Antiviral Drugs for Seasonal Influenza 2014-2015

Antiviral drugs can be used for treatment of influenza and as an adjunct to influenza vaccination1 for prophylaxis. Frequently updated information on influenza activity and antiviral resistance is available from the CDC at www.cdc.gov/flu.

NEURAMINIDASE INHIBITORS — Oseltamivir (Tamiflu), which is taken orally, and zanamivir (Relenza), which is inhaled, can be used for chemoprophylaxis and treatment of influenza. When used for prophylaxis after exposure to susceptible strains of seasonal influenza A or B viruses, they have generally been about 70-90% effective.2

In patients with mild illness caused by a susceptible strain of influenza, starting treatment with a neuraminidase inhibitor within 48 hours after the onset of illness can decrease the duration of fever and symptoms and may also reduce the risk of complications such as pneumonia.3 In hospitalized and critically ill patients, observational studies indicate that these drugs can decrease the risk of death when started soon after symptom onset; the results of some studies suggest that treatment within 4-5 days after symptoms appear may still have some benefit.4 The usual duration of treatment with a neuraminidase inhibitor is 5 days, but a prolonged treatment course (e.g., 10 days) is often used for critically ill or immunocompromised patients, in whom viral replication may be protracted.

Resistance to oseltamivir can occur,7 especially in immunocompromised patients with prolonged viral shedding, but recently almost all of the circulating influenza A and B viruses tested by the CDC and the World Health Organization have been susceptible to both oseltamivir and zanamivir. The rare oseltamivir-resistant isolates have remained susceptible to zanamivir.

In critically ill patients, oseltamivir capsules can be opened and dissolved in water and given by nasogastric tube.8 An IV formulation of zanamivir is available for hospitalized patients with severe influenza under an

Table 1. Antiviral Drugs for Seasonal Influenza

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulations</th>
<th>Adult Dosage</th>
<th>Pediatric Dosage</th>
<th>Cost1</th>
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</thead>
<tbody>
<tr>
<td>Oseltamivir – Tamiflu (Genentech)</td>
<td>30, 45, 75 mg caps; 6 mg/mL oral suspension</td>
<td>Prophylaxis: 75 mg PO once/d1 Treatment: 75 mg PO bid x 5d,7</td>
<td>Prophylaxis: 30-75 mg PO once/d4 Treatment: 30-75 mg PO bid x 5d4</td>
<td>$120.60</td>
</tr>
<tr>
<td>Peramivir – Rapivab (BioCryst)</td>
<td>200 mg/20 mL single-use vials</td>
<td>Prophylaxis: Not approved Treatment: 600 mg IV once4</td>
<td>Prophylaxis: Not approved Treatment: Not approved</td>
<td>$950.00</td>
</tr>
<tr>
<td>Zanamivir – Relenza11(GSK)</td>
<td>5 mg/blister for inhalation11</td>
<td>Prophylaxis:2 2 inhalations once/d Treatment: 2 inhalations bid x 5d</td>
<td>Prophylaxis:2 ≥5 yrs: 2 inhalations once/d Treatment:2 ≥7 yrs: 2 inhalations bid x 5d</td>
<td>$59.00</td>
</tr>
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</table>

1. Approximate WAC for 5 days’ treatment at adult dosage. WAC = wholesaler acquisition cost or manufacturer’s published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. November 5, 2014. Reprinted with permission by First Databank, Inc. All rights reserved. ©2014. www.fdbhealth.com/policies/drug-pricing-policy.
2. For post-exposure prophylaxis in households, a 10-day course is recommended. For prophylaxis of exposures in institutions, the drug should be taken for at least 2 weeks and continued for 1 week after the end of the outbreak. For prophylaxis during community outbreaks, oseltamivir has been shown to be effective and safe when taken for up to 42 days, and zanamivir for up to 28 days. Some expert clinicians would use twice-daily therapeutic doses for post-exposure prophylaxis in highly immunocompromised persons.
3. Dosage for patients with CrCl ≥30-60 mL/min: 30 mg every other day; end-stage renal disease on hemodialysis (HD): 30 mg after every other HD; continuous ambulatory peritoneal dialysis (CAPD): 30 mg once/wk immediately following exchange.
4. For children ≥1 year old: ≥15 kg: 30 mg; 15.1-23 kg: 45 mg; 23.1-40 kg: 60 mg; ≥40.1 kg: 75 mg. The FDA-approved dose for treatment of infants ≥2 weeks to less than 1 year old is 3 mg/kg bid. Although not FDA-approved for prophylaxis for children <1 year, the ACIP and CDC recommend that children 3-11 months old receive 3 mg/kg once/day.
5. In adults with pneumonia or severe lower respiratory tract disease, some expert clinicians recommend 150 mg bid x 10 days for treatment (off-label).
6. Approximate WAC for 3 single-use vials.
7. Not recommended for use in patients with underlying respiratory disease such as asthma or COPD.
8. Available in a carton containing 5 rotadisks (each rotadisk contains four 5-mg blisters of the active drug in a lactose carrier) and a Diskhaler inhalation device. Zanamivir should not be used in a nebulizer.
emergency investigational new drug request to the manufacturer (GSK: 1-877-626-8019); it has been used successfully to treat some severely ill patients with proven or suspected oseltamivir resistance.9

