HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RELENZA safely and effectively. See full prescribing information for RELENZA.

RELENZA® (zanamivir) Inhalation Powder, for oral inhalation
Initial U.S. Approval: 1999

----------RECENT MAJOR CHANGES----------

Indications and Usage
Important Limitations on Use of RELENZA (1.3) October 2008
Warnings and Precautions
Neuropsychiatric Events (5.3) February 2008

----------INDICATIONS AND USAGE----------

RELENZA, an influenza neuraminidase inhibitor, is indicated for:
Treatment of influenza in patients 7 years of age and older who have been symptomatic for no more than 2 days. (1.1)
Prophylaxis of influenza in patients 5 years of age and older. (1.2)

Important Limitations on Use of RELENZA:
Not recommended for treatment or prophylaxis of influenza in:
- Individuals with underlying airways disease. (5.1)

Not proven effective for:
- Treatment in individuals with underlying airways disease. (1.3)
- Prophylaxis in nursing home residents. (1.3)

Not a substitute for annual influenza vaccination. (1.3)
Consider available information on influenza drug susceptibility patterns and treatment effects when deciding whether to use RELENZA. (1.3)

----------DOSAGE AND ADMINISTRATION----------

Indication	Dose
Treatment of Influenza (2.2)	10 mg twice daily for 5 days
Prophylaxis: (2.3)	
Household Setting	10 mg once daily for 10 days
Community Outbreaks	10 mg once daily for 28 days

Note: The 10 mg dose is provided by 2 inhalations (one 5 mg blister per inhalation). (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Four 5 mg blisters of powder on a ROTADISK® for oral inhalation via DISKHALER®. Packaged in carton containing 5 ROTADISKs (total of 10 doses) and 1 DISKHALER inhalation device. (3)

----------CONTRAINDICATIONS----------

Do not use in patients with history of allergic reaction to any ingredient of RELENZA, including lactose (which contains milk proteins). (4)

---------- WARNINGS AND PRECAUTIONS ----------

- **Bronchospasm:** Serious, sometimes fatal, cases have occurred. Not recommended in individuals with underlying airways disease. Discontinue RELENZA if bronchospasm or decline in respiratory function develops. (5.1)
- **Allergic Reactions:** Discontinue RELENZA and initiate appropriate treatment if an allergic reaction occurs or is suspected. (5.2)
- **Neuropsychiatric Events:** Patients with influenza, particularly pediatric patients, may be at an increased risk of seizures, confusion, or abnormal behavior early in their illness. Monitor for signs of abnormal behavior. (5.3)
- **High-risk Underlying Medical Conditions:** Safety and effectiveness have not been demonstrated in these patients. (5.4)

---------- ADVERSE REACTIONS ----------

The most common adverse events reported in >1.5% of patients treated with RELENZA and more commonly than in patients treated with placebo are:
- Treatment Studies – sinusitis, dizziness.
- Prophylaxis Studies – fever and/or chills, arthralgia and articular rheumatism. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Live attenuated influenza vaccine, intranasal (7):
- Do not administer until 48 hours following cessation of RELENZA.
- Do not administer RELENZA until 2 weeks following administration of the live attenuated influenza vaccine, unless medically indicated.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: October 2008
RLZ:xPI

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Influenza

RELENZA 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.

1.2 Prophylaxis of Influenza

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

1.3 Important Limitations 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) due to risk of serious bronchospasm *[see Warnings and Precautions (5.1)]*.
- RELENZA has not been proven effective for treatment of influenza in individuals with underlying airways disease.
- RELENZA has not been proven effective for prophylaxis of influenza in the nursing home setting.
- RELENZA is not a substitute for early influenza vaccination on an annual basis as recommended by the Centers for Disease Control's Immunization Practices Advisory Committee.
- Influenza viruses change over time. Emergence of resistance mutations could decrease drug effectiveness. Other factors (for example, changes in viral virulence) might also diminish clinical benefit of antiviral drugs. Prescribers should consider available information on influenza drug susceptibility patterns and treatment effects when deciding whether to use RELENZA.
- There is no evidence for efficacy of zanamivir in any illness caused by agents other than influenza virus A and B.
- Patients should be advised that the use of RELENZA for treatment of influenza has not been shown to reduce the risk of transmission of influenza to others.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Considerations

