PRODUCT MONOGRAPH

PrRELENZA

zanamivir dry powder for inhalation

for use with the DISKHALER Inhalation Device

5 mg/blister

Antiviral Agent

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for use with the DISKHALER Inhalation Device

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral inhalation	Dry powder 5 mg/blister	lactose *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Treatment of Influenza
RELENZA (zanamivir dry powder for inhalation) is indicated for treatment of uncomplicated acute illness due to influenza A and B virus in adults and pediatric patients 7 years of age and older, who have been symptomatic for no more than 2 days. No data are available to support zanamivir safety and efficacy in patients who receive treatment after 48 hours of symptoms.

This indication is based on placebo controlled studies conducted in North America, the Southern Hemisphere, and Europe during their respective influenza seasons. The magnitude of treatment effect varied between studies, with possible relationships to population-related factors including amount of symptomatic relief medication used.

RELENZA, when taken as recommended for treatment of influenza, alleviates the symptoms and reduces their duration.

Prophylaxis of Influenza
RELENZA is indicated in adults and pediatric patients 7 years of age and older for prophylaxis of influenza.

Important Information on Use of RELENZA
RELENZA is not recommended for treatment or prophylaxis of influenza in individuals with underlying airways disease (such as asthma or chronic obstructive pulmonary disease [see WARNINGS AND PRECAUTIONS]) due to risk of serious bronchospasm.

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

RELENZA is not a substitute for influenza vaccination on an annual basis as recommended by the National Advisory Committee on Immunization (NACI).

Geriatrics (≥ 65 years of age):
In clinical trials, the safety profile of RELENZA did not appear to vary with increasing age and no overall differences in the safety and efficacy were observed between the elderly and younger patients. A brief discussion can be found in WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics.

Pediatrics:
Safety and effectiveness of RELENZA for treatment of influenza have not been established in pediatric patients under 7 years of age. Safety and effectiveness of RELENZA for prophylaxis of influenza have not been assessed in pediatric patients under 5 years of age. Efficacy data from the age of 5 to 7 years are limited.

CONTRAINDICATIONS

RELENZA (zanamivir) is contraindicated in patients with a known or suspected hypersensitivity to zanamivir or any component of the zanamivir inhalation powder (including lactose, which contains milk protein).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

There have been reports of patients being treated for influenza who have experienced bronchospasm and decline in respiratory function. Many but not all of these patients had underlying airways disease such as asthma or chronic obstructive pulmonary disease. There have been cases of respiratory arrest, including deaths, in which a contribution from RELENZA (zanamivir) cannot be excluded. RELENZA should be discontinued in any patient who develops bronchospasm or a decline in respiratory function; immediate treatment and hospitalization may be required. All patients should be advised of the risk of bronchospasm with RELENZA.

RELENZA is not generally recommended for treatment of patients with severe underlying airways disease because of the risk of serious adverse events and because efficacy has not been demonstrated in this population (see WARNINGS AND PRECAUTIONS, Respiratory).

General
Due to the limited number of patients with severe asthma or other severe chronic respiratory diseases, patients with chronic illnesses or immunocompromised patients who have been treated, it has not been possible to demonstrate the efficacy and safety of RELENZA in these groups.

Vaccination of persons at high risk each year before the influenza season is currently recognized as the most effective measure for reducing the impact of influenza. The use of zanamivir should not affect the evaluation of individuals for annual influenza vaccination, in accordance to *"Health Canada, An Advisory Committee Statement, National Advisory Committee on Immunization (NACI), Statement on Influenza Vaccination for the current Year/Season"*.

Patients should be instructed in the use of the DISKHALER inhalation device and instructions should include a demonstration wherever possible. Patients should be advised to read and follow carefully the patient instructions to ensure safe and effective use. Patients should be advised to finish the full course of treatment or prophylaxis therapy as prescribed.

RELENZA (zanamivir) dry powder for inhalation must not be made into an extemporaneous solution for administration by nebulization or mechanical ventilation. There have been reports of hospitalised patients with influenza who received a solution made with RELENZA (zanamivir) dry powder for inhalation administered by nebulization or mechanical ventilation, including a fatal case where it was reported that the lactose in this formulation obstructed the proper functioning of the equipment. RELENZA (zanamivir) dry powder for inhalation must only be administered using the device provided (see DOSAGE AND ADMINISTRATION, Administration).

Carcinogenesis and Mutagenesis
See Part II, TOXICOLOGY.

Hepatic/Biliary/Pancreatic
The pharmacokinetics of zanamivir have not been investigated in patients with impaired hepatic function; doses of up to 1200 mg IV in healthy adults did not show evidence of hepatic metabolism.

Immune/Infection
Serious bacterial infections may begin with influenza-like symptoms or may co-exist with or occur as complications during the course of influenza. RELENZA has not been shown to prevent such complications.

Allergic-like reactions, including facial and oropharyngeal edema, bronchospasm, laryngospasm, dyspnea, urticaria, serious skin rashes and anaphylaxis have been reported in post-marketing experience. RELENZA should be discontinued and immediate medical attention sought by any patient who develops an allergic reaction or if one is suspected.

Neurologic

There have been post-marketing reports (mostly from Japan) of delirium and abnormal behaviour leading to injury in patients with influenza who were receiving neuraminidase inhibitors, including RELENZA. 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 RELENZA. These events were reported primarily among pediatric patients and often had an abrupt onset. The contribution of RELENZA to these events has not been established. Patients with influenza receiving RELENZA should be closely monitored for signs of abnormal behaviour. If neuropsychiatric symptoms occur, the risks and benefits of continuing treatment should be evaluated for each patient.

It should be noted that influenza infection itself can be complicated with a variety of neurologic and behavioural symptoms which can include events such as seizures, hallucinations, delirium, and abnormal behaviour, 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.

Renal

At the therapeutic daily dose of inhaled zanamivir of 20 mg, bioavailability is low (4-17%), and as a result, systemic exposure of patients to RELENZA is limited. However, after a single IV dose of 4 mg or 2 mg of zanamivir in volunteers with mild or moderate, or severe renal impairment, respectively, significant decreases in renal clearance (and hence total clearance: normal 5.3 L/h, mild/moderate 2.7 L/h, and severe 0.8 L/h; median values) and significant increases in half life (normals 3.1 h, mild/moderate 4.7 h, and severe 18.5 h; median values) and systemic exposure were observed. Safety and efficacy have not been documented in patients with end stage renal disease.

Respiratory

Safety and efficacy of RELENZA have not been demonstrated in patients with severe underlying chronic pulmonary disease or severe asthma due to limited number of patients treated. Therefore, RELENZA is not generally recommended for treatment in such patients. Serious adverse events have been reported in patients with underlying chronic pulmonary disease and in patients with severe or decompensated chronic obstructive pulmonary disease or asthma (see Serious Warnings and Precautions).

If treatment with RELENZA is considered for a patient with an underlying airway disease, the potential risks and benefits should be carefully weighed. The patients should be advised of the risk of bronchospasm. If a decision is made to prescribe RELENZA 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. Patients should be instructed to contact their physician if they experience increased respiratory

symptoms during treatment such as worsening wheezing, shortness of breath, or other signs or symptoms of bronchospasm (see Serious Warnings and Precautions) and to discontinue RELENZA. Patients scheduled to take inhaled bronchodilators at the same time as RELENZA should be advised to use their bronchodilators before taking RELENZA.

