Drug Information Newsletter
Summer 2013

In this issue...

- A Review of Canagliflozin for the Treatment of Type 2 Diabetes Mellitus
  Katie Spence, PharmD

- Antihypertensive Timing and Cardiovascular Risk in Patients with Type 2 Diabetes Mellitus
  Michael Parker, PharmD, BS

- Plan B Becomes Plan OTC
  Anthony Weiland, PharmD

- Reversal Agents for Novel Oral Anticoagulants
  Michael Parker, PharmD, BS

- 2013 Influenza Recommendations: Making a Difference in the Outpatient Setting
  Jason Hou, PharmD, BA

The UB School of Pharmacy and Pharmaceutical Sciences Drug Information Newsletter is dedicated to providing timely information relevant to healthcare practitioners in New York. The newsletter supplies information on clinical practice guidelines, medication safety issues, new drug approvals / medications under development, medication shortages, and drug class reviews. While the newsletter is published quarterly, supplements may be issued for important breaking information.

A Review of Canagliflozin for the Treatment of Type 2 Diabetes Mellitus
Katie Spence, PharmD

Background
Canagliflozin, brand name Invokana™, is a novel drug indicated for the treatment of patients with type 2 diabetes mellitus (T2DM) in combination with diet and exercise.¹ Canagliflozin may be used either as monotherapy or as add-on therapy to metformin, sulfonylureas, a thiazolidinedione (e.g., pioglitazone), or insulin.

In the kidneys, glucose is freely filtered across the glomerulus, but all of it is reabsorbed by 2 transporters: sodium-glucose co-transporter 1 and sodium-glucose co-transporter 2 (SGLT2).² SGLT2 is expressed in the proximal renal tubules and is responsible for the majority of glucose reabsorption. Canagliflozin is a reversible, competitive, SGLT2 inhibitor. By inhibiting the reabsorption of glucose, canagliflozin increases its urinary excretion and induces an osmotic diuresis.

The mean absolute oral bioavailability of canagliflozin is approximately 65%.² Following single-dose oral administration of canagliflozin 100 mg and 300 mg, peak plasma concentrations occur within 1 to 2 hours post-dose. Protein binding of canagliflozin is extensive at approximately 98% to 99%, primarily to albumin. As such, removal via dialysis is negligible. Canagliflozin is metabolized by O-glucuronidation via UGT1A9 and UGT2B4 to 2 inactive O-glucuronide metabolites. Cytochrome P450 3A4-mediated metabolism of canagliflozin is approximately 7% in humans. The terminal half-life is 10.6 hours and 13.1 hours for the 100 mg and 300 mg doses, respectively.
Dosage, Administration, and Dose Adjustments
Canagliflozin is initially dosed 100 mg by mouth once daily, taken before the first meal of the day, and may be administered with or without food. Administration before the first meal of the day is recommended based on the potential to reduce postprandial plasma glucose excursions due to delayed intestinal glucose absorption. The dose can be increased to 300 mg orally once daily (the maximum daily dose) in those who require additional glycemic control. Canagliflozin is supplied as 100 mg and 300 mg tablets.

Renal dose adjustment is necessary because as renal function decreases, less glucose is filtered across the glomerulus. Also, the total exposure to canagliflozin, as measured by area under the curve (AUC), increases. For patients with estimated glomerular filtration rate (eGFR) ≥60 mL/min, no dosage adjustment is needed; in patients with eGFR 45—59 mL/min, dosage should not exceed 100 mg/day. For patients with eGFR <45 mL/min, canagliflozin should not be initiated. If a patient’s eGFR falls below 45 mL/min while on canagliflozin, the drug should be discontinued. Dosage adjustments are not required in patients with mild to moderate hepatic impairment; however, canagliflozin is not recommended in those patients with severe hepatic impairment.

Contraindications, Warnings & Precautions, and Adverse Reactions
Canagliflozin is contraindicated in patients who have hypersensitivity to canagliflozin or any of its components, patients receiving dialysis, and patients with severe renal impairment (eGFR <30 mL/min). Warnings include hypotension, renal dysfunction, hyperkalemia, hypoglycemia when used in combination with other agents, genital mycotic infections, hypersensitivity reactions, and increased low-density lipoprotein cholesterol (LDL-C).

