Emergency Use Authorization (EUA) Review
Oseltamivir Phosphate for Swine Influenza A

Identifying Information:

- Trade name: Tamiflu
- Manufacturer: Roche Laboratories (NDA 21087 & 21246)
- Established name: oseltamivir phosphate
- Formulations: capsules 30 mg, 45 mg, and 75 mg
  powder for suspension (12 mg/mL when reconstituted)
- Product in the Strategic National Stockpile: Yes
- EUA sponsor: Centers for Disease Control and Prevention, Atlanta, GA 30333

We have received a request for emergency use authorization from the CDC for Tamiflu (oseltamivir phosphate) in the Strategic National Stockpile (SNS). The CDC is asking for an EUA for the following purposes:

1. to allow for treatment and prophylaxis of swine influenza A (H1N1) in pediatric patients 1 year and younger
2. to allow for the distribution of Fact Sheets for Health Care Providers and Recipients
3. to allow for dispensing of TAMIFLU® unit of use (UoU) bottles by state and local health jurisdictions without all of the required information on the prescription label
4. to allow for the distribution, use, and labeling of TAMIFLU® products that are part of the Shelf Life Extension Program (SLEP)

Background

Tamiflu (oseltamivir phosphate) is a neuraminidase inhibitor that is approved for the treatment and prophylaxis of influenza as described in the Indications and Usage section of the product labeling:[1]

> **INDICATIONS AND USAGE**
>
> **Treatment of Influenza**
> TAMIFLU is indicated for the treatment of uncomplicated acute illness due to influenza infection in patients 1 year and older who have been symptomatic for no more than 2 days.
>
> **Prophylaxis of Influenza**
> TAMIFLU is indicated for the prophylaxis of influenza in patients 1 year and older. The following points should be considered before initiating treatment or prophylaxis with TAMIFLU:

[1] Tamiflu (oseltamivir phosphate) labeling (accessed 4/26/2009)

- TAMIFLU is not a substitute for early vaccination on an annual basis as recommended by the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices.
- Influenza viruses change over time. Emergence of resistance mutations could decrease drug effectiveness. Other factors (for example, changes in viral virulence) might also diminish clinical benefit of antiviral drugs. Prescribers should consider available information on influenza drug susceptibility patterns and treatment effects when deciding whether to use TAMIFLU.

Recently, there have been reports of cases of human infection with a novel strain of swine influenza A (H1N1).[2] These cases were initially reported from California, Texas and Mexico. Although the exact diagnosis for a cluster of influenza like illness cases in Mexico has not been established for all of the cases, some of the cases have been associated with Swine influenza A (H1N1). The reports out of Mexico include reports of severe illness including fatalities.[3] Over the last day or two, cases have also been confirmed in Kansas, Ohio, and New York City. NYC reported approximately 100 students complaining of flu-like symptoms from a single school; eight cases have been confirmed as swine influenza A (H1N1) at this point in time. The Director-General of the World Health Organization (WHO) has determined that the current events constitute a public health emergency of international concern, under the WHO regulations.[4]

The current situation with human infections with swine influenza A (H1N1) is a rapidly evolving situation for which there currently is incomplete information. While we are in a state of incomplete information, the current situation with this novel strain of swine influenza (H1N1) is concerning. This document represents our best efforts to provide appropriate recommendations within the time limitations and limitations of the currently available information to address response efforts to human infections with swine influenza A (H1N1).

There are four main issues that CDC requests be addressed in their EUA.

1. to allow for treatment and prophylaxis of swine influenza A (H1N1) in pediatric patients 1 year and younger

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[2] http://www.cdc.gov/swineflu/investigation.htm (accessed 4/26/2009)

[3] The WHO provides the following information as of April 24, 2009 re: Swine flu cases. "The Government of Mexico has reported three separate events. In the Federal District of Mexico, surveillance began picking up cases of ILI starting 18 March. The number of cases has risen steadily through April and as of 23 April there are now more than 854 cases of pneumonia from the capital. Of those, 59 have died. In San Luis Potosi, in central Mexico, 24 cases of ILI, with three deaths, have been reported. And from Mexicali, near the border with the United States, four cases of ILI, with no deaths, have been reported.
Of the Mexican cases, 18 have been laboratory confirmed in Canada as Swine Influenza A/H1N1, while 12 of those are genetically identical to the Swine Influenza A/H1N1 viruses from California." Source: http://www.who.int/csr/don/2009_04_24/en/index.html (accessed 4/26/2009).