In a placebo controlled study in patients with predominantly mild/moderate asthma and/or Chronic Obstructive Pulmonary Disease (COPD), RELENZA was shown to be effective and well tolerated for the treatment of influenza. There was no evidence of a difference between RELENZA and placebo in forced expiratory volume in one second (FEV_1) or peak expiratory flow rate (PEFR) measured after the end of treatment.

Skin

Severe skin reactions including erythema multiforme, Stevens-Johnnson syndrome and toxic epidermal necrolysis have been reported in post-marketing experience.

Special Populations

Fertility: Animal studies indicate no clinically meaningful effects of zanamivir on male or female fertility (see TOXICOLOGY).

Pregnant Women: There are insufficient data on the use of zanamivir in pregnant women to inform drug associated risk. Data from several studies have not found an increased risk of adverse pregnancy outcomes following in utero exposure to inhaled zanamivir, but due to limited sample sizes, no definitive conclusions can be drawn regarding the safety of zanamivir in pregnancy. There is no information on placental transfer in humans.

Reproductive studies performed in rats and rabbits indicated that placental transfer of zanamivir occurs and there was no evidence of teratogenicity. In these animals, fetal blood concentrations of zanamivir were significantly lower than zanamivir concentrations in the maternal blood. Results from a rat peri- and postnatal study showed no clinically meaningful impairment of offspring development. One embryo/fetal study was conducted using subcutaneous administration of zanamivir, 3 times daily at doses of 1, 9 or 80 mg/kg during days 7 to 17 of pregnancy. Based on AUC measurements, the high dose in the study produced an exposure greater than 1000 times the human exposure at the proposed clinical dose. There was an increase in the incidence rates of a variety of minor skeleton alterations and variants in the exposed offspring in this study. The individual incidence rates of each skeletal alteration or variant, in many but not in all cases, remained within the range of background rates of the historical occurrence in the rat strain studied.

As experience is limited, RELENZA should not be used in pregnancy unless the possible benefit to the patient is thought to outweigh any possible risk to the fetus.

Nursing Women: Studies in rats have demonstrated that zanamivir is excreted in milk. Nursing mothers, however, should be instructed that it is not known whether zanamivir is excreted in human milk. As experience is limited, the use of zanamivir in nursing mothers should be considered only if the possible benefit to the mother is thought to outweigh any possible risk to the child.

Pediatrics: Safety and effectiveness of RELENZA for treatment of influenza have not been established in pediatric patients under 7 years of age. Safety and effectiveness of RELENZA for prophylaxis of influenza have not been assessed in pediatric patients under 5 years of age. Efficacy data from the age of 5 to 7 years are limited. Prescribers should carefully evaluate the ability of young children to use the delivery system if prescription of RELENZA is considered. When RELENZA is prescribed for children, it should be used only under adult supervision and with attention to proper use of the delivery system.

Geriatrics (≥ 65 years of age): At the therapeutic daily dose of 20 mg, bioavailability of zanamivir in young healthy adults is low (10-20%), and as a result, systemic exposure of patients to zanamivir is limited. The bioavailability of zanamivir in elderly individuals has not been determined. However, a total of 83 elderly patients (aged ≥ 65 years old) received inhaled zanamivir at a dose of 10 mg twice daily, or greater, for the treatment of symptomatic influenza in completed clinical trials. Of the total number of patients who received zanamivir 10 mg once daily for prophylaxis of influenza in households and community settings in 4 clinical studies of RELENZA, 954 were aged 65 and over. The safety profile did not appear to vary with increasing age and no overall differences in the safety and efficacy were observed between the elderly and younger patients. However, greater sensitivity of some older patients to medications in general, cannot be ruled out. In 2 additional studies of RELENZA for prophylaxis of influenza in the nursing home setting, efficacy was not demonstrated. Elderly subjects may need assistance with use of the device.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

See WARNINGS AND PRECAUTIONS for information about risk of serious adverse events such as bronchospasm and allergic-like reactions, and for safety information in patients with underlying respiratory disease.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Because the placebo consisted of inhaled lactose powder which is also the vehicle for the inhaled active drug (zanamivir), some adverse events occurring at similar frequencies in different treatment groups could be related to lactose vehicle inhalation.

Treatment of Influenza
Clinical studies were conducted predominately in young adults, in pediatric patients 5 to 12 years old, and in high risk patients (mostly patients with underlying respiratory disease and/or elderly ≥ 65 years old). The incidence of adverse events in these trials appeared similar in the RELENZA (zanamivir) and placebo groups. No differences in adverse reactions were observed between these patient groups.

Adverse events that occurred with an incidence ≥ 1.5% in treatment studies in adults and adolescents are listed in Table 1 below.

Table 1 Summary of Adverse Events ≥ 1.5% Incidence During Treatment in Adults and Adolescents

Adverse Event	RELENZA		Placebo (Lactose Vehicle) (n=1520)
	10 mg b.i.d. **Inhaled** (n=1132)	All Dosing Regimens* (n=2289)	
Body as a Whole			
Headaches	2%	2%	3%
Digestive			
Diarrhea	3%	3%	4%
Nausea	3%	3%	3%
Vomiting	1%	1%	2%
Respiratory			
Nasal signs and symptoms	2%	3%	3%
Bronchitis	2%	2%	3%
Cough	2%	2%	3%
Sinusitis	3%	2%	2%
Ear, nose and throat infections	2%	1%	2%
Nervous system			
Dizziness	2%	1%	<1%

* Includes studies where RELENZA was administered intranasally (6.4 mg 2 to 4 times per day in addition to inhaled preparation) and/or inhaled more frequently (q.i.d.) than the currently recommended dose.

Additional adverse reactions occurring in less than 1.5% of patients receiving RELENZA and placebo included malaise, fatigue, fever, abdominal pain, myalgia, arthralgia, and urticaria. Other side effects that have been reported, but are not as common include allergic reactions and rashes.

Adverse events that occurred with an incidence ≥ 1.5% in children receiving treatment doses of RELENZA in two Phase 3 studies are listed in Table 2.

Table 2 Summary of Adverse Events ≥ 1.5% Incidence During Treatment in Pediatric Patients*

Adverse Event	RELENZA 10 mg b.i.d. Inhaled (n=291)	Placebo (Lactose Vehicle) (n=318)
Respiratory		
Ear, nose, and throat infections	5%	5%
Ear, nose, and throat hemorrhage	<1%	2%
Asthma	<1%	2%
Cough	<1%	2%
Digestive		
Vomiting	2%	3%
Diarrhea	2%	2%
Nausea	<1%	2%

*Includes a subset of patients receiving RELENZA for treatment of influenza in a prophylaxis study.

Prophylaxis of influenza

Family/Household Prophylaxis Studies: Adverse events that occurred with an incidence of ≥ 1% in the 2 prophylaxis studies are listed in Table 3. This table shows adverse events occurring in patients ≥ 5 years of age receiving RELENZA 10 mg or placebo inhaled once daily for 10 days.

