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Antiviral Drugs for Seasonal Influenza for 2024-2025

Influenza is generally a self-limited illness, but pneumonia, respiratory failure, and death can occur, especially in persons at increased risk for influenza complications (see Table 1). Updated information on influenza activity and antiviral resistance is available from the CDC at cdc.gov/flu.

TREATMENT OF INFLUENZA — Three neuraminidase inhibitors (oral oseltamivir, IV peramivir, and inhaled zanamivir) and the oral cap-dependent endonuclease inhibitor baloxavir marboxil are available in the US for treatment of influenza this season (see Table 2).

Antiviral treatment is recommended as soon as possible for any patient with suspected or confirmed influenza who is hospitalized, has severe, complicated, or progressive illness, or is at increased risk for complications (see Table 1), even if it is started >48 hours after illness onset.[1-3] False-negative results can occur with influenza tests; patients with suspected influenza in the aforementioned groups should receive antiviral treatment despite a negative test, especially when influenza viruses are known to be circulating in the community.[4]

Antiviral treatment can be considered for otherwise healthy symptomatic outpatients with suspected or confirmed influenza who are not at increased risk for influenza complications if it can be started within 48 hours after illness onset.

Table 1: Persons at Increased Risk for Influenza Complications

- Children <5 years old (especially children <2 years old)
- Patients <19 years old receiving long-term treatment with aspirin or salicylate-containing drugs
- Adults ≥65 years old
- Persons with obesity (BMI ≥40 kg/m^2)
- Women who are pregnant or ≤2 weeks postpartum
- Non-Hispanic Black persons, Hispanic or Latino persons, or persons of American Indian or Alaska Native heritage
- Residents of nursing homes or other long-term care facilities
- Patients who are immunosuppressed
- Patients with a chronic medical condition[1]

1. Including asthma, neurologic and neurodevelopmental conditions, stroke, blood disorders, chronic lung disease, endocrine disorders, heart disease, kidney disease, liver disorders, metabolic disorders, and certain disabilities (especially those affecting muscle function or lung function, or causing difficulty coughing, swallowing, or clearing fluids from airways).

Key Points: Antiviral Drugs for Seasonal Influenza

- Influenza antiviral drugs available this season include three neuraminidase inhibitors (oral oseltamivir, IV peramivir, and inhaled zanamivir) and the oral cap-dependent endonuclease inhibitor baloxavir marboxil. They are all active against influenza A and B viruses.
- Antiviral treatment is most effective when started within 48 hours after illness onset.
- Antiviral treatment is recommended for patients with suspected or confirmed influenza who are hospitalized, have severe, complicated, or progressive illness, or are at increased risk for complications, even if it is started more than 48 hours after illness onset.
- Antiviral treatment can be considered for otherwise healthy symptomatic outpatients with suspected or confirmed influenza who are not at increased risk for influenza complications if it can be started within 48 hours after illness onset.
- Oseltamivir is preferred for treatment of children, pregnant women, hospitalized patients, and outpatients with severe, complicated or progressive illness.
- Post-exposure prophylaxis with oseltamivir, zanamivir, or baloxavir should be considered within 48 hours for persons at very high risk of complications who have not received an annual influenza vaccine or when influenza vaccination may be ineffective; it is not recommended for healthy persons exposed to influenza.

Oseltamivir is preferred for treatment of influenza in pregnant women, children, hospitalized patients, and outpatients with severe, complicated, or progressive illness.[1,3]

Guidelines for treatment of community-acquired pneumonia (CAP) recommend antiviral treatment for patients with CAP who test positive for influenza regardless of the duration of illness before diagnosis.[5]

Effectiveness – Neuraminidase inhibitors and baloxavir are active against influenza A and B viruses. Use of a neuraminidase inhibitor or baloxavir for treatment of acute uncomplicated influenza in adults shortens the duration of symptoms by about one day.[6-9] Although most controlled trials of antiviral drugs have not been powered to assess their efficacy in preventing serious influenza complications, experts have generally concluded from the combined results of observational studies, controlled trials, and meta-analyses that early antiviral treatment of influenza in high-risk and hospitalized patients can reduce the risk of complications.[6,10-13]

In a randomized, double-blind trial (CAPSTONE-2) in 2184 **outpatients** ≥12 years old with uncomplicated

influenza who were at high risk of developing complications, the median time to symptom improvement was similar with a single dose of baloxavir or 5 days' treatment with oseltamivir (both started within 48 hours after illness onset) in the overall population and in those infected with influenza A(H3N2), but was statistically significantly shorter with baloxavir in those infected with influenza B (74.6 vs 101.6 hours). Use of either drug was associated with a lower incidence of influenza-related complications and fewer antibiotic prescriptions compared to placebo.[9]

