

Zanamivir

VIRENZA

For oral inhalation only

For use with the **Revolizer** Inhalation Device

COMPOSITION

Each capsule contains

Zanamivir...5 mg

DOSAGE FORM

Dry powder for inhalation

PHARMACOLOGY

Pharmacodynamics

Mechanism of Action

Zanamivir is an inhibitor of influenza virus neuraminidase affecting release of viral particles.

Antiviral Activity

The antiviral activity of zanamivir against laboratory and clinical isolates of influenza virus was determined in cell culture assays. The concentrations of zanamivir required for inhibition of influenza virus were highly variable depending on the assay method used and virus isolate tested. The 50% and 90% effective concentrations (EC₅₀ and EC₉₀) of zanamivir were in the range of 0.005 to 16.0 µM and 0.05 to >100 µM, respectively (1 µM = 0.33 mcg/mL). The relationship between the cell culture inhibition of influenza virus by zanamivir and the inhibition of influenza virus replication in humans has not been established.

Resistance

Influenza viruses with reduced susceptibility to zanamivir have been selected in cell culture by multiple passages of the virus in the presence of increasing concentrations of the drug. Genetic analysis of these viruses showed that the reduced susceptibility in cell culture to zanamivir is associated with mutations that result in amino acid changes in the viral neuraminidase or viral hemagglutinin or both. Resistance mutations selected in cell culture which result in neuraminidase amino acid substitutions include E119G/A/D and R292K. Mutations selected in cell culture in hemagglutinin include: K68R, G75E, E114K, N145S, S165N, S186F, N199S, and K222T.

In an immunocompromised patient infected with influenza B virus, a variant virus emerged after treatment with an investigational nebulized solution of zanamivir for 2 weeks. Analysis of this variant showed a hemagglutinin substitution (T198I) which resulted in a reduced affinity for human cell receptors, and a substitution in the neuraminidase active site (R152K) which reduced the enzyme's activity to zanamivir by 1,000-fold. Insufficient information is available to characterize the risk of emergence of zanamivir resistance in clinical use.

Cross-Resistance

Cross-resistance has been observed between some zanamivir-resistant and some oseltamivir-resistant influenza virus mutants generated in cell culture. However, some of the in cell culture zanamivir-induced resistance mutations, E119G/A/D and R292K, occurred at the same neuraminidase amino acid positions as in the clinical isolates resistant to oseltamivir, E119V and R292K. No studies have been performed to assess risk of emergence of cross-resistance during clinical use.

Influenza Vaccine Interaction Study

An interaction study (n = 138) was conducted to evaluate the effects of zanamivir (10 mg once daily) on the serological response to a single dose of trivalent inactivated influenza vaccine, as measured by hemagglutination inhibition titers. There was no difference in hemagglutination inhibition antibody titers at 2 weeks and 4 weeks after vaccine administration between zanamivir and placebo recipients.

Influenza Challenge Studies

Antiviral activity of zanamivir was supported for infection with influenza A virus, and to a more limited extent for infection with influenza B virus, by Phase I studies in volunteers who received intranasal inoculations of challenge strains of influenza virus, and received an intranasal formulation of zanamivir or placebo starting before or shortly after viral inoculation.

Pharmacokinetics

Absorption and Bioavailability

Pharmacokinetic studies of orally inhaled zanamivir indicate that approximately 4% to 17% of the inhaled dose is systemically absorbed. The peak serum concentrations ranged from 17-142 ng/mL within 1 to 2 hours following a 10-mg dose. The area under the serum concentration versus time curve (AUC_{∞}) ranged from 111 to 1,364 ng·hr/mL.

Distribution

Zanamivir has limited plasma protein binding (<10%).

Metabolism

Zanamivir is renally excreted as unchanged drug. No metabolites have been detected in humans.

Elimination

The serum half-life of zanamivir following administration by oral inhalation ranges from 2.5 to 5.1 hours. It is excreted unchanged in the urine with excretion of a single dose completed within 24 hours. Total clearance ranges from 2.5 to 10.9 L/hr. Unabsorbed drug is excreted in the feces.

Impaired Hepatic Function

The pharmacokinetics of zanamivir has not been studied in patients with impaired hepatic function.

Impaired Renal Function

After a single intravenous dose of 4 mg or 2 mg of zanamivir in volunteers with mild/moderate or severe renal impairment, respectively, significant decreases in renal clearance (and hence total clearance: normals 5.3 L/hr, mild/moderate 2.7 L/hr, and severe 0.8 L/hr; median values) and significant increases in half-life (normals 3.1 hr, mild/moderate 4.7 hr, and severe 18.5 hr; median values) and systemic exposure were observed. Safety and efficacy have not been documented in the presence of severe renal insufficiency. Due to the low systemic bioavailability of zanamivir following oral inhalation, no dosage adjustments are necessary in patients with renal impairment. However, the potential for drug accumulation should be considered.

