

## Zanamivir

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

■ Zanamivir, a sialic acid derivative, is a neuraminidase inhibitor antiviral agent that is pharmacologically related to oseltamivir and active against influenza A and B viruses.

#### Uses

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

Zanamivir is used for the symptomatic *treatment* of uncomplicated acute illness caused by influenza A or B virus in adults, adolescents, and children 7 years of age or older who have been symptomatic for no longer than 2 days.

Emergence of zanamivir-resistant influenza virus may decrease effectiveness of the drug. Clinicians should consider local viral surveillance data before deciding to use zanamivir.

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 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).

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 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. Treatment with zanamivir has not been shown to reduce the risk of transmission of influenza to others.

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

##### Clinical Experience

Efficacy of zanamivir for the treatment of influenza has been established in randomized placebo-controlled studies in which the predominant influenza infection was *seasonal* influenza A; a smaller number of patients in these studies were infected with *seasonal* influenza B. When used within 2 days of onset of symptoms in otherwise healthy adults, adolescents, and children with uncomplicated influenza, the drug has decreased viral shedding in adults and adolescents and reduced the degree and duration of fever, headache, myalgia, cough, and sore throat in adults, adolescents, and children. Zanamivir therapy generally has been associated with a median 1- to 1.5-day decrease in the duration of symptoms, although those who initiate therapy sooner (i.e., no later than 30 hours after symptom onset) and those with more pronounced illness may exhibit greater benefit (e.g., a 3-day decrease in symptom duration).

Efficacy of zanamivir for the treatment of influenza is *not* established in patients with underlying airways disease (e.g., asthma, chronic obstructive pulmonary disease [COPD]). In addition, zanamivir is *not* recommended for use in patients with underlying airways disease because of the risk of serious bronchospasm. (See Individuals with Asthma or COPD under Cautions.)

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

Zanamivir is used for the *prophylaxis* of influenza virus infection in adults, adolescents, and children 5 years of age and older.

Safety and efficacy of zanamivir have been established for prophylaxis of seasonal influenza in household settings and during community outbreaks; efficacy of the drug has *not* been established for prophylaxis of seasonal influenza in nursing home settings.

Emergence of zanamivir-resistant influenza virus may decrease effectiveness of the drug. Clinicians should consider local viral surveillance data before deciding to use zanamivir.

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 amantadine and rimantadine *not* be used for prevention of 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 adamantanes (amantadine, 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.

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

##### Clinical Experience

Efficacy of zanamivir for prevention of *seasonal* influenza was demonstrated in postexposure prophylaxis studies in households and seasonal prophylaxis studies during community outbreaks of influenza. The primary efficacy endpoint in these studies was the incidence of symptomatic, laboratory-confirmed influenza, which was defined as the presence of at least 2 symptoms (oral temperature 37.8°C or higher, feverishness, cough, headache, sore throat, myalgia) and laboratory confirmation by culture, polymerase chain reaction (PCR), or seroconversion.

In the placebo-controlled studies evaluating zanamivir for postexposure prophylaxis in household contacts of an index case, each household (including all household members 5 years of age or older) was randomized to receive zanamivir (10 mg once daily for 10 days) or placebo initiated within 1.5 days of symptom onset in the index cases. The proportion of households with at least 1 new case of symptomatic, laboratory-confirmed influenza was 4.1% in the groups that received zanamivir and 19% in the groups that received placebo.

In a placebo-controlled seasonal prophylaxis study in university students (86% were unvaccinated), the incidence of symptomatic, laboratory-confirmed influenza was 2% in those who received zanamivir (10 mg once daily for 28 days) and 6.1% in those who received placebo during a community outbreak. In another seasonal prophylaxis study in adults and children 12-94 years of age (33% were unvaccinated), the incidence of symptomatic, laboratory-confirmed influenza was 0.2% in those who received zanamivir and 1.4% in those who received placebo during a community outbreak.

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

Zanamivir 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 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. 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 this drug is absorbed systemically; 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 breast-feeding.

Oseltamivir and zanamivir are available under EUAs issued by FDA that allow emergency use of the drugs for the treatment and prophylaxis of influenza in individuals exposed to the 2009 influenza A (H1N1) virus. These EUAs 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 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

No clinical data are available to date regarding the use of zanamivir for the treatment of avian influenza A virus infections. Oseltamivir is considered the drug of choice for the treatment of strongly suspected or clinically confirmed cases of avian influenza A (H5N1) infection.