The most common adverse reactions reported were female genital mycotic infections (10.4%), urinary tract infections (UTIs, 5.9%), increased urination (5.3%), male genital mycotic infection (4.2%), vulvovaginal pruritus (1.6%), thirst (2.8%), constipation (1.8%), and nausea (2.2%). Canagliflozin may increase LDL-C by 4.5% at the 100 mg dose and 8.0% at the 300 mg dose. Canagliflozin can also cause a dose-dependent increase in the incidence of orthostatic hypotension-related adverse reactions, especially in patients on loop diuretics, patients with moderate renal impairment (eGFR 30 – 60 mL/min), and patients ≥75 years of age. This medication can also cause mild weight loss (a decrease of 2.2% from baseline) and decrease in systolic blood pressure (SBP; -3.7%). Hyperkalemia and hypermagnesemia can also occur. Increases in serum potassium of greater than 5.4 mEq/L and 15% above baseline occurred in 16.1%, 12.4%, and 27% of patients treated with placebo, canagliflozin 100 mg/day, and canagliflozin 300 mg/day, respectively, within 3 weeks of initiation. Within 6 weeks of initiation, the mean change in serum magnesium levels was 8.1% and 9.3% with canagliflozin 100 mg/day and canagliflozin 300 mg/day, respectively, compared to -0.6% with placebo.

Canagliflozin has not been evaluated in pregnant women; as such, it is classified as pregnancy category C. Though it is unknown if canagliflozin is excreted in human milk, due to a potential for serious adverse reactions in the nursing infant, it is recommended to avoid breast-feeding, or to discontinue the drug, taking into account the importance of the therapy to the mother.

Drug Interactions
Co-administration with UGT enzyme inducers such as rifampin, ritonavir, phenytoin, and phenobarbital may require a dose increase of canagliflozin to 300 mg once daily due to decreased canagliflozin concentrations (as long as renal function is adequate). When canagliflozin is initiated in patients already receiving diuretics, angiotensin converting enzyme inhibitors, or angiotensin II receptor blockers, symptomatic hypotension can occur. Patients taking digoxin and canagliflozin should have their digoxin serum concentrations monitored, as studies suggest a moderate increase in digoxin AUC (20%) may occur.

Studies
A double-blind, active-controlled study of canagliflozin 300 mg in combination with metformin and a sulfonylurea vs. sitagliptin 100 mg in combination with metformin and a sulfonylurea was conducted. Patients were required to have a glycosylated hemoglobin (HgA1c) ≥7.5% and ≤10.5% for inclusion. Additional antihyperglycemic agents were titrated to ≥2,000 mg metformin and a minimum dose of sulfonylurea (based on drug) during an adjustment period (up to 4 weeks) prior to randomization. Subjects were excluded if their eGFR at baseline was <60 mL/min/1.73 m² or serum creatinine was ≥1.4 mg/dL for men or ≥1.3 mg/dL for women. Change in HgA1c from baseline through week 52 was the primary endpoint of the study. Secondary endpoints included percent of patients with HgA1c <7%, percent body weight change, and change...
Antihypertensive Timing and Cardiovascular Risk in Patients with Type 2 Diabetes Mellitus

Michael Parker, PharmD, BS

Background: Type 2 Diabetes, Blood Pressure, and Associated Cardiovascular Risk
When uncontrolled, T2DM may lead to significant morbidity and mortality due to micro- and macrovascular complications. Myocardial infarction (MI), cerebrovascular accidents (CVA), and peripheral vascular disease (PVD) are macrovascular complications that often manifest in patients with T2DM. Cardiovascular (CV) disease is the biggest contributor to both direct and indirect costs associated with T2DM. Due to the progressive nature of diabetes, preventing CV manifestations in these patients is an important goal. In order to mitigate the increased CV risk, clinicians focus on controlling hypertension (HTN), dyslipidemia, and hyperglycemia. The majority of the CV risk can be attributed to HTN and dyslipidemia. We know that statins play a major role in CV risk reduction by directly lowering low density lipoprotein levels in addition to other pleiotropic effects. HTN also plays a major role in the risk of CV events. There is a great need for an efficacious and cost effective method of reducing HTN-related CV risk in patients with T2DM.

