FDA Update on the H1N1 Flu Vaccine and Antiviral Medications

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Introduction

The 2009 H1N1 flu virus (referred to as "swine flu" early on) is a new influenza virus strain that is causing illness in people. This new virus strain was first detected in people in the US in April 2009 and is spreading from person-to-person worldwide, probably in much the same way that regular seasonal influenza viruses spread. On June 11, 2009, the World Health Organization (WHO) declared that a pandemic of 2009 H1N1 flu was underway.

As the situation developed, the Food and Drug Administration (FDA) instituted an H1N1 incident management system to coordinate actions to protect the public's health. Through the incident management system, FDA has created seven cross-cutting teams to mitigate an H1N1 outbreak. The seven teams consist of the vaccine team, the antiviral team, the *in vitro* diagnostics team, the personal protective equipment team, the blood team, the drug shortage team and the consumer protection team. This article will focus on the work of the vaccine and antiviral teams with the recent approval of the H1N1 vaccines and the recommendations for safely using the vaccines and antiviral medications.

H1N1 Flu Vaccine

On September 15, 2009, FDA approved four Influenza A (H1N1) 2009 Monovalent Vaccines for the active immunization of individuals against influenza disease caused by pandemic (H1N1) 2009 virus. As noted in Table 1, for the injectable vaccines, the virus is inactivated, split, and further purified while the intranasal vaccines contain a live, attenuated virus. The vaccines are available in formulations that contain thimerosal, a mercury-containing preservative, as well as preservative-free formulations.

Table 1: FDA Approved H1N1 Vaccines

Proper Name	Route of Administration	Virus	Manufacturer	How Supplied	Indication
Influenza A (H1N1) 2009 Monovalent Vaccine	Injectable	Inactivated	CSL Limited	0.5 mL preservative-free single-dose, prefilled syringe 5 mL multi-dose vial[1]	Active immunization of persons ages 18 years of age and older against influenza disease caused by pandemic (H1N1) 2009 virus.
Influenza A (H1N1) 2009 Monovalent Vaccine	Injectable	Inactivated	Novartis Vaccines and Diagnostics Limited	0.5 mL single-dose, prefilled syringe[2] 5 mL multi-dose vial[1]	Active immunization of persons 4 years of age and older against influenza disease caused by pandemic (H1N1) 2009 virus.
Influenza A (H1N1) 2009 Monovalent Vaccine	Injectable	Inactivated	Sanofi Pasteur, Inc.	0.25 mL preservative-free, single-dose, prefilled syringe and single-dose vial 0.5 mL preservative-free, single-dose, prefilled syringe and single-dose vial 5 mL multi-dose vial[1]	Active immunization of persons 6 months of age and older against influenza disease caused by pandemic (H1N1) 2009 virus.
Influenza A (H1N1) 2009 Monovalent Vaccine	Intranasal	Live, attenuated	MedImmune LLC	0.2 mL pre-filled, single-dose intranasal sprayer	Active immunization of individuals 2-49 years of age against influenza disease caused by pandemic (H1N1) 2009 virus.

[1] contains Thimerosal as preservative
[2] Thimerosal, a mercury derivative used during the manufacture, is removed by subsequent purification steps to a trace amount (≤ 1 mcg mercury per 0.5 mL dose)

Influenza A (H1N1) 2009 Monovalent Vaccines Lot Release

Lot release information will be updated weekly.

For updated information on lot release, visit FDA's website at: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/LotReleases/ucm181956.htm

Who Should Get Vaccinated?

In past pandemics, groups at increased risk for serious illness and death have differed by age and health status. With the current outbreak, the most vulnerable groups are:

- Pregnant women
- Health care workers and emergency medical responders
- Any household contacts of children six months of age and younger
- Children and young adults from six months to 24 years
- People aged 25 to 64 years with underlying medical conditions (e.g. asthma, diabetes)

Immunizing these groups first will help contain the spread of the flu during the vaccination roll-out which may take a few months. Once public health authorities at the local level determine that the H1N1 influenza vaccine demand for the five target groups has been met, providers will be notified that they can administer the vaccine to healthy people ages 25 through 64 years. Once demand for H1N1 influenza vaccine among younger age groups is met, vaccination should be expanded to all people age 65 and older. Infants younger than six months should not receive the flu vaccine; therefore, it is important for infant caregivers be vaccinated and for families to take everyday actions to stay healthy.

