. Both the small joints of the hands and feet, and the larger joints such as the knees and wrists, are damaged in RA, ultimately leading to serious functional impairment. More aggressive forms of RA also involve extra-articular tissues to cause lung inflammation, splenomegaly with cytopenias (reduced number of blood cells), skin nodules, and vasculitis. The disease is associated with considerable morbidity, premature mortality, disability and diminished quality of life, and imposes a substantial economic burden on patients and society. Treatment aims at terminating the inflammatory response before permanent damage occurs.

**Mechanism of Action.** Tofacitinib is a novel small molecule Janus kinase (JAK) inhibitor. JAKs are intracellular enzymes that transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis (formation and development of blood cells) and immune cell function. Within the signaling pathway, JAKs phosphorylate and activate receptors which, in turn, modulate intracellular activity including gene expression. Tofacitinib modulates the signaling pathway at the point of JAKs, preventing phosphorylation and activation.

**Safety.** Safety of Xeljanz was evaluated in seven clinical trials in adult patients with moderately to severely active RA. The new drug was associated with an increased risk of serious infections, including opportunistic infections (ones that occur primarily when the immune system is suppressed), TB, cancers and lymphoma. The drug was also associated with increases in lipids and liver enzymes and decreases in blood counts and hemoglobin. As noted in Table 1, the most common adverse reactions in all seven clinical trials were upper respiratory tract infections, headache, diarrhea, and inflammation of the nasal passages and the upper areas of the pharynx. The proportion of patients who discontinued treatment due to any adverse reaction during exposure in the double-blind, placebo-controlled trials was 4 percent for patients taking Xeljanz and 3 percent for those taking a placebo.

To study the long-term effects of Xeljanz on heart disease, cancer, and serious infections, FDA is requiring a postmarketing study that will evaluate two doses of Xeljanz and include a group of patients on an alternate approved treatment to serve as a comparison.

**Warnings, Precautions and Contraindications.** The following warnings and precautions are listed:

- **Serious infections:** serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral or other opportunistic pathogens have been reported in persons with RA who are receiving Xeljanz. Patients should not receive Xeljanz during an active infection, including localized infections. If a serious infection develops, Xeljanz administration should be interrupted until the problem is controlled.

- **Lymphomas and other malignancies:** these have been reported in patients treated with Xeljanz.

- **Gastrointestinal perforations:** the drug should be used with caution in patients who may be at increased risk (e.g., persons with a history of diverticulitis). Patients presenting with new-onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforations.

- **Laboratory monitoring:** close monitoring is recommended due to potential changes in lymphocytes, neutrophils, hemoglobin, liver enzymes and lipids.

- **Immunizations:** live vaccines should not be given concurrently with Xeljanz.

- **Severe hepatic impairment:** Xeljanz use is not recommended.

- **A Boxed Warning** emphasizes the importance of these warnings and precautions.

There are no contraindications listed.

**Drug Interactions.** With potent inhibitors of CYP3A4 (e.g., ketoconazole), the dose of Xeljanz should be reduced to 5 mg once daily. With one or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole), Xeljanz dose should be reduced to 5 mg once daily. Potent CYP inducers (e.g., rifampin): may result in loss of or reduced clinical response.

**Patient Counseling Information.** An FDA-approved Medication Guide must be dispensed with Xeljanz. Specific points for counseling are summarized in Table 5.

**Overview and Summary**

Four unrelated human pathologies that represent significant therapeutic challenges are profiled in this lesson. While each disorder is associated with a variety of signs and symptoms that are independent of those characteristic of the other conditions, there is one common element that is shared by all four pathologies: each can now be treated with a new drug recently approved for its therapy.
The author, the Ohio Pharmacists Foundation and the Ohio Pharmacists Association disclaim any liability to you or your patients resulting from reliance solely upon the information contained herein. Bibliography for additional reading and inquiry is available upon request.

This lesson is a knowledge-based CE activity and is targeted to pharmacists in all practice settings.

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New Drugs: Eliquis, Fulyzaq, Sirturo, and Xeljanz

1. All of the following are true about atrial fibrillation EXCEPT:
   a. it is the most common cardiac arrhythmia.
   b. it occurs in 15 to 20 percent of the general population.
   c. it is associated with a 5-fold increased risk of stroke.
   d. hospitalization of patients with AF is very common.

2. All of the following are true about apixaban EXCEPT:
   a. it is a clotting factor Xa inhibitor.
   b. it indirectly inhibits platelet aggregation.
   c. it has a longer half-life than warfarin.
   d. weekly INR monitoring is not needed.

3. The most common reason for discontinuation of apixaban in pre-marketing clinical trials was:
   a. bleeding-related events.
   b. the large number of drug interactions.
   c. intense nausea with vomiting.

4. Which of the following drugs is reported to increase blood levels of apixaban?
   a. Rifampin
   b. Phenytoin
   c. Ketocanazole
   d. St. John’s Wort

5. For patients whose multi-drug resistant TB isolate is susceptible in vitro, Sirturo should only be used in combination with at least how many other antimycobacterial drugs?
   a. One
   b. Two
   c. Three
   d. Four

6. Which of the following is inhibited by bedaquiline?
   a. Janus kinase
   b. ATP synthase
   c. Chlorine transportase
   d. Endodeoxyribonuclease

7. A Boxed Warning with Situro alerts about:
   a. possible QT prolongation.
   b. lymphoma.
   c. increased liver enzymes and lipids.

8. Counseling information for Situro includes all of the following EXCEPT:
   a. take with other antimycobacterial drugs as directed.
   b. swallow the tablets whole with water.
   c. take with food and abstain from alcohol.
   d. missed doses during the first two weeks of treatment should be made up.

9. Which of the following drugs is a proanthocyanidin oligomer isolated and purified from a plant growing in South America?
   a. Apixaban
   b. Bedaquiline
   c. Crofelemer
   d. Tofacitinib

10. Fulyzaq was approved to treat diarrhea associated with which of the following?
    a. HIV/AIDS
    b. Tuberculosis
    c. Influenza
    d. Filariasis

11. All of the following are true about RA EXCEPT:
    a. it is a chronic autoimmune disease.
    b. the pannus destroys bone adjacent to the joint.
    c. the joints of the hands, feet, knees and wrists are damaged.
    d. aggressive disease is confined to articular tissue.

12. Janus kinases are enzymes that:
    a. destroy intra-articular membranes that protect joint capsules.
    b. influence cellular processes of hematopoiesis and immune cell function.
    c. block phosphorylation and activation of receptors in the signaling pathway.

13. Xeljanz may be used concurrently with which of the following drugs?
    a. Azathioprine
    b. Methotrexate
    c. Cyclosporine
    d. A biologic DMARD

14. Which of the following drugs has a contraindication listed in its label?
    a. Eliquis
    b. Sirturo
    c. Fulyzaq
    d. Xeljanz

15. An FDA-approved Medication Guide must be dispensed with all of the following EXCEPT?
    a. Eliquis
    b. Sirturo
    c. Xeljanz
    d. Fulyzaq

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