

## 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](http://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

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2 **FULL PRESCRIBING INFORMATION**

3 **1 INDICATIONS AND USAGE**

4 **1.1 Treatment of Influenza**

5 RELENZA is indicated for treatment of uncomplicated acute illness due to influenza A  
6 and B virus in adults and pediatric patients 7 years of age and older who have been symptomatic  
7 for no more than 2 days.

8 **1.2 Prophylaxis of Influenza**

9 RELENZA is indicated for prophylaxis of influenza in adults and pediatric patients  
10 5 years of age and older.

11 **1.3 Important Limitations on Use of RELENZA**

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

31 **2 DOSAGE AND ADMINISTRATION**

32 **2.1 Dosing Considerations**

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

38 only under adult supervision and instruction, and the supervising adult should first be  
39 instructed by a healthcare professional [see Patient Counseling Information (17.4)].  
40 • Patients scheduled to use an inhaled bronchodilator at the same time as RELENZA should  
41 use their bronchodilator before taking RELENZA [see Patient Counseling Information  
42 (17.2)].

## 43 **2.2 Treatment of Influenza**

- 44 • The recommended dose of RELENZA for treatment of influenza in adults and pediatric  
45 patients 7 years of age and older is 10 mg twice daily (approximately 12 hours apart) for  
46 5 days.
- 47 • Two doses should be taken on the first day of treatment whenever possible provided there is  
48 at least 2 hours between doses.
- 49 • On subsequent days, doses should be about 12 hours apart (e.g., morning and evening) at  
50 approximately the same time each day.
- 51 • The safety and efficacy of repeated treatment courses have not been studied.

## 52 **2.3 Prophylaxis of Influenza**

### 53 Household Setting:

- 54 • The recommended dose of RELENZA for prophylaxis of influenza in adults and pediatric  
55 patients 5 years of age and older in a household setting is 10 mg once daily for 10 days.
- 56 • The dose should be administered at approximately the same time each day.
- 57 • There are no data on the effectiveness of prophylaxis with RELENZA in a household setting  
58 when initiated more than 1.5 days after the onset of signs or symptoms in the index case.

### 59 Community Outbreaks:

- 60 • The recommended dose of RELENZA for prophylaxis of influenza in adults and adolescents  
61 in a community setting is 10 mg once daily for 28 days.
- 62 • The dose should be administered at approximately the same time each day.
- 63 • There are no data on the effectiveness of prophylaxis with RELENZA in a community  
64 outbreak when initiated more than 5 days after the outbreak was identified in the community.
- 65 • The safety and effectiveness of prophylaxis with RELENZA have not been evaluated for  
66 longer than 28 days' duration.

## 67 **3 DOSAGE FORMS AND STRENGTHS**

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

## 71 **4 CONTRAINDICATIONS**

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

75 **5 WARNINGS AND PRECAUTIONS**

76 **5.1 Bronchospasm**

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

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

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

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

87 Bronchospasm was documented following administration of zanamivir in 1 of 13 patients  
88 with mild or moderate asthma (but without acute influenza-like illness) in a Phase I study. In a  
89 Phase III study in patients with acute influenza-like illness superimposed on underlying asthma  
90 or chronic obstructive pulmonary disease, 10% (24 of 244) of patients on zanamivir and 9% (22  
91 of 237) on placebo experienced a greater than 20% decline in FEV<sub>1</sub> following treatment for  
92 5 days.

93 If use of RELENZA is considered for a patient with underlying airways disease, the  
94 potential risks and benefits should be carefully weighed. If a decision is made to prescribe  
95 RELENZA for such a patient, this should be done only under conditions of careful monitoring of  
96 respiratory function, close observation, and appropriate supportive care including availability of  
97 fast-acting bronchodilators.

98 **5.2 Allergic Reactions**

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

103 **5.3 Neuropsychiatric Events**

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

108 There have been postmarketing reports (mostly from Japan) of delirium and abnormal  
109 behavior leading to injury in patients with influenza who were receiving neuraminidase  
110 inhibitors, including RELENZA. Because these events were reported voluntarily during clinical  
111 practice, estimates of frequency cannot be made, but they appear to be uncommon based on  
112 usage data for RELENZA. These events were reported primarily among pediatric patients and  
113 often had an abrupt onset and rapid resolution. The contribution of RELENZA to these events  
114 has not been established. Patients with influenza should be closely monitored for signs of

115 abnormal behavior. If neuropsychiatric symptoms occur, the risks and benefits of continuing  
116 treatment should be evaluated for each patient.

#### 117 **5.4 Limitations of Populations Studied**

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

#### 122 **5.5 Bacterial Infections**

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

#### 126 **5.6 Importance of Proper Use of DISKHALER**

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

### 130 **6 ADVERSE REACTIONS**

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

#### 134 **6.1 Clinical Trials Experience**

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

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

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

146

147 **Table 1. Summary of Adverse Events  $\geq 1.5\%$  Incidence During Treatment in Adults and**  
 148 **Adolescents**

| Adverse Event                    | RELENZA                                       |  | Placebo<br>(Lactose Vehicle)<br>(n = 1,520) |
|----------------------------------|---|--|---|
|                                  | 10 mg b.i.d.<br><b>Inhaled</b><br>(n = 1,132) | All Dosing<br>Regimens*<br>(n = 2,289) |   |
| <b>Body as a whole</b>           |   |  |   |
| Headaches                        | 2%  | 2%                                     | 3%  |
| <b>Digestive</b>                 |   |  |   |
| Diarrhea                         | 3%  | 3%                                     | 4%  |
| Nausea                           | 3%  | 3%                                     | 3%  |
| Vomiting                         | 1%  | 1%                                     | 2%  |
| <b>Respiratory</b>               |   |  |   |
| 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%  |
| <b>Nervous system</b>            |   |  |   |
| Dizziness                        | 2%  | 1%                                     | <1%   |

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

152  
 153 Additional adverse reactions occurring in less than 1.5% of patients receiving RELENZA  
 154 included malaise, fatigue, fever, abdominal pain, myalgia, arthralgia, and urticaria.

