New therapeutic agents marketed in the first half of 2010: Part 1

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Abstract

Objective: To provide information regarding the most important properties of the new therapeutic agents marketed in the first half of 2010.

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: 13 new therapeutic agents were marketed in the United States during the first half of 2010, 6 of which are reviewed in this article (part 1 of a two-part series): tocilizumab, pitavastatin calcium, liraglutide, dalfampridine, denosumab, and polidocanol. 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: Three of the new drugs have mechanisms of action and/or other properties that distinguish them from previously marketed drugs. Tocilizumab is the first drug to inhibit the action of interleukin-6 and may be effective in some patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more tumor necrosis factor antagonists. Denosumab has a unique mechanism of action and is indicated for the treatment of postmenopausal women with osteoporosis who are at high risk of fracture or who have failed or are intolerant to agents such as the bisphosphonates. Dalfampridine is a potassium channel blocker that increases walking speed in some patients with multiple sclerosis. An understanding of the properties of these medications is important for the pharmacist 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, risk assessment.

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**Antiarthritic agent**

Rheumatoid arthritis is a chronic, debilitating autoimmune disorder that is characterized by inflammation and joint damage. Traditional treatment has included the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX), leflunomide, and hydroxychloroquine. The more recent development of biologic agents for the treatment of rheumatoid arthritis represents an important advance in the treatment of this condition, and these agents have been used in combination with one of the older drugs and, in some situations, as monotherapy. These biologicals include tumor necrosis factor (TNF) antagonists (etanercept [Enbrel], infliximab [Remicade], adalimumab [Humira], golimumab [Simponi], certolizumab pegol [Cimzia]), the interleukin (IL)-1 antagonist anakinra (Kineret), the T-cell costimulatory inhibitor abatacept (Orencia), and the anti-CD20 monoclonal antibody rituximab (Rituxan).

IL-6 is a naturally occurring proinflammatory cytokine that is produced by synovial and endothelial cells and contributes to the local inflammation that is experienced by individuals with rheumatoid arthritis. **Tocilizumab** (Actemra—Genentech) is a recombinant humanized monoclonal antibody that binds to soluble and membrane-bound IL-6. The new drug is administered via intravenous infusion and is indicated as monotherapy or in combination with DMARDs for adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonists. However, concurrent use of tocilizumab with a biological DMARD should be avoided because their similar risks increase the possibility of serious complications.

The efficacy of tocilizumab was demonstrated in five studies with four regimens studied: monotherapy, in combination with MTX, in combination with other DMARDs, and in combination with MTX in patients who failed TNF antagonist therapy. Overall, more than 50% of the patients treated with tocilizumab achieved an ACR20 response (i.e., representing a 20% improvement in criteria established by the American College of Rheumatology [ACR]) at 24 weeks compared with approximately 30% of the patients receiving placebo. Patients treated with tocilizumab also had higher ACR50 and ACR70 responses compared with placebo (29% vs. 14% and 15% vs. 5%, respectively). The new drug has not been directly compared with other antirheumatic drugs in clinical studies.

The adverse events associated with tocilizumab are generally similar to those of other biological therapies for rheumatoid arthritis. Similar to the TNF antagonists, the labeling for tocilizumab includes a boxed warning regarding the risk of serious infections. The risk is highest in patients concomitantly treated with other agents having immunosuppressive activity. Tocilizumab should not be administered if the patient has a clinically important infection, including localized infections, and its use should be withheld until the infection resolves.

Before treatment, patients should be screened for tuberculosis (TB). Patients with active or latent TB should be treated before initiating tocilizumab therapy, and antitubercular treatment should also be considered for patients with a negative test for latent TB but who have risk factors for TB. Patients should not receive live vaccines while being treated with tocilizumab, and recommended vaccinations should be provided before initiation of therapy.

Like other agents with immunosuppressant activity, tocilizumab may increase the risk of malignancies. A risk with regard to demyelinating disorders also exists, and rare cases of multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported in clinical trials. Therefore, patients should be monitored for signs and symptoms of such disorders.

In the clinical trials, a risk of gastrointestinal perforation, primarily as a complication of diverticulitis, was reported. Multiple laboratory abnormalities were also observed, including neutropenia, thrombocytopenia, elevated liver function tests, and elevated lipids. Treatment with tocilizumab should not be initiated in patients with an absolute neutrophil count (ANC) less than 2,000/mm³, with a platelet count less than 100,000/mm³, or who have alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values above 1.5 times the upper limit of normal. Neutrophils, platelets, ALT, AST, and lipids should be monitored every 4 to 8 weeks. Treatment with tocilizumab is not recommended in patients with hepatic impairment or active hepatic disease.

The adverse events most commonly observed in the clinical trials with tocilizumab (and the incidence reported with monotherapy) include upper respiratory tract infection (7%), nasopharyngitis (7%), headache (7%), hypertension (6%), and elevated ALT (6%). Infusion reactions were reported in approximately 7% of the patients treated with the new drug, and 0.1% experienced a clinically significant hypersensitivity reaction that typically occurred during the second to fourth infusion.