Pediatric Patients

The pharmacokinetics of zanamivir was evaluated in pediatric patients with signs and symptoms of respiratory illness. Sixteen patients, 6 to 12 years of age, received a single dose of 10-mg zanamivir dry powder. Five patients had either undetectable zanamivir serum concentrations or had low drug concentrations (8.32 to 10.38 ng/mL) that were not detectable after 1.5 hours. Eleven patients had C_{max} median values of 43 ng/mL (range 15 to 74) and AUC_∞ median values of 167 ng·hr/mL (range 58 to 279). Low or undetectable serum concentrations were related to lack of measurable PIFR in individual patients.

Geriatric Patients

The pharmacokinetics of zanamivir has not been studied in patients over 65 years of age.

Gender, Race, and Weight

In a population pharmacokinetic analysis in patient studies, no clinically significant differences in serum concentrations and/or pharmacokinetic parameters (V/F, CL/F, k_a, AUC₀₋₃, C_{max}, T_{max}, CL_r, and % excreted in urine) were observed when demographic variables (gender, age, race, and weight) and indices of infection (laboratory evidence of infection, overall symptoms, symptoms of upper respiratory illness, and viral titers) were considered. There were no significant correlations between measures of systemic exposure and safety parameters.

INDICATIONS

Treatment of Influenza

VIRENZA is indicated for treatment of uncomplicated acute illness due to influenza A and B virus in adults and pediatric patients 5 years and older who have been symptomatic for no more than 2 days.

Prophylaxis of Influenza

VIRENZA is indicated in adults and pediatric patients 5 years of age and older for prophylaxis of influenza.

VIRENZA is not recommended for treatment of patients with underlying airways disease (such as asthma or chronic obstructive pulmonary disease)

DOSAGE AND ADMINISTRATION

VIRENZA is for administration to the respiratory tract by oral inhalation using the **Revolizer** device only.

Patients scheduled to use an inhaled bronchodilator at the same time as **VIRENZA** should use their bronchodilator before taking **VIRENZA**.

Treatment of Influenza

The recommended dose of **VIRENZA** for treatment of influenza in adults and pediatric patients aged 5 years and older is 2 inhalations (one 5-mg capsule per inhalation for a total dose of 10 mg) twice daily (approximately 12 hours apart) for 5 days.

Two doses should be taken on the first day of treatment whenever possible provided there is at least 2 hours between doses.

On subsequent days, doses should be about 12 hours apart (e.g., morning and evening) at approximately the same time each day.

Prophylaxis of Influenza

Household Setting:

The recommended dose of **VIRENZA** for prophylaxis of influenza in adults and pediatric patients 5 years of age and older in a household setting is 10 mg once daily for 10 days. The 10-mg dose is provided by 2 inhalations (one 5-mg rotacap per inhalation).

The dose should be administered at approximately the same time each day.

There are no data on the effectiveness of prophylaxis with **Virenza** in a household setting when initiated more than 1.5 days after the onset of signs or symptoms in the index case.

Community Outbreaks:

The recommended dose of **VIRENZA** for prophylaxis of influenza in adults and adolescents in a community setting is 10 mg once daily for 28 days. The 10-mg dose is provided by 2 inhalations (one 5-mg rotacap per inhalation).

The dose should be administered at approximately the same time each day.

There are no data on the effectiveness of prophylaxis with **VIRENZA** in a community outbreak when initiated more than 5 days after the outbreak was identified in the community.

The safety and effectiveness of prophylaxis with **VIRENZA** have not been evaluated for longer than 28 days duration.

CONTRAINDICATIONS

VIRENZA is contraindicated in patients with a known hypersensitivity to any component of the formulation.

WARNINGS AND PRECAUTIONS

VIRENZA has not been proven effective for treatment of influenza in individuals with underlying airways disease. If use with **VIRENZA** is considered for a patient with underlying airways disease, the potential risks and benefits should be carefully weighed. If a decision is made to prescribe **VIRENZA** for such a patient, this should be done only under conditions of careful monitoring of respiratory function, close observation, and appropriate supportive care including availability of fast-acting bronchodilators.

VIRENZA has not been proven effective for prophylaxis of influenza in the nursing home setting.

VIRENZA is not a substitute for early influenza vaccination on an annual basis.

Patients should be advised that the use of **VIRENZA** for treatment of influenza has not been shown to reduce the risk of transmission of influenza to others.

There is no evidence for efficacy of zanamivir in any illness caused by agents other than influenza virus A and B.

Safety and efficacy of repeated treatment courses have not been studied.

