

# Oseltamivir (Systemic)

Antiviral; neuraminidase inhibitor; sialic acid analog.

**Class:** 8:18.28 Neuraminidase Inhibitors (AHFS primary); am800 (VA primary)

**Brands:** Tamiflu®

## Uses

### Treatment of Seasonal Influenza A and B Virus Infections

- Symptomatic treatment of uncomplicated acute illness caused by susceptible influenza A or B virus in adults, adolescents, and children ≥1 year of age who have been symptomatic for ≤2 days.
- Although efficacy has not been established in immunocompromised patients, oseltamivir has been used to treat *seasonal* influenza A or B virus infections in bone marrow transplant (BMT) recipients†. Oseltamivir also has been used for the treatment of *seasonal* influenza infections in hematopoietic stem cell transplant (HSCT) recipients†.
- CDC, AAP, and IDSA recommend treatment of influenza illness in all individuals with suspected or confirmed influenza who require hospitalization or have severe, complicated, or progressive illness (regardless of vaccination status or underlying illness). Treatment also recommended in individuals with suspected or confirmed influenza who are at high risk of influenza-related complications, including children <2 years of age, adults ≥65 years of age, pregnant women and women up to 2 weeks postpartum (including following pregnancy loss), individuals of any age with certain chronic medical or immunosuppressive conditions, individuals <19 years of age receiving long-term aspirin therapy, American Indians, Alaskan natives, individuals with a body mass index (BMI) ≥40, and residents of any age in nursing homes or other long-term care facilities. If indicated, initiate treatment as early as possible since benefit is greatest if started within 48 hours of symptom onset; do not delay initiation of treatment while waiting for laboratory confirmation.
- Consider viral surveillance data available from local and state health departments and the CDC when selecting an antiviral for treatment of seasonal influenza. Strains of circulating influenza viruses and the antiviral susceptibility of these strains constantly evolve, and emergence of oseltamivir-resistant influenza virus may decrease effectiveness of the drug. When treatment of seasonal influenza is indicated, oseltamivir or zanamivir usually is recommended. Although influenza A and B viruses circulating in the US during the last few years generally have been susceptible to oseltamivir, consult the most recent information.
- CDC issues recommendations concerning the use of antiviral agents for the treatment of influenza, and these recommendations are updated as needed during each influenza season. Information regarding influenza surveillance and updated recommendations for treatment of seasonal influenza are available from CDC at <http://www.cdc.gov/flu>.

### Prevention of Seasonal Influenza A and B Virus Infections

- Prevention of illness caused by influenza A or B virus in adults, adolescents, and children ≥1 year of age.
- Although efficacy not established in immunocompromised patients, oseltamivir has been used for prophylaxis of *seasonal* influenza in immunocompromised individuals†, including cancer patients, BMT recipients, HSCT recipients, and solid organ transplant recipients.
- Annual vaccination with seasonal influenza virus vaccine, as recommended by the US Public Health Service Advisory Committee on Immunization Practices (ACIP), is the primary means of preventing seasonal influenza and its severe complications. Prophylaxis with an appropriate antiviral active against circulating influenza strains is considered an adjunct to vaccination for control and prevention of influenza.
- When seasonal influenza viruses are circulating in the community, postexposure prophylaxis with oseltamivir or zanamivir can be considered for certain individuals, including those at high risk of developing influenza complications for whom influenza vaccine is contraindicated, unavailable, or expected to have low efficacy (e.g., immunocompromised individuals). Other possible candidates for antiviral prophylaxis include unvaccinated health care personnel, public health workers, and first responders with unprotected, close-contact exposure to a patient with confirmed, probable, or suspected influenza during the time when the patient was infectious. Also consider antiviral prophylaxis for controlling influenza outbreaks in nursing and long-term care facilities or other closed or semi-closed settings with large numbers of individuals at high risk for influenza complications. In individuals at high risk of influenza complications who receive influenza virus vaccine inactivated, use of prophylaxis can be considered during the 2 weeks after vaccination to provide protection until an adequate immune response develops. (See Specific Drugs under Interactions.)
- Consider viral surveillance data available from local and state health departments and the CDC when selecting an antiviral for the prophylaxis of influenza. The most appropriate antiviral for prevention of influenza is based on the likelihood that the influenza strain is susceptible and the known adverse effects of the drug. Strains of circulating influenza

viruses and the antiviral susceptibility of these strains constantly evolve, and emergence of oseltamivir-resistant influenza virus may decrease effectiveness of the drug.

