

# New drug update: Review of 2009 and 2010 preview

## INTRODUCTION

The Food and Drug Administration monitors more than \$1 trillion worth of products, including drugs, cosmetics and food, such that 25 cents out of every \$1 spent by consumers is regulated by the FDA. Over the past decade, more than 500 drugs have been approved, and in 2009, 39 agents were introduced to the market. The estimated cost to develop each new drug is approximately \$500 million. To put this in perspective, there are approximately 5,000 to 10,000 compounds that don't make their way to the FDA or to your patients. Last year, more than \$50 billion was spent in new drug development.<sup>1</sup> Few blockbusters hit the shelves in 2009, with heart and psychiatric medications prevailing. 2010 appears to be a year for treatments for diabetes and such neurological disorders as multiple sclerosis. This lesson will discuss 10 of the most impactful new drug approvals of 2009 and 2010 for various disease states. Each drug will be summarized to include indication, similar agents, dosing and drug interactions, as well as the highlights of cautions and adverse effects that impact patients. The evidence for each drug will be summarized to aid in decisions being made for its place in therapy.

## HEART

### Dronedarone

Dronedarone (Multaq®) is an antiarrhythmic agent approved to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation, or AF, or atrial flutter, or AFL, with a recent episode of AF/AFL and associated cardiovascular risk factors who are in sinus rhythm or who will be cardioverted. This drug is similar to amiodarone; however, it has fewer adverse effects. The dose of this drug is 400 mg twice daily with no dosage adjustment needed in renal failure. The drug's bioavailability is significantly impacted when not given with food, so it should be taken with meals.<sup>2</sup>

Dronedarone does not interact with warfarin, like amiodarone, but should not be used with drugs that impact the CYP3A, most notably digoxin. Concurrent use with digoxin may increase the action of both agents, such that the dose should be decreased by one-half. Patients on a beta-blocker (e.g., metoprolol) or calcium channel blocker (e.g., diltiazem) should be carefully monitored and lower doses utilized initially in these patients. Dronedarone may increase the action of such

CYP3A substrates as simvastatin and such CYP2D6 substrates as fluoxetine.<sup>2</sup>

Studies with dronedarone showed an increased risk of mortality for heart failure patients, thus causing a black box warning for patients with severe heart failure or recent decompensation of heart failure.<sup>2,3</sup> This drug may increase the QT interval, so potassium and magnesium should be normalized prior to starting this agent and monitored thereafter. In trials, it was common to see a small, but not clinically significant, increase in serum creatinine with the start of this drug. Dronedarone is contraindicated for use in patients with second- or third-degree atrioventricular block, except for patients with a pacemaker. Dronedarone is Pregnancy Category X. The adverse effects of this agent are minimal, with diarrhea (8%), asthenia (7%) and nausea (5%) reported most frequently.<sup>2</sup>

Studies with dronedarone showed a positive impact on reducing cardiovascular hospitalizations due to atrial fibrillation.<sup>4</sup> In a head-to-head study with amiodarone, dronedarone was less effective in reducing the recurrence of atrial fibrillation but was better tolerated.<sup>5</sup> This drug may provide a good

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**This program is accredited for 1.25 (one and one-quarter) hours of continuing education credit, of which 1.25 (one and one-quarter) hours are considered pharmacology credit.**

**Program Goal:** To improve the clinician's ability to prescribe new therapeutic agents approved for use in 2009 and investigate the drug pipeline for 2010.

**Learning Objectives:**  
Upon completion of this program, the clinician should be able to:

1. List the new therapeutic agents approved for use in 2009.
2. Discuss newly approved pharmacologic agents giving their indication and mechanism of action.
3. Compare new agents with currently available agents stating advantages of new agents over current agents.
4. List brand name medications that will become generic in 2010 stating implications for prescribing.
5. Preview current pharmacological agents that may be approved in 2010 giving their therapeutic indication in clinical practice.

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option for patients who cannot tolerate rate control with beta-blockers and calcium channel blockers, and experience adverse effects to amiodarone.

### Prasugrel

Prasugrel (Effient®) is a P2Y<sub>12</sub> platelet inhibitor indicated for the reduction of thrombotic cardiovascular events in patients with acute coronary syndrome, or ACS, including patients with non-ST-elevation myocardial infarction, or NSTEMI, and ST-elevation myocardial infarction when managed with primary or delayed PCI. This drug is similar to clopidogrel (Plavix®), which recently has been scrutinized for its genetic influences and possible drug interaction to proton-pump inhibitors. The initial loading dose is 60 mg, followed by 10 mg once daily with 75 mg to 325 mg aspirin. Dosage adjustment for renal or hepatic impairment is not necessary, but patients <60 kg should take a lower dose of 5 mg daily.<sup>6</sup>

Like other thienopyridine derivatives, the most notable adverse event with prasugrel is bleeding. In trials, prasugrel had an increased risk of bleeding (4.5% with prasugrel versus 3.4% with clopidogrel), with bleeding risk the highest in the initial seven days of treatment. For this reason, prasugrel is contraindicated in patients with active pathological bleeding and previous TIA or stroke. Patients with other risk factors for bleeding — body weight less than 60 kg; propensity to bleed, such as recent trauma; concomitant use of medications that increase risk of bleeding, such as heparin, warfarin and NSAIDs; age greater than 75 years — should be carefully monitored. If bleeding does occur, prasugrel actually should not be discontinued as it may increase the risk of subsequent cardiovascular events.<sup>6</sup>

Drug interactions are minimal with this agent, with no interaction to omeprazole or other proton-pump inhibitors. The drug is relatively well tolerated, and adverse events were similar to clopidogrel, with hypertension (7.5%), hyperlipidemia (7%) and headache (5.5%) being the most reported adverse events for both agents.<sup>6</sup>

## PATIENT CASE 1

Sandy Huston presents to your anticoagulation clinic today for a routine follow-up of her INR. She was a new-onset atrial fibrillation patient four months ago, who has been stable on a dose of warfarin 7.5 mg daily. She does not have any other medical conditions. Most medications make her sick, so she prefers to take them with food. You learn from Sandy that at her recent cardiology appointment her healthcare provider discussed the initiation of an antiarrhythmic agent because her blood pressure cannot tolerate the diltiazem or atenolol therapies she has tried for rate control of her atrial fibrillation. Her father died from pulmonary fibrosis, a side effect from the amiodarone he was taking, so she is very scared about taking amiodarone. Would Sally be a good candidate for the new drug dronedarone (Multaq®)?

