

Relenza™

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-dispensed quantity of inhalation powder (one blister) contains 5 mg zanamivir. Each delivered inhalation (the amount that leaves the mouthpiece of the Diskhaler) contains 4.0 mg zanamivir.

Excipients with known effect:

Lactose monohydrate (approximately 20 mg which contains milk protein).

For the full list of excipients, see section 11.

1 INDICATIONS AND USAGE

1.1 Treatment of Influenza

RELENZA is indicated for treatment of both uncomplicated acute illness due to influenza A and B virus in adults and adolescents (> or = 12 years) who have been symptomatic for no more than 48 hours and pediatric patients 7 years and older who have been symptomatic for no more than 36 hours.

1.2 Important Limitations on Use of RELENZA

- RELENZA is not recommended for treatment 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.
- 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 [*see Warnings and Precautions (5.6)*].
- 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)*]. 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 Treatment of Influenza

- The recommended dose of RELENZA for treatment of influenza in adults and pediatric patients aged 7 years 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.

3 DOSAGE FORMS AND STRENGTHS

Blister for oral inhalation: 5 mg. 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 milk proteins [*see Warnings and Precautions (5.2), Description (11)*].

5 WARNINGS AND PRECAUTIONS

5.1 Bronchospasm

RELENZA is not recommended for treatment 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 subjects with mild or moderate asthma (but without acute influenza-like illness) in a Phase I trial. In a Phase III trial in subjects with acute influenza-like illness superimposed on underlying asthma or chronic obstructive pulmonary disease, 10% (24 of 244) of subjects on zanamivir and 9% (22 of 237) on placebo experienced a greater than 20% decline in FEV₁ 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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

5.6 Importance of Proper Route of Administration

RELENZA Inhalation Powder must not be made into an extemporaneous solution for administration by nebulization or mechanical ventilation. There have been reports of hospitalized patients with influenza who received a solution made with RELENZA Inhalation Powder 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 Inhalation Powder must only be administered using the device provided [*see Dosage and Administration (2.1)*].

5.7 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 trials 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 $\geq 1.5\%$ in treatment trials are listed in Table 1. This table shows adverse events occurring in subjects aged 12 years and older 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 $\geq 1.5\%$ Incidence During Treatment in Adults and Adolescents

Adverse Event	RELENZA		Placebo (Lactose Vehicle) (n = 1,520)
	10 mg b.i.d. <u>Inhaled</u> (n = 1,132)	All Dosing Regimens ^a (n = 2,289)	
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%

^a Includes trials 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 subjects receiving RELENZA included malaise, fatigue, fever, abdominal pain, myalgia, arthralgia, and urticaria.

The most frequent laboratory abnormalities in Phase III treatment trials 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 Subjects: Adverse events that occurred with an incidence $\geq 1.5\%$ in children receiving treatment doses of RELENZA in 2 Phase III trials are listed in Table 2. This table shows adverse events occurring in pediatric *Subjects* aged 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 $\geq 1.5\%$ Incidence During Treatment in Pediatric Subjects^a

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%

^a Includes a subset of subjects receiving RELENZA for treatment of influenza in a prophylaxis trial.

In 1 of the 2 trials described in Table 2, some additional information is available from children (aged 5 to 12 years) 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.

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. Vasovagal-like episodes have been reported shortly following inhalation of zanamivir.

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

Skin: Facial edema; rash, including serious cutaneous reactions (e.g., erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis); urticaria [*see Warnings and Precautions (5.2)*].

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

<http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il>

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 younger than 7 years, but were studied in a Phase III treatment trial in pediatric subjects, where 471 children aged 5 to 12 years received zanamivir or placebo [see *Clinical Studies (14.1)*]. Adolescents were included in the 3 principal Phase III adult treatment trials. In these trials, 67 patients were aged 12 to 16 years. No definite differences in safety and efficacy were observed between these adolescent patients and young adults.

In a Phase I trial of 16 children aged 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 younger than 8 years) 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.

