

# Oseltamivir (Systemic)

Antiviral; neuraminidase inhibitor; sialic acid analog.

**Class:** Neuraminidase Inhibitors 8:18.28 (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 influenza A or B virus in adults, adolescents, and children  $\geq 1$  year of age who have been symptomatic for  $\leq 2$  days.
- Emergence of oseltamivir-resistant influenza virus may decrease effectiveness of the drug.
- CDC issued interim recommendations concerning the use of antiviral agents during the 2009-2010 influenza season. CDC recommends treatment of influenza illness for all individuals with suspected or confirmed influenza who require hospitalization. CDC also states that early empiric treatment should be considered for individuals with suspected or confirmed influenza who are at high risk for influenza-related complications, including children  $< 2$  years of age, adults  $\geq 65$  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, and individuals  $< 19$  years of age who are receiving long-term aspirin therapy. If treatment is indicated, initiate as early as possible; do not delay initiation of treatment while waiting for laboratory confirmation. As of October 2009, 99% of influenza viruses circulating in the US were the 2009 influenza A (H1N1) virus. (See 2009 Influenza A (H1N1) Virus Infections under Uses.) When treatment of influenza is indicated and seasonal influenza is suspected, oseltamivir or zanamivir is recommended. If viral surveillance indicates that seasonal influenza A (H1N1) resistant to oseltamivir is circulating and treatment is indicated, CDC states that zanamivir should be used; oseltamivir in conjunction with rimantadine or amantadine is an alternative.
- CDC recommends that health-care providers review local surveillance data, if available, to determine whether influenza A or B is most likely and which subtype of influenza A (H1N1 or H3N2) is prominent in the community. Use of diagnostic tests to distinguish influenza A and B should be considered.
- 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†.
- 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  $\geq 1$  year of age.
- Emergence of oseltamivir-resistant influenza virus may decrease effectiveness of the drug.
- CDC issued interim recommendations concerning the use of antiviral agents for prophylaxis of influenza during the 2009-2010 influenza season. Postexposure prophylaxis with oseltamivir or zanamivir can be considered for certain individuals. Candidates for antiviral prophylaxis include those at high risk for influenza-related complications following close contact with a patient with confirmed, probable, or suspected influenza during the time when the patient was infectious; other candidates include 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. Antiviral prophylaxis also can be considered for controlling influenza outbreaks in assisted living facilities or other closed or semi-closed settings with large numbers of individuals at high risk for influenza complications. Early recognition of influenza illness and treatment is an alternative to postexposure prophylaxis. Postexposure prophylaxis is not indicated if  $> 48$  hours has elapsed since contact with the patient with influenza.
- Although efficacy not established in immunocompromised patients, oseltamivir has been used for prophylaxis of seasonal influenza in immunocompromised individuals† (e.g., cancer or BMT patients).
- Not a substitute for annual vaccination with seasonal influenza virus vaccine inactivated or seasonal influenza virus vaccine live intranasal. Vaccination is the primary means of preventing seasonal influenza and its complications; antiviral agents are considered adjuncts for control and prevention of influenza. (See Influenza Virus Vaccines under Interactions.)
- Information regarding influenza surveillance and updated recommendations for prevention of seasonal influenza are available from CDC at <http://www.cdc.gov/flu>.

### 2009 Influenza A (H1N1) Virus Infections

- Treatment or prevention of infections caused by the 2009 influenza A (H1N1) virus, previously referred to as the novel 2009 influenza A (H1N1) virus or swine-origin influenza A (H1N1) virus†.
- Beginning in March and April 2009, cases of human infection with 2009 influenza A (H1N1) virus were reported in Mexico and other countries, including the US. As of October 2009, 99% of circulating influenza viruses in the US were identified as 2009 influenza A (H1N1).