**Peramivir** (BioCryst), an investigational IV neuraminidase inhibitor that was available under an emergency use authorization during the 2009-2010 influenza season, has been approved by the FDA for treatment of influenza. A review of peramivir will appear in our February 2, 2015 issue.

**Adverse Effects** – Nausea, vomiting, and headache are the most common adverse effects of oseltamivir; taking the drug with food may improve its gastrointestinal tolerability. Neuropsychiatric events including self-injury and delirium have occurred in some patients taking neuraminidase inhibitors, particularly children treated with oseltamivir.10 Bronchospasm can occur with inhaled zanamivir; the drug should not be used in patients with underlying airway disease.

Neuraminidase inhibitors administered within 48 hours before or <2 weeks after administration of the intranasal live-attenuated influenza vaccine (Flumist Quadrivalent) may interfere with the vaccine’s efficacy. Inactivated influenza vaccine can be given at any time relative to use of a neuraminidase inhibitor.

**ADAMANTANES** – Amantadine and rimantadine (Flumadine, and generics) have activity against some influenza A viruses, but not against influenza B viruses. They have not been active against most circulating influenza A viruses in recent years and are currently not recommended for treatment or chemoprophylaxis of influenza.

**INDICATIONS FOR TREATMENT** – Antiviral treatment is recommended as soon as possible for patients with suspected influenza who are at high risk for complications, including children <2 years old, persons <19 years old receiving long-term aspirin therapy, adults ≥65 years old, morbidly obese patients (BMI ≥40), women who are pregnant or ≤2 weeks postpartum, persons of American Indian/Alaska Native heritage, residents of nursing homes and other chronic care facilities, and persons of any age who have certain chronic medical conditions or are immunosuppressed. Treatment is also recommended for patients with suspected or confirmed influenza who show signs of clinical deterioration, develop symptoms of lower respiratory tract infection, or require hospitalization. Antiviral treatment could be considered for previously healthy persons with uncomplicated influenza if it can be started within 48 hours of symptom onset.11

**INDICATIONS FOR PROPHYLAXIS** – Chemoprophylaxis with antiviral drugs is not recommended for healthy persons exposed to influenza. It can be considered after exposure for persons at high risk of complications who are unvaccinated or unlikely to respond to vaccination or who have received the influenza vaccine within the last 2 weeks, for unvaccinated healthcare workers who are exposed to influenza, and to help control outbreaks in nursing homes. When indicated, chemoprophylaxis should be started within 48 hours after exposure to the virus.

**PREGNANCY** – Pregnant women are at high risk for complications of influenza, including death.12 Even though oseltamivir and zanamivir are both classified as category C (some fetal toxicity in animals; no adequate studies in pregnant women) for use during pregnancy, prompt treatment with one of these antiviral medications is recommended. Chemoprophylaxis can be considered for women who are pregnant or ≤2 weeks postpartum who have had close contact with someone likely to have been infected with influenza. Oseltamivir appears to be safe for use during pregnancy.13

**CONCLUSION** – Chemoprophylaxis with antiviral drugs is not recommended for healthy persons exposed to influenza. A neuraminidase inhibitor, either oseltamivir (Tamiflu) or zanamivir (Relenza), remains the drug of choice for treatment of patients with influenza. Oseltamivir is preferred for use in pregnant women and in patients with underlying airway disease.

9. AH Gaur et al. Intravenous zanamivir for oseltamivir-resistant