- CDC issues recommendations concerning the use of antiviral agents for prophylaxis of influenza, and these recommendations are updated as needed during each influenza season. Information regarding influenza surveillance and updated recommendations for prevention of seasonal influenza are available from CDC at <http://www.cdc.gov/flu>.

### Avian Influenza A Virus Infections

- Has been used in a limited number of patients for treatment of avian influenza A virus infections† (H5N1, H7N3, H7N7).
- Drug of choice for treatment of clinically confirmed cases of avian influenza A (H5N1) infection. Early treatment is likely to provide the greatest clinical benefit. Virus continues to replicate for prolonged periods; treatment warranted even in patients who present in later stages of illness. High doses and prolonged duration of therapy may be needed in some patients.
- Concomitant use of a neuraminidase inhibitor (oseltamivir) and an adamantane (amantadine, rimantadine) can be considered in a patient with pneumonic disease or clinical progression if local surveillance data indicate the H5N1 virus is known or likely to be susceptible to an adamantane.
- Has been used for prophylaxis of avian influenza A infections† (H5N1, H7N7). Drug of choice for postexposure prophylaxis in high-risk exposure groups (household or close family contacts of individuals with strongly suspected or confirmed H5N1 illness). Can be used for postexposure prophylaxis in moderate-risk exposure groups (individuals with unprotected exposure to infected animals or affected environments; health-care workers with unprotected close contact with individuals with strongly suspected or confirmed H5N1 illness).
- May be considered for preexposure prophylaxis in certain individuals in high-risk situations (e.g., individuals directly involved in control and eradication of poultry outbreaks).
- Whenever possible, choice of antiviral for treatment or prophylaxis of avian influenza A infections should be based on results of in vitro susceptibility testing; in the absence of such testing, oseltamivir is drug of first choice.

### Pandemic Influenza

- Treatment or prevention of pandemic influenza† caused by susceptible strains of influenza virus.
- Influenza viruses can cause pandemics, during which rates of illness and death from influenza-related complications can increase dramatically worldwide. Most recent influenza pandemic occurred during 2009 and was related to a novel influenza A (H1N1) strain.
- On June 11, 2009, the WHO declared the first global influenza pandemic in 41 years and issued a phase 6 pandemic alert regarding 2009 influenza A (H1N1). A phase 6 pandemic is characterized by human-to-human spread of an animal or human-animal reassortant virus and sustained community level outbreaks of the virus in at least 2 countries in a single WHO region and sustained community level outbreaks in at least one other country in a different WHO region. Cases of human infection with 2009 influenza A (H1N1) virus were first reported in Mexico and other countries (including the US) beginning in March and April 2009. In the US, the pandemic was characterized by a substantial increase in influenza activity that peaked in late October and early November 2009 and returned to seasonal baseline levels by January 2010. During that time, more than 99% of influenza viruses circulating in the US were the 2009 pandemic influenza A (H1N1) virus. In August 2010, the WHO declared that the world was in a post-pandemic period; however, the 2009 influenza A (H1N1) virus continued to circulate during the 2010–2011 influenza season and is expected to continue to circulate during the 2011–2012 season.
- The spread of the highly pathogenic H5N1 strain of avian influenza A in poultry in Asia and other countries that was identified in 2003 represents a potential future pandemic threat.

## Dosage and Administration

### Administration

#### Oral Administration

Administer orally without regard to meals; administration with meals may improve GI tolerability.

Commercially available as 30-, 45-, and 75-mg capsules and as a powder for oral suspension that is reconstituted to provide an oral suspension containing 6 mg/mL.

A powder for oral suspension that is reconstituted to provide an oral suspension containing 12 mg/mL was previously available from the manufacturer. In July 2011, the manufacturer discontinued the 12 mg/kg concentration and began supplying the 6 mg/mL concentration. The reconstituted 6 mg/mL preparation is less frothy when shaken (allowing for more accurate dosage measurements) and the oral dosing device provided by the manufacturer with the 6 mg/mL preparation is labeled in volume (mL) instead of dosage (mg). Although the manufacturer implemented a voluntary take back program to facilitate removal of the 12 mg/mL preparation from the marketplace, it still may be available from some distributors and still may be in state or national stockpiles. There are no quality issues with the 12 mg/mL preparation; any remaining supplies can be used until their expiration date. Since both preparations (6 mg/mL and 12 mg/mL) may be available during the 2011–2012 influenza season, healthcare providers should take precautions to avoid potential medication errors. Prescribers are encouraged to include the new

strength (6 mg/mL) and dosage in mLs on each prescription for oseltamivir for oral suspension. Pharmacists should ensure that dosage instructions and oral dosing device provided to the patient are consistent with the concentration of oral suspension (6 mg/mL or 12 mg/mL) that the patient receives.