### CASE DISCUSSION

Reasons why Sandy is a good candidate for dronedarone therapy:

- Sandy has failed rate control with calcium channel blockers and beta blockers;
- Dronedarone is similar in mechanism to amiodarone (i.e., it affects all four Vaughan-Williams classes of antiarrhythmic agents) but is less likely to cause pulmonary, thyroid, hepatic or ocular adverse effects;
- Dronedarone does not interact with warfarin;
- Sandy does not have heart failure, a contraindication to dronedarone therapy;
- Dronedarone is less likely than rate control agents to cause hypotension; and
- Sandy prefers to take her medications with food. Dronedarone has a low bioavailability (4%) when not taken with food. This increases more than three-fold to 15% when administered with a high-fat meal.

Although this drug had an increased bleeding risk, it showed a greater reduction in cardiovascular events, with the most notable reduction seen in nonfatal myocardial infarction (19% relative risk reduction) and stent thrombosis (50% relative risk reduction).<sup>7,8</sup> It is important to note that the differences in effectiveness could have been influenced by the possibility that the action of clopidogrel could have been reduced in patients due to genetic influences of the CYP2C19 metabolic pathway or the concurrent use of proton-pump inhibitors that are CYP2C19 inhibitors. The risk-to-benefit ratio is important to consider with drugs like prasugrel. While prasugrel appears to be more effective than clopidogrel, there was an increased risk of bleeding, in addition to being more expensive. One must weigh the risk of bleeding considering patient-specific variables with the benefit of reduction in cardiovascular events when prescribing these agents.

### Ticagrelor

Ticagrelor (expected brand name of Brilinta®) is another antiplatelet agent that has shown very positive results in clinical trials compared with clopidogrel. This drug is expected to come to the market in 2010 and may be more effective than both clopidogrel and prasugrel.

## DIABETES

### Saxagliptin

Saxagliptin (Onglyza®) is the next agent in the incretin class approved for monotherapy or combination therapy as an adjunct to diet and exercise in Type 2 diabetes mellitus. This drug is a dipeptidyl peptidase-4, or DPP-4, inhibitor similar to sitagliptin (Januvia®). This class of medications targets the incretin hormones, whose role is to increase insulin release from beta cells and suppress glucagon release by alpha cells following meals. The DPP-4 enzyme inactivates these hormones, so the inhibition of

DPP-4 is an effort to sustain the activity of the incretin hormones thus increasing insulin secretion and decreasing glucose output. The dose of saxagliptin is 5 mg with a dose of 2.5 mg recommended in renal failure or when used in combination with strong CYP3A4/5 inhibitors, such as ketoconazole. An advantage of this class of drugs is that it is well tolerated by patients, with minimal side effects. The most frequently reported adverse effect was headache (6.5%). Both approved agents in the class have reported an increase in upper respiratory tract and urinary tract infections. Saxagliptin may cause less hypersensitivity reactions that have been seen with sitagliptin. It is unknown whether this drug will cause an increased risk of pancreatitis like other agents in this family. Saxagliptin is said to be weight neutral, unlike its incretin cousin exenatide and liraglutide, which may aid in weight loss.<sup>9</sup>

In clinical trials, saxagliptin lowered hemoglobin A1c levels by 0.6% as monotherapy with similar clinical improvement when used in combination with metformin, glyburide and rosiglitazone for 24 weeks.<sup>10-12</sup> In patients naive to drug therapy with an average A1c of 9.4%, a greater A1c lowering of 2.5% was seen with saxagliptin and metformin, compared with 2% when metformin was used alone.<sup>13</sup> This drug adds another option in the incretin class but may not have many advantages over current, less-expensive agents.

#### Liraglutide [rDNA origin] injection

Liraglutide [rDNA origin] injection (Victoza<sup>®</sup>) was approved this year for Type 2 diabetes mellitus. This agent is a glucagon-like peptide-1, or GLP-1, receptor agonist similar to exenatide (Byetta<sup>®</sup>) but administered once daily without regard to food. Like exenatide, it is a subcutaneous injection ranging from 0.6 mg to 1.8 mg daily. The starting dose should be 0.6 mg per day for one week to reduce the incidence of gastrointestinal symptoms, titrated to the effective dose of 1.2 mg daily with an option to increase

to 1.8 mg daily for optimal glycemic control. There are minimal contraindications, or warnings, with liraglutide. The only contraindication being for patients with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2; however, this finding was only seen in animal models. Like exenatide, there is an increased risk for pancreatitis, so caution should be used for patients with a history of pancreatitis. Nausea (15% to 35%) and diarrhea (10% to 15%) were frequently reported; however, the percentage of patients who reported nausea declined over time, and only 7.8% of patients withdrew from studies with liraglutide due to side effects.<sup>14</sup>

The clinical studies with liraglutide are known as the LEAD series, with six clinical trials in the series. Liraglutide showed an average hemoglobin A1c reduction of approximately 1% (0.8% with 1.2 mg and 1.1% with 1.8 mg) in the various clinical trials. There was not a significantly lower A1c seen when liraglutide was used in combination with single agents, but a 1.5% decrease in A1c was seen when used with two additional agents. Although the drug is not indicated for weight loss, a weight loss of approximately 5 kg was seen with liraglutide, with even larger weight loss (5.7 to 6.2 kg) seen in combination with metformin.<sup>15,16</sup> This drug is very similar to exenatide; however, it provides a significant advantage of once-daily dosing without regard to meals.

