

Oseltamivir Phosphate

Neuraminidase Inhibitors 8:18.28 (AHFS primary)

■ Oseltamivir phosphate is a prodrug of oseltamivir carboxylate, a sialic acid analog and neuraminidase inhibitor antiviral agent that is pharmacologically related to zanamivir and active against influenza A and B viruses.

Uses

In this monograph, the term influenza A virus refers to those virus subtypes that occur widely in humans (known as seasonal influenza); there are 3 known subtypes of human influenza A viruses (H1, H2, H3). The term avian influenza virus refers to influenza A subtypes that occur mainly in birds, but have also rarely caused infection in humans (H5N1, H7N2, H7N3, H7N7, H9N2). The term 2009 influenza A (H1N1) refers to a virus containing a unique combination of gene segments not previously reported in the US or elsewhere prior to 2009.

■ Treatment of Seasonal Influenza A and B Virus Infections

Oseltamivir is used for the symptomatic *treatment* of uncomplicated acute illness caused by influenza A or B virus in adults, adolescents, and children 1 year of age or older who have been symptomatic for no longer than 2 days. Efficacy of oseltamivir for the symptomatic treatment of influenza infection in patients whose symptoms have been present for more than 40 hours has not been established.

Emergence of oseltamivir-resistant influenza virus may decrease effectiveness of the drug.

The US Centers for Disease Control and Prevention (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 younger than 2 years of age, adults 65 years of age or older, 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 younger than 19 years of age who are receiving long-term aspirin therapy. If treatment is indicated, it should be initiated as early as possible; initiation of treatment should not be delayed 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 Uses: 2009 Influenza A (H1N1) Virus Infections.) 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.

When assessing a possible case of influenza, 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. The use of diagnostic tests to distinguish influenza A and B should be considered.

CDC recommends that adamantanes (amantadine, rimantadine) *not* be used alone for the treatment of *seasonal* influenza in the US until susceptibility to these antiviral agents has been reestablished in circulating influenza A viruses. During the 2005-2006 influenza season, most influenza A (H3N2) strains circulating in the US were resistant to amantadine and rimantadine. Resistance to amantadine and rimantadine among influenza A isolates remained high during the 2006-2007 and 2007-2008 influenza seasons, especially in influenza A (H3N2).

There currently are 4 antivirals available in the US for the treatment of influenza infection, the adamantanes (amantadine, rimantadine) and the neuraminidase inhibitors (oseltamivir, zanamivir). The most appropriate antiviral is selected based on information regarding the likelihood that the influenza strain is susceptible and the known adverse effects of the drug. The fact that strains of circulating influenza viruses and the antiviral susceptibility of these strains constantly evolves should be considered. The neuraminidase inhibitors generally are active against both influenza A and B and are considered less toxic and less likely than the adamantanes to promote development of drug-resistant influenza. The adamantanes are only active against influenza A; in addition, the adamantanes are associated with several clinically important adverse effects and with rapid emergence of drug-resistant viral variants. The comparative efficacy of the neuraminidase inhibitors versus the adamantanes in the treatment of influenza A infections caused by susceptible strains and the comparative efficacy of oseltamivir versus zanamivir in the treatment of influenza A or B virus infections caused by susceptible strains have not been evaluated.

Information regarding influenza surveillance and updated recommendations for treatment of seasonal influenza are available from CDC at <http://www.cdc.gov/flu>.

Adults and Adolescents

Efficacy of oseltamivir for the treatment of seasonal influenza in adults has been established in randomized placebo-controlled studies in which the predominant influenza infection was influenza A; only a limited number of adults in studies to date have been infected with influenza B. When initiated within 40 hours of onset

of symptoms in otherwise healthy adults with uncomplicated influenza, the drug has decreased the severity of influenza symptoms (i.e., nasal congestion, sore throat, cough, aches, fatigue, headache, chills/sweats) and shortened the average duration of these symptoms by about 1.3 days. When used in geriatric patients 65 years of age or older, oseltamivir has reduced the time to symptom improvement by 1 day.

Analysis of data from several studies indicated that adults who received oseltamivir for seasonal influenza had a lower incidence of respiratory complications requiring anti-infective therapy and hospitalization. Individuals who initiate therapy sooner (i.e., no later than 24 hours after symptom onset) exhibit greater benefit (e.g., a 2-day decrease in symptom duration). Oseltamivir therapy also has reduced the magnitude and duration of viral replication.

Children 1-12 Years of Age

Efficacy of oseltamivir for the treatment of seasonal influenza in children 1-12 years of age has been established in a placebo-controlled study in children infected with influenza A (67%) or influenza B (33%). When used in these children within 48 hours of symptom onset, the drug reduced influenza symptoms (i.e., cough, coryza, duration of fever) and shortened the average duration of illness by about 1.5 days. Data from this study also indicate that children who received oseltamivir had a lower incidence of newly diagnosed otitis media (a common secondary complication of influenza) than those who received placebo.

In a study in children 6-12 years of age with asthma who received oseltamivir or placebo for the treatment of acute influenza virus infection, use of oseltamivir improved pulmonary function and reduced the risk of influenza-induced asthma exacerbations. When initiated within 48 hours of symptom onset, oseltamivir shortened the duration of illness in these children by about 24 hours; however, if initiated within 24 hours of symptom onset, oseltamivir shortened the duration of illness by about 40 hours.

Immunocompromised Individuals

Although the manufacturer states that efficacy of oseltamivir for the treatment of influenza in immunocompromised patients has not been established, oseltamivir has been used to treat seasonal influenza A or B virus infections in bone marrow transplant recipients† in a prospective, uncontrolled study. This study provides some evidence that oseltamivir treatment (75 mg twice daily for 5 days) may prevent influenza complications and is not associated with any unusual adverse effects in these patients. Oseltamivir also has been used for the treatment of influenza infections in hematopoietic stem cell transplant (HSCT) recipients†. Treatment with oseltamivir prevented progression to pneumonia in influenza-infected HSCT recipients in a small study.

■ Prevention of Seasonal Influenza A and B Virus Infections

Oseltamivir is used for the *prophylaxis* of influenza A or B virus infection in adults, adolescents, and children 1 year of age or older.

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. Individuals who are 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 more than 48 hours has elapsed since contact with the patient with influenza.

CDC recommends that adamantanes (amantadine, rimantadine) *not* be used for prevention of seasonal influenza in the US until susceptibility to these antiviral agents has been reestablished in circulating influenza A viruses. During the 2005-2006 influenza season, most influenza A (H3N2) strains circulating in the US were resistant to amantadine and rimantadine. Resistance to amantadine and rimantadine among influenza A isolates remained high during the 2006-2007 and 2007-2008 influenza seasons, especially in influenza A (H3N2).

Annual vaccination with seasonal influenza virus vaccine is considered the primary means of preventing seasonal influenza and its severe complications. However, prophylaxis with an appropriate antiviral agent is an important adjunct for the control and prevention of influenza.

For information on prevention and control of influenza, including CDC guidelines, see Prevention of Influenza A Virus Infections under Uses, in Amantadine 8:18.04.

Information regarding influenza surveillance and updated recommendations for prevention of seasonal influenza are available from CDC at <http://www.cdc.gov/flu>.

Adults and Adolescents

Results of community studies in healthy, unvaccinated adults indicate that oseltamivir is about 82% effective in preventing febrile, laboratory-confirmed influenza illness. Efficacy of oseltamivir in preventing naturally occurring influenza illness has been demonstrated in seasonal prophylaxis studies and in postexposure prophylaxis studies in households. The primary efficacy parameter for these studies was the incidence of laboratory-confirmed clinical influenza, which was defined as oral

temperature exceeding 37.2°C with at least one respiratory symptom (cough, sore throat, nasal congestion) and at least one constitutional symptom (aches and pain, fatigue, headache, chills/sweats) all occurring within a single 24-hour period and either a positive virus isolation or a fourfold increase in virus antibody titer from baseline.