Reconstituted oseltamivir oral suspension is the preferred preparation for individuals unable to swallow capsules. Alternatively, if the oral suspension is not available, the appropriate dosage of oseltamivir capsules can be administered by opening the capsules and mixing the contents with a sweet liquid (e.g., regular or sugar-free chocolate syrup, corn syrup, caramel topping, light brown sugar dissolved in water).

If the commercially available powder for oral suspension is not available (e.g., shortage during an emergency), a pharmacist can prepare an extemporaneous oral suspension using oseltamivir capsules and simple syrup, cherry syrup vehicle (Humco), or Ora-Sweet® SF (Paddock). Consult the oseltamivir prescribing information for specific instructions. Consider that current prescribing information for oseltamivir capsules and powder for suspension (6 mg/mL) includes instructions for emergency compounding of a suspension of the same strength (6 mg/mL). However, prescribing information for oseltamivir capsules and powder for suspension (12 mg/mL) that still may remain in the marketplace includes instructions for emergency compounding of oseltamivir oral suspension containing 15 mg/mL.

In emergency situations (e.g., pandemic), if oseltamivir is administered as an extemporaneous oral preparation prepared using oseltamivir powder from bulk storage containers (not commercially available in the US), the bitter taste of the drug can be ameliorated by drinking a strongly flavored fruit drink or chewing flavored chewing gum following ingestion of the preparation.

When dispensing the commercially available oral suspension or an extemporaneous oral suspension, ensure that the units of measure on the oral dosing dispenser provided to the patient match the preparation being dispensed and the patient's dosage and prescription instructions. (See Reconstitution under Dosage and Administration.)

### Reconstitution

Reconstitute commercially available powder for oral suspension at the time of dispensing. Tap bottle to thoroughly loosen powder and then add the amount of water specified on the bottle; shake well for 15 seconds. Consider that a powder for oral suspension that is reconstituted to provide 6 mg/mL and a powder for oral suspension that is reconstituted to provide 12 mg/mL both may be available during the 2011–2012 influenza season.

Use graduated oral dosing dispenser provided by the manufacturer to administer reconstituted oral suspension; alternatively, some other oral dosing device marked with units of measure that correspond to the required dose may be used.

Shake suspension well prior to each dose.

### Dosage

Available as oseltamivir phosphate; dosage expressed in terms of oseltamivir.

### Pediatric Patients

#### Treatment of Seasonal Influenza A and B Virus Infections

**Oral:** Initiate oseltamivir treatment within 2 days after onset of symptoms. Although efficacy not established, antiviral treatment initiated >48 hours after onset of symptoms still may be beneficial in those who are hospitalized or have moderate to severe, complicated, or progressive influenza. Although usual duration of antiviral treatment is 5 days, patients hospitalized with severe infections (e.g., those with prolonged infection or admitted into an intensive care unit) may require >5 days of treatment.

Adolescents ≥13 years of age: 75 mg twice daily for 5 days.

**Table 1. Oseltamivir Dosage for Treatment of Seasonal Influenza A and B in Children 1–12 Years of Age**

Weight (kg)	Daily Dosage (mg)	Daily Dosage (Volume of Reconstituted Oral Suspension Containing 6 mg/mL)	Daily Dosage (Volume of Reconstituted Oral Suspension Containing 12 mg/mL)
≤15	30 mg twice daily for 5 days	5 mL twice daily for 5 days	2.5 mL twice daily for 5 days
16 to 23	45 mg twice daily for 5 days	7.5 mL twice daily for 5 days	3.8 mL twice daily for 5 days

<sup>a</sup>12 mg/mL concentration no longer being manufactured, but still may be available from some distributors or may be in state or national stockpiles until current supplies expire.

**Table 1. Oseltamivir Dosage for Treatment of Seasonal Influenza A and B in Children 1–12 Years of Age**

24 to 40	60 mg twice daily for 5 days	10 mL twice daily for 5 days	5 mL twice daily for 5 days
≥41	75 mg twice daily for 5 days	12.5 mL twice daily for 5 days	6.2 mL twice daily for 5 days

<sup>a</sup>12 mg/mL concentration no longer being manufactured, but still may be available from some distributors or may be in state or national stockpiles until current supplies expire.