Bronchospasm

VIRENZA is not recommended for treatment or prophylaxis of influenza in individuals with underlying airways disease (such as asthma or chronic obstructive pulmonary disease) due to risk of serious bronchospasm.

Serious cases of bronchospasm, including fatalities, have been reported during treatment with zanamivir in patients with and without underlying airways disease. Many of these cases were reported during post-marketing and causality was difficult to assess.

Zanamivir should be discontinued in any patient who develops bronchospasm or decline in respiratory function; immediate treatment and hospitalization may be required.

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

Allergic Reaction

Allergic-like reactions, including oropharyngeal edema and serious skin rashes, have been reported in post-marketing experience with zanamivir. **Virenza** should be stopped

and appropriate treatment instituted if an allergic reaction occurs or is suspected.

Bacterial Infections

Serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza. Zanamivir has not been shown to prevent such complications.

Neuropsychiatric Events

Influenza can be associated with a variety of neurologic and behavioral symptoms which can include events such as seizures, hallucinations, delirium, and abnormal behavior, in some cases resulting in fatal outcomes. These events may occur in the setting of encephalitis or encephalopathy but can occur without obvious severe disease.

There have been post-marketing reports (mostly from Japan) of delirium and abnormal behavior leading to injury in patients with influenza who were receiving neuraminidase inhibitors, including zanamivir. Because these events were reported voluntarily during clinical practice, estimates of frequency cannot be made, but they appear to be uncommon based on usage data for zanamivir. These events were reported primarily among pediatric patients and often had an abrupt onset and rapid resolution. The contribution of zanamivir to these events has not been established. Patients with influenza should be closely monitored for signs of abnormal behavior. If neuropsychiatric symptoms occur, the risks and benefits of continuing treatment should be evaluated for each patient.

Limitations of Populations Studied

Safety and efficacy have not been demonstrated in patients with high-risk underlying medical conditions. No information is available regarding treatment of influenza in patients with any medical condition sufficiently severe or unstable to be considered at imminent risk of requiring inpatient management

Drug Interactions

Zanamivir is not a substrate nor does it affect cytochrome P450 (CYP) isoenzymes (CYP1A1/2, 2A6, 2C9, 2C18, 2D6, 2E1, and 3A4) in human liver microsomes. No clinically significant pharmacokinetic drug interactions are predicted based on data from in vitro studies.

The concurrent use of zanamivir with live attenuated influenza vaccine (LAIV) intranasal has not been evaluated. However, because of potential interference between these products, LAIV should not be administered within 2 weeks before or 48 hours after administration of zanamivir, unless medically indicated. The concern about possible interference arises from the potential for antiviral drugs to inhibit replication of live vaccine virus.

Trivalent inactivated influenza vaccine can be administered at any time relative to use of zanamivir.

Pregnancy

Pregnancy Category C. There are no adequate and well-controlled studies of zanamivir in pregnant women. **VIRENZA** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation

Studies in rats have demonstrated that zanamivir is excreted in milk. However, lactating mothers should be instructed that it is not known whether zanamivir is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when **VIRENZA** is administered to a lactating mother.

Paediatric use

Zanamivir has been studied in children 5 to 12 years of age. No definite differences in safety and efficacy were observed between these adolescent patients and young adults.

Prescribers should carefully evaluate the ability of young children to use the delivery system if prescription of **VIRENZA** is considered.

Geriatric use

No overall differences in safety or effectiveness were observed between these subjects and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

UNDESIRABLE EFFECTS

Zanamivir is generally well tolerated. The most common adverse events include nasal signs and symptoms, diarrhoea, nausea, vomiting, headache, bronchitis, cough, sinusitis, dizziness and ear, nose, throat infections. Additional adverse reactions occurring in less than 1.5% of patients receiving zanamivir included malaise, fatigue, fever, abdominal pain, myalgia, arthralgia, and urticaria.

Postmarketing Experience

Bronchospasm and allergic-like reactions, including oropharyngeal edema, facial edema, rash, serious cutaneous reactions and urticaria have been reported.

Psychiatric:

Delirium, including symptoms such as altered level of consciousness, confusion, abnormal behavior, delusions, hallucinations, agitation, anxiety, nightmares.

Cardiac

Arrhythmias, syncope.

Neurologic

Seizures.

Skin:

Facial edema; rash, including serious cutaneous reactions; urticaria.

OVERDOSAGE

There have been no reports of overdosage from administration of zanamivir. Doses of zanamivir up to 64 mg/day have been administered by nebulizer. Additionally, doses of up to 1,200 mg/day for 5 days have been administered intravenously. Adverse effects were similar to those seen in clinical studies at the recommended dose.

PACKAGING INFORMATION

VIRENZA is available in a container with 20 capsules and the Revolizer device.

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