In 2 seasonal prophylaxis studies in healthy, unvaccinated adults and adolescents 13–65 years of age who received oseltamivir (75 mg once daily) or placebo for 42 days during a community outbreak, the incidence of laboratory-confirmed clinical influenza was 1.2 or 4.8% of those receiving oseltamivir or placebo, respectively. In a seasonal prophylaxis study in geriatric residents of skilled nursing facilities (80% vaccinated, 14% with chronic airway obstructive disorders, 43% with cardiac disorders) who received oseltamivir (75 mg once daily) or placebo for 42 days, the incidence of laboratory-confirmed clinical influenza was 0.4 or 4.4% of those receiving oseltamivir or placebo, respectively.

In a postexposure prophylaxis study in household contacts (13 years of age or older) of influenza-infected index cases (not treated with antivirals) who received oseltamivir (75 mg once daily) or placebo for 7 days within 2 days of onset of symptoms in the index case, the incidence of laboratory-confirmed clinical influenza was 1 or 12% of those receiving oseltamivir or placebo, respectively. In another postexposure prophylaxis study, there was evidence that oseltamivir prophylaxis effectively reduced the secondary spread of influenza within households when given to household contacts of index patients who were receiving the drug for treatment.

Children 1–12 Years of Age

Efficacy of oseltamivir in preventing naturally occurring influenza illness in children 1–12 years of age was evaluated in a randomized, open-label, postexposure prophylaxis study. In this study, oseltamivir prophylaxis was used during a documented community influenza outbreak and was given to adults and children 1 year of age or older residing in households that had an index patient with an influenza-like illness who was receiving oseltamivir for treatment. The primary efficacy parameter for this study was the incidence of laboratory-confirmed clinical influenza (defined as oral temperature 37.8°C or higher with cough and/or coryza occurring within a single 48-hour period and either a positive virus isolation or a fourfold or greater increase in virus antibody titer from baseline). In household contacts 1–12 years of age not shedding virus at baseline, the incidence of laboratory-confirmed clinical influenza was 3 or 17% in those receiving oseltamivir or placebo, respectively. The overall incidence of influenza illness in children who received oseltamivir prophylaxis was higher than that in adults and adolescents 13 years of age or older who received such prophylaxis.

Immunocompromised Individuals

Although the manufacturer states that efficacy of oseltamivir for prevention of influenza in immunocompromised patients has not been established, the drug has been used in some immunocompromised individuals† for influenza prophylaxis. In a prospective, uncontrolled study, oseltamivir was used for prophylaxis of influenza in cancer patients‡ 6.3–23.4 years of age who were immunocompromised because of current or recent chemotherapy or bone marrow transplantation. There were no laboratory-confirmed cases of influenza in the study participants; however, a few patients withdrew from the study because of adverse GI effects.

■ **2009 Influenza A (H1N1) Virus Infections**

Oseltamivir is recommended for the 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. The 2009 influenza A (H1N1) virus appears to be a triple-reassortant swine influenza virus containing genes from human, swine, and avian influenza A viruses. The virus contains a unique combination of gene segments not previously reported among human or swine influenza A in the US or elsewhere. As of October 2009, 99% of circulating influenza viruses in the US were identified as 2009 influenza A (H1N1).

The 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 younger than 2 years of age, adults 65 years of age or older, 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 younger than 19 years of age who are receiving long-term aspirin therapy. If treatment is indicated, it should be initiated as early as possible; initiation of treatment should not be delayed 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 US Food and Drug Administration (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. Individuals who are 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 more than 48 hours has elapsed since contact with the individual with influenza.

CDC states that adults and adolescents with human immunodeficiency virus (HIV) infection 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, CDC states that oseltamivir may be preferred for treatment of 2009 influenza A (H1N1) in pregnant women because of its systemic activity; the drug of choice for prophylaxis in these patients is less clear. (See Pregnancy under Warnings/Precautions: Specific Populations, in Cautions.) CDC states that antiviral treatment or prophylaxis is not a contraindication for breastfeeding.

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 the 2009 influenza A (H1N1) virus. Although safety and efficacy of oseltamivir have not been established in children younger than 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 on use of antiviral agents for the treatment or prevention of infections caused by the 2009 influenza A (H1N1) virus may change as additional data become available (e.g., additional antiviral susceptibility data, efficacy data). The CDC website should be consulted for the most recent information regarding case definitions of confirmed, probable, and suspected 2009 influenza A (H1N1) infections and recommendations regarding diagnosis, treatment, and prophylaxis (including outbreak control) of these infections (<http://www.cdc.gov/h1n1flu/>).

■ **Avian Influenza A Virus Infections**

Oseltamivir has been used in a limited number of patients for the treatment of avian influenza A virus infections† (H5N1, H7N3, H7N7). Oseltamivir also has been used for prophylaxis of avian influenza A infections† (H5N1, H7N7).

Risk of Exposure and Infection

Although avian influenza A viruses usually do not infect humans, infection with these viruses has been reported following exposure to infected poultry. It can be anticipated that human cases of avian influenza A will continue to be detected in countries where these viruses circulate in wild birds, outbreaks occur in poultry, and close human contact with poultry is common (e.g., backyard flocks, markets).

Since 2003, highly pathogenic avian influenza A (H5N1) infection in poultry or wild birds has been reported in Asia (Cambodia, China, Hong Kong, Indonesia, Japan, Laos, Malaysia, Mongolia, Myanmar, South Korea, Thailand, Vietnam), Africa (Benin, Burkina Faso, Cameroon, Djibouti, Ghana, Ivory Coast, Niger, Nigeria, Sudan, Togo), Europe and Eurasia (Albania, Austria, Azerbaijan, Bosnia and Herzegovina, Bulgaria, Czech Republic, Croatia, Denmark, France, Georgia, Germany, Greece, Hungary, Italy, Mongolia, Poland, Romania, Russia, Serbia and Montenegro, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, Ukraine, United Kingdom), and in Afghanistan, Bangladesh, Egypt, India, Iran, Iraq, Israel, Jordan, Kazakhstan, Kuwait, Nepal, Pakistan, and Saudi Arabia. Spread to poultry in additional countries is likely. There also have been documented reports of avian influenza (H5N1) infection in pigs in China and in tigers and leopards in Thailand. Although avian influenza A (H5N1) also has been reported recently in several domestic cats in Germany and Austria and in a stone marten (a mammal) on the German island of Ruegen, these infections appear to have been associated with local outbreaks of influenza A (H5N1) in domestic or wild birds and probably were acquired through ingestion of infected birds.

The first human cases of avian influenza A (H5N1) infection were reported in Hong Kong in 1997. Between December 2003 and August 2009, there have been a total of 440 laboratory-confirmed human cases of avian influenza A (H5N1) infection (including 262 fatalities) reported to the World Health Organization (WHO). These human cases occurred in Azerbaijan, Bangladesh, Cambodia, China, Djibouti, Egypt, Indonesia, Iraq, Laos, Myanmar, Nigeria, Pakistan, Thailand, Turkey, and Vietnam.

In addition to confirmed human cases of avian influenza A (H5N1) illness, confirmed human cases of H7N2, H7N3, H7N7, and H9N2 avian influenza A infection and illness have been reported in other countries (including a few cases in Canada and the US). There was a large outbreak of avian influenza A (H7N7) in commercial poultry

farms in the Netherlands in 2003 that resulted in large numbers of human cases of H7N7 infection (principally conjunctivitis and influenza-like illnesses).