Table 3 Summary of Adverse Events ≥ 1% Incidence During 10 Day Prophylaxis Studies in Adults and Pediatric Patients*

Adverse Event	Contact Cases	
	RELENZA (n=1068)	Placebo (n=1059)
Lower respiratory		
Viral respiratory infections	13%	19%
Cough	7%	9%
Neurologic		
Headaches	13%	14%
Ear, nose, and throat		
Nasal signs and symptoms	12%	12%
Throat and tonsil discomfort and pain	8%	9%
Nasal inflammation	1%	2%
Musculoskeletal		
Muscle pain	3%	3%
Musculoskeletal pain	1%	1%
Endocrine and metabolic		
Feeding problems (decreased or increased appetite and anorexia)	2%	2%
Gastrointestinal		
Nausea and vomiting	1%	2%
Diarrhea	1%	< 1%
Non-site specific		
Malaise and fatigue	5%	5%
Temperature regulation disturbances (fever and/or chills)	5%	4%

* In prophylaxis studies, symptoms associated with influenza-like illness were captured as adverse events; subjects were enrolled during a winter respiratory season during which time any symptoms that occurred were captured as adverse events.

Community Prophylaxis Studies: Adverse events that occurred with an incidence of ≥1% in 2 prophylaxis studies are listed in Table 4. This table shows adverse events occurring in patients ≥ 12 years of age receiving RELENZA 10 mg or placebo inhaled once daily for 28 days.

Table 4 Summary of Adverse Events ≥ 1% Incidence During 28 Day Prophylaxis Studies in Adults and Adolescents*

Adverse Event	RELENZA (n=2231)	Placebo (n=2239)
Neurologic		
Headaches	24%	26%
Ear, nose, and throat		
Throat and tonsil discomfort and pain	19%	20%
Nasal signs and symptoms	12%	13%
Ear, nose, and throat infections	2%	2%
Viral ear, nose, and throat infections	1%	1%
Sinusitis	1%	1%
Lower respiratory		
Cough	17%	18%
Viral respiratory infections	3%	4%
Bronchitis	1%	1%
Asthma	< 1%	1%
Musculoskeletal		
Muscle pain	8%	8%
Musculoskeletal pain	6%	6%
Arthralgia and articular rheumatism	2%	< 1%
Endocrine and metabolic		
Feeding problems (decreased or increased appetite and anorexia)	4%	4%
Gastrointestinal		
Nausea and vomiting	2%	3%
Diarrhea	2%	2%
Reproduction		
Menstruation symptoms	1%	1%
Non-site specific		
Temperature regulation disturbances (fever and/or chills)	9%	10%
Malaise & fatigue	8%	8%

* In prophylaxis studies, symptoms associated with influenza like illness were captured as adverse events; subjects were enrolled during a winter respiratory season during which time any symptoms that occurred were captured as adverse events.

Abnormal Hematologic and Clinical Chemistry Findings

The most frequent laboratory abnormalities in Phase 3 treatment studies included elevations of liver enzymes and CPK, lymphopenia, and neutropenia. These were reported in similar proportions of zanamivir and lactose vehicle placebo recipients with acute influenza-like illness.

Post-Market Adverse Drug Reactions

Reporting rates determined on the basis of spontaneously reported post-marketing adverse events are generally presumed to underestimate the risks associated with drug treatments.

The following adverse events have been reported spontaneously during post-marketing experience with inhaled RELENZA. However, a causal relationship to RELENZA cannot be clearly established for spontaneously reported events.

Cardiac: Arrhythmias, syncope, tachycardia

Gastrointestinal: Diarrhea, nausea, vomiting

General: Allergic or allergic-like reactions, including anaphylactic and anaphylactoid reactions, facial and oropharyngeal oedema, laryngospasm (see WARNINGS AND PRECAUTIONS)

Neurologic: Dizziness, headaches, insomnia, seizures, vasovagal-like reactions have been reported in patients shortly following inhalation of zanamivir

Psychiatric: Delirium, including symptoms such as altered level of consciousness, confusion, abnormal behaviour, delusions, hallucinations, agitation, anxiety, nightmares (see WARNINGS AND PRECAUTIONS)

Respiratory: Bronchospasm, dyspnea (see WARNINGS AND PRECAUTIONS)

Skin: Rash, urticaria, and severe skin reactions including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (see WARNINGS AND PRECAUTIONS).

DRUG INTERACTIONS

Drug-Drug Interactions

Zanamivir is less than 15% protein bound. There is no evidence of hepatic metabolism, and zanamivir is not a substrate nor does it affect hepatic cytochrome P450 (CYP) isoenzymes (CYP1A1/2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4). It is not a substrate of P-glycoprotein (P-gp) or renal transporters, nor does it affect human transporters (organic anion, cation or urate transporters). *In vivo*, zanamivir is excreted in urine as unchanged drug and there is no evidence that zanamivir is hepatically metabolized or modified. Therefore, based on data from *in vitro* studies, clinically significant drug interactions are unlikely. RELENZA (zanamivir), when given for 28 days (10 mg once daily), did not impair the immune response to the influenza vaccine.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Treatment of Influenza
The recommended dose of RELENZA (zanamivir) for treatment of influenza in adults and pediatric patients ≥ 7 years of age is 2 inhalations (one 5 mg blister per inhalation for a total dose of 10 mg) twice daily (approximately 12 hours apart) for 5 days. A second dose 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 RELENZA when initiated more than 2 days after the onset of signs or symptoms. For maximum benefit, treatment must begin within two days after the onset of symptoms.

Prophylaxis of Influenza

Household setting: The recommended dose of RELENZA for prophylaxis of influenza in adults and pediatric patients 7 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 RELENZA 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 RELENZA 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 RELENZA 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 RELENZA have not been evaluated for longer than 28 days duration.

Missed Dose
In case of a missed dose, RELENZA should be taken immediately, except if it is near the next dose (within 2 hours). Then, RELENZA should be continued at the usual times.

Administration
RELENZA is for administration to the respiratory tract by oral inhalation only using the device provided. The contents of each blister are inhaled using a specially designed breath-activated plastic device for inhaling powder called the DISKHALER inhalation device.

Patients scheduled to use an inhaled bronchodilator at the same time as RELENZA should use their bronchodilator before taking RELENZA (see WARNINGS AND PRECAUTIONS, Respiratory).

OVERDOSAGE

Symptoms and Signs
Reports of overdoses with inhaled RELENZA have been received during postmarketing experience. The reported clinical signs or symptoms were similar to those observed with therapeutic doses of inhaled RELENZA. Doses of an investigational (lactose-free) aqueous solution of RELENZA up to 64 mg/day (approximately 3 times the maximum daily recommended dose) have been administered by oral inhalation (by nebuliser). Additionally, systemic administration by intravenous route of up to 1200 mg/day for five days in 12 healthy adults caused no adverse effect.

Treatment
As zanamivir has a low molecular weight, low protein binding, and small volume of distribution, it is expected to be removed by hemodialysis. Further management should be as clinically indicated or as recommended by your regional Poison Control Centre.

For management of a suspected drug overdose contact your regional Poison Control Centre

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
RELENZA (zanamivir) is a selective inhibitor of neuraminidase, the influenza virus surface enzyme. It is believed that viral neuraminidase aids the release of newly formed virus particles from infected cells and may facilitate access of virus through mucus to epithelial cell surfaces, to allow viral infection of other cells. It is believed that the inhibition of this enzyme is reflected in both *in vitro* and *in vivo* (in animals) activity against influenza A and B virus replication, and encompasses all of the known neuraminidase subtypes of influenza A viruses.