- CDC issued interim recommendations concerning the use of antiviral agents during the 2009-2010 influenza season. CDC recommends treatment of influenza illness for all individuals with suspected or confirmed influenza who require hospitalization. CDC also states that early empiric treatment should be considered for individuals with suspected or confirmed influenza who are at high risk for complications, including children  $< 2$  years of age, adults  $\geq 65$  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, and individuals  $< 19$  years of age who are receiving long-term aspirin therapy. Initiate treatment as early as possible; do not delay initiation of treatment while waiting for laboratory confirmation. When treatment of influenza is indicated in patients with known or suspected influenza A (H1N1) infection, oseltamivir or zanamivir is recommended. For certain hospitalized adult or pediatric patients when an IV antiviral is clinically appropriate, IV peramivir became available under an Emergency Use Authorization (EUA) issued by the FDA in October 2009. Information on peramivir is available at <http://www.cdc.gov/h1n1flu/eua/peramivir.htm>.
- CDC issued interim recommendations concerning the use of antiviral agents for prophylaxis of influenza during the 2009-2010 influenza season. Postexposure prophylaxis with oseltamivir or zanamivir can be considered for certain individuals. Candidates for antiviral prophylaxis include those at high risk for influenza-related complications following close contact with a patient with confirmed, probable, or suspected influenza during the time when the patient was infectious; other candidates include 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. Antiviral prophylaxis also can be considered for controlling influenza outbreaks in assisted living facilities or other closed or semi-closed settings with large numbers of individuals at high risk for influenza complications. Early recognition of influenza illness and treatment is an alternative to postexposure prophylaxis. Postexposure prophylaxis is not indicated if  $> 48$  hours has elapsed since contact with the individual with influenza.
- CDC states that HIV-infected adults and adolescents who meet current case definitions for confirmed, probable, or suspected 2009 influenza A (H1N1) infection should receive empiric antiviral treatment and those who are in close contact (e.g., household contact) with a probable or confirmed case should receive antiviral prophylaxis. Oseltamivir or zanamivir regimens recommended for treatment or prophylaxis of 2009 influenza A (H1N1) in HIV-infected individuals are the same as those for individuals who are not HIV-infected.
- Pregnant women are at increased risk for severe influenza-related complications and death. CDC states that pregnant women and women up to 2 weeks postpartum (including after pregnancy loss) who meet current case definitions for confirmed, probable, or suspected 2009 influenza A (H1N1) infection should receive prompt empiric antiviral treatment and pregnant women who are in close contact with an individual with suspected, probable, or confirmed infection should receive antiviral prophylaxis. Oseltamivir or zanamivir regimens recommended for treatment or prophylaxis of these infections in pregnant women are the same as those recommended for other adults. However, because of its systemic absorption, CDC states that oseltamivir may be preferred for treatment of 2009 influenza A (H1N1) in pregnant women; the drug of choice for prophylaxis in these patients is less clear. (See Pregnancy under Cautions.) CDC states that antiviral treatment or prophylaxis is not a contraindication for breast-feeding.
- Oseltamivir and zanamivir are available under EUAs issued by FDA that allow emergency use of the drugs for the treatment and prophylaxis of influenza in individuals exposed to 2009 influenza A (H1N1). Although safety and efficacy of oseltamivir have not been established in children  $< 1$  year of age, the EUA allows emergency use of the drug in this age group. The EUA will end when the declaration of emergency is terminated or the EUA is revoked.
- Recommendations for use of antiviral agents for treatment or prevention of infections caused by 2009 influenza A (H1N1) may change as additional data become available. Consult the CDC website for the most recent information regarding 2009 influenza A (H1N1) infections (<http://www.cdc.gov/h1n1flu>).

### 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 in patients who present in late stages of illness.
- 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

- Beginning in March and April 2009, cases of human infection with 2009 influenza A (H1N1) virus were reported in Mexico and other countries, including the US. 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. (See 2009 Influenza A (H1N1) Virus Infections under Uses.)
- The spread of the highly pathogenic H5N1 strain of avian influenza A in poultry in Asia and other countries that occurred in 2004–2008 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 12 mg/mL.

Oseltamivir oral suspension is the preferred preparation for individuals who are unable to swallow capsules. Alternatively, if the oral suspension is not available, each dose can be administered by opening the appropriate capsules corresponding to the dose and mixing the contents with a sweet liquid (e.g., regular or sugar-free chocolate syrup).

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 either cherry syrup vehicle (Humco) or Ora-Sweet® SF (Paddock). Consult the oseltamivir prescribing information for specific instructions. The oral dosing dispenser (oral syringe) provided with the commercially available powder for oral suspension should not be used to administer the extemporaneous preparation (extemporaneous suspension contains 15 mg/mL; suspension prepared using the powder for oral suspension contains 12 mg/mL).

In the event of a pandemic, if oseltamivir is administered as an extemporaneous oral preparation prepared from bulk storage containers of the drug (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 (oral syringe) provided to the patient match 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.