Similar to other biologicals, the potential for immunogenicity is a concern. Of the more than 2,600 patients in the studies who were tested, 46 (2%) developed anti-tocilizumab antibodies. Of these patients, five experienced hypersensitivity reactions that required discontinuation of treatment.

Tocilizumab is classified in Pregnancy Category C and should only be used during pregnancy if the anticipated benefit justifies the risk to the fetus. In the situations in which using tocilizumab during pregnancy is justified, patients should be enrolled in the pregnancy registry for the drug by calling 1-877-311-8972. The effectiveness and safety of tocilizumab in patients younger than 18 years have not been established.

Like infliximab, abatacept, and rituximab, tocilizumab is administered intravenously, whereas the other biologicals used in the treatment of rheumatoid arthritis are administered subcutaneously. The new drug is administered via an intravenous drip infusion over a period of 60 minutes. The recommended starting dosage is 4 mg/kg once every 4 weeks, that may be increased to 8 mg/kg once every 4 weeks based on the clinical response. Doses exceeding 800 mg are not recommended. The product labeling should be consulted for the recommendations for adjusting the dosage or interrupting/discontinuing treatment based on decreases in ANC or platelets or increases in ALT or AST.
Tocilizumab is supplied as a sterile solution in a concentration of 20 mg/mL in single-use vials containing 4 mL (80 mg), 10 mL (200 mg), and 20 mL (400 mg) solution. The vials should be stored in a refrigerator and protected from light. The volume of solution needed to provide the appropriate dose should be diluted to 100 mL in 0.9% Sodium Chloride Injection.

**Lipid-regulating agent**

**Pitavastatin calcium** (Livalo—Kowa; Lilly) is the eighth 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) to be marketed in the United States, joining atorvastatin (Lipitor), fluvastatin (e.g., Lescol XL), lovastatin, pravastatin, rosuvastatin (Crestor), and simvastatin. Cerivastatin (Baycol) was marketed from 1998 to 2001 but was withdrawn from the market because of concern regarding serious adverse events (i.e., myopathy, rhabdomyolysis).

Like the other statins, pitavastatin is indicated as an adjunctive therapy to diet to reduce elevated total cholesterol, low-density lipoprotein (LDL) cholesterol, apolipoprotein B, and triglycerides and to increase high-density lipoprotein cholesterol in adult patients with primary hyperlipidemia or mixed dyslipidemia. The effectiveness of pitavastatin was demonstrated in placebo-controlled studies and in studies in which it was compared with atorvastatin, simvastatin, and pravastatin. In the determinations of the percent reductions in LDL cholesterol from baseline to endpoint, pitavastatin (in a dosage of 4 mg once a day) was noninferior to atorvastatin (20 mg once a day) and simvastatin (40 mg once a day) and more effective than pravastatin (40 mg once a day). However, the dosage of 4 mg once a day for pitavastatin represents the maximum recommended dosage for the new drug, whereas the maximum daily dosage identified in the labeling for atorvastatin, simvastatin, and pravastatin is 80 mg. Although higher dosages of the latter three agents were not evaluated in the comparative studies, it can be anticipated that, when used within the recommended dosage range, the action of pitavastatin on blood lipid concentrations will be less pronounced than the action of atorvastatin, simvastatin, and rosuvastatin (with which it has not been directly compared).

The labeled indications for pitavastatin are also more limited than those for the other statins. As selected examples, atorvastatin and simvastatin have been demonstrated to reduce the risk of myocardial infarction, stroke, and revascularization procedures in patients without clinically evident coronary heart disease but with multiple risk factors for such, as well as in patients with clinically evident coronary heart disease. However, these are not labeled indications for pitavastatin at the present time. In addition, the older statins have been approved for a larger number of dyslipemias than the new drug.

The contraindications, warnings, and precautions for pitavastatin are generally similar to those for the other statins. The statins may cause fetal harm if administered during pregnancy. Accordingly, they are classified in Pregnancy Category X and are contraindicated in pregnant women, as well as in nursing mothers.

Like the other statins, pitavastatin is contraindicated in patients with active liver disease, including unexplained persistent elevations of serum transaminases (ALT and AST). It must be used with caution in patients who have a history of liver disease or who consume substantial quantities of alcohol. Liver enzyme tests should be performed before and at 12 weeks following the initiation of therapy and any increase in dosage, then periodically (e.g., semiannually) thereafter. If ALT and/or AST values of more than three times the upper limit of normal persist, the dosage of pitavastatin should be reduced or treatment suspended.

All of the statins have been associated with the occurrence of adverse events involving the skeletal muscles, including myalgia, myopathy, and rhabdomyolysis, a rare but potentially fatal complication associated with damage to skeletal muscle, leakage of muscle contents (e.g., myoglobin) into the blood and urine, and possibly acute renal failure and cardiac dysrhythmias or arrest. Patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Treatment should be discontinued if markedly elevated creatine kinase concentrations occur or if myopathy is diagnosed or suspected. Therapy should also be temporarily withheld in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., sepsis, hypotension, dehydration, electrolyte disorders, major surgery). In the premarketing clinical studies of pitavastatin, an increased risk for severe myopathy was associated with the use of dosages greater than 4 mg once a day, and it is this risk that limits the recommended dosage to a maximum of 4 mg once a day.

