

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

RECENT MAJOR CHANGES

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

INDICATIONS AND USAGE

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

Prophylaxis of influenza in patients 5 years of age and older. (1.2)

Important Limitations on Use of RELENZA:

Not recommended for treatment or prophylaxis of influenza in:

- Individuals with underlying airways disease. (5.1)

Not proven effective for:

- Treatment in individuals with underlying airways disease. (1.3)
- Prophylaxis in nursing home residents. (1.3)

Not a substitute for annual influenza vaccination. (1.3)

Consider available information on influenza drug susceptibility patterns and treatment effects when deciding whether to use RELENZA. (1.3)

DOSAGE AND ADMINISTRATION

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

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

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

The most common adverse events reported in >1.5% of patients treated with RELENZA and more commonly than in patients treated with placebo are:

- Treatment Studies – sinusitis, dizziness.
- Prophylaxis Studies – fever and/or chills, arthralgia and articular rheumatism. (6.1)

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

DRUG INTERACTIONS

Live attenuated influenza vaccine, intranasal (7):

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

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

Revised: October 2008
RLZ:xPI

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

1

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 FEV₁ 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 ≥ 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 (Lactose Vehicle) (n = 1,520)
	10 mg b.i.d. Inhaled (n = 1,132)	All Dosing Regimens* (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%

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 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%

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

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 ≥ 5 years of age receiving RELENZA 10 mg inhaled once daily for 28 days.

192
193
194

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

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

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)*].

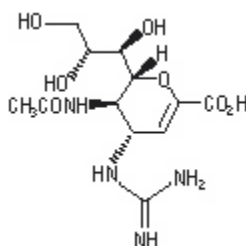
291 **10 OVERDOSAGE**

292 There have been no reports of overdose 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_{∞}) 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_{∞} 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 (EC₅₀ and EC₉₀) 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 ≥ 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
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