



NEW YORK CITY DEPARTMENT OF
HEALTH AND MENTAL HYGIENE
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Interim Guidance on Dosage, Precautions, and Adverse Effects of Antiviral Medications used to Treat or Prevent Infection with Novel Influenza H1N1

Last Updated 5/11/2009

Novel H1N1 Influenza is an emerging virus and there is an ongoing intensive investigation of its clinical and epidemiologic features. In the United States, most cases of novel influenza H1N1 have been mild.

Providers should monitor the New York City Department of Health and Mental Hygiene (DOHMH) Health Alerts and check www.nyc.gov/health and www.cdc.gov for updates as they become available.

This document specifically addresses dosages, precautions, and adverse effects of antiviral medications for the treatment and prevention of influenza H1N1 (SO). For more information on:

- Case definitions
- Diagnostic testing
- Specimen collection
- Indications for antiviral treatment and prophylaxis
- Infection control
- Reporting , and
- Patient information and educational materials

Please refer to the DOHMH's Novel H1N1 Influenza website at <http://www.nyc.gov/html/doh/html/cd/cd-h1n1flu.shtml#2> and look under the heading, **Information for Health Care Professionals**. Providers can also access the Provider Access Line at 1-866-NYC-DOH1 for specific questions or to report suspected cases.

Treatment

What Antiviral Drugs Should Be Used For Treatment?

- On the basis of antiretroviral susceptibility testing at CDC, Novel H1N1 Influenza virus is currently sensitive to the neuraminidase inhibitors zanamivir (Relenza®) and oseltamivir (Tamiflu®). It is resistant to the adamantanes, amantadine and rimantadine.

- Novel H1N1 Influenza infection should be treated with either oseltamivir or zanamivir. Recommendations may change as more information on effectiveness or adverse events becomes available, or if the virus develops new patterns of antiviral resistance.

Who Should Be Treated with Antiviral Medications?

- Since the outbreak is still ongoing, please consult the NYC DOHMH website for the latest health alert for recommendations on whom to treat.
- Please see the NYC DOHMH website Information for Providers at <http://www.nyc.gov/html/doh/html/cd/cd-h1n1flu.shtml#2> for the latest recommendations. Best practices for clinical management of influenza and influenza-like illness can also be found at in the IDSA guidelines at <http://www.journals.uchicago.edu/doi/full/10.1086/598513>.

When to Start Treatment?

- Treatment is most effective when started early in the course of illness, and ideally should be initiated within 48 hours after symptom onset.
- Studies have shown modest benefit in hospitalized patients even when antiviral medications are started later in the course of illness. The Food and Drug Administration issued an emergency use authorization (EUA) permitting the use of antiviral medications even when initiated at later times in the illness. Particularly for patients with severe illness or substantial underlying comorbidities, DOHMH recommends starting antiviral treatment even if initiated more than 48 hours after illness onset.

Medications

- The recommended duration of treatment is 5 days for either oseltamivir or zanamivir. The two antivirals should NOT be given together.
- Oseltamivir can be used in persons of all ages. The FDA has authorized its use for infants under its EUA. It is available in capsules and oral suspension.
 - For dosages and frequency of administration, see the tables at the end of this document.
 - Consult the FDA website at http://www.fda.gov/cder/drug/antivirals/influenza/Tamiflu/EUA_Tamiflu_FS%20HCP_4%2027%2009%20final.pdf for more information.
- Zanamivir should only be used in persons aged 7 years and older. It is administered by oral inhalation via a special delivery device.
 - For dosages and frequency of administration, see the tables at the end of this document.
 - Consult the FDA website at [http://www.fda.gov/cder/drug/antivirals/influenza/Relenza/EUA_Zanamivir_FS%20HCP_CDCrev_27Apr09%20\(2\)%20\(3\).pdf](http://www.fda.gov/cder/drug/antivirals/influenza/Relenza/EUA_Zanamivir_FS%20HCP_CDCrev_27Apr09%20(2)%20(3).pdf) for more information.