8.5 Geriatric Use

Of the total number of subjects in 6 clinical trials of RELENZA for treatment of influenza, 59 subjects were aged 65 years and older, while 24 subjects were aged 75 years and older. Of the total number of subjects in 4 clinical trials of RELENZA for prophylaxis of

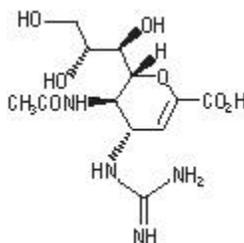
influenza in households and community settings, 954 subjects were aged 65 years and older, while 347 subjects were aged 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out. Elderly patients may need assistance with use of the device.

10 OVERDOSAGE

There have been no reports of overdose 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-galactonon-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•h/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/h. 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/h \ddagger , mild/moderate 2.7 L/h \ddagger , and severe 0.8 L/h \ddagger ; median values) and significant increases in half-life (normals 3.1 h \ddagger , mild/moderate 4.7 h \ddagger , and severe 18.5 h \ddagger ; 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 subjects with signs and symptoms of respiratory illness. Sixteen subjects, aged 6 to 12 years, received a single dose of 10 mg zanamivir dry powder via DISKHALER. Five subjects 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 subjects had C_{max} median values of 43 ng/mL (range: 15 to 74) and AUC_{∞} median values of 167 ng•h/mL (range: 58 to 279). Low or undetectable serum concentrations were related to lack of measurable PIFR in individual subjects [see *Use in Specific Populations (8.4), Clinical Studies (14.1)*].

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

Gender, Race, and Weight: In a population pharmacokinetic analysis in patient trials, no clinically significant differences in serum concentrations and/or pharmacokinetic parameters (V/F , CL/F , k_a , AUC_{0-3} , C_{max} , T_{max} , CL_r , and % excreted in urine) were observed when demographic variables (gender, age, race, and weight) and indices of infection (laboratory evidence of infection, overall symptoms, symptoms of upper respiratory illness, and viral titers) were considered. There were no significant correlations between measures of systemic exposure and safety parameters.

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 (EC₅₀ and EC₉₀) of zanamivir were in the range of 0.005 to 16.0 μM and 0.05 to >100 μM, respectively (1 μM = 0.33 mcg/mL). The relationship between the cell culture inhibition of influenza virus by zanamivir and the inhibition of influenza virus replication in humans has not been established.

Resistance: Influenza viruses with reduced susceptibility to zanamivir have been selected in cell culture by multiple passages of the virus in the presence of increasing concentrations of the drug. Genetic analysis of these viruses showed that the reduced susceptibility in cell culture to zanamivir is associated with mutations that result in amino acid changes in the viral neuraminidase or viral hemagglutinin or both. Resistance mutations selected in cell cultures 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 trials have been performed to assess risk of emergence of cross-resistance during clinical use.

Influenza Vaccine Interaction Trial: An interaction trial (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 Trial: 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 trials 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•h/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 trials conducted in North America, the Southern Hemisphere, and Europe during their respective influenza seasons. The magnitude of treatment effect varied between trials, with possible relationships to population-related factors including amount of symptomatic relief medication used.

Populations Studied: The principal Phase III trials enrolled 1,588 subjects aged 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 subjects with confirmed influenza, 89% had influenza A and 11% had influenza B. These trials 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 subjects 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 trial conducted in North America (total of over

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

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

In general, subjects 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 subjects 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 trial 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 trial conducted in North America and Europe, enrolling 471 subjects, aged 5 to 12 years (55% male, 90% Caucasian), within 36 hours of symptom onset. Of 346 subjects 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 subjects 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 trial endpoint in both treatment groups.

Although this trial was designed to enroll children aged 5 to 12 years, the product is indicated only for children aged 7 years 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 trial population, and evidence of inadequate inhalation through the DISKHALER in a pharmacokinetic trial [*see Use in Specific Populations (8.4), Clinical Pharmacology (12.3)*]

6 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 below 30°C Keep out of reach of children. Do not puncture any RELENZA ROTADISK blister until taking a dose using the DISKHALER.

Shelf life

The expiry date of the product is indicated on the label and packaging.

Manufacturer

Glaxo Wellcome Production, Marly-Le-Roi, France.

GlaxoSmithKline Australia PTY Ltd., Boronia, Australia.

Licence Holder

GlaxoSmithKline (Israel) Ltd., 25 Bazel St., Petach Tikva.

Licence Number

116-29-29741

Relz DR v2