Dosage recommendations:

Children Age Nine and Under

Currently available data suggest that children six months to nine years of age have little or no evidence of protective antibodies to the H1N1 2009 virus[1]. Based on these data, children nine years of age and younger should be administered two doses of the monovalent pandemic (H1N1) 2009 virus vaccine.

Adults and Children 10 Years of Age and Older
Adults should be administered one dose, as should children and adolescents 10 years of age and older, as they are expected to respond similarly to adults. Clinical studies are underway and will provide additional information about the optimal number of doses.

Contraindications:

The manufacturers of the H1N1 vaccines use the same well-established, egg-based manufacturing processes that are used in the manufacturing of the seasonal influenza vaccine. Therefore, people who have a severe (life-threatening) allergy to chicken eggs or to any other substance in the vaccine should not be vaccinated. Patients should be advised to talk to their doctor before getting a flu vaccine if they:

- Have ever had a severe allergic reaction to eggs;
- Have ever had a severe allergic reaction to a previous flu vaccine; or
- Have a history of Guillain-Barr Syndrome (GBS).

[1] Centers for Disease Control and Prevention. Serum Cross-Reactive Antibody Response to a Novel Influenza A (H1N1) Virus After Vaccination with Seasonal Influenza Vaccine. *MMWR 2009*; 58(19): 521-524.

The Advisory Committee on Immunization Practices suggests using inactivated influenza vaccine for immunosuppressed persons and for household members, healthcare personnel, and others who have close contact with severely immunosuppressed individuals.

Adverse Events:

The expected adverse events associated with H1N1 vaccine will be similar to those of the seasonal vaccine, potentially including a mild fever, body aches, and fatigue for a few days after the vaccine, and soreness at the injection site. The most common adverse events seen with administration of the nasal vaccine include runny nose or nasal congestion in recipients of all ages, fever more than 100 degrees Fahrenheit in children two to six years of age, and sore throat in adults. As with any medical product, serious adverse events may occur. Health professionals may report serious adverse events for
vaccines to the Vaccine Adverse Event Reporting System (VAERS).

- Online: Vaccine Adverse Event Reporting System
  https://secure.vaers.org/VaersDataEntryintro.htm

- Regular Mail: Download postage-paid Form VAERS-1 at
  http://vaers.hhs.gov/pdf/vaers_form.pdf and mail to VAERS, P.O. Box 1100, Rockville, MD 20849-1100

H1N1 Vaccine vs. Seasonal Influenza Vaccine

The H1N1 vaccine is not part of the seasonal influenza vaccine that is recommended every year. This is a stand-alone monovalent vaccine and is separate from the seasonal influenza vaccine.

Although the currently licensed seasonal trivalent influenza vaccines contain an H1N1 subtype, their subtype differs from the 2009 H1N1 influenza virus strain, which is a new virus strain that has never before circulated among humans. The 2009 H1N1 influenza virus strain is not the same as previous or current human seasonal influenza viruses and seasonal influenza vaccine does not provide protection against the 2009 H1N1 influenza virus strain.

Use of Antiviral Drugs for the H1N1 Flu Virus:

Tamiflu (oseltamivir) and Relenza (zanamivir) are two FDA-approved antiviral drugs indicated for the prevention and treatment of influenza.

On September 24, 2009, FDA issued a Public Health Advisory alerting health care professionals that the Agency has received reports of dosing errors with Tamiflu for Oral Suspension, specifically where dosing instructions for the patient do not match the dosing dispenser.

In general, prescriptions for liquid medicines are written in milliliters (mL) or teaspoons, while Tamiflu is dosed in milligrams (mg). The dosing dispenser packaged with Tamiflu has markings only in 30, 45, and 60 mg.

Pharmacists should ensure that the units of measure on the prescription instructions match the dosing device provided with the drug.

If prescription instructions specify administration using mL, the dosing device accompanying the product should be replaced with a measuring device (e.g., a syringe) calibrated in mL.

Specific Considerations for Tamiflu Dosing for Children over One Year of Age:

- Dosing should be prescribed in mg according to information provided in the table below. Caregivers for children should use the dosing dispenser packaged with the medication, unless otherwise directed by a health care provider.