#### Exenatide

Exenatide (expected name Bydureon<sup>®</sup>) has filed a new drug application for a once-weekly formulation, which will add even more options within this class of drugs. The pathophysiology of diabetes supports the mechanism of action of these agents, and their glucose improvement, coupled with weight loss, provides an excellent therapeutic option for patients who can tolerate the side effects and are willing to give a subcutaneous injection.

## PAIN AND ASSOCIATED ILLNESSES

### Febuxostat

Febuxostat (Uloric<sup>®</sup>) is the first approved agent for gout in nearly 40 years. Febuxostat is similar in structure to allopurinol, a xanthine-oxidase inhibitor. Patients with gout have high uric acid levels and xanthine oxidase partially is responsible for the breakdown of uric acid. By inhibiting xanthine oxidase, febuxostat and allopurinol decrease uric acid production and lower elevated serum concentrations of uric acid. The starting dose for febuxostat is 40 mg once daily, with an increase after two weeks to 80 mg daily for patients who do not achieve a serum uric acid less than 6 mg/dL. When starting drugs that lower uric acid, there is an increase risk for a gout flare. When initiating therapy, it is recommended that a NSAID or colchicines be given with febuxostat for the first six months. If a gout flare does occur, febuxostat should not be discontinued. Febuxostat is contraindicated with other xanthine oxidase substrates, such as azathioprine, mercaptopurine or theophylline. Febuxostat is safe in mild to moderate renal or hepatic impairment, whereas allopurinol must be adjusted for patients with renal failure.<sup>17</sup>

The clinical effectiveness of febuxostat at the 40 mg dose is similar to allopurinol. When the dose is optimized to 80 mg, febuxostat was more effective than allopurinol 300 mg.<sup>18,19</sup> It should be noted, however, that this dose is less than the 400- to 800-mg doses of allopurinol commonly seen in practice. In clinical trials, liver enzyme elevations greater than three times the upper limit of normal was noted in a small (2%) number of patients. For this reason, liver function tests should be assessed at two and four months after initiation of the drug, and periodically thereafter. Febuxostat has very few adverse effects, with no other adverse reactions occurring in more than 2% of patients on the drug.<sup>17</sup> One troubling result from early studies of febuxostat was a higher rate of cardiovascular thromboembolic events

(e.g., cardiovascular deaths, nonfatal myocardial infarctions and nonfatal strokes) in patients treated with febuxostat. The results of the trials showed an increased incidence with both allopurinol and febuxostat but a nonsignificant relationship (relative risk 0.74, confidence interval 0.36 to 1.37 for febuxostat), but it is important to consider this risk when treating patients with gout.<sup>18,19</sup> While febuxostat may offer some advantages for patients with renal failure, it is similar in effectiveness to allopurinol, and the cost of this new agent is significantly greater than generically available allopurinol.

### Tapentadol

Tapentadol (Nucynta<sup>®</sup>) is an opioid analgesic indicated for the relief of moderate to severe acute pain in patients 18 years of age and older. This drug has a mechanism of action similar to tramadol, being a  $\mu$ -opioid receptor agonist and norepinephrine-reuptake inhibitor, but has potency similar to oxycodone. The drug is available in 50-, 75- and 100-mg tablets to be dosed every four to six hours with a daily maximum dose of 600 mg. There is no dosage adjustment needed for renal failure, but a lower dose of 50 mg every eight hours is recommended in patients with hepatic impairment. Tapentadol 100 mg is similar in potency to oxycodone 15 mg. Tapentadol currently is approved only for acute pain, and unlike tramadol, tapentadol is a Schedule II controlled substance. It has similar warnings and adverse effects as other opioid analgesics, with nausea (30%), dizziness (24%), vomiting (18%) and somnolence (15%) the most frequently reported side effects. Unlike tramadol, tapentadol is not metabolized via the CYP450 pathway, leading to few drug interactions. Alcohol and other central-acting drugs (e.g., other analgesics, antiemetics and sedatives) may increase central nervous system depression similar to other opioid analgesics. Tapentadol should not be taken with, or within 14 days of, monoamine-oxidase inhibitors. Due to the indication, which is limited

## PATIENT CASE 2

John Christiansen is one of your favorite patients at your clinic. He is a 68-year-old man with a past medical history significant for gout, hypertension and a previous myocardial infarction. He currently takes allopurinol 200 mg daily, lisinopril 10 mg daily, metoprolol 50 mg twice daily, simvastatin 20 mg daily and aspirin 81 mg. He has had three acute episodes of gout in the past year. His uric acid level today in your clinic is 9.2 mg/dL and has been greater than 6 mg/dL for the past nine months. He has experienced minimal success with appropriate doses of allopurinol 200 mg daily. You recently attended a continuing education lecture on gout where febuxostat (Uloric<sup>®</sup>) was discussed. Is this a good option for John?