Children ≥1 year of age: Use graduated oral dosing dispenser (oral syringe) provided by the manufacturer to administer reconstituted oral suspension; alternatively, some other oral dosing syringe or similar device may be used.

Children <1 year of age receiving oseltamivir oral suspension for treatment or prevention of 2009 influenza A (H1N1) infections†: Use an oral syringe (e.g., a 5-mL oral syringe) that will deliver a 2-mL dose (approximately 25 mg), a 1.6-mL dose (approximately 20 mg), or a 1-mL dose (12 mg). The graduated oral dosing dispenser (oral syringe) provided by the manufacturer should *not* be used to measure dosages for children <1 year of age and should *not* be dispensed with the reconstituted oral suspension.

Shake suspension well prior to each dose.

### Dosage

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

Systemic availability of oseltamivir carboxylate from an extemporaneous oral preparation prepared from a bulk storage containers of the drug (not commercially available in the US) is expected to be the same as that from the commercially available preparations.

#### Pediatric Patients

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

Oral:

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

Weight (kg)	Daily Dosage	Daily Dosage (Volume of Reconstituted Commercially Available Suspension Containing Oseltamivir 12 mg/mL)
≤15	30 mg twice daily for 5 days	2.5 mL twice daily for 5 days
>15 to 23	45 mg twice daily for 5 days	3.8 mL twice daily for 5 days
>23 to 40	60 mg twice daily for 5 days	5 mL twice daily for 5 days
>40	75 mg twice daily for 5 days	6.2 mL twice daily for 5 days

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

Age	Daily Dosage	Daily Dosage (Volume of Reconstituted Commercially Available Suspension Containing Oseltamivir 12 mg/mL)
≤15	30 mg twice daily for 5 days	2.5 mL twice daily for 5 days
>15 to 23	45 mg twice daily for 5 days	3.8 mL twice daily for 5 days
>23 to 40	60 mg twice daily for 5 days	5 mL twice daily for 5 days
>40	75 mg twice daily for 5 days	6.2 mL twice daily for 5 days

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

Initiate oseltamivir treatment within 2 days after onset of symptoms; efficacy not established if treatment begins >40 hours after symptoms have been established.

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

Oral:

**Table 2. Dosage for Prevention of Seasonal Influenza A and B in Children 1–12 Years of Age**

Weight (kg)	Daily Dosage	Daily Dosage (Volume of Reconstituted Commercially Available Suspension Containing Oseltamivir 12 mg/mL)
≤15	30 mg once daily for 10 days	2.5 mL once daily for 10 days
>15 to 23	45 mg once daily for 10 days	3.8 mL once daily for 10 days
>23 to 40	60 mg once daily for 10 days	5 mL once daily for 10 days
>40	75 mg once daily for 10 days	6.2 mL once daily for 10 days

Children 1–12 years of age: Initiate oseltamivir prophylaxis within 2 days after exposure (e.g., close contact with infected individual). Usual duration is 10 days; duration >10 days not evaluated in this age group.

Adolescents ≥13 years of age: 75 mg once daily for ≥10 days. Initiate oseltamivir prophylaxis within 2 days after exposure (e.g., close contact with infected individual). Individualize duration of prophylaxis. For maximum effectiveness, must be taken every day during influenza activity in the community. May be continued for up to 6 weeks during a community influenza outbreak.

##### Oral Treatment of 2009 Influenza A (H1N1) Virus Infections†

Antiviral treatment of confirmed, probable, and suspected cases of 2009 influenza A (H1N1) virus infection† should be prioritized for those hospitalized with influenza and those at high risk of influenza complications. (See 2009 Influenza A (H1N1) Virus Infections under Uses.)

When indicated, treatment should preferably begin within 2 days of symptom onset and be continued for 5 days. CDC states that some studies in hospitalized patients suggest benefit, including decreased mortality or duration of hospitalization, even when treatment is started >48 hours after illness onset. In addition, CDC states that hospitalized patients with severe infections (e.g., those with prolonged infection or those admitted into an intensive care unit) may require a longer duration of treatment.

Although safety and efficacy of oseltamivir not established in children <1 year of age, the EUA issued by FDA allows emergency use of the drug in this age group for treatment of 2009 influenza A (H1N1) infections†. The EUA will end when the declaration of emergency is terminated or the EUA is revoked.

