

New therapeutic agents marketed in the first half of 2009: Part 1

Daniel A. Hussar

Abstract

Objective: To provide information regarding the most important properties of the new therapeutic agents marketed in the first half of 2009.

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

Study selection: By the author.

Data extraction: By the author.

Data synthesis: 16 new therapeutic agents were marketed in the United States during the first half of 2009, 8 of which are reviewed in this article (part 1 of a two-part series): tapentadol hydrochloride, golimumab, febuxostat, lacosamide, rufinamide, milnacipran hydrochloride, fesoterodine fumarate, and silodosin. Indications and information on dosage and administration for these agents are reviewed, as are the most important pharmacokinetic properties, adverse events, drug interactions, and other precautions. Practical considerations for the use of the new agents are also discussed. When possible, the properties of the new drugs are compared with those of older drugs marketed for the same indications.

Conclusion: Most of the new drugs discussed in this article have properties and uses that are very similar to those of older drugs. Consequently, most of them do not have important advantages compared with the older drugs, but they may have benefits for selected patients. An understanding of the properties of these agents is important for the pharmacist to appropriately compare them with older agents used for the same conditions, to effectively counsel patients about their use, and to serve as a valuable source of information for other health professionals regarding these drugs.

Keywords: New drugs, Food and Drug Administration, drug development, pharmaceutical marketing.

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Part 2 of this series will appear in the October 2009 issue of *Pharmacy Today*. The two parts are separate opportunities for obtaining continuing pharmacy education.

Learning objectives

At the conclusion of this program, the pharmacist will be able to:

- Identify the new therapeutic agents marketed during January to June 2009 and explain their appropriate use.
- Describe the indications and the most important adverse events and other risks of each of the new therapeutic agents.
- State the route of administration for each new drug and the important considerations regarding dosage and administration.
- Demonstrate appropriate patient counseling regarding the use of the new medications and the precautions to be observed.

ACPE Activity Type: Knowledge-Based

Analgesic

Tapentadol hydrochloride (Nucynta—PriCara) is a centrally acting analgesic that acts via two mechanisms to relieve pain. Like the opioid analgesics (e.g., morphine, oxycodone), it is a mu-opioid receptor agonist, but unlike these agents, it also inhibits norepinephrine reuptake. The pharmacological actions of tapentadol are most similar to those of tramadol (e.g., Ultram), which has an opioid agonist action and also inhibits norepinephrine and serotonin reuptake. However, the opioid agonist action of tapentadol is stronger than that of tramadol, and the new drug also has a greater potential for dependence and abuse. This risk is reflected by the inclusion of tapentadol in Schedule II under the provisions of the Controlled Substances Act, as are the opioid analgesics, whereas tramadol is not a controlled substance.

Tapentadol is supplied in an immediate-release tablet formulation (a controlled-release formulation is under development) and has been approved for the relief of moderate to severe acute pain in patients 18 years or older. Both tramadol and oxycodone are also available in controlled-release formulations (e.g., Ultram ER, OxyContin) that are used over longer periods of time in the management of chronic pain. The indication for certain of these formulations (Ultram ER, OxyIR) is for the relief of moderate to moderately severe pain.

The effectiveness of tapentadol has been demonstrated in studies in which it was compared with placebo and, to a more limited extent, with oxycodone. The percentages of patients who showed reduction in pain intensity of 30% or greater, or 50% or greater, were significantly higher in the patients treated with the new drug compared with placebo. The results of one study suggest that the analgesic benefit of tapentadol in a dose of 100 mg is similar to that provided by oxycodone in a dose of 15 mg.

The primary risk of the opioid agonists including tapentadol is respiratory depression, and these agents are contraindicated in patients with considerable respiratory depression or with acute or severe bronchial asthma or hypercapnia, in unmonitored settings, or in the absence of resuscitative equipment. Caution must be exercised when tapentadol is used in patients with less serious underlying pulmonary problems, as well as in elderly or debilitated patients who are at greater risk of experiencing impaired pulmonary function. Opioid analgesics may increase cerebrospinal fluid pressure as a result of respiratory depression, and they must be used with caution in patients with head injury, intracranial lesions, or other sources of increased intracranial pressure.

Like the other opioid agonists, tapentadol is contraindicated in patients with paralytic ileus. Because these agents may cause spasm of the sphincter of Oddi, caution must be exercised when they are used in patients with biliary tract disease, including acute pancreatitis.

The adverse events most often reported in the clinical studies of tapentadol include nausea (30%), vomiting (18%), constipation (8%), dizziness (24%), and somnolence (15%). In the studies in which some patients received oxycodone, the incidence of gastrointestinal events was lower with tapentadol.

Because of its central nervous system (CNS) depressant action, patients should be advised that tapentadol may impair the mental and/or physical abilities required for potentially hazardous tasks such as driving or operating machinery. The concurrent use of other CNS depressants, including alcoholic beverages, may result in an additive depressant effect, and consideration should be given to reducing the dosage of the agents implicated in such interactions. Patients with seizure disorders were excluded from the clinical studies of tapentadol, and the new drug must be used with caution in patients with a history of seizures or who are otherwise at greater risk of these problems. A more prominent warning regarding the risk of seizures is included in the labeling for tramadol, but insufficient data are available comparing the two drugs with respect to this risk.

Tapentadol has an abuse potential that is considered similar to that of hydromorphone (e.g., Dilaudid), and it is classified in Schedule II. Although concerns about addiction and abuse should not prevent the proper management of pain, patients should be informed about these risks, and appropriate cautions regarding the use of tapentadol should be observed.

Tapentadol is classified in Pregnancy Category C and should only be used during pregnancy if the anticipated benefit outweighs the risk to the fetus. The drug should not be used in women during and immediately before labor and delivery or in women who are breast-feeding. The effectiveness and safety of the new drug in patients younger than 18 years have not been established.

Serotonin syndrome has been reported infrequently in patients treated with medications that inhibit reuptake of serotonin and/or norepinephrine. The risk is increased by the concurrent use of serotonergic drugs such as selective serotonin reuptake inhibitors (SSRIs; e.g., fluoxetine [e.g., Prozac]), serotonin and norepinephrine reuptake inhibitors (e.g., venlafaxine [e.g., Effexor]), tricyclic antidepressants (e.g., amitriptyline), and triptans (e.g., sumatriptan [e.g., Imitrex]), as well as monoamine oxidase inhibitors (MAOIs [e.g., tranylcypromine {e.g., Parnate}]), which inhibit the metabolism of serotonin. Use of tapentadol is contraindicated in patients currently taking an MAOI or who have been treated with an MAOI within the previous 14 days.

Following oral administration, the absolute bioavailability of tapentadol is approximately 32% because of extensive first-pass metabolism. Most of a dose of the drug is metabolized via glucuronidation, and it is metabolized to only a limited extent via cytochrome P450 (CYP) metabolic pathways. Tapentadol is not likely to interact with other medications via pharmacokinetic mechanisms, whereas tramadol is extensively metabolized via CYP pathways and has a greater potential to interact with other medications that inhibit, induce, or compete for these pathways.