It is believed that the activity of zanamivir is extracellular. It reduces the propagation of both influenza A and B viruses by inhibiting the release of infectious influenza virions from the epithelial cells of the respiratory tract. Influenza viral replication is primarily

confined to the superficial epithelium of the respiratory tract. The efficacy of topical administration of zanamivir to this site has been confirmed in clinical studies.

Pharmacokinetics

Absorption: Pharmacokinetic studies in humans have shown that the absolute oral absorption of zanamivir, as compared to IV administration of the drug, was low (mean 2%). Similar studies of orally inhaled RELENZA (zanamivir) indicate that approximately 4-17% of the dose is systemically absorbed, with serum concentrations generally peaking within 1-2 hours. The peak serum concentrations ranged from 17 to 142 ng/mL following a 10 mg dose. The area under the serum concentration versus time curve (AUC to infinity) ranged from 111 to 1364 ng•hr/mL.

Distribution: In healthy adults, after oral inhalation, RELENZA is widely deposited at high concentrations throughout the respiratory tract, thus delivering the drug to the site of influenza infection. The high concentrations of RELENZA in the respiratory tract will result in the rapid onset of inhibition of the viral neuraminidase. The two major sites of deposition are the oropharynx and the lungs (mean 77.6% and 13.2 %, respectively), from where zanamivir is eliminated via the gastrointestinal tract. Following twice daily administration of zanamivir 10 mg by oral inhalation, the median trough concentrations of zanamivir measured at the epithelial layer of the airways, (the major sites of influenza viral replication) ranged from 326 ng/mL to 891 ng/mL. These trough concentrations are multiple-fold in excess of the in vitro IC_{50} (<1 to 4 ng/mL) and IC_{90} (1.7 to 7.8 ng/mL) values for influenza virus neuraminidase for various influenza subtypes. The high concentrations of zanamivir in the respiratory tract will result in the rapid onset of inhibition of the viral neuraminidase.

Metabolism: Zanamivir has been shown to be renally excreted as unchanged drug. There is no evidence of metabolism of orally inhaled drug.

Excretion: The serum half life of zanamivir following administration by oral inhalation ranges from 2.6 to 5.05 hours. It is entirely excreted unchanged in the urine. Total clearance ranges from 2.5 to 10.9 L/h as approximated by urinary clearance. Renal elimination is completed within 24 hours. The unabsorbed drug is excreted in the feces.

Special Populations and Conditions

Pediatrics: The pharmacokinetics of zanamivir were 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 via the DISKHALER inhalation device. 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 peak inspiratory flow rates (PIFR) in individual patients (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).

Geriatrics: At the therapeutic daily dose of inhaled zanamivir of 20 mg, bioavailability is low (4-17%), and as a result systemic exposure of patients to RELENZA is limited. The bioavailability of zanamivir in elderly individuals has not been determined (see WARNINGS AND PRECAUTIONS).

Hepatic Insufficiency: The pharmacokinetics of zanamivir have not been investigated in patients with impaired hepatic function; doses of up to 1200 mg IV in healthy adults did not show evidence of hepatic metabolism.

Renal Insufficiency: At the therapeutic daily dose of inhaled zanamivir of 20 mg, bioavailability is low (4-17%), and as a result systemic exposure of patients to RELENZA is limited. However, after a single IV dose of 4 mg or 2 mg of zanamivir in volunteers with mild or moderate, or severe renal impairment, respectively, significant decreases in renal clearance (and hence total clearance: normal 5.3 L/h, mild/moderate 2.7 L/h, and severe 0.8 L/h; median values) and significant increases in half life (normal 3.1 h, mild/moderate 4.7 h, and severe 18.5 h; median values) and systemic exposure were observed. Safety and efficacy have not been documented in patients with end stage renal disease.

STORAGE AND STABILITY

Store at room temperature (15 to 30°C) in a dry place.

SPECIAL HANDLING INSTRUCTIONS

Use the ROTADISK disks before the expiration date. Do not puncture any ROTADISK disk blister until taking a dose using the DISKHALER inhalation device.

DOSAGE FORMS, COMPOSITION AND PACKAGING

RELENZA (zanamivir) ROTADISK disks consist of a circular foil disk with four regularly distributed blisters each containing 5 mg of zanamivir and lactose (which contains milk protein). A DISKHALER inhalation device is provided to administer the medication. Box of 5 ROTADISK disks.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

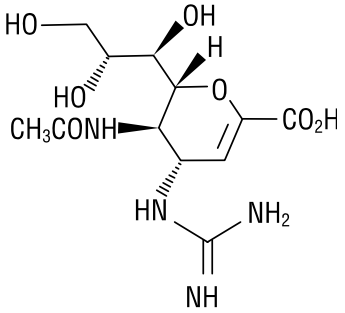
Proper name: zanamivir

Chemical name: 5-(acetylamino)-4-[(aminoiminomethyl)-amino]-2,6-anhydro-3,4,5-trideoxy-D-glycero-D-galacto-non-2-enonic acid.

Molecular formula: $C_{12}H_{20}N_4O_7$

Molecular mass: 332.3

Structural formula:



Physicochemical properties: White to off-white powder with a solubility of approximately 18 mg/mL in water at 20ºC.

CLINICAL TRIALS

Treatment of Influenza

Studies in Adults: The efficacy of RELENZA (zanamivir) 10 mg inhaled twice daily for 5 days in the treatment of influenza has been evaluated in placebo controlled studies conducted in North America, the Southern Hemisphere, and Europe during their respective influenza seasons. The magnitude of treatment effect varied between studies, with possible relationships to population related factors including amount of symptomatic relief medication used.

Four phase 3 randomized, double blind, placebo controlled clinical studies recruited a total of 2113 patients aged 12 years and older (mean age 37 years, 47% male, 91% Caucasian), of which 1075 subjects received zanamivir. One thousand three hundred and twenty-one subjects were infected with influenza A and 155 with influenza B. Treatment was initiated in patients with uncomplicated influenza-like illness within 48 hours of the onset of symptoms. Influenza was confirmed by culture, hemagglutination inhibition antibodies, or investigational direct tests. The patients were given a 5 day course of therapy (10 mg zanamivir b.i.d by oral inhalation). The primary efficacy measure was the length of median time to alleviation of symptoms and signs of influenza, focusing on the key features of influenza: fever/feverish, headache, myalgia, cough and sore throat. The results of these studies are shown in Table 5 below.

