

# Zanamivir (Systemic)

Antiviral; neuraminidase inhibitor; sialic acid analog.

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

**Brands:** Relenza®

## Uses

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

- Symptomatic treatment of uncomplicated acute illness caused by influenza A or B virus in adults, adolescents, and children  $\geq 7$  years of age who have been symptomatic for  $\leq 2$  days.
- Emergence of zanamivir-resistant influenza virus may decrease effectiveness of the drug. Consider local viral surveillance data before deciding to use zanamivir.
- CDC issued interim recommendations concerning the use of antiviral agents during the 2009-2010 influenza season. CDC recommends treatment of influenza illness for all individuals with suspected or confirmed influenza who require hospitalization. CDC also states that early empiric treatment should be considered for individuals with suspected or confirmed influenza who are at high risk for influenza-related complications, including children  $< 2$  years of age, adults  $\geq 65$  years of age, pregnant women and women up to 2 weeks postpartum (including following pregnancy loss), individuals of any age with certain chronic medical or immunosuppressive conditions, and individuals  $< 19$  years of age who are receiving long-term aspirin therapy. If treatment is indicated, initiate as early as possible; do not delay initiation of treatment while waiting for laboratory confirmation. As of October 2009, 99% of influenza viruses circulating in the US were the 2009 influenza A (H1N1) virus. (See 2009 Influenza A (H1N1) Virus Infections under Uses.) When treatment of influenza is indicated and seasonal influenza is suspected, oseltamivir or zanamivir is recommended. If viral surveillance indicates that seasonal influenza A (H1N1) resistant to oseltamivir is circulating and treatment is indicated, CDC states that zanamivir should be used; oseltamivir in conjunction with rimantadine or amantadine is an alternative.
- CDC recommends that health-care providers review local surveillance data, if available, to determine whether influenza A or B is most likely and which subtype of influenza A (H1N1 or H3N2) is prominent in the community. Use of diagnostic tests to distinguish influenza A and B should be considered.
- Efficacy of zanamivir for treatment of influenza *not* established in patients with underlying airways disease (e.g., asthma, COPD). Also *not* recommended for those with underlying airways disease because of risk of serious bronchospasm. (See Individuals with Asthma or COPD under Cautions.)
- 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>.

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

- Prophylaxis of influenza in adults, adolescents, and children  $\geq 5$  years of age.
- Emergence of zanamivir-resistant influenza virus may decrease effectiveness of the drug. 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. Candidates for antiviral prophylaxis include those at high risk for influenza-related complications following close contact with a patient with confirmed, probable, or suspected influenza during the time when the patient was infectious; other candidates include health care personnel, public health workers, and first responders with unprotected, close-contact exposure to a patient with confirmed, probable, or suspected influenza during the time when the patient was infectious. Antiviral prophylaxis also can be considered for controlling influenza outbreaks in assisted living facilities or other closed or semi-closed settings with large numbers of individuals at high risk for influenza complications. Early recognition of influenza illness and treatment is an alternative to postexposure prophylaxis. Postexposure prophylaxis is not indicated if  $> 48$  hours has elapsed since contact with the patient with influenza.
- Zanamivir has been effective for prophylaxis of influenza in household settings and during community outbreaks; efficacy *not* established for prophylaxis of influenza in nursing home settings.
- *Not* recommended for those with underlying airways disease (e.g., asthma, COPD) because of risk of serious bronchospasm. (See Individuals with Asthma or COPD under Cautions.)
- Not a substitute for annual vaccination with seasonal influenza virus vaccine inactivated or seasonal influenza virus vaccine live intranasal. Vaccination is the primary means of preventing seasonal influenza and its complications; antiviral agents are considered adjuncts for control and prevention of influenza. (See Influenza Virus Vaccines under Interactions.)
- Information regarding influenza surveillance and updated recommendations for prevention of seasonal influenza are available from CDC at <http://www.cdc.gov/flu>.

