

Oseltamivir Phosphate

8:18.28 Neuraminidase Inhibitors (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

■ Treatment of Seasonal Influenza A and B Virus Infections

Oseltamivir is used for the symptomatic *treatment* of uncomplicated acute illness caused by susceptible 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 48 hours has not been established.

The US Centers for Disease Control and Prevention (CDC), American Academy of Pediatrics (AAP), and Infectious Diseases Society of America (IDSA) recommend treatment of influenza illness in all individuals with suspected or confirmed influenza if they require hospitalization or have severe, complicated, or progressive illness (regardless of vaccination status or underlying illness). Early empiric treatment also is recommended for individuals with suspected or confirmed influenza who are at increased 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, individuals younger than 19 years of age receiving long-term aspirin therapy, American Indians, Alaskan natives, individuals with a body mass index (BMI) of 40 or greater, and residents of any age in nursing homes or other long-term care facilities. If treatment is indicated, it should be initiated as early as possible since benefit is greatest if started within 48 hours of symptom onset; initiation of treatment should not be delayed while waiting for laboratory confirmation.

Viral surveillance data available from local and state health departments and the CDC should be considered when selecting an antiviral for treatment of seasonal influenza. Strains of circulating influenza viruses and the antiviral susceptibility of these strains constantly evolve, and the possibility that emergence of oseltamivir-resistant influenza virus may decrease effectiveness of the drug should be considered. When treatment of seasonal influenza is indicated, oseltamivir or zanamivir usually is recommended. Although influenza A and B viruses circulating in the US during the last few years generally have been susceptible to oseltamivir (see Resistance), clinicians should consult the most recent information.

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

Clinical Experience

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 (BMT) 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.

Annual vaccination with seasonal influenza virus vaccine, as recommended by the US Public Health Service Advisory Committee on Immunization Practices (ACIP), is the primary means of preventing seasonal influenza and its severe complications. Prophylaxis with an appropriate antiviral agent active against circulating influenza strains is considered an adjunct to vaccination for the control and prevention of influenza.

When seasonal influenza viruses are circulating in the community, postexposure prophylaxis with oseltamivir or zanamivir can be considered for certain individuals, including those at high risk of developing influenza complications for whom influenza vaccine is contraindicated, unavailable, or expected to have low efficacy (e.g., immunocompromised individuals). Other possible candidates for antiviral prophylaxis include unvaccinated health care personnel, public health workers, and first responders with unprotected, close-contact exposure to a patient with confirmed, probable, or suspected influenza during the time when the patient was infectious. Antiviral prophylaxis also can be considered for controlling influenza outbreaks in nursing and long-term care facilities or other closed or semi-closed settings with large numbers of individuals at high risk for influenza complications. In individuals at high risk of influenza complications who receive influenza virus vaccine inactivated, use of prophylaxis can be considered during the 2 weeks after vaccination to provide protection until an adequate immune response develops. (See Drug Interactions: Influenza Virus Vaccines.)

Viral surveillance data available from local and state health departments and the CDC should be considered when selecting an antiviral for the prophylaxis of influenza. The most appropriate antiviral for prevention of influenza is selected based on information regarding the likelihood that the influenza strain is susceptible and the known adverse effects of the drug. Strains of circulating influenza viruses and the antiviral susceptibility of these strains constantly evolve, and the possibility that emergence of oseltamivir-resistant influenza virus may decrease effectiveness of the drug should be considered.

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

Clinical Experience

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, pooled analysis indicates that the incidence of laboratory-confirmed clinical influenza was 1 or 5% in 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 less than 1 or 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 for prophylaxis of influenza in some immunocompromised individuals†, including cancer patients, BMT recipients, HSCT recipients, and solid organ transplant recipients.

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 BMT. 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.

Safety and efficacy of oseltamivir for prevention of seasonal influenza in immunocompromised patients were evaluated in a double-blind, placebo-controlled study that included 475 immunocompromised adults, adolescents, and pediatric patients 1–12 years of age who had received solid organ transplants (liver, kidney, liver and kidney) or HSCT. The median time since solid organ transplant was 1105 days in those randomized to placebo and 1379 days in those randomized to oseltamivir prophylaxis; the median time since HSCT transplant was 424 days in those randomized to placebo and 367 days in those randomized to oseltamivir. Approximately 40% of patients had received influenza vaccine prior to study entry. The primary efficacy endpoint was the incidence of confirmed clinical influenza, defined as oral temperature exceeding 37.2°C plus cough and/or coryza (all recorded within 24 hours) plus either a positive virus culture or a fourfold increase in virus antibody titers from baseline. The incidence of confirmed clinical influenza was 3% in the placebo group and 2% in the oseltamivir group; this difference was not statistically significant. The safety profile of oseltamivir reported in these immunocompromised patients (up to 12 weeks of prophylaxis) was similar to that reported in other clinical trials evaluating oseltamivir prophylaxis.