In a randomized, double-blind trial (miniSTONE-2) in 173 otherwise healthy children 1-11 years old with influenza, the median time to symptom improvement was similar with a single dose of baloxavir or 5 days' treatment with oseltamivir (138 vs 150 hours; both started within 48 hours after illness onset).[14]

A meta-analysis of 5 randomized trials in children with influenza found that starting oseltamivir within 48 hours after illness onset reduced illness duration by about 18 hours (by about 30 hours when trials that enrolled children with asthma were excluded) and decreased the risk of otitis media.[15]

In a retrospective cohort study in 542 adults **hospitalized** with laboratory-confirmed influenza, time to defervescence, duration of hospital and intensive care unit stay, and mortality rates were similar with oral oseltamivir and IV peramivir.[16]

In a meta-analysis of 6 randomized controlled trials in hospitalized patients with severe influenza (mean age 36-60 years) treatment with oseltamivir or peramivir was associated with small reductions in the duration of hospitalization compared to placebo or standard care (-1.63 days with oseltamivir and -1.73 days with peramivir).[17]

In an observational cohort study in hospitalized children (with underlying conditions or admitted to the ICU) with laboratory-confirmed influenza, the duration of hospitalization was shorter with antiviral treatment started within 48 hours after illness onset than with no antiviral treatment.[18]

In a randomized, double-blind trial (FLAGSTONE) in 366 patients ≥12 years old hospitalized with severe influenza, the median time to clinical improvement was not statistically significantly different between a **combination** of a neuraminidase inhibitor (primarily oseltamivir) and baloxavir and a neuraminidase inhibitor alone (97.5 vs 100.2 hours).[19]

Timing – Neuraminidase inhibitors are most effective when started within 48 hours after 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 shorten the duration of hospitalization and reduce the risk of pneumonia, respiratory failure, and death.[20-22]

No data are available on the efficacy of baloxavir started >48 hours after illness onset.

In a retrospective cohort study of 23,233 hospitalized adults with laboratory-confirmed influenza and pneumonia, delayed initiation of antiviral treatment was associated with a higher risk of death; compared to patients who started antiviral treatment on day 0, the adjusted odds ratio for death was 1.14 (95% CI 1.01-1.27) in those who started treatment on day 1 and 1.40 (95% CI 1.17-1.66) in those who started on days 2-5.[23]

CHEMOPROPHYLAXIS — Oseltamivir, zanamivir, and baloxavir are FDA-approved for chemoprophylaxis of influenza. Post-exposure prophylaxis should be considered within 48 hours of exposure for persons at very high risk of complications who have not received an annual influenza vaccine for the current season, received one within the previous 2 weeks, or might not respond to vaccination, or when the match between the vaccine and circulating strains is poor. It is not recommended for healthy persons exposed to influenza or when >48 hours have elapsed since exposure.[2]

Antiviral chemoprophylaxis with oral oseltamivir or inhaled zanamivir is recommended by the CDC for control of institutional influenza outbreaks.[1]

Effectiveness – Oseltamivir, zanamivir, and baloxavir have generally been about 70-90% effective in preventing influenza caused by susceptible strains of influenza A or B viruses.[1,24] A meta-analysis of 33 trials found that prompt post-exposure prophylaxis with zanamivir, oseltamivir, or baloxavir can reduce the risk of symptomatic seasonal influenza in patients at high risk for severe disease.[25]

Timing – When indicated, chemoprophylaxis with oseltamivir or zanamivir should be started no later than 48 hours after exposure and continued for 7 days after the last known exposure. A single dose of baloxavir within 48 hours after exposure is also an option.

For institutional influenza outbreaks, the CDC recommends chemoprophylaxis with oral oseltamivir