Although safety and efficacy not established in infants <1 year of age† (see Pediatric Use under Cautions), if treatment of influenza is considered necessary in this age group, 3 mg/kg twice daily for 5 days is recommended for *full-term* infants <1 year of age†.

Although weight-based dosage is preferred if oseltamivir is used in infants <1 year of age†, dosage for treatment of influenza in *full-term* infants may be determined based on age, if necessary. (See Table 2.)

Data are insufficient to make dosage recommendations for treatment of influenza in *premature* infants <3 months of age†; dosage recommended for *full-term* infants may result in high and variable oseltamivir concentrations in *premature* infants because of immature renal function.

**Table 2. Age-based Oseltamivir Dosage for Treatment of Seasonal Influenza A or B in Infants <1 Year of Age with Unknown Weight†**

Age	Daily Dosage (mg)	Daily Dosage (Volume of Reconstituted Oral Suspension Containing 6 mg/mL)
0–3 months (full-term)	12 mg twice daily for 5 days	2 mL twice daily for 5 days
4–5 months	17 mg twice daily for 5 days	2.8 mL twice daily for 5 days
6–11 months	24 mg twice daily for 5 days	4 mL twice daily for 5 days

### Prevention of Seasonal Influenza A and B Virus Infections

**Oral:** Initiate oseltamivir prophylaxis within 2 days after exposure (e.g., close contact with infected individual). Usual duration is 10 days. May be continued for up to 6 weeks during a community influenza outbreak.

Adolescents ≥13 years of age: 75 mg once daily for at least 10 days.

**Table 3. Oseltamivir Dosage for Prevention of Seasonal Influenza A and B in Children 1–12 Years of Age**

Weight (kg)	Daily Dosage (mg)	Daily Dosage (Volume of Reconstituted Oral Suspension Containing 6 mg/mL)	Daily Dosage (Volume of Reconstituted Oral Suspension Containing 12 mg/mL)
≤15	30 mg once daily for 10 days	5 mL once daily for 10 days	2.5 mL once daily for 10 days
16 to 23	45 mg once daily for 10 days	7.5 mL once daily for 10 days	3.8 mL once daily for 10 days
24 to 40	60 mg once daily for 10 days	10 mL once daily for 10 days	5 mL once daily for 10 days
≥41	75 mg once daily for 10 days	12.5 mL once daily for 10 days	6.2 mL once daily for 10 days

<sup>a</sup>12 mg/mL concentration no longer being manufactured, but still may be available from some distributors or may be in state or national stockpiles until current supplies expire.

Although safety and efficacy not established in infants <1 year of age† (see Pediatric Use under Cautions), if prevention of influenza is considered necessary in this age

group, 3 mg/kg once daily for 10 days is recommended in *full-term* infants 3 months to <1 year of age†.

Although weight-based dosage is preferred if oseltamivir is used in infants <1 year of age†, dosage for prevention of influenza in *full-term* infants 3 months to <1 year of age† may be determined based on age, if necessary. (See Table 4.)

Data are insufficient to make dosage recommendations for prevention of influenza in *full-term* or *premature* infants <3 months of age†.

**Table 4. Age-based Oseltamivir Dosage for Prevention of Seasonal Influenza A or B in Infants <1 Year of Age with Unknown Weight†**

Age	Daily Dosage (mg)	Daily Dosage (Volume of Reconstituted Oral Suspension Containing 6 mg/mL)
0–3 months	Not recommended unless situation judged critical	
4–5 months	17 mg once daily for 10 days	2.8 mL once daily for 10 days
6–11 months	24 mg once daily for 10 days	4 mL once daily for 10 days

### Treatment of Avian Influenza A Virus Infections†

**Oral:** Dosage usually recommended for treatment of seasonal influenza A and B virus infections has been recommended. This dosage may be reasonable for early, mild cases of influenza A (H5N1) infection, but WHO and others state that severely ill patients may benefit from higher dosage and/or longer duration of therapy (i.e., 7–10 days).

Initiate treatment as early as possible. Treatment is most beneficial if initiated within 2 days of symptom onset, but is warranted even in patients who present for care in the later stages of illness.

### Prevention of Avian Influenza A Virus Infections†

**Oral:** Dosage usually recommended for prophylaxis of seasonal influenza A and B virus infections has been recommended.

High-risk and moderate-risk exposure groups: Initiate as soon as possible and continue for 7–10 days after last known exposure.

### Pandemic Influenza†

**Oral:** Dosage usually recommended for treatment or prophylaxis of seasonal influenza A and B virus infections is considered the *minimum* dosage required for treatment or prophylaxis of influenza in a pandemic situation.