### Table 1. New therapeutic agents marketed in the United States from January to June 2010

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Manufacturer</th>
<th>Therapeutic classification</th>
<th>Route of administration</th>
<th>FDA classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalfampridine</td>
<td>Ampyra</td>
<td>Acorda</td>
<td>Agent for multiple sclerosis</td>
<td>Oral</td>
<td>1-P</td>
</tr>
<tr>
<td>Denosumab</td>
<td>Prolia</td>
<td>Amgen</td>
<td>Agent for osteoporosis</td>
<td>Subcutaneous</td>
<td>S</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Victoza</td>
<td>Novo Nordisk</td>
<td>Antidiabetic agent</td>
<td>Subcutaneous</td>
<td>1-S</td>
</tr>
<tr>
<td>Pitavastatin calcium</td>
<td>Livalo</td>
<td>Kowa; Lilly</td>
<td>Lipid-regulating agent</td>
<td>Oral</td>
<td>1-S</td>
</tr>
<tr>
<td>Polidocanol</td>
<td>Asclera</td>
<td>BioForm Medical</td>
<td>Sclerosing agent</td>
<td>Intravenous</td>
<td>1-S</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>Actemra</td>
<td>Genentech</td>
<td>Antiarthritic agent</td>
<td>Intravenous</td>
<td>1-S</td>
</tr>
</tbody>
</table>

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

*FDA classification of new drugs: 1 = new molecular entity; P = priority review; S = standard review.

*A biological approved through an FDA procedure that does not assign a numerical classification.
The concurrent use of a statin with a fibrate (fenofibrate, gemfibrozil) or lipid-lowering doses of niacin is likely to increase the risk of myopathy and other skeletal muscle effects. However, in some patients in whom the use of a statin alone does not provide the desired regulation of blood lipids, the anticipated benefit of such combination regimens (e.g., an additional reduction in triglyceride concentrations) may outweigh the increased risk. Caution should be exercised if pitavastatin is used concurrently with a fibrate, and a reduction in dosage of the new drug should be considered in patients who are also to be treated with lipid-lowering doses of niacin.

The adverse events most often reported with the use of pitavastatin include back pain (4%), constipation (4%), diarrhea (3%), myalgia (3%), and pain in extremity (2%). The incidences of these events were only slightly higher than those reported in the individuals receiving placebo.

Pitavastatin is metabolized to only a limited extent via cytochrome P450 (CYP) metabolic pathways and is less likely than lovastatin, simvastatin, and atorvastatin to interact with other medications via this mechanism. However, it has been implicated in several other interactions that warrant particular caution. Cyclosporine significantly increases pitavastatin exposure, and concurrent use is contraindicated. Lopinavir/ritonavir (Kaletra) are thought to have the potential to significantly increase pitavastatin exposure, and the use of these agents in combination should be avoided. Erythromycin and rifampin have also been reported to increase pitavastatin exposure considerably, and the dosage of the new drug should be reduced in patients who are also being treated with one of these agents. Although studies of the concurrent use of pitavastatin and warfarin have not been associated with any substantial change in prothrombin time or the international normalized ratio (INR), it is recommended that patients treated with warfarin have their prothrombin time and INR monitored when pitavastatin is added to their therapy.

Following oral administration, peak plasma concentrations of pitavastatin are attained within approximately 1 hour. The absolute bioavailability of pitavastatin oral solution is 51%. The primary route of metabolism of the new drug is glucuronidation in the liver via uridine 5'-diphosphate glucuronosyltransferase (UGT1A3 and UGT2B7), resulting in the formation of pitavastatin lactone. Approximately 15% of a dose of the new drug is excreted in the urine and approximately 80% in the feces. Its bioavailability is considerably higher in patients with moderate renal impairment and in patients with end-stage renal disease receiving hemodialysis, and a lower dosage is recommended in these patients. Because pitavastatin has not been studied in patients with severe renal impairment but who are not on hemodialysis, it is recommended that it not be used in these patients.

Pitavastatin is administered once a day at any time of the day with or without food. The recommended starting dosage is 2 mg once a day. Blood lipid concentrations should be determined when initiating treatment and after 4 weeks, at which time the dosage may be adjusted accordingly. The maximum recommended dosage of pitavastatin is 4 mg once a day. In patients with moderate renal impairment or with end-stage renal disease receiving hemodialysis, the recommended initial dosage is 1 mg once a day and the maximum dosage 2 mg once a day. In patients treated concurrently with erythromycin, the dosage of pitavastatin should not exceed 1 mg once a day, and in patients treated with rifampin, the dosage should not exceed 2 mg once a day.

Pitavastatin calcium is supplied in tablets in quantities that provide the equivalent of 1, 2, and 4 mg of the drug as the free base.

Antidiabetic agent

Liraglutide (Victoza—Novo Nordisk) is an analog of glucagon-like peptide-1 (GLP-1) and acts as a GLP-1 receptor agonist. Its properties are most similar to those of exenatide (Byetta), and both agents are administered subcutaneously. Liraglutide and exenatide reduce blood glucose concentrations via several mechanisms that include increased insulin release in the presence of elevated glucose concentrations, decreased glucagon secretion, and delayed gastric emptying.

