

Special points of interest:

- **Drug class review** of antivirals used in the treatment of novel H1N1 influenza and seasonal influenza
- **Drug Information Corner:** Who should receive H1N1 and seasonal influenza vaccine?
- **FDA Alert:** Emergency use authorization of peramivir

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Pharmacotherapy Update



Editor Notes

This edition of the newsletter focuses on influenza. This year, growing concerns about novel influenza A (H1N1) have caused an increase in efforts to prevent the spread of illness. Vaccination is one way that influenza can be averted.

This newsletter’s Drug Information section focuses on targeting priority groups for vaccination, and explains how the two influenza vaccines should be given.

On [page 2](#) you will find an article on the safety of acetaminophen, which has recently been in the news. The literature on the use of acetaminophen post-immunization is also reviewed.

The Drug Class Review below focuses on a review of the Antiviral class of medications used to treat influenza. An additional section on [page 4](#) includes information on the FDA’s emergency use authorization

of the intravenous antiviral drug peramivir.

The PBM alerts section features an alert on the look-alike packaging of live attenuated seasonal influenza vaccine and novel influenza A (H1N1) vaccines. This section also provides information about the neuropsychological effects associated with leukotriene inhibitors.

Stay warm this winter!
Denise Alexander, Pharm.D. and Dina Norris, Pharm.D., BCPS, Editors

Drug Class Review: Antivirals

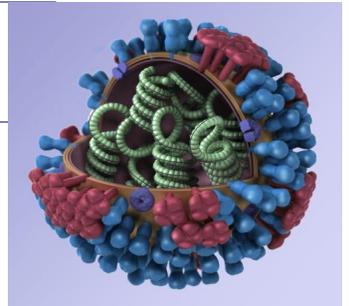
By: Lou Portas, Pharm.D.

Every year when the mercury begins to drop we are reminded to prepare our patients for the upcoming influenza season. Vaccination is the cornerstone of therapy, but despite adequate prevention, many people are still infected with the influenza virus. There are several explanations for vaccine failure, with the most common being infection with an influenza strain not included in the vaccine. Patients may also decide not to get the vaccine, or as in recent years, a novel viral strain may appear. When prevention fails, many pharmacological treatment options are available, which vary based on current resistance patterns and the strain of virus causing the infection.

Three types of influenza virus exist in nature: types A, B, and C. These types are further differentiated by hemagglutinin and neuraminidase proteins, which

surround the outer membrane of the virus and play an important role in infecting human cells. Hemagglutinin allows the virus to “stick” to human cells, and neuraminidase facilitates the breakdown of our body’s defensive barrier of mucin (mucus layer protecting human cells). Influenza A is further classified with sequential numbers based on the activity of these two proteins. Hemagglutinin subtypes range from 1-16 and neuraminidase subtypes range from 1-9. One example of a common seasonal influenza A strain is H3N2.

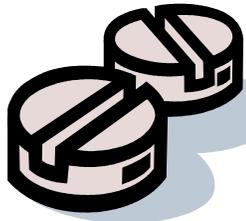
Adamantanes and neuraminidase inhibitors are two classes of drugs that are used to treat and prevent influenza. Amantadine and rimantadine are FDA-approved adamantanes that are available but are no longer recommended by the Center for Disease Control and Prevention (CDC) for treatment or prophylaxis due to increasing resistance



patterns. Neuraminidase inhibitors available for use include zanamivir and oseltamivir. Recently, the Food and Drug Administration (FDA) granted an Emergency Use Authorization for peramivir, an experimental intravenous neuraminidase inhibitor (see [page 4](#) for more information). Because viral resistance patterns are constantly shifting, recommendations regarding the use of antiviral medications are subject to change.

The adamantane drug class is useful for the treatment and prophylaxis of influenza A virus only. Adamantanes work by preventing viral access into human cells via inhibition of the uncoating of the virus, but despite the similar mechanism of action, several differences exist between rimantadine and amantadine. Rimantadine has

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Literature Review: Acetaminophen Limits and Limitations

By: Susan Sincavage, Pharm. D.

“Acetaminophen was found to be the leading cause of acute liver failure in recent years, affecting some 56,000 individuals.”