Table 5 Comparison of Median Time (Days) to Alleviation of Clinically Significant Influenza Symptoms: Intent to Treat (ITT) and Influenza Positive Population (IPP) - Adult Studies

Study	Population	Placebo	Zanamivir 10 mg inhaled twice daily	Differences in Days	(95% CI) p value
NAIB3001 (Australian Study)	ITT	n=228 6.5	n=227 5.0	1.5	(0.5, 2.25) 0.011
	IPP	n=160 6.0	n=161 4.5	1.5	(0.5, 2.5) 0.004
NAIA3002 (North American Study)	ITT	n=365 6.0	n=412 5.5	0.5	(-0.5, 1.0) 0.228
	IPP	n=257 6.0	n=312 5.0	1	(0.0, 1.5) 0.078
NAIB3002 (European Study	ITT	n=182 7.5	n=174 5.0	2.5	(0.75, 3.5) <0.001
	IPP	n=141 7.5	n=136 5.0	2.5	(1.0, 4.0) <0.001
NAI30008 (High Risk – Asthma/COPD Study)	ITT	n=263 7.0	n=262 6.0	1	(0.0, 2.0) 0.123
	IPP	n=153 7.0	n=160 5.5	1.5	(0.50, 3.25) 0.009

In general, patients with lower temperature (e.g. 38.2°C or less) or investigator-rated as having less severe symptoms at entry derived less benefit from therapy.

No consistent differences in rate of development of complications were observed between treatment groups.

The four adult and adolescent phase 3 studies recruited a total of 742 high risk patients (mostly patients with underlying respiratory disease and/or elderly ≥ 65 years old) of which 361 received zanamivir. The safety profile in these patients, as far as adverse events and laboratory parameters, was similar to that of placebo, and no specific safety issues were identified.

It has not been possible to demonstrate that RELENZA is safe and effective in patients with severe asthma or other severe chronic respiratory diseases, patients with unstable chronic illnesses or immunocompromised patients due to the limited number of such patients who have been treated.

The safety and efficacy of repeated treatment courses have not been studied.

Study in Pediatric Patients: The efficacy of RELENZA 10 mg inhaled twice daily for 5 days in the treatment of influenza in pediatric patients has been evaluated in a randomized, double blind, placebo controlled study enrolling 471 patients aged 5 to 12 years, of which 224 subjects received zanamivir. Two hundred and twenty-six subjects were infected with influenza A and 120 with influenza B. The results of this study are shown in Table 6 below**.**

Table 6 Comparison of Median Time (Days) to Alleviation of Clinically Significant Influenza Symptoms: Intent to Treat (ITT) and Influenza Positive Population (IPP) - Pediatric Study

Study	Population	Placebo	Zanamivir 10 mg inhaled twice daily	Differences in Days	(95% CI) p value
NAI30009 (Pediatric Study)	ITT	n=247 5.0	n=224 4.5	0.5	(0.0, 1.5) 0.011
	IPP	n=182 5.25	n=164 4.0	1.25	(0.5, 2.0) < 0.001

The definition of time to improvement included no fever and parental assessment of no or mild cough and absent/minimal muscle and joint aches or pains, sore throat, chills/feverishness and headache. No consistent differences in rate of development of complications were observed between treatment groups.

Although this study was designed to enrol children aged 5 to 12 years old, the product is indicated only in children 7 years and older. This evaluation is based on the combination of lower estimates of treatment effect in 5 and 6 year old children compared with the overall study population, and evidence of inadequate inhalation through the DISKHALER inhalation device in a pharmacokinetic study (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Pediatrics).

Prophylaxis of Influenza

The efficacy of RELENZA in preventing naturally occurring influenza illness has been demonstrated in 2 post-exposure prophylaxis studies in households and 2 seasonal prophylaxis studies during community outbreaks of influenza. The primary efficacy endpoint in these studies was the incidence of symptomatic, laboratory confirmed influenza, defined as the presence of 2 or more of the following symptoms: oral temperature ≥ 100°F/37.8°C or feverishness, cough, headache, sore throat and myalgia; and laboratory confirmation of influenza A or B by culture, PCR, or seroconversion (defined as a 4-fold increase in convalescent antibody titer from baseline).

Two studies assessed post-exposure prophylaxis in household contacts of an index case. Within 1.5 days of onset of symptoms in an index case, each household (including all family members ≥ 5 years of age) was randomized to RELENZA 10 mg inhaled once daily or placebo inhaled once daily for 10 days. In the first study only, each index case was randomized to RELENZA 10 mg inhaled twice daily for 5 days or inhaled placebo twice daily for 5 days. In this study, the proportion of households with at least 1 new case of symptomatic laboratory confirmed influenza was reduced from 19.0% (32 of 168 households) for the placebo group to 4.1% (7 of 169 households) for the group receiving RELENZA ($p<0.001$, relative risk 0.21 [95% CI: 0.11, 0.43]).

In the second study, index cases were not treated. The incidence of symptomatic laboratory confirmed influenza was reduced from 19.0% (46 of 242 households) for the placebo group to 4.1% (10 of 245 households) for the group receiving RELENZA ($p<0.001$, relative risk 0.19 [95% CI: 0.10, 0.36]).

Two seasonal prophylaxis studies assessed RELENZA 10 mg inhaled once daily versus placebo inhaled once daily for 28 days during community outbreaks. The first study enrolled subjects 18 years of age or greater (mean age 29 years) from two university communities. The majority of subjects were unvaccinated (86%). In this study, the incidence of symptomatic laboratory confirmed influenza was reduced from 6.1% (34 of 554) for the placebo group to 2.0% (11 of 553) for the group receiving RELENZA ($p<0.001$, relative risk 0.33 [95% CI: 0.17, 0.61]).

The second seasonal prophylaxis study enrolled subjects 12 to 94 years of age (mean age 60 years) with 56% of them older than 65 years of age. Sixty-seven percent of the subjects were vaccinated. In this study, the incidence of symptomatic laboratory-confirmed influenza was reduced from 1.4% (23 of 1685) for the placebo group to 0.2% (4 of 1678) for the group receiving RELENZA ($p<0.001$, relative risk 0.17 [95% CI: 0.07, 0.44]).

DETAILED PHARMACOLOGY

Animal - Pharmacokinetics

Studies of the absorption, distribution, metabolism and excretion of zanamivir in animal species used in the toxicological evaluation of this compound have demonstrated that the species used were appropriate for predicting the safety of zanamivir in humans. Interspecies scaling of the pharmacokinetic data from animals to man indicate that the kinetics of zanamivir in man are entirely predictable from the animal data (Table 7). In the rat and dog, zanamivir is excreted in the urine entirely in the form of unchanged drug. *In vitro* and *in vivo* drug interaction studies have shown zanamivir to have a low potential for interactions with drugs likely to be co administered in the clinic.

Table 7 Pharmacokinetic Data for Zanamivir

Species	Half-life (min)	Plasma Clearance (mL/min)	Renal Clearance (mL/min)	Volume of Distribution (mL)	Oral Bioavailability (%)
Rat	15	1.57	1.42	36.6	2.7
Dog	50	41.0	36.5	3100	10.0
Man	100	111	94.8	16000	2

VIROLOGY

Influenza A and B viruses both have two surface glycoproteins, hemagglutinin and neuraminidase, which protrude from the lipid envelope. The hemagglutinin mediates the attachment of the virus to the host cell by binding to the sialic acids present on glycoconjugates at the surface of the cell. The neuraminidase hydrolyses sialic acids from glycoconjugates, thereby destroying the cellular receptor for the virus and allowing the release of mature virus particles to propagate the infection.

In Vitro Activity

Zanamivir is a highly potent and selective inhibitor of neuraminidases. The antiviral activity *in vitro* of zanamivir has been assessed using a variety of assay methodologies, including plaque formation, viral yields and antigen expression. Zanamivir is equiactive against influenza A viruses and influenza B viruses with IC_{50} values in the range of 4 nM – 16 μM.