Experience to date indicates that human cases of avian influenza infection are rare and that these viruses do not transmit easily from poultry to humans. The majority of human cases have occurred in rural areas; however, cases have been reported in urban areas. Most, but not all, human cases reported to date have been linked to direct contact with infected poultry, uncooked poultry products, or surfaces contaminated with infected poultry feces or respiratory secretions. Exposure risk appears greatest during slaughter, defeathering, butchering, and preparation of poultry for cooking. Although transmission of H5N1 viruses to 2 individuals through consumption of uncooked duck blood has been reported, there is no evidence that properly cooked poultry or poultry products are a source of infection. Sustained person-to-person transmission of avian influenza viruses has not been reported to date, but limited person-to-person transmission of H5N1 viruses has been reported in Vietnam and Thailand. In addition, person-to-person transmission of H7N7 occurred among household contacts during the outbreak of that virus that occurred in the Netherlands.

In humans, avian influenza A viruses can cause typical influenza illness (fever, cough, sore throat, muscle aches), conjunctivitis, or respiratory disease; however, severe illness can occur, especially with H5N1. The fatality rate in patients hospitalized with H5N1 infection has been high (exceeding 50%). In one group of patients in Vietnam with severe H5N1 infections, the median time to death was 9 days (range[†] 6–17 days) with or without treatment.

Avian influenza A virus strains isolated during the past several years (including the H5N1 strains that infected poultry in 2005 and caused human illness) are resistant to adamantanes (amantadine, rimantadine). Many avian influenza A virus strains (e.g., H5N1, H7N7, H9N2) have been susceptible to oseltamivir *in vitro* and H5N1 and H9N2 have been susceptible to oseltamivir *in vivo* in animal studies. However, avian influenza A (H5N1) isolates that have reduced susceptibility or are resistant to oseltamivir *in vitro* have been reported. (See Spectrum and see Resistance.)

Travelers.

The CDC does *not* currently recommend that the general public avoid travel to any of the countries that have had poultry outbreaks or human cases of avian influenza A (H5N1). However, the CDC and WHO recommend that travelers to these areas avoid direct contact with poultry and practice careful and frequent handwashing. The CDC recommends that such travelers avoid direct contact with poultry (including touching well-appearing, sick, or dead chickens and ducks), avoid places such as poultry farms and bird markets where live poultry are raised or kept, and avoid handling surfaces contaminated with poultry feces or secretions. Because influenza viruses are destroyed by heat, all foods from poultry that comes from these areas (including eggs and poultry blood) should be thoroughly cooked; egg yolks should not be runny or liquid and poultry meat should be cooked to a temperature of 74°C. Additional information for travelers can be obtained at the CDC website (<http://www.cdc.gov/travel>).

Treatment and Prevention

Because the continuing spread of highly pathogenic avian influenza A (H5N1) in poultry and wild waterfowl has increased the opportunities for transmission of the virus to humans, WHO has provided guidance on use of antiviral agents for treatment of H5N1-infected patients and for chemoprophylaxis. Recommendations were developed by an expert panel and apply to the current pre-pandemic situation. These recommendations take into account different specific patients and exposure groups and make recommendations for or against specific actions regarding treatment and chemoprophylaxis of H5N1 virus infection. Evidence for these recommendations is based on small observational case studies of H5N1 patients, *in vitro* and animal model studies of H5N1, and studies that evaluated treatment and prophylaxis of seasonal influenza. The quality of evidence for these recommendations is considered low.

Treatment.

For the *treatment* of patients with clinically confirmed or strongly suspected avian influenza A (H5N1) illness[†], the WHO recommends initiation of therapy with oseltamivir as soon as possible. When neuraminidase inhibitors are available, amantadine and rimantadine should *not* be used alone for the treatment of these infections. Clinicians can consider treatment with a neuraminidase inhibitor (i.e., oseltamivir) and an adamantane (amantadine, rimantadine) in a patient with pneumonic disease or clinical progression if local surveillance data indicates that the H5N1 virus is known or likely to be susceptible to an adamantane.

Only limited data are available to date regarding treatment of human cases of avian influenza A virus infections. Data from observational studies indicate that early initiation of oseltamivir therapy is associated with a reduction in mortality in influenza A (H5N1)-infected patients. Because this virus continues to replicate for prolonged periods of time, treatment with oseltamivir also is warranted in patients who present for care in the late stages of illness. The optimum dosage and duration of oseltamivir therapy for H5N1 infections are unknown. Although some individuals with avian influenza A (H5N1) infections who were treated with oseltamivir died, it is unclear whether these deaths were related to a lack of efficacy, a delay in diagnosis and initiation of oseltamivir treatment, or the dosage regimen used.

Prevention.

Oseltamivir is used for *prophylaxis* of influenza A infections[†] under certain exposure situations. When neuraminidase inhibitors are available, WHO states that oseltamivir should be used for postexposure chemoprophylaxis in high-risk exposure groups (household or close family contacts of individuals with strongly suspected or confirmed H5N1 illness); zanamivir is considered an alternative agent. WHO states

that use of oseltamivir or zanamivir for postexposure prophylaxis can be considered in moderate-risk exposure groups (personnel who handled sick animals or were involved in decontamination of affected environments when appropriate protective equipment was not used properly; individuals with unprotected close direct exposure to sick or dead animals infected with H5N1 virus or birds implicated in human cases; health-care workers with unprotected or insufficiently protected close contact with strongly suspected or confirmed H5N1-infected patients [e.g., those involved in aerosol-generating procedures, those exposed to body fluids, laboratory personnel with exposure to virus-containing samples]).

WHO states that chemoprophylaxis with oseltamivir or zanamivir probably should not be used for low-risk exposure groups (health-care workers not in close contact with strongly suspected or confirmed H5N1-infected patients and having no direct contact with infectious material from such patients; health-care workers who used appropriate protective equipment during exposure to an infected patient; personnel involved in culling non-infected or likely non-infected animal populations as a control measure; personnel who handled sick animals or were involved in decontamination of affected environments who used appropriate protective equipment). Pregnant women in the low-risk group should not receive oseltamivir or zanamivir for chemoprophylaxis.

The CDC recommends that individuals involved in activities to control and eradicate outbreaks of avian influenza in poultry in the US receive an influenza antiviral agent daily during the time the individual is in direct contact with infected poultry or contaminated surfaces. When possible, the choice of antiviral agents should be based on *in vitro* susceptibility testing; in the absence of susceptibility testing, oseltamivir is the first choice because it is less likely that the virus will be resistant to a neuraminidase inhibitor than to adamantanes (amantadine, rimantadine).

Oseltamivir was used for the treatment and prophylaxis of human influenza A (H7N7) infections (principally conjunctivitis and influenza-like illnesses) that occurred in the Netherlands as the result of an outbreak in poultry.

The role of H5N1 influenza vaccine in preventing or reducing the risk of severe illness in individuals exposed to influenza A H5N1 virus remains to be determined.

■ Pandemic Influenza

Influenza viruses cause seasonal epidemics and, occasionally, global pandemics (an epidemic that affects the whole population). Three recent influenza pandemics include one that occurred in 1918 (origination not identified), 1957 (originated in China), and 1968 (originated in Hong Kong).

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. The 2009 influenza A (H1N1) virus contains a unique combination of gene segments not previously reported in the US or elsewhere. On June 11, 2009, the WHO declared that the first global influenza pandemic in 41 years was occurring 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 Uses: 2009 Influenza A (H1N1) Virus Infections.)

The spread of the highly pathogenic H5N1 strain of avian influenza A in poultry in Asia and other countries that occurred in 2004–2009 represents a potential future pandemic threat.

Dosage and Administration

■ Administration

Oseltamivir phosphate is administered orally without regard to meals, although administration with meals may improve GI tolerability.

Oseltamivir phosphate is 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 of oseltamivir per mL.