■ 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 or 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 parts of Asia, Africa, Europe, and the Middle East. 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 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 2010, there were more than 500 laboratory-confirmed human cases of avian influenza A (H5N1) infection (including 300 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. The most recent information regarding worldwide reports of avian influenza A (H5N1) is available at the WHO website at http://www.who.int/csr/disease/avian_influenza/en/ and the CDC website at <http://www.cdc.gov/flu/avian/outbreaks/current.htm>.

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 clustering and limited person-to-person transmission of H5N1 viruses has been reported in a few countries (Indonesia, Vietnam, China, Thailand). Most clusters of human infection with avian influenza A (H5N1) reported to date have included documented exposure to birds. Person-to-person transmission of H7N7 has 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 recommends that travelers to these areas take certain precautions. The CDC recommends that travelers to countries with known outbreaks of H5N1 avoid direct contact with all birds (poultry such as chickens and ducks, wild birds), especially contact with sick or dead poultry. Travelers also should avoid places such as poultry farms and markets where live poultry or animals are raised or kept and avoid contact with surfaces that might be contaminated with poultry feces or secretions. Uncooked (raw) or undercooked poultry or poultry products should *not* be consumed, and care should be taken when preparing these foods. 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 at <http://www.cdc.gov/flu/avian/index.htm> or <http://www.cdc.gov/travel/content/avian-flu-asia.aspx>.

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. Some data indicate a survival rate of 83% when oseltamivir treatment is initiated within 2 days of symptom onset compared with a survival rate of 21% if initiated 3–8 days after symptom onset. Because this virus continues to replicate for prolonged periods of time, treatment with oseltamivir is warranted even in patients who present for care in the later stages of illness. The optimum dosage and duration of

oseltamivir therapy for H5N1 infections are unknown, but high doses and prolonged duration of therapy may be needed in some patients. 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

Oseltamivir is used for the treatment or prevention of pandemic influenza† caused by susceptible strains of influenza virus.

Influenza viruses can cause seasonal epidemics and, occasionally, pandemics during which rates of illness and death from influenza-related complications can increase dramatically worldwide. The most recent influenza pandemic occurred during 2009 and was related to a novel influenza A (H1N1) strain. Influenza A strains also were involved in prior influenza pandemics occurring in 1918 (H1N1; origination not identified), 1957 (H2N2; originated in China), and 1968 (H3N2; originated in Hong Kong).

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. Cases of human infection with 2009 influenza A (H1N1) virus were first reported in Mexico and other countries (including the US) beginning in March and April 2009. The 2009 pandemic influenza A (H1N1) virus is a triple-reassortant swine influenza virus with genes from human, swine, and avian influenza A viruses, and contains a unique combination of gene segments not previously reported among human or swine influenza A in the US or elsewhere. In the US, the 2009 influenza A (H1N1) pandemic was characterized by a substantial increase in influenza activity that peaked in late October and early November 2009 and returned to seasonal baseline levels by January 2010. During that time, more than 99% of influenza viruses circulating in the US were the 2009 pandemic influenza A (H1N1) virus. In August 2010, the WHO declared that the world was in a post-pandemic period; however, the 2009 influenza A (H1N1) virus continued to circulate during the 2010–2011 influenza season and is expected to continue to circulate during the 2011–2012 season.

The spread of the highly pathogenic H5N1 strain of avian influenza A in poultry in Asia and other countries that was identified in 2003 represents a potential future pandemic threat. (See Uses: Avian Influenza A Virus Infections.)

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 6 mg of oseltamivir per mL.

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

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

If the commercially available powder for oral suspension is 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 simple syrup, a cherry syrup vehicle (Humco), or a sugar-free vehicle (Ora-Sweet® SF, Paddock). Pharmacists should be aware that current prescribing information for oseltamivir capsules and powder for suspension (6 mg/mL) includes instructions for emergency compounding of an oral suspension of the same strength (6 mg/mL). However, prescribing information for oseltamivir capsules and powder for suspension (12 mg/mL) that may still remain in the marketplace includes instructions for emergency compounding of an oral suspension containing 15 mg/mL.

