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Antiviral Drugs for Treatment and Prophylaxis of Seasonal Influenza

Antiviral drugs can be used for treatment and prophylaxis of seasonal influenza (see Table 1). Frequently updated information on influenza activity, influenza testing, and antiviral resistance is available from the CDC at www.cdc.gov/flu.

ANTIVIRAL DRUGS — The neuraminidase inhibitors oseltamivir (Tamiflu, and generics), which is taken orally, and zanamivir (Relenza), which is inhaled, are FDA-approved for prophylaxis and treatment of acute uncomplicated influenza. The IV neuraminidase inhibitor peramivir (Rapivab) and the oral polymerase acidic (PA) endonuclease inhibitor baloxavir marboxil (Xofluza) are FDA-approved only for treatment of acute uncomplicated influenza. The neuraminidase inhibitors and baloxavir are active against both influenza A and B viruses.

TREATMENT — The CDC recommends antiviral treatment as soon as possible after illness onset for all people with suspected or confirmed influenza infection who have severe, complicated, or progressive illness, require hospitalization, or are at higher risk for complications, including children <5 years old (children ≤2 years old are at highest risk), people ≤19 years old receiving long-term aspirin therapy, adults ≥65 years old, extremely obese people (BMI ≥40), women who are pregnant or ≤2 weeks postpartum, people of American Indian or Alaska Native heritage, residents of nursing homes or other chronic care facilities, and people who are immunosuppressed or have chronic medical conditions (including pulmonary, cardiovascular, renal, hepatic, hematologic, metabolic, neurologic, or neurodevelopmental disorders).

In previously healthy people with suspected or confirmed influenza who are not at high risk for complications, antiviral treatment can be considered if it can be started within 48 hours of illness onset.

For treatment of outpatients with acute uncomplicated influenza, the CDC recommends treatment with oseltamivir, zanamivir, peramivir, or baloxavir. There are no data that suggests superiority of one drug over another in such patients; choice of drug should be based on patient characteristics (e.g., comorbidities, pregnancy), dosing schedule, adverse effects, and cost. Oseltamivir is preferred for treatment of hospitalized patients and outpatients with severe, complicated, or progressive influenza illness (off-label use).

Because false negative results can occur with some influenza tests, patients with severe or complicated illness and those at higher risk for complications should be treated with an antiviral drug despite a negative test result, especially when influenza is known to be circulating in the community.

CHEMOPROPHYLAXIS — Antiviral prophylaxis is recommended to help control institutional influenza outbreaks, and can be considered after exposure for people at high risk for complications who have not received the influenza vaccine this season, received it within the previous 2 weeks, or are unlikely to have responded to vaccination, such as those who are immunosuppressed. It is not recommended for healthy people exposed to influenza or if >48 hours have elapsed since exposure.

EFFECTIVENESS — Treatment — Use of neuraminidase inhibitors for treatment of uncomplicated influenza shortens the duration of symptoms by about one day.
Table 1. Antiviral Drugs for Seasonal Influenza

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulations</th>
<th>Usual Treatment Dosage</th>
<th>Usual Prophylaxis Dosage</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuraminidase Inhibitors</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Oseltamivir (generic)</td>
<td>30, 45, 75 mg caps; 6 mg/mL oral susp</td>
<td>&lt;1 yr: 3 mg/kg PO bid^6 x 5 d'</td>
<td>&lt;1 yr: 3 mg/kg PO once/d^6 x 7 d'^10</td>
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<tr>
<td>(Genentech)</td>
<td></td>
<td>1-12 yrs: 30-75 mg PO bid^6 x 5 d'</td>
<td>1-12 yrs: 30-75 mg PO once/d^6 x 7 d'^10</td>
<td>$93.30</td>
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<tr>
<td></td>
<td></td>
<td>≥13 yrs: 75 mg PO bid^6 x 5 d'</td>
<td>≥13 yrs: 75 mg PO once/d^6 x 7 d'^10</td>
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<tr>
<td></td>
<td>Renal Impairment: See footnote 12</td>
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<tr>
<td>Tamiflu (Genentech)</td>
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<tr>
<td></td>
<td>200 mg/20 mL single-use vials</td>
<td>2-12 yrs: 12 mg/kg (max 600 mg) IV once^7,14</td>
<td>Not FDA-approved for prophylaxis</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>≥13 yrs: 600 mg IV once^7,14</td>
<td></td>
<td>950.00</td>
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<tr>
<td></td>
<td>Renal Impairment: See footnote 15</td>
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<tr>
<td>Zanamivir^16-18 – Relenza</td>
<td>5 mg/blisters of powder for inhalation^17</td>
<td>≥7 yrs: 2 inhalations bid x 5 d</td>
<td>≥5 yrs: 2 inhalations once/d x 7 d'^13</td>
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<tr>
<td>(GSK)</td>
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<tr>
<td>Polymeric Acidic (PA) Endonuclease Inhibitor</td>
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<tr>
<td>Baloxavir marboxil^13 – Xofluza</td>
<td>20, 40 mg tabs in 2-tablet blister packs</td>
<td>≥12 yrs and &lt;80 kg: 40 mg PO once^18</td>
<td>Not FDA-approved for prophylaxis</td>
<td></td>
</tr>
<tr>
<td>(Shionogi/Genentech)</td>
<td></td>
<td>≥12 yrs and ≥80 kg: 80 mg PO once^18</td>
<td></td>
<td>150.00</td>
</tr>
</tbody>
</table>