Tapentadol and its metabolites are excreted almost entirely via the kidneys. Only 3% of a dose of the drug is excreted in unchanged form. An adjustment in dosage is not considered necessary in patients with mild or moderate renal impairment or with mild hepatic impairment. The drug has not been studied in patients with severe renal or severe hepatic impairment, and

Table 1. New therapeutic agents marketed in the United States from January to June 2009^a

Generic name	Trade name	Manufacturer	Therapeutic classification	Route of administration	FDA classification ^b
Febuxostat	Uloric	Takeda	Agent for gout	Oral	1-S
Fesoterodine fumarate	Toviaz	Pfizer	Agent for overactive bladder	Oral	1-S
Golimumab	Simponi	Centocor Ortho Biotech	Antiarthritic agent	Subcutaneous	S ^c
Lacosamide	Vimpat	UCB	Antiepileptic drug	Oral; intravenous	1-S
Milnacipran hydrochloride	Savella	Forest; Cypress	Agent for fibromyalgia	Oral	1-S
Rufinamide	Banzel	Eisai	Antiepileptic drug	Oral	1-S
Sildenafil	Rapaflo	Watson	Agent for benign prostatic hyperplasia	Oral	1-S

^aAdditional agents marketed during this time period are considered in part 2 of this two-part series.

^bFDA classification of new drugs: 1 = new molecular entity; S = standard review.

^cA biological approved through an FDA procedure that does not assign a numerical classification.

its use is not recommended in these patients.

The dosage of tapentadol should be individualized according to the severity of the patient's pain, the previous experience of the patient with similar drugs, and the ability to monitor the patient. The usual dosage is 50, 75, or 100 mg every 4 to 6 hours depending on the intensity of the pain. When initiating treatment, if adequate pain relief is not attained with the first dose, the second dose may be administered as soon as 1 hour later. Subsequent doses should be administered every 4 to 6 hours. Total daily doses greater than 700 mg on the first day and 600 mg on subsequent days have not been studied and are not recommended.

In patients with moderate hepatic impairment, the recommended initial dosage is 50 mg with the interval between doses no less than 8 hours. In elderly patients, consideration should also be given to starting treatment with a dose of 50 mg.

Tapentadol immediate-release tablets are supplied in 50-, 75-, and 100-mg potencies.

Antiarthritic agent

Golimumab (Simponi—Centocor Ortho Biotech) is the fifth tumor necrosis factor (TNF) blocker (inhibitor) to be marketed for the treatment of rheumatoid arthritis, joining etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), and certolizumab pegol (Cimzia). The latter agent was initially marketed in 2008 for the treatment of Crohn's disease and was subsequently approved in May 2009 for the treatment of rheumatoid arthritis. Golimumab is a humanized monoclonal antibody that prevents the binding of TNF alpha to its receptors, thereby inhibiting its activity.

Like etanercept, adalimumab, and certolizumab, golimumab is administered subcutaneously, whereas infliximab is administered intravenously. The new drug is specifically indicated for use in adult patients for the treatment of moderately to severely active rheumatoid arthritis (in combination with methotrexate), active psoriatic arthritis (alone or in combination with methotrexate), and active ankylosing spondylitis. Etanercept, adalimumab, and infliximab are also indicated for the three conditions for which golimumab has been approved,

although the specifics of these indications vary in some instances. For example, in the treatment of rheumatoid arthritis, the indication for golimumab and infliximab involves use in combination with methotrexate, whereas such combination use is not required with etanercept and adalimumab (or certolizumab). The labeled indications for etanercept and adalimumab in the treatment of rheumatoid arthritis also reflect the benefits of inducing major clinical response, inhibiting the progression of structural damage, and improving physical function, and the latter two are included in the labeled indication for infliximab.

In the treatment of psoriatic arthritis, the labeled indication for etanercept, adalimumab, and infliximab, but not for golimumab, includes reference to inhibiting the progression of structural damage and improving physical function.

The effectiveness of golimumab in the treatment of rheumatoid arthritis was demonstrated in three controlled trials. One of these studies included patients who had been previously treated with one or more doses of another TNF blocker without a serious adverse event but who had discontinued this treatment for a variety of reasons. In all three studies, a higher percentage of patients who were treated with the combination of golimumab and methotrexate experienced improvement at the week 14 and 24 evaluation points compared with patients treated with methotrexate alone. Golimumab has not been directly compared with other TNF blockers in clinical studies, and data are not sufficient to conclude that it is effective in patients in whom response with other TNF blockers has been inadequate.

In patients with psoriatic arthritis or ankylosing spondylitis, the use of golimumab resulted in significant improvement in signs and symptoms. Including methotrexate in the regimen for treating psoriatic arthritis did not provide a consistent benefit, and golimumab may be used alone or in combination with methotrexate in the treatment of this disorder.

Certain of the TNF blockers have also been approved for other indications. Etanercept and adalimumab are indicated for the treatment of juvenile idiopathic arthritis, and these agents, as well as infliximab, are indicated for the treatment

of plaque psoriasis. Infliximab, adalimumab, and certolizumab are indicated for the treatment of patients with Crohn's disease, and infliximab is also indicated for the treatment of patients with ulcerative colitis. However, these are not labeled indications for golimumab currently.

The risks and adverse events associated with the use of golimumab are generally similar to those of the other TNF blockers. Of greatest concern is the potential for serious infection (e.g., tuberculosis [TB], invasive fungal infections, other opportunistic infections), some of which have been fatal and which are the subject of a boxed warning in the product labeling. Treatment with golimumab should not be initiated in patients with an active infection, including clinically important localized infection. Patients should be evaluated for TB risk factors and tested for latent TB infection. A risk of reactivation of hepatitis B virus in patients who are chronic carriers of this virus also exists. The risk of serious infections is increased if a TNF blocker is used concomitantly with abatacept (Orencia) or anakinra (Kineret). Accordingly, golimumab should not be used concurrently with one of these agents.

The TNF blockers have also been associated with a risk of malignancies (e.g., lymphomas). The risks and benefits of golimumab should be carefully evaluated before initiating treatment in a patient with a known malignancy or when considering whether to continue treatment in a patient who develops a malignancy.

Other risks with the use of golimumab, as well as the other TNF blockers, include exacerbation or new onset of congestive heart failure, exacerbation or new onset of CNS demyelinating disorders (e.g., multiple sclerosis), and hematologic reactions (e.g., pancytopenia, leukopenia). Live vaccines should not be used during treatment with golimumab.

The adverse events experienced most often in the clinical studies of golimumab include upper respiratory tract infection (7%), nasopharyngitis (6%), injection-site erythema (3%), and hypertension (3%). Elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were reported in 4% and 3% of patients, respectively.

Antibodies to golimumab were detected in 4% of patients in the clinical studies but were reported less frequently in patients who received methotrexate concurrently. Whether the formation of antibodies influences the effectiveness of the new drug is unknown. Development of a lupus-like syndrome in patients treated with TNF blockers has been rarely reported.

Golimumab is classified in Pregnancy Category B and should only be used during pregnancy if the anticipated benefit outweighs the risk to the fetus. Whether the drug is excreted in human milk is unknown, and a decision should be made whether to discontinue nursing or not use the drug. The effectiveness and safety of golimumab have not been established in patients younger than 18 years. Etanercept and adalimumab are indicated for use in the treatment of juvenile idiopathic arthritis in children as young as 2 and 4 years, respectively, and infliximab is indicated for the treatment of Crohn's disease in children as young as 6 years.

Golimumab is administered subcutaneously, and the rec-

ommended dosage is 50 mg once a month. It is used in combination with methotrexate in patients with rheumatoid arthritis. In patients with psoriatic arthritis or ankylosing spondylitis, it may be used with or without methotrexate or other nonbiologic disease-modifying antirheumatic drugs. The once-a-month dosage regimen is an advantage over the other TNF blockers that are administered subcutaneously, as etanercept is usually administered every week and adalimumab and certolizumab are usually administered every other week. Consideration may be given to administering certolizumab once every 4 weeks for maintenance treatment, which is the dosage regimen recommended for its use in the treatment of Crohn's disease. Infliximab is administered intravenously every 8 weeks for maintenance treatment. If a patient develops a serious infection or sepsis while being treated with golimumab or another TNF blocker, therapy should be discontinued.