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

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

Reconstitution

The commercially available oseltamivir phosphate powder for oral suspension should be reconstituted at the time of dispensing. The bottle should be tapped to thoroughly loosen the powder and then the amount of water specified on the bottle should be added; the bottle should be shaken for 15 seconds. Pharmacists should consider that a powder for oral suspension that is reconstituted to provide a preparation containing 6 mg/mL and a powder for oral suspension that is reconstituted to provide a preparation containing 12 mg/mL both may be available during the 2011–2012 influenza season. (See Dosage and Administration: Administration.)

The graduated oral dosing dispenser provided by the manufacturer should be used to administer the appropriate dosage of reconstituted oral suspension. If this dosing dispenser is not available, some other appropriate oral dosing device marked with units of measure that correspond to the required dose may be used.

■ Dosage

Dosage of oseltamivir phosphate is expressed in terms of oseltamivir.

Treatment of Seasonal Influenza A and B Virus Infections

When indicated for the *treatment* of seasonal influenza, oseltamivir should be initiated within 2 days of symptom onset and usually is continued for 5 days. Although

efficacy has not been established if treatment begins more than 2 days after onset of symptoms, studies in patients hospitalized with influenza suggest that antiviral treatment initiated more than 48 hours after onset of symptoms still may be beneficial in hospitalized patients and those with moderate to severe, complicated, or progressive influenza. In addition, 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.

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.

Children 1–12 Years of Age.

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

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

^a12 mg/mL concentration no longer being manufactured, but still may be available from some distributors or may be in state or national stockpiles until current supplies expire.

Infants Younger than 1 Year of Age.

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

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

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

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

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

Prevention of Seasonal Influenza A and B Virus Infections

When indicated for *prophylaxis* of seasonal influenza, oseltamivir should be initiated within 2 days of exposure. Protection lasts as long as oseltamivir therapy is continued. Safety and efficacy of oseltamivir prophylaxis was demonstrated for up to 6 weeks in immunocompetent individuals; safety of oseltamivir prophylaxis was demonstrated for up to 12 weeks in immunocompromised individuals.

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.

Children 1–12 Years of Age.

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

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

^a12 mg/mL concentration no longer being manufactured, but still may be available from some distributors or may be in state or national stockpiles until current supplies expire.

Infants Younger than 1 Year of Age.

Although safety and efficacy have not been established in infants younger than 1 year of age† (see Cautions: Pediatric Precautions), if prevention of influenza is considered necessary in this age group, 3 mg/kg of oseltamivir once daily for 10 days is recommended in *full-term* infants 3 months to less than 1 year of age†.

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

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

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

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

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 and may be most beneficial if initiated within 2 days of symptom onset. However, because this virus continues to replicate for prolonged periods of time, treatment with oseltamivir is warranted even in patients who present for care in the later 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.

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 infants 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 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 Seasonal Influenza A and B Virus Infections and see Prevention of Seasonal Influenza A and B Virus 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.

Dosage adjustment is not needed in individuals with mild to moderate hepatic impairment (Child-Pugh score 9 or less). The safety and pharmacokinetics of the drug in patients with severe hepatic impairment have not been evaluated.

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.

■ **Dermatologic and Hypersensitivity Reactions**

Anaphylaxis and serious dermatologic reactions (toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme) have been reported 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.

■ **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.

Neuropsychiatric Events

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.

Adverse neuropsychiatric events (e.g., self-injury, delirium, hallucinations, confusion, abnormal behavior, seizures), which occasionally were fatal, have been reported in patients receiving oseltamivir. Cases generally had an abrupt onset and rapid resolution.

Postmarketing reports of self-injury and delirium principally have involved children in Japan. The contribution of oseltamivir to these events has not been established. (See Cautions: Pediatric Precautions.)

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

■ **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.

■ **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.

■ **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, hypothermia, 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 the drug or 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 Neuropsychiatric Events under Cautions: Nervous System Effects), 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 symptoms 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 48 hours.

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

There is no evidence that oseltamivir is effective for illness caused by any organisms other than influenza A or B. Serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications of influenza. There is no evidence that oseltamivir prevents such complications.