The oral suspension is preferred for patients who have difficulty swallowing 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 unavailable (e.g., a shortage occurs during an emergency situation), a pharmacist can prepare an oral suspension extemporaneously using the commercially available capsules of the drug. These extemporaneous oral suspensions should *not* be used for convenience or when the commercial powder for oral suspension is available. The manufacturer's information should be consulted for specific information on how to prepare extemporaneous oral suspensions using the commercially available capsules and a cherry syrup vehicle (Humco) or a sugar-free vehicle (Ora-Sweet[®] SF, Paddock). The graduated oral dosing dispenser (oral syringe) provided by the manufacturer with the commercially available powder for oral suspension should *not* be used to administer the extemporaneous oral suspensions prepared from the capsules since the extemporaneous suspensions contain 15 mg of oseltamivir per mL and those prepared from the powder for oral suspension contain 12 mg/mL.

Alternatively, 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, the pharmacist should 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: Administration.)

Reconstitution

The commercially available powder for oral suspension should be reconstituted at the time of dispensing. Tap the bottle to thoroughly loosen the powder and then add the amount of water specified on the bottle; shake well for 15 seconds. Following reconstitution as directed, oseltamivir phosphate oral suspension contains 12 mg of oseltamivir per mL.

For children 1 year of age or older, the graduated oral dosing dispenser (oral syringe) provided by the manufacturer should be used to administer the appropriate dosage of reconstituted oral suspension; alternatively, some other appropriate oral dosing syringe or similar device marked with units of measure that correspond to the required dose may be used.

When the manufacturer's oral dosing dispenser is used for children 1 year of age or older, the container of reconstituted suspension should be shaken for about 5 seconds and the child-resistant cap removed. The plunger of the oral dosing dispenser should be pushed completely down toward the tip of dispenser and the tip inserted firmly into the opening of the bottle adapter. The assembled unit (bottle and oral dispenser) should then be inverted and the appropriate dose withdrawn into the dispenser by slowly pulling the plunger out. In some cases, it may be necessary to withdraw 2 volumes to deliver the desired dose (e.g., a 30- and 45-mg withdrawal to deliver a 75-mg dose). The unit should be turned right side up and the oral dispenser removed slowly from the bottle. The suspension should be dispensed directly into the mouth; it should *not* be mixed with any liquid prior to administration. Following administration, the dispenser should be disassembled, rinsed under running tap water, and air dried prior to subsequent use.

If the reconstituted oral suspension is used for the treatment or prevention of 2009 influenza A (H1N1) virus infections in children younger than 1 year of age†, 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) *must* be used. The oral dosing dispenser (oral syringe) provided by the manufacturer should *not* be used to measure dosages for children younger than 1 year of age and should *not* be dispensed with the reconstituted oral suspension.

■ Dosage

Dosage of oseltamivir phosphate is expressed in terms of oseltamivir.

Systemic availability of oseltamivir carboxylate from an extemporaneous oral preparation prepared from 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.

Treatment of Seasonal Influenza A and B Virus Infections

Adults and Adolescents.

For the *treatment* of influenza infection in adults (including geriatric adults) and adolescents 13 years of age and older, the usual dosage of oseltamivir is 75 mg twice daily for 5 days. Oseltamivir treatment should be initiated within 2 days after the onset of symptoms.

Children 1–12 Years of Age.

For the *treatment* of influenza infection in children 1–12 years of age, the recommended dosage of oseltamivir is 30 mg twice daily for children weighing up to 15 kg, 45 mg twice daily for those weighing more than 15 up to 23 kg, 60 mg twice daily for those weighing more than 23 up to 40 kg, and 75 mg twice daily for those weighing more than 40 kg. Oseltamivir treatment should be initiated within 2 days after the onset of symptoms and continued for 5 days.

Prevention of Seasonal Influenza A and B Virus Infections

Adults and Adolescents.

For the *prophylaxis* of influenza infection in adults (including geriatric adults) and adolescents 13 years of age or older following close contact with an infected individual or during community outbreaks, the usual dosage of oseltamivir is 75 mg once daily for at least 10 days. Oseltamivir prophylaxis should be initiated within 2 days of exposure. Protection lasts as long as oseltamivir therapy is continued. In clinical studies used to establish safety and efficacy for this indication, oseltamivir prophylaxis was continued for up to 6 weeks. Duration of antiviral prophylaxis should be individualized. For maximum effectiveness, the antiviral agent must be taken every day during influenza activity in the community.

Children 1–12 Years of Age.

For the *prophylaxis* of influenza infection in children 1–12 years of age, the recommended dosage of oseltamivir is 30 mg once daily for children weighing up to 15 kg, 45 mg once daily for those weighing more than 15 up to 23 kg, 60 mg once daily for those weighing more than 23 up to 40 kg, and 75 mg once daily for those weighing more than 40 kg. Oseltamivir prophylaxis in these children should be initiated within 2 days of exposure and continued for 10 days. Oseltamivir prophylaxis for longer than 10 days has not been evaluated in pediatric patients 1–12 years of age. Duration of antiviral prophylaxis should be individualized. For maximum effectiveness, the antiviral agent must be taken every day during influenza activity in the community.

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 Uses: 2009 Influenza A (H1N1) Virus Infections.)

When antiviral treatment is indicated, treatment should preferably begin within 2 days of symptom onset and be continued for 5 days. The CDC states that some studies in hospitalized patients suggest benefit, including decreased mortality or duration of hospitalization, even when treatment is started more than 48 hours after illness onset. In addition, the 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.

Adults and Adolescents 13 Years of Age or Older.

For the treatment of 2009 influenza A (H1N1) virus infection† in adults and adolescents 13 years of age or older, CDC recommends an oseltamivir dosage of 75 mg twice daily for 5 days.

Children 1–12 Years of Age.

For the treatment of 2009 influenza A (H1N1) virus infection† in children 1–12 years of age, the US Centers for Disease Control and Prevention (CDC) recommends the following oseltamivir dosage based on weight and age (see Table 1).

Table 1. 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

Children Younger than 1 Year of Age.

Although safety and efficacy of oseltamivir have not been established in children younger than 1 year of age, an Emergency Use Authorization (EUA) issued by the US Food and Drug Administration (FDA) allows emergency use of the drug in this age group for the treatment of 2009 influenza A (H1N1) infections†. The EUA will end when the declaration of emergency is terminated or the EUA is revoked.

For the treatment of 2009 influenza A (H1N1) virus infection in children younger than 1 year of age†, CDC recommends the following oseltamivir dosage based on age (see Table 2).

Table 2. Dosage for Treatment of 2009 Influenza A (H1N1) in Children Younger than 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

Prevention of 2009 Influenza A (H1N1) Virus Infections

Antiviral prophylaxis against 2009 influenza A (H1N1) virus infections† should be considered only in certain situations and in certain individuals. (See Uses: 2009 Influenza A (H1N1) Infections.) If prophylaxis is initiated, it should be continued for 10 days after the last known exposure to a confirmed case. The CDC website should be consulted 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>).

Adults and Adolescents 13 Years of Age or Older.

For the prophylaxis of 2009 influenza A (H1N1) virus infection† in adults and adolescents 13 years of age or older, CDC recommends an oseltamivir dosage of 75 mg once daily for 10 days after the last known exposure to a confirmed case.

Children 1–12 Years of Age.

For the prophylaxis of 2009 influenza A (H1N1) virus infection† in children 1–12 years of age, CDC recommends the following oseltamivir dosage based on weight and age (see Table 3) and for 10 days after the last known exposure to a confirmed case:

Table 3. 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

Children Younger than 1 Year of Age.