[4] http://www.who.int/mediacentre/news/statements/2009/h1n1_20090425/en/index.html (accessed 4/26/2009)

While TAMIFLU® has been demonstrated to be safe and effective in treating patients as young as 1 year of age, preclinical findings in juvenile rats raised possible concerns regarding the use of TAMIFLU® in infants less than 1 year of age. In a juvenile rat toxicology study, a single dose of 657 mg/kg oseltamivir phosphate (about 55 times the recommended dose in children ≥1 year old) administered to 7-day-old rats resulted in death in some animals. The cause of death was undetermined. Other studies showed no deaths or other significant effects in older juvenile rats given the same or higher doses of TAMIFLU®. The exposures to oseltamivir phosphate and oseltamivir carboxylate, the active metabolite, associated with no adverse effects in the juvenile rats correspond to approximately 300- and 20-fold, respectively, the exposure expected in a 1-year-old child. The clinical significance of the preclinical data to human infants was uncertain but limited drug development in the setting of routine, seasonal influenza. The current evolving swine influenza situation and the possibility of an influenza pandemic lead to a different risk/benefit conclusion regarding potential dosing of patients < 1 year of age and it is appropriate to determine dosing recommendations in this age group at this time.

CDC has provided information culled from the scientific literature on administration of doses of Tamiflu in the pediatric population of less than one year of age. We have also examined other available sources of data on safety of oseltamivir phosphate in pediatric patients less than one year of age. These include unpublished data from an NIH-sponsored retrospective chart review of off-label Tamiflu use in 180 infants less than 1 year of age from 15 US medical facilities. In addition, we have reviewed information available from another prospective NIH study evaluating pharmacokinetics and safety of Tamiflu in pediatric patients less than one year of age. This study is ongoing and no data are available in the youngest age cohort (less than 3 months) and very limited data are available in infants 3 to 5 months of age. We have been in contact with the investigators for this NIH Collaborative Antivirals Study Group study regarding dosing recommendations based upon the available data from the study. Based upon our clinical safety and Clinical Pharmacology review of the above information we have derived dosing recommendations for the pediatric patients less than one year of age. The recommended dosing ranges are shown in Table 1. Dosing by weight is preferred for children older than 1 year of age but dosing by age is acceptable if a child's weight is not known.

Body Weight (kg)	**Body Weight (lbs)**	**Dose by Age**	**Recommended Treatment Dose for 5 Days**
>40 kg	>88 lbs	≥ 10 years	75 mg twice daily
>23 kg to 40 kg	>51 lbs to 88 lbs	6-9 years	60 mg twice daily
>15 kg to 23 kg	>33 lbs to 51 lbs	3-5 years	45 mg twice daily
≤15 kg	≤33 lbs	1-2 year	30 mg twice daily
Dosing for infants younger than 1 year not based on weight		6-11 months	25 mg twice daily
		3-5 months	20 mg twice daily
		< 3 months	12 mg twice daily

Tamiflu oral suspension is dispensed with a measuring device marked for 30, 45, or 60 mg. For children who weigh more than 40 kg (or 88 lbs) or adults who can not swallow capsules, the caregiver is required to measure out a dose of 30 mg plus another dose of 45 mg. For infants less than 1 year of age, a different measuring device (such as a 5 mL oral syringe) will need to be provided to dispense 2 mL (about 25 mg), 1.6 mL (about 20 mg) or 1 mL (12 mg).

Recommendations for use of Tamiflu as prophylaxis in patients less than one year of age are similar to those for treatment but given once daily rather than twice daily. Because there is no pharmacokinetic data to guide dosing in infants less than 3 months of age, we do not believe Tamiflu should be routinely used for prophylaxis in this age group but should be reserved in cases where the exposure is significant and the risk of severe illness is considered high. Local health care providers should be given some discretion in making decisions regarding prophylaxis in infants less than 3 months.