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

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

163

164 **Table 2. Summary of Adverse Events  $\geq 1.5\%$  Incidence During Treatment in Pediatric**  
 165 **Patients\***

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

166 \* Includes a subset of patients receiving RELENZA for treatment of influenza in a prophylaxis  
 167 study.  
 168

169 In 1 of the 2 studies described in Table 2, some additional information is available from  
 170 children (5 to 12 years old) without acute influenza-like illness who received an investigational  
 171 prophylaxis regimen of RELENZA; 132 children received RELENZA and 145 children received  
 172 placebo. Among these children, nasal signs and symptoms (zanamivir 20%, placebo 9%), cough  
 173 (zanamivir 16%, placebo 8%), and throat/tonsil discomfort and pain (zanamivir 11%, placebo  
 174 6%) were reported more frequently with RELENZA than placebo. In a subset with chronic  
 175 pulmonary disease, lower respiratory adverse events (described as asthma, cough, or viral  
 176 respiratory infections which could include influenza-like symptoms) were reported in 7 of 7  
 177 zanamivir recipients and 5 of 12 placebo recipients.

178 Prophylaxis of Influenza: Family/Household Prophylaxis Studies: Adverse events  
 179 that occurred with an incidence of  $\geq 1.5\%$  in the 2 prophylaxis studies are listed in Table 3. This  
 180 table shows adverse events occurring in patients  $\geq 5$  years of age receiving RELENZA 10 mg  
 181 inhaled once daily for 10 days.  
 182

183 **Table 3. Summary of Adverse Events  $\geq 1.5\%$  Incidence During 10-Day Prophylaxis Studies**  
 184 **in Adults, Adolescents, and Children\***

| Adverse Event   | Contact Cases          |                        |
|---|------------------------|------------------------|
|   | RELENZA<br>(n = 1,068) | Placebo<br>(n = 1,059) |
| <b>Lower respiratory</b>  |                        |                        |
| Viral respiratory infections                                    | 13%                    | 19%                    |
| Cough   | 7%                     | 9%                     |
| <b>Neurologic</b>   |                        |                        |
| Headaches   | 13%                    | 14%                    |
| <b>Ear, nose, and throat</b>                                    |                        |                        |
| Nasal signs and symptoms  | 12%                    | 12%                    |
| Throat and tonsil discomfort and pain                           | 8%                     | 9%                     |
| Nasal inflammation  | 1%                     | 2%                     |
| <b>Musculoskeletal</b>  |                        |                        |
| Muscle pain   | 3%                     | 3%                     |
| <b>Endocrine and metabolic</b>                                  |                        |                        |
| Feeding problems (decreased or increased appetite and anorexia) | 2%                     | 2%                     |
| <b>Gastrointestinal</b>   |                        |                        |
| Nausea and vomiting   | 1%                     | 2%                     |
| <b>Non-site specific</b>  |                        |                        |
| Malaise and fatigue   | 5%                     | 5%                     |
| Temperature regulation disturbances (fever and/or chills)       | 5%                     | 4%                     |

185 \* In prophylaxis studies, symptoms associated with influenza-like illness were captured as  
 186 adverse events; subjects were enrolled during a winter respiratory season during which time  
 187 any symptoms that occurred were captured as adverse events.  
 188

189 *Community Prophylaxis Studies:* Adverse events that occurred with an incidence of  
 190  $\geq 1.5\%$  in 2 prophylaxis studies are listed in Table 4. This table shows adverse events occurring  
 191 in patients  $\geq 5$  years of age receiving RELENZA 10 mg inhaled once daily for 28 days.

192  
193  
194

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

| Adverse Event   | RELENZA<br>(n = 2,231) | Placebo<br>(n = 2,239) |
|---|------------------------|------------------------|
| <b>Neurologic</b>   |                        |                        |
| Headaches   | 24%                    | 26%                    |
| <b>Ear, nose, and throat</b>                                    |                        |                        |
| Throat and tonsil discomfort and pain                           | 19%                    | 20%                    |
| Nasal signs and symptoms  | 12%                    | 13%                    |
| Ear, nose, and throat infections                                | 2%                     | 2%                     |
| <b>Lower respiratory</b>  |                        |                        |
| Cough   | 17%                    | 18%                    |
| Viral respiratory infections                                    | 3%                     | 4%                     |
| <b>Musculoskeletal</b>  |                        |                        |
| Muscle pain   | 8%                     | 8%                     |
| Musculoskeletal pain  | 6%                     | 6%                     |
| Arthralgia and articular rheumatism                             | 2%                     | <1%                    |
| <b>Endocrine and metabolic</b>                                  |                        |                        |
| Feeding problems (decreased or increased appetite and anorexia) | 4%                     | 4%                     |
| <b>Gastrointestinal</b>   |                        |                        |
| Nausea and vomiting   | 2%                     | 3%                     |
| Diarrhea  | 2%                     | 2%                     |
| <b>Non-site specific</b>  |                        |                        |
| Temperature regulation disturbances (fever and/or chills)       | 9%                     | 10%                    |
| Malaise and fatigue   | 8%                     | 8%                     |

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

198

## 199 **6.2 Postmarketing Experience**

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

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

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

210            **Cardiac:** Arrhythmias, syncope.

211            **Neurologic:** Seizures.