### CASE DISCUSSION

Febuxostat should not be initiated during a flare of gout. John's flare should be treated with a NSAID (e.g., naproxen 250 mg twice daily) or colchicine (0.6 mg one to two times daily). If febuxostat is started after resolution of his flare, one of these agents should be continued for up to six months. It is possible that the dose of allopurinol that John is taking is not a large enough dose. In comparison trials, febuxostat 40 mg and 80 mg was compared with allopurinol 300 mg. The larger 40 mg dose was similar to allopurinol, so if febuxostat was started, the 80 mg dose should be used. The maximum dose of allopurinol is 800 mg daily, so the most cost-effective option may be to simply increase his allopurinol dose.

to acute pain and lack of controlled release tablets at this time, there may not be many advantages of this agent when compared with less expensive oxycodone and tramadol.<sup>20</sup>

### Milnacipran

Milnacipran (Savella<sup>®</sup>) is a selective serotonin and norepinephrine-reuptake inhibitor, or SNRI, indicated for the management of fibromyalgia. It is similar to duloxetine and venlafaxine; however, it is not approved for depression and is more selective toward norepinephrine than either of these agents. The dose of milnacipran is 50 mg, twice daily. The drug is safe in renal and hepatic failure, which is one advantage of its use over duloxetine. Milnacipran undergoes minimal metabolism via CYP450 pathways and is less likely than duloxetine to interact with other medications. Milnacipran carries the same risks and warnings as antidepressants, such as risk of suicidal thinking and behavior, due to its mechanism of action. Nausea (35%), constipation (16%), insomnia (12%), dizziness

(11%) and hot flashes (11%) were common adverse effects of this medication. There is a gradual starting dose titration in an effort to decrease nausea and other side effects. In clinical trials among patients who were not hypertensive at baseline, approximately twice as many patients (20%) in the milnacipran group became hypertensive. This elevation in blood pressure, as well as an increase in heart rate, has been seen with other SNRIs, but not to this extent. Similar to other SNRI medications, milnacipran may increase the risk of bleeding for patients on aspirin or anticoagulants, may activate mania, may cause hyponatremia and should not be used in patients with BPH or a history of dysuria. In clinical trials, milnacipran has not been compared with other agents approved for fibromyalgia.<sup>21</sup> Compared with placebo, significantly more patients in the milnacipran group experienced a 30% reduction in pain (75% versus 38%) and considered themselves globally improved.<sup>22,23</sup> Fibromyalgia continues to be a disease with new drug therapies. While milnacipran

may be more potent than other SNRIs, it has definite risks and minimal advantages over current approved treatments.

## NEUROLOGY

### Lacosamide

Lacosamide (Vimpat®) is indicated as adjunctive therapy for partial-onset seizures in patients 17 years and older. This drug is similar to carbamazepine, oxcarbazepine and lamotrigine in its oral formulation, and levetiracetam in its oral and intravenous formulations. Lacosamide selectively enhances slow inactivation of sodium channels and binds to collapsing response mediator protein-2, which may play a role in seizure control. The initial dose of lacosamide is 50 mg, twice daily, and can be increased at weekly intervals to a maintenance dose of 200 mg to 400 mg daily in divided doses. Doses above 400 mg did not show any additional benefit in clinical trials.<sup>24</sup> In clinical trials, patients continued on one to three other antiepileptic medications and saw a 40% decrease in seizures with lacosamide 400 mg, compared with 25% seizure reduction when no new drug therapy was added.<sup>25</sup> Lacosamide does not have any known drug interactions or contraindications. Dizziness was very common, occurring in close to one-third of all patients in clinical trials. Nausea (11%), vomiting (9%) and ataxia (7%) were more frequent when compared with placebo-controlled patients. Lacosamide, like other antiepileptic drugs, carries a warning of increased suicidal behavior and ideation. Higher doses of lacosamide may cause euphoria similar to when taking alprazolam. While the incidence of euphoria is low (<1%), the FDA has classified lacosamide as a Schedule V drug.<sup>24</sup> The niche for this drug is for patients who have failed other drug therapies.

### Vigabatrin

Vigabatrin (Sabril®) is another adjunctive therapy option for patients with refractory seizures. Vigabatrin also is the first drug approved for infantile spasms.

The drug is similar to adrenocorticotrophic hormone, or ACTH, which has been used "off-label" for infantile spasms. This drug carries a black-box warning for vision loss as it causes progressive and permanent bilateral concentric visual field constriction in a high percentage (30%) of patients. In some cases, it also may reduce visual acuity. The risk increases with total dose and duration of use, but any exposure may cause vision loss even after discontinuing the drug. All patients should have their vision assessed every three months. Because of the risk of permanent vision loss, vigabatrin is available only through a special restricted distribution program. The starting dose of vigabatrin is 50 mg/kg/day in two divided doses initially, and may be increased to a maximum of 150 mg/kg/day for infantile spasms. The dose for refractory complex partial seizures is 500 mg, twice daily, titrated to 1,500 mg, twice daily.<sup>26</sup> More than half of patients on vigabatrin saw a 50% decrease in seizures per month, but the risks associated with this drug must be carefully weighed with these benefits.<sup>27</sup> In clinical trials, vigabatrin was effective in decreasing infantile spasms but may be less effective than ACTH.<sup>28</sup> A new drug application, or NDA, has been filed for an ACTH formulation for infantile spasms, which may provide a safer option for the treatment of this devastating condition for infants.

### Dalfampridine

Dalfampridine (Ampyra®) recently was approved to improve walking in patients with multiple sclerosis. There are few oral agents available to improve lifestyle factors in patients with MS. Dalfampridine is dosed 10 mg, twice daily. Seizures were seen at larger doses and a history of seizures is a contraindication to this treatment. Dalfampridine also is contraindicated in patients with moderate to severe renal impairment.<sup>29</sup> During the double-blind treatment period, a significantly greater proportion of patients taking dalfampridine twice daily had

increases in walking speed from baseline (35% versus 8%), compared with placebo.<sup>30</sup> This drug was well tolerated by patients and was safe when combined with immunomodulatory drugs (interferons, glatiramer acetate or natalizumab).<sup>29</sup> Several additional drugs are in the pipeline for MS, including fingolimod and cladribine. These new drugs for MS most likely will be costly to patients but may improve ambulatory disability that these patients experience.