- If the dosing dispenser packaged with Tamiflu oral suspension is lost or damaged, or if the prescriber wishes to use volume-based dosing, appropriate dosages in mL are also provided in the table. In these cases the prescriber and pharmacist should ensure that a dosing dispenser, such as an oral syringe calibrated in mL, is given to the patient or caregiver with instructions for use. The dosing dispenser packaged with the product should be discarded.

- Prescribers should avoid prescribing Tamiflu oral suspension in teaspoons. This can lead to inaccurate dosing. If a prescription is written in teaspoons, the pharmacist should convert the volume to mL and ensure that an appropriate measuring device, such as an oral syringe calibrated in mL, is provided. The dosing dispenser packaged with the product should be discarded.

Dose of Tamiflu for Oral Suspension (12 mg/mL) for Treatment of Influenza in Pediatric Patients One Year or Older by Weight

Body Weight (kg)	**Body Weight** (lbs)	**Recommended Dose for 5 Days** (If using the dosing device supplied with the product)	**Dose** (mL) (If using a syringe marked in mL or cc)	**Number of Bottles of Tamiflu needed to Obtain the Recommended Doses for a 5 Day Regimen**
≤ 15 kg	≤ 33 lbs	30 mg twice daily	2.5 mL	1
>15 kg to 23 kg	>33 lbs to 51 lbs	45 mg twice daily	3.8 mL	2
>23 kg to 40 kg	>51 lbs to 88 lbs	60 mg twice daily	5.0 mL	2
>40 kg	>88 lbs	75 mg twice daily	6.2 mL	3

Emergency Use of Tamiflu in Infants Less than One Year of Age

Tamiflu for Oral Suspension is approved for use in treatment and prophylaxis of influenza in pediatric patients 1 year of age and older. In certain cases, FDA has authorized emergency use of Tamiflu in infants less than one year of age.

Health care providers should be aware that there are limited data on safety and dosing when considering Tamiflu use in a seriously ill, infant with confirmed 2009 H1N1 influenza virus infection, or in one that has been exposed to a confirmed 2009 H1N1 influenza case. Infants should be carefully monitored for adverse events when Tamiflu is used.

The pharmacokinetic data to guide dosing in infants less than 3 months of age are also extremely limited. Therefore, Tamiflu should **not** be routinely used for prophylaxis in this age group. Tamiflu should be reserved for cases in which the exposure is significant and the risk of severe illness is considered high.

Current age-based dosing recommendations are not intended for premature infants. Premature infants may have slower clearance of drug due to immature renal function, and doses recommended for full term infants may lead to very high drug concentrations in this age group. Dose recommendations for premature infants are currently being evaluated.

The following table provides dosing instructions for the emergency use of Tamiflu in Infants less than one year of age:

Recommended Doses* for Infants Less than One year of age Using Tamiflu Oral Suspension

Age	Dose (mg)	Volume per Dose (12 mg/mL)	Treatment Dose Required (for 5 days)	Prophylaxis Dose Required (for 10 days)
6 - 11 months	25 mg	2 mL	2 mL twice daily	2 mL once daily
3 - 5 months	20 mg	1.6 mL	1.6 mL twice daily	1.6 mL once daily
< 3 months	12 mg	1.0 mL	1.0 mL twice daily	Not recommended unless critical

* Doses recommended for treatment of infants in the FDA Emergency Use Authorization are based on data from an ongoing NIH study evaluating treatment doses of 3.0 to 3.5 mg/kg twice daily.

When dispensing Tamiflu oral suspension for infants younger than one year of age, **the oral dosing dispenser included in the product package should always be removed and replaced with an appropriate measuring device.** The pharmacist or other health care provider should provide an oral syringe capable of accurately measuring the prescribed milliliter (mL) dose and counsel the caregiver on how to administer the prescribed dose.