Although safety and efficacy of oseltamivir have not been established in children younger than 1 year of age, an EUA issued by FDA allows emergency use of oseltamivir in this age group for the prophylaxis of 2009 influenza A (H1N1) infections†. The EUA will end when the declaration of emergency is terminated or the EUA is revoked. Because there is limited data on use of oseltamivir for prophylaxis in children younger than 3 months of age, CDC does not recommend the drug for prophylaxis in this age group unless such use is judged to be critical.

For the prophylaxis of 2009 influenza A (H1N1) virus infection in children younger than 1 year of age†, CDC recommends the following oseltamivir dosage based on age (see Table 4) and for 10 days after the last known exposure to a confirmed case:

Table 4. Dosage for Prevention of 2009 Influenza A (H1N1) in Children Younger than 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

Avian Influenza A Virus Infections**Treatment.**

Only limited data are available to date regarding *treatment* of avian influenza A virus infection†, and the optimum dosage and duration of oseltamivir for treatment of these infections are unknown.

Some clinicians suggest that the oseltamivir dosage usually recommended for the treatment of seasonal influenza A and B virus infection can be used for the *treatment* of avian influenza A virus infection† in adults and pediatric patients. (See Treatment of Seasonal Influenza A and B Virus Infections under Dosage and Administration: Dosage.) Although this dosage may be reasonable for the treatment of early, mild cases of influenza A (H5N1) infection, the World Health Organization (WHO) and others state that severely ill patients may benefit from treatment with a higher dosage (i.e., 150 mg twice daily in adults) and/or longer duration of therapy (i.e., 7–10 days).

Treatment should be initiated as early as possible. Because this virus continues to replicate for prolonged periods of time, treatment with oseltamivir also is warranted in patients who present for care in the late stages of illness.

Prevention.

WHO states that the oseltamivir dosage usually recommended for prophylaxis of seasonal influenza A and B virus infection can be used for postexposure *prophylaxis* of avian influenza A virus infection† in adults and pediatric patients. There is no evidence to date that an increase in dosage or duration of oseltamivir prophylaxis is necessary in individuals who have had a single exposure to influenza A (H5N1); however, a longer duration of prophylaxis may be necessary in those with repeated or prolonged exposure.

For high-risk exposure groups (household or close family contacts of individuals with strongly suspected or confirmed H5N1 illness), the recommended adult dosage of oseltamivir is 75 mg once daily; oseltamivir should be started as soon as possible after exposure and continued for 7–10 days after the last known exposure. In children 1 year of age or older, the recommended dosage of oseltamivir is 30 mg once daily for those weighing up to 15 kg, 45 mg once daily for those weighing more than 15 up to 23 kg, 60 mg once daily for those weighing more than 23 up to 40 kg, and 75 mg once daily for those weighing more than 40 kg. Data are not available regarding use of oseltamivir prophylaxis in children younger than 1 year of age.

This dosage regimen may be used when chemoprophylaxis with oseltamivir is used in moderate-risk groups (personnel who handled sick animals or were involved in decontamination of affected environments when appropriate protective equipment was not used properly; individuals with unprotected or close direct exposure to sick or dead animals infected with H5N1 virus or birds implicated in human cases; health-care workers with unprotected or insufficiently protected close contact with strongly suspected or confirmed H5N1-infected patients [e.g., those involved in aerosol-generating procedures, those exposed to body fluids, laboratory personnel with exposure to virus-containing samples]). In certain individuals in high-risk situations (e.g., health-care workers if influenza A (H5N1) is being transmitted from person-to-person with increased efficacy, health-care workers involved in high-risk procedures, individuals directly involved in control and eradication of poultry outbreaks), preexposure prophylaxis or repeated or continuous postexposure prophylaxis with the drug may be necessary. Oseltamivir prophylaxis given in a dosage of 75 mg daily generally is well tolerated when given for up to 6 weeks.

Oseltamivir has been given in a dosage of 75 mg daily for prophylaxis in exposed individuals during an outbreak of avian influenza A (H7N7).

Pandemic Influenza

Oseltamivir dosage usually recommended for the treatment or prophylaxis of seasonal influenza A or B infections is considered the *minimum* dosage required for the treatment or prophylaxis of influenza in a pandemic situation†. (See Treatment of 2009 Influenza A [H1N1] Virus Infections and see Prevention of 2009 Influenza A [H1N1] Infections under Dosage and Administration: Dosage.)

■ Dosage in Renal and Hepatic Impairment

For the *treatment* of influenza infection, the recommended oseltamivir dosage for adults with a creatinine clearance of 10–30 mL/minute is 75 mg once daily for 5 days. For *prophylaxis* of influenza infection in adults with a creatinine clearance of 10–30 mL/minute, the recommended dosage is 75 mg every other day or 30 mg daily. Dosage recommendations for patients with end-stage renal failure undergoing routine hemodialysis or continuous peritoneal dialysis are not available.

If oseltamivir is used for the treatment of 2009 influenza A (H1N1) infections† in patients with creatinine clearances of 10–30 mL/minute, the recommended dosage is 75 mg once daily for 5 days. If the drug is used for the prevention of 2009 influenza A (H1N1) infections† in patients with creatinine clearances of 10–30 mL/minute, the recommended dosage is 75 mg once every other day or 30 mg once daily and for 10 days after the last known exposure to a confirmed case. Dosage recommendations for patients with end-stage renal failure or undergoing routine hemodialysis or continuous peritoneal dialysis are not available.

Dosage adjustment is not needed in individuals with mild to moderate hepatic impairment (Child-Pugh score 9 or less).

Cautions

Oseltamivir generally is well tolerated. Adverse effects occurring in 1% or more of adults and at an incidence greater than that with placebo include GI effects (nausea, vomiting, diarrhea, abdominal pain), headache, bronchitis, insomnia, and vertigo. In one study in frail older individuals residing in residential homes or sheltered accommodations, the incidence of adverse effects reported in those receiving oseltamivir was similar to that reported in those receiving placebo.

Safety data from dose-ranging studies indicate that a 5-day course of oseltamivir 150 mg twice daily or a 6-week course of oseltamivir 75 mg twice daily are tolerated as well as the usual recommended dosage for treatment or prophylaxis of influenza.

Adverse effects occurring in 1% or more of children receiving oseltamivir for the treatment of influenza include vomiting, abdominal pain, epistaxis, otic disorder, and conjunctivitis. GI effects, especially vomiting, were the most frequently reported adverse effects in children receiving the drug for prophylaxis of influenza.

Adverse neurologic and/or psychiatric effects have been reported in patients receiving oseltamivir (principally children in Japan). The contribution of oseltamivir to these events has not been established. There have been reports of deaths (12 as of November 2005) in Japanese children 16 years of age or younger receiving oseltamivir for the treatment of influenza. The level of detail in these reports is highly variable, and the role of oseltamivir in these events remains to be determined. (See Cautions: Pediatric Precautions.)

GI Effects

Nausea, with or without vomiting, has been reported in up to 10% of adults or 15% of children receiving oseltamivir and has resulted in discontinuance in less than 1% of adults. Nausea usually occurs after the initial dose and resolves within 1–2 days; administration of the drug with food improves GI tolerance. Diarrhea or abdominal pain has occurred in up to 7 or 2%, respectively, of adults and in 10 or 5%, respectively, of pediatric patients receiving oseltamivir in clinical studies.

Pseudomembranous colitis has been reported rarely in oseltamivir-treated adults.

Nervous System Effects

Headache has occurred in about 2% of adults receiving oseltamivir for treatment of influenza and in about 18% of adults receiving the drug for prophylaxis of influenza. Dizziness, insomnia, vertigo, or fatigue has occurred in up to 2, 1, 1, or 8%, respectively, of adults receiving oseltamivir in clinical studies for the treatment or prevention of influenza. Seizure or confusion has been reported during postmarketing surveillance.