- RELENZA is for administration to the respiratory tract by oral inhalation only, using the DISKHALER device provided.
- The 10 mg dose is provided by 2 inhalations (one 5 mg blister per inhalation).
- Patients should be instructed in the use of the delivery system. Instructions should include a demonstration whenever possible. If RELENZA is prescribed for children, it should be used

only under adult supervision and instruction, and the supervising adult should first be instructed by a healthcare professional *[see Patient Counseling Information (17.4)]*.

- Patients scheduled to use an inhaled bronchodilator at the same time as RELENZA should use their bronchodilator before taking RELENZA *[see Patient Counseling Information (17.2)]*.

2.2 Treatment of Influenza

- The recommended dose of RELENZA for treatment of influenza in adults and pediatric patients 7 years of age and older is 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.
- The safety and efficacy of repeated treatment courses have not been studied.

2.3 Prophylaxis of Influenza

Household Setting:

- The recommended dose of RELENZA 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 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 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.

3 DOSAGE FORMS AND STRENGTHS

Four 5 mg blisters of powder on a ROTADISK for oral inhalation via DISKHALER. Packaged in carton containing 5 ROTADISKs (total of 10 doses) and 1 DISKHALER inhalation device *[see How Supplied/Storage and Handling (16)]*.

4 CONTRAINDICATIONS

Do not use in patients with history of allergic reaction to any ingredient of RELENZA including lactose (which contains milk proteins) *[see Warnings and Precautions (5.2), Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Bronchospasm

RELENZA is not recommended for treatment or prophylaxis of influenza in individuals with underlying airways disease (such as asthma or chronic obstructive pulmonary disease).

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

RELENZA 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.

Bronchospasm was documented following administration of zanamivir in 1 of 13 patients with mild or moderate asthma (but without acute influenza-like illness) in a Phase I study. In a Phase III study in patients with acute influenza-like illness superimposed on underlying asthma or chronic obstructive pulmonary disease, 10% (24 of 244) of patients on zanamivir and 9% (22 of 237) on placebo experienced a greater than 20% decline in FEV_1 following treatment for 5 days.

If use of RELENZA 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 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.

5.2 Allergic Reactions

Allergic-like reactions, including oropharyngeal edema, serious skin rashes, and anaphylaxis have been reported in postmarketing experience with RELENZA. RELENZA should be stopped and appropriate treatment instituted if an allergic reaction occurs or is suspected.

5.3 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 postmarketing reports (mostly from Japan) of delirium and abnormal behavior 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 and rapid resolution. The contribution of RELENZA 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.

5.4 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.

5.5 Bacterial Infections

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

5.6 Importance of Proper Use of DISKHALER

Effective and safe use of RELENZA requires proper use of the DISKHALER to inhale the drug. Prescribers should carefully evaluate the ability of young children to use the delivery system if use of RELENZA is considered *[see Use in Specific Populations (8.4)]*.

6 ADVERSE REACTIONS

See Warnings and Precautions for information about risk of serious adverse events such as bronchospasm (5.1) and allergic-like reactions (5.2), and for safety information in patients with underlying airways disease (5.1).

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The placebo used in clinical studies consisted of inhaled lactose powder, which is also the vehicle for the active drug; therefore, some adverse events occurring at similar frequencies in different treatment groups could be related to lactose vehicle inhalation.