Liraglutide is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes and may be used as monotherapy or in conjunction with one or more oral antidiabetic drugs, such as metformin, glimepiride, or a thiazolidinedione. However, it is not recommended as first-line therapy for patients inadequately controlled on diet and exercise, whereas the labeling for exenatide does not include this limitation.

The effectiveness of liraglutide was demonstrated in studies in which it was used alone or in patients also treated with metformin and/or glimepiride or with metformin and rosiglitazone (Avandia). In the study in which liraglutide monotherapy was compared with glimepiride monotherapy, the new drug provided significantly greater reductions in glycosylated hemoglobin (A1C; −0.8% and −1.1% with daily doses of 1.2 and 1.8 mg liraglutide, respectively, compared with −0.5% with 8 mg daily glimepiride, after 52 weeks). In one study, either liraglutide (1.8 mg once a day) or exenatide (10 µg twice a day) was added to a regimen of metformin and/or glimepiride. After 26 weeks, patients receiving liraglutide achieved a statistically greater reduction in A1C from baseline (−1.12%) compared with −0.79% in patients receiving exenatide. Liraglutide also provided significantly greater reductions in fasting plasma glucose, but patients treated with exenatide experienced a greater reduction in postprandial glucose after breakfast and dinner.

As with exenatide, many patients treated with liraglutide lose weight (~3 kg on average): this is an added benefit for these medications, which are often used in patients who are overweight. In contrast, use of glimepiride and other sulfonylureas is often associated with weight gain.

The adverse events reported most often in the study in which liraglutide was used as monotherapy included nausea (28%), diarrhea (17%), vomiting (11%), constipation (10%), upper respiratory tract infection (10%), and headache (9%). As with exenatide, pancreatitis has been reported infrequently. Caution should be exercised in patients with a history of pan-
creatitis, particularly when treatment is initiated and following increases in dosage. If symptoms suspected to be associated with pancreatitis develop, treatment should be discontinued. If pancreatitis is confirmed, liraglutide should not be resumed.

Liraglutide has been reported to cause malignant thyroid C-cell tumors in rodents, and this is the subject of a boxed warning in the labeling for the drug. Although whether liraglutide causes such tumors, including medullary thyroid carcinoma (MTC), in humans is unknown, the new drug is contraindicated in patients with a personal or family history of MTC or in patients with multiple endocrine neoplasia syndrome type 2. The labeling for exenatide does not address this problem, although recent observations suggested the possibility of an increased cancer risk with its use.

Many of the patients in the clinical studies were tested for the presence of anti-liraglutide antibodies at the end of treatment. These antibodies were detected in approximately 9% of those tested, but the potential for significant neutralization of the clinical benefit was not assessed. Although experienced infrequently, immunogenicity-related events, including urticaria, were reported more often in patients treated with liraglutide (0.8%) than with other antidiabetic agents.

Liraglutide 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 drug is excreted in human milk is not known, and a decision should be made whether to discontinue nursing or not use the drug. The effectiveness and safety of liraglutide in pediatric patients have not been established.

Liraglutide is not likely to cause hypoglycemia. However, serious hypoglycemia may result when it is used concurrently with an insulin secretagogue such as a sulfonylurea. The risk of hypoglycemia may be reduced by decreasing the dosage of the latter agent when treatment with liraglutide is initiated. Because liraglutide delays gastric emptying, a potential exists for altered absorption of oral medications used concurrently. Although interactions of this type were not reported in the clinical studies, the potential for changes in absorption and activity of orally administered drugs should be monitored.

Liraglutide is administered subcutaneously in the abdomen, thigh, or upper arm. Following administration, maximum concentrations are attained within 12 hours, and the absolute bioavailability is approximately 55%. As with other proteins, the drug is endogenously metabolized in a manner in which no specific organ has a prominent role. None of the parent drug and only limited quantities of metabolites are identified in the urine and feces. Because experience with liraglutide in patients with impaired hepatic or renal function has been limited, it should be used with caution in these patients.

The duration of action of liraglutide is longer than that of exenatide, and the new drug is administered once a day, whereas exenatide is administered twice a day. This advantage may, however, be short-lived because an application is pending at the Food and Drug Administration (FDA) for a longer-acting formulation of exenatide that will be administered just once a week.

Daily injections of liraglutide may be administered at any time of day, but the general time of administration should be consistent from day to day. Treatment should be initiated with a dosage of 0.6 mg once a day for 1 week. Although this initial dosage is not considered effective in providing glycemic control, gastrointestinal adverse events will be reduced when therapy is started. After 1 week, the dosage should be increased to 1.2 mg once a day. If this dosage does not provide the anticipated glycemic control, the dosage may be increased to 1.8 mg once a day.

Liraglutide solution is supplied for subcutaneous injection in prefilled multidose pens that deliver doses of 0.6, 1.2, or 1.8 mg (6 mg/mL; 3 mL). The product should be stored in a refrigerator. After initial use of the pen unit, it may be stored for 30 days at controlled room temperature or in a refrigerator.

Agent for multiple sclerosis

Approximately 400,000 Americans have been diagnosed with multiple sclerosis (MS), a chronic autoimmune disease of the central nervous system. Symptoms often include fatigue, visual problems, numbness in the limbs, loss of balance/coordination, and difficulty walking. Some patients become paralyzed or otherwise disabled as a consequence of the disease. MS affects more women than men, and the onset of the disease is usually between 20 and 40 years of age.