Table 2. Antiviral Drugs for Seasonal Influenza

Drug/Formulations	Usual Dosage	Comments	Cost[1]
Cap-Dependent Endonuclease Inhibitor			
Baloxavir marboxil – *Xofluza* (Genentech) 40, 80 mg tabs; 40 mg/20 mL oral suspension[2]	**Treatment:** ≥5 yrs and 20-<80 kg: 40 mg PO x 1 dose ≥5 yrs and ≥80 kg: 80 mg PO x 1 dose **Chemoprophylaxis:** ≥5 yrs and 20-<80 kg: 40 mg PO x 1 dose ≥5 yrs and ≥80 kg: 80 mg PO x 1 dose	▸ FDA-approved for treatment of acute uncomplicated influenza in patients ≥5 years old who are otherwise healthy or at high risk of developing influenza-related complications and have been symptomatic for ≤48 hours ▸ FDA-approved for post-exposure prophylaxis in patients ≥5 years old ▸ No data in patients with severe influenza ▸ Not recommended for use in severely immuno-compromised patients or pregnant women ▸ Avoid coadministration of dairy products, calcium-fortified beverages, and products containing polyvalent cations	$164.00
Neuraminidase Inhibitors			
Oseltamivir – generic *Tamiflu* (Genentech) 30, 45, 75 mg caps; 6 mg/mL oral suspension[3]	**Treatment:** ≥2 wks-<1 yr: 3 mg/kg PO bid[4] x 5 days[5] 1-12 yrs: 30-75 mg[6] PO bid x 5 days[5] ≥13 yrs: 75 mg PO bid x 5 days[5] Renal impairment: See footnote 7 **Chemoprophylaxis:** 3 months-<1 yr: 3 mg/kg PO once/day[8] x 7 days[9] 1-12 yrs: 30-75 mg[6] PO once/day x 7 days[9] ≥13 yrs: 75 mg PO once/day x 7 days[9] Renal impairment: See footnote 7	▸ FDA-approved for treatment of acute uncomplicated influenza in patients ≥2 weeks old who have been symptomatic for ≤48 hours ▸ FDA-approved for chemoprophylaxis of influenza in patients ≥1 year old ▸ Preferred for treatment of influenza in pregnant women, children, hospitalized patients, and outpatients with severe, complicated, or progressive illness ▸ Taking oseltamivir with food may improve tolerability ▸ Contents of capsules can be mixed in a thick sweetened liquid to mask the bitter taste	27.00 152.00
Peramivir – *Rapivab* (BioCryst) 200 mg/20 mL single-use vials	**Treatment:** 6 months-12 yrs: 12 mg/kg (max 600 mg) IV over 15-30 minutes once ≥13 yrs: 600 mg IV over 15-30 minutes once Renal impairment: See footnote 10	▸ FDA-approved for treatment of acute uncomplicated influenza in otherwise healthy patients ≥6 months old who have been symptomatic for ≤48 hours ▸ Not recommended for treatment of severe influenza[11] ▸ Not FDA-approved for chemoprophylaxis	950.00
Zanamivir – *Relenza* (GSK) 5 mg blisters of powder for inhalation	**Treatment:** ≥7 yrs: 2 inh bid x 5 days **Chemoprophylaxis:** ≥5 yrs: 2 inh once/day x 7 days[9]	▸ FDA-approved for treatment of acute uncomplicated influenza in patients ≥7 years old who have been symptomatic for ≤48 hours ▸ FDA-approved for chemoprophylaxis of influenza in patients ≥5 years old ▸ Contraindicated in patients with lactose or milk protein allergy ▸ Not recommended for patients with underlying airway disease ▸ Not recommended for treatment of severe influenza	59.00

1. Approximate WAC for 5 days' treatment with oseltamivir capsules or zanamivir, or for a single treatment dose of peramivir or baloxavir marboxil, 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. November 5, 2024. Reprinted with permission by First Databank, Inc. All rights reserved. ©2024. www.fdbhealth.com/policies/drug-pricing-policy.
2. For patients <20 kg, the oral suspension is given as a single 2-mg/kg dose. The suspension must be used within 10 hours after reconstitution.
3. Oseltamivir can be administered by oro/nasogastric tube to patients who are unable to swallow.
4. Although not FDA-approved for use in children <2 weeks old, the CDC recommends that children <2 weeks old receive 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 (www.cdc.gov/flu).
5. In hospitalized, critically ill, or immunocompromised patients, a longer treatment course of oseltamivir (e.g., 10 days) is often used.
6. FDA-approved doses for children 1-12 years old who weigh ≤15 kg: 30 mg; >15-23 kg: 45 mg; >23-40 kg: 60 mg; >40 kg: 75 mg.
7. Oseltamivir renal dosage adjustment for adults and children who weigh >40 kg (recommended by the CDC): CrCl 31-60 mL/min: 30 mg bid for treatment and 30 mg once/day for prophylaxis; CrCl 11-30 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): single 30-mg dose 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.
8. Although not FDA-approved for chemoprophylaxis in children <1 year old, the American Academy of Pediatrics and the CDC recommend that children 3 months-<1 year old receive 3 mg/kg once/day. Chemoprophylaxis is generally not recommended for premature infants or infants <3 months old (refer to CDC recommendations at: www.cdc.gov/flu).
9. Duration of chemoprophylaxis 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 after the last known exposure. For control of outbreaks in institutions, the CDC recommends that chemoprophylaxis be given for at least 2 weeks and continued for up to 1 week after the end of the outbreak. Some experts would use twice-daily therapeutic doses for post-exposure prophylaxis in highly immunocompromised patients.
10. 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.
11. IV peramivir (for at least 5 days) may be considered for hospitalized, critically ill, or immunocompromised patients who cannot tolerate or absorb oral or enterically administered oseltamivir because of gastric stasis, malabsorption, or GI bleeding.

or inhaled zanamivir for at least 2 weeks; prophylaxis should be continued for up to 1 week after the end of the outbreak.