Zanamivir was found to be substantially more active (up to 2800 times) than the reference antiviral agents, amantadine, rimantadine and ribavirin against most of the influenza viruses tested (Table 8). Studies of the compound's mode of action are consistent with inhibition of the viral neuraminidase being the mechanism by which zanamivir exerts its antiviral effect.

Table 8 Antiviral Activity (IC50) of Zanamivir and Amantadine in MDCK Cells Infected With Laboratory Adapted Strains of Influenza A and B Viruses, Measured By Inhibition of Plaque Formation

Plaque Reduction IC_{50}		
Virus	**Zanamivir**	**Amantadine**
	IC_{50}	**IC_{50}**
Influenza Virus A Strains	0.004 - 0.014	1.1 - 7.3
Influenza Virus B/Victoria/102/85	0.005	> 26.7

The effect of a range of likely concomitant drugs on the antiviral activity of zanamivir was determined *in vitro* in plaque reduction assays. Aspirin, ibuprofen, acetaminophen and codeine, oxymetazoline, phenylephrine, diphenhydramine, promethazine and amoxicillin-clavulanic acid all at concentrations of peak serum or local topical levels during clinical use, do not interfere adversely with the antiviral activity of zanamivir.

***In Vivo* Activity**

The antiviral activity of zanamivir *in vivo* has been investigated in mouse and ferret models.

In mice, when administered intranasally b.i.d at 18 hours prior to infection and continuing for 4 days, zanamivir inhibited the replication of influenza A with an ED_{AUC10} value (the dose of drug required to reduce lung virus titres by 90% when given bid) of 0.027 mg/kg. This value was much lower ($p < 0.01$) than the ED_{AUC10} for amantadine (3.5 mg/kg) using the same dosing regimen. Similar activity against influenza B was also observed in the mouse model.

Studies in mice have demonstrated that the lung virus titres did not rebound up after drug treatment was stopped three days after infection.

Intranasal administration of zanamivir bid at 0.39 mg/kg and 12.5 mg/kg with the first dose of compound administered up to 3 hours after infection, was shown to reduce the lung virus titre AUC by more than 90% in mice.

In ferrets, zanamivir when administered intranasally b.i.d 26 hours prior to infection and continuing until the fifth day after infection, was shown to inhibit the replication of the influenza A and B viruses with ED_{AUC10} values of 0.32 mg/kg and 0.59 mg/kg respectively.

Zanamivir when administered intranasally b.i.d at 1.5 mg/kg or 0.3 mg/kg for five days in the ferret model beginning either 5 hours or 22 hours after infection showed reductions in the antiviral efficacy of influenza. The mouse and ferret models of influenza infection therefore demonstrate that zanamivir has both prophylactic and therapeutic antiviral activity against influenza A and B virus replication.

***In Vitro* Viral Resistance**

The *in vitro* replication of influenza viruses in MDCK cells in the presence of zanamivir led to the selection of viruses which are resistant to the compound *in vitro*. Biological studies and sequence analysis of these viruses has shown that *in vitro* resistance to zanamivir can result from amino acid sequence changes to the viral hemagglutinin, or the viral neuraminidase, or both. Of these viruses, only variants with neuraminidase mutations have shown reduced susceptibility (no greater than 10 fold) to zanamivir *in vivo*. The clinical relevance of the resistant genotypes, which were selected from *in vitro* experiments, has not been established.

Cross resistance has been observed between zanamivir resistant and oseltamivir resistant influenza mutants generated *in vitro*.

***In Vivo* Viral Resistance**

Emergence of virus with reduced susceptibility to zanamivir in the clinical trials of zanamivir was rare.

In an 18 month old child who had received a bone marrow transplant and whose zanamivir therapy was started 7 days after the diagnosis of influenza pneumonia, a variant virus was detected in nasopharyngeal secretions two weeks after the treatment with an investigational nebulized solution of zanamivir was started. Analysis of this variant identified two mutations: one in the neuraminidase active site (R152K) which reduced the enzymes activity to zanamivir 1000 fold, and one in the hemagglutinin molecule (T198I) which significantly reduced the virus affinity for human cell receptors. Given the condition of the patient, and the late initiation of the therapy, the clinical significance of these changes is unknown.

No studies have been performed to assess the risk of emergence of cross resistance during clinical use. However, the zanamivir mutation (R152K) and one of the three oseltamivir mutations (R292K) induced in the viral neuraminidase from clinical isolates produces some *in vitro* cross resistance. For the other two oseltamivir mutations (E119V and H274Y) cross resistance has not been observed *in vitro* to zanamivir.

TOXICOLOGY

Acute Toxicity

In male and female mice, a non-lethal oral dose of 2040 mg/kg was established. The non-lethal intravenous dose in mice was considered to be < 90 mg/kg. With the exception of one male who died after receiving a dose of 90 mg/kg, no clinical signs attributable to treatment with zanamivir were seen in any other animal. No target organ toxicity was detected in any single dose study.

In male and female rats, non-lethal doses of > 1740 mg/kg orally and > 90 mg/kg intravenously were established. An acute inhaled dose, generated from a nebulized

solution of zanamivir, at dosages up to 56 mg/kg, caused no deaths and no respiratory tract irritancy in rats.

Long-Term Toxicity

No clinically important systemic toxicity was observed in the Wistar rat or Beagle dog following repeated intravenous administration at systemic exposures between 345 and 552 times that achieved following clinical use of zanamivir. Dosages of 864 mg/kg/day and above, given by continuous infusion for 14 days to rats, caused potentially severe pathological changes in the kidney. At the clear no effect level of 432 mg/kg/day, systemic exposure is approximately 1340 times that following an inhaled dose in man. Therefore, this finding was considered to have no relevance to the clinical use of zanamivir. In inhalation studies, no significant toxicity or respiratory tract irritancy was observed in the rat or Beagle dog following chronic administration, with achieved plasma exposures between 21 (rat) and 40 (dog) times those expected from the clinical use of zanamivir. There were no significant findings following intranasal exposure to the dog.

Carcinogenicity and Mutagenicity

Zanamivir was not genotoxic in a battery of *in vitro* genetic toxicity tests. Zanamivir was negative when tested at the maximum concentration required for each test (up to 5000 μg/plate) both in the presence and absence of a metabolizing system.

In the intravenous micronucleus test, at the maximum achievable dose of zanamivir (90 mg/kg), there was no evidence of clastogenic activity.

In two-year carcinogenicity studies conducted with zanamavir in rats and mice using a powder formulation administered through inhalation, there was an increase in lymphoma incidence over controls in male rats, only at the high dose (30 to 50 mg/kg/day); there was no dose relationship. No increase in lymphoma incidence was seen in mice or female rats. The maximum daily exposures in rats and mice were approximately 23 to 25 and 20 to 22 times, respectively, greater than those in humans at the proposed clinical dose based on AUC comparisons.

Zanamivir was not mutagenic in *in vitro* and *in vivo* genotoxicity assays which included bacterial mutation assays in S. typhimurium and E. coli, mammalian mutation assays in mouse lymphoma, chromosomal aberration assays in human peripheral blood lymphocytes, and the *in vivo* mouse bone marrow micronucleus assay.