**Table 3. Dosage for Treatment of 2009 Influenza A (H1N1) in Children <1 Year of Age†**

Age	Daily Dosage	Daily Dosage (Volume of Reconstituted Commercially Available Suspension Containing Oseltamivir 12 mg/mL)
<3 months	12 mg twice daily for 5 days	1 mL twice daily for 5 days
3–5 months	20 mg twice daily for 5 days	1.6 mL twice daily for 5 days
6–11 months	25 mg twice daily for 5 days	2 mL twice daily for 5 days

**Table 4. Dosage for Treatment of 2009 Influenza A (H1N1) in Children 1–12 Years of Age†**

Weight (kg)	Age	Daily Dosage	Daily Dosage (Volume of Reconstituted Commercially Available Suspension Containing Oseltamivir 12 mg/mL)
≤15	1–2 Years	30 mg twice daily for 5 days	2.5 mL twice daily for 5 days
>15 to 23	3–5 Years	45 mg twice daily for 5 days	3.8 mL twice daily for 5 days
>23 to 40	6–9 Years	60 mg twice daily for 5 days	5 mL twice daily for 5 days
>40	≥10 Years	75 mg twice daily for 5 days	6.2 mL twice daily for 5 days

**Table 5. Dosage for Treatment of 2009 Influenza A (H1N1) in Adolescents ≥13 Years of Age†**

75 mg twice daily for 5 days.

**Oral Prevention of 2009 Influenza A (H1N1) Virus Infections†**

Consider antiviral prophylaxis against 2009 influenza A (H1N1) virus infections† only in certain situations and in certain individuals. (See 2009 Influenza A (H1N1) Infections under Uses.) Continue prophylaxis (if indicated) for 10 days after the last known exposure to a confirmed case. Consult CDC website for the most recent information regarding who should receive prophylaxis for these infections, including information on outbreak control (<http://www.cdc.gov/h1n1flu/recommendations.htm>).

Continue prophylaxis for 10 days after last known exposure to a confirmed case.

**Table 6. Dosage for Prevention of 2009 Influenza A (H1N1) in Children <1 Year of Age†**

Age	Daily Dosage	Daily Dosage (Volume of Reconstituted Commercially Available Suspension Containing Oseltamivir 12 mg/mL)
<3 months	Not recommended unless situation judged critical	
3–5 months	20 mg once daily for 10 days	1.6 mL once daily for 10 days
6–11 months	25 mg once daily for 10 days	2 mL once daily for 10 days

**Table 7. Dosage for Prevention of 2009 Influenza A (H1N1) in Children 1–12 Years of Age†**

Weight (kg)	Age	Daily Dosage	Daily Dosage (Volume of Reconstituted Commercially Available Suspension Containing Oseltamivir 12 mg/mL)
≤15	1–2 Years	30 mg once daily for 10 days	2.5 mL once daily for 10 days
>15 to 23	3–5 Years	45 mg once daily for 10 days	3.8 mL once daily for 10 days
>23 to 40	6–9 Years	60 mg once daily for 10 days	5 mL once daily for 10 days
>40	≥10 Years	75 mg once daily for 10 days	6.2 mL once daily for 10 days

**Table 8. Dosage for Prevention of 2009 Influenza A (H1N1) in Adolescents ≥13 Years of Age†**

75 mg once daily for at least 10 days following close contact with an infected individual.

**Treatment of Avian Influenza A Virus Infections†**

**Oral:** Children: 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 also warranted in patients who present for care in the late stages of illness.

**Prevention of Avian Influenza A Virus Infections†**

**Oral:** Children: Dosage usually recommended for prophylaxis of seasonal influenza A and B virus infections has been recommended. No evidence to date that an increase in dosage or duration is necessary in individuals who have had a single exposure to influenza A (H5N1), but a longer duration of prophylaxis may be necessary in those with repeated or prolonged exposure.

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:** Children: 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. (See Treatment of 2009 Influenza A (H1N1) Virus Infections and Prevention of 2009 Influenza A (H1N1) Virus Infections under Dosage: Pediatric Patients.)

**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; efficacy not established if treatment begins >40 hours after symptoms have been established.

**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).

75 mg once daily has been given for up to 6 weeks during a community outbreak of influenza. Individualize duration of prophylaxis. For maximum effectiveness, must be taken every day during influenza activity in the community.