PREGNANCY AND LACTATION — Pregnant and postpartum women are at increased risk for severe complications of influenza. Empiric antiviral **treatment** should be started as soon as possible in those with suspected or confirmed influenza. Oseltamivir and zanamivir appear to be safe for use during pregnancy; insufficient data are available on use of peramivir.[26-29] Oseltamivir is preferred for treatment of pregnant and breastfeeding women.[28-30] Baloxavir is not recommended for treatment of pregnant or breastfeeding women because of a lack of data.[29]

Antiviral **chemoprophylaxis** can be considered for pregnant women and those who are ≤2 weeks postpartum who cannot receive an influenza vaccine or have severe immunodeficiencies or other medical conditions that make them unlikely to respond to influenza vaccination and have had close contact with someone suspected or confirmed to have influenza. Oseltamivir is preferred for post-exposure prophylaxis in such patients.[28,29]

RESISTANCE — Over 99% of recently circulating influenza virus strains tested by the World Health Organization (WHO) have been susceptible to neuraminidase inhibitors.[31] Reduced susceptibility of some influenza virus strains, particularly influenza A(H1N1) viruses, to oseltamivir or peramivir can emerge during or after treatment, especially in young children and immunocompromised patients with prolonged viral shedding.[32-37] Resistant isolates have usually remained susceptible to zanamivir, but reduced susceptibility to the drug has been reported.[38] In immunocompromised patients, a double dose of oseltamivir reduced the incidence of oseltamivir resistance compared to standard dosing, but it did not improve efficacy and caused more adverse effects.[39]

Amino acid substitutions associated with reduced susceptibility to baloxavir have occurred following treatment with a single dose of the drug.[8,40] Reduced susceptibility to baloxavir appears to be more frequent in persons infected with influenza A(H3N2) and A(H1N1)pdm09 viruses, particularly children.[41,42] Baloxavir monotherapy is not recommended for severely immunocompromised patients because of concerns that prolonged viral replication in such patients could lead to emergence of resistance.[1] Oseltamivir and peramivir may be active against influenza virus strains with reduced susceptibility to baloxavir.[43] Baloxavir is active against neura-minidase inhibitor-resistant strains of influenza A and B viruses, including A(H1N1), A(H5N1), A(H3N2), and A(H7N9).

The adamantanes amantadine and rimantadine are active against influenza A viruses, but not influenza B viruses. Resistance to these drugs has been reported in recent years and remains high (>99%) among circulating influenza A(H3N2) and A(H1N1) pdm09 viruses; neither amantadine nor rimantadine is recommended for treatment or chemoprophylaxis of influenza.

ADVERSE EFFECTS — Nausea, vomiting, and headache are the most common adverse effects of **oseltamivir**; taking the drug with food may minimize GI adverse effects. Oseltamivir has been associated with bradycardia in critically ill patients.[44] 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**.[45]

Baloxavir appears to cause less nausea and vomiting than oseltamivir.[46]

Neuropsychiatric events, including self-injury and delirium, have been reported in patients taking neuraminidase inhibitors or baloxavir, but a causal relationship has not been established, and neuro-psychiatric dysfunction can be a complication of influenza itself.[47] Hypersensitivity reactions, includ-ing anaphylaxis, have been reported with all of these drugs.

DRUG INTERACTIONS — Coadministration of dairy products, beverages, antacids, laxatives, multivitamins, or other products containing polyvalent cations (e.g., calcium, aluminum, iron, magnesium, selenium, zinc) can reduce serum concentrations of **baloxavir** and should be avoided.

USE WITH THE LIVE-ATTENUATED VACCINE — Use of oseltamivir or zanamivir within 48 hours before, perami-vir within 5 days before, or baloxavir within 17 days before administration of the live-attenuated intranasal influenza vaccine *(FluMist)* could inhibit replication of the vaccine virus, reducing the vaccine's effectiveness, and is not recommended.[48] Persons who receive any of these antiviral drugs during these specified times or within 2 weeks after receiving the live-attenuated vaccine should be revaccinated with an inactivated or recombinant age-appropriate influenza vaccine.[49] ■

Additional Content Available Online

Comparison Chart: Antiviral Drugs for Seasonal Influenza for 2024-2025
http://medicalletter.org/TML-article-1717d

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