## Adults

### Treatment of Seasonal Influenza A and B Virus Infections

**Oral:** 75 mg twice daily for 5 days.

Initiate oseltamivir treatment within 2 days after onset of symptoms. Although efficacy not established, antiviral treatment initiated >48 hours after onset of symptoms may still be beneficial in those with moderate to severe or progressive influenza. Although usual duration of antiviral treatment is 5 days, patients hospitalized with severe infections (e.g., those with prolonged infection or admitted into an intensive care unit) may require >5 days of treatment.

### Prevention of Seasonal Influenza A and B Virus Infections

**Oral:** 75 mg once daily given for at least 10 days. Initiate prophylaxis within 2 days after exposure (e.g., close contact with infected individual). Safety and efficacy of prophylaxis demonstrated for up to 6 weeks in immunocompetent individuals; safety of prophylaxis demonstrated for up to 12 weeks in immunocompromised individuals.

### Treatment of Avian Influenza A Virus Infections†

**Oral:** 75 mg twice daily for 5 days has been recommended.

Dosage usually recommended for treatment of seasonal influenza A and B virus infections has been recommended. This dosage may be reasonable for early, mild cases of influenza A (H5N1) infection, but WHO and others state that severely ill patients may benefit from higher dosage (i.e., 150 mg twice daily in adults) and/or longer duration of therapy (i.e., 7–10 days).

Initiate treatment as early as possible. Treatment is most beneficial if initiated within 2 days of symptom onset, but is warranted even in patients who present for care in the later stages of illness.

### Prevention of Avian Influenza A Virus Infections†

**Oral:** Dosage usually recommended for prophylaxis of seasonal influenza A and B virus infections has been recommended.

High-risk and moderate-risk exposure groups: Initiate as soon as possible and continue for 7–10 days after last known exposure.

Preexposure prophylaxis or repeated or continuous postexposure prophylaxis may be necessary in individuals in high-risk situations (e.g., individuals directly involved in control and eradication of poultry outbreaks).

During avian influenza A (H7N7) outbreaks, 75 mg daily has been used for prophylaxis in exposed individuals.

### Pandemic Influenza†

**Oral:** Dosage recommended for treatment or prophylaxis of seasonal influenza A and B virus infections is considered the *minimum* dosage required for treatment or prophylaxis of influenza in a pandemic situation.

## Special Populations

### Hepatic Impairment

Usual dosage can be used in those with mild to moderate hepatic impairment (Child-Pugh score ≤9).

### Renal Impairment

Treatment of influenza A or B virus infections in patients with  $Cl_{cr}$  10–30 mL/minute: 75 mg once daily for 5 days.

Prevention of influenza A or B virus infections in patients with  $Cl_{cr}$  10–30 mL/minute: 75 mg once every other day or 30 mg once daily for 10 days after last known exposure to a confirmed case.

Dosage recommendations not available for patients with end-stage renal disease ( $Cl_{cr}$  <10 mL/minute) or for those undergoing routine hemodialysis or CAPD.

### Geriatric Patients

No dosage adjustments except those related to renal impairment.

## Cautions

### Contraindications

- Known hypersensitivity to oseltamivir or any ingredient in the formulations.

### Warnings/Precautions

#### Sensitivity Reactions

##### Dermatologic and Hypersensitivity Reactions

Anaphylaxis and serious skin reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme, reported.

If an allergic reaction occurs or is suspected, discontinue oseltamivir and institute appropriate therapy.

#### Neuropsychiatric Events

Adverse neuropsychiatric events (e.g., self-injury, delirium, hallucinations, confusion, abnormal behavior, seizures) and death reported.

Postmarketing reports of delirium and abnormal behavior leading to injury mainly involved children from Japan. Cases generally had an abrupt onset and rapid resolution. Role of oseltamivir not determined.

Influenza itself can be associated with neurologic and behavioral symptoms (e.g., hallucinations, delirium, abnormal behavior) and fatalities can occur. Although such events may occur in the setting of encephalitis or encephalopathy, they can occur without obvious severe disease.

Closely monitor patients with influenza for signs of abnormal behavior. If neuropsychiatric symptoms develop, consider risks versus benefits of continued therapy.

#### Bacterial Infections

Serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications of influenza. No evidence that oseltamivir prevents such complications.

No evidence of efficacy in illness caused by any organisms other than influenza A or B.

#### Concomitant Illness

Efficacy for treatment of influenza in patients with chronic cardiac disease and/or underlying pulmonary disease not established; no evidence to date of increased risk of adverse effects in this population.