## PSYCHOLOGY

### Asenapine and iloperidone

Asenapine (Saphris®) and iloperidone (Fanapt®) were approved in 2009 for the acute treatment of schizophrenia in adults. Asenapine also has an approved indication for bipolar disorder. Asenapine is a sublingual tablet similar to olanzapine. The starting dose is 5 mg (schizophrenia) and 10 mg (bipolar), twice daily, which must be taken 10 minutes apart from eating and drinking. A large problem with antipsychotic medications is their metabolic effects. While asenapine appears to have less metabolic effects compared with olanzapine, it was more likely to cause dizziness, nausea, akathisia and oral hypoesthesia. In trials with asenapine, 15% of patients experienced a  $\geq 7\%$  increase in body weight.<sup>31</sup> Clinical trials with asenapine have been modest, with a recent comparison trial failing to show a benefit over olanzapine therapy.<sup>32</sup>

Iloperidone is similar to risperidone and ziprasidone. Significant orthostatic hypotension was seen with iloperidone in clinical trials, resulting in a titration starting at 1 mg, twice daily, slowly increased to the recommended dose of 6 mg to 12 mg, twice daily. In addition to orthostatic hypotension, iloperidone may cause QT interval prolongation. The labeling for the drug states, "consider using other antipsychotics first," which summarizes the place in therapy for iloperidone. Like other antipsychotics, both of these drugs have a risk for extrapyramidal symptoms, most notably somnolence.<sup>33</sup>

### UROLOGY

#### Fesoterodine

Fesoterodine (Toviaz<sup>®</sup>) is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency. It is the sixth drug approved for this indication and most similar to tolterodine (Detrol<sup>®</sup>), sharing the same active metabolite. The dose of fesoterodine is 4 mg to 8 mg daily. Patients with renal failure should not take more than 4 mg, and it should not be used in patients with hepatic insufficiency. The most common adverse effects with these agents are due to their anticholinergic activity, with dry mouth (19% to 35%) and constipation (5%) as the most common complaints.

The higher dose of fesoterodine has significantly more side effects than the lower dose and other agents in this class. This drug has similar warnings and contraindications as other drugs in this class but does not prolong the QT interval, which has been reported with tolterodine.<sup>34</sup> Placebo-controlled trials of fesoterodine showed significant improvement, with a more than 50% decrease of incontinence episodes.<sup>35,36</sup> A recent trial directly comparing with tolterodine also showed positive results; however, the high dose of fesoterodine (8 mg) was compared with 4 mg of tolterodine, which may have less active drug.<sup>37</sup> Fesoterodine may be indicated for patients who have not had adequate control on other agents, but is very similar to other drugs in its class.

#### Silodosin

Silodosin (Rapaflo<sup>®</sup>) is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia, or BPH. Although it is an alpha-blocker and similar to tamsulosin, it is not approved for hypertension and is less likely to cause orthostatic hypotension compared with other alpha-blockers used for BPH. Silodosin does not require a dose titration and has a starting dose of 8 mg daily with a meal. The 4 mg dose should be used in patients

with renal impairment, but it should not be used in severe renal or severe hepatic impairment. Silodosin has similar drug interactions (CYP3A4) and adverse effects with other drugs in its class, but is more likely to cause retrograde or abnormal ejaculation. Nearly 30% of patients in clinical trials experienced this side effect, rarely seen with tamsulosin. Placebo-controlled trials showed similar results to other agents.<sup>38</sup> In one comparison trial, silodosin appeared to be more effective; however, the dose of tamsulosin was used at a lower (0.2 mg) dose than commonly seen in practice.<sup>39</sup> Tamsulosin will be generic in 2010, providing a cheaper option with similar effectiveness to silodosin.

### OPHTHALMOLOGY

#### Bepotastine and besifloxacin

Bepotastine and besifloxacin are two new agents approved for the eye. Bepotastine (Bepreve<sup>®</sup>) is indicated for treatment of itching associated with signs and symptoms of allergic conjunctivitis. Bepotastine is a twice-daily drop that should not be used to treat contact lens-related irritation. There are minimal side effects; however, mild taste was reported in 25% of patients. It is similar to other antihistamine and mast cell-stabilizing agents, with little apparent advantage

over current products.<sup>40</sup> Besifloxacin (Besivance<sup>®</sup>) ophthalmic suspension is a quinolone antimicrobial indicated for the treatment of bacterial conjunctivitis. It has the advantage of being dosed three times daily with other quinolone solutions (e.g., ciprofloxacin, levofloxacin, etc.) that are dosed four or more times daily. Because it is the sixth quinolone ophthalmic product, its place of therapy most likely will be for patients who have failed other therapies, as it does target a broader spectrum of bacteria.<sup>41</sup>

### BENZYL ALCOHOL

Benzyl alcohol (Ulesfia<sup>®</sup>) has been formulated as a new topical treatment for head lice infestation in patients 6 months of age and older. The drug works by causing asphyxiation of lice, and showed a 75% eradication rate after 14 days of therapy. The dose depends on length of hair and will range from three to six bottles applied to dry hair and rinsed off after 10 minutes. A second treatment is recommended one week after the first treatment.<sup>42</sup> No studies have looked at benzyl alcohol compared with permethrin (Nix<sup>®</sup>) or pyrethrin/piperonyl butoxide (RID<sup>®</sup>), but these older agents report successful treatment in 90% of patients.<sup>43,44</sup> There has been an increase

## PATIENT CASE 3

Ella Jones is a 7-year-old who presents to your clinic with an episode of head lice. You counsel her mother on nonpharmacologic treatment, then start to discuss shampoos. Ella has responded well to permethrin (Nix<sup>®</sup>) in the past. Mrs. Jones pulls out an ad from a parenting magazine for Ulesfia<sup>®</sup> and asks if this would be a good option for her. You have heard about the unique mechanism of Ulesfia<sup>®</sup> causing asphyxiation of head lice but are unsure whether or not to recommend the product.