The most common form of MS is the relapsing/remitting form, in which acute symptoms (designated as relapses, attacks, or exacerbations) occur and subsequently diminish or resolve (remissions). The remissions may continue for months or years before the next relapse occurs. Several medications have been used to decrease the frequency of clinical exacerbations in patients with relapsing/remitting MS, including interferon beta-1a (Avonex, Rebif), interferon beta-1b (Betaseron), and glatiramer acetate (Copaxone). Mitoxantrone (Novantrone), a drug initially approved for the treatment of certain neoplastic disorders, has also been approved for reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening relapsing/remitting MS. In 2004, natalizumab (Tysabri), a monoclonal antibody with a unique mechanism of action, was marketed for the treatment of patients with relapsing forms of MS to reduce the frequency of clinical exacerbations. However, because of the risk of a rare but potentially fatal adverse event (progressive multifocal leukoencephalopathy), its use should generally be reserved for patients who have had an inadequate response to or are unable to tolerate other therapies for MS.

Dalfampridine (Ampyra—Acorda), which is also known as fampridine and by its chemical name, 4-aminopyridine, is a potassium channel blocker that, in animal studies, has been shown to increase conduction of action potentials in demyelinated axons. It has been approved for oral use to improve walking in patients with MS, a benefit that was demonstrated by an increase in walking speed. Dalfampridine was evaluated in two clinical trials in which the primary measure of efficacy was walking speed as measured by the Timed 25-foot Walk. A
significantly greater percentage of patients treated with the new drug showed faster walking speed compared with patients receiving placebo (35% vs. 8% and 43% vs. 9% in the two studies). However, of note, more than one-half of the patients treated with dalfampridine did not experience benefit.

The most important concern with using dalfampridine is the risk of seizures, which is dose related. It is contraindicated in patients with a history of seizures, and its use should be discontinued in patients who experience a seizure during treatment. Because approximately 90% of a dose of the drug is excreted in unchanged form in the urine, its clearance is reduced in patients with renal impairment and seizure risk is increased as a result. Accordingly, dalfampridine is contraindicated in patients with moderate or severe renal impairment (creatinine clearance ≤50 mL/minute). The risk of seizures in patients with mild renal impairment (creatinine clearance 51–80 mL/minute) is not known, but the plasma concentrations of dalfampridine in these patients may approximate those seen with a dosage of 15 mg twice a day—a dosage that is associated with an increased risk of seizures and is higher than the recommended dosage of 10 mg twice a day. An estimated creatinine clearance should be known before initiating treatment with dalfampridine, particularly in elderly patients who are more likely to experience decreased renal function.

The most commonly reported adverse events with the use of dalfampridine included urinary tract infections (12%), insomnia (9%), dizziness (7%), headache (7%), nausea (7%), asthenia (7%), back pain (5%), and balance disorder (5%). Unlike most new drugs, dalfampridine was available (as 4-aminopyridine) before it was officially approved by FDA, and some physicians have prescribed it in formulations compounded by pharmacists. Precautions must be observed to prevent patients from taking more than one product containing this active ingredient.

Dalfampridine 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 drug is excreted in human milk is not known, and a decision should be made whether to discontinue nursing or not use the drug. The effectiveness and safety of dalfampridine in patients younger than 18 years of age have not been established.

Following oral administration, dalfampridine is rapidly and completely absorbed. It undergoes only limited metabolism and most of a dose is eliminated as the parent drug in the urine.

Dalfampridine extended-release tablets are supplied in a 10-mg potency and are only available through a limited network of specialty pharmacies and Kaiser Permanente. The recommended dosage is 10 mg twice a day, taken approximately 12 hours apart. This dosage should not be exceeded, and if a dose is missed, double or extra doses should not be taken.

**Agent for osteoporosis**

Osteoporosis is characterized by decreased bone mass and an increased risk of fracture, most often at the spine, hip, and wrist. Because of the reduction in estrogen production that occurs following menopause, women are more likely than men to experience osteoporosis, and one of every two women older than 50 years will experience a bone fracture as a consequence. Bisphosphonates such as alendronate (e.g., Fosamax), ibandronate (Boniva), and risedronate (Actonel) have been widely prescribed for the treatment and prevention of osteoporosis. These agents are administered orally, and ibandronate is also available in a formulation that is administered intravenously every 3 months. Another bisphosphonate, zoledronic acid (Reclast), is administered intravenously once a year for the treatment (and every 2 years for prevention) of osteoporosis in postmenopausal women.

**Denosumab** (Prolia—Amgen) is a human monoclonal antibody that binds to receptor activator of nuclear factor kappa-B ligand (RANKL), a protein that is essential for the formation, function, and survival of osteoclasts, the cells that are responsible for bone resorption. Denosumab prevents RANKL from activating its receptor on the surface of osteoclasts and their precursors, with a resultant decrease in bone resorption and increase in bone mass and strength.