### 2009 Influenza A (H1N1) Virus Infections

- Treatment or prevention of infections caused by the 2009 influenza A (H1N1) virus, previously referred to as the novel 2009 influenza A (H1N1) or swine-origin influenza A (H1N1) virus†.
- Beginning in March and April 2009, cases of human infection with 2009 influenza A (H1N1) virus were reported in Mexico and other countries, including the US. As of October 2009, 99% of circulating influenza viruses in the US were identified as 2009 influenza A (H1N1).
- CDC issued interim recommendations concerning the use of antiviral agents during the 2009-2010 influenza season. CDC recommends treatment of influenza illness for all individuals with suspected or confirmed influenza who require hospitalization. CDC also states that early empiric treatment should be considered for individuals with suspected or confirmed influenza who are at high risk for complications, including children  $< 2$  years of age, adults  $\geq 65$  years of age, pregnant women and women up to 2 weeks postpartum (including following pregnancy loss), individuals of any age with certain chronic medical or immunosuppressive conditions, and individuals  $< 19$  years of age who are receiving long-term aspirin therapy. If treatment is indicated, initiate as early as possible; do not delay initiation of treatment while waiting for laboratory confirmation. When treatment of influenza is indicated in patients with known or suspected influenza A (H1N1) infection, oseltamivir or zanamivir is recommended. For certain hospitalized adult or pediatric patients when an IV antiviral is clinically appropriate, IV peramivir became available under an Emergency Use Authorization (EUA) issued by the FDA in October 2009. Information on peramivir is available at <http://www.cdc.gov/h1n1flu/eua/peramivir.htm>.
- CDC issued interim recommendations concerning the use of antiviral agents for prophylaxis of influenza during the 2009-2010 influenza season. Postexposure prophylaxis with oseltamivir or zanamivir can be considered for certain individuals. Candidates for antiviral prophylaxis include those at high risk for influenza-related complications following close contact with a patient with confirmed, probable, or suspected influenza during the time when the patient was infectious; other candidates include health care personnel, public health workers, and first responders with unprotected, close-contact exposure to a patient with confirmed, probable, or suspected influenza during the time when the patient was infectious. Antiviral prophylaxis also can be considered for controlling influenza outbreaks in assisted living facilities or other closed or semi-closed settings with large numbers of individuals at high risk for influenza complications. Early recognition of influenza illness and treatment is an alternative to postexposure prophylaxis. Postexposure prophylaxis is not indicated if  $> 48$  hours has elapsed since contact with the individual with influenza.
- CDC states that HIV-infected adults and adolescents who meet current case definitions for confirmed, probable, or suspected 2009 influenza A (H1N1) infection should receive empiric antiviral treatment and those who are in close contact (e.g., household contact) with a probable or confirmed case should receive antiviral prophylaxis. Oseltamivir or zanamivir regimens recommended for treatment or prophylaxis of 2009 influenza A (H1N1) in HIV-infected individuals are the same as those for individuals who are not HIV-infected.
- Pregnant women are at increased risk for severe influenza-related complications and death. CDC states that pregnant women and women up to 2 weeks postpartum (including after pregnancy loss) who meet current case definitions for confirmed, probable, or suspected 2009 influenza A (H1N1) infection should receive prompt empiric antiviral treatment and pregnant women who are in close contact with an individual with suspected, probable, or confirmed infection should receive antiviral prophylaxis. Oseltamivir or zanamivir regimens recommended for treatment or prophylaxis of these infections in pregnant women are the same as those recommended for other adults. However, because of its systemic absorption, CDC states that oseltamivir may be preferred for treatment of 2009 influenza A (H1N1) in pregnant women; the drug of choice for prophylaxis in these patients is less clear. (See Pregnancy under Cautions.) CDC states that antiviral treatment or prophylaxis is not a contraindication for breast-feeding.
- Oseltamivir and zanamivir are available under EUAs issued by FDA that allow emergency use of the drugs for the treatment and prophylaxis of influenza in individuals exposed to 2009 influenza A (H1N1). 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) may change as additional data become available. Consult the CDC website for the most recent information regarding 2009 influenza A (H1N1) infections (<http://www.cdc.gov/h1n1flu>).

