

Zanamivir (Systemic)

Antiviral; neuraminidase inhibitor; sialic acid analog.

Class: 8:18.28 Neuraminidase Inhibitors (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 ≥ 7 years of age who have been symptomatic for ≤ 2 days.
- Efficacy of zanamivir for treatment of influenza is *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.
- CDC, AAP, and IDSA recommend treatment of influenza illness in all individuals with suspected or confirmed influenza who require hospitalization (regardless of vaccination status or underlying illness) and in individuals with suspected or confirmed influenza who are at high risk of developing complications (regardless of vaccination status or influenza severity). Early empiric treatment also should be considered for individuals with suspected or confirmed influenza who are at increased risk for influenza-related complications, including children < 2 years of age, adults ≥ 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, individuals < 19 years of age who are receiving long-term aspirin therapy, and residents of any age in nursing homes or other long-term care facilities. If indicated, initiate treatment as early as possible since benefit is greatest if started within 48 hours of symptom onset; do not delay initiation of treatment while waiting for laboratory confirmation.
- Consider viral surveillance data available from local and state health departments and the CDC when selecting an antiviral for treatment of seasonal influenza. Strains of circulating influenza viruses and the antiviral susceptibility of these strains constantly evolve, and emergence of zanamivir-resistant influenza virus may decrease effectiveness of the drug. When treatment of seasonal influenza is indicated, oseltamivir or zanamivir usually is recommended. If viral surveillance indicates that influenza strains resistant to oseltamivir are circulating and treatment is indicated, zanamivir should be used.
- 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>.

Prevention of Seasonal Influenza A and B Virus Infections

- Prophylaxis of influenza in adults, adolescents, and children ≥ 5 years of age.
- Has been effective for prophylaxis of influenza in household settings and during community outbreaks; efficacy is *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.)
- 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 active against circulating influenza strains is considered an adjunct to vaccination for 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. Also consider antiviral prophylaxis 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 parenteral inactivated influenza vaccine, use of prophylaxis can be considered during the 2 weeks after vaccination to provide protection until an adequate immune response develops. (See Influenza Virus Vaccines under Interactions.)
- Consider viral surveillance data available from local and state health departments and the CDC when selecting an antiviral for prophylaxis of influenza. The most appropriate antiviral for prevention of influenza is based on 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 zanamivir-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>.

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.

Pandemic Influenza

- Treatment or prevention of pandemic influenza† caused by susceptible strains of influenza virus.
- Influenza viruses can cause pandemics, during which rates of illness and death from influenza-related complications can increase dramatically worldwide. Most recent influenza pandemic occurred during 2009 and was related to a novel influenza A (H1N1) strain.
- 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. In the US, the 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. As of August 2010, the WHO declared that the world was in a post-pandemic period; however, the 2009 influenza A (H1N1) virus is expected to continue to circulate during the 2010–2011 influenza 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.

Dosage and Administration

Administration

Administer commercially available powder for inhalation *only* by oral inhalation using the inhaler (Diskhaler®) provided by the manufacturer. Do *not* administer using a nebulizer or mechanical ventilator.

Zanamivir has been administered IV†; but a parenteral dosage form of the drug is not commercially available in the US.

Oral Inhalation

Zanamivir powder for inhalation is commercially available in a disk containing 4 foil blisters of the drug (Rotadisk®) and is provided with an inhaler (Diskhaler®) that is used to deliver the drug to the respiratory tract.

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.)

Consult the manufacturer's instructions for information on how to load the Rotadisk® onto the drug delivery system (Diskhaler®) and how to use the Diskhaler® to administer the drug.

Patients should be instructed in the safe and effective use of the Diskhaler®; instructions should include a demonstration whenever possible.

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 ≥ 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.

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.

Initiate zanamivir treatment within 2 days after onset of symptoms. Although efficacy not established, antiviral treatment initiated >48 hours after onset of symptoms may still be beneficial in those with moderate to severe or progressive influenza. In addition, although usual duration of antiviral treatment is 5 days, patients hospitalized with severe infections (e.g., those with prolonged infection or admitted into an intensive care unit) may require >5 days of antiviral treatment.

Prevention of Seasonal Influenza A and B Virus Infections

>Household Setting

Oral Inhalation: Adolescents and children ≥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.

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.

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.

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.