**Treatment of 2009 Influenza A (H1N1) Virus Infections†**

**Oral:** 75 mg twice daily for 5 days. CDC states that hospitalized patients with severe infections (e.g., those with prolonged infection or those admitted into an intensive care unit) may require a longer duration of treatment.

When indicated, treatment should preferably begin within 2 days of symptom onset. CDC states that some studies in hospitalized patients suggest benefit, including decreased mortality or duration of hospitalization, even when treatment is started >48 hours after illness onset.

**Prevention of 2009 Influenza A (H1N1) Virus Infections†**

**Oral:** 75 mg once daily for 10 days following close contact with an infected individual.

Consider antiviral prophylaxis against 2009 influenza A (H1N1) virus infections† only in certain situations and in certain individuals. (See 2009 Influenza A (H1N1) Infections under Uses.) Continue prophylaxis (if initiated) for 10 days after the last known exposure to a confirmed case. Consult CDC website for the most recent information regarding who should receive prophylaxis for these infections, including information on outbreak control (<http://www.cdc.gov/h1n1flu/recommendations.htm>).

**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 also warranted in patients who present for care in the late 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. No evidence to date that an increase in dosage or duration is necessary in individuals who have had a single exposure to influenza A (H5N1), but a longer duration of prophylaxis may be necessary in those with repeated or prolonged exposure.

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). Oseltamivir prophylaxis in a dosage of 75 mg daily generally well tolerated for up to 6 weeks.

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. (See Treatment of 2009 Influenza A

## Special Populations

### Hepatic Impairment

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

### 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.

Treatment of 2009 influenza A (H1N1) infections† in patients with  $Cl_{cr}$  10–30 mL/minute: 75 mg once daily for 5 days.

Prevention of 2009 influenza A (H1N1) 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.

No dosage recommendations 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

#### Warnings

##### **Nervous System Effects**

Adverse neuropsychiatric events (e.g., self-injury, delirium, hallucinations, confusion, abnormal behavior, seizures) and death reported. Influenza also may be associated with neurologic and behavioral symptoms. Events may occur in the setting of encephalitis or encephalopathy; events also have occurred in those without clinically apparent severe disease. Role of oseltamivir not determined.

Postmarketing reports of self-injury and delirium reported mainly in children from Japan. Monitor patients with influenza for signs of abnormal behavior. If neuropsychiatric adverse effects develop, consider risks versus benefits of continued therapy.

#### Sensitivity Reactions

##### **Hypersensitivity Reactions**

Anaphylaxis reported rarely. If an allergic reaction occurs or is suspected, discontinue drug and institute appropriate therapy as indicated.

##### **Dermatologic Effects**

Toxic epidermal necrosis, Stevens-Johnson Syndrome, or erythema multiforme reported rarely.

#### General Precautions

##### **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.

Manufacturer states efficacy for treatment or prevention of influenza not established in immunocompromised patients. Has been used in some immunocompromised individuals†, including BMT recipients, hematopoietic stem cell 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.

##### **Prior Use**

No data available regarding safety and efficacy of repeated courses of oseltamivir for treatment or prevention of influenza.

##### **Differential Diagnosis**

When making treatment decisions in patients with suspected influenza, consider the possibility of primary or concomitant bacterial infection for which oseltamivir would be ineffective.

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

##### **Influenza Vaccination**

Oseltamivir is not a substitute for annual vaccination with seasonal influenza virus vaccine inactivated or seasonal influenza virus vaccine live intranasal and is not a substitute for vaccination with influenza A (H1N1) 2009 monovalent vaccine inactivated or influenza A (H1N1) 2009 monovalent vaccine live intranasal.

Seasonal influenza virus vaccines used for the 2009-2010 influenza season are not expected to provide protection against infection with 2009 influenza A (H1N1) virus. Influenza A (H1N1)

2009 monovalent vaccines are not expected to provide protection against infection with seasonal influenza A or B viruses.

Antiviral agents used for treatment or prevention of influenza (amantadine, oseltamivir, rimantadine, zanamivir) may be used concomitantly with parenteral inactivated seasonal influenza virus vaccine or parenteral inactivated influenza A (H1N1) 2009 vaccine if indicated.

Intranasal live influenza virus vaccine or intranasal live influenza A (H1N1) 2009 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. (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.