### Avian Influenza A Virus Infections

- No clinical data to date regarding use for treatment of avian influenza A virus infections. Drug of choice for treatment of strongly suspected or clinically confirmed cases of avian influenza A (H5N1) infection is oseltamivir.
- May be an alternative to oseltamivir for prophylaxis of avian influenza A infections since in vitro studies indicate some avian influenza A (H5N1) strains resistant to oseltamivir are susceptible to zanamivir.
- Whenever possible, choice of antiviral for treatment or prophylaxis of avian influenza A infections should be based on results of in vitro susceptibility testing; in the absence of such testing, oseltamivir is drug of first choice.

### Pandemic Influenza

- Beginning in March and April 2009, cases of human infection with 2009 influenza A (H1N1) virus were reported in Mexico and other countries, including the US. On June 11, 2009, the WHO declared the first global influenza pandemic in 41 years and issued a phase 6 pandemic alert regarding 2009 influenza A (H1N1). A phase 6 pandemic is characterized by human-to-human spread of an animal or human-animal reassortant virus and sustained community level outbreaks of the virus in at least 2 countries in a single WHO region and

sustained community level outbreaks in at least one other country in a different WHO region. (See 2009 Influenza A (H1N1) Virus Infections under Uses.)

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

## Dosage and Administration

### Administration

#### Oral Inhalation

Administer by oral inhalation using the inhaler (Diskhaler<sup>®</sup>) provided by the manufacturer. The Diskhaler<sup>®</sup> delivers zanamivir powder for inhalation from foil blisters (Rotadisk<sup>®</sup>).

Do *not* remove zanamivir powder for inhalation from its foil blister packaging.

Do *not* attempt to dissolve or reconstitute the powder for inhalation in any liquid.

Do *not* attempt to administer using a nebulizer or mechanical ventilator. (See Administration Precautions under Cautions.)

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

### Dosage

#### Pediatric Patients

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

**Oral Inhalation:** Adolescents and children  $\geq 7$  years of age: 2 inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) twice daily (approximately 12 hours apart) for 5 days. Initiate zanamivir treatment within 2 days after onset of symptoms.

Whenever possible, the first day of treatment should include 2 doses provided there is at least 2 hours between doses; on subsequent days, doses should be given about 12 hours apart (morning and evening) at approximately the same time each day.

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

###### >Household Setting

**Oral Inhalation:** Adolescents and children  $\geq 5$  years of age: 2 inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) once daily for 10 days. Administer at approximately the same time each day. Efficacy in household settings not established if zanamivir prophylaxis initiated  $>1.5$  days after onset of symptoms in the index case.

###### >Community Outbreak

**Oral Inhalation:** Adolescents: 2 inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) once daily for 28 days. Administer at approximately the same time each day. Individualize duration of prophylaxis. For maximum effectiveness, must be taken every day during influenza activity in the community. Efficacy in community outbreaks not established if zanamivir prophylaxis initiated  $>5$  days after the outbreak is identified in the community. Safety and efficacy of prophylaxis given for  $>28$  days not evaluated.

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

**Oral Inhalation:** Adolescents and children  $\geq 7$  years of age: 2 inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) twice daily for 5 days. CDC states that hospitalized patients with severe infections (e.g., those with prolonged infection or those admitted into an intensive care unit) may require a longer duration of treatment.

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

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

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

**Oral Inhalation:** Adolescents and children  $\geq 5$  years of age: 2 inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) once daily for 10 days after known exposure to 2009 influenza A (H1N1).

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

#### Adults

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

**Oral Inhalation:** 2 inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) twice daily (approximately 12 hours apart) for 5 days. Initiate zanamivir treatment within 2 days after onset of symptoms.

Whenever possible, the first day of treatment should include 2 doses provided there is at least 2 hours between doses; on subsequent days, doses should be given about 12 hours apart (morning and evening) at approximately the same time each day.

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

###### >Household Setting

**Oral Inhalation:** 2 inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) once daily for 10 days. Administer at approximately the same time each day. Efficacy in household settings not established if zanamivir prophylaxis initiated  $>1.5$  days after onset of symptoms in the index case.