Acetaminophen has been considered a safe and effective remedy for mild pain for many years, having been used widely in infants, pregnant women, and the elderly when taken as directed. It is also commonly combined with opioids to provide relief from moderate to severe pain. However, acetaminophen was found to be the leading cause of acute liver failure in recent years, affecting some 56,000 individuals. In 2006, a randomized, controlled trial of healthy adults consuming the maximum recommended daily dose of acetaminophen of 4 grams per day demonstrated the increased risk of serum aminotransferase elevations, an indicator of liver cell damage. This study raised concerns about dosage limits, especially in elderly or medically complicated patients. The maximum daily dose of acetaminophen in frail populations may need to be as little as 2-3 grams per day to prevent liver toxicity. Nonprescription product labeling for adults currently states that when taken in excess, acetaminophen can lead to liver damage, and that this risk increases if consuming three or more alcoholic beverages a day. When taken for pain or fever, the duration of therapy is limited to ten and three days, respectively. Some organizations have released their own recommendations for susceptible populations, including the American Liver Foundation, who warns: “Do not exceed three grams of acetaminophen daily for any prolonged period.” While the American Geriatrics Society states that for most older people the maximum daily dose of acetaminophen is 4 grams, for older individuals with a history of alcohol abuse or hepatic insufficiency, the daily dose should be reduced by 25-50% or 2-3 grams per day. In June, a Food and Drug Administration (FDA) advisory panel voted to lower the maximum daily dose of nonprescription acetaminophen. They also recommend reducing the maximum single dose to 650 mg which would likely make the 1000 mg dose available by prescription only. Furthermore, the FDA recommends a “black box” warning on narcotic drugs that contain acetaminophen since these drugs are linked to the majority of fatal acetaminophen overdoses. As a result of the FDA’s recommendations, combination cold and flu products containing more than 650 mg of acetaminophen may be reformulated as well.

To date, conflicting information exists regarding the use of prophylactic acetaminophen to prevent adverse effects such as fever, soreness, and flu-like symptoms post-immunization. While fever and inflammation is the body’s natural response to vaccination, the use of acetaminophen to ameliorate this process may have the potential to reduce vaccine effectiveness in some populations. Two studies performed in infants receiving four standard childhood immunizations compared the use of concomitant acetaminophen for 24 hours with no antipyretic prophylaxis on reduction of febrile reactions greater than or equal to 38.0 degrees Celsius and immunogenicity. Findings from these trials showed a significant decrease of febrile reactions and reduced antibody response.

To further explore whether the use of acetaminophen may blunt immune system response rates and reduce the number of antibodies which are produced, the adult population was also examined. In a study of elderly patients 65 years and older immunized with seasonal influenza strains, prophylactic acetaminophen did not affect vaccine protection rates nor improve adverse effects. A similar study of health care workers receiving seasonal influenza vaccine demonstrated that acetaminophen significantly reduced the incidence of nausea and sore arm without influencing antibody response. In a study of 60 healthy, elderly subjects and 20 infirm, elderly subjects randomly treated with 1000 mg of acetaminophen or placebo every six hours for two days following influenza vaccination, the healthy subjects demonstrated a significantly better immune response than the infirm subjects while the serum antibody response was unaffected in either group.

Administering prophylactic acetaminophen is not recommended in children being immunized as it has the potential to reduce vaccine effectiveness. Conversely, acetaminophen use in adults and the elderly does not seem to negatively impact immune development of serum antibodies but may decrease systemic response in those with poor health.

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Prymula R, Siegrist CA, Chlibek R et al. Effect of prophylactic paracetamol administration at time of vaccination on febrile reactions and antibody responses in children: two open-label, randomised controlled trials. *Lancet.* 2009 Oct 17;374(9698):1339-50.

Chernesky M, O'Neill D, Pickard L et al. Immunogenicity and adverse reactions of influenza vaccination in elderly patients given acetaminophen or placebo. *Clin Diagn Virol.* 1993 Jul;1(2):129-36.

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Drug Information Corner: Novel Influenza A (H1N1) Vaccine and Seasonal Influenza Vaccine

By Denise Alexander, PharmD

This year, vaccines for both seasonal influenza and novel influenza A (H1N1) are available. Due to the limited supply, high-risk groups should be a priority when distributing the vaccine. Despite the similarities in symptomatology and presentation, there are various differences in priority for seasonal and novel H1N1 influenza vaccines.