Although efficacy for treatment or prevention of influenza not established in immunocompromised patients, safety of oseltamivir prophylaxis has been demonstrated for up to 12 weeks in immunocompromised patients. Has been used for treatment or prevention of influenza in some immunocompromised individuals†, including BMT recipients, HSCT recipients, solid organ transplant recipients, and chemotherapy patients. (See Uses.)

No data available regarding use for treatment of influenza in patients with any medical condition severe or unstable enough to require inpatient care.

#### Influenza Vaccination

Oseltamivir is not a substitute for annual vaccination with seasonal influenza virus vaccine inactivated or seasonal influenza virus vaccine live intranasal.

Antiviral agents used for treatment or prevention of influenza (amantadine, oseltamivir, rimantadine, zanamivir) may be used concomitantly with parenteral inactivated seasonal influenza virus vaccine.

Intranasal live influenza virus vaccine should not be administered until at least 48 hours after influenza antiviral agents are discontinued and these antiviral agents should not be administered

until at least 2 weeks after administration of an intranasal live influenza virus vaccine, unless medically indicated. (See Influenza Virus Vaccines under Interactions.)

**Sorbitol**

When the commercially available oral suspension is used, each 75-mg dose of oseltamivir contains 2 g of sorbitol. This amount of sorbitol exceeds the maximum daily limit of sorbitol for individuals with hereditary fructose intolerance and may result in dyspepsia and diarrhea.

**Specific Populations**

**Pregnancy**

Category C.

Pregnant women are at increased risk for severe complications and death from influenza.

CDC states that pregnancy is not considered a contraindication to use of oseltamivir for treatment or prevention of influenza; oseltamivir regimens recommended for such infections in pregnant women are the same as those for other adults.

Because of its systemic absorption, CDC states that oseltamivir may be preferred when a neuraminidase inhibitor is indicated for treatment of influenza in a pregnant woman, but the drug of choice for prophylaxis of these infections is less clear. Zanamivir may be preferred for prophylaxis in pregnant women because of its limited systemic absorption; however, respiratory complications that may be associated with zanamivir because of its route of administration should be considered, especially in women at risk for respiratory problems.

**Lactation**

Distributed into milk in rats; not known whether distributed into human milk.

Use with caution and only if potential benefits justify possible risks to breast-fed infant.

CDC states that antiviral treatment or prophylaxis is not a contraindication for breastfeeding.

**Pediatric Use**

Safety and efficacy not established in infants <1 year of age.

Manufacturer states oseltamivir is not indicated for treatment or prevention of influenza in infants <1 year of age because it is not known whether toxicology data reported in animals are clinically relevant for human infants.

Young children, especially those <2 years of age, are at increased risk of influenza infection, hospitalization, and complications. During the 2009 influenza A (H1N1) pandemic, FDA issued an emergency use authorization (EUA) that temporarily allowed use of oseltamivir for emergency treatment or prevention of 2009 influenza A (H1N1) infection in infants <1 year of age†. Although the EUA expired in June 2010, the AAP states that use of oseltamivir in infants <1 year of age† is appropriate when indicated. (See Pediatric Patients under Dosage.)

Unusual adverse neurologic and/or psychiatric effects (e.g., self-injury, delirium, hallucinations, mental confusion, abnormal behavior, seizures) and deaths reported in Japanese children (≤16 years of age) receiving oseltamivir for treatment of influenza; role of oseltamivir not determined. (See Neuropsychiatric Events under Cautions.)

**Geriatric Use**

No overall differences in safety or efficacy compared with younger adults, but increased sensitivity cannot be ruled out.

**Hepatic Impairment**

Safety and pharmacokinetics not evaluated in patients with severe hepatic impairment.

**Renal Impairment**

Decreased clearance. Dosage adjustment is recommended if Cl<sub>cr</sub> is 10–30 mL/minute. (See Renal Impairment under Dosage and Administration.)

**Common Adverse Effects**

GI effects (nausea, vomiting, diarrhea, abdominal pain), headache, bronchitis, insomnia, vertigo.

**Interactions**

Oseltamivir phosphate and its active metabolite not metabolized by and do not inhibit CYP isoenzymes; drug interactions with drugs that are substrates or inhibitors of these enzymes unlikely.

**Drugs Eliminated by Renal Excretion**

Potential pharmacokinetic interaction when used concomitantly with other drugs eliminated by renal tubular secretion (e.g., probenecid); clinically important interactions unlikely.