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**Oral Inhalation:** 2 inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) once daily for 28 days. Administer at approximately the same time each day. Individualize duration of prophylaxis. For maximum effectiveness, must be taken every day during influenza activity in the community. Efficacy in community outbreaks not established if zanamivir prophylaxis initiated  $>5$  days after the outbreak is identified in the community. Safety and efficacy of prophylaxis given for  $>28$  days not evaluated.

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

**Oral Inhalation:** 2 inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) twice daily for 5 days. CDC states that hospitalized patients with severe infections (e.g., those with prolonged infection or those admitted into an intensive care unit) may require a longer duration of treatment.

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

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

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

**Oral Inhalation:** 2 inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) once daily for 10 days after known exposure to 2009 influenza A (H1N1).

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

### Special Populations

#### Renal Impairment

Dosage adjustment not needed in patients with renal impairment.

## Cautions

### Contraindications

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

### Warnings/Precautions

#### Warnings

##### Respiratory Effects

Serious bronchospasm, including fatalities, reported when used in patients with or without underlying airways disease. (See Individuals with Asthma or COPD under Cautions.) Many such cases were reported during postmarketing surveillance and causality to the drug 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 use if bronchospasm develops or respiratory function declines; immediate treatment and hospitalization may be required.

##### Individuals with Asthma or COPD

Efficacy for treatment of influenza not established in patients with underlying airways disease.

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

When tested in patients with mild or moderate asthma (but without acute influenza-like illness), bronchospasm documented in 1/13 patients. When used in patients with acute influenza-like illness superimposed on underlying asthma or COPD, a  $>20\%$  decline in FEV<sub>1</sub> or peak expiratory flow rate occurred in more patients receiving the drug than in those receiving placebo.

The benefits and risks should be considered carefully if use of zanamivir is considered in patients with underlying airways 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 reported mainly in Japanese children receiving neuraminidase inhibitors, including zanamivir. Role of zanamivir not determined. Monitor patients with influenza for signs of abnormal behavior. If adverse neuropsychiatric effects develop, consider risks versus benefits of continued therapy.

## **Sensitivity Reactions**

### **Hypersensitivity Reactions**

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

Discontinue immediately and initiate appropriate treatment if an allergic reaction occurs or is suspected.

## **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 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 Pediatric Use under Cautions.)

### **Concomitant Illness**

Safety and efficacy for treatment or prophylaxis of influenza not established in patients with high-risk underlying medical conditions. (See Individuals with Asthma or COPD under Cautions.)

No data available regarding use in patients with severe or unstable medical conditions that may require inpatient care.

### **Prior Use**

No data 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.

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 2009-2010 influenza season are not expected to provide protection against infection with the 2009 influenza A (H1N1) virus. Influenza A (H1N1) 2009 monovalent vaccines are not expected to provide protection against infection with seasonal influenza A or B viruses.

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

Intranasal live seasonal influenza virus vaccine or intranasal live influenza A (H1N1) 2009 vaccine should not be administered until at least 48 hours after influenza antiviral agents are discontinued and these antiviral agents should not be administered until at least 2 weeks after administration of a live intranasal influenza vaccine. (See Influenza Virus Vaccines under Interactions.)

## **Specific Populations**

### **Pregnancy**

Category C.

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

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>; 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 treatment of seasonal influenza or 2009 influenza A (H1N1) infection in a pregnant woman, but the drug of choice for prophylaxis of these infections is less clear. Zanamivir may be preferred for prophylaxis in pregnant women because of its limited systemic absorption; however, respiratory complications that may be associated with zanamivir because of its route of administration should be considered, especially in women at risk for respiratory problems.

### **Lactation**

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

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 <7 years of age.

Safety and efficacy for *prophylaxis* of influenza not established in children <5 years of age.

Safety and efficacy in adolescents and children ≥7 years of age for *treatment* of influenza and safety and efficacy in adolescents and children ≥5 years of age for *prophylaxis* of influenza similar to adults.