Denosumab is administered subcutaneously and is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture or multiple risk factors for fracture, or of patients who have failed or are intolerant to other available therapies for osteoporosis. The effectiveness of the new drug was demonstrated in placebo-controlled studies, in which it reduced the incidence (identified as new fractures at year 3 for the denosumab and placebo groups, respectively) of vertebral (2.3%, 7.2%), nonvertebral (6.5%, 8%), and hip (0.7%, 1.2%) fractures. Treatment with denosumab significantly increased bone mineral density (BMD) at all anatomic sites measured at 3 years. Following discontinuation of treatment, BMD returned to approximately baseline levels within 12 months.

Whereas the labeled indication for denosumab is for the treatment of women who are considered to be at high risk of fracture, the indications for alendronate, ibandronate, risedronate, and zoledronic acid include the prevention, as well as treatment, of osteoporosis in postmenopausal women, and the indication is not limited to those at high risk of fracture. The indications for alendronate, risedronate, and zoledronic acid also include the treatment of osteoporosis in men and women, and Paget’s disease in men and women.

Denosumab is also being evaluated to determine whether it may reduce the risk of fractures in patients with certain cancers (e.g., prostate cancer) that have metastasized to bone tissue or whether it may prevent tumors from metastasizing to bone. However, these are not labeled indications at the present time.

The use of denosumab may exacerbate hypocalcemia, and it is contraindicated in patients with hypocalcemia. Preexisting hypocalcemia should be corrected before initiating treatment with the new drug. In patients who are predisposed to hypocalcemia and disturbances of mineral metabolism (e.g., history of hypoparathyroidism, malabsorption syndromes, severe renal impairment), concentrations of calcium and minerals (e.g.,
phosphorus, magnesium) should be monitored. Supplementation with calcium and vitamin D should be provided during treatment.

In the clinical studies, serious infections (e.g., skin, abdominal, urinary tract, ear, endocarditis) that necessitated hospitalization were reported more frequently in patients treated with denosumab than in those receiving placebo. Patients who are also being treated with immunosuppressive agents or who have impaired immune function should be considered at greater risk for serious infection. Patients should be advised to promptly report signs or symptoms of severe infection.

Denosumab has been reported to cause dermatologic adverse events (e.g., dermatitis, eczema, rash) at a significantly higher incidence than was observed in the placebo group. The discontinuation of treatment should be considered if severe symptoms occur.

As with the bisphosphonates, some patients treated with denosumab have experienced osteonecrosis of the jaw (ONJ) that may be related, in part, to suppression of bone remodeling. A routine oral exam should be performed by the prescriber before initiating treatment. In patients with risk factors for ONJ (e.g., tooth extraction, oral surgery, poor oral hygiene), a dental examination with appropriate preventive dentistry should be considered. Patients should be advised to inform their dentists that they are taking denosumab before having dental work done.

The most frequently experienced adverse events with denosumab include back pain (35%), pain in extremity (12%), musculoskeletal pain (8%), cystitis (6%), and hypercholesterolemia (7%), although the incidences of these events were only slightly higher than those reported in participants receiving placebo. The percent of patients who withdrew from the study because of adverse events was 2.1% in the placebo group and 2.4% in the denosumab group. As with other therapeutic proteins, a possibility exists for immunogenicity with denosumab, although none of the patients tested positive for neutralizing antibodies.

Because denosumab is indicated only for use in postmenopausal women, it would not be considered for use in a pregnant woman unless it was being used off label. It is classified in Pregnancy Category C, and if used in pregnant women, they should be encouraged to enroll in Amgen’s Pregnancy Surveillance Program.

Denosumab should be administered by a health professional and is administered subcutaneously in the upper arm, upper thigh, or abdomen. The recommended dosage is 60 mg once every 6 months. Patients should receive calcium (1,000 mg/day) and vitamin D (at least 400 IU daily).

Denosumab is supplied in single-use prefilled syringes and single-use vials containing 1 mL of a solution containing the drug in a concentration of 60 mg/mL. The formulations should be stored in a refrigerator. After removal from the refrigerator, the drug should be used within 14 days. Before administering, denosumab should be removed from the refrigerator and brought to room temperature by standing in its original container for 15 to 30 minutes. The product should not be warmed/

Sclerosing agent

Varicose veins are swollen, twisted veins that are just under the surface of the skin and are readily visible. Veins have one-way valves that keep blood flowing toward the heart. However, if these valves are weak or damaged, blood may back up and pool in the veins, resulting in swelling that leads to varicose veins. Although varicose veins may not be associated with the occurrence of symptoms, some individuals experience mild to moderate pain, blood clots, and/or skin ulcers.

Varicose veins most commonly occur in the legs. Spider veins involve the capillaries and often have the appearance of a spider web or tree branch. Reticular veins are flat blue veins that are usually seen behind the knees. Certain other vein problems (e.g., telangiectasias, hemorrhoids) that are related to varicose veins occur in other parts of the body.

Treating varicose veins is often unnecessary. However, if symptoms persist and/or concern exists that the varicose veins present an unacceptable appearance, treatment with lifestyle changes (e.g., avoiding standing or sitting for long periods without taking a break, physical activities, compression stockings) or medical procedures may be considered. Medical procedures involve removing or closing the varicose veins. This will not usually cause problems with blood flow because the blood starts moving through other veins. Sclerotherapy with the use of agents such as sodium tetradecyl sulfate (Sotradecol) and morrhuate sodium (Scleromate) has been used in the treatment of smaller varicose veins. These sclerosing agents are injected into the vein and cause irritation and scarring inside the vein. This action results in the vein closing off and fading away.