These dosing recommendations are also provided in the accompanying Fact Sheets for Patients and Parents and Health Care Providers.

In cell culture testing, the recent isolates of swine influenza A (H1N1) have been susceptible to the neuraminidase inhibitors oseltamivir and zanamivir and resistant to the adamantanes (amantadine and rimantidine). Therefore the only option for treatment and or prophylaxis in patients less than 1 year of age is Tamiflu (oseltamivir). Relenza (zanamivir) is a dry powder for inhalation using a device that is not approved for use in this age group and would not be feasible in this age group. Considering the current situation and uncertainties, the current risk/benefit assessment supports the use of oseltamivir in pediatric patients less than one year of age for treatment or prophylaxis of known or suspected swine influenza A.

2. to allow for the distribution of Fact Sheets for Health Care Providers and Recipients

We have reviewed and edited the Fact Sheets for Health Care Provider and Patients and Parents. The versions attached in the Appendices to this review provide information to health care providers and Tamiflu recipients and describe conditions of use for oseltamivir. They also provide other useful information, including some information about the disease, recommended dosing for all age groups, previously described adverse effects of the drug and how to report suspected new adverse events to the FDA. Much of the information included in the Fact Sheets is derived from the product labeling.

The Fact Sheets describe that Tamiflu oral suspension is the preferred formulation for patients who can not swallow capsules and if the oral suspension is not available, Tamiflu capsules may be opened and mixed with sweetened liquids such as regular or sugar-free chocolate syrup. The Fact Sheets also provide for dosing of pediatric patients greater than 1 year of age according to age in the event that a a child's weight is not known. This information and the recommended dosing regimen is consistent with information in the product label.

The known and potential benefits and risks and the uncertainties of the evolving public health emergency support the inclusion of the Fact Sheets for Patients and Parents and Health Care providers. They provide useful dosing instructions and other advice on the use of the product in the populations covered under the proposed use under EUA.

3. to allow for dispensing of TAMIFLU® UoU bottles by state and local health jurisdictions without all of the required information on the prescription label

During an emergency situation, when it is essential to provide larger quantities of medication to a population, dispensing may not be able to include all of the information that is stipulated be included on the labeling for the product in 503(b)(2) of the FD&CA. The SNS plans to dispense medication in manufacturers UoU bottles without a traditional pharmacists label affixed to the bottle. UoU bottles designated for federal, state or other stockpiles contain on the bottle label the appropriate dosing directions for standard adult dosing. We have considered the known and potential risks and benefits along with the uncertainties of the current situation and believe the dispensing of UoU bottles without all of the required information is supported under the current circumstances of this proposed use under EUA.

4. to allow for the distribution, use, and labeling of TAMIFLU® products that are part of the Shelf Life Extension Program (SLEP)

Some oseltamivir phosphate products in the SNS may have undergone testing under the Shelf-life extension program (SLEP). Product that passes testing under SLEP has its expiry dating extended. The known and potential risk and benefits for using product that has had its expiry dating extended under SLEP supports the use of product that has undergone SLEP under this EUA.

5. to allow for use of Tamiflu for patients who are symptomatic for more than 2 days and/or in patients sick enough to require hospitalization (i.e., patients who do not have "uncomplicated acute illness" per se)

Another issue that warrants discussion is that of the scope of the approved indication for influenza treatment which is as follows:

> TAMIFLU is indicated for the treatment of uncomplicated acute illness due to influenza infection in patients 1 year and older who have been symptomatic for no more than 2 days.

The indication for oseltamivir treatment is for acute uncomplicated illness with treatment initiated within 2 days of onset. Experience with treatment at later time points and/or in patients sick enough to require hospitalization is extremely limited. For example, a cohort study from Ontario [5] reported decreased mortality in influenza patients treated with oseltamivir on hospital admission, including those with treatment initiated more than

[5] McGeer A et al, Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. Clinical Infectious Diseases 2007;45:1568-1575.