What Additional Therapy Should Be Considered?

- Additional therapy such as antibacterial agents should be used at the discretion of the clinician depending on the patient's clinical presentation and course of illness (e.g., development of secondary bacterial pneumonia). Agents active against *Streptococcus pneumoniae* and methicillin-resistant *Staphylococcus aureus* should be chosen if empiric antibacterial therapy is started.
- Providers should administer pneumococcal vaccine to patients who meet current vaccine indication as outlined in the ACIP guidelines at <http://www.cdc.gov/vaccines/recs/provisional/downloads/pneumo-Oct-2008-508.pdf> and <http://www.cdc.gov/mmwr/preview/mmwrhtml/00047135.htm> .
- According to the CDC, the 2008-9 seasonal influenza vaccine probably does not provide protection against Novel H1N1 Influenza virus. However, seasonal influenza is still circulating (outbreaks in previous years have even occurred in late May or early June), so for individuals with indications for influenza vaccine who have not been vaccinated this season, providers should still offer the annual influenza vaccine.

Oseltamivir Supplies

- The possible increased demand for oseltamivir may lead to occasional shortages, and anecdotal reports suggest that the local supply may be unevenly distributed. However, wholesale suppliers report plenty of antiviral medications in stock, and patients and hospitals should be able to locate medicines through normal commercial routes. If hospitals have shortages of antiviral medications, they should call their usual suppliers.
- While there is a national and state stockpile of oseltamivir, it is not currently available for use by the public and is reserved for use during a severe pandemic. We are **urging providers to use prudent clinical judgment** when evaluating patients and deciding if antiviral treatment or prophylaxis is indicated. Generally, previously healthy individuals between the ages of 5 and 65 years of age who present with mild signs and symptoms do not require treatment with antiviral medication for influenza.

Do Not Prescribe Personal Stockpiles of Antivirals

Personal stockpiling of antivirals (e.g., oseltamivir) for use during a pandemic is not recommended. Physicians are advised not to write prescriptions for oseltamivir for their patients to stockpile now in the event of a future pandemic due to novel H1N1 or other viruses for the following reasons:

- Efficacy of antivirals for a future pandemic strain is unknown at this time.
- Inappropriate or inconsistent use of antivirals may increase the risk of drug resistance.
- Use of antivirals without the guidance of a physician may increase the risk of adverse effects or drug interactions.
- Poorly timed and/or inappropriate use of antivirals may leave individuals without medication when they most need it.
- Antivirals have a limited shelf life (< 5 years) and medications may be wasted if they expire before a pandemic.
- Oseltamivir is considered Category C risk for pregnant patients.

Antiviral Chemoprophylaxis

Who Should Receive Chemoprophylaxis to Prevent Novel H1N1 Influenza Virus Infection?

- As this is a newly recognized virus with a still undefined epidemiology, please refer to the relevant NYC DOHMH Health Alert at <http://www.nyc.gov/html/doh/html/cd/cd-h1n1flu.shtml#2> for more detailed recommendations on who should receive prophylaxis.

Children Under 1 Year of Age

- Oseltamivir use for children < 1 year old was recently approved by the U.S. Food and Drug Administration (FDA) under an Emergency Use Authorization (EUA), and dosing for children under 1 year is age- rather than weight-based (Table 2). More detail is available at http://www.fda.gov/cder/drug/antivirals/influenza/Tamiflu/EUA_Tamiflu_FS%20HCP_4%2027%2009%20final.pdf.