Treatment of Influenza: *Clinical Trials in Adults and Adolescents:* Adverse events that occurred with an incidence ≥1.5% in treatment studies are listed in Table 1. This table shows adverse events occurring in patients ≥12 years of age receiving RELENZA 10 mg inhaled twice daily, RELENZA in all inhalation regimens, and placebo inhaled twice daily (where placebo consisted of the same lactose vehicle used in RELENZA).

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

Adverse Event	RELENZA 10 mg b.i.d. **Inhaled** (n = 1,132)	RELENZA All Dosing Regimens* (n = 2,289)	Placebo (Lactose Vehicle) (n = 1,520)
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 included malaise, fatigue, fever, abdominal pain, myalgia, arthralgia, and urticaria.

The most frequent laboratory abnormalities in Phase III 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.

Clinical Trials in Pediatric Patients: Adverse events that occurred with an incidence ≥1.5% in children receiving treatment doses of RELENZA in 2 Phase III studies are listed in Table 2. This table shows adverse events occurring in pediatric patients 5 to 12 years old receiving RELENZA 10 mg inhaled twice daily and placebo inhaled twice daily (where placebo consisted of the same lactose vehicle used in RELENZA).

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.

In 1 of the 2 studies described in Table 2, some additional information is available from children (5 to 12 years old) without acute influenza-like illness who received an investigational prophylaxis regimen of RELENZA; 132 children received RELENZA and 145 children received placebo. Among these children, nasal signs and symptoms (zanamivir 20%, placebo 9%), cough (zanamivir 16%, placebo 8%), and throat/tonsil discomfort and pain (zanamivir 11%, placebo 6%) were reported more frequently with RELENZA than placebo. In a subset with chronic pulmonary disease, lower respiratory adverse events (described as asthma, cough, or viral respiratory infections which could include influenza-like symptoms) were reported in 7 of 7 zanamivir recipients and 5 of 12 placebo recipients.

Prophylaxis of Influenza: *Family/Household Prophylaxis Studies:* Adverse events that occurred with an incidence of ≥1.5% 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 inhaled once daily for 10 days.

Table 3. Summary of Adverse Events ≥1.5% Incidence During 10-Day Prophylaxis Studies in Adults, Adolescents, and Children*

Adverse Event	Contact Cases	
	RELENZA (n = 1,068)	Placebo (n = 1,059)
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%
Endocrine and metabolic		
Feeding problems (decreased or increased appetite and anorexia)	2%	2%
Gastrointestinal		
Nausea and vomiting	1%	2%
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 ≥1.5% in 2 prophylaxis studies are listed in Table 4. This table shows adverse events occurring in patients ≥5 years of age receiving RELENZA 10 mg inhaled once daily for 28 days.

Table 4. Summary of Adverse Events ≥1.5% Incidence During 28-Day Prophylaxis Studies in Adults, Adolescents, and Children*

Adverse Event	RELENZA (n = 2,231)	Placebo (n = 2,239)
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%
Lower respiratory		
Cough	17%	18%
Viral respiratory infections	3%	4%
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%
Non-site specific		
Temperature regulation disturbances (fever and/or chills)	9%	10%
Malaise and 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.

6.2 Postmarketing Experience

In addition to adverse events reported from clinical trials, the following events have been identified during postmarketing use of zanamivir (RELENZA). Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to zanamivir (RELENZA).

Allergic Reactions: Allergic or allergic-like reaction, including oropharyngeal edema *[see Warnings and Precautions (5.2)]*.

Psychiatric: Delirium, including symptoms such as altered level of consciousness, confusion, abnormal behavior, delusions, hallucinations, agitation, anxiety, nightmares *[see Warnings and Precautions (5.3)]*.

Cardiac: Arrhythmias, syncope.

Neurologic: Seizures.

Respiratory: Bronchospasm, dyspnea *[see Warnings and Precautions (5.1)]*.

Skin: Facial edema; rash, including serious cutaneous reactions; urticaria *[see Warnings and Precautions (5.2)]*.