The high-priority groups for vaccination typically include those with the highest risk of mortality from the disease. Seasonal influenza mortality is highest in the elderly, whereas novel H1N1 is more dangerous to the younger population. This shift in mortality is often seen with influenza pandemics, such as the Spanish Influenza of 1918.

Because of the unusual characteristics of novel H1N1 influenza, the Centers for Disease Control and Prevention (CDC) recommend that the following groups be vaccinated against H1N1 with high priority:

- Pregnant women;
- People caring for children less than 6 months of age;
- Children, adolescents, and adults age 6 months – 24 years;
- Healthcare and emergency medical personnel;
- Ages 25 – 64 with a chronic medical condition or weakened immune system (including asthma, heart disease, kidney or liver disease, diabetes, HIV/AIDS, chemotherapy recipients, etc.)

The VA also recommends immunizing those of American Indian/Alaskan Native descent with high priority, as this indigenous population has demonstrated a 4-fold increase in mortality due to H1N1 influenza compared to all other ethnic groups combined. An increase in mortality in indigenous populations was documented during the pandemic Spanish Influenza as well.

After priority groups have been immunized, the vaccine may be offered to non-priority groups, such as ages 65+ and healthy persons age 25 – 64. In contrast to H1N1 influenza vaccine priority, seasonal influenza vaccine targets the older population. The high-priority groups for vaccination with seasonal influenza are as follows:

- Adults age 50 years and older;
- Residents of nursing homes or chronic care facilities;
- Caregivers or household contacts of people age 50 years or older;
- Pregnant women;
- Children and adolescents age 6 months – 18 years;
- People caring for children up to 5 years of age;
- Healthcare and emergency medical personnel;
- Anyone with a chronic medical condition, weakened immune system, or muscle or nerve disorders (including cerebral palsy or seizure disorder)

Additional groups that may be offered the vaccination include those who live in crowded areas such as dormitories and anyone else who would like to be protected from the disease. Children 6 months through 9 years of age require 2 doses at least 21 days apart if they are receiving the vaccine for the first time, whereas adults and children older than 9 years of age require a single dose. Although the inactivated vaccine and live attenuated intranasal vaccine are available for both seasonal and H1N1 influenza, the live intranasal vaccine is indicated only in non-pregnant healthy persons age 2 – 49 years.

The inactivated influenza vaccines may be administered in combination with any other inactivated vaccines at any time. However, administration of two live influenza vaccines requires four weeks' separation. Other live vaccines (i.e., varicella) can be administered on the same day as a live influenza vaccine, but need to be separated by four weeks if not given concurrently.

In summary, to prevent the spread of influenza this season, encourage your patients, family, and friends to get vaccinated, especially if they are in a high-priority group.

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- CDC. Deaths related to 2009 pandemic influenza A (H1N1) among American Indian/Alaskan Natives—12 states, 2009. *MMWR* 2009 Dec 11;58(48):1341-1344.

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Clinical Pharmacist Corner: Inpatient Clinical Pharmacy Specialist

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Food and Drug Administration: Emergency Use Authorization of Peramivir

EMERGENCY USE AUTHORIZATION OF PERAMIVIR IV FACT SHEET FOR HEALTH CARE PROVIDERS

Peramivir, a neuraminidase inhibitor, is an intravenous (IV) drug authorized for emergency use for the treatment of certain hospitalized patients with known or suspected 2009 H1N1 influenza.

The standard adult dose of Peramivir is 600 mg once daily, administered intravenously for 5 to 10 days.

Commonly reported adverse events in Peramivir IV clinical trials were diarrhea, nausea, vomiting, and neutropenia.

Patients with known or suspected renal insufficiency must have creatinine clearance determined prior to Peramivir IV dose calculation and first administration.

Patients with a history of severe allergic reaction to any other neuraminidase inhibitor (zanamivir or oseltamivir) or any ingredient of Peramivir IV must not receive Peramivir IV.