Special Considerations for Pregnant Women

- Oseltamivir and zanamavir are Category C agents for use in pregnancy. However, pregnancy also places women at high risk for complications due to influenza.
- Pregnant women who meet the current case-definition for confirmed or probable Novel H1N1 Influenza infection should receive antiviral treatment.
- Pregnant women with influenza-like illness should be tested for influenza before antiviral treatment is considered. However, due to the insensitivity of most rapid tests for influenza, and the risk of severe disease due to influenza in pregnant women, clinical judgment should be used to decide whether to treat pregnant women with influenza-like illness empirically, including when a rapid influenza test is negative.
- Antiviral prophylaxis should be considered for pregnant women who are close contacts of persons with influenza A, including probable or confirmed cases of Novel H1N1 Influenza and seasonal influenza. Obstetricians caring for pregnant women with suspected Novel H1N1 Influenza may wish to consult with an infectious diseases specialist for advice on whether to use prophylactic antiviral medications in individual cases.
- Recommendations for use of antiviral medications for pregnant women might change as additional data on the benefits and risks of antiviral therapy in pregnant women become available. For more information, see the CDC website at http://www.cdc.gov/h1n1flu/clinician_pregnant.htm.

Breastfeeding Considerations

- Women who are breastfeeding should continue to do so while receiving antiviral medications.
- Women who have influenza, including probable or confirmed Novel H1N1 Influenza, should take steps to reduce the risk of transmitting influenza to their infants, such as frequent hand washing. They should consider wearing a surgical mask when close contact with the infant is unavoidable. Information on how to use a surgical mask can be found on the CDC website at http://www.cdc.gov/h1n1flu/general_info.htm.
- Additional information on Novel H1N1 Influenza for breastfeeding patients can be found at <http://www.cdc.gov/h1n1flu/breastfeeding.htm>.

Special Dosage Considerations

Oseltamivir

- For treatment of persons with chronic renal disease, dose adjustment of oseltamivir is recommended for patients with a creatinine clearance between 10 and 30 ml/min. Treatment dose should be reduced to 75 mg once daily for 5 days. No recommended dosing regimens are available for patients undergoing routine hemodialysis or continuous peritoneal dialysis treatment with end-stage renal disease.
- For prophylaxis of persons with chronic renal disease, it is recommended that the dose be reduced to 75 mg of oseltamivir every other day or 30 mg oseltamivir every day. No recommended dosing regimens are available for patients undergoing routine hemodialysis or continuous peritoneal dialysis treatment with end-stage renal disease.
- No dosage adjustment is necessary for persons with mild-moderate liver disease and geriatric patients.

Zanamivir

- The safety and efficacy of zanamivir have not been documented in the presence of severe renal insufficiency. However, due to the low systemic bioavailability of zanamivir following oral inhalation, no dosage adjustments are necessary in patients with renal impairment.

HIV-Infected Adults and Adolescents

- Recommendations for the treatment and chemoprophylaxis of Novel H1N1 Influenza infection in HIV-infected persons are the same ones used for others who are at higher risk of complications from influenza, whether novel H1N1 or seasonal influenza strains.
- There are no known absolute contraindications for co-administration of oseltamivir or zanamivir with currently available antiretroviral medications.

- CDC has issued specific recommendations on novel H1N1 influenza for HIV-infected persons. They can be found at http://www.cdc.gov/h1n1flu/guidance_HIV.htm.

Drug Interactions

Package inserts of the Physician Desk Reference manual/website should be consulted for more information about potential drug interactions.

Oseltamivir

- Limited clinical data are available regarding drug interactions with oseltamivir. Because oseltamivir and oseltamivir carboxylate are excreted in the urine by glomerular filtration and tubular secretion, a potential exists for interaction with other agents excreted by this pathway.

Zanamivir

- Clinical data are limited regarding drug interactions with zanamivir. However, no known drug interactions have been reported, and no clinically critical drug interactions have been predicted on the basis of in vitro and animal study data.
- Package inserts of the Physician Desk Reference manual/website should be consulted for more information about potential drug interactions.