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

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

## 215 **7 DRUG INTERACTIONS**

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

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

225            Trivalent inactivated influenza vaccine can be administered at any time relative to use of  
226 RELENZA [*see Clinical Pharmacology (12.4)*].

## 227 **8 USE IN SPECIFIC POPULATIONS**

### 228 **8.1 Pregnancy**

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

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

240            An additional embryo/fetal study, in a different strain of rat, was conducted using  
241 subcutaneous administration of zanamivir, 3 times daily, at doses of 1, 9, or 80 mg/kg during  
242 days 7 to 17 of pregnancy. There was an increase in the incidence rates of a variety of minor  
243 skeleton alterations and variants in the exposed offspring in this study. Based on AUC  
244 measurements, the 80 mg/kg dose produced an exposure greater than 1,000 times the human  
245 exposure at the proposed clinical dose. However, in most instances, the individual incidence rate

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

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

### 251 **8.3 Nursing Mothers**

252 Studies in rats have demonstrated that zanamivir is excreted in milk. However, nursing  
253 mothers should be instructed that it is not known whether zanamivir is excreted in human milk.  
254 Because many drugs are excreted in human milk, caution should be exercised when RELENZA  
255 is administered to a nursing mother.

### 256 **8.4 Pediatric Use**

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

264 In a Phase I study of 16 children ages 6 to 12 years with signs and symptoms of  
265 respiratory disease, 4 did not produce a measurable peak inspiratory flow rate (PIFR) through the  
266 DISKHALER (3 with no adequate inhalation on request, 1 with missing data), 9 had measurable  
267 PIFR on each of 2 inhalations, and 3 achieved measurable PIFR on only 1 of 2 inhalations.  
268 Neither of two 6-year-olds and one of two 7-year-olds produced measurable PIFR. Overall, 8 of  
269 the 16 children (including all those under 8 years old) either did not produce measurable  
270 inspiratory flow through the DISKHALER or produced peak inspiratory flow rates below the  
271 60 L/min considered optimal for the device under standardized in vitro testing; lack of  
272 measurable flow rate was related to low or undetectable serum concentrations [see *Clinical*  
273 *Pharmacology (12.3)*, *Clinical Studies (14.1)*]. Prescribers should carefully evaluate the ability  
274 of young children to use the delivery system if prescription of RELENZA is considered.

275 Prophylaxis of Influenza: The safety and effectiveness of RELENZA for prophylaxis of  
276 influenza have been studied in 4 Phase III studies where 273 children 5 to 11 years of age and  
277 239 adolescents 12 to 16 years of age received RELENZA. No differences in safety and  
278 effectiveness were observed between pediatric and adult subjects [see *Clinical Studies (14.2)*].

### 279 **8.5 Geriatric Use**

280 Of the total number of patients in 6 clinical studies of RELENZA for treatment of  
281 influenza, 59 patients were 65 years of age and older, while 24 patients were 75 years of age and  
282 older. Of the total number of patients in 4 clinical studies of RELENZA for prophylaxis of  
283 influenza in households and community settings, 954 patients were 65 years of age and older,  
284 while 347 patients were 75 years of age and older. No overall differences in safety or  
285 effectiveness were observed between these patients and younger patients, and other reported

286 clinical experience has not identified differences in responses between the elderly and younger  
287 patients, but greater sensitivity of some older individuals cannot be ruled out. Elderly patients  
288 may need assistance with use of the device.

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

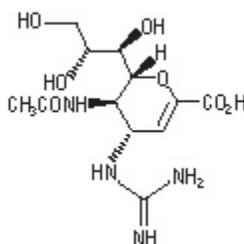
## 291 **10 OVERDOSAGE**

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

## 293 **11 DESCRIPTION**

294 The active component of RELENZA is zanamivir. The chemical name of zanamivir is 5-  
295 (acetylamino)-4-[(aminoiminomethyl)-amino]-2,6-anhydro-3,4,5-trideoxy-D-glycero-D-galacto-  
296 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  
297 has the following structural formula:

298



299

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

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

## 313 **12 CLINICAL PHARMACOLOGY**

### 314 **12.1 Mechanism of Action**

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

### 316 **12.3 Pharmacokinetics**

317 Absorption and Bioavailability: Pharmacokinetic studies of orally inhaled zanamivir  
318 indicate that approximately 4% to 17% of the inhaled dose is systemically absorbed. The peak

319 serum concentrations ranged from 17 to 142 ng/mL within 1 to 2 hours following a 10 mg dose.  
320 The area under the serum concentration versus time curve ( $AUC_{\infty}$ ) ranged from 111 to  
321 1,364 ng•hr/mL.

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

323 Metabolism: Zanamivir is renally excreted as unchanged drug. No metabolites have  
324 been detected in humans.

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

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

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

340 Pediatric Patients: The pharmacokinetics of zanamivir were evaluated in pediatric  
341 patients with signs and symptoms of respiratory illness. Sixteen patients, 6 to 12 years of age,  
342 received a single dose of 10 mg zanamivir dry powder via DISKHALER. Five patients had either  
343 undetectable zanamivir serum concentrations or had low drug concentrations (8.32 to  
344 10.38 ng/mL) that were not detectable after 1.5 hours. Eleven patients had  $C_{max}$  median values of  
345 43 ng/mL (range 15 to 74) and  $AUC_{\infty}$  median values of 167 ng•hr/mL (range 58 to 279). Low or  
346 undetectable serum concentrations were related to lack of measurable PIFR in individual patients  
347 [see *Use in Specific Populations (8.4), Clinical Studies (14.1)*].

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

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

## 357 **12.4 Microbiology**

358 Mechanism of Action: Zanamivir is an inhibitor of influenza virus neuraminidase  
359 affecting release of viral particles.