Zanamivir has been suggested as an alternative to oseltamivir for prophylaxis of avian influenza A infections when chemoprophylaxis is indicated in certain exposure situations. (See Prevention under Avian Influenza A Virus Infections: Treatment and Prevention, in Uses in Oseltamivir 8:18.28.)

Whenever possible, the choice of antiviral for the treatment or prophylaxis of avian influenza A infections should be based on results of *in vitro* susceptibility testing; in the absence of such testing, oseltamivir is the drug of first choice.

For information on avian influenza A virus infections, including current recommendations for treatment and prevention, see Uses: Avian Influenza A Virus Infections in Oseltamivir 8:18.28.

## ■ Pandemic Influenza

Influenza viruses can cause pandemics, during which rates of illness and death from influenza-related complications can increase dramatically worldwide.

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. If the avian influenza virus reassorts with a human virus (e.g., H3N2) in a dually infected individual or nonhuman mammal or if virus mutations that foster transmission occur, the resulting new virus variant could be capable of sustained human-to-human transmission.

## Dosage and Administration

### ■ Administration

Zanamivir is administered by oral inhalation using the inhaler (Diskhaler<sup>®</sup>) provided by the manufacturer that delivers the powdered drug from foil blisters (Rotadisk<sup>®</sup>).

Zanamivir powder for inhalation should *not* be removed from its foil blister packaging. The powder should *not* be dissolved or reconstituted in any liquid and should *not* be administered using a nebulizer or mechanical ventilator. (See Administration Precautions under Warnings/Precautions: General Precautions, in Cautions.)

Patients scheduled to use an inhaled bronchodilator at the same time as zanamivir should use the bronchodilator before zanamivir.

### ■ Dosage

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

For the *treatment* of influenza infection in adults, adolescents, and children 7 years of age or older, the usual dosage of zanamivir is 2 inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) twice daily (about 12 hours apart) for 5 days. Two doses should be administered the first day provided there is an interval of at least 2 hours between doses. On subsequent days, zanamivir doses should be administered about 12 hours apart (e.g., morning and evening) at about the same time each day.

Zanamivir therapy should be initiated within 2 days after the onset of symptoms.

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

##### **Household Setting.**

For the *prophylaxis* of influenza in adults, adolescents, and children 5 years of age or older in household settings, the usual dosage of zanamivir is 2 inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) once daily for 10 days. The daily dose should be administered at approximately the same time each day.

Efficacy of zanamivir for prophylaxis in household settings is not established if the drug is initiated more than 1.5 days after the onset of symptoms in the index case.

##### **Community Outbreak.**

For the *prophylaxis* of influenza in adults and adolescents in community settings, the usual dosage of zanamivir is 2 inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) once daily for 28 days. The daily dose should be administered at approximately the same time each day.

Efficacy of zanamivir for prophylaxis in community outbreaks is not established if the drug is initiated more than 5 days after the outbreak is identified in the community. Duration of antiviral prophylaxis should be individualized. For maximum effectiveness, the antiviral agent must be taken every day during influenza activity in the community. The safety and efficacy of zanamivir prophylaxis given for longer than 28 days have not been evaluated.

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

For the treatment of 2009 influenza A (H1N1) virus infections<sup>†</sup> in adults, adolescents, and children 7 years of age or older, the US Centers for Disease Control and Prevention (CDC) recommends a zanamivir dosage of 2 inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) twice daily for 5 days. 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.

Antiviral treatment of confirmed, probable, and suspected cases of 2009 influenza A (H1N1) virus infection<sup>†</sup> 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. 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.

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

For the prophylaxis of 2009 influenza A (H1N1) virus infections<sup>†</sup> in adults, adolescents, and children 5 years of age or older, CDC recommends a zanamivir dosage of 2 inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) once daily for 10 days.

Antiviral prophylaxis against 2009 influenza A (H1N1) virus infections<sup>†</sup> 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>).

### ■ Special Populations

Dosage adjustment is not needed in patients with renal impairment.