Blood Pressure – It’s Not That Simple
Ambulatory blood pressure monitoring (ABPM) is superior to clinic BP pressure monitoring in predicting CV events in patients with and without T2DM. As far back as 1998, ABPM has been shown to be reproducible, a predictor of end-organ damage, and this method may avert the “white coat” phenomenon. Around the clock ABPM allows for analysis of arterial BP during waking and sleeping periods of the day. Sturrock et al. describe a phenomenon of BP reduction during times of sleep that occurs in some patients. Patients whose BP decreases by ≥10% overnight, exhibiting a diurnal pattern, are
Influence of Time of Day of BP-Lowering Treatment on Cardiovascular Risk in Hypertensive Patients with Type 2 Diabetes

This was a prospective single-center, randomized, open-label, blinded endpoint trial conducted in Spain. Inclusion criteria were a history of HTN, T2DM, age ≥18 years, and had ≥6 months of follow-up in order to evaluate events. Exclusion criteria included a history of alcohol or illicit drug abuse, night-shift work, a diagnosis of acquired immune deficiency syndrome, type 1 diabetes, secondary HTN, existing CV disorders, intolerance to ABPM, or inability to comply with all study requirements. Patients were randomized to receive all of their BP lowering medications upon awakening or ≥1 of these medications at bedtime. ABPM was measured for 48 hours at baseline and again annually or more frequently if any BP medication adjustments were made (as often as every 3 months); blood draws were performed at the same intervals. During ABPM, BP was monitored every 20 minutes between 7:00 AM and 11:00 PM, and every 30 minutes overnight. Actigraphy (a physical movement monitor worn on the wrist) and patient diaries were used to corroborate and define daytime versus sleeping hours and to ensure BPs were accurately categorized in their respective categories. CV morbidity and mortality were assessed at least yearly by investigators blinded to the timed treatment assignment. Events recorded included all-cause mortality, MI, angina pectoris, coronary revascularization, heart failure, PVD, retinal artery occlusion, CVA, and transient ischemic attack.

A total of 448 patients were assessed. There were no statistically significant between-group differences in baseline characteristics including demographics, anthropometric, BP, and laboratory values. Additionally, there were no statistically significant between group differences for the use of statins, low-dose aspirin, or the number or type of antihypertensive medications used. Between 55% and 59% of patients were male, with a mean age of 62.5 years and body mass index of 32. After a median follow-up of 5.4 years, patients in the bedtime group showed an age and sex-adjusted reduction in CV risk that was statistically significant (hazard ratio [HR] 0.33; 95% confidence interval [CI] 0.21-0.54; p<0.001). At the final follow-up visit, the percent of patients in the bedtime administration group who took 1, 2, or ≥3 medications at bedtime were 56.5%, 25%, and 18.5%, respectively. The between-group difference for the adjusted risk of major CV events (CV death, MI, and CVA) was also statistically significant in the favor of the bedtime group (HR 0.25; 95% CI 0.10-0.61; p=0.003). For ambulatory BP, there was a 12% and 23% CV risk reduction for each 5 mmHg decrease in asleep systolic or diastolic BP, respectively (p<0.001 for both).

<table>
<thead>
<tr>
<th>Last Follow-Up Blood Pressure Differences Between Groups for Ambulatory Blood Pressure Monitoring</th>
<th>Bedtime Administration</th>
<th>AM Administration</th>
<th>Statistical Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of Non-Dipper Patients</td>
<td>49.5%</td>
<td>76.3%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Proportion of Patients at ABPM Goal for both SBP &amp; DBP</td>
<td>62.5%</td>
<td>50.9%</td>
<td>p=0.013</td>
</tr>
<tr>
<td>Proportion of Patients with controlled awake ABPM</td>
<td>72.2%</td>
<td>75.4%</td>
<td>p=0.439</td>
</tr>
<tr>
<td>Proportion of Patient with controlled asleep ABPM</td>
<td>70.8%</td>
<td>54.7%</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure; ABPM = Ambulatory Blood Pressure Monitoring

Limitations: This study was completed in older Spanish residents. The population in the United States is more racially diverse and the patients we treat have a much broader age range. While one may not be able to guarantee the same results in a variety of racial groups, there is no evidence that applying this intervention to other patient populations would be harmful.

Conclusion

The bedtime administration group exhibited a 67% and 75% relative risk reduction for total and major CV events, respectively. The bedtime group had poorer ambulatory awake-time BP control, but this was not statistically significant. Despite this finding, the study revealed greater overall ambulatory (day and night combined) and asleep BP control in patients taking ≥1 BP medications at bedtime versus those conventionally taking all BP medications in the morning. Switching a non-diuretic BP medication from the morning to bedtime is a simple, cost effective intervention that a practitioner can suggest to their patients with HTN. This intervention may have the added benefit of reducing side effects,
such as dizziness and orthostatic hypotension. It may be helpful to reproduce these results in patients with diabetes or singular hypertension, with greater demographic diversity.