Adverse neuropsychiatric events (e.g., self-injury, delirium, hallucinations, confusion, abnormal behavior, seizures), which occasionally were fatal, have been reported in patients receiving oseltamivir. These events may occur in the setting of encephalitis or encephalopathy; events also have occurred in those without clinically apparent severe disease. Postmarketing reports of self-injury and delirium principally have involved children in Japan. The contribution of oseltamivir to these events has not been established. Patients should be monitored for abnormal behavior. (See Cautions: Pediatric Precautions.)

Dermatologic and Sensitivity Reactions

Anaphylaxis and serious dermatologic reactions (toxic epidermal necrosis, Stevens-Johnson syndrome, erythema multiforme) have been reported rarely in patients receiving oseltamivir, including pediatric patients.

Rash, swelling of the face or tongue, allergy, dermatitis, eczema, or urticaria has been reported during postmarketing surveillance.

Respiratory Effects

Bronchitis or cough has been reported in up to 2 or 5%, respectively, of adults receiving oseltamivir in clinical studies. Pneumonia has occurred in less than 1% of adults receiving oseltamivir. Otitis media, asthma, or epistaxis has occurred in up to 9, 3, or 3% respectively, of oseltamivir-treated pediatric patients. Pneumonia, ear disorder, sinusitis, bronchitis, or tympanic membrane disorder has been reported in less than 2% of pediatric patients receiving oseltamivir for the treatment of influenza.

Other Adverse Effects

Hepatitis or abnormal liver function test values have been reported during postmarketing surveillance.

Unstable angina, anemia, fracture (humerus), pyrexia, or peritonsillar abscess has been reported in less than 1% of oseltamivir-treated adults.

Conjunctivitis or lymphadenopathy has occurred in 1% of oseltamivir-treated children.

Arrhythmia or metabolic events (e.g., deterioration in diabetes control) has been reported during postmarketing surveillance.

■ Precautions and Contraindications

Oseltamivir is contraindicated in patients with known hypersensitivity to any ingredient in the formulation. If an allergic reaction occurs or is suspected, oseltamivir should be discontinued and appropriate treatment initiated.

Because there have been postmarketing reports of neuropsychiatric events (e.g., self-injury, delirium) in influenza patients receiving oseltamivir (see Cautions: Pediatric Precautions), patients with influenza (especially children) should be closely monitored for signs of abnormal behavior during oseltamivir treatment. Patients and/or their caregivers should be instructed to immediately contact a health-care professional if there are any signs of unusual behavior during oseltamivir treatment. If neuropsychiatric adverse effects develop, the risks and benefits of continued therapy with oseltamivir should be evaluated.

Efficacy of oseltamivir has not been established in patients with chronic cardiac disease and/or underlying pulmonary disease; however, no difference in incidence of complications between drug and placebo has been observed in these populations. Safety and efficacy have not been established in those with any medical condition severe or unstable enough to require inpatient care. In addition, efficacy of oseltamivir treatment of influenza has not been established in patients whose symptoms have been present for longer than 40 hours.

The manufacturer states that efficacy of oseltamivir for treatment or prevention of influenza in immunocompromised patients has not been established. The drug has been used in some immunocompromised individuals[†], including bone marrow transplant recipients, hematopoietic stem cell transplant (HSCT) recipients, and chemotherapy patients. (See Uses.)

Safety and efficacy of repeated courses of oseltamivir for treatment or prevention of influenza have not been studied.

When making treatment decisions in patients with suspected influenza, the possibility of primary or concomitant bacterial infection for which oseltamivir would be ineffective should be considered. There is no evidence that oseltamivir is effective for illness caused by any organisms other than influenza A or B.

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 the 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.

Although antiviral agents used for treatment or prevention of influenza (oseltamivir, amantadine, rimantadine, zanamivir) may be used concomitantly with parenteral inactivated influenza virus vaccines if indicated, intranasal live influenza virus vaccines 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 Drug Interactions.)

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.

Safety of oseltamivir has not been systematically evaluated in patients with severe hepatic impairment.

Dosage adjustments are recommended for patients with a creatinine clearance of 10–30 mL/minute. Dosage recommendations are not available for patients with end-stage renal failure (i.e., creatinine clearance less than 10 mL/minute) and those undergoing hemodialysis or continuous peritoneal dialysis.

■ Pediatric Precautions

Safety and efficacy of oseltamivir have not been established in children younger than 1 year of age.

An Emergency Use Authorization (EUA) issued by the US Food and Drug Administration (FDA) allows emergency use of oseltamivir for the treatment or prevention of infections caused by 2009 influenza A (H1N1) in children younger than 1 year of age[†]. The EUA will end when the declaration of emergency is terminated or the EUA is revoked. (See Uses: 2009 Influenza A (H1N1) Virus Infections.)

Although oseltamivir has been used in a limited number of Japanese children younger than 1 year of age without evidence of increased mortality or encephalopathy, the drug is *not* indicated in children younger than 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. Administration of a single oseltamivir dose of 1 g/kg (250 times the recommended dose in children) in juvenile rats 7 days old resulted in deaths associated with high brain concentrations of the prodrug (1500 times higher than concentrations seen in adult rats).

Unusual adverse neurologic and/or psychiatric effects, including self-injury, delirium, hallucinations, mental confusion, abnormal behavior, seizures, and encephalitis, have been reported in children 16 years of age and younger receiving oseltamivir. These effects have been reported principally in children in Japan. There also have been reports of deaths (12 as of November 2005) in Japanese children receiving oseltamivir. These deaths were attributed to sudden death (4), cardiorespiratory arrest (4), suicide (1), pneumonia (1), asphyxiation (1), and acute pancreatitis with cardiopulmonary arrest (1). In many cases, a relationship to oseltamivir was difficult to assess because of concomitantly used drugs, comorbid conditions, and/or lack of adequate detail in reports.

There is no evidence that Japanese patients have a pharmacodynamic predisposition for adverse effects since they do not metabolize oseltamivir differently or achieve higher drug concentrations compared with US patients. However, unusual neurologic manifestations of influenza (influenza-associated encephalitis or encephalopathy) have been documented in Japan, and Japanese pediatricians describe a syndrome of rapid onset of fever accompanied by seizures and altered consciousness that progresses to coma within a few days of flu symptom onset. This syndrome has frequently resulted in death or substantial neurologic sequelae. Currently available information suggests that increased reports of neuropsychiatric events in Japanese children receiving oseltamivir are most likely related to an increased awareness of influenza-associated encephalopathy, increased access to the drug in the Japanese population, and a coincident period of intensive monitoring for potential adverse effects. Therefore, based on currently available information, the FDA states that it is unable to conclude that a causal relationship exists between oseltamivir and reported pediatric deaths.

■ Geriatric Precautions

Safety of oseltamivir for the treatment of influenza in geriatric individuals has been established in clinical studies. In addition, safety and efficacy were demonstrated in frail geriatric individuals (many with cardiac and/or respiratory disease) residing in nursing homes who received oseltamivir for up to 42 days for the prevention of influenza.

Oseltamivir dosage adjustments based solely on age are not necessary for geriatric patients older than 65 years of age.

■ Mutagenicity and Carcinogenicity

Oseltamivir was not mutagenic in the Ames microbial test, the human lymphocyte chromosome assay, or the mouse micronucleus test; oseltamivir was mutagenic in the Syrian hamster embryo cell transformation assay. Oseltamivir carboxylate was not mutagenic in the Ames microbial test, the L5178Y mouse lymphoma assay, or the Syrian hamster embryo cell transformation assay.

Oseltamivir was not carcinogenic in studies in rats or mice.