360 Antiviral Activity: The antiviral activity of zanamivir against laboratory and clinical  
361 isolates of influenza virus was determined in cell culture assays. The concentrations of zanamivir  
362 required for inhibition of influenza virus were highly variable depending on the assay method  
363 used and virus isolate tested. The 50% and 90% effective concentrations (EC<sub>50</sub> and EC<sub>90</sub>) of  
364 zanamivir were in the range of 0.005 to 16.0 μM and 0.05 to >100 μM, respectively  
365 (1 μM = 0.33 mcg/mL). The relationship between the cell culture inhibition of influenza virus by  
366 zanamivir and the inhibition of influenza virus replication in humans has not been established.

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

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

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

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

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

397 **13 NONCLINICAL TOXICOLOGY**

398 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

399 Carcinogenesis: In 2-year carcinogenicity studies conducted in rats and mice using a  
400 powder formulation administered through inhalation, zanamivir induced no statistically  
401 significant increases in tumors over controls. The maximum daily exposures in rats and mice  
402 were approximately 23 to 25 and 20 to 22 times, respectively, greater than those in humans at the  
403 proposed clinical dose based on AUC comparisons.

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

408 Impairment of Fertility: The effects of zanamivir on fertility and general reproductive  
409 performance were investigated in male (dosed for 10 weeks prior to mating, and throughout  
410 mating, gestation/lactation, and shortly after weaning) and female rats (dosed for 3 weeks prior  
411 to mating through Day 19 of pregnancy, or Day 21 post partum) at IV doses 1, 9, and  
412 90 mg/kg/day. Zanamivir did not impair mating or fertility of male or female rats, and did not  
413 affect the sperm of treated male rats. The reproductive performance of the F1 generation born to  
414 female rats given zanamivir was not affected. Based on a subchronic study in rats at a  
415 90 mg/kg/day IV dose, AUC values ranged between 142 and 199 mcg•hr/mL (>300 times the  
416 human exposure at the proposed clinical dose).

417 **14 CLINICAL STUDIES**

418 **14.1 Treatment of Influenza**

419 Adults and Adolescents: The efficacy of RELENZA 10 mg inhaled twice daily for  
420 5 days in the treatment of influenza has been evaluated in placebo-controlled studies conducted  
421 in North America, the Southern Hemisphere, and Europe during their respective influenza  
422 seasons. The magnitude of treatment effect varied between studies, with possible relationships to  
423 population-related factors including amount of symptomatic relief medication used.

424 Populations Studied: The principal Phase III studies enrolled 1,588 patients ages  
425 12 years and older (median age 34 years, 49% male, 91% Caucasian), with uncomplicated  
426 influenza-like illness within 2 days of symptom onset. Influenza was confirmed by culture,  
427 hemagglutination inhibition antibodies, or investigational direct tests. Of 1,164 patients with  
428 confirmed influenza, 89% had influenza A and 11% had influenza B. These studies served as the  
429 principal basis for efficacy evaluation, with more limited Phase II studies providing supporting  
430 information where necessary. Following randomization to either zanamivir or placebo (inhaled  
431 lactose vehicle), all patients received instruction and supervision by a healthcare professional for  
432 the initial dose.

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

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

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

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

447 No consistent treatment effect was demonstrated in patients with underlying chronic  
448 medical conditions, including respiratory or cardiovascular disease [*see Warnings and*  
449 *Precautions (5.4)*].

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

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

454 **Pediatric Patients:** The efficacy of RELENZA 10 mg inhaled twice daily for 5 days in  
455 the treatment of influenza in pediatric patients has been evaluated in a placebo-controlled study  
456 conducted in North America and Europe, enrolling 471 patients, ages 5 to 12 years (55% male,  
457 90% Caucasian), within 36 hours of symptom onset. Of 346 patients with confirmed influenza,  
458 65% had influenza A and 35% had influenza B. The definition of time to improvement included  
459 no fever and parental assessment of no or mild cough and absent/minimal muscle and joint aches  
460 or pains, sore throat, chills/feverishness, and headache. Median time to symptom improvement  
461 was 1 day shorter in patients receiving zanamivir compared with placebo. No consistent  
462 differences in rate of development of complications were observed between treatment groups.  
463 Some fluctuation of symptoms was observed after the primary study endpoint in both treatment  
464 groups.

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

## 470 **14.2 Prophylaxis of Influenza**

471 The efficacy of RELENZA in preventing naturally occurring influenza illness has been  
472 demonstrated in 2 post-exposure prophylaxis studies in households and 2 seasonal prophylaxis  
473 studies during community outbreaks of influenza. The primary efficacy endpoint in these studies  
474 was the incidence of symptomatic, laboratory-confirmed influenza, defined as the presence of 2  
475 or more of the following symptoms: oral temperature  $\geq 100^{\circ}\text{F}/37.8^{\circ}\text{C}$  or feverishness, cough,

476 headache, sore throat, and myalgia; and laboratory confirmation of influenza A or B by culture,  
477 PCR, or seroconversion (defined as a 4-fold increase in convalescent antibody titer from  
478 baseline).

479 **Household Prophylaxis Studies:** Two studies assessed post-exposure prophylaxis in  
480 household contacts of an index case. Within 1.5 days of onset of symptoms in an index case,  
481 each household (including all family members  $\geq 5$  years of age) was randomized to RELENZA  
482 10 mg inhaled once daily or placebo inhaled once daily for 10 days. In the first study only, each  
483 index case was randomized to RELENZA 10 mg inhaled twice daily for 5 days or inhaled  
484 placebo twice daily for 5 days. In this study, the proportion of households with at least 1 new  
485 case of symptomatic laboratory-confirmed influenza was reduced from 19.0% (32 of  
486 168 households) for the placebo group to 4.1% (7 of 169 households) for the group receiving  
487 RELENZA.