Initiate zanamivir treatment within 2 days after onset of symptoms. Although efficacy not established, antiviral treatment initiated >48 hours after onset of symptoms may still be beneficial in those with moderate to severe or progressive influenza. In addition, although usual duration of antiviral treatment is 5 days, patients hospitalized with severe infections (e.g., those with prolonged infection or admitted into an intensive care unit) may require >5 days of antiviral treatment.

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.

>Community Outbreak

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.

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.

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

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

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 FEV₁ 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 β-adrenergic bronchodilators.

Sensitivity Reactions

Hypersensitivity Reactions

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

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

Neuropsychiatric Events

Postmarketing reports of delirium and abnormal behavior leading to self-injury reported mainly in Japanese children receiving neuraminidase inhibitors, including zanamivir. Role of zanamivir not determined.

Influenza itself can be associated with a variety of neurologic and behavioral symptoms (e.g., seizures, 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.

Closely monitor patients with influenza for signs of abnormal behavior. If neuropsychiatric symptoms develop, consider risks versus benefits of continued therapy.

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.

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.

Serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications of influenza. No evidence that zanamivir prevents such complications.

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

Administration Precautions

Administer zanamivir powder for inhalation using *only* the inhaler (Diskhaler[®]) provided by the manufacturer. Do *not* remove the powder from its foil blister packaging (Rotadisk[®]). 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 or mechanical ventilation. 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[®]) 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.)

Prior Use

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

Influenza Vaccination

Zanamivir is not a substitute for annual vaccination with seasonal influenza virus vaccine inactivated or seasonal influenza virus vaccine live intranasal.

Antiviral agents used for treatment or prevention of influenza may be used concomitantly with parenteral inactivated seasonal influenza virus vaccine if indicated.

Intranasal live seasonal 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 live intranasal influenza vaccine, unless medically indicated. (See Influenza Virus Vaccines under Interactions.)

Specific Populations

Pregnancy

Category C.

Pregnant women are at increased risk for severe complications and death from influenza.

CDC states that pregnancy should not be considered a contraindication to use of zanamivir for the treatment or prevention of influenza; 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 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.

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.

Some young children may have suboptimal inspiratory flow rates through the drug delivery system (Diskhaler®). 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®).

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.

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

Drug	Interaction	Comments
Influenza virus vaccines	Parenteral inactivated influenza vaccine: No evidence of interference with the antibody response to the vaccine	Parenteral inactivated influenza vaccine: May be administered concomitantly with or at any interval before or after zanamivir
	Intranasal live influenza vaccine: Potential interference with antibody response to the vaccine; no specific studies	Intranasal live influenza vaccine: Do not administer the live intranasal vaccine until at least 48 hours after zanamivir is discontinued; do not administer zanamivir until at least 2 weeks after administration of the live intranasal vaccine, unless

medically indicated; repeat vaccination if influenza antiviral is given 2 days before to 14 days after the vaccine

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).
- Active against some influenza strains resistant to oseltamivir. To date, isolates of 2009 pandemic influenza A (H1N1) virus, including some oseltamivir-resistant strains, have been susceptible to zanamivir. Some isolates of influenza A (H5N1) with reduced susceptibility or resistance to oseltamivir remain susceptible to zanamivir.
- Influenza viruses with reduced susceptibility to zanamivir have been produced in vitro. Resistance reported rarely in clinical isolates of influenza A or B, but risk of emergence of resistant isolates with clinical use has not been quantified.
- Influenza strains cross-resistant to zanamivir and oseltamivir have been generated in cell culture; only limited data available regarding possible emergence of clinical isolates with cross-resistance to both drugs.

Advice to Patients

- Importance of understanding proper inhalation technique and use of the drug delivery system (Diskhaler®); 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 β-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 immediately contacting a clinician if patient demonstrates signs of unusual behavior. Influenza patients, particularly children and adolescents, may be at increased risk of seizures, confusion, or abnormal behavior early in their illness and should be closely observed for signs of unusual behavior. Such events are uncommon, but may occur after starting zanamivir treatment or when influenza is not treated and can result in accidental injury to the patient.
- 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® foil pack)

5 mg per inhalation

Relenza® (with
Diskhaler®),
GlaxoSmithKline

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

Selected Revisions November 2010, © Copyright, May 2004, American Society of Health-System Pharmacists, Inc.