7 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 RELENZA 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 RELENZA, 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 RELENZA *[see Clinical Pharmacology (12.4)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

Embryo/fetal development studies were conducted in rats (dosed from days 6 to 15 of pregnancy) and rabbits (dosed from days 7 to 19 of pregnancy) using the same IV doses (1, 9, and 90 mg/kg/day). Pre- and post-natal developmental studies were performed in rats (dosed from day 16 of pregnancy until litter day 21 to 23). No malformations, maternal toxicity, or embryotoxicity were observed in pregnant rats or rabbits and their fetuses. Because of insufficient blood sampling timepoints in rat and rabbit reproductive toxicity studies, AUC values were not available. In a subchronic study in rats at the 90 mg/kg/day IV dose, the AUC values were greater than 300 times the human exposure at the proposed clinical dose.

An additional embryo/fetal study, in a different strain of rat, 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. There was an increase in the incidence rates of a variety of minor skeleton alterations and variants in the exposed offspring in this study. Based on AUC measurements, the 80 mg/kg dose produced an exposure greater than 1,000 times the human exposure at the proposed clinical dose. However, in most instances, the individual incidence rate

of each skeletal alteration or variant remained within the background rates of the historical occurrence in the strain studied.

Zanamivir has been shown to cross the placenta in rats and rabbits. In these animals, fetal blood concentrations of zanamivir were significantly lower than zanamivir concentrations in the maternal blood.

8.3 Nursing Mothers

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 RELENZA is administered to a nursing mother.

8.4 Pediatric Use

Treatment of Influenza: Safety and effectiveness of RELENZA for treatment of influenza have not been assessed in pediatric patients less than 7 years of age, but were studied in a Phase III treatment study in pediatric patients, where 471 children 5 to 12 years of age received zanamivir or placebo *[see Clinical Studies 14.1)]*. Adolescents were included in the 3 principal Phase III adult treatment studies. In these studies, 67 patients were 12 to 16 years of age. No definite differences in safety and efficacy were observed between these adolescent patients and young adults.

In a Phase I study of 16 children ages 6 to 12 years with signs and symptoms of respiratory disease, 4 did not produce a measurable peak inspiratory flow rate (PIFR) through the DISKHALER (3 with no adequate inhalation on request, 1 with missing data), 9 had measurable PIFR on each of 2 inhalations, and 3 achieved measurable PIFR on only 1 of 2 inhalations. Neither of two 6-year-olds and one of two 7-year-olds produced measurable PIFR. Overall, 8 of the 16 children (including all those under 8 years old) either did not produce measurable inspiratory flow through the DISKHALER or produced peak inspiratory flow rates below the 60 L/min considered optimal for the device under standardized in vitro testing; lack of measurable flow rate was related to low or undetectable serum concentrations *[see Clinical Pharmacology (12.3), Clinical Studies (14.1)]*. Prescribers should carefully evaluate the ability of young children to use the delivery system if prescription of RELENZA is considered.

Prophylaxis of Influenza: The safety and effectiveness of RELENZA for prophylaxis of influenza have been studied in 4 Phase III studies where 273 children 5 to 11 years of age and 239 adolescents 12 to 16 years of age received RELENZA. No differences in safety and effectiveness were observed between pediatric and adult subjects *[see Clinical Studies (14.2)]*.

8.5 Geriatric Use

Of the total number of patients in 6 clinical studies of RELENZA for treatment of influenza, 59 patients were 65 years of age and older, while 24 patients were 75 years of age and older. Of the total number of patients in 4 clinical studies of RELENZA for prophylaxis of influenza in households and community settings, 954 patients were 65 years of age and older, while 347 patients were 75 years of age and older. No overall differences in safety or effectiveness were observed between these patients 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. Elderly patients may need assistance with use of the device.