1. Use of amantadine or rimantadine is not recommended because of high levels of resistance to these drugs among currently circulating influenza A viruses; they are not active against influenza B viruses.

2. Approximate WAC for 5 days’ treatment with oseltamivir capsules or zanamivir, or for a single treatment dose of peramivir or baloxavir, at the usual adult dosage. WAC = wholesaler acquisition cost, or manufacturer’s published price to wholesalers; WAC represents published catalogue or list prices and may not represent an actual transactional price. Source: AnalySource® Monthly. December 5, 2018. Reprinted with permission by First Databank, Inc. All rights reserved. ©2018. www.fdbhealth.com/policies/drug-pricing-policy.


4. Capsules can be opened and the contents mixed in a thickened liquid (e.g., chocolate syrup, corn syrup, caramel topping, or brown sugar dissolved in water) to mask the bitter taste and consumed immediately.

5. Although not FDA-approved for use in children <2 weeks old, the CDC recommends children <2 weeks old be treated with 3 mg/kg bid. The American Academy of Pediatrics has recommended a dose of 3.5 mg/kg for infants 9-11 months old based on the results of a study showing that a higher dose was needed to achieve the target exposure in this age group (DW Kimberlin et al. J Infect Dis 2013; 207:709). For treatment of premature infants, refer to CDC recommendations at: www.cdc.gov/flu.

6. Taking oseltamivir with food may improve tolerability.

7. In hospitalized, critically ill, or immunocompromised patients, a longer treatment course of oseltamivir (e.g., 10 days) is often used. Oseltamivir can be administered by oro/nasogastric tube to patients who are unable to swallow. IV peramivir (for at least 5 days) may be considered for those who cannot tolerate oral or enterically administered oseltamivir because of gastric stasis, malabsorption, or GI bleeding.

8. Although not FDA-approved for prophylaxis in children <1 year old, the Advisory Committee on Immunization Practices (ACIP) and CDC recommend that children 3 months–<1 year old receive 3 mg/kg once/day. Prophylaxis is generally not recommended for premature infants or infants <3 months old (refer to CDC recommendations at: www.cdc.gov/flu).

9. Duration of prophylaxis recommended by the CDC is 7 days after the last known exposure. The recommended duration in the labeling of oseltamivir and zanamivir is 10 days.

10. For control of outbreaks in institutions, the CDC recommends prophylaxis be given for at least 2 weeks and continued for 1 week after the end of the outbreak. Some experts would use twice-daily therapeutic doses for post-exposure prophylaxis in highly immunocompromised patients.

11. FDA-approved doses for children 1-12 years old: ≤15 kg: 30 mg; ≤15-23 kg: 45 mg; ≤23-40 kg: 60 mg; >40 kg: 75 mg.

12. Oseltamivir renal dosage adjustment for adults and children who weigh >40 kg (recommended by the CDC); CrCl >30-60 mL/min: 30 mg bid for treatment and 30 mg once/day for prophylaxis; CrCl 10-30 mL/min: 30 mg once/day for treatment and 30 mg every other day for prophylaxis; hemodialysis (HD): 30 mg after every HD for treatment (may be started immediately if influenza symptoms develop between HD sessions) and 30 mg after every other HD for prophylaxis (initial dose can be given before start of HD); continuous ambulatory peritoneal dialysis (CAPD): 30 mg once after exchange for treatment and 30 mg once/week after exchange for prophylaxis; end-stage renal disease (ESRD) not on HD: not recommended for treatment or prophylaxis.


15. Peramivir renal dosage adjustment for patients 2-12 years old: CrCl 30-49 mL/min: 4 mg/kg once; CrCl 10-29 mL/min: 2 mg/kg once. For patients ≥13 years old: CrCl 30-49 mL/min: 200 mg once; CrCl 10-29 mL/min: 100 mg once; hemodialysis (HD): administer dose (based on CrCl) after HD.

16. Inhaled zanamivir is not recommended for use in patients with underlying respiratory disease such as asthma or COPD, or in patients with severe influenza, including hospitalized patients. It is contraindicated in patients with a history of milk protein allergy.

17. 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.