Golimumab is supplied in a single-dose prefilled syringe and in a single-dose prefilled SmartJect autoinjector. Both products contain 50 mg golimumab in 0.5 mL solution. The needle cover on the prefilled syringe, as well as the syringe in the autoinjector, contains dry natural rubber (a derivative of latex), which should not be handled by individuals who are sensitive to latex.

Golimumab should be stored in a refrigerator and protected from light. When preparing to administer the medication, the product should be allowed to sit at room temperature for 30 minutes prior to injection.

Agent for gout

Approximately 5 million Americans suffer from gout, which is the most common inflammatory arthritis in men older than 40 years. Gout is a chronic condition characterized by attacks, or "flares," that are marked by intense pain, redness, swelling, and heat in the affected joint. These symptoms result from an acute inflammatory response to the presence of crystallized uric acid in the joint(s). Uric acid is an end product formed when the body breaks down purines. Hyperuricemia occurs when this process results in elevated uric acid concentrations as a consequence of overproduction and/or underexcretion of uric acid. Hyperuricemia is a precursor to gout, and the higher an individual's uric acid concentration, the greater the risk for developing gout. A goal in treating chronic gout is reducing and maintaining serum uric acid concentrations less than 6 mg/dL.

Febuxostat (Uloric—Takeda) is the first new treatment option for patients with chronic gout in more than 40 years. Like allopurinol (e.g., Zyloprim), it is classified as a xanthine oxidase inhibitor. Xanthine oxidase is responsible for the breakdown of the purine base, hypoxanthine, to xanthine, and then to uric acid. By inhibiting this enzyme, febuxostat and allopurinol reduce uric acid production and lower elevated concentrations of serum uric acid.

Febuxostat is specifically indicated for the chronic management of hyperuricemia in patients with gout. Neither the new drug nor allopurinol is recommended for treating asymptomatic hyperuricemia. In the largest clinical study, febuxostat in a dosage of 80 mg once a day was more effective than al-

lopurinol in a dosage of 300 mg once a day (or 200 mg once a day in patients with moderate renal impairment) in lowering serum uric acid concentrations to less than 6 mg/dL at the final visit (67% vs. 42% of patients, respectively). However, the results with febuxostat in a dosage of 40 mg once a day (45% of patients) were similar to those with allopurinol. Although this and other studies demonstrate the effectiveness of febuxostat in lowering elevated serum uric acid concentrations, it cannot be concluded that the new drug is more effective than allopurinol because the 300 mg/day dosage of the latter agent that was used in the clinical studies is considerably less than the maximum dosage (800 mg/day) that has been evaluated and approved for patients who experienced an inadequate response with the usual lower dosage.

The labeled indications for febuxostat are more limited than those for allopurinol, which also has indications for managing patients with leukemia, lymphoma, and malignancies who are receiving cancer therapy that causes elevations of serum and urinary uric acid concentrations, and for managing patients with recurrent calcium oxalate calculi whose daily uric acid excretion exceeds 800 mg/day in male patients and 750 mg/day in female patients.

After febuxostat or allopurinol treatment is initiated, gout flares may be experienced because the reduction in serum uric acid concentrations results in mobilization of urate from tissue deposits. When initiating treatment, flare prophylaxis with a nonsteroidal anti-inflammatory drug (e.g., naproxen 250 mg twice a day) or colchicine (0.6 mg once or twice a day) may be beneficial for up to 6 months. If a gout flare occurs, it should be managed concurrently while continuing treatment with febuxostat.

The adverse events experienced most often in the clinical studies with febuxostat included nausea (1%), arthralgia (1%), and rash (1%). With the use of allopurinol, serious and even fatal skin reactions/hypersensitivity responses have been reported, and use of this agent should be discontinued immediately if a rash develops. Use of febuxostat has not been associated with these severe reactions and subsequent warnings, but the occurrence of dermatological adverse events should be carefully evaluated. A small number of patients in the clinical studies experienced cardiovascular thromboembolic events (e.g., myocardial infarction [MI], stroke) at a rate that was higher with febuxostat than with allopurinol. However, a causal relationship has not been established. It is recommended that patients be monitored for symptoms of MI (e.g., chest pain, shortness of breath) and stroke (e.g., neurologic symptoms suggestive of a stroke).

Liver function test abnormalities (ALT and AST elevations) were reported in approximately 6% of patients treated with febuxostat and at a higher rate than with allopurinol. Although a dose-effect relationship has not been identified, liver function tests should be performed (e.g., at 2 and 4 months after initiation of treatment and periodically thereafter).

Febuxostat is classified in Pregnancy Category C and should be used during pregnancy only if the anticipated benefit justifies the risk to the fetus. Whether the drug is excreted in human

milk is unknown, and caution should be exercised if it is used in a nursing woman. The effectiveness and safety of febuxostat in patients younger than 18 years have not been established.

As xanthine oxidase inhibitors, febuxostat and allopurinol will inhibit the metabolism of other medications (azathioprine [e.g., Imuran], mercaptopurine [e.g., Purinethol], theophylline) that are substrates for this enzyme. The resultant increased concentrations may cause serious toxicity. The use of febuxostat is contraindicated in patients being treated with one of these xanthine oxidase substrates, whereas the labeling for allopurinol includes a warning about these interactions and recommendations for dosage reductions to decrease the risk of concurrent use.

Following oral administration, febuxostat is absorbed to an extent of approximately 50%. It may be administered without regard to food or use of an antacid. Febuxostat is extensively metabolized via both glucuronidation and oxidation pathways. At least four of its metabolites are pharmacologically active, but their concentrations in the plasma are much lower than that of the parent compound. The drug is eliminated to an approximately equal extent via hepatic and renal pathways, primarily in the form of metabolites. Dosage adjustment is not necessary in patients with mild or moderate hepatic or renal impairment. Experience with using febuxostat in patients with severe hepatic or renal impairment is limited, and if the drug is to be used in these patients, caution must be exercised.

The recommended initial dosage of febuxostat is 40 mg once a day. In patients who do not achieve a serum uric acid concentration less than 6 mg/dL after 2 weeks with the 40-mg dosage, the dosage should be increased to 80 mg once a day. With allopurinol, higher dosages (>300 mg/day) should be administered in divided doses rather than once a day.

Febuxostat tablets are supplied in 40- and 80-mg potencies.

Antiepileptic drugs

Lacosamide

Approximately 3 million Americans have epilepsy, a general designation that includes many different seizure types and syndromes. Almost 20 antiepileptic drugs (AEDs) are available for treating these disorders, but an estimated 25% of patients with epilepsy experience either uncontrolled seizures or significant adverse events caused by the medications. Two new AEDs were marketed in early 2009.

Lacosamide (Vimpat—UCB) has been approved as adjunctive therapy in treating partial-onset seizures in patients with epilepsy aged 17 years or older. In addition to a tablet formulation, a formulation for intravenous administration is available for use when oral administration is temporarily not feasible. Partial-onset seizures are usually treated with a combination of AEDs. Some of the already-marketed AEDs for treating partial-onset seizures include carbamazepine (e.g., Tegretol), lamotrigine (e.g., Lamictal), levetiracetam (Keppra), and oxcarbazepine (Trileptal), which are considered by many to be first-line treatment options, and topiramate (e.g., Topamax), valproate (e.g., Depakene), zonisamide (Zonegran), gabapentin (e.g.,

Neurontin), pregabalin (Lyrica), and phenytoin (e.g., Dilantin).