Oseltamivir is not a substitute for annual vaccination with seasonal influenza virus vaccine inactivated or seasonal influenza virus vaccine live intranasal. Although antiviral agents used for treatment or prevention of influenza (oseltamivir, amantadine, rimantadine, zanamivir) may be used concomitantly with parenteral inactivated influenza virus vaccine if indicated, intranasal live influenza virus vaccine should *not* be administered until at least 48 hours after influenza antiviral agents are discontinued, and these antiviral agents should not be administered until at least 2 weeks after administration of 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) or for those undergoing hemodialysis or continuous peritoneal dialysis. (See Dosage and Administration: Dosage in Renal and Hepatic Impairment.)

■ Pediatric Precautions

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

The manufacturer states that oseltamivir is *not* indicated in infants younger than 1 year of age because it is not known whether toxicology data reported in animals are clinically relevant for human infants. Administration of a single oseltamivir dose of 657 mg/kg or greater in juvenile rats 7 days old resulted in toxicity, including death, but had no effect on adult rats.

Young children, especially those younger than 2 years of age, are at increased risk of influenza infection, hospitalization, and complications. During the 2009 influenza A (H1N1) pandemic, the US Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) that temporarily allowed use of oseltamivir for emergency treatment or prevention of 2009 influenza A (H1N1) infection in infants younger than 1 year of age†. Although the EUA expired in June 2010, the American Academy of Pediatrics (AAP) states that use of oseltamivir in infants younger than 1 year of age† is appropriate when indicated. (See Dosage and Administration: Dosage.)

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 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 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.

When the total number of patients studied in oseltamivir clinical trials is considered, 19% of those in studies evaluating the drug for the treatment of influenza were 65 years of age or older (7% were 75 years of age or older) and 25% of those in studies evaluating the drug for the prevention of influenza were 65 years or older (18% were 75 years of age or older). Although no overall differences in efficacy or safety were observed between geriatric and younger adults, and other clinical experience revealed no evidence of age-related differences, the possibility that some older patients may exhibit increased sensitivity to the drug cannot be ruled out.

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.

Pregnant women are at increased risk for severe complications and death from influenza. The CDC states that pregnancy is not considered a contraindication to use of oseltamivir for treatment or prevention of influenza 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 influenza in a pregnant woman, but the drug of choice for prophylaxis of these infections is less clear. Zanamivir may be preferred for prophylaxis in pregnant women because of its limited systemic absorption; however, respiratory complications that may be associated with zanamivir because of its route of administration should be considered, especially in women at risk for respiratory problems.

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.

■ Anticoagulants

Concomitant use of oseltamivir and warfarin has not revealed any pharmacokinetic interactions between the drugs.

■ 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. 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 with oseltamivir have not been studied. Because influenza antiviral agents reduce replication of influenza viruses, seasonal influenza virus 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. 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 with influenza virus vaccine live intranasal.

■ 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

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

Osetamivir 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

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

Osetamivir 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.

Although most isolates of the 2009 pandemic influenza A (H1N1) virus have been susceptible to osetamivir in vitro, resistance has been reported rarely. (See Resistance.)

Osetamivir 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 osetamivir has been reported rarely. Osetamivir generally has been active against influenza A (H5N1) in vivo in animal studies. (See Resistance.)

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

Resistance

The major mechanisms of resistance to neuraminidase inhibitors (i.e., osetamivir, zanamivir) that have been identified in vitro are viral neuraminidase mutations that affect the ability of the drugs to inhibit the enzyme and hemagglutinin mutations that reduce viral dependence on neuraminidase activity.

Influenza A and B viruses with decreased susceptibility to osetamivir due to mutations in viral neuraminidase have been produced in vitro and observed in clinical isolates. Influenza A virus variants with reduced susceptibility to osetamivir that have been recovered from patients receiving the drug or identified during viral surveillance include substitutions in neuraminidase N1 (i.e., H275Y, N294S) and in neuraminidase N2 (i.e., R292K, E119V, N294S, I222V, SASG245–248 deletion). Influenza B virus variants with reduced susceptibility to osetamivir recovered from patients receiving the drug or identified during viral surveillance include I222T, D198N, D198E, R371K, and G402S. The H275Y substitution in influenza A (H1N1) has been the major substitution associated with resistance to osetamivir. 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 osetamivir 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, person-to-person transmission of osetamivir-resistant variants of influenza A (H1N1) has been documented.

Influenza virus with mutations in the viral hemagglutinin that confer reduced susceptibility have been produced in vitro.