Adverse Events and Overdose

Oseltamivir

- Oseltamivir is generally safe and well-tolerated, and can be safely used in persons with underlying medical conditions and impaired renal function.
- While there have been no reported adverse events of oseltamivir on the fetus when administered to pregnant women, oseltamivir and zanamivir are "Pregnancy Category C" medications, indicating that no clinical studies have been conducted to assess the safety of these medications for pregnant women. Because of the unknown effects of influenza antiviral drugs on pregnant women and their fetuses, oseltamivir or zanamivir should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus.
- Side effects to oseltamivir are infrequently reported, generally mild, and respond to supportive management; they include:
 - Nausea and vomiting, with vomiting most commonly reported in children, and generally during the first 2 days.
 - Delirium and behavioral changes have also been reported, mostly in children, so parents and family members should observe patients receiving oseltamivir closely and report behavioral changes to their doctor.

Zanamivir

- Some patients, especially those with underlying respiratory disorders, may experience bronchospasm or serious breathing problems when using zanamivir.
- Children should take zanamivir under the supervision of an adult.

Overdose

- Overdose of oseltamivir generally results in nausea and/or vomiting.
- Treatment of overdose is supportive; make the patient comfortable, hydrate if indicated, prevent aspiration, and observe carefully.
- To report an overdose or suspected poisoning due to any medication, and for clinical guidance, call the New York City Poison Control Center at 1-212-764-7667 or 1-800-222-1222.

Contraindications

- As with any medication, oseltamivir and zanamivir should not be used in persons with known allergy to oseltamivir phosphate, zanamivir or other ingredients contained in the formulation or in persons with history of previous hypersensitivity reactions.
- Persons with underlying airway disease should use zanamivir with caution.

Additional Resources for Providers

CDC Swine Influenza Page - <http://www.cdc.gov/h1n1flu/>

NYC DOHMH Swine Flu Information - <http://www.nyc.gov/html/doh/html/cd/cd-swineflu.shtml>

New York State Swine Flu Resources -

http://www.nyhealth.gov/diseases/communicable/influenza/seasonal/swine_flu/index.htm

IDSA Clinical Practice Guidelines for Seasonal Influenza -

<http://www.journals.uchicago.edu/doi/full/10.1086/598513>

Table 1: Antiviral Medication Dosing Recommendations for Treatment and Chemoprophylaxis of Novel H1N1 Influenza Virus

Antiviral Agent		Treatment	Chemoprophylaxis
		OSELTAMIVIR*	
Adults		75 mg capsule twice per day for 5 days	75 mg capsule once per day
Children (age, 12 months or older), weight*	15 kg or less¶	30 mg twice per day	30 mg once per day
	15-23 kg	45 mg twice per day	45 mg once per day
	24-40 kg	60 mg twice per day	60 mg once per day
	>40 kg	75 mg twice per day	75 mg once per day
ZANAMIVIR**			
Adults		Two 5 mg inhalations (10 mg total) twice per day	Two 5 mg inhalations (10 mg total) once per day
Children (ZANAMAVIR SHOULD NOT BE GIVEN TO CHILDREN < 7 YEARS OF AGE)		Two 5 mg inhalations (10 mg total) twice per day (age, 7 years or older)	Two 5 mg inhalations (10 mg total) once per day (age, ≥ 5 yrs.)
Duration of Treatment	Treatment	Recommended duration for antiviral treatment is 5 days.	
	Chemoprophylaxis	Recommended duration is 10 days.	
* . For additional recommendations, see the oseltamivir Fact Sheet for Healthcare Providers, available at http://www.cdc.gov/h1n1flu/EUA/pdf/tamiflu-hcp.pdf			
** For additional recommendations, see the Zanamivir Fact Sheet for Healthcare Providers, available at http://www.cdc.gov/h1n1flu/eua/pdf/relenza-hcp.pdf			

Dosing Recommendations for Children Younger than One Year

Table 2: Recommended Daily Dosage of Tamiflu® (Oseltamivir) for Treatment and Chemoprophylaxis of Influenza in Infants Under the Age of 1		
Age	Treatment (x 5 days)	Prophylaxis (x 10 days)
< 3 months	12 mg twice daily	Not recommended unless critical
3-5 months	20 mg twice daily	20 mg once daily
6-11 months	25 mg twice daily	25 mg once daily