Lacosamide is a functionalized amino acid that is used in the form of its R-enantiomer that is at least 10-fold more active than the S-enantiomer. Although its precise mechanisms of action have not been determined, it is thought to selectively enhance slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes. In addition, it binds to collapsin response mediator protein-2, a phosphoprotein that is mainly expressed in the nervous system, although whether this binding contributes to a reduction in seizures is not known. Because the structure and mechanisms of action of lacosamide differ from those of other AEDs, the new drug may be of value in patients who have had an inadequate response or intolerable adverse events with other agents.

The effectiveness of lacosamide was demonstrated in three 12-week placebo-controlled studies in patients with partial-onset seizures that were not adequately controlled with one to three concomitant AEDs. The patients enrolled in the studies had a median baseline seizure frequency ranging from 10 to 17 seizures per month. Almost all were taking two or three AEDs, and 45% of the patients had previously tried seven or more AEDs to control their seizures. Of the patients treated with lacosamide (400 mg/day), 40% experienced a 50% or greater reduction in seizure frequency compared with 23% of the patients receiving placebo with concomitant AEDs. Approximately 3% of the patients treated with lacosamide were seizure free throughout the 12 weeks of the study compared with 1% of those receiving placebo.

Many of the AEDs already on the market are also indicated for treating other types of epilepsy, as well as other clinical disorders. However, currently, the only labeled indication for lacosamide is adjunctive therapy for partial-onset seizures. Lacosamide also has been studied for management of neuropathic pain in patients with diabetes, but the Food and Drug Administration (FDA) has declined to approve the drug for this use.

AEDs, including lacosamide, increase the risk of suicidal thoughts or behaviors. Patients should be advised of this risk and monitored for the emergence or worsening of depression, unusual changes in mood or behavior, and/or suicidal thoughts or behavior.

The adverse events experienced most frequently in the clinical studies of lacosamide include dizziness (30%), headache (14%), nausea (11%), vomiting (9%), diplopia (11%), blurred vision (9%), somnolence (8%), ataxia (7%), and fatigue (7%). The onset of dizziness and ataxia was most commonly observed during dosage titration. Because of the possibility of these reactions and other CNS effects, patients should be advised not to drive a car or operate complex machinery until they have assessed the effects of the drug on their ability to perform such activities. Caution must also be exercised when other AEDs and other medications having CNS-depressant activity, as well as alcoholic beverages, are used concurrently.

Dose-dependent prolongations in the PR interval of the electrocardiogram have been observed in patients treated with lacosamide, and asymptomatic first-degree atrioventricular

(AV) block was reported in 0.4% of the patients randomized to receive the new drug but in none of the patients receiving placebo. Therapy must be closely monitored when lacosamide is used in patients with known conduction problems (e.g., marked first-degree AV block, second-degree or higher AV block and sick sinus syndrome without pacemaker) or with severe cardiac disease such as myocardial ischemia or heart failure. In these patients, obtaining an electrocardiogram is recommended before starting treatment with lacosamide and after the dosage is titrated to a steady state.

In the studies of lacosamide in patients with epilepsy, syncope did not increase compared with the patients receiving placebo. However, in a study in patients with diabetic neuropathy, 1.2% of patients treated with lacosamide experienced syncope compared with 0% of those receiving placebo. Patients should be advised that, if they experience syncope, that they should contact their physician and lie down with their legs raised until recovered.

One of the healthy volunteers receiving lacosamide in a clinical study experienced symptomatic hepatitis and nephritis, a response that is consistent with a delayed multiorgan hypersensitivity reaction. Such reactions have also been reported with other AEDs, and if this reaction is suspected, treatment should be discontinued and alternative treatment initiated.

Lacosamide has been evaluated with respect to its abuse potential, and higher doses have produced euphoria-type responses similar to those associated with alprazolam (e.g., Xanax). The incidence of euphoria reported as an adverse event in the clinical studies is less than 1%. However, as with pregabalin, lacosamide has been classified in Schedule V under the provisions of the Controlled Substances Act.

Based on results in animal studies, concerns exist about using lacosamide, as well as other AEDs, during pregnancy. The new agent is classified in Pregnancy Category C and should only be used during pregnancy if the anticipated benefit outweighs the risk to the fetus. If it is considered necessary to use lacosamide during pregnancy, enrolling the patient in the UCB AED Pregnancy Registry (888-537-7734) and the North American Antiepileptic Drug Pregnancy Registry (888-233-2334) is recommended.

Whether lacosamide is excreted in human milk is unknown, and a decision should be made whether to discontinue nursing or not use the drug. The effectiveness and safety of the new drug have not been evaluated in patients younger than 17 years.

The potential for lacosamide to interact with other medications has been studied in healthy patients, and interactions via pharmacokinetic mechanisms appear unlikely to occur. However, a response that is at least additive should be anticipated when lacosamide is used concurrently with other AEDs or other medications having a CNS-depressant action.

Following oral administration, lacosamide is completely absorbed and has an absolute bioavailability of approximately 100%. Food does not affect the rate and extent of absorption. Lacosamide is a substrate for the CYP2C19 metabolic pathway, but more than 40% of a dose is eliminated in unchanged form. The major metabolite does not have pharmacologic activity. Ap-

proximately 95% of a dose of the drug is eliminated in the urine as unchanged drug and metabolites. The dosage should be adjusted in patients with severe renal impairment and in patients with hepatic impairment.

The recommended initial dosage of lacosamide is 50 mg twice a day. The dosage can be increased at weekly intervals by 100 mg/day given as two divided doses up to the recommended maintenance dosage of 200 to 400 mg/day (i.e., 100–200 mg twice a day), based on individual patient response and tolerability. In the clinical studies, a dosage of 600 mg/day was not more effective than 400 mg/day but was associated with a substantially higher rate of adverse events. Dosage adjustment is not necessary in patients with mild to moderate renal impairment, but a dosage of 300 mg/day should not be exceeded in patients with severe renal impairment (creatinine clearance \leq 30 mL/min) and in patients with end-stage renal disease. Because lacosamide is effectively removed from plasma by hemodialysis, dosage supplementation of up to 50% should be considered following a 4-hour hemodialysis treatment. In patients with mild to moderate hepatic impairment, the maximum recommended dosage of lacosamide is 300 mg/day. The drug has not been evaluated in patients with severe hepatic impairment, and its use in these patients is not recommended.

If the use of lacosamide in a patient with a seizure disorder is to be discontinued, it should be withdrawn gradually over a period of at least 1 week to minimize the potential for increased seizure frequency.

Lacosamide is supplied in tablets in 50-, 100-, 150-, and 200-mg potencies and in vials containing 200 mg of the drug in 20 mL solution. Administration via intravenous infusion is indicated for short-term use when oral administration is not feasible. The oral and intravenous formulations are bioequivalent and may be used in the same dosage. The parenteral formulation can be administered without dilution, or it may be mixed with a diluent (Sodium Chloride Injection 0.9%, Dextrose Injection 5%, Lactated Ringer's Injection). The drug should be infused intravenously over a period of 30 to 60 minutes.

Rufinamide

Lennox-Gastaut syndrome is a severe form of childhood epilepsy that is characterized by frequent episodes of multiple types of seizures such as atypical absence seizures, tonic seizures, and atonic seizures in which the patient has a loss of muscle tone and falls suddenly (a "drop attack"). Valproate (e.g., Depakene) is often considered a first-line drug for treating Lennox-Gastaut syndrome, although this is not a labeled indication for its use. Treatment usually requires a multiple-AED regimen, and the AEDs with labeled indications for this syndrome include lamotrigine (e.g., Lamictal), topiramate (e.g., Topamax), and felbamate (Felbatol).

Rufinamide (Banzel—Eisai) has been approved for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in children 4 years or older and adults. The new drug is structurally unrelated to other AEDs and is thought to act primarily by modulating the action of sodium channels. More specifically, rufinamide appears to prolong the inactive state of sodium channels by slowing the recovery of these channels

from inactivation.