■ Resistance in Influenza A and B Virus

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

There is some evidence that selection of influenza A viruses resistant to osetamivir may occur at higher frequencies in children receiving the drug than in adults. Strains of seasonal influenza with decreased in vitro susceptibility to osetamivir 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 pediatric treatment studies, the rate of treatment-emergent resistance to osetamivir was 27–37% in children with influenza A (H1N1) and 3–18% in children with influenza A (H3N2). In one group of Japanese children who received osetamivir for the treatment of seasonal influenza, osetamivir-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 osetamivir therapy.

Viral surveillance between October 2010 and May 2011 indicated that all but a few influenza A (H3N2) isolates tested were susceptible to osetamivir and zanamivir. In addition, all influenza B isolates tested were susceptible to osetamivir and zanamivir.

Beginning in the 2007–2008 influenza season, a significant increase in the prevalence of osetamivir-resistant seasonal influenza A (H1N1) was reported worldwide. In the US, almost all seasonal influenza A (H1N1) strains tested in 2008, 2009, and the beginning of 2010 were resistant to osetamivir. During the 2010–2011 influenza season, the former seasonal influenza A (H1N1) was rarely detected and almost all circulating influenza A (H1N1) were the 2009 pandemic influenza A (H1N1) virus.

Osetamivir-resistant strains of 2009 pandemic influenza A (H1N1) virus have been reported rarely. Resistance in 2009 pandemic influenza A (H1N1) has emerged during therapy with the drug, and may develop rapidly in immunocompromised patients. During the 2010–2011 influenza season, more than 99% of circulating 2009 pandemic influenza A (H1N1) tested were susceptible to osetamivir. To date, almost all osetamivir-resistant 2009 influenza A (H1N1) have had the H275Y N1 amino acid substitution and were susceptible to zanamivir.

■ Resistance in Avian Influenza A Virus

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

Although osetamivir 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 osetamivir doses and more prolonged administration to induce similar antiviral effects and survival rates.

■ Cross-resistance

Osetamivir and zanamivir bind to different sites on the neuraminidase enzyme, and cross-resistance between the drugs is variable.

Influenza strains cross-resistant to osetamivir and zanamivir have been generated in cell culture.

Neuraminidase mutations at position 152 (influenza B) or 292 (influenza A N2) can confer cross-resistance between osetamivir and zanamivir; mutations in influenza A at positions 119 (influenza A N2), 275 (influenza A N1), or 294 (influenza A N1 or N2) usually do not confer cross-resistance. Reduced susceptibility to both osetamivir and zanamivir have been observed in vitro with substitutions at 292 in influenza A N2 and 198, 222, 371, or 402 in influenza B neuraminidase. To date, isolates with the H275Y mutation that are resistant to osetamivir have remained susceptible to zanamivir. Influenza A (H5N1) isolates obtained from a patient in Vietnam during 2005 had mutations associated with osetamivir resistance but remained susceptible to zanamivir.

Pharmacokinetics

■ Absorption

Osetamivir phosphate is readily absorbed following oral administration and then extensively converted by hepatic esterases to the active metabolite, osetamivir carboxylate. Following oral administration of osetamivir 75 mg twice daily for multiple days in healthy adults, peak plasma concentrations of osetamivir or osetamivir carboxylate were 65 or 348 ng/mL, respectively. Following oral administration of osetamivir phosphate, osetamivir carboxylate is detectable in plasma within 30 minutes; peak concentrations of osetamivir carboxylate are attained within 3–4 hours. The absolute bioavailability of osetamivir carboxylate is 80% following oral administration of osetamivir phosphate. Plasma concentrations of osetamivir carboxylate are proportional to dosage up to an osetamivir dosage of 500 mg twice daily.

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

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

Because renal clearance of osetamivir 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 osetamivir

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.

Oseltamivir phosphate powder for oral suspension should be stored at 25°C, but may be exposed to temperatures ranging from 15–30°C. The reconstituted oral suspension should be stored at 2–8°C for up to 17 days. Alternatively, the reconstituted suspension may be stored for up to 10 days at 25°C and may be exposed to 15–30°C during this time. The reconstituted oral suspension should not be frozen.

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).

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

Preparations

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

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

Oseltamivir Phosphate

Oral

Capsules

30 mg (of oseltamivir)

Tamiflu[®], Genentech

45 mg (of oseltamivir)

Tamiflu[®], Genentech

75 mg (of oseltamivir)

Tamiflu[®], Genentech

For suspension

6 mg (of oseltamivir) per mL

Tamiflu[®], Genentech

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

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