488 In the second study, index cases were not treated. The incidence of symptomatic  
489 laboratory-confirmed influenza was reduced from 19.0% (46 of 242 households) for the placebo  
490 group to 4.1% (10 of 245 households) for the group receiving RELENZA.

491 **Seasonal Prophylaxis Studies:** Two seasonal prophylaxis studies assessed RELENZA  
492 10 mg inhaled once daily versus placebo inhaled once daily for 28 days during community  
493 outbreaks. The first study enrolled subjects 18 years of age or greater (mean age 29 years) from 2  
494 university communities. The majority of subjects were unvaccinated (86%). In this study, the  
495 incidence of symptomatic laboratory-confirmed influenza was reduced from 6.1% (34 of 554)  
496 for the placebo group to 2.0% (11 of 553) for the group receiving RELENZA.

497 The second seasonal prophylaxis study enrolled subjects 12 to 94 years of age (mean age  
498 60 years) with 56% of them older than 65 years of age. Sixty-seven percent of the subjects were  
499 vaccinated. In this study, the incidence of symptomatic laboratory-confirmed influenza was  
500 reduced from 1.4% (23 of 1,685) for the placebo group to 0.2% (4 of 1,678) for the group  
501 receiving RELENZA.

## 502 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

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

## 509 **17 PATIENT COUNSELING INFORMATION**

510 *See FDA-Approved Patient Labeling (17.6).*

### 511 **17.1 Bronchospasm**

512 **Patients should be advised of the risk of bronchospasm, especially in the setting of**  
513 **underlying airways disease, and should stop RELENZA and contact their physician if they**  
514 **experience increased respiratory symptoms during treatment such as worsening wheezing,**

515 **shortness of breath, or other signs or symptoms of bronchospasm [see Warnings and**  
516 **Precautions (5.1)]. If a decision is made to prescribe RELENZA for a patient with asthma**  
517 **or chronic obstructive pulmonary disease, the patient should be made aware of the risks**  
518 **and should have a fast-acting bronchodilator available.**

#### 519 **17.2 Concomitant Bronchodilator Use**

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

#### 522 **17.3 Neuropsychiatric Events**

523 Patients with influenza (the flu), particularly children and adolescents, may be at an  
524 increased risk of seizures, confusion, or abnormal behavior early in their illness. These events  
525 may occur after beginning RELENZA or may occur when flu is not treated. These events are  
526 uncommon but may result in accidental injury to the patient. Therefore, patients should be  
527 observed for signs of unusual behavior and a healthcare professional should be contacted  
528 immediately if the patient shows any signs of unusual behavior [see Warnings and Precautions  
529 (5.3)].

#### 530 **17.4 Instructions for Use**

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

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

#### 537 **17.5 Risk of Influenza Transmission to Others**

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

#### 540 **17.6 FDA-Approved Patient Labeling and Instructions for Use**

541 See separate leaflet.

542  
543 RELENZA, DISKHALER, and ROTADISK are registered trademarks of GlaxoSmithKline.  
544  
545



546 GlaxoSmithKline  
547 Research Triangle Park, NC 27709  
548

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550

1 **Patient Labeling**

2  
3 **RELENZA® (zanamivir) Inhalation Powder**

4  
5 This leaflet contains important patient information about RELENZA (zanamivir)  
6 Inhalation Powder, and should be read completely before beginning treatment. It does not,  
7 however, take the place of discussions with your healthcare provider about your medical  
8 condition or your treatment. This summary does not list all benefits and risks of RELENZA. The  
9 medication described here can only be prescribed and dispensed by a licensed healthcare  
10 provider, who has information about your medical condition and more information about the  
11 drug, including how to take it, what to expect, and potential side effects. If you have any  
12 questions about RELENZA, talk with your healthcare provider.

13  
14 **What is RELENZA?**

15 RELENZA (ruh-LENS-uh) is a medicine for the treatment of influenza (flu, infection  
16 caused by influenza virus) and for reducing the chance of getting the flu in community and  
17 household settings. It belongs to a group of medicines called neuraminidase inhibitors. These  
18 medications attack the influenza virus and prevent it from spreading inside your body.  
19 RELENZA treats the cause of influenza at its source, rather than simply masking the symptoms.

20  
21 **Important Safety Information About RELENZA**

22 Some patients have had bronchospasm (wheezing) or serious breathing problems when  
23 they used RELENZA. Many but not all of these patients had previous asthma or chronic  
24 obstructive pulmonary disease. RELENZA has not been shown to shorten the duration of  
25 influenza in people with these diseases. Because of the risk of side effects and because it has not  
26 been shown to help them, RELENZA is not recommended for people with chronic respiratory  
27 disease such as asthma or chronic obstructive pulmonary disease.

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

30 If you have chronic respiratory disease such as asthma and chronic obstructive pulmonary  
31 disease and your healthcare provider has prescribed RELENZA, you should have a fast-acting,  
32 inhaled bronchodilator available for your use. If you are scheduled to use an inhaled  
33 bronchodilator at the same time as RELENZA, use the inhaled bronchodilator **before** using  
34 RELENZA.

35 Read the rest of this leaflet for more information about side effects and risks.

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

39  
40 **Who should not take RELENZA?**

41 RELENZA is not recommended for people who have chronic lung disease such as  
42 asthma or chronic obstructive pulmonary disease. RELENZA has not been shown to shorten the  
43 duration of influenza in people with these diseases, and some people have had serious side  
44 effects of bronchospasm and worsening lung function. (See the section of this Patient  
45 Information entitled “**Important Safety Information About RELENZA.**”)

46 You should not take RELENZA if you are allergic to zanamivir or any other ingredient of  
47 RELENZA. Also tell your healthcare provider if you have any type of chronic condition  
48 including lung or heart disease, if you are allergic to any other medicines or food products, or if  
49 you are pregnant.