The effectiveness of rufinamide was demonstrated in a 12-week placebo-controlled study in which the enrolled patients had experienced at least 90 seizures in the month before entering the study and were already taking one to three AEDs that were providing inadequate seizure control. In the patients in whom rufinamide was added to their AED regimen, total seizure frequency decreased 33% in 28 days and tonic-atonic seizure frequency decreased 43% in 28 days compared with a 12% decrease and 1% increase, respectively, in the patients in whom placebo was added to their AED regimen. In addition, seizure severity rating from global evaluation was improved in 53% of patients receiving rufinamide compared with 31% of those receiving placebo. Therefore, the new drug represents a useful addition to the small group of AEDs that are effective in the treatment of Lennox-Gastaut syndrome.

Rufinamide has also been studied as adjunctive treatment for partial-onset seizures. However, this is not a labeled indication currently.

AEDs, including rufinamide, increase the risk of suicidal thoughts or behavior. Patients should be advised of this risk and monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or unusual changes in mood or behavior.

CNS-related adverse events are often associated with the use of rufinamide and have been classified into two general categories: (1) somnolence or fatigue and (2) coordination abnormalities, dizziness, gait disturbances, and ataxia. Patients should be advised not to drive a car or operate machinery until they have assessed whether the drug adversely affects their mental and/or motor performance. They should also be informed that the concurrent use of other CNS-active medications, as well as alcoholic beverages, may cause additive CNS effects.

The most frequent adverse events of all types experienced by children in the clinical studies include somnolence (17%), vomiting (17%), headache (16%), fatigue (9%), dizziness (8%), and nausea (7%). In adults, the most frequent adverse events include dizziness (19%), fatigue (16%), nausea (12%), somnolence (11%), and diplopia (9%). Headache was also reported by 27% of adult patients but at essentially the same rate (26%) as in those receiving placebo. The occurrence of leukopenia was more commonly observed in patients treated with rufinamide (4%) than in patients in the placebo group (1%). Of the patients treated with rufinamide, 9% discontinued therapy as a consequence of an adverse event compared with 4% of those receiving placebo.

Rufinamide has been reported to cause a shortening of the QT interval of the electrocardiogram, although the degree to which this shortening has occurred has not been associated with clinical risk. The new drug is contraindicated in patients with Familial Short QT syndrome, and caution should be exercised when rufinamide is used concurrently with other drugs that shorten the QT interval (e.g., lamotrigine, digoxin).

As has been reported with the use of other AEDs, multi-organ hypersensitivity reactions (e.g., urticaria, hepatitis) have been infrequently experienced by patients treated with

rufinamide. If this reaction is suspected, rufinamide should be discontinued and alternative treatment initiated. Patients who experience a rash should be closely monitored.

Rufinamide is classified in Pregnancy Category C and should only be used during pregnancy if the anticipated benefit outweighs the risk to the fetus. The new agent is likely to be excreted in human milk, and a decision should be made whether to discontinue nursing or not use the drug. The effectiveness and safety of rufinamide in children younger than 4 years have not been established.

Although rufinamide is not a substrate for the oxidizing CYP enzymes, its concentration is decreased by up to 46% by the concurrent use of potent enzyme inducers such as carbamazepine (e.g., Tegretol), phenobarbital, phenytoin (e.g., Dilantin), and primidone (e.g., Mysoline). Conversely, its concentration is increased by up to 70% when valproate is used concurrently. When treatment with either of these agents is to be started in a patient who is already stabilized on the other agent, a lower dosage of the second drug should be used when initiating treatment.

Rufinamide is a weak inhibitor of CYP2E1 and a weak inducer of CYP3A4 enzymes. Its use may reduce the effectiveness of hormonal contraceptives, and women using these products should be advised to use additional nonhormonal forms of contraception.

Rufinamide is well absorbed following oral administration, but the extent of its absorption decreases as the dosage is increased. The extent of absorption was approximately 85% following administration of a single dose of 600 mg under fed conditions. Food increases the extent of absorption, and doses of the drug should be administered with food.

Rufinamide is extensively metabolized, primarily via carboxylesterase-mediated hydrolysis to inactive metabolites. Approximately 85% of a dose of the drug, almost entirely in the form of metabolites, is eliminated via renal pathways. Adjusting the dosage in patients with impaired renal function is not necessary; however, patients undergoing hemodialysis within 3 hours after a dose of rufinamide are likely to experience a reduction in exposure of approximately 30%, and adjusting the dosage to compensate for the loss of the drug should be considered. Rufinamide has not been studied in patients with hepatic impairment. It is not recommended for use in patients with severe hepatic impairment, and caution should be exercised when it is used in patients with mild to moderate hepatic impairment.

Rufinamide tablets are supplied in 200- and 400-mg potencies. The tablets are scored on both sides and may be cut in half for dosing flexibility; however, the tablets may not readily provide the exact milligram/kilogram dosage that has been calculated for use in children, and these dosages have been designated as "approximate." The tablets can be administered whole, as half tablets, or crushed. The recommended initial dosage of rufinamide in children 4 years or older is approximately 10 mg/kg/day administered in two equally divided doses with food. The dosage should be increased by approximately 10 mg/kg/day increments every other day to a target dosage of 45 mg/kg/day or 3,200 mg/day, whichever is less, administered in two equally

divided doses with food. In adult patients, treatment with rufinamide should be initiated at a dosage of 400 to 800 mg/day administered in two equally divided doses with food. The dosage should be increased by 400 to 800 mg/day every 2 days until a maximum daily dosage of 3,200 mg/day in two equally divided doses with food is reached.

Agent for fibromyalgia

Fibromyalgia is one of the most common types of chronic widespread muscle pain, affecting an estimated 3 to 6 million Americans. Most patients with this disorder are women (>80%) who typically develop the condition in early-to-middle adulthood. Patients may experience different types of symptoms, the most common of which include muscle soreness, tenderness, flu-like aching, dull pain in the muscles, morning stiffness, fatigue, and problems sleeping. The American College of Rheumatology has identified criteria for a diagnosis of fibromyalgia that include widespread pain lasting for at least 3 months, plus pain present at 11 or more of the 18 parts of the body called "tender points."

Medications such as analgesics, muscle relaxants, antidepressants, AEDs, and agents for insomnia have been used in the management of fibromyalgia, but often without success. In 2007, pregabalin (Lyrica) was the first drug to be approved by FDA for managing fibromyalgia. It had already been on the market with indications that included managing neuropathic pain associated with diabetic peripheral neuropathy, managing postherpetic neuralgia, and adjunctive therapy for adult patients with partial-onset seizures. Duloxetine (Cymbalta) was the second agent to be approved (in 2008) for managing fibromyalgia, having already been marketed for the management of neuropathic pain associated with diabetic peripheral neuropathy, the acute and maintenance treatment of major depressive disorder, and the acute treatment of generalized anxiety disorder.

Milnacipran hydrochloride (Savella—Forest; Cypress) is the third drug to be approved for managing fibromyalgia, which is its only indication in the United States, although it is marketed in certain other countries for treating depression. Like duloxetine, venlafaxine (e.g., Effexor XR), and desvenlafaxine (Pristiq), the new drug is classified pharmacologically as a serotonin norepinephrine reuptake inhibitor (SNRI). The new drug is a racemic mixture, and its active enantiomer, d-milnacipran, inhibits norepinephrine uptake with approximately threefold higher potency in vitro than serotonin uptake.