References

Plan B Becomes Plan OTC

*Anthony Weiland, PharmD*

**Background**

A landmark ruling by US District Judge Edward Korman has greatly affected Plan B’s place within the pharmacy and who will have access to the drug.¹ Since then, the Food and Drug Administration has come out with its guidance on the matter and President Obama has also weighed in.² These rulings, stays and appeals have confused this issue and have brought Plan B into the spotlight. This article will discuss how the events unfolded, where the issue currently stands and what opinions fall on either side of the issue. It is important to note these changes affect only Plan B One-Step, the single dose formulation for emergency contraception. The 2 dose formulation is unaffected by these changes and requires a prescription for women under 17 years of age.

In December 2011, the FDA was prepared to lift a controversial age limit (≥17 years) and make Teva’s Plan B One-Step (levonorgestrel) available for purchase without a prescription.³ However, the Department of Health and Human Services’ Secretary Kathleen Sebelius blocked the move stating, “While young girls are physically capable of bearing children, they might not properly understand how to use the emergency contraception without guidance from an adult.” Events were rekindled this year on April 5th when Judge Edward Korman of the Eastern District of New York issued a ruling to make Plan B available over the counter without age restriction which came as a result of a lawsuit brought by reproductive-rights advocates. This decision overruled the age restriction implemented by Secretary Sebelius and the FDA so Plan B would be available to women of all ages within 30 days of the ruling.

**Opinions**

Numerous groups, including the federal government, Planned Parenthood, US Senators to the March of Life Education & Defense fund and the Concerned Women of America have voiced opinions regarding the changes being made with Plan B (decrease in age requirement and moving the product out of the pharmacy).³ The groups’ opinions on the topics seem to mesh into 2 main categories, overall agreement or disagreement with changes.

**Considerations of Selected Groups in Agreement and Disagreement with Plan B Changes.³**

<table>
<thead>
<tr>
<th>Overall Agreement</th>
<th>Overall Disagreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>• May have significant impact on teen pregnancy rates</td>
<td>• High dose of hormones (upwards of 40x amount in daily use birth control);</td>
</tr>
<tr>
<td>• Could create a real opportunity for parents to</td>
<td>• questionable effect on younger patients</td>
</tr>
<tr>
<td>communicate with kids about sex</td>
<td>• Removes prescribers from the equation and</td>
</tr>
</tbody>
</table>
• Step in right direction for increased access to a “safe and effective” method in preventing unintended pregnancies

leads to young girls put in situations that need adult guidance

• May exacerbate STDs as Plan B does not prevent spread of disease and may become a primary form of contraception

• Parents should be involved in health decisions that impact their daughters. Removing this barrier eliminates parents from being involved in these decisions

STDs = sexually transmitted diseases

On April 30th, 2013 the FDA announced an approval independent of the April 5th ruling for Plan B One-Step, where men and women 15 years of age and older can buy Plan B One-Step over the counter with proof of identification and age (e.g., a driver’s license, birth certificate or passport). Labeling changes will be required as well, placed on the packaging stating “not for sale to those under 15 years of age *proof of age required* not for sale where age cannot be verified”. An additional product code prompting cashier to request and verify customer’s age and a security tag is placed on all product cartons to prevent theft. Plan B will be available at retail outlets with an onsite pharmacy, placed within the family planning or female health aisle, without regard to pharmacy hours of operation.

Since then, further changes have been implemented. A summary of events is described below:

2013 Timeline

May 1st: Obama administration filed a notice of appeal and a motion to stay the April 5th ruling and asked the U.S. Court of Appeals for the Second Circuit to overturn the ruling along with having Judge Korman stay his order pending the appeal.

May 10th: Judge Korman denied the stay concluding, “The appeal is frivolous and is taken for the purpose of delay.”

May 13th: The government filed a motion for stay pending appeal in US Court of appeals for the second circuit, which the appeals court ordered the stay of original ruling extended to May 28th.

May 28th: Pending the results of the government’s appeal, Judge Korman’s decision to make Plan B available without an age restriction went into effect.

June 10th: The government drops the appeal, enabling Plan B to be sold OTC without age restrictions.

June 20th: FDA officially approves Plan B One-Step to be sold OTC without age restrictions.

Though this issue is currently settled, it is possible future challenges to the ruling may arise based on different groups’ opinions. Plan B One-Step® is available over the counter to all patrons regardless of age or gender, and without the need to consult a healthcare provider.