50 RELENZA was not effective in reducing the chance of getting the flu in 2 studies in  
51 nursing home patients.

52 RELENZA does not treat flu-like illness that is not caused by influenza virus.

53

#### 54 **Who should consider taking RELENZA?**

55 Adult and pediatric patients at least 7 years of age who have influenza symptoms that  
56 appeared within the previous day or two. Typical symptoms of influenza include sudden onset of  
57 fever, cough, headache, fatigue, muscular weakness, and sore throat.

58 RELENZA can also help reduce the chance of getting the flu in adults and children at  
59 least 5 years of age who have a higher chance of getting the flu because they spend time with  
60 someone who has the flu. RELENZA can also reduce the chance of getting the flu if there is a flu  
61 outbreak in the community.

62 The use of RELENZA for the treatment of flu has not been shown to reduce the risk of  
63 spreading the virus to others.

64

#### 65 **Can I take other medications with RELENZA?**

66 RELENZA has been shown to have an acceptable safety profile when used as labeled,  
67 with minimal risk of drug interactions. Your healthcare provider may recommend taking other  
68 medications, including over-the-counter medications, to reduce fever or other symptoms while  
69 you are taking RELENZA. Before starting treatment, make sure that your healthcare provider  
70 knows if you are taking other medicines. If you are scheduled to use an inhaled bronchodilator at  
71 the same time as RELENZA, you should use the inhaled bronchodilator **before** using  
72 RELENZA.

73 Before taking RELENZA, please let your healthcare provider know if you received live  
74 attenuated influenza vaccine (FLUMIST<sup>®</sup>) intranasal in the past 2 weeks.

75

#### 76 **How and when should I take RELENZA?**

77 RELENZA is packaged in medicine disks called ROTADISKS<sup>®</sup> and is inhaled by mouth  
78 using a delivery device called a DISKHALER<sup>®</sup>. Each ROTADISK contains 4 blisters. Each  
79 blister contains 5 mg of active drug and 20 mg of lactose powder (which contains milk proteins).

80           You should receive a demonstration on how to use RELENZA in the DISKHALER from  
81 a healthcare provider. Before taking RELENZA, read the “Patient Instructions for Use.” Make  
82 sure that you understand these instructions and talk to your healthcare provider if you have any  
83 questions. Children who use RELENZA should always be supervised by an adult who  
84 understands how to use RELENZA. Proper use of the DISKHALER to inhale the drug is  
85 necessary for safe and effective use of RELENZA.

86           If you have the flu the usual dose for treatment is 2 inhalations of RELENZA (1 blister  
87 per inhalation) twice daily (in the morning and evening) for 5 days. It is important that you begin  
88 your treatment with RELENZA as soon as possible from the first appearance of your flu  
89 symptoms. Take 2 doses on the first day of treatment whenever possible if there are at least  
90 2 hours between doses.

91           To reduce the chance of getting the flu, the usual dose is 2 inhalations of RELENZA  
92 (1 blister per inhalation) once daily for 10 or 28 days as prescribed by your healthcare provider.

93           Never share RELENZA with anyone, even if they have the same symptoms. If you feel  
94 worse or develop new symptoms during treatment with RELENZA, or if your flu symptoms do  
95 not start to get better, stop using the medicine and contact your healthcare provider.

96

#### 97 **What if I miss a dose?**

98           If you forget to take your medicine at any time, take the missed dose as soon as you  
99 remember, except if it is near the next dose (within 2 hours). Then continue to take RELENZA at  
100 the usual times. You do not need to take a double dose. If you have missed several doses, inform  
101 your healthcare provider and follow the advice given to you.

102

#### 103 **What are important or common possible side effects of taking RELENZA?**

104           Some patients have had breathing problems while taking RELENZA. This can be very  
105 serious and need treatment right away. Most of the patients who had this problem had asthma or  
106 chronic obstructive pulmonary disease, but some did not. If you have trouble breathing or have  
107 wheezing after your dose of RELENZA, stop taking RELENZA and get medical attention.

108           In studies, the most common side effects with RELENZA have been headaches; diarrhea;  
109 nausea; vomiting; nasal irritation; bronchitis; cough; sinusitis; ear, nose, and throat infections;  
110 and dizziness. Other side effects that have been reported, but were not as common, include  
111 rashes and allergic reactions, some of which were severe.

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

118            This list of side effects is not complete. Your healthcare provider or pharmacist can  
119 discuss with you a more complete list of possible side effects with RELENZA. Talk to your  
120 healthcare provider promptly about any side effects you have.

121            Please refer to the section entitled "**Important Safety Information About RELENZA**"  
122 for additional information.

123

124 **Should I get a flu shot?**

125            RELENZA is not a substitute for a flu shot. You should receive an annual flu shot  
126 according to guidelines on immunization practices that your healthcare provider can share with  
127 you.

128

129 **What if I am pregnant or nursing?**

130            If you are pregnant or planning to become pregnant while taking RELENZA, talk to your  
131 healthcare provider before taking this medication. RELENZA is normally not recommended for  
132 use during pregnancy or nursing, as the effects on the unborn child or nursing infant are  
133 unknown.

134

135 **How and where should I store RELENZA?**

136            RELENZA should be stored at room temperature below 77°F (25°C). RELENZA is not  
137 in a childproof container. Keep RELENZA out of the reach of children. Discard the  
138 DISKHALER after finishing your treatment.