**Specific Drugs**

Drug	Interaction	Comments
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<b>Acetaminophen</b>	No evidence of pharmacokinetic interaction	
<b>Amoxicillin</b>	No evidence of pharmacokinetic interaction	
<b>Antacids (containing magnesium, aluminum, or calcium carbonate)</b>	No clinically important effect on oseltamivir pharmacokinetics	
<b>Anticoagulants, oral</b>	No evidence of pharmacokinetic interaction	
<b>Aspirin</b>	Pharmacokinetic interactions unlikely	
<b>Cimetidine</b>	No evidence of pharmacokinetic interaction	
<b>Influenza virus vaccines</b>	Parenteral inactivated influenza vaccine: Oseltamivir does not interfere with the antibody response to the vaccine  Intranasal live influenza vaccine: Potential interference with antibody response to the live vaccine; no specific studies	Parenteral inactivated influenza vaccine: May be administered concomitantly with or at any interval before or after oseltamivir  Intranasal live influenza vaccine: Do not administer the live intranasal vaccine until at least 48 hours after oseltamivir is discontinued; do not administer oseltamivir until at least 2 weeks after administration of the live intranasal vaccine; repeat vaccination if influenza antiviral is given 2 days before to 14 days after the vaccine
<b>Probenecid</b>	Potential increased systemic exposure to oseltamivir carboxylate because of decreased renal tubular secretion	Not expected to be clinically important; use usual dosages

**Pharmacokinetics**

**Absorption**

**Bioavailability**

Oseltamivir phosphate readily absorbed following oral administration and then extensively converted to the active metabolite (oseltamivir carboxylate).

Absolute bioavailability of oseltamivir carboxylate 80% following oral administration of oseltamivir phosphate; peak concentrations of active metabolite attained within 3–4 hours.

**Food**

Administration of oseltamivir phosphate with food has no effect on peak plasma concentrations or AUC of oseltamivir carboxylate.

**Distribution**

**Extent**

Following oral administration of oseltamivir phosphate, oseltamivir carboxylate distributed throughout body, including upper and lower respiratory tract.

Placental transfer of oseltamivir carboxylate demonstrated in rats and rabbits; not known whether oseltamivir or oseltamivir carboxylate crosses the placenta in humans.

Distributed into milk in rats; not known whether oseltamivir or oseltamivir carboxylate distributed into human milk.

**Plasma Protein Binding**

Oseltamivir phosphate 42% bound to plasma proteins; oseltamivir carboxylate 3% bound to plasma proteins.

## Elimination

### Metabolism

Oseltamivir phosphate extensively converted to oseltamivir carboxylate, principally by hepatic esterases.

Oseltamivir phosphate and oseltamivir carboxylate not metabolized by CYP enzymes.

### Elimination Route

Oseltamivir phosphate principally (>90%) eliminated by conversion to oseltamivir carboxylate. No further metabolism.

Oseltamivir carboxylate principally eliminated by glomerular filtration and tubular secretion; <20% of dose eliminated in feces.

### Half-life

Plasma half-life of oseltamivir phosphate 1–3 hours; half-life of oseltamivir carboxylate 6–10 hours.

### Special Populations

Renal clearance decreased in patients with impaired renal function.

Systemic exposure to oseltamivir carboxylate in individuals with mild or moderate hepatic impairment is comparable to that in individuals without hepatic impairment.

Clearance of both oseltamivir phosphate and oseltamivir carboxylate increased in younger pediatric patients compared with adults. Total clearance of oseltamivir carboxylate decreases linearly with increasing age (up to 12 years of age); pharmacokinetics in those >12 years of age similar to adults.

Exposure to oseltamivir carboxylate at steady-state approximately 25–35% higher in geriatric individuals (65–78 years of age) compared with younger adults; similar plasma half-life.

## Stability

### Storage

#### Oral

##### Capsules

25°C (may be exposed to 15–30°C).

##### For Suspension

25°C (may be exposed to 15–30°C).

Following reconstitution, store suspension at 2–8°C for up to 17 days. Alternatively, may be stored for up to 10 days at 25°C (may be exposed to 15–30°C). Do not freeze.

##### Extemporaneous Oral Suspension

Extemporaneous oral suspensions prepared by dissolving contents of oseltamivir capsules in simple syrup, cherry syrup vehicle, or Ora-Sweet<sup>®</sup> SF are stable for 5 weeks (35 days) at 2–8°C or 5 days at 25°C.