References


Reversal Agents for Novel Oral Anticoagulants

Michael Parker, PharmD, BS

Background

For many years, warfarin, a vitamin K antagonist (VKA), has been the sole oral anticoagulant marketed in the United States. Over the past several years, novel oral anticoagulants (NOACs) have been approved by the Food and Drug Administration (FDA). These include the direct thrombin inhibitor, dabigatran, and the factor Xa inhibitors rivaroxaban and apixaban. At times, a patient on warfarin may require urgent anticoagulant reversal due to a severely elevated international normalized ratio (INR), major bleeding, or the need for surgery. Vitamin K is an established antidote for warfarin reversal which may be used alone or in combination with other agents depending on the level of urgency. This is not the case for the NOACs, where comparatively little evidence exists to guide the clinician’s selection of the most appropriate and efficacious agent. This review will provide a guide to reversal of warfarin and the NOACs based on the latest evidence.

General Advice

The first step in reversing the effects of an oral anticoagulant is to stop the drug. Depending on the severity/risk of a bleed or the timing of surgery, interruption of therapy may be enough to reach the desired level of hemostasis. Factors such as agent used, timing of last dose, half-life, and renal function may play a role in this decision. Baseline and periodic coagulation studies, complete blood count (CBC), renal function, and vital signs should be monitored as clinically appropriate. The characteristics of the NOACs may be found in Table 1 below.

Table 1: Characteristics of Novel Oral Anticoagulants

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Half-life (hours)</th>
<th>Time to maximum plasma concentration (hours)</th>
<th>Dosing frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>8-13</td>
<td>3</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>14-17</td>
<td>2-3</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>5-9</td>
<td>2-4</td>
<td>VTE treatment: twice daily x3 weeks, then daily Stroke prevention: daily</td>
</tr>
</tbody>
</table>

Reversal of Warfarin with Vitamin K

Warfarin exerts its anticoagulant effects by inhibiting vitamin K-dependent clotting factors II, VII, IX, and X. The anticoagulant proteins C and S are also inhibited by warfarin. Vitamin K effectively promotes the hepatic production of these factors. Vitamin K does not reverse the effect of the NOACs.

Reversal of Warfarin

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Action</th>
<th>Dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR ≤ 10 w/no bleeding</td>
<td>Hold warfarin &amp; monitor INR</td>
<td>N/A</td>
<td>Unnecessary use of vitamin K may lead to warfarin resistance for up to 1 week</td>
</tr>
<tr>
<td>INR &gt; 10 w/no bleeding</td>
<td>Hold warfarin &amp; give vitamin K</td>
<td>2 to 2.5 mg PO</td>
<td>Larger doses will lead to resistance</td>
</tr>
<tr>
<td>Active bleed at any INR</td>
<td>Hold warfarin &amp; give vitamin K &amp; 4-factor PCC</td>
<td>Vitamin K 5 to 10 mg IV</td>
<td>Give vitamin K slowly IV and protect from light. Four-factor PCC should be used over FFP. This combination offers complimentary PK.</td>
</tr>
<tr>
<td>Need for surgery</td>
<td>Use clinical judgment</td>
<td>N/A</td>
<td>Based on level of urgency, holding warfarin alone, or the use of vitamin K and/or PCC may be appropriate</td>
</tr>
</tbody>
</table>

INR = international normalized ratio; N/A = not applicable; PO = oral; PCC = Prothrombin complex concentrate; FFP = Fresh Frozen Plasma; PK = pharmacokinetics
Coagulation Factor Replacement

The NOACs work by inhibiting specific clotting factors in the coagulation cascade, namely factor IIa or Xa. If specific approved antidotes were available and geared towards the NOAC, this would be ideal. However, this is not the case; until these antidotes are commercially available, the use of PCC is appropriate in emergency situations, even though it may seem excessive. Many of the agents below are FDA-approved for management of bleeding in patients with hemophilia.