The effectiveness of milnacipran was demonstrated in two placebo-controlled studies in which a larger proportion of patients treated with the drug (compared with placebo) experienced a simultaneous reduction in pain from baseline of at least 30% (using a visual analog scale) and rated themselves as much improved or very much improved based on a patient global assessment. In addition, a larger proportion of patients treated with milnacipran met the criteria for treatment response, as measured by the composite endpoint that concurrently evaluated improvement in pain, physical function, and patient global assessment.

The different mechanisms of action of milnacipran and pregabalin offer the possibility that the concurrent use of the two drugs may be more effective in managing fibromyalgia than either agent alone. Although preliminary studies have been initiated, use in such combination regimens is not a labeled indication for these agents or duloxetine.

The drug-related problems, warnings, and precautions associated with use of milnacipran are generally similar to those of duloxetine and the other SNRIs, as well as those of the SSRIs (e.g., fluoxetine [e.g., Prozac]). The labeling for each of these agents includes a boxed warning regarding the increased risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (aged 18–24 years). All patients treated with one of these agents should be closely observed for clinical worsening, suicidality, and unusual changes in behavior, particularly during the first several months of therapy and when the dosage is changed.

The use of milnacipran is contraindicated in patients treated with an MAOI or within 14 days after discontinuing an MAOI. Treatment with an MAOI should not be initiated for at least 5 days following discontinuation of therapy with milnacipran. The development of a life-threatening serotonin syndrome (e.g., mental status changes, autonomic instability, neuromuscular aberrations), as well as neuroleptic malignant syndrome–like reactions, may occur with milnacipran, other SNRIs, and SSRIs, particularly if another serotonergic drug (e.g., triptans, tramadol [e.g., Ultram]) is used concurrently. The concomitant use of these agents must be closely monitored, especially when treatment is being initiated and when dosages are increased. The concurrent use of milnacipran with tryptophan, a serotonin precursor, is not recommended. As with other CNS-active drugs, patients should be advised to avoid consuming alcoholic beverages while being treated with milnacipran.

Some patients treated with milnacipran, other SNRIs, or a SSRI have experienced seizures, hyponatremia, and abnormal bleeding, and treatment should be closely monitored in patients who are at greater risk of these complications. The risk of bleeding events is increased by concurrent use of warfarin (e.g., Coumadin) and other anticoagulants, aspirin, and nonsteroidal anti-inflammatory drugs.

The SNRIs, including milnacipran, have been associated with increases in heart rate and blood pressure. Preexisting hypertension or other cardiovascular disease should be treated before starting therapy with milnacipran. Blood pressure should be determined before starting treatment with the new drug and periodically thereafter. If patients experience a sustained increase in blood pressure while being treated with milnacipran, consideration should be given to decreasing the dosage or discontinuing treatment.

In the clinical trials with milnacipran, some patients (~5%) experienced mild elevations of ALT and/or AST (one to three times the upper limit of normal) at an incidence that was approximately twice that reported in those receiving placebo. Milnacipran should be discontinued in patients who develop jaundice or other evidence of liver dysfunction. Because milnacipran can aggravate preexisting liver disease, the new agent

should not be used in patients with substantial alcohol use or evidence of chronic liver disease.

The adverse events experienced most frequently with the use of milnacipran (and their incidence with the recommended maintenance dosage of 100 mg/day) include nausea (35%), constipation (16%), dizziness (11%), hot flush (11%), hyperhidrosis (8%), palpitations (8%), hypertension (7%), vomiting (6%), dry mouth (5%), and increased heart rate (5%). Headache was reported by 19% of the patients treated with milnacipran but was reported at a similar incidence by those receiving placebo. In the clinical studies of the new drug, 23% of patients discontinued treatment prematurely because of adverse events compared with 12% of those receiving placebo.

Because of their noradrenergic effect, the SNRIs may affect urethral resistance and micturition, and dysuria occurred more frequently in patients treated with milnacipran (1%) than in placebo-treated patients (0.5%). Caution must be observed when the new drug is used in patients with a history of dysuria, particularly in male patients with benign prostatic hyperplasia (BPH), prostatitis, or other lower urinary tract obstructive disorders. Male patients treated with milnacipran have also experienced other genitourinary adverse events (e.g., erectile dysfunction, ejaculation disorder, decreased libido, urinary retention) at a rate (2%) greater than that in placebo-treated male patients.

Mydriasis may occur in patients treated with a SNRI, including milnacipran. The use of the new drug is contraindicated in patients with uncontrolled narrow-angle glaucoma and must be used with caution in those with controlled narrow-angle glaucoma.

Although milnacipran is not a controlled substance, withdrawal symptoms may be experienced when treatment is discontinued—a response that also occurs with the other SNRIs and SSRIs. The drug should not be abruptly discontinued following extended use; instead, the dosage should be reduced gradually.

Milnacipran is classified in Pregnancy Category C and should only be used during pregnancy if the anticipated benefit justifies the risk to the fetus. Whether the new drug is excreted in human milk is unknown, and nursing while being treated with the drug is not recommended. The effectiveness and safety of milnacipran in patients younger than 17 years have not been established, and its use is not recommended in pediatric patients.

Following oral administration, the absolute bioavailability of milnacipran is approximately 85 to 90%. The drug may be administered without regard to food, but administration with food may improve tolerability. Milnacipran undergoes minimal metabolism via CYP pathways, and approximately 55% of a dose is excreted unchanged in the urine. Dosage adjustment is not necessary in patients with mild renal impairment, but caution should be exercised in patients with moderate renal impairment. A reduction in dosage is recommended in patients with severe renal impairment (i.e., creatinine clearance <30 mL/min), but its use is not recommended in patients with end-stage renal disease. In patients with mild or moderate hepatic

impairment, an adjustment in dosage is not necessary, but caution should be exercised in patients with severe hepatic impairment.

The recommended maintenance dosage of milnacipran is 50 mg twice a day. Treatment should be initiated with a single dose of 12.5 mg on the first day, followed by 12.5 mg twice a day on days 2 and 3, 25 mg twice a day on days 4 through 7, and 50 mg twice a day thereafter. Although use of a higher dosage of 100 mg twice a day in the clinical studies did not confer greater benefit than a dosage of 50 mg twice a day, based on individual patient response, the dosage may be increased to 100 mg twice a day. In patients with severe renal impairment, the usual maintenance dosage should be reduced by 50% to 25 mg twice a day.

Milnacipran hydrochloride film-coated tablets are supplied in 12.5-, 25-, 50-, and 100-mg potencies.

Agent for overactive bladder

Overactive bladder is characterized by contraction of the detrusor muscle while the bladder is filling with urine rather than when it is full. The condition is a common cause of incontinence in the elderly and affects many individuals between the ages of 35 and 64 years.

Urinary bladder contraction is mediated via cholinergic muscarinic receptors, with anticholinergic agents representing the primary treatment for overactive bladder. **Fesoterodine fumarate** (Toviaz—Pfizer) is the sixth muscarinic receptor antagonist to be approved for treating overactive bladder, joining tolterodine (e.g., Detrol LA), oxybutynin (e.g., Ditropan XL), trospium (e.g., Sanctura XR), darifenacin (Enblex), and solifenacin (Vesicare). The new drug is most closely related to tolterodine, and both drugs are converted to the same active metabolite, 5-hydroxymethyl tolterodine. Following oral administration, fesoterodine is rapidly and extensively hydrolyzed to this active metabolite, which is responsible for the antimuscarinic activity.