139

140

**PATIENT INSTRUCTIONS FOR USE**



141

142

**IMPORTANT: Read Step-by-Step Instructions  
before using the DISKHALER®.**

143

144

145

**Be sure to take the dose your healthcare provider has prescribed.**

146

147

**BEFORE YOU START:**

148

149

**Please read the entire Patient Labeling for important information about the effects of RELENZA including the section “Important Safety Information About RELENZA” for information about the risk of breathing difficulties.**

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**If RELENZA is prescribed for a child, dosing should be supervised by an adult who understands how to use RELENZA and has been instructed in its use by a healthcare provider.**

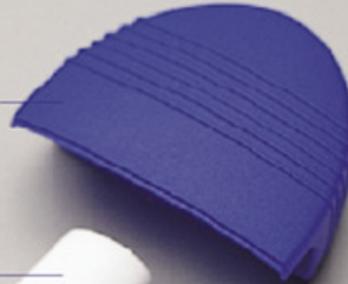
154

155

## Parts of the DISKHALER:

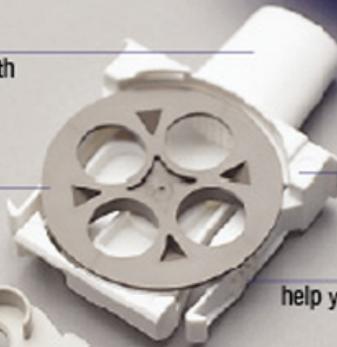
### COVER

keeps the DISKHALER clean and free of foreign matter; replace cover when not in use



### WHITE MOUTHPIECE

where the medicine is inhaled by mouth



### DARK BROWN WHEEL

rotates to the next plister of medicine



### WHITE TRAY

pulls in and out of DISKHALER body

### RAISED RIDGES

help you pull out the tray for loading

### NEEDLE

punctures the plister to release medicine

### DISKHALER BODY

### HALF-CIRCLE FLAP

lifts up and down to operate plastic needle



### SILVER MEDICINE DISK

contains 4 plisters of medicine; the disk fits into the dark brown wheel inside the DISKHALER



156 **Step-by-step instructions for using the DISKHALER®**

157

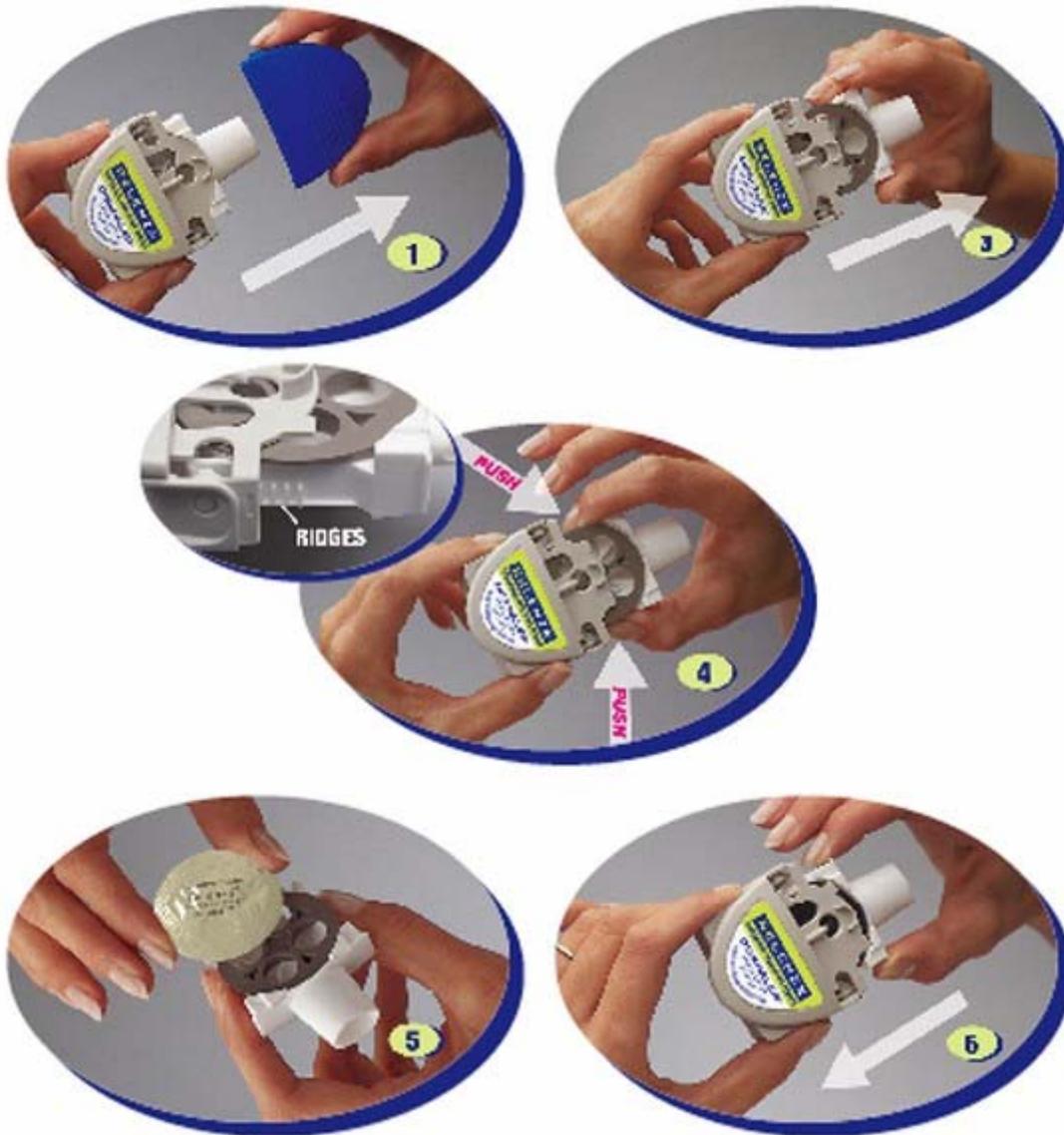
158 **Step A: Load the medicine into the DISKHALER**

159

160 1. Start by pulling off the blue cover.

