

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

Zanamivir acts by the inhibition of influenza virus neuraminidase with the possibility of alteration of virus particle aggregation and release.

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% inhibitory concentrations (IC₅₀ and IC₉₀) 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 in vitro inhibition of influenza virus by zanamivir and the inhibition of influenza virus replication in humans has not been established.

Influenza viruses with reduced susceptibility to zanamivir have been recovered in vitro by passage of the virus in the presence of increasing concentrations of the drug. Genetic analysis of these viruses showed that the reduced susceptibility in vitro to zanamivir is associated with mutations that result in amino acid changes in the viral neuraminidase or viral hemagglutinin or both.

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 mutation (Thr 198 Ile) which resulted in a reduced affinity for human cell receptors, and a mutation in the neuraminidase active site (Arg 152 Lys) which reduced the enzyme's activity to zanamivir by 1000-fold.

Insufficient information is available to characterize the risk of emergence of zanamivir resistance in clinical use.

Cross-resistance has been observed between zanamivir-resistant and oseltamivir-resistant influenza virus mutants generated in vitro. No studies have been performed to assess risk of emergence of cross-resistance during clinical use. There was no clear difference in hemagglutination inhibition antibody titers at 2 weeks and 4 weeks after vaccine administration between zanamivir and placebo recipients.

Antiviral activity of zanamivir was supported for influenza A, and to a more limited extent for influenza B, by Phase 1 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 ($AUC_{(infinity)}$) 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.

Special Populations

Impaired Hepatic Function: The pharmacokinetics of zanamivir has not been studied in patients with impaired hepatic function.

Impaired Renal Function: Systemic exposure is limited after inhalation. 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.

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 $AUC_{(infinity)}$ 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 , AUC_{0-3} , C_{max} , T_{max} , CLr , 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. There are no data on the effectiveness of treatment with Zanamivir when initiated more than 2 days after the onset of signs or symptoms.

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 blister 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 blister 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 & PRECAUTIONS

VIRENZA IS NOT RECOMMENDED FOR TREATMENT OR PROPHYLAXIS OF INFLUENZA IN INDIVIDUALS WITH UNDERLYING AIRWAYS DISEASE (SUCH AS ASTHMA OR CHRONIC OBSTRUCTIVE PULMONARY DISEASE)

Some patients with serious adverse events during treatment with Zanamivir have had fatal outcomes, although 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

If treatment 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.

General

Patients should be instructed in the use of the delivery system. Instructions should include a demonstration whenever possible. Patients should read and follow carefully the Patient Instructions for Use accompanying the product.

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

No data are available to support safety or efficacy in patients who begin treatment after 48 hours of symptoms.

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

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.

Prevention of Influenza

Use of zanamivir should not affect the evaluation of individuals for annual influenza vaccination in accordance with guidelines of the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices. Safety and efficacy of zanamivir have not been established for prophylactic use of zanamivir to prevent influenza.

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

No clinically significant pharmacokinetic drug interactions are predicted based on data from in vitro studies.

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, nursing 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 nursing mother.

Pediatric Use

Safety and effectiveness of zanamivir have not been established in pediatric patients under 5 years of age.

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

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.

SHELF-LIFE

24 months

STORAGE & HANDLING INSTRUCTIONS

Store in a cool dry place

PACKAGING INFORMATION

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

Last updated: May 2010