Like its predecessors, fesoterodine is indicated for treating overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. Its effectiveness was demonstrated in two placebo-controlled studies, and the improvement of symptoms was greater with the use of a dosage of 8 mg once a day than with a dosage of 4 mg once a day. In a study in which fesoterodine was compared with tolterodine extended release, fesoterodine was reported to be significantly better than tolterodine in improving a number of endpoints; however, the dosage of fesoterodine was 8 mg once a day and the dosage of tolterodine was 4 mg once a day. Although the amounts of the active metabolite cannot be quantified exactly, an 8-mg dose of fesoterodine has considerably more active drug than a 4-mg dose of tolterodine. This is also reflected in the higher incidence of adverse events reported with fesoterodine in this study (e.g., a 34% incidence of dry mouth with the 8-mg dose of fesoterodine compared with a 17% incidence with the 4-mg dose of tolterodine).

Most of the risks and adverse events associated with the use of fesoterodine and the other agents for overactive bladder are related to their anticholinergic activity. All six agents are

contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma, and they must be used with caution in patients with conditions that place them at risk of these complications (e.g., bladder outflow obstruction, decreased gastrointestinal motility [such as those with severe constipation]).

The most common adverse events (and the incidences in patients receiving 8 mg once a day and 4 mg once a day, respectively) reported in the clinical studies with fesoterodine include dry mouth (35% and 19%), constipation (6% and 4%), dry eyes (4% and 1%), and dyspepsia (2% and 2%). Because anticholinergic agents may cause blurred vision, patients should exercise caution when engaged in potentially hazardous activities (e.g., driving) until they are able to identify whether the drug has any effect on their vision. These agents may also reduce sweating and, when used in a hot environment, the risk of heat stroke is increased. The concurrent use of fesoterodine with another agent having anticholinergic activity (e.g., certain antihistamines [e.g., diphenhydramine], tricyclic antidepressants [e.g., imipramine]) is likely to increase the frequency and severity of anticholinergic adverse events. Conversely, concurrent use with an agent exhibiting cholinergic activity may reduce the action of both agents. Drugs with anticholinergic activity, including fesoterodine, must be used with caution in patients with myasthenia gravis—a condition characterized by decreased cholinergic activity at the neuromuscular junction.

The labeling for tolterodine and solifenacin includes a precaution regarding use in patients with acquired or congenital QT prolongation. However, no evidence exists of prolongation of the QT interval in the cardiac electrophysiology studies of fesoterodine.

Fesoterodine is classified in Pregnancy Category C and should be used during pregnancy only if the anticipated benefit justifies the risk to the fetus. Whether the drug is excreted in human milk is unknown, and avoiding its use in a nursing mother is recommended. The effectiveness and safety of fesoterodine in pediatric patients have not been established.

Following oral administration, fesoterodine is well absorbed, but because of its rapid and extensive hydrolysis by nonspecific esterases to its active metabolite, the parent compound is not detected in the plasma. The bioavailability of the active metabolite is approximately 50%. The active metabolite is further metabolized in the liver, primarily via the CYP2D6 and CYP3A4 pathways. The additional metabolites do not contribute considerably to the pharmacological activity of the primary metabolite. In patients also being treated with a potent CYP3A4 inhibitor (e.g., clarithromycin [e.g., Biaxin], ketoconazole [e.g., Nizoral], itraconazole [e.g., Sporanox]), the dosage of fesoterodine should not exceed 4 mg once a day; however, a dosage adjustment is not considered necessary in patients receiving concurrent treatment with a CYP2D6 inhibitor.

Hepatic metabolism and renal excretion contribute substantially to the elimination of the active metabolite of fesoterodine. Approximately 70% of a dose of the drug, in the form of metabolites, is eliminated in the urine. An adjustment in dosage is not necessary in patients with mild or moderate renal

impairment, but the dosage should not exceed 4 mg once a day in patients with severe renal impairment (creatinine clearance <30 mL/min). Dosage adjustment is not necessary in patients with mild or moderate hepatic impairment. The drug has not been studied in patients with severe hepatic impairment and therefore is not recommended for use in these patients.

The recommended initial dosage of fesoterodine is 4 mg once a day. Based on the individual response and tolerability, the dosage may be increased to 8 mg once a day, except in patients with severe renal impairment or those who are being simultaneously treated with a potent CYP3A4 inhibitor.

Fesoterodine fumarate is supplied in an extended release tablet formulation in 4- and 8-mg potencies. Patients should be advised that the tablets should not be chewed, divided, or crushed.

Agent for benign prostatic hyperplasia

Most men older than 50 years experience an enlargement of the prostate gland (BPH) that is characterized by symptoms such as urinary urgency or hesitancy, incomplete bladder emptying, incontinence, and/or nocturia. These symptoms can be effectively managed with medications in many men, but BPH may worsen and necessitate surgery in others.

Two classes of medications have been used in men with BPH. The steroid 5-alpha-reductase inhibitors, dutasteride (Avodart) and finasteride (Proscar), reduce the size of the prostate and reduce BPH symptoms, but maximum clinical benefit may not be attained until at least several months after initiation of therapy.

Alpha-1-adrenergic receptor antagonists often provide prompt relief of BPH symptoms but do not reduce the size of the prostate. **Silodosin** (Rapaflo—Watson) is the fifth “alpha-blocker” approved for treating the signs and symptoms of BPH, joining tamsulosin (Flomax), alfuzosin (Uroxatral), doxazosin (e.g., Cardura XL), and terazosin (e.g., Hytrin). The properties and actions of silodosin are most similar to those of tamsulosin. Doxazosin and terazosin were initially approved for treating hypertension and, subsequently, BPH. A sixth alpha-blocker, prazosin (e.g., Minipress), is indicated only for treating hypertension. Silodosin, tamsulosin, and alfuzosin exhibit greater selectivity than the other alpha-blockers for alpha-1-adrenergic receptors in the lower urinary tract (e.g., prostate) and are indicated for treating BPH but not hypertension. The selectivity of the alpha-blockers does not considerably influence their efficacy in treating BPH, but it is a factor with respect to certain safety considerations.

The effectiveness of silodosin was demonstrated in two placebo-controlled studies in which the primary efficacy assessment was the International Prostate Symptom Score (IPSS), which evaluated irritative (frequency, urgency, and nocturia) and obstructive (hesitancy, incomplete emptying, intermittency, and weak stream) symptoms. The change in the total IPSS score was considerably greater in those treated with silodosin than in those receiving placebo. Studies that directly compare silodosin with other alpha-blockers are limited. The results of one study conducted in Japan demonstrated that silodosin

was more effective than placebo and not inferior to tamsulosin, although the latter agent was used in a lower dosage (0.2 mg once a day) than is generally used in the United States (0.4 mg once a day).

The alpha-blockers often are used concurrently with finasteride or dutasteride to reduce the symptoms of BPH via two mechanisms of action. In 2008, FDA approved use of tamsulosin and dutasteride in combination based on the results of studies that demonstrated greater effectiveness compared with use of either agent alone. However, studies of the use of silodosin in combination with dutasteride or finasteride have not been conducted.

Because the action and risk of adverse events of silodosin may be significantly increased, its use is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min) or severe hepatic impairment and in patients being treated with medications that are strong inhibitors of the CYP3A4 metabolic pathway (e.g., clarithromycin [e.g., Biaxin], ketoconazole [e.g., Nizoral], itraconazole [e.g., Sporanox], ritonavir [Norvir]).