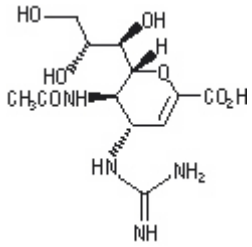
In 2 additional studies of RELENZA for prophylaxis of influenza in the nursing home setting, efficacy was not demonstrated *[see Indications and Usage (1.3)]*.

10 OVERDOSAGE

There have been no reports of overdosage from administration of RELENZA.

11 DESCRIPTION

The active component of RELENZA is zanamivir. The chemical name of zanamivir is 5-(acetylamino)-4-[(aminoiminomethyl)-amino]-2,6-anhydro-3,4,5-trideoxy-D-glycero-D-galacto-non-2-enonic acid. It has a molecular formula of $C_{12}H_{20}N_4O_7$ and a molecular weight of 332.3. It has the following structural formula:



Zanamivir is a white to off-white powder for oral inhalation with a solubility of approximately 18 mg/mL in water at 20°C.

RELENZA is for administration to the respiratory tract by oral inhalation only. Each RELENZA ROTADISK contains 4 regularly spaced double-foil blisters with each blister containing a powder mixture of 5 mg of zanamivir and 20 mg of lactose (which contains milk proteins). The contents of each blister are inhaled using a specially designed breath-activated plastic device for inhaling powder called the DISKHALER. After a RELENZA ROTADISK is loaded into the DISKHALER, a blister that contains medication is pierced and the zanamivir is dispersed into the air stream created when the patient inhales through the mouthpiece. The amount of drug delivered to the respiratory tract will depend on patient factors such as inspiratory flow. Under standardized in vitro testing, RELENZA ROTADISK delivers 4 mg of zanamivir from the DISKHALER device when tested at a pressure drop of 3 kPa (corresponding to a flow rate of about 62 to 65 L/min) for 3 seconds.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Zanamivir is an antiviral drug *[see Clinical Pharmacology (12.4)]*.

12.3 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 to 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 have 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 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 DISKHALER. 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 *[see Use in Specific Populations (8.4), Clinical Studies (14.1)]*.

Geriatric Patients: The pharmacokinetics of zanamivir have not been studied in patients over 65 years of age *[see Use in Specific Populations (8.5)]*.

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, ka, 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.

12.4 Microbiology

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 (EC_{50} and EC_{90}) 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: In 2-year carcinogenicity studies conducted in rats and mice using a powder formulation administered through inhalation, zanamivir induced no statistically significant increases in tumors over controls. 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.

Mutagenesis: 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.

Impairment of Fertility: The effects of zanamivir on fertility and general reproductive performance were investigated in male (dosed for 10 weeks prior to mating, and throughout mating, gestation/lactation, and shortly after weaning) and female rats (dosed for 3 weeks prior to mating through Day 19 of pregnancy, or Day 21 post partum) at IV doses 1, 9, and 90 mg/kg/day. Zanamivir did not impair mating or fertility of male or female rats, and did not affect the sperm of treated male rats. The reproductive performance of the F1 generation born to female rats given zanamivir was not affected. Based on a subchronic study in rats at a 90 mg/kg/day IV dose, AUC values ranged between 142 and 199 mcg•hr/mL (>300 times the human exposure at the proposed clinical dose).

14 CLINICAL STUDIES

14.1 Treatment of Influenza

Adults and Adolescents: The efficacy of RELENZA 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.

Populations Studied: The principal Phase III studies enrolled 1,588 patients ages 12 years and older (median age 34 years, 49% male, 91% Caucasian), with uncomplicated influenza-like illness within 2 days of symptom onset. Influenza was confirmed by culture, hemagglutination inhibition antibodies, or investigational direct tests. Of 1,164 patients with confirmed influenza, 89% had influenza A and 11% had influenza B. These studies served as the principal basis for efficacy evaluation, with more limited Phase II studies providing supporting information where necessary. Following randomization to either zanamivir or placebo (inhaled lactose vehicle), all patients received instruction and supervision by a healthcare professional for the initial dose.