<table>
<thead>
<tr>
<th>NOAC Reversal Agent Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product/Procedure</strong></td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>Fresh Frozen Plasma (FFP)</td>
</tr>
<tr>
<td>3 or 4 factor Prothrombin Complex Concentrate (PCC)</td>
</tr>
<tr>
<td>rFVIIa</td>
</tr>
<tr>
<td>Hemodialysis</td>
</tr>
<tr>
<td>aPCC</td>
</tr>
<tr>
<td>Activated Charcoal</td>
</tr>
</tbody>
</table>

**FFP = fresh frozen plasma; N/A = not applicable; NOACs = novel oral anticoagulants; VKA = vitamin K antagonist; PCC = prothrombin complex concentrate; IV = intravenous; rFVIIa = recombinant factor VIIa; Tx = treatment; ICH = intracranial hemorrhage; HTN = hypertension; HA = headache; aPCC = activated prothrombin complex concentrate; Inh = Inhibitor;**

Reversal of the direct thrombin inhibitor dabigatran

No specific antidote exists. Generally, drug is 35% plasma protein bound and 65% exists free in plasma. Dabigatran is dialyzable (hemodialysis) with 62-68% removed over 2 to 4 hours. The manufacturer recommends factor VIII inhibitor bypassing activity (FEIBA; aPCC), rFVIIa, or PCC. Four factor PCC is supported by animal data. More in vivo human data are needed to determine safety and efficacy.
Reversal of the factor Xa Inhibitors apixaban and rivaroxaban
No specific antidote exists. Laboratory parameters were improved with 4-factor PCC, however bleeding outcomes did not change. More in vivo human data are needed to determine safety and efficacy.

Kcentra
This 4-factor PCC was approved by the FDA in April 2013 for the immediate reversal of vitamin K antagonists in patients with acute major bleeding. One pivotal efficacy trial found Kcentra to be non-inferior to FFP. A second pivotal safety trial is ongoing with interim safety data reported. When combined with results of the first trial, mortality is similar between the active treatment and FFP arms; however, the first trial revealed a statistically significant higher mortality rate in the Kcentra group (p=0.0466). FDA is requiring a Phase IV post-marketing trial to look further into safety concerns, including thromboembolic events.

Emerging Therapies
A humanized monoclonal antibody fragment (Fab) was developed to reverse the effects of dabigatran and is currently under investigation. Van Ryn et al. described a trial in rats in which Fab successfully reduced blood loss and corrected clotting assays. Additionally, a recombinant factor Xa derivative is in development for the reversal of factor Xa inhibitors. It has shown promise by reducing blood loss and anti-factor Xa activity.

Summary
As more patients begin taking NOACs, more bleeding events will occur. Warfarin remains the only oral anticoagulant with an effective antidote. Though different therapies, including FFP, PCC, and rFVIIa may be used to help suppress emergent bleeding associated with the NOACs, none have been studied for this use. Though antidotes may become available, until this time clinicians should use their best judgment in selecting the most appropriate agent.

References
Background
As a provider, it is important to determine the difference between patients who present with colds and those who present with influenza (the flu). The following table outlines the differences between a cold and the flu.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Cold</th>
<th>Flu</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Rare</td>
<td>Characteristic, high (100-102°F); lasts 3 to 4 days</td>
</tr>
<tr>
<td>Headache</td>
<td>Rare</td>
<td>Prominent</td>
</tr>
<tr>
<td>General aches, pains</td>
<td>Slight</td>
<td>Usual; often severe</td>
</tr>
<tr>
<td>Fatigue, weakness</td>
<td>Quite mild</td>
<td>Can last up to 2 to 3 weeks</td>
</tr>
<tr>
<td>Extreme exhaustion</td>
<td>Never</td>
<td>Early and prominent</td>
</tr>
<tr>
<td>Stuffy nose</td>
<td>Common</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Sneezing</td>
<td>Usual</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Sore throat</td>
<td>Common</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Chest discomfort, cough</td>
<td>Mild to moderate; hacking cough</td>
<td>Common; can become severe</td>
</tr>
<tr>
<td>Complications</td>
<td>Sinus congestion or earache</td>
<td>Bronchitis, pneumonia; can be life-threatening</td>
</tr>
<tr>
<td>Prevention</td>
<td>None</td>
<td>Annual vaccination; rimantadine, zanamivir, or oseltamivir (antiviral drugs)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Only temporary relief of symptoms</td>
<td>Amantadine, rimantadine, zanamivir, or oseltamivir within 24-48 hours after onset of symptoms</td>
</tr>
</tbody>
</table>

The Centers for Disease Control and Prevention (CDC) has published recommendations for providers regarding the prevention and treatment of the influenza virus. These guidelines highlight the different formulations of the influenza virus vaccine available, as well as the suggested dose and interval for each vaccine. The treatments for active influenza and in the population they should be used are also outlined.