Polidocanol

Polidocanol (Asclera—BioForm Medical) is a nonionic detergent that consists of two components: a polar hydrophilic (dodecyl alcohol) chain and an apolar hydrophobic (polyethylene oxide) chain. It is a sclerosing agent with properties and uses that are most similar to those of sodium tetradecyl sulfate, an anionic surface active agent. When injected into varicose veins, polidocanol damages the endothelium of blood vessels. Platelets aggregate at the site of the damage, and eventually a dense network of platelets, cellular debris, and fibrin occludes the vessel. The occluded vein is subsequently replaced with connective fibrous tissue.

Polidocanol is specifically indicated to sclereose uncomplicated spider veins (varicose veins ≤1 mm diameter) and uncomplicated reticular veins (varicose veins 1–3 mm diameter) in the lower extremity. Its effectiveness was demonstrated in a study in which it was compared with sodium tetradecyl sulfate or placebo (0.9% isotonic saline solution). Digital images of the treated area were taken before treatment and at 12 and 24 weeks following treatment and were judged by a blinded panel. Treatment was determined to be successful at both 12 and 24 weeks in more than 90% of the patients treated with polidocanol or sodium tetradecyl sulfate but in less than 10% of those receiving placebo. Patient satisfaction was also evaluated, and
approximately 85%, 64%, and 15% were satisfied or very satisfied with their treatment with polidocanol, sodium tetradecyl sulfate, and placebo, respectively.

The use of polidocanol is contraindicated in patients with acute thromboembolic diseases and in those with a known allergy (anaphylaxis) to the drug. Severe allergic reactions, including anaphylactic reactions, have been reported following the use of polidocanol, some of which have been fatal. The risk of severe reactions is greater with the use of volumes greater than 3 mL of the injection, and the smallest effective volume at each injection site should be used. Following injection, patients should be under supervision for at least 20 minutes so that any emerging allergic response may be appropriately treated.

When administering polidocanol, particular caution must be observed in the intravenous needle placement. Accidental intra-arterial injection may result in severe necrosis, ischemia, or gangrene, and inadvertent perivascular injection may cause pain. If the resulting pain is severe, a local anesthetic (without epinephrine) may be administered.

The most frequently reported adverse events (and the incidences with polidocanol and sodium tetradecyl sulfate, respectively) in the clinical study include the following, usually mild in injection site reactions: hematoma (42%, 65%), irritation (41%, 73%), discoloration (38%, 74%), pain (24%, 31%), pruritus (19%, 27%), and warmth (16%, 21%). Ultrasound examinations at 1 and 12 weeks following treatment did not reveal deep-vein thrombosis in any treatment group.

Polidocanol is classified in Pregnancy Category C and should not be used during pregnancy or in nursing mothers. Its effectiveness and safety in pediatric patients have not been established.

Polidocanol is supplied in ampules containing 5 mg (0.5%) and 10 mg (1%) of the drug in water for injection with 5% (vol/vol) ethanol. The 0.5% solution should be used for the treatment of spider veins and the 1% solution for reticular veins. A syringe with a fine needle (typically 26 or 30 gauge) should be used, and the solution should be injected slowly. A volume of 0.1 to 0.3 mL should be used for each injection, and no more than 10 mL should be injected per session. Repeat treatments may be needed if the extent of the varicose veins requires more than 10 mL solution. These treatments should be separated by 1 to 2 weeks.

Following the removal of the needle and the covering of the injection site, compression in the form of a stocking or bandage should be applied. The patient should be encouraged to walk for 15 to 20 minutes while being kept under observation because of the potential for an allergic response. To reduce the risk of deep-vein thrombosis, compression should be maintained for 2 to 3 days following treatment of spider veins and for 5 to 7 days for reticular veins. For extensive varicosities, longer treatment with compression bandages or a gradient compression stocking of a higher compression class is recommended.
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, 2010.

1. Which of the following agents is administered intravenously?
   a. Liraglutide
   b. Tocilizumab
   c. Denosumab
   d. Dalfampridine

2. Which of the following agents is administered twice a day?
   a. Dalfampridine
   b. Pitavastatin
   c. Liraglutide
   d. Polidocanol

3. Which of the following agents is contraindicated in patients with hypocalcemia?
   a. Liraglutide
   b. Tocilizumab
   c. Polidocanol
   d. Denosumab

4. With the use of which of the following agents is the risk of seizures the most important concern?
   a. Pitavastatin
   b. Dalfampridine
   c. Tocilizumab
   d. Denosumab

5. Which of the following agents is most likely to be associated with weight loss?
   a. Pitavastatin
   b. Polidocanol
   c. Liraglutide
   d. Tocilizumab

6. Which of the following agents has been associated with the occurrence of osteonecrosis of the jaw?
   a. Dalfampridine
   b. Liraglutide
   c. Pitavastatin
   d. Denosumab

7. Which of the following agents is contraindicated in patients with moderate or severe renal impairment?
   a. Pitavastatin
   b. Tocilizumab
   c. Dalfampridine
   d. Polidocanol

8. Which of the following agents is classified as an interleukin-6 antagonist?
   a. Tocilizumab
   b. Denosumab
   c. Dalfampridine
   d. Polidocanol

9. Which of the following statements is correct regarding tocilizumab?
   a. Its labeled indications include severe rheumatoid arthritis and severe plaque psoriasis.
   b. It must be used in combination with methotrexate.
   c. It must be used in combination with etanercept.
   d. It is administered every 4 weeks.