Principal Results: The definition of time to improvement in major symptoms of influenza included no fever and self-assessment of “none” or “mild” for headache, myalgia, cough, and sore throat. A Phase II and a Phase III study conducted in North America (total of

over 600 influenza-positive patients) suggested up to 1 day of shortening of median time to this defined improvement in symptoms in patients receiving zanamivir compared with placebo, although statistical significance was not reached in either of these studies. In a study conducted in the Southern Hemisphere (321 influenza-positive patients), a 1.5-day difference in median time to symptom improvement was observed. Additional evidence of efficacy was provided by the European study.

Other Findings: There was no consistent difference in treatment effect in patients with influenza A compared with influenza B; however, these trials enrolled smaller numbers of patients with influenza B and thus provided less evidence in support of efficacy in influenza B.

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 treatment effect was demonstrated in patients with underlying chronic medical conditions, including respiratory or cardiovascular disease *[see Warnings and Precautions (5.4)]*.

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

Some fluctuation of symptoms was observed after the primary study endpoint in both treatment groups.

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 placebo-controlled study conducted in North America and Europe, enrolling 471 patients, ages 5 to 12 years (55% male, 90% Caucasian), within 36 hours of symptom onset. Of 346 patients with confirmed influenza, 65% had influenza A and 35% had influenza B. 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. Median time to symptom improvement was 1 day shorter in patients receiving zanamivir compared with placebo. No consistent differences in rate of development of complications were observed between treatment groups. Some fluctuation of symptoms was observed after the primary study endpoint in both treatment groups.

Although this study was designed to enroll children ages 5 to 12 years, the product is indicated only for children 7 years of age and older. This evaluation is based on the combination of lower estimates of treatment effect in 5- and 6-year-olds compared with the overall study population, and evidence of inadequate inhalation through the DISKHALER in a pharmacokinetic study *[see Use in Specific Populations (8.4), Clinical Pharmacology (12.3)]*.

14.2 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).

Household Prophylaxis Studies: 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.

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.

Seasonal Prophylaxis Studies: 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 2 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.

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 1,685) for the placebo group to 0.2% (4 of 1,678) for the group receiving RELENZA.

16 HOW SUPPLIED/STORAGE AND HANDLING

RELENZA is supplied in a circular double-foil pack (a ROTADISK) containing 4 blisters of the drug. Five ROTADISKs are packaged in a white polypropylene tube. The tube is packaged in a carton with 1 blue and gray DISKHALER inhalation device (NDC 0173-0681-01).

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP Controlled Room Temperature). Keep out of reach of children. Do not puncture any RELENZA ROTADISK blister until taking a dose using the DISKHALER.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.6).

17.1 Bronchospasm

Patients should be advised of the risk of bronchospasm, especially in the setting of underlying airways disease, and should stop RELENZA and 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 Warnings and Precautions (5.1)]*. If a decision is made to prescribe RELENZA for a patient with asthma or chronic obstructive pulmonary disease, the patient should be made aware of the risks and should have a fast-acting bronchodilator available.

17.2 Concomitant Bronchodilator Use

Patients scheduled to take inhaled bronchodilators at the same time as RELENZA should be advised to use their bronchodilators before taking RELENZA.

17.3 Neuropsychiatric Events

Patients with influenza (the flu), particularly children and adolescents, may be at an increased risk of seizures, confusion, or abnormal behavior 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 behavior and a healthcare professional should be contacted immediately if the patient shows any signs of unusual behavior *[see Warnings and Precautions (5.3)]*.

17.4 Instructions for Use

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

If RELENZA is prescribed for children, it should be used only under adult supervision and instruction, and the supervising adult should first be instructed by a healthcare professional *[see Dosage and Administration (2.1)]*.

17.5 Risk of Influenza Transmission to Others

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

17.6 FDA-Approved Patient Labeling and Instructions for Use

See separate leaflet.

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