Recommendations
Influenza Virus Vaccine
Fluvirin® (inactivated)
Adults, Adolescents, and Children 9-12 years: 0.5 ml IM as a single dose.
- Children 4-8 years: 0.5 ml IM. Repeat the dose in ≥ 4 weeks for those who are receiving the flu vaccine for the first time. For those who were first vaccinated last season with only 1 dose, a second dose is recommended ≥ 4 weeks after the first dose.
- Neonates, Infants, and Children <4 years: Safety/efficacy has not been established.

Fluzone® High-Dose only (inactivated)
- Geriatric ≥65 years: 0.5 ml IM

Fluzone® (inactivated)
- Infants and Children 6-35 months: 0.25 ml IM. Repeat the dose in ≥ 4 weeks for those who are receiving the flu vaccine for the first time. For those who were first vaccinated last season with only 1 dose, the manufacturer recommends a
**Immunization Schedule:**

- **Annual vaccination is recommended for patients ≥6 months of age.** Type of vaccine recommended (i.e., live attenuated vs. inactivated) varies per patient age.
- **≥65 years:** inactivated or high dose inactivated
- **50 - 64 years:** Inactivated
- **2 - 49 years, not initial dose:** Inactivated or live attenuated
  - Live attenuated should not be given to those with asthma, children 2-4 years with wheezing within the past 12 months, or those with medical conditions that would predispose them to influenza complications
- **6 months - 8 years, first time receiving:** Inactivated only
  - 2 doses at least 4 weeks apart
- **<6 months:** not recommended

**Egg Allergies**

- Can the person eat lightly cooked eggs without a reaction?
  - Administer vaccine as usual
- Does the person experience ONLY hives after eating eggs or egg-containing foods?
  - Administer IIV; observe for at least 30 minutes after vaccination
- Does the person experience symptoms consistent with anaphylaxis: cardiovascular changes, respiratory distress, nausea, vomiting, a reaction requiring epinephrine or emergency medical attention?
  - Refer to a physician with expertise in management of allergic conditions

**Treatment**

- Neuraminidase inhibitor (active against Influenza A & B) - Tamiflu® (oseltamivir)
- Geriatric, adult, and adolescent (≥13 years): 75 mg twice daily
- Children ≥1 year:
  - ≤15 kg – 30 mg twice daily
  - 15-23 kg – 45 mg twice daily
  - >23 kg – 60 mg twice daily
  - >40 kg – 75 mg twice daily
- Infants and Children 2 weeks-1 year:
  - 3mg/kg twice daily

- Neuraminidase inhibitor (active against Influenza A & B) - Relenza® (zanamivir)
- Geriatric, adult, adolescents, and children (≥7 years): 10 mg (2 inhalations) twice daily

- Amantadine - Symmetrel® - approved for only Influenza A virus
- Due to high resistance among Influenza A viruses, not recommended
- Rimantadine - Flumadine® - approved for only Influenza A virus
- Due to high resistance among Influenza A viruses, not recommended

IM = intramuscular; IIV = inactivated influenza vaccine
The Advisory Committee on Immunization Practices (ACIP) provides recommendations for patients with specific indications for vaccination, including pregnancy, immunocompromized individuals, those with chronic conditions, and healthcare personnel.\(^4\)\(^5\)

<table>
<thead>
<tr>
<th>Indications</th>
<th>Pregnancy</th>
<th>Immunocompromising conditions (excluding human immunodeficiency virus [HIV])</th>
<th>HIV infection</th>
<th>CD4+ T lymphocyte count</th>
<th>Men who have sex with men (MSM)</th>
<th>Heart disease, chronic lung disease, chronic alcoholism</th>
<th>Asplenia (including complement deficiencies)</th>
<th>Chronic liver disease</th>
<th>Kidney failure, end-stage renal disease, receipt of hemodialysis</th>
<th>Diabetes</th>
<th>Healthcare personnel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>1 DOSE IIV ANNUALLY</td>
<td></td>
<td>≥ 200 cells/μL</td>
<td>≥ 200 cells/μL</td>
<td>1 DOSE IIV ANNUALLY</td>
<td>1 DOSE IIV ANNUALLY</td>
<td>1 DOSE IIV ANNUALLY</td>
<td>1 DOSE IIV ANNUALLY</td>
<td>1 DOSE IIV ANNUALLY</td>
<td>1 DOSE IIV ANNUALLY</td>
<td>1 DOSE IIV ANNUALLY</td>
</tr>
</tbody>
</table>

2013-2014 Season Updates

- Quadrivalent influenza vaccines have been approved (Fluarix\(^\text{®}\) Quadrivalent, Flumist\(^\text{®}\) Quadrivalent).\(^5\) There are 4 virus strains in the quadrivalent influenza vaccine: 2 influenza A (H3N2 & H1N1), and 2 influenza B vaccine virus strains, 1 from each lineage of circulating influenza B viruses
  - Live attenuated: only the quadrivalent formulation will be available. Manufacture of the trivalent formulation will cease.
  - Inactivated: Available in both trivalent and quadrivalent formulations.