### CASE DISCUSSION

Benzyl alcohol (Ulesfia<sup>®</sup>) does not offer advantages over other common therapies that are available to Mrs. Jones over the counter. The over-the-counter agents are known to be very effective in more than 90% of patients. You assure Mrs. Jones that permethrin (Nix<sup>®</sup>) may be more effective, and because Ella responded well to that treatment in the past and has not shown any signs of resistance, you would recommend that treatment again.

in resistance to older agents, which may provide the most appropriate place in therapy for benzyl alcohol.

#### OTHER AGENTS AND GENERIC CONVERSIONS

Several additional agents have been approved over the last year but may be prescribed less often in the ambulatory care setting. These drugs are listed in Table 1. Several frequently prescribed drugs will become generic in 2010, including Flomax<sup>®</sup>, Mirapex<sup>®</sup>, Cozaar<sup>®</sup>, Coreg XR<sup>®</sup>, Effexor XR<sup>®</sup> and Aricept<sup>®</sup>. Drugs with promise in the pipeline include dabigatran and rivaroxaban for thrombosis prevention, formoterol/fluticasone for asthma, cethromycin for community-acquired pneumonia, lorcaserin for obesity and a combination esomeprazole/naproxen for gastric ulcer prevention. It appears that neurology, heart and diabetes drug pipelines also will remain strong for the coming year.

#### CONCLUSION

The constant and ever-evolving drug market requires clinicians to stay up to date with new drug therapies and potential agents. When a new agent is introduced, the package insert provides the most essential information for the prescriber. These have become significantly easier to read over the past couple of years. The FDA Web site, FDA.gov, also can serve as an excellent reference for all healthcare practitioners. These resources may assist clinicians who always will have the challenge of keeping up to date on new drugs.

**TABLE 1**

**Additional new drug approvals for 2009**

Drug	Indication
Abobotulinumtoxin A (Dysport <sup>®</sup> )	Cervical dystonia, temporary improvement in the appearance of moderate to severe glabellar lines
Artemether/lumefantrine (Coartem <sup>®</sup> )	Acute, uncomplicated malaria
Canakinumab (Ilaris <sup>®</sup> )	Cryopyrin-Associated Periodic Syndromes
Degarelix (Firmagon <sup>®</sup> )	Advanced prostate cancer
Everolimus (Afinitor <sup>®</sup> )	Advanced renal-cell carcinoma after failure of treatment with sunitinib or sorafenib
Golimumab (Simponi <sup>®</sup> )	Moderate to severe active rheumatoid arthritis, active psoriatic arthritis and active ankylosing spondylitis
Ofatumumab (Arzerra <sup>®</sup> )	Chronic lymphocytic leukemia refractory to fludarabine and alemtuzumab
Pazopanib (Votrient <sup>®</sup> )	Advanced renal-cell carcinoma
Plerixafor (Mozobil <sup>®</sup> )	Non-Hodgkin's lymphoma and multiple myeloma
Pralatrexate (Folotyn <sup>®</sup> )	Relapsed or refractory peripheral T-cell lymphoma
Rufinamide (Banzel <sup>®</sup> )	Seizures associated with Lennox-Gastaut syndrome
Telavancin (Vibativ <sup>®</sup> )	Complicated skin infections caused by susceptible isolates of certain Gram-positive bacteria
Tolvaptan (Samsca <sup>®</sup> )	Hypervolemic and euvolemic hyponatremia
Ustekinumab	Moderate to severe plaque psoriasis in patients who are candidates for phototherapy or systemic therapy

#### PRACTICE POINTS

- Dronedarone is a new agent approved for atrial fibrillation that has fewer side effects than amiodarone.
- Prasugrel and ticagrelor are new antiplatelet agents similar to clopidogrel.
- Febuxostat is the first agent approved for gout in more than 40 years. It is similar to allopurinol and should not be initiated during a flare of gout.
- Liraglutide and saxagliptin are diabetes drugs affecting incretin hormones.
- Milnacipran is a SNRI approved for fibromyalgia that has been associated with increases in blood pressure.