48 hours after symptom onset. A brief report from Hong Kong [6] noted decreased mortality in hospitalized patients receiving oseltamivir within 96 hours after symptom onset. A case series from Indonesia [7] reported progressively lower mortality for patients with H5N1 influenza receiving treatment at greater than 6 days, 5-6 days, 2-4 days, or less than 2 days after symptom onset. These limited data provide little information to support treatment decisions. However, depending on available products and susceptibility data, clinicians may wish to make individual risk-benefit assessments regarding the appropriate use of this product under this emergency use authorization.

6. to allow for distribution by those other than licensed health care providers

It is conceivable under the emergency circumstances that not only licensed health care providers, but also other public health officials or other volunteers might distribute products to recipients, if permitted, in accordance with applicable state and local law and/or in accordance with the public health and medical emergency response of the Authority Having Jurisdiction to prescribe, administer, deliver, distribute, or dispense the covered countermeasures, and their officials, agents, employees, contractors, or volunteers following a declaration of an emergency. The benefits of receiving Tamiflu under such conditions would outweigh any risks in this emergency setting.

Summary
Swine influenza A can cause influenza, a serious or life-threatening disease or condition. Based on the totality of scientific evidence available, it is reasonable to believe that Tamiflu may be effective for treatment and prophylaxis of Swine Influenza A under the circumstances described in 1-6 above. There is no adequate, available, approved alternative product that includes Fact Sheets for Patients and Parents and Health Care Providers with information on the proposed uses (including dosing recommendations for children less than 1 year of age). In addition, under the circumstances described in 1-6 above, the known and potential benefits of Tamiflu when used for the treatment and prophylaxis of influenza, outweigh the known and potential risks . The use of Tamiflu is supported by a favorable risk/benefit assessment based on our current knowledge of the evolving public health situation and knowledge of the drug from clinical trials, observational cohorts, clinical practice guidelines, and spontaneous adverse reporting. Depending on available products and susceptibility data, clinicians may wish to make individual risk-benefit assessments regarding the appropriate use of this product in individual patients. Therefore, we recommend that the emergency use of Tamiflu for the treatment and prophylaxis of Swine Influenza A be authorized subject to the following conditions:

CDC

[6] Lee N et al, Antiviral treatment for patients hospitalized with severe influenza infection may affect clinical outcomes. Clinical Infectious Diseases 2008;46:1323-4.
[7] Kandun IN et al, Factors associated with case fatality of human H5N1 virus infections in Indonesia: a case series. Lancet 2008;372:744-9.

A. CDC will verify that authorized oseltamivir phosphate products distributed to the Receive, Stage, Storage (RSS) sites are within their labeled (or SLEP-relabeled) expiration dates.

B. CDC will ensure that the local public health authority(ies) are informed of this EUA, including the terms and conditions herein.

C. CDC will make available to local public health authority(ies) through appropriate means the authorized Fact Sheet for Health Care Providers, Fact Sheet for Recipients, and at least one representative FDA-approved package insert that covers the dosage forms and strengths of authorized oseltamivir phosphate products.

D. Only CDC may request changes to the authorized Fact Sheet for Health Care Providers and authorized Fact Sheet for Recipients. Such requests will be made by contacting FDA concerning FDA review and approval.

State and/or Local Public Health Authority(ies)

E. The appropriate state and/or local public health authority(ies) will ensure that authorized oseltamivir phosphate products are distributed to recipients in accordance with applicable state and local laws and/or in accordance with the public health and medical emergency response of the Authority Having Jurisdiction to prescribe, administer, deliver, distribute, or dispense the covered countermeasures, and their officials, agents, employees, contractors, or volunteers following a declaration of an emergency.

F. The appropriate state and/or local public health authority(ies) will make available through appropriate means authorized Fact Sheets for Health Care Providers, Fact Sheets for Recipients, and at least one representative FDA-approved package insert that covers the dosage forms and strengths of authorized oseltamivir phosphate products.

CDC and State and/or Local Public Health Authority(ies)

G. CDC and the appropriate state and/or local public health authority(ies) are also authorized to make available additional information relating to the emergency use of authorized oseltamivir phosphate products that is consistent with, and does not exceed, the terms of this letter of authorization.

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