## Cautions

### ■ Contraindications

History of a hypersensitivity reaction to zanamivir or any ingredient in the formulation (e.g., lactose).

### ■ Warnings/Precautions

#### Warnings

##### Respiratory Effects.

Serious bronchospasm, including fatalities, have been reported in patients receiving zanamivir; some (but not all) of these patients had chronic underlying pulmonary disease (e.g., asthma, chronic obstructive pulmonary disease [COPD]). (See Individuals with Asthma or COPD under Cautions.) Many of these cases were reported during postmarketing surveillance and causality to the drug is difficult to assess.

Some patients without prior respiratory disease also may have respiratory abnormalities from acute respiratory infection that could resemble adverse drug reactions or increase vulnerability to adverse drug reactions.

Discontinue zanamivir in any patient who experiences bronchospasm or decline in respiratory function; immediate treatment and hospitalization may be required.

##### Individuals with Asthma or COPD.

Efficacy of zanamivir for the treatment of influenza has not been established in patients with underlying airways disease.

Use of zanamivir for the treatment or prophylaxis of influenza in individuals with underlying airways disease (e.g., asthma, COPD) is not recommended because of the risk of serious bronchospasm. (See Respiratory Effects under Cautions.)

Bronchospasm has occurred when zanamivir was used in patients with mild or moderate asthma (but without acute influenza-like illness).

The benefits and risks should be considered carefully if use of zanamivir is considered for a patient with underlying respiratory disease. If a decision is made to use the drug in such patients, monitor respiratory function carefully and have appropriate supportive care available, including short-acting  $\beta$ -adrenergic bronchodilators.

##### Nervous System Effects.

Postmarketing reports of self-injury and delirium principally have involved children in Japan. The contribution of zanamivir to these events has not been established. Patients should be monitored for abnormal behavior. If neuropsychiatric adverse effects develop, the risks and benefits of continued therapy with zanamivir should be evaluated.

## Sensitivity Reactions

##### Hypersensitivity Reactions.

Bronchospasm and allergic-like reactions (e.g., oropharyngeal edema, serious skin rash) reported.

If an allergic reaction occurs or is suspected, zanamivir should be discontinued immediately and appropriate treatment initiated.

## General Precautions

##### Administration Precautions.

Administer zanamivir powder for inhalation using *only* the inhaler (Diskhaler<sup>®</sup>) provided by the manufacturer. Do *not* remove the powder from its foil blister packaging (Rotadisk<sup>®</sup>). Do *not* attempt to reconstitute or solubilize the powder in liquid; do *not* attempt to administer the drug in a nebulizer or mechanical ventilator.

Safety and efficacy have not been established for administration by nebulization. Lactose in the formulation may obstruct or interfere with proper functioning of mechanical ventilator equipment. At least 1 death has been reported when a patient received the drug by mechanical ventilation after solubilization in a liquid.

Patients should be instructed in the safe and effective use of the drug delivery system (Diskhaler<sup>®</sup>) provided by the manufacturer. Instructions on use of the inhaler should include a demonstration whenever possible.

Some geriatric patients may need assistance with the inhaler. Children should be under adult supervision with close attention to use of the inhaler. (See Cautions: Pediatric Use.)

##### Concomitant Illness.

Safety and efficacy for treatment or prophylaxis of influenza have not established in patients with high-risk underlying medical conditions (see Individuals with Asthma or COPD under Cautions) and no data are available regarding use in patients with severe or unstable medical conditions that may require inpatient care.

##### Prior Use.

No data are available regarding safety and efficacy of repeated courses of zanamivir for treatment of influenza.

##### Differential Diagnosis.

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

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

##### Influenza Vaccination.

Zanamivir 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 2008-2009 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 (amantadine, oseltamivir, rimantadine, zanamivir) may be used concomitantly with seasonal influenza virus vaccine inactivated or influenza A (H1N1) 2009 monovalent vaccine inactivated if indicated, 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 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.)

## Specific Populations

##### Pregnancy.

Category C. (See Users Guide.)

Pregnant women are at increased risk for severe complications and death from seasonal influenza or 2009 influenza A (H1N1). The US Centers for Disease Control and Prevention (CDC) states that pregnancy should not be considered a contraindication to use of zanamivir for the treatment or prevention of seasonal influenza or 2009 influenza A (H1N1) infections<sup>†</sup> and that zanamivir regimens recommended for such infections in pregnant women are the same as those for other adults.