■ Pregnancy, Fertility, and Lactation

Pregnancy

An increased incidence of a variety of minor skeletal abnormalities and variants has been observed in exposed offspring in reproductive studies in rats and rabbits; however, the individual incidence rate of each skeletal abnormality or variant was within the background rate of occurrence in the specific species.

There are no adequate and well-controlled studies using oseltamivir in pregnant women, and the drug should be used during pregnancy only when the potential benefits outweigh the possible risks to the fetus. 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 the potential risks to the fetus.

Pregnant women are at increased risk for severe complications and death from seasonal influenza or 2009 influenza A (H1N1). The 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† and that oseltamivir regimens recommended for such infections in pregnant women are the same as those for other adults.

Because of its systemic absorption, the CDC states that oseltamivir may be preferred when a neuraminidase inhibitor is indicated for the 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.

Fertility

No effects on fertility, mating performance, or early embryonic development were observed in rats given oseltamivir at doses up to 100 times the human systemic exposure of oseltamivir carboxylate.

Lactation

Oseltamivir and oseltamivir carboxylate are distributed into milk in rats. It is not known whether oseltamivir or oseltamivir carboxylate is distributed into human milk. Oseltamivir should be used in a nursing woman only if potential benefits to the woman outweigh the potential risks to the infant.

Drug Interactions

■ **Drugs Affected or Metabolized by Hepatic Microsomal Enzymes**

Oseltamivir phosphate and its active metabolite, oseltamivir carboxylate, are not metabolized by and do not inhibit cytochrome P-450 (CYP) isoenzymes; interactions with drugs that are substrates for or inhibitors of these enzymes are unlikely.

■ **Drugs Eliminated by Renal Excretion**

Concomitant use of oseltamivir with other drugs eliminated by renal tubular secretion (e.g., probenecid) may result in pharmacokinetic interactions; however, clinically important interactions are unlikely.

■ **Acetaminophen**

Oseltamivir does not affect the pharmacokinetics of acetaminophen.

■ **Amoxicillin**

Pharmacokinetic interactions are unlikely if oseltamivir is used concomitantly with amoxicillin.

■ **Antacids**

Concomitant use of oseltamivir and antacids containing magnesium hydroxide, aluminum hydroxide, or calcium carbonate does not have a clinically important effect on the pharmacokinetics of the antiviral agent.

■ **Aspirin**

Pharmacokinetic interactions are unlikely if oseltamivir is used concomitantly with aspirin.

■ **Cimetidine**

Concomitant use of cimetidine does not affect plasma concentrations of oseltamivir or oseltamivir carboxylate.

■ **Influenza Virus Vaccines**

Oseltamivir may be used concomitantly with seasonal influenza virus vaccine inactivated or influenza A (H1N1) 2009 monovalent vaccine inactivated if indicated. Although drug interaction studies have not been conducted to evaluate the immune response to influenza virus vaccine inactivated in patients receiving oseltamivir, oseltamivir therapy does not appear to impair normal humoral antibody response to infection in patients with naturally or experimentally acquired influenza.

Safety and efficacy of concomitant use of seasonal influenza virus vaccine live intranasal or influenza A (H1N1) 2009 monovalent vaccine live intranasal with antiviral agents used for the treatment or prevention of influenza (e.g., amantadine, oseltamivir, rimantadine, zanamivir) have not been studied. Because influenza antiviral agents reduce replication of influenza viruses, seasonal influenza virus vaccine live intranasal or influenza A (H1N1) 2009 monovalent vaccine live intranasal should not be administered until at least 48 hours after oseltamivir is discontinued, and oseltamivir should not be administered until at least 2 weeks after administration of an intranasal live influenza vaccine. If oseltamivir and influenza A (H1N1) 2009 monovalent vaccine live intranasal are administered concomitantly, revaccination should be considered if appropriate; in recommendations regarding seasonal influenza virus vaccine live intranasal, the US Public Health Service Advisory Committee on Immunization Practices (ACIP) recommends revaccination if an influenza antiviral was given 2 days before to 14 days after vaccination.

■ **Probenecid**

Concomitant use of oseltamivir with probenecid may result in increased systemic exposure to oseltamivir carboxylate because of decreased renal tubular secretion. However, this pharmacokinetic interaction is not expected to be clinically important and the usual oseltamivir dosage can be used in patients receiving probenecid.

Mechanism of Action

Oseltamivir phosphate is a prodrug and has little, if any, pharmacologic activity until hydrolyzed in vivo to oseltamivir carboxylate. Oseltamivir is pharmacologically related to zanamivir; oseltamivir, like zanamivir, differs pharmacologically from other currently available antiviral agents.

Oseltamivir carboxylate is a potent selective competitive inhibitor of the influenza virus neuraminidase, an enzyme essential for viral replication in vivo. Neuraminidase cleaves terminal sialic acid residues from glycoconjugates to enable the release of virus from infected cells, prevents the formation of viral aggregates after release from host cells, and possibly facilitates viral invasion of the upper airways.

Neuraminidase inhibitors interfere with the release of progeny influenza virus from infected host cells, thus preventing infection of new host cells and halting the spread of infection. Because replication of influenza virus in the respiratory tract reaches its peak between 24 and 72 hours after the onset of illness, neuraminidase inhibitors must be administered as early as possible.

Spectrum

Oseltamivir (as oseltamivir carboxylate, the active metabolite of oseltamivir phosphate) exhibits potent antiviral activity in vitro against both influenza A and B viruses. Oseltamivir appears to be a potent and selective inhibitor of all influenza A neuraminidase subtypes (i.e., N1–N9) tested to date.

Oseltamivir has been shown to be active in vitro and in vivo in animal studies against a recombinant influenza A virus containing the H1 and N1 genes of the 1918 pandemic human influenza virus.

Oseltamivir was active in vitro against strains of avian influenza A (H5N1) virus isolated from Vietnam and Thailand patients during 2004. However, influenza A (H5N1) with reduced in vitro susceptibility or resistance to oseltamivir were isolated from several oseltamivir-treated patients in Vietnam during 2005. Oseltamivir generally has been active against influenza A (H5N1) in vivo in animal studies. (See Resistance.)

Oseltamivir has been active in vitro against avian influenza A (H7N7) virus. In addition, oseltamivir was active against avian influenza A (H9N2) in vivo in animal studies.

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. To date, isolates of 2009 influenza A (H1N1) virus have been susceptible to zanamivir and resistant to amantadine and rimantadine. Although most isolates of 2009 influenza A (H1N1) virus have been susceptible to oseltamivir, a few isolates have been resistant to oseltamivir.

Resistance

The major mechanisms of resistance to neuraminidase inhibitors (i.e., oseltamivir, zanamivir) that have been identified in vitro are hemagglutinin mutations that reduce viral dependence on neuraminidase activity and neuraminidase mutants that alter inhibition of the enzyme by the drugs.

Influenza A virus with decreased susceptibility to oseltamivir due to mutations in the viral neuraminidase N1 and N2 have been produced in vitro. Virus variants with reduced susceptibility to oseltamivir that have been recovered from patients receiving the drug include H274Y (in neuraminidase N1), R292K (in neuraminidase N2), and E119V (in neuraminidase N2). In the event of an H5N1 pandemic, the N1 mutation at position 274 would be important because this is associated with a greater than 600-fold increase in inhibitory concentrations for oseltamivir in enzyme inhibition assays.

Viruses that have neuraminidase mutations generally have reduced virulence. Although it has been suggested that these mutant viruses may have some degree of compromised infectivity and transmissibility compared with wild-type viruses, transmission of an oseltamivir-resistant virus has been documented in at least one animal model.

Influenza virus with mutations in the viral hemagglutinin that confer reduced susceptibility have been produced in vitro; however, such mutations have not been documented in practice and are unlikely to be clinically important.