1 Lipsky MS, Sharp LK. From idea to market: the drug approval process. *J Am Board Fam Pract* 2001;14:362-7. 2 MULTAQ® (dronedarone) Prescribing Information. Sanofi-aventis U.S. LLC. 2009 Bridgewater, NJ. <http://products.sanofi-aventis.us/multaq/multaq.html>. Accessed March 22, 2010. 3 Køber L, Torp-Pedersen C, McMurray JJ, et al. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med*. 2008 Jun 19;358(25):2678-87. 4 Hohnloser SH, Crijns HJ, Van Eickels M et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med*. 2009 Feb 12;360(7):668-78. 5 Singh BN, Connolly SJ, Crijns HJ, et al. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med*. 2007 Sep 6;357(10):987-99. 6 Effient® (prasugrel) Prescribing Information. Eli Lilly. 2009 Indianapolis, IN. <http://pi.lilly.com/us/effient.pdf>. Accessed March 22, 2010. 7 Montalescot G, Wiviott SD, Braunwald E, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. *Lancet*. 2009 Feb 28;373(9665):723-31. 8 Morrow DA, Wiviott SD, White HD, et al. Effect of the novel thienopyridine prasugrel compared with clopidogrel on spontaneous and procedural myocardial infarction in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38: an application of the classification system from the universal definition of myocardial infarction. *Circulation*. 2009 Jun 2;119(21):2758-64. Epub 2009 May 18. 9 Onglyza® (saxagliptin) Prescribing Information. Bristol-Myers Squibb Company. 2009 Princeton, NJ. [http://packageinserts.bms.com/pi/pi\\_onglyza.pdf](http://packageinserts.bms.com/pi/pi_onglyza.pdf). Accessed March 22, 2010. 10 Rosenstock J, Sankoh S, List JF. Glucose-lowering activity of the dipeptidyl peptidase-4 inhibitor saxagliptin in drug-naïve patients with type 2 diabetes. *Diabetes Obes Metab*. 2008 May;10(5):376-86. 11 Hollander P, Li J, Allen E, Chen R. Saxagliptin added to a thiazolidinedione improves glycemic control in patients with type 2 diabetes and inadequate control on thiazolidinedione alone. *J Clin Endocrinol Metab*. 2009 Dec;94(12):4810-9. 12 DeFronzo RA, Hissa MN, Garber AJ, et al. The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes with metformin alone. *Diabetes Care*. 2009 Sep;32(9):1649-55. 13 Rosenstock J, Aguilar-Salinas C, Klein E, et al. Effect of saxagliptin monotherapy in treatment-naïve patients with type 2 diabetes. *Curr Med Res Opin* 2009 Oct;25(10):2401-11. 14 Victoza® (liraglutide) Prescribing Information. Novo Nordisk. 2010 Princeton, NJ. [http://www.victoza.com/clinical\\_resources.aspx](http://www.victoza.com/clinical_resources.aspx). Accessed March 22, 2010. 15 Nauck M, Frid A, Hermansen K, et al; for the LEAD-2 Study Group. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. *Diabetes Care*. 2009;32(1):84-90. 16 Garber A, Henry R, Ratner R, et al; for the LEAD-3 (Mono) Study Group. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomized, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet*. 2009;373(9662):473-481. 17 Uloric® (febuxostat) Prescribing Information. Takeda Pharmaceuticals. 2009 Deerfield, IL. <http://www.uloiric.com/hcp/default.aspx>. Accessed March 22, 2010. 18 Becker MA, Schumacher HR Jr, Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med*. 2005 Dec 8;353(23):2450-61. 19 Schumacher HR Jr, Becker MA, Wortmann RL, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. *Arthritis Rheum*. 2008 Nov 15;59(11):1540-8. 20 Nucynta® (tapentadol) Prescribing Information. Ortho-McNeil-Janssen Pharmaceuticals. 2008 Raritan, NJ. <http://www.nucynta.com/nucynta/assets/Nucynta-PI.pdf>. Accessed March 22, 2010. 21 Savella® (milnacipran) Prescribing Information. Forest Laboratories. 2009 New York, NY. [http://www.frx.com/pi/Savella\\_pi.pdf](http://www.frx.com/pi/Savella_pi.pdf). Accessed March 22, 2010. 22 Clauw DJ, Mease P, Palmer RH, Gendreau RM, Wang Y. Milnacipran for the treatment of fibromyalgia in adults: a 15-week, multicenter, randomized, double-blind, placebo-controlled, multiple-dose clinical trial. *Clin Ther*. 2008 Nov;30(11):1988-2004. 23 Vitton O, Gendreau M, Gendreau J, Kranzler J, Rao SG. A double-blind placebo-controlled trial of milnacipran in the treatment of fibromyalgia. *Hum Psychopharmacol*. 2004 Oct;19 Suppl 1:S27-35. 24 Vimpat® (lacosamide) Prescribing Information. UCB 2009. Smyrna, GA. <http://www.vimpat.com/hcp/pdfs/VIMPAT%20PI.pdf>. Accessed March 22, 2010. 25 Halász P, Kälviäinen R, Mazurkiewicz-Beldziska M, et al. Adjunctive lacosamide for partial-onset seizures: Efficacy and safety results from a randomized controlled trial. *Epilepsia*. 2009 Mar;50(3):443-53. 26 Sabril® (vigabatrin) Prescribing Information. Lundbeck Inc. 2010 Deerfield, IL. [http://www.lundbeckinc.com/USA/products/CNS/Sabril/sabril\\_PI\\_IS.pdf](http://www.lundbeckinc.com/USA/products/CNS/Sabril/sabril_PI_IS.pdf). Accessed March 22, 2010. 27 Guberman A, Bruni J. Long-term open multicentre, add-on trial of vigabatrin in adult resistant partial epilepsy. *The Canadian Vigabatrin Study Group. Seizure*. 2000 Mar;9(2):112-8. 28 Cohen-Sadan S, Kramer U, Ben-Zeev B, et al. Multicenter long-term follow-up of children with idiopathic West syndrome: ACTH versus vigabatrin. *Eur J Neurol*. 2009 Apr;16(4):482-7. 29 Ampyra® (dalfampridine) Prescribing Information. Acorda Therapeutics. 2010 Hawthorne, NY. <http://www.ampyra.com/local/files/PI.pdf>. Accessed March 22, 2010. 30 Goodman AD, Brown TR, Krupp LB, Schapiro RT, et al. Sustained-release oral fampridine in multiple sclerosis: a randomized, double-blind, controlled trial. *Lancet*. 2009 Feb 28;373(9665):732-8. 31 Saphris® (asenapine) Prescribing Information. Schering-Plough Corporation 2009. Kenilworth, NJ. <http://www.spfiles.com/pisaphriv1.pdf> 32 Schoemaker J, Naber D, Vrijland P, Panagides J, Emsley R. Long-Term Assessment of Asenapine vs. Olanzapine in Patients with Schizophrenia or Schizoaffective Disorder. *Pharmacopsychiatry*. 2010 Mar 4. 33 Fanapt® (iloperidone) Prescribing Information. Vanda Pharmaceuticals Inc. 2009 Rockville, MD. <http://www.pharma.us.novartis.com/product/pi/pdf/fanapt.pdf>. Accessed March 22, 2010. 34 Toviaz® (fesoterodine) Prescribing Information. Pfizer Inc. 2008 New York, NY. [http://media.pfizer.com/files/products/uspi\\_toviaz.pdf](http://media.pfizer.com/files/products/uspi_toviaz.pdf). Accessed March 22, 2010. 35 Chapple C, Van Kerrebroeck P, Tubaro A, et al. A 12-Week, randomized, double-blind, placebo- and active-controlled trial to assess the efficacy and safety of fesoterodine 4 mg and 8 mg extended-release tablets. *Eur Urol*. 2007;52:1204-1212. 36 Nitti V, Dmochowski R, Sand P, et al. A 12-week, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of fesoterodine 4-mg and 8-mg extended-release tablets. *J Urol*. 2007;178:2488-2494. 37 Herschorn S, Swift S, Guan Z, et al. Comparison of fesoterodine and tolterodine extended release for the treatment of overactive bladder: a head-to-head placebo-controlled trial. *BJU Int*. 2010 Jan;105(1):58-66. 38 Rapaflo® (silodosin) Prescribing Information. Watson Pharma, Inc. 2009 Morristown, NJ. [http://pi.watson.com/data\\_stream.asp?product\\_group=1630&p=pi&language=E](http://pi.watson.com/data_stream.asp?product_group=1630&p=pi&language=E) 39 Kawabe K, Yoshida M, Homma Y. Silodosin, a new alpha1A-adrenoceptor-selective antagonist for treating benign prostatic hyperplasia: results of a phase III randomized, placebo-controlled, double-blind study in Japanese men. *BJU Int*. 2006 Nov;98(5):1019-24. 40 Bepreve® (bepotastine) Prescribing Information. Itsa Pharmaceuticals. 2009 Irvine, CA. [http://www.istavision.com/pdf/Bepreve\\_insert.pdf](http://www.istavision.com/pdf/Bepreve_insert.pdf). Accessed March 22, 2010. 41 Besivance® (besifloxacin) Prescribing Information. Bausch & Lomb Incorporated. 2009 Tampa, FL. <http://www.besivance.com/Besivance-Full-Prescribing-Info.pdf>. Accessed March 22, 2010. 42 Ulesfia Lotion® (benzyl alcohol) Prescribing Information. Shionogi Pharma, Inc. 2009 Atlanta, GA. <https://www.ulesfialotion.com/ulesfia/default.aspx>. Accessed March 22, 2010. 43 Nix® (permethrin) Prescribing Information. Insight Pharmaceuticals Corp. Langhorne, PA. <http://www.nixlice.com/index.php>. Accessed March 22, 2010. 44 RID® (piperonyl butoxide) Prescribing Information. Bayer HealthCare LLC. Morristown, NJ. <http://www.ridlice.com/healthcare.html>. Accessed March 22, 2010.