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

##### Lactation.

Zanamivir is distributed into milk in rats; caution if used in nursing women.

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

##### Pediatric Use.

Safety and efficacy for *treatment* of influenza not established in children younger than 7 years of age. Some clinical studies evaluating zanamivir have included children 5–6 years of age<sup>†</sup>; however, there is some evidence that the drug is not as effective in these children as in older children and adults. In addition, inadequate inhalation through the Diskhaler<sup>®</sup> has been observed in young children (i.e., younger than 8 years of age).

Safety and efficacy for *prophylaxis* of influenza not established in children younger than 5 years of age. Safety and efficacy in adolescents and children 5 years of age or older for *prophylaxis* of influenza are similar to adults.

An Emergency Use Authorization (EUA) issued by the US Food and Drug Administration (FDA) allows emergency use of zanamivir in children 7 years of age or older for the treatment of 2009 influenza A (H1N1) infections<sup>†</sup> and emergency use of the drug in children 5 years of age or older for the prevention of 2009 influenza A (H1N1) infections<sup>†</sup>. The EUA will end when the declaration of emergency is terminated or the EUA is revoked. (See Uses: 2009 Influenza A (H1N1) Virus Infections.)

Children should receive zanamivir only under adult supervision and with close attention to proper use of the inhaler. The supervising adult should be instructed on proper use of the inhaler.

##### Geriatric Use.

No substantial differences in safety and efficacy relative to younger adults, but increased sensitivity cannot be ruled out.

Safety and efficacy for *prophylaxis* of influenza in those 65 years of age or older in household or community settings are similar to that reported in younger adults. Efficacy has not been established for *prophylaxis* of influenza in geriatric individuals in nursing home settings.

Some geriatric patients may need assistance with the drug delivery system (Diskhaler<sup>®</sup>).

##### Hepatic Impairment.

Pharmacokinetics not studied in the presence of hepatic impairment.

##### Renal Impairment.

Safety and efficacy not documented in presence of severe renal impairment, but systemic exposure is limited after oral inhalation. Potential for drug accumulation should be considered.

## ■ Common Adverse Effects

Adverse effects occurring in 1–3% or more of adults and children 12 years of age or older include diarrhea; nausea; vomiting; nasal signs and symptoms; bronchitis; sinusitis; cough; ear, nose, and throat infections; headache; and dizziness. No adverse effect occurred at an incidence greater than 3%. Adverse effects occurring in up to 5% of children 5–12 years of age include ear, nose, and throat infections; vomiting; nausea; and diarrhea. Some adverse effects may be secondary to lactose vehicle inhalation. Bronchospasm and allergic-like reactions, including oropharyngeal edema and serious rash, have been reported.

## Drug Interactions

Zanamivir not metabolized by and does not affect cytochrome P-450 (CYP) enzymes, including CYP1A1, 1A2, 2A6, 2C9, 2C18, 2D6, 2E1, or 3A4. Drug interactions with drugs that are substrates or inhibitors of these enzymes unlikely.

### ■ Influenza Virus Vaccines

Zanamivir (10 mg daily) does not appear to interfere with the antibody response to influenza virus vaccine inactivated. Inactivated influenza vaccines may be administered concomitantly with zanamivir.

Safety and efficacy of concomitant use of seasonal influenza virus vaccine live intranasal or influenza A (H1N1) monovalent vaccine live intranasal with antiviral agents used for treatment or prevention of influenza (e.g., amantadine, oseltamivir, rimantadine, zanamivir) have not been studied. Because influenza antiviral agents reduce replication of influenza viruses, do not administer seasonal influenza virus vaccine live intranasal or influenza A (H1N1) 2009 monovalent vaccine live intranasal until at least 48 hours after zanamivir is discontinued, and do not administer zanamivir until at least 2 weeks after administration of an intranasal live influenza vaccine. If zanamivir and influenza A (H1N1) 2009 monovalent vaccine live intranasal are administered concomitantly, consider revaccination 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.

## Pharmacokinetics

### ■ Absorption

#### **Bioavailability**

Following oral inhalation of zanamivir, approximately 4–17% of the inhaled dose is absorbed systemically.