Reference:

FDA. Emergency Use Authorization Fact Sheet for Health Care Providers [Monograph on the Internet]. Rockville (MD): FDA; 2009 Oct 23. Available at: <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM187811.pdf>

**Peramivir Injection 200 mg/20mL (10 mg/mL) is an unapproved product
Peramivir must be administered intravenously**

The Secretary of the Department of Health and Human Services (HHS) has declared the rapid and extensive incidence of 2009 H1N1 infection a public health emergency that justifies the emergency use of certain drugs to treat 2009 H1N1 influenza. In response to this emergency, the Food and Drug Administration (FDA) has authorized the use of the unapproved drug, Peramivir IV, to treat certain adult and pediatric patients with suspected or laboratory confirmed 2009 H1N1 infection or infection due to nonsubtypable influenza A virus suspected to be 2009 H1N1 based on community epidemiology.

Do not use Peramivir IV for the treatment of seasonal influenza A or B virus infections, for outpatients with acute uncomplicated 2009 H1N1 virus infection or for pre- or post-exposure chemoprophylaxis (prevention) of influenza.

The prescribing health care provider and/or their designee is/are responsible for mandatory FDA MedWatch reporting of all medication errors and selected adverse events occurring during Peramivir IV treatment within 7 calendar days from the onset of the event. **See the Adverse Reactions and Medication Errors section below for details on the required FDA MedWatch reporting.**

To request Peramivir IV under Emergency Use Authorization (EUA) go to:
www.cdc.gov/h1n1flu/eua.

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**Drug Safety Notice: NATIONAL PBM COMMUNICATION
Leukotriene Inhibitors and Neuropsychiatric Events
June 15, 2009**

In April 2009, the Food and Drug Administration (FDA) reviewed post-marketing reports and clinical trial data on mood and behavioral changes associated with the use of leukotriene inhibitors. Neuropsychiatric events reported in patients taking montelukast (Singulair), zafirlukast (Accolate), and zileuton (Zyflo and Zyflo CR) include: agitation, aggression, anxiousness, dream abnormalities and hallucinations, depression, insomnia, irritability, restlessness, tremor, and suicidal thinking and behavior (including suicide). FDA has requested that manufacturers revise the drug prescribing information to include a precaution addressing the above events. Limited literature exists regarding suicidality and leukotriene inhibitors. One study reviewed available reports of suicidality and treatment of allergy with leukotriene inhibitors and found insufficient data associating montelukast with suicidality. Another population-based cohort study showed no cases of suicide in patients receiving montelukast during the study time period. 23,500 patients received over 250,000 montelukast prescriptions from February 1998 –March 2007. No cases of suicide were identified.



FDA recommends:

Patients and healthcare professionals should be aware of the potential for neuropsychiatric events with these medications.

Patients should talk with their healthcare providers if these events occur.

Healthcare professionals should consider discontinuing these medications if patients develop neuropsychiatric symptoms.

VA Center for Medication Safety (VAMedSAFE) will monitor and analyze reports of adverse events with leukotriene inhibitors to better characterize the adverse event profile in the veteran population.

References:

FDA. <http://www.fda.gov/Drugs/DrugSafety/postmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm165489.htm>. (Accessed June 12, 2009).

Manalai P, Woo JM, Postolache TT. Suicidality and montelukast. *Expert Opin Drug Saf.* 2009 May; 8(3):273-282.

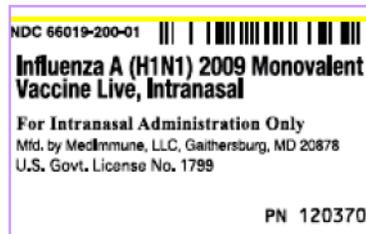
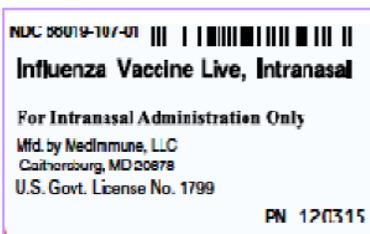
Jick H, Hagberg KW, Egger P. Rate of suicide in patients taking montelukast. *Pharmacotherapy.* 2009 Feb; 29(2):165-166.