Reproduction and Teratology

No drug-related malformations, maternal toxicity or embryotoxicity were observed in pregnant rats or rabbits or their foetuses following intravenous administration of zanamivir at doses up to 90 mg/kg/day. Following subcutaneous administration of zanamivir in an additional rat embryofoetal development study, there was an increase in the incidence rates of a variety of minor skeletal and visceral alterations and variants in the exposed offspring at the highest dose 80 mg/kg, three times daily (240 mg/kg/day; total daily dose), most of which remained within the background rates of the historical occurrence in the strain studied. Based on AUC measurements, the 80 mg/kg dose (240

mg/kg/day) produced an exposure approximately 3 or 1000 times the human exposure at the clinical intravenous or inhaled dose, respectively. In the peri- and post-natal developmental study conducted in rats, there was no clinically meaningful impairment of development of offspring.

Intravenous doses of up to 90mg/kg/day zanamivir produced no effect on fertility and reproductive function of the treated or subsequent generation in male and female rats.

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PART III: CONSUMER INFORMATION

[Pr]RELENZA
zanamivir dry powder for inhalation

This leaflet is Part III of a three-part "Product Monograph" published when RELENZA (zanamivir dry powder for inhalation) was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about RELENZA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
RELENZA is an antiviral medicine for the treatment of influenza and for reducing the chance of getting the flu in community and household settings, in adults and children 7 years of age and older.

RELENZA is not a substitute for the flu shot. You should receive an annual flu shot according to guidelines on immunization practices that your doctor can share with you.

What influenza is:
The flu, or influenza, is an illness caused by a virus in your respiratory tract. Although the flu virus stays in your respiratory tract and is not carried by the blood, it can often make you feel sick all over.

True influenza is often confused with:
- the common cold (also caused by viruses)
- infections caused by bacteria, which may require antibiotics.

Antibiotics have no effect on viruses like the ones that cause influenza or colds. "Stomach flu" that causes vomiting and diarrhea is not related to influenza.

If you have the flu – You might need to be in bed for several days. You probably feel terrible. You will often have a fever, plus some or all of these symptoms:

- Chills
- Muscle aches
- Headache
- Sore throat
- Runny or stuffy nose
- Dry cough
- Tiredness

These symptoms are caused by your body's defense system trying to fight the flu virus in your respiratory tract.

There are 2 main types of influenza viruses - A and B with several subtypes for each. These viruses change, or mutate, over time. Annual flu shot protects 80 to 85% of the time against one or more of the subtypes of flu that cause infections.

You might be surprised to find that you are still susceptible to flu even though you got your flu shot this year.

There are a few reasons why you may still have the flu:
- You were infected with the flu before the vaccine could protect you
- The flu vaccine did not completely protect you against the virus because:
  - the virus may have mutated or changed since the vaccine was developed
  - you may have a weakened immune system

What the medication does:
The influenza virus infects cells that line the inside of your respiratory tract. When RELENZA is inhaled, it helps stop the spread of the influenza virus to healthy cells in your respiratory tract.

With less flu virus in your respiratory tract, **you should experience a less severe disease because** your body's defense system doesn't have to work too hard to fight the virus. That means your flu symptoms should improve.

RELENZA should alleviate the symptoms you are feeling, shorten the duration of your flu (i.e. reduces duration of flu symptoms by about 1 or 2 days) and help you feel better sooner.

RELENZA can also help reduce the chance of getting the flu in persons who have a higher chance of getting the flu because they spend time with someone who has the flu. RELENZA can also reduce the chance of getting the flu if there is a flu outbreak in the community.

When it should not be used:
You should not take RELENZA if you are allergic to zanamivir or any component of the zanamivir inhalation powder (see section entitled **"What the important nonmedicinal ingredients are"**).

What the medicinal ingredient is:
RELENZA contains the active ingredient zanamivir *(zah-NA-mih-veer)*.

What the important nonmedicinal ingredients are:
RELENZA contains the nonmedicinal ingredient lactose (which contains milk protein).

What dosage forms it comes in:
RELENZA is a dry powder for inhalation. Each blister of RELENZA contains a dry loose powder mixture of zanamivir and lactose. The lactose acts as a carrier to deliver the medicine to the respiratory tract. The blister protects the powder from the air (until you inhale the powder). The DISKHALER inhalation device is used to inhale RELENZA directly into your respiratory tract.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Some patients have had bronchospasm (wheezing) or serious breathing problems when they used RELENZA. Many but not all of these patients had asthma or chronic obstructive pulmonary disease. There is limited data on the use of RELENZA in patients with severe asthma or severe chronic obstructive pulmonary disease. Therefore, RELENZA is not generally recommended for such patients.

If you develop worsening respiratory symptoms such as wheezing or shortness of breath, stop using RELENZA and contact your doctor right away.

If you have chronic respiratory disease such as asthma or chronic obstructive pulmonary disease and your doctor has prescribed RELENZA, you should have a fast-acting, inhaled bronchodilator available for your use. If you are scheduled to use an inhaled bronchodilator at the same time as RELENZA, use the inhaled bronchodilator before using RELENZA.

Other kinds of infections can appear like influenza or occur along with influenza and need different kinds of treatment. Contact your doctor if you feel worse or develop new symptoms during or after treatment, or if your influenza symptoms do not start to get better.

BEFORE you use RELENZA talk to your doctor or pharmacist if:

- you suffer from asthma or chronic respiratory disease.
  Similar to other non-bronchodilator medications that are inhaled as a dry powder, a bronchospasm can occur when using RELENZA and a fast-acting inhaled bronchodilator (e.g. salbutamol) should be available if this occurs.
- you are pregnant, or likely to become pregnant soon, or if you are breast feeding.
  If you are pregnant or breast feeding, your doctor will help you decide whether you should take RELENZA.
- you have any type of chronic condition including lung, kidney or heart disease.
- you are allergic to lactose or milk protein.

INTERACTIONS WITH THIS MEDICATION

It is unlikely that RELENZA will interact with any medications you might be taking. Always be sure to tell your doctor what medications you are using.

PROPER USE OF THIS MEDICATION

Usual dose:
For the Treatment of Influenza: You need to inhale two blisters in the morning and two blisters in the evening. You will use 1 ROTADISK disk each day for 5 days. RELENZA works best when you start taking it **as soon as** you begin to feel symptoms and no later than 2 days after flu symptoms start. Take the entire dosage (all 5 ROTADISK disks) of RELENZA **even if** you start to feel better before you've finished all your medicine.

For the Prevention of Influenza: To reduce the chance of getting the flu, the usual dose is two blisters once daily for 10 or 28 days as prescribed by your doctor.

If you are scheduled to use an inhaled bronchodilator at the same time as RELENZA, you should use your bronchodilator first, before using RELENZA.

See also section entitled "How to take RELENZA" for instructions on how to use the DISKHALER inhalation device.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose, don't worry. Take a dose as soon as you remember, except if it is near the next dose (within 2 hours). Then continue to take RELENZA at the usual times. You do not need to take a double dose. If you have missed several doses, inform your doctor or pharmacist and follow the advice given to you.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

In studies, the most common side effects during treatment with RELENZA have been headaches, diarrhea, nausea, vomiting, appetite problems, nasal irritation, bronchitis, cough, sinusitis, ear, nose and throat infections, fever, chills, body pain, fatigue and dizziness. Other side effects that have been reported, but are not as common include allergic reactions and rashes.