Emergency Compounding of an Oral Suspension from Tamiflu 75 mg Capsules (Final Concentration 15 mg/mL)

Commercially manufactured Tamiflu for Oral Suspension (12 mg/mL) is the preferred product for pediatric and adult patients who have difficulty swallowing capsules or where lower doses are needed. In the event that Tamiflu for Oral Suspension is not available, pharmacists may compound a suspension (15 mg/mL) from Tamiflu (oseltamivir phosphate) Capsules 75 mg using Cherry Syrup (Humco) or Ora-Sweet Sugar-Free (SF; Paddock Laboratories). Other vehicles have not been studied. **This compounded suspension should not be used for convenience or when the FDA-approved Tamiflu for Oral Suspension is available.**

The approved compounding procedure is included in the professional prescribing information and results in a 15 mg/mL suspension. Healthcare providers should note that the compounded suspension is a different concentration compared to commercially available Tamiflu for Oral Suspension, which has a concentration of 12 mg/mL. Pharmacists and health care providers should ensure that an appropriate dispensing device (i.e., one that measures volume in mL) is provided with the compounded suspension of Tamiflu.

The following tables provide the volume of compounded suspension (15 mg/mL) made from Tamiflu Capsules needed for a full treatment course based on the patient's weight, and the dosing chart for pharmacy-compounded Tamiflu suspension.

Total Volume of Suspension Needed for Correct Dosing

Body Weight (kg)	Body Weight (lbs)	Total Volume to Compound per patient (mL)
≤ 15 kg	≤ 33 lbs	30 mL
16 to 23 kg	34 to 51 lbs	40 mL
24 to 40 kg	52 to 88 lbs	50 mL
≥ 41 kg	& ≥ 89 lbs	60 mL

Dosing Chart for Pharmacy-compounded Tamilfu

Body Weight (kg)	Body Weight (lbs)	Dose (mg)	Volume per Dose (15 mg/mL)	Treatment Dose Required (for 5 days)	Prophylaxis Dose Required (for 10 days)
≤ 15 kg	≤ 33 lbs	30 mg	2 mL	2 mL twice daily	2 mL once daily
16 to 23 kg	34 to 51 lbs	45 mg	3 mL	3 mL twice daily	3 mL once daily
24 to 40 kg	52 to 88 lbs	60 mg	4 mL	4 mL twice daily	4 mL once daily
≥ 41 kg	≥ 89 lbs	75 mg	5 mL	5 mL twice daily	5 mL once daily

Healthcare professionals and consumers can access complete compounding directions and other information on emergency compounding of an oral suspension from Tamiflu Capsules in the Tamiflu package insert at: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=11065

Treatment of Influenza During Pregnancy

The Centers for Disease Control and Prevention (CDC) recommends women in any trimester of their pregnancy who have a suspected or confirmed influenza infection receive prompt antiviral therapy with Tamiflu (oseltamavir) or Relenza (zanamivir).

Are Tamiflu and Relenza safe to use in pregnancy?

Relenza and Tamiflu are both FDA approved for treatment of influenza. Both drugs have been carefully looked at to understand their safety profile in pregnancy and we are continuing to monitor them closely. For a pregnant woman and her developing baby, the benefit of any drug needs to be considered in light of the risks from the drug and the risks from not treating the disease or condition.

Both drugs are designated "Pregnancy Category C," which means that they have not been studied in pregnant women. However, Pregnancy Category C does NOT mean the drug cannot be used in pregnant women. Pregnant women can and should receive a category C drug when the possible benefits of using the drug are more likely than the possible risk of harm to the woman or her baby.

What else should pregnant women know?

Antiviral drugs are most beneficial if treatment starts within 2 days of the start of influenza symptoms. The medicine will probably need to be taken for at least 5 days.
Pregnant women should not avoid getting a flu shot. Antiviral therapy is not a substitute for vaccination against seasonal and or H1N1 influenza.

MedWatch

Health care professionals may report serious adverse events (side effects) concerning drug products (e.g. antivirals) to the FDA's MedWatch Adverse Event Reporting program either online, by regular mail, fax or phone. Please include the name of the product, the manufacturer, and lot number (if known).

- Online: MedWatch Online Voluntary Reporting Form (3500)
- Regular Mail: Download postage-paid FDA Form 3500 and mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787
- Fax: (800) FDA-0178
- Phone: (800) FDA-1088

For additional information on the H1N1 Flu Virus, visit FDA's website at:

- FDA 2009 H1N1 (Swine) Flu Page
  http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm150305.htm
- Influenza A (H1N1) 2009 Monovalent Vaccine
  http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm181950.htm

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