161

- 162 2. **Always check inside the mouthpiece to make sure it is clear before each use. If foreign**  
163 **objects are in the mouthpiece, they could be inhaled and cause serious harm.**  
164
- 165 3. Pull the white mouthpiece by the edges to extend the white tray all the way.  
166
- 167 4. Once the white tray is extended all the way, find the raised ridges on each side of it. Press in  
168 these ridges, both sides at the same time, and **pull the whole white tray out of the**  
169 **DISKHALER body.**  
170
- 171 5. Place one silver medicine disk onto the dark brown wheel, flat side up. The four silver  
172 blisters on the underside of the medicine disk will drop neatly into the four holes in the  
173 wheel.  
174
- 175 6. Push in the white tray as far as it will go. Now the DISKHALER is loaded with medicine.  
176



177

178 **Step B: Puncture the blister**

179

180 **Be sure to keep the DISKHALER level.**

181

182 **The DISKHALER punctures one blister of medicine at a time so you can inhale the right**  
 183 **amount. It does not matter which blister you start with. Check to make sure that the silver**  
 184 **foil is unbroken.**

185

186 1. Be sure to keep the DISKHALER level so the medicine does not spill out.

187

188 2. Locate the half-circle flap with the name “RELENZA” on top of the DISKHALER.

189  
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3. Lift this flap from the outer edge until it cannot go any farther. Flap must be **straight up** for the plastic needle to puncture both the **top** and **bottom** of the silver medicine disk inside.
4. Keeping the DISKHALER level, click the flap down into place.



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### Step C: Inhale

1. Before putting the white mouthpiece into your mouth, breathe all the way out (exhale).

200 **Then put the white mouthpiece into your mouth. Be sure to keep the DISKHALER level so**  
201 **the medicine does not spill out.**

202  
203  
204  
205

2. Close your lips firmly around the mouthpiece. Be sure not to cover the small holes on either side of it.

3. Breathe in through your mouth steadily and as deeply as you can. Your breath pulls the medicine into your airways and lungs.

208

4. Hold your breath for a few seconds to help RELENZA stay in your lungs where it can work.

210

**To take another inhalation, move to the next blister by following Step D below.**

212

213 **Once you've inhaled the number of blisters prescribed by your healthcare provider,**  
214 **replace the cover until your next dose.**



215  
216

**Step D: Move the medicine disk to the next blister**

218

219  
220

1. **Pull** the mouthpiece to extend the white tray, without removing it.

221  
222

2. Then **push** it back until it clicks. This pull-push motion rotates the medicine disk to the next blister.

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224  
225

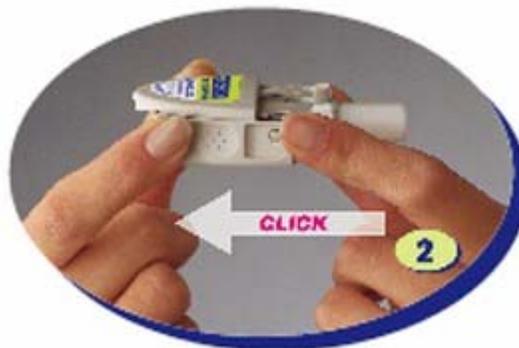
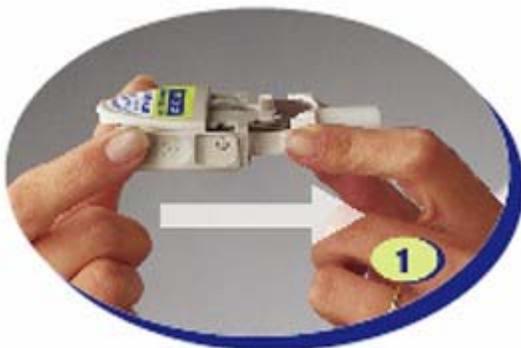
3. To take your next inhalation, repeat Steps B and C.

226

**If all four blisters in the medicine disk have been used, you are ready to start a new medicine disk (see Step A). Check to make sure that the silver foil is unbroken each time you are ready to puncture the next blister.**

227

228



229

**IMPORTANT INSTRUCTIONS**

Read this entire leaflet before using RELENZA. Even if you have had a previous prescription for RELENZA, read this leaflet to see if any information has changed.

If you have the flu, the usual dose is 2 inhalations twice daily. To reduce the chance of getting the flu, the usual dose is 2 inhalations once daily. However, you must take the

number of inhalations your healthcare provider has prescribed.

If you feel worse or develop new symptoms during or after treatment, or if your flu symptoms do not start to improve, stop using the medicine and contact your healthcare provider.

Keep out of reach of children.

Always check inside the mouthpiece to make sure it is clear before each use. If foreign objects are in the mouthpiece, they could be inhaled and cause serious harm.

Always replace the cover after each use.

Throw away the DISKHALER after treatment is completed.

This DISKHALER is for use only with RELENZA. Do not use the RELENZA DISKHALER device with FLOVENT<sup>®</sup> (fluticasone propionate) and do not use RELENZA with the FLOVENT DISKHALER device.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP Controlled Room Temperature).

**REMEMBER:** This medicine has been prescribed for you by your healthcare provider. **DO NOT** give this medicine to anyone else.

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