If you are feeling unwell when you take RELENZA you may faint or become lightheaded after inhaling RELENZA. You must sit down in a relaxed position before inhaling the dose of RELENZA, and you must only hold your breath for as long as is comfortable after inhaling the dose. If you are feeling unwell, you are advised to have someone with you while you are inhaling the dose of RELENZA.

People with influenza (the flu), particularly children and adolescents, may be at an increased risk of seizures, confusion, delirium, hallucinations, or abnormal behaviour early in their illness. These events may occur after beginning RELENZA or may occur when flu is not treated. These events are uncommon but may result in accidental injury to the patient. Therefore, patients should be observed for signs of unusual behaviour and a healthcare professional should be contacted immediately if the patient shows any signs of unusual behaviour.

Serious Warnings and Precautions are described above, and Serious Side Effects are in the table below.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very rare	Breathing Problems. Bronchospasm (involuntary contraction of the smooth muscles of the airway passages) with symptoms such as difficulty in breathing and wheezing.		✓	✓
Very rare	Allergic reaction such as swelling of the face or in the mouth or throat; or itchy, raised skin rash (hives); or breathing problems (shortness of breath or wheezing), or collapse.		✓	✓
Very rare	Skin rash, which may blister, and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) (erythema multiforme)		✓	✓
Very rare	Widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens Johnson Syndrome)		✓	✓
Very rare	Extensive peeling of the skin on much of the body surface (toxic epidermal necrolysis)		✓	✓

If you notice any of the symptoms listed in the table above stop taking RELENZA and contact a doctor urgently.

This is not a complete list of side effects. For any unexpected effects while taking RELENZA, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature (15 to 30°C) in a dry place. Use the ROTADISK disk before the expiration date. Do not puncture any RELENZA ROTADISK disk blister until you are ready to inhale a dose of RELENZA.

Keep RELENZA and the DISKHALER inhalation device in a safe place away from children.

HOW TO TAKE RELENZA

The medicine in the ROTADISK disk must only be inhaled using the DISKHALER inhalation device. Follow the instructions as shown below. Children (7 years and older) who use RELENZA should always be supervised by an adult who understands how to use RELENZA. It is important that you inhale, not swallow, each dose as instructed by your doctor or pharmacist. If you have any problems taking this medicine, or do not understand the instructions below, tell your doctor or pharmacist.

The parts of your DISKHALER inhalation device are:

- Half-Circle Flap - Lifts up and down to operate the plastic needle.
- Needle - Punctures the blister to release medicine.
- Brown Wheel - Rotates to the next blister.
- White Tray - Pulls in and out.
- Raised Ridges - Help you pull out the tray for loading.
- Air Holes.
- White Mouthpiece - Where medicine is inhaled.
- Cover - Keeps the DISKHALER inhalation device clean when not in use.
- ROTADISK Medicine Disk - Contains 4 blisters of medicine; the disk fits onto the brown wheel inside the DISKHALER inhalation device.
- Blister of Medicine - Contains dry loose powder medicine.

PATIENT INSTRUCTIONS

Each disk contains 4 blisters of medicine.

- ROTADISK disk
- Blister of dry loose powder medicine

Don't puncture any blisters until you've read all of the instructions and you're ready to inhale your medicine.
Important Instructions! Read instructions before using.

Step 1● Step 2● Step 3● Step 4● TO INHALE RELENZA

Step 1 To Load Medicine
Pull off the blue cover

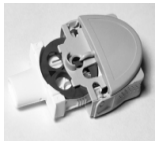
Remove cover

Check that the mouthpiece is clean, inside and outside.

Pull and Extend
Hold the white sliding tray by the edges as shown and pull it out until it stops.

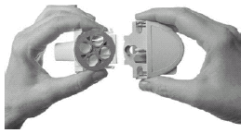
Pull to extend

Find 4 Ridges
Find the 4 raised ridges (finger grips) on each side of the white tray.



4 raised ridges

Squeeze and Remove
Press in these ridges, both sides at the same time, and pull the whole tray out of the DISKHALER inhalation device. The white tray should come out easily.

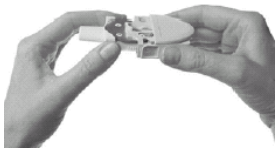


Squeeze 4 ridges to remove tray

Drop in ROTADISK disk
Place one ROTADISK disk onto the brown wheel, **flat side up**. Make sure the printed side is up, with the blisters facing downwards. The 4 blisters will drop neatly into the 4 holes in the wheel.

Drop in disk

Close
Push in the white tray, until it clicks firmly back into place. If you're not ready to inhale a dose straight away, replace the blue cover.



Push to close (Click!)

Step 2 To Puncture Blister
Find Flap
Find the half-circle flap of the DISKHALER device.

Find flap

From this point on-- KEEP THE DISKHALER inhalation device LEVEL.
(The medicine in the blister is loose powder, so you don't want it to spill out!)

Lift and Puncture
Lift this flap **straight up**--all the way— so the needle pierces the blister at both top and bottom.

Lift flap **straight up**

REMEMBER--Keep the DISKHALER inhalation device level! Do not turn it over or drop it as there is loose powder in the blister and it may spill out. Should you accidently spill out the powder in the blister proceed to Step 4.

Close Flap
Click the flap back down into place.

Close flap

Step 3 To get your dose ready
Don't do this until just before you inhale a dose. Sit down in a comfortable position. Before putting the white mouthpiece into your mouth, breathe all the way out as far as is comfortable (exhale). Keep the DISKHALER away from your mouth.

Now put the white mouthpiece into your mouth and **keep the DISKHALER inhalation device level!**

Keep it level!

Close your lips firmly around the mouthpiece. Do not block the airholes on the side of the mouthpiece. Don't blow into the DISKHALER (if you do, you'll blow the powder out).

Take one quick deep breath in.

Hold your breath for 3 seconds or as long as is comfortable to help RELENZA stay in your respiratory tract where it can work. (Your breath will pull the medicine into your respiratory tract.)

Breathe in

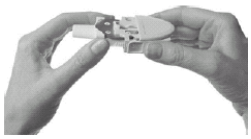
You will feel some powder in your throat. This is normal. The powder may have a sweet taste. It's O.K. to take a drink of water.

Go to Step 4 to inhale your next blister now.

Step 4 Next Blister
To automatically advance to the next blister, just pull the white tray by the edges until it stops. (Don't remove it.)

Pull to extend

Then push it back until it clicks. Repeat if necessary until a full blister is positioned under the piercing needle.



Push to close (Click!)

This pull-push motion rotates the ROTADISK disk to the next blister.

Now you need to **puncture** this blister by lifting then closing the flap - See STEP 2.

Then you need to **inhale** with a quick deep breath- See STEP 3.

Once you have inhaled 2 blisters, wipe the mouthpiece with a tissue and put the blue cover back on the DISKHALER inhalation device to keep it clean until your next dose.

When all 4 blisters have been used, replace the disk with a fresh one - See STEP 1.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- **Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or**
- **Calling toll-free at 1-866-234-2345.**

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

The current version of this document plus the full product monograph, prepared for health professionals can be found at: http://www.gsk.ca or by contacting the sponsor,

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