10. Which of the following statements is correct regarding pitavastatin?
    a. Neutralizing antibodies develop in most patients who have been treated for more than one year.
    b. Neutrophils, platelets, alanine aminotransferase, aspartate aminotransferase, and lipids should be monitored during treatment.
    c. Severe hypersensitivity reactions are the most important concern with its use.
    d. Its action is increased by the concurrent use of a cytochrome P450 (CYP)3A4 inhibitor.

11. Which of the following statements is correct regarding pitavastatin?
    a. It is a prodrug that is converted to simvastatin following administration.
    b. It is more effective than atorvastatin in reducing low-density lipoprotein cholesterol concentrations.
    c. Its labeled indications are more limited than those for the other statins.
    d. Its maximum recommended dosage is 40 mg once a day.

12. Which of the following statements is correct regarding pitavastatin?
    a. It is less likely than the other statins to cause musculoskeletal adverse events.
    b. It is excreted in unchanged form in the urine.
    c. Concurrent use with cyclosporine is contraindicated.
    d. It should be administered with the evening meal.

13. Which of the following statements is correct regarding liraglutide?
    a. It acts as a glucagon-like peptide-1 receptor agonist.
    b. It acts as a dipeptidyl peptidase-4 inhibitor.
    c. It is indicated as an adjunct to diet in patients with type 1 and type 2 diabetes.
    d. Its properties are most similar to those of glimepiride.
14. Which of the following statements is correct regarding liraglutide?
   a. It is extensively metabolized via the CYP3A4 metabolic pathway.
   b. Hypoglycemia is the most important concern associated with its use.
   c. It must be administered with the morning meal.
   d. Its labeling contains a boxed warning about the occurrence of thyroid tumors in studies in animals.

15. Which of the following statements is correct regarding dalfampridine?
   a. It is a prodrug that is converted to 4-aminopyridine following administration.
   b. Its properties are most similar to those of natalizumab.
   c. It is indicated to reduce the frequency and severity of relapses in patients with multiple sclerosis.
   d. It acts as a potassium channel blocker.

16. Which of the following statements is correct regarding dalfampridine?
   a. An estimated creatinine clearance should be known before initiating treatment.
   b. Its use is contraindicated in patients with impaired hepatic function.
   c. Its action is increased by the concurrent use of a CYP3A4 inhibitor.
   d. It should be administered at least 1 hour before or 2 hours after a meal.

17. Which of the following statements is correct regarding denosumab?
   a. It has been demonstrated to reduce the incidence of vertebral fractures but not the incidence of nonvertebral or hip fractures.
   b. It should be used concurrently with a bisphosphonate derivative.
   c. It acts by preventing receptor activator of nuclear factor kappa-B ligand from activating its receptor on the surface of osteoclasts.
   d. It is indicated for the treatment and prevention of osteoporosis.

18. Which of the following statements is correct regarding denosumab?
   a. Musculoskeletal adverse events are the most important concern associated with its use.
   b. Calcium and vitamin D supplementation should be provided during treatment.
   c. It is administered every 3 months.
   d. It should not be used in patients who are allergic to latex.

19. Which of the following statements is correct regarding polidocanol?
   a. Musculoskeletal adverse events are the most important concern associated with its use.
   b. Calcium and vitamin D supplementation should be provided during treatment.
   c. It is administered every 3 months.
   d. It should not be used in patients who are allergic to latex.

20. Which of the following statements is correct regarding polidocanol?
   a. It should be used in a higher concentration for the treatment of spider veins than in the treatment of reticular veins.
   b. Compression should be maintained for at least 2 days following administration.
   c. Patients should avoid walking for at least 4 hours following administration to reduce the severity of injection site reactions.
   d. The incidence of injection site reactions is significantly higher than with the use of sodium tetradecyl sulfate.

CPE Information
To obtain 2.0 contact hours of CPE credit (0.2 CEUs) for this activity, complete and submit the CPE exam online at www.pharmacist.com/education. A Statement of Credit will be awarded for a passing grade of 70% or better. You will have two opportunities to successfully complete the CPE exam. Pharmacists who successfully complete this activity before September 15, 2013, can receive credit.
Your Statement of Credit will be available online immediately upon successful completion of the CPE exam.
CPE instructions: Get your documentation of credit now! Completing a posttest at www.pharmacist.com/education is as easy as 1-2-3.
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2. Log in. APhA members enter your user name and password. Not an APhA member? Just click “Create one now” to open an account. No fee is required to register.
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Live step-by-step assistance is available Monday through Friday 8:30 am to 5:00 pm ET at APhA Member Services at 800-237-APhA (2742) or by e-mailing InfoCenter@pharmacist.com.