Absolute bioavailability averages 2% following oral inhalation; peak serum concentrations attained within 1–2 hours.

#### **Special Populations**

In pediatric patients younger than 12 years of age with signs and symptoms of respiratory illness, zanamivir serum concentrations may be low or undetectable following oral inhalation because of inadequate or absent inspiratory flow rates. (See Pediatric Use under Cautions.)

### ■ Distribution

#### **Extent**

Delivered to epithelial lining of the respiratory tract following oral inhalation. Amount of drug in respiratory tract depends on patient factors such as inspiratory flow rate. May be present in sputum and nasal washings for at least 12 hours after a dose.

Crosses the placenta in animals.

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

#### **Plasma Protein Binding**

Less than 10% bound to plasma proteins.

### ■ Elimination

#### **Metabolism**

Not metabolized.

Not a substrate for and does not affect CYP isoenzymes.

#### **Elimination Route**

Following oral inhalation, absorbed drug is excreted unchanged in urine within 24 hours; unabsorbed drug excreted in feces.

#### **Half-life**

Serum half-life following oral inhalation is 2.5–5.1 hours.

#### **Special Populations**

Half-life prolonged in those with renal impairment; studies using IV zanamivir indicate half-life is 4.7 hours if mild to moderate impairment and 18.5 hours if severe impairment.

## Description

Zanamivir, a sialic acid derivative, is a neuraminidase inhibitor antiviral agent. Zanamivir is pharmacologically related to oseltamivir and, like oseltamivir, is pharmacologically unrelated to other currently available antiviral agents.

Zanamivir is a potent selective competitive inhibitor of the influenza virus neuraminidase, an enzyme essential for viral replication. Neuraminidase cleaves terminal sialic acid residues from glycoconjugates to enable the release of virus from infected cells, prevent the formation of viral aggregates after release from host cells, and possibly decrease viral inactivation by respiratory mucus.

Zanamivir exhibits potent antiviral activity in vitro against both influenza A and B viruses, including amantadine- and rimantadine-resistant isolates. In vitro studies indicate that zanamivir is active against avian influenza A viruses, including influenza A H5N1, H6N1, H7N7, and H9N2.

Resistance to zanamivir has been produced in vitro by serial passage of influenza virus in the presence of increasing concentrations of the drug, and strains of influenza B with in vitro resistance to zanamivir have emerged rarely during therapy with the drug.

Experience with zanamivir is limited, and the risk of emergence of resistant isolates with clinical use has not been quantified.

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.

Zanamivir and oseltamivir bind to different sites on the neuraminidase enzyme, and cross-resistance between the drugs is variable. Mutations at positions 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 isolated from a patient in Vietnam during 2005 had mutations associated with oseltamivir resistance but remained susceptible to zanamivir.

## Advice to Patients

Importance of understanding proper storage, preparation, and inhalation techniques, including use of the delivery system (Diskhaler<sup>®</sup>); importance of reading the patient instructions for use.

Importance of initiating zanamivir treatment as soon as possible after appearance of influenza symptoms (within 2 days after symptom onset).

Advise patients that zanamivir treatment does not reduce the risk of transmission of influenza virus to others.

Advise patients of the possible risk of bronchospasm, especially in those with chronic underlying respiratory disease (e.g., asthma, chronic obstructive pulmonary disease [COPD]); importance of patients with asthma or COPD having a short-acting inhaled  $\beta$ -adrenergic bronchodilator readily available.

Advise patients using an inhaled bronchodilator at the same time as zanamivir of the importance of using the bronchodilator first.

Importance of discontinuing zanamivir and promptly contacting a clinician if there is an increase in respiratory symptoms (e.g., wheezing, dyspnea, signs or symptoms of bronchospasm) or if symptoms of an allergic reaction occur.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs as well as any concomitant illnesses.

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of informing patients of other important precautionary information. (See Cautions.)

**Overview (see Users Guide). For additional information until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is essential that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.**

## Preparations

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

### Zanamivir

#### Oral Inhalation

Powder for inhalation (contained in Rotadisk<sup>®</sup> foil pack)

5 mg per inhalation

Relenza<sup>®</sup> (with Diskhaler<sup>®</sup>),  
GlaxoSmithKline

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

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