Decisions to use oseltamivir during pregnancy should be made on a case-by-case basis.

For treatment or prevention of seasonal influenza infections, the USPHS Advisory Committee on Immunization Practices (ACIP) states that oseltamivir should be used during pregnancy only if potential benefits justify potential risks to the fetus.

Pregnant women are at increased risk for severe complications and death from seasonal influenza or 2009 influenza A (H1N1).

CDC states that pregnancy is not considered a contraindication to use of oseltamivir for treatment or prevention of seasonal influenza or 2009 influenza A (H1N1) infections†; 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 seasonal influenza or 2009 influenza A (H1N1) infection 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 children <1 year of age.

Not indicated for treatment or prevention of influenza in children <1 year of age because of uncertainties regarding the rate of development of the human blood-brain barrier and because it is not known whether toxicology data reported in animals are clinically relevant for human infants.

Temporarily authorized by FDA for emergency treatment or prevention of 2009 influenza A (H1N1) infections† in children <1 year of age. (See 2009 Influenza A (H1N1) Virus Infections under Uses.)

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

##### **Geriatric Use**

Safety and efficacy profiles similar to those in younger adults.

##### **Hepatic Impairment**

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

##### **Renal Impairment**

Decreased clearance. Reduce dosage if  $Cl_{cr}$  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.

## Drug 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
<b>Acetaminophen</b>	No pharmacokinetic interaction	
<b>Amoxicillin</b>	No pharmacokinetic interaction	
<b>Antacids (containing magnesium, aluminum, or calcium carbonate)</b>	No clinically important effect on oseltamivir pharmacokinetics	
<b>Aspirin</b>	Pharmacokinetic interactions unlikely	
<b>Cimetidine</b>	No pharmacokinetic interaction	
<b>Influenza virus vaccines</b>	No interference with antibody response to parenteral inactivated influenza virus vaccines Potential interference with antibody response to intranasal live influenza virus vaccines; no specific studies	Parenteral inactivated influenza vaccines may be administered concomitantly with oseltamivir Do not administer an intranasal live influenza virus vaccine until at least 48 hours after oseltamivir is discontinued; do not administer oseltamivir until at least 2 weeks after administration of an intranasal live influenza vaccine  If oseltamivir and intranasal live influenza A (H1N1) 2009 vaccine are administered concomitantly, consider revaccination if appropriate; in recommendations regarding seasonal intranasal live influenza vaccine, experts recommend revaccination if an influenza antiviral was given 2 days before to 14 days after vaccination
<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; do not freeze. Reconstituted oral suspension should be used within 10 days.

#### Extemporaneous Oral Suspension

Extemporaneous oral suspensions prepared by dissolving contents of oseltamivir capsules in 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.

#### Bulk Storage Containers

Oseltamivir phosphate in bulk storage containers (not commercially available in the US) for extemporaneous preparation of oral preparations in pandemic situations is expected to be stable for 8 years. Extemporaneous oral preparations, prepared by dissolving the bulk powder 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 and 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.
- Influenza viruses with reduced susceptibility to oseltamivir carboxylate reported. Almost all influenza A (H1N1) viruses circulating in the US in late 2008 and early 2009 were resistant to oseltamivir. Avian influenza A (H5N1) with reduced in vitro susceptibility or resistance to oseltamivir isolated from a few oseltamivir-treated patients in Vietnam during 2005; some isolates remained susceptible to zanamivir.
- To date, isolates of 2009 influenza A (H1N1) virus have been susceptible to zanamivir and resistant to amantadine and rimantadine. Although most isolates have been susceptible to oseltamivir, a few isolates have been resistant to oseltamivir.
- Oseltamivir and zanamivir bind to different sites on the neuraminidase enzyme, and cross-resistance between the drugs is variable.

## Advice to Patients

- 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 >40 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 using the graduated oral dosing dispenser provided with the commercially available powder for oral suspension.
- 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

#### Oral

#### Capsules

30 mg (of oseltamivir)

**Tamiflu**<sup>®</sup>, Roche

45 mg (of oseltamivir)

**Tamiflu**<sup>®</sup>, Roche

75 mg (of oseltamivir)

**Tamiflu**<sup>®</sup>, Roche

#### For suspension

12 mg (of oseltamivir) per mL

**Tamiflu**<sup>®</sup>, Roche

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

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