■ **Resistance in Influenza A and B Virus**

Resistance to oseltamivir (as oseltamivir carboxylate, the active metabolite of oseltamivir phosphate) has been produced in vitro by serial passage of influenza A virus in the presence of increasing concentrations of the drug.

Strains of influenza with decreased in vitro susceptibility to oseltamivir have emerged in posttreatment isolates obtained from 1.3% of adults and adolescents and 8.6% of pediatric patients 1–12 years of age who received the drug in clinical studies of naturally acquired influenza infection. In one group of Japanese children who received oseltamivir for the treatment of influenza, oseltamivir-resistant mutants were detected in 18% of patients posttreatment. Resistant strains of influenza A and influenza B viruses have emerged in immunocompromised patients who received oseltamivir therapy.

In the 2007–2008 influenza season, an increased incidence of resistance to oseltamivir was reported in influenza A (H1N1) virus isolates in many countries. In the US, about 10% of influenza A (H1N1) viruses were resistant to oseltamivir during the 2007–2008 season. Almost all *seasonal* influenza A (H1N1) viruses circulating in the US in late 2008 and early 2009 were resistant to oseltamivir; these viruses were susceptible to zanamivir, amantadine, and rimantadine. Strains of *seasonal* influenza A (H3N2) circulating during the 2008–2009 influenza season have been susceptible to oseltamivir and zanamivir, but resistant to amantadine and rimantadine. All influenza B viruses tested this season have been susceptible to oseltamivir and zanamivir; influenza

B viruses are resistant to amantadine and rimantadine. A few isolates of 2009 influenza A (H1N1) virus have been resistant to oseltamivir.

■ Resistance in Avian Influenza A Virus

Avian influenza A (H5N1) with reduced in vitro susceptibility or resistance to oseltamivir were isolated from several oseltamivir-treated patients in Vietnam during 2005. One patient had received prophylaxis with oseltamivir (75 mg once daily for 3 days) immediately followed by oseltamivir treatment (75 mg twice daily for 7 days); the patient recovered from her influenza A (H5N1) infection but isolates obtained on the third day of oseltamivir prophylaxis had mutations associated with oseltamivir resistance (these isolates remained susceptible to zanamivir). In 2 other patients in Vietnam who received oseltamivir for treatment of avian influenza A (H5N1) infection, isolates had an amino acid substitution (H274Y) associated with high-level oseltamivir resistance; both patients subsequently died.

Although oseltamivir generally has been active against influenza A (H5N1) in vivo in animal studies, data from a murine model study indicated that, compared with an H5N1 strain isolated in 1997, an influenza A (H5N1) strain isolated in 2004 required higher oseltamivir doses and more prolonged administration to induce similar antiviral effects and survival rates.

■ Cross-resistance

Oseltamivir and zanamivir bind to different sites on the neuraminidase enzyme, and cross-resistance between the drugs is variable. Mutations at position 152 or 292 generally confer cross-resistance between oseltamivir and zanamivir; mutations at positions 119 or 274 usually do not confer cross-resistance. Isolates with the H274Y mutation that are resistant to oseltamivir have remained susceptible to zanamivir. Influenza A (H5N1) isolates obtained from a patient in Vietnam during 2005 had mutations associated with oseltamivir resistance but remained susceptible to zanamivir.

Pharmacokinetics

■ Absorption

Oseltamivir phosphate is readily absorbed following oral administration and then extensively converted by hepatic esterases to the active metabolite, oseltamivir carboxylate. Following oral administration of oseltamivir 75 mg twice daily for multiple days in healthy adults, peak plasma concentrations of oseltamivir or oseltamivir carboxylate were 65.2 or 348 ng/mL, respectively. Following oral administration of oseltamivir phosphate, oseltamivir carboxylate is detectable in plasma within 30 minutes; peak concentrations of oseltamivir carboxylate are attained within 3–4 hours. The absolute bioavailability of oseltamivir carboxylate is 80% following oral administration of oseltamivir phosphate. Plasma concentrations of oseltamivir carboxylate are proportional to dosage up to an oseltamivir dosage of 500 mg twice daily.

Administration of oseltamivir phosphate with food has no effect on peak plasma concentrations or area under the plasma concentration-time curve (AUC) of oseltamivir carboxylate.

Following oral administration of oseltamivir phosphate in geriatric individuals (65–78 years of age), systemic exposure to oseltamivir carboxylate at steady-state is about 25–35% higher compared with younger adults receiving the same dosage.

Because renal clearance of oseltamivir carboxylate decreases with declining renal function, an increase in plasma concentrations of the active metabolite can be expected in patients with severe renal impairment (creatinine clearance less than 30 mL/minute).

Limited data in patients with cirrhosis indicate that hepatic carboxylesterase activity in patients with moderate hepatic impairment is sufficient to metabolize oseltamivir phosphate to oseltamivir carboxylate. Systemic exposure to oseltamivir carboxylate in individuals with mild or moderate hepatic impairment is comparable to that in individuals without hepatic impairment.

■ Distribution

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

It is not known whether oseltamivir or oseltamivir carboxylate crosses the placenta in humans; placental transfer of oseltamivir carboxylate has been demonstrated in rats and rabbits.

Oseltamivir and oseltamivir carboxylate are distributed into milk in rats; it is not known whether oseltamivir and oseltamivir carboxylate are distributed into human milk.

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

■ Elimination

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

Oseltamivir phosphate and oseltamivir carboxylate are not metabolized by cytochrome P450 (CYP) enzymes.

Oseltamivir phosphate is principally (greater than 90%) eliminated by conversion to oseltamivir carboxylate. Oseltamivir carboxylate is eliminated principally by glomerular filtration and tubular secretion; less than 20% of an oral radiolabeled dose is eliminated in feces.

The plasma half-life of oseltamivir phosphate is 1–3 hours; the half-life of oseltamivir carboxylate is 6–10 hours in both young and geriatric adults.

Clearance of both oseltamivir phosphate and oseltamivir carboxylate is 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 or older is similar to that in adults.

Renal clearance of oseltamivir carboxylate decreases linearly with creatinine clearance.

Chemistry and Stability

■ Chemistry

Oseltamivir phosphate is a carbocyclic transition state sialic acid analog. Oseltamivir differs structurally from zanamivir (another sialic acid analog) by the absence of glycerol and guanidino groups. These structural modifications in oseltamivir result in a compound with substantially improved oral bioavailability compared with that of zanamivir.

Oseltamivir phosphate occurs as a white, crystalline solid with a bitter taste. Oseltamivir phosphate has an aqueous solubility of 588 mg/mL at 25°C.

■ Stability

Oseltamivir phosphate capsules should be stored at 25°C, but may be exposed to temperatures ranging from 15–30°C. Commercially available oseltamivir phosphate capsules are stable for 5 years after the date of manufacturer when stored as specified in the product labeling.

Oseltamivir phosphate powder for oral suspension should be stored at 25°C, but may be exposed to temperatures ranging from 15–30°C. Commercially available oseltamivir phosphate powder for oral suspension is stable for 2 years after the date of manufacture when stored as specified in the product labeling. The reconstituted oral suspension should be stored at 2–8°C and should not be frozen; any unused suspension should be discarded after 10 days.

Extemporaneous oral suspensions of oseltamivir phosphate prepared according to the manufacturer's directions (i.e., using commercially available capsules of the drug and one of the vehicles specified) are stable for 5 weeks (35 days) when refrigerated at 2–8°C or for 5 days when stored at room temperature (25°C).

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 of oseltamivir phosphate, 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.

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[®], Roche

45 mg (of oseltamivir)

Tamiflu[®], Roche

75 mg (of oseltamivir)

Tamiflu[®], Roche

For suspension

12 mg (of oseltamivir) per mL

Tamiflu[®], Roche

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

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