##### Powder in Bulk Storage Containers

Extemporaneous oral preparations, prepared by dissolving oseltamivir powder from bulk storage containers (not commercially available in the US) in water at a concentration of 15 mg of oseltamivir per mL and adding sodium benzoate as a preservative, are stable for 3 weeks at 25°C or for 6 weeks at 5°C.

## Actions

- Oseltamivir phosphate is an inactive prodrug until hydrolyzed by hepatic esterases to oseltamivir carboxylate, the active metabolite.
- Oseltamivir carboxylate is a potent selective competitive inhibitor of influenza virus neuraminidase, an enzyme essential for viral replication; possibly alters virus particle aggregation and release.
- Active against influenza A and B viruses, including amantadine- and rimantadine-resistant isolates.
- Active in vitro and in vivo in animal studies against some avian influenza A viruses (some strains of H5N1, H7N2, H9N2); active against influenza A (H5N1) isolated from patients in Vietnam and Thailand during 2004. However, avian influenza A (H5N1) with reduced in vitro susceptibility or resistance to oseltamivir have been isolated from a few oseltamivir-treated patients; some of these isolates remained susceptible to zanamivir.
- Beginning in the 2007–2008 influenza season, a significant increase in the prevalence of oseltamivir-resistant seasonal influenza A (H1N1) was reported worldwide; almost all seasonal influenza A (H1N1) strains tested in the US in 2008, 2009, and beginning of 2010 were resistant to oseltamivir. During the 2010–2011 influenza season, the former seasonal influenza A (H1N1) was rarely detected and almost all circulating influenza A (H1N1) were the 2009 pandemic influenza A (H1N1) virus.
- Although most isolates of the 2009 pandemic influenza A (H1N1) virus (>99% of isolates from the 2010–2011 influenza season) have been susceptible to oseltamivir in vitro, oseltamivir-resistance has been reported rarely. These oseltamivir-resistant strains generally were susceptible to zanamivir.

- Influenza strains cross-resistant to zanamivir and oseltamivir have been generated in cell culture; only limited data available regarding possible emergence of clinical isolates with cross-resistance to both drugs.

## Advice to Patients

- Importance of using the *appropriate* graduated oral dosing dispenser for the strength of powder for oral suspension being dispensed. Importance of informing patient of appropriate dosage for the strength of oseltamivir suspension being dispensed.
- Importance of initiating oseltamivir treatment as soon as possible after appearance of influenza symptoms (within 2 days after symptom onset); efficacy not established if treatment begins >48 hours after symptoms have been established.
- Importance of initiating oseltamivir prophylaxis as soon as possible after exposure to influenza (within 2 days after exposure).
- Importance of complying with the entire drug regimen. Importance of taking missed dose as soon as remembered, except if within 2 hours of the next scheduled dose.
- Importance of informing clinician if signs of unusual behavior develop.
- Advise patients that oseltamivir is not a substitute for annual vaccination with influenza virus vaccine.
- Importance of informing clinicians of existing or contemplated therapy, including prescription and OTC drugs, as well as any concomitant illnesses.
- Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.
- Importance of advising patients of other important precautionary information. (See Cautions.)

## Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Oseltamivir phosphate powder for oral suspension that is reconstituted to provide an oral suspension containing 12 mg of oseltamivir per mL was previously available from the manufacturer. In July 2011, the manufacturer discontinued the 12 mg/mL preparation and began supplying a powder for oral suspension that is reconstituted to provide an oral suspension containing 6 mg/mL. Although the manufacturer implemented a voluntary take back program during July and August 2011 to facilitate removal of the 12 mg/mL preparation from the marketplace, it still may be available from some distributors and still may be in state or national stockpiles. There are no quality issues with the 12 mg/mL preparation; any remaining supplies can be used until their expiration date. Since both strengths (6 mg/mL and 12 mg/mL) may be available during the 2011–2012 influenza season and since dosage recommendations for these preparations differ (i.e., volume of reconstituted oral suspension), precautions should be taken to avoid potential medication errors. (See Dosage and Administration.)

### Oseltamivir Phosphate

#### Oral

##### Capsules

30 mg (of oseltamivir)

**Tamiflu<sup>®</sup>**, Genentech

45 mg (of oseltamivir)

**Tamiflu<sup>®</sup>**, Genentech

75 mg (of oseltamivir)

**Tamiflu<sup>®</sup>**, Genentech

##### For suspension

6 mg (of oseltamivir) per mL

**Tamiflu<sup>®</sup>**, Genentech

† Use is not currently included in the labeling approved by the US Food and Drug Administration.

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