18. Coadministration of dairy products, calcium-fortified beverages, or products containing polyvalent cations such as calcium, aluminum, iron, magnesium, selenium, or zinc should be avoided.

day in adults. A meta-analysis of randomized trials in children with influenza found that treatment with oseltamivir within 48 hours of symptom onset reduced illness duration by about 18 hours (by 30 hours when trials that enrolled only children with asthma were excluded from the analysis) and reduced the risk of developing otitis media. Although most controlled trials of these drugs have not been powered to assess their efficacy in preventing serious influenza complications, experts have generally interpreted the combined results of controlled trials, observational studies, and meta-analyses as showing that early antiviral treatment of influenza in high-risk patients can reduce the risk of complications.

In clinical trials in otherwise healthy outpatients ≥12 years old with uncomplicated influenza, administration of baloxavir within 48 hours of symptom onset shortened the duration of influenza symptoms by about one day compared to placebo; the time to alleviation of symptoms was about the same with baloxavir and oseltamivir. Similar results
were reported in a trial of patients at higher risk for influenza complications.14

**Prophylaxis** – Neuraminidase inhibitors have generally been about 70-90% effective when used for prophylaxis against susceptible strains of seasonal influenza A or B viruses.3

**TIMING – Treatment** – Neuraminidase inhibitors are most effective when started within 48 hours of illness onset, but the results of some observational studies in hospitalized and critically ill patients suggest that treatment started as late as 4-5 days after illness onset can reduce the risk of complications such as pneumonia, respiratory failure, and death.15-17 Baloxavir should also be given within 48 hours of symptom onset; there are no data on the efficacy of baloxavir started >48 hours after symptom onset. In clinical trials, the time to alleviation of symptoms was shorter in patients who started baloxavir within 24 hours of symptom onset than in those who started it later.13

**Prophylaxis** – When indicated, prophylaxis with oseltamivir or zanamivir should be started within 48 hours after exposure to the influenza virus and continued for 7 days after the last known exposure. Longer durations of prophylaxis are often recommended for institutional and community outbreaks (see Table 1).

**PREGNANCY** – Pregnant women are at increased risk for severe complications of influenza, including death. Oseltamivir and zanamivir appear to be safe for use during pregnancy.18,19 Prompt treatment, preferably with oseltamivir, is recommended for women with suspected or confirmed influenza who are pregnant or ≤2 weeks postpartum.20-22

Antiviral prophylaxis can be considered for pregnant women who have had close contact with someone likely to have been infected with influenza. Zanamivir may be preferred for prophylaxis because of its limited systemic absorption, but oseltamivir is a reasonable alternative, especially for women at increased risk for respiratory problems.

**LACTATION** – Oseltamivir, which is poorly excreted in breast milk, is preferred for treatment of women who are breastfeeding.

**RESISTANCE** – Nearly all (≥99%) of the recently circulating influenza virus strains tested by World Health Organization have been susceptible to neuraminidase inhibitors.23 Reduced susceptibility of some influenza strains (particularly influenza A [H1N1]) to oseltamivir or peramivir can emerge sporadically or during or after treatment, especially in immunocompromised patients with prolonged viral shedding.24,25 Resistant isolates have generally remained susceptible to zanamivir, but reduced susceptibility to zanamivir has also been reported.26,27

**Baloxavir** is active against neuraminidase inhibitor-resistant strains of influenza, including A(H1N1), A(H5N1), A(H3N2), and B viruses. Amino acid substitutions associated with reduced susceptibility to baloxavir have occurred following treatment with a single dose (in 9.7% of patients in one trial).13 Oseltamivir may be active against influenza strains with reduced susceptibility to baloxavir.

**ADVERSE EFFECTS** – Nausea, vomiting, and headache are the most common adverse effects of oseltamivir; taking the drug with food may minimize GI adverse effects. Diarrhea, nausea, sinusitis, fever, and arthralgia have been reported with zanamivir. Inhalation of zanamivir can cause bronchospasm; the drug should not be used in patients with underlying airway disease. Diarrhea and neutropenia have occurred with peramivir.

Neuropsychiatric events, including self-injury and delirium, have been reported in patients taking neuraminidase inhibitors, but a causal relationship has not been established, and neuropsychiatric dysfunction is a complication of influenza illness itself.28

**Baloxavir** was well tolerated in clinical trials. It appears to cause less nausea and vomiting than oseltamivir.2

**DRUG INTERACTIONS** – Use of a neuraminidase inhibitor or baloxavir within 48 hours before or <2 weeks after administration of the intranasal live-attenuated influenza vaccine (FluMist Quadrivalent) could inhibit replication of the vaccine virus, reducing the vaccine’s efficacy.

Coadministration of antacids, laxatives, multivitamins, or other products containing polyvalent cations such as calcium, aluminum, iron, magnesium, selenium, or zinc can reduce serum concentrations of baloxavir and should be avoided.

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