An EUA issued by FDA allows emergency use of zanamivir in children ≥7 years of age for the treatment of 2009 influenza A (H1N1) infections<sup>†</sup> and for emergency use of the drug in children ≥5 years of age 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 2009 Influenza A (H1N1) Virus Infections under Uses.)

Some young children may have suboptimal inspiratory flow rates through the drug delivery system (Diskhaler<sup>®</sup>). When considering use of zanamivir in pediatric patients, clinicians should carefully evaluate the ability of the child to use the inhaler.

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**

Safety and efficacy for *treatment* of influenza in those ≥65 years of age similar to younger adults.

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

Possibility exists of greater sensitivity to the drug in some older individuals.

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

### **Hepatic Impairment**

Pharmacokinetics not studied in patients with hepatic impairment.

### **Renal Impairment**

Safety and efficacy not documented in patients with severe renal impairment, but systemic exposure is limited after oral inhalation. Consider potential for drug accumulation.

## **Common Adverse Effects**

Diarrhea, nausea, vomiting, headache, dizziness, nasal signs and symptoms, bronchitis, sinusitis, cough, and ear, nose, and throat infections. Some adverse effects may be related to lactose vehicle contained in the powder for oral inhalation.

## **Drug Interactions**

Zanamivir not metabolized by and does not affect 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.

## **Specific Drugs**

| <b>Drug</b>                     | <b>Interaction</b>   | <b>Comments</b>   |
|---------------------------------|--|---|
| <b>Influenza virus vaccines</b> | No evidence of interference with antibody response to parenteral inactivated influenza virus vaccines          | Parenteral inactivated influenza vaccines may be administered concomitantly with zanamivir  |
|                                 | Potential interference with antibody response to intranasal live influenza virus vaccines; no specific studies | Do not administer an intranasal live influenza virus vaccine until at least 48 hours after zanamivir is discontinued; do not administer zanamivir until at least 2 weeks after administration of an intranasal live influenza vaccine<br><br>If zanamivir and intranasal live influenza A (H1N1) 2009 vaccine are administered concomitantly, consider revaccination if appropriate; in recommendations regarding seasonal intranasal live influenza vaccine, experts recommend revaccination if an influenza antiviral was |

given 2 days before to  
14 days after vaccination

## 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 <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

<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.

## Stability

### Storage

#### Oral Inhalation

##### **Powder for Inhalation**

25°C (may be exposed to 15–30°C).

## Actions

- Zanamivir is a potent selective competitive inhibitor of influenza virus neuraminidase, an enzyme essential for viral replication; possibly alters virus particle aggregation and release.
- Active against influenza A and B viruses, including amantadine- and rimantadine-resistant isolates. Active in vitro against avian influenza A viruses (including H5N1, H6N1, N7N7, H9N2). Some isolates of influenza A (H5N1) with reduced susceptibility or resistance to oseltamivir remain susceptible to zanamivir.
- To date, isolates of 2009 influenza A (H1N1) virus have been susceptible to zanamivir and resistant to amantadine and rimantadine. Although most isolates have been susceptible to oseltamivir, a few isolates have been resistant to oseltamivir.
- Influenza viruses with reduced susceptibility to zanamivir have been produced in vitro; resistance reported rarely in clinical isolates, but risk of emergence of resistant isolates with clinical use has not been quantified.
- Zanamivir and oseltamivir bind to different sites on the neuraminidase enzyme, and cross-resistance between the drugs is variable.
- Some zanamivir-resistant influenza viruses may be cross-resistant to oseltamivir.

## Advice to Patients

- Importance of understanding proper inhalation technique and use of the drug delivery system (Diskhale<sup>®</sup>); importance of reading patient instructions for use.
- Importance of initiating zanamivir treatment as soon as possible after appearance of influenza symptoms (within 2 days after symptom onset); efficacy not established if treatment begins after 48 hours of symptoms.

- 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 underlying respiratory disease; 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 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 advising patients of other important precautionary information. (See Cautions.)

## Preparations

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

### Zanamivir

#### **Oral Inhalation**

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

5 mg per inhalation

**Relenza<sup>®</sup>** (with  
Diskhale<sup>®</sup>),  
GlaxoSmithKline

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

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