Additional information

- Additional guidance for the use of the vaccines described in this supplement is available at [http://www.cdc.gov/vaccines/pubs/acip-list.htm](http://www.cdc.gov/vaccines/pubs/acip-list.htm)
- Information on vaccination recommendations when vaccination status is unknown and other general immunization information can be found in the General Recommendations on Immunization at [http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.htm)
- Information on travel vaccine requirements and recommendations (e.g., for hepatitis A and B, meningococcal, and other vaccines) are available at [http://wwwn.cdc.gov/travel/page/vaccinations.htm](http://wwwn.cdc.gov/travel/page/vaccinations.htm)

FDA Updates on Tamiflu\(^\text{®}\) Shortage

The oral suspension for oseltamivir remains on intermittent backorder.\(^8\) Some supplies may be found at distributors, wholesalers, or pharmacies. Further updates regarding the availability of the oseltamivir suspension may be found on the FDA drug shortage website, listed in the references. In lieu of this product, the FDA has issued instructions for the compounding of the oral suspension from the 75 mg oseltamivir capsules. These instructions may be found below in the prescribing information. The specific weight-based dosing guidelines may be found below.

### Tamiflu\(^\text{®}\) Weight-Based Dosing\(^6\)

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geriatric, Adults, Adolescents (≥ 13 years)</td>
<td>75 mg twice daily</td>
</tr>
<tr>
<td>Children ≥ 1 year</td>
<td>≤15 kg: 30 mg twice daily</td>
</tr>
<tr>
<td></td>
<td>15-23 kg: 45 mg twice daily</td>
</tr>
<tr>
<td></td>
<td>&gt;23-40 kg: 60 mg twice daily</td>
</tr>
<tr>
<td></td>
<td>&gt;40 kg: 75 mg twice daily</td>
</tr>
<tr>
<td>Infants and Children 2 weeks-1 year</td>
<td>3 mg/kg twice daily</td>
</tr>
</tbody>
</table>

Summary

It is important for practitioners to recognize the differences between influenza and the common cold, as treatment for influenza may reduce the duration and severity of the symptoms. Furthermore, practitioners should be aware of the
current guidelines and recommendations for the influenza prevention, as these vary based on patient characteristics. Vaccination remains the primary preventive strategy for reducing the morbidity and mortality associated with influenza infection. Pharmacists can identify patients who are candidates for vaccination, and administer the influenza vaccination, thereby reducing the incidence of infection.

References

Author Biographies
Katie Spence graduated from UB School of Pharmacy and Pharmaceutical Sciences in 2012 and is a PGY1 resident at Buffalo Medical Group in Buffalo, NY. Her current research interests include pharmacists’ impact on diabetes, dyslipidemia, and hypertension outcomes in a patient-centered medical home.

Michael Parker graduated with his BS in biology from George Mason University in 1998 and his PharmD from Wingate University in 2012. He is currently a PGY1 Ambulatory Pharmacy resident at Lifetime Health in Buffalo, NY. His current research involves disparities in standards of care among patients with type 2 diabetes.

Anthony Weiland graduated from Ohio Northern University College of Pharmacy in 2011 and is a PGY1 resident at Middleport Family Health Center in Buffalo, NY. His current research interests include perceptions of New York pharmacists on the change in the prescription drug monitoring program.

Jason Hou graduated with a BA in Cell Molecular Biology from Skidmore College in 2006 and a PharmD from UB School of Pharmacy and Pharmaceutical Sciences in 2012. He is currently a PGY1 resident at VascuScript Pharmacy in Buffalo, NY, and his current research interests include patient satisfaction with community pharmacies.

Editor
Drew Lambert graduated from UB School of Pharmacy and Pharmaceutical Sciences in 2011 and completed a PGY1 residency at Millcreek Community Hospital in Erie, PA in 2012. He is currently a PGY2 Drug Information resident at the UB Drug Information Response Center, and his current research interests include drug information perceptions among IPPE and APPE students and preceptors.

Please address any comments or corrections to Drew Lambert at lambert7@buffalo.edu.