# New drug update: Review of 2009 and 2010 preview

## Learning Assessment

Successful completion of "New drug update: Review of 2009 and 2010 preview" is accredited for 1.25 (one and one-quarter) hours of continuing education credit, of which 1.25 (one and one-quarter) hours are considered pharmacology credit. To obtain credit, answer the following questions and complete the evaluation online at RetailClinician.com.

- Which of the following is a contraindication to dronedarone therapy?
  - Patients on warfarin
  - Atrial fibrillation
  - Renal insufficiency
  - Heart failure
- Prasugrel is most similar to which of the following drugs?
  - Warfarin
  - Clopidogrel
  - Aspirin
  - Heparin
- Which of the following statements reflects a difference between liraglutide and exenatide?
  - Liraglutide is a once-daily injection, while exenatide is a twice-daily injection.
  - Liraglutide is an oral tablet, while exenatide is an injection.
  - Liraglutide has a Food and Drug Administration indication for weight loss.
  - Liraglutide has minimal side effects, while exenatide may cause nausea.
- Which of the following statements is true regarding febuxostat?
  - Naproxen should not be used with febuxostat.
  - Febuxostat is more effective than allopurinol.
  - Febuxostat 80 mg does not offer any greater benefit than 40 mg.
  - Febuxostat is safe in renal impairment.
- Tapentadol 100 mg is similar in potency to what dose of oxycodone?
  - 10 mg
  - 15 mg
  - 25 mg
  - 30 mg
- Which of the following is an adverse effect of milnacipran?
  - Diarrhea
  - Hyponatremia
  - Hypertension
  - Hypertriglyceridemia
- Which of the following statements about vigabatrin is true?
  - Vigabatrin is the first drug approved for infantile spasms.
  - Vigabatrin may cause vision loss.
  - Vigabatrin decreased seizures by 50% in more than half of patients.
  - All of the above statements are true.
- Which of the following is the correct indication for dalfampridine?
  - Multiple sclerosis
  - Fibromyalgia
  - Schizophrenia
  - Epilepsy
- Which of the following is an advantage of asenapine over olanzapine?
  - Asenapine is less likely to cause dizziness and nausea.
  - Asenapine is less likely to cause weight gain.
  - Asenapine is more effective than olanzapine in clinical trials.
  - All of the following are advantages of asenapine over olanzapine.
- Which of the following brand-name agents will become generic in 2010?
  - Flomax®
  - Cozaar®
  - Aricept®
  - All of the above drugs will become generic in 2010.