Look-alike Influenza Vaccines: Live Attenuated Intranasal Vaccines Similar for Novel H1N1 and Seasonal Influenza Manufactured by MedImmune, Inc.



Read labels carefully and verify which vaccine you are administering!

The labels on the boxes as well as syringes are similar.



Note: This includes only the live intranasal influenza vaccines.

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Continued from page 1: Drug Review: Antivirals

been shown to yield higher concentrations in respiratory secretions, and for this reason may be up to 8 times more active in the treatment of influenza. Dose adjustments are not required with rimantadine in mild or moderate renal impairment due to having primarily hepatic metabolism, whereas 80-90% of amantadine is renally excreted and does require a reduction in dose in these patients. Amantadine also has the propensity to cause more central nervous system side effects than rimantadine, and should be used with caution in elderly patients. Interestingly, amantadine is also indicated for the treatment of Parkinson's disease, which is mostly derived from the medication's dopaminergic activity. Unfortunately, this unique action also causes unwanted effects, such as agitation, confusion, delirium, dizziness, somnolence and nausea.

Unlike the adamantanes, the neuraminidase inhibitors may be used for the treatment and prophylaxis of both influenza A and B. These agents are most beneficial when initiated within 48 hours of symptom onset, but can be started after this window depending on individual patients' clinical severity and the time of presentation. There are several differences that set the neuraminidase inhibitors apart. Oseltamivir is available as an oral capsule or suspension, whereas zanamivir is only available as an inhaler. The manufacturer of zanamivir cautions against using this drug in patients with chronic obstructive pulmonary disease (COPD) or asthma due to the ability of the drug to cause bronchospasm. If no alternative to zanamivir is available, close monitoring of respiratory function is required, and a rescue inhaler should be readily accessible. The dose of zanamivir varies depending on the indication. A typical treatment dose for seasonal influenza is 2 inhalations twice daily; whereas the dose used for prophylaxis is 2 inhalations once daily. Prophylaxis dosing of oseltamivir is 75 mg once daily; when treatment is required, 75 mg twice daily for 5 days is recommended. Dose adjustments are required for oseltamivir use in patients with a creatinine clearance less than 30 mL/min due to the drug's renal elimination. Nausea is the most common side effect of oseltamivir. Although some strains of seasonal influenza are susceptible to oseltamivir, resistance has been as high as 97% in late 2008 and early 2009.

This influenza season, the prevention, diagnosis, and treatment of a novel strain of influenza A, known as the H1N1 "swine" flu has been a priority. This virus is composed of a unique combination of genes from swine, avian, and human sources. As recommended by the CDC, treatment should be initiated in patients presenting with suspected or confirmed novel H1N1 influenza if they have comorbidities placing them at increased risk for complications. In otherwise healthy patients, treatment can be considered if the patient presents within 48 hours of symptom onset. Hospitalized patients with suspected novel H1N1 influenza should receive treatment regardless of symptom onset, as some benefit may be recognized in this subset. The current agents of choice for the virus are the neuraminidase inhibitors. It is important to remember that preferred agents are subject to change due to resistance patterns, which vary based on location and year. It is necessary to follow the CDC's recommendations on appropriate prophylaxis and treatment strategies during each influenza season. Despite the availability of pharmacological treatment options available for influenza, we should not forget the age old adage, an ounce of prevention is worth a pound of cure.

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2. Lacy CF, Armstrong LL, Goldman MP, Lance LL. Drug Information Handbook, 17th ed. Hudson (OH): Lexi-Comp Inc.; 2008.
3. CDC. Updated Interim Recommendations for the Use of Antiviral Medications in the Treatment and Prevention of Influenza for the 2009-2010 Season [Internet]. Atlanta: Centers for Disease Control and Prevention; 2009 Dec 07 [cited 2009 Dec 31]. Available from: <http://www.cdc.gov/H1N1flu/recommendations.htm>.
4. CDC. Flu View: Influenza Season, Week 39 ending October 3, 2009 [Internet]. Atlanta: Centers for Disease Control and Prevention; 2009 Oct 09 [cited 2009 Dec 31]. Available from: <http://www.cdc.gov/flu/weekly/weeklyarchives2008-2009/weekly39.htm>.



Goodbye, Marketa!
We'll Miss You!