Like tamsulosin, silodosin causes retrograde/abnormal ejaculation in many patients (28% incidence in the clinical studies), probably as a result of the selectivity of these two agents for receptors in the prostate. The other most common adverse events include orthostatic hypotension (3%), dizziness (3%), and diarrhea (3%). Orthostatic hypotension and dizziness are most likely to occur when treatment is initiated and in older patients (i.e., 5% incidence of orthostatic hypotension in patients >75 years). Patients should be cautioned about driving, operating machinery, or engaging in hazardous activities when beginning treatment. Because of the potential for an excessive reduction in blood pressure, silodosin should not be used concurrently with another alpha-blocker, and caution should be exercised when any alpha-blocker is used in patients treated with antihypertensive medications. Although concurrent use of silodosin and a phosphodiesterase type 5 inhibitor (sildenafil [Viagra], tadalafil [Cialis], vardenafil [Levitra]) was not associated with the occurrence of symptomatic orthostasis in the clinical studies, caution must be exercised with respect to the potential for such a response.

Reports have appeared of intraoperative floppy iris syndrome during cataract surgery in some patients treated with alpha-1-blockers, including silodosin. Accordingly, patients treated with silodosin for whom cataract surgery is planned should inform their ophthalmologist regarding their use of this medication.

BPH and carcinoma of the prostate often coexist and cause many of the same symptoms. Patients who are thought to have BPH should be examined before starting treatment with a medication such as silodosin to rule out the presence of prostate cancer.

Following oral administration, the absolute bioavailability of silodosin is approximately 32%. The peak concentration and bioavailability are decreased when silodosin is administered with food. However, the therapeutic benefit of the drug is not compromised, and administering the drug with a meal to reduce the risk of adverse events is recommended.

Sildenafil is extensively metabolized via glucuronidation, alcohol and aldehyde dehydrogenase, and CYP3A4 pathways. The main metabolite is formed from direct conjugation via the UDP-glucuronosyltransferase (UGT)2B7 pathway and is pharmacologically active. Concurrent use of an inhibitor of UGT2B7 (e.g., valproic acid [e.g., Depakene], fluconazole [e.g., Diflucan]) may increase the exposure to sildenafil, but the interaction may not be of clinical importance because both the parent compound and metabolite are pharmacologically active. The concurrent use of sildenafil and a strong CYP3A4 inhibitor is contraindicated. The new drug also is a substrate for P-glycoprotein (P-gp), and its use with a strong P-gp inhibitor (e.g., cyclosporine [e.g., Neoral]) is not recommended. Caution must be exercised if sildenafil is used concurrently with moderate CYP3A4 inhibitors, particularly those that also inhibit P-gp (e.g., verapamil).

Approximately 34% and 55% of a dose of sildenafil is eliminated in the urine and feces, respectively. In patients with moderate renal impairment, the bioavailability, peak concentration, and elimination half-life were two- to threefold higher than in patients with normal renal function, and the dosage should be reduced in these patients. The drug is contraindicated in patients with severe renal impairment. An adjustment in dosage is not necessary in patients with mild or moderate hepatic impairment. However, the use of sildenafil has not been evaluated in patients with severe hepatic impairment, and it is contraindicated in patients with this degree of hepatic dysfunction.

The recommended dosage of sildenafil is 8 mg once a day with a meal. In patients with moderate renal impairment, a dosage of 4 mg once a day is recommended.

Sildenafil capsules are supplied in 4- and 8-mg potencies.

Assessment Questions

Instructions: The assessment test for this activity must be taken online; please see “CPE processing” below for further instructions. There is only one correct answer to each question. This CPE will be available at www.pharmacist.com no later than September 30, 2009.

- 1. Which of the following agents is administered twice a day for maintenance treatment?**

 - Fesoterodine
 - Milnacipran
 - Febuxostat
 - Silodosin
- 2. Which of the following agents is included in Schedule V under the provisions of the Controlled Substances Act?**

 - Tapentadol
 - Milnacipran
 - Rufinamide
 - Lacosamide
- 3. Which of the following drug : indication pairings is correct?**

 - Golimumab : ankylosing spondylitis
 - Milnacipran : bipolar disorder
 - Rufinamide : tonic-clonic seizures
 - Lacosamide : Lennox-Gastaut syndrome
- 4. Which of the following drug : classification pairings is correct?**

 - Golimumab : interleukin-2 receptor antagonist
 - Fesoterodine : acetylcholinesterase inhibitor
 - Febuxostat : xanthine oxidase inhibitor
 - Silodosin : beta-2-adrenergic receptor agonist
- 5. Which of the following statements is correct regarding tapentadol?**

 - It is administered parenterally for the relief of moderate to severe acute pain.
 - It is a mu-opioid receptor agonist and serotonin reuptake inhibitor.
 - Nausea and dizziness are the adverse events most often associated with its use.
 - It is the active metabolite of tramadol.
- 6. Which of the following statements is correct regarding tapentadol?**

 - It is extensively metabolized via cytochrome P450 (CYP) metabolic pathways.
 - It interacts with numerous other medications via pharmacokinetic mechanisms.
 - It is contraindicated in patients with renal impairment.
 - It is administered every 4 to 6 hours.
- 7. Which of the following statements is correct regarding golimumab?**

 - When used in the treatment of rheumatoid arthritis, its indication is for use in combination with methotrexate.
 - It has been demonstrated to be effective in patients whose arthritis is refractory to etanercept and adalimumab.
 - It is the first monoclonal antibody to be approved for the treatment of systemic lupus erythematosus.
 - Its labeled indications include juvenile idiopathic arthritis.

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“New therapeutic agents marketed in the first half of 2009: Part 1” is a home-study continuing education activity for pharmacists developed by the American Pharmacists Association.

- 8. Which of the following statements is correct regarding golimumab?**
- It is administered intravenously.
 - It is administered once a month.
 - Most patients experience the development of neutralizing antibodies with continued use that limit its long-term effectiveness.
 - Its use is contraindicated in patients who are allergic to eggs.
- 9. Which of the following statements is correct regarding febuxostat?**
- It is classified as a uricosuric agent.
 - Its properties are most similar to those of allopurinol.
 - It is indicated for the chronic management of gout and to treat acute gout flares.
 - It causes an increase in blood glucose concentrations and should not be used in patients with diabetes.
- 10. Which of the following statements is correct regarding febuxostat?**
- It reduces the action of mercaptopurine, and the dosage of mercaptopurine must be increased when the two agents are used concurrently.
 - It should be administered at least 1 hour before a meal.
 - It is excreted in the urine in unchanged form.
 - It has caused liver function test abnormalities, and liver function tests should be performed.
- 11. Which of the following statements is correct regarding lacosamide?**
- It should be used as monotherapy because of the risk of serious drug interactions with other antiepileptic drugs (AEDs).
 - Its labeled indications include the treatment of neuropathic pain in patients with diabetes.
 - It is supplied in formulations for oral and intravenous administration.
 - It is classified as a gamma-aminobutyric acid antagonist.
- 12. Which of the following statements is correct regarding lacosamide?**
- Dizziness is the adverse event experienced most often with its use.
 - It causes dose-dependent prolongation of the QT interval of the electrocardiogram.
 - It is converted to an active metabolite that is responsible for its pharmacologic action.
 - Its use should be avoided in patients with renal impairment.
- 13. Which of the following statements is correct regarding rufinamide?**
- It is a prodrug that is converted to zonisamide following oral administration.
 - It is indicated for use in children as young as 2 years of age.
 - It is indicated for use in combination with other AEDs.
 - Rash is the adverse event experienced most often with its use.
- 14. Which of the following statements is correct regarding rufinamide?**
- It causes prolongation of the QT interval of the electrocardiogram.
 - It should be administered with food.
 - It is extensively metabolized via CYP metabolic pathways.
 - Its use is contraindicated in patients with impaired renal function.
- 15. Which of the following statements is correct regarding milnacipran?**
- It is a selective serotonin reuptake inhibitor.
 - Its properties are most similar to those of pregabalin.
 - It is often used in combination with duloxetine.
 - It may increase blood pressure, and blood pressure should be periodically monitored.

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