

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**-----
Warnings and Precautions (5.6) 12/2010

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

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

Prophylaxis of influenza in patients aged 5 years 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**-----

Blister for oral inhalation: 5 mg. Four 5-mg blisters of powder on a ROTADISK® for oral inhalation via DISKHALER®. Packaged in carton containing 5 ROTADISKS (total of 10 doses) and 1 DISKHALER inhalation device. (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: 12/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

- 1.1 Treatment of Influenza
- 1.2 Prophylaxis of Influenza
- 1.3 Important Limitations on Use of RELENZA

2 DOSAGE AND ADMINISTRATION

- 2.1 Dosing Considerations
- 2.2 Treatment of Influenza
- 2.3 Prophylaxis of Influenza

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Bronchospasm
- 5.2 Allergic Reactions
- 5.3 Neuropsychiatric Events
- 5.4 Limitations of Populations Studied
- 5.5 Bacterial Infections
- 5.6 Importance of Proper Route of Administration
- 5.7 Importance of Proper Use of DISKHALER

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics
- 12.4 Microbiology

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Treatment of Influenza
- 14.2 Prophylaxis of Influenza

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

- 17.1 Bronchospasm
- 17.2 Concomitant Bronchodilator Use
- 17.3 Neuropsychiatric Events
- 17.4 Instructions for Use
- 17.5 Risk of Influenza Transmission to Others

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

1 FULL PRESCRIBING INFORMATION

2 1 INDICATIONS AND USAGE

3 1.1 Treatment of Influenza

4 RELENZA[®] (zanamivir) Inhalation Powder is indicated for treatment of uncomplicated
5 acute illness due to influenza A and B virus in adults and pediatric patients aged 7 years and
6 older who have been symptomatic for no more than 2 days.

7 1.2 Prophylaxis of Influenza

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

10 1.3 Important Limitations on Use of RELENZA

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

30 2 DOSAGE AND ADMINISTRATION

31 2.1 Dosing Considerations

- 32 • RELENZA is for administration to the respiratory tract by *oral inhalation only*, using the
33 DISKHALER device provided [*see Warnings and Precautions (5.6)*].
- 34 • The 10-mg dose is provided by 2 inhalations (one 5-mg blister per inhalation).
- 35 • Patients should be instructed in the use of the delivery system. Instructions should include a
36 demonstration whenever possible. If RELENZA is prescribed for children, it should be used
37 only under adult supervision and instruction, and the supervising adult should first be
38 instructed by a healthcare professional [*see Patient Counseling Information (17.4)*].

- 39 • Patients scheduled to use an inhaled bronchodilator at the same time as RELENZA should
40 use their bronchodilator before taking RELENZA [see Patient Counseling Information
41 (17.2)].

42 **2.2 Treatment of Influenza**

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

51 **2.3 Prophylaxis of Influenza**

52 Household Setting:

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

58 Community Outbreaks:

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

66 **3 DOSAGE FORMS AND STRENGTHS**

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

70 **4 CONTRAINDICATIONS**

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

74 **5 WARNINGS AND PRECAUTIONS**

75 **5.1 Bronchospasm**

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

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

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

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

86 Bronchospasm was documented following administration of zanamivir in 1 of 13 patients
87 with mild or moderate asthma (but without acute influenza-like illness) in a Phase I study. In a
88 Phase III study in patients with acute influenza-like illness superimposed on underlying asthma
89 or chronic obstructive pulmonary disease, 10% (24 of 244) of patients on zanamivir and 9% (22
90 of 237) on placebo experienced a greater than 20% decline in FEV₁ following treatment for
91 5 days.

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

97 **5.2 Allergic Reactions**

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

102 **5.3 Neuropsychiatric Events**

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

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

116 **5.4 Limitations of Populations Studied**

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

121 **5.5 Bacterial Infections**

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

125 **5.6 Importance of Proper Route of Administration**

126 RELENZA Inhalation Powder must not be made into an extemporaneous solution for
127 administration by nebulization or mechanical ventilation. There have been reports of hospitalized
128 patients with influenza who received a solution made with RELENZA Inhalation Powder
129 administered by nebulization or mechanical ventilation, including a fatal case where it was
130 reported that the lactose in this formulation obstructed the proper functioning of the equipment.
131 RELENZA Inhalation Powder must only be administered using the device provided [*see Dosage
132 and Administration (2.1)*].

133 **5.7 Importance of Proper Use of DISKHALER**

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

137 **6 ADVERSE REACTIONS**

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

141 **6.1 Clinical Trials Experience**

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

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

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

153

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

Adverse Event	RELENZA		Placebo (Lactose Vehicle) (n = 1,520)
	10 mg b.i.d. Inhaled (n = 1,132)	All Dosing Regimens ^a (n = 2,289)	
Body as a whole			
Headaches	2%	2%	3%
Digestive			
Diarrhea	3%	3%	4%
Nausea	3%	3%	3%
Vomiting	1%	1%	2%
Respiratory			
Nasal signs and symptoms	2%	3%	3%
Bronchitis	2%	2%	3%
Cough	2%	2%	3%
Sinusitis	3%	2%	2%
Ear, nose, and throat infections	2%	1%	2%
Nervous system			
Dizziness	2%	1%	<1%

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

159

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

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

165 *Clinical Trials in Pediatric Patients:* Adverse events that occurred with an incidence
166 $\geq 1.5\%$ in children receiving treatment doses of RELENZA in 2 Phase III studies are listed in
167 Table 2. This table shows adverse events occurring in pediatric patients 5 to 12 years old
168 receiving RELENZA 10 mg inhaled twice daily and placebo inhaled twice daily (where placebo
169 consisted of the same lactose vehicle used in RELENZA).

170

171 **Table 2. Summary of Adverse Events $\geq 1.5\%$ Incidence During Treatment in Pediatric**
172 **Patients^a**

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

173 ^a Includes a subset of patients receiving RELENZA for treatment of influenza in a prophylaxis
174 study.

175

176 In 1 of the 2 studies described in Table 2, some additional information is available from
177 children (5 to 12 years old) without acute influenza-like illness who received an investigational
178 prophylaxis regimen of RELENZA; 132 children received RELENZA and 145 children received
179 placebo. Among these children, nasal signs and symptoms (zanamivir 20%, placebo 9%), cough
180 (zanamivir 16%, placebo 8%), and throat/tonsil discomfort and pain (zanamivir 11%, placebo
181 6%) were reported more frequently with RELENZA than placebo. In a subset with chronic
182 pulmonary disease, lower respiratory adverse events (described as asthma, cough, or viral
183 respiratory infections which could include influenza-like symptoms) were reported in 7 of 7
184 zanamivir recipients and 5 of 12 placebo recipients.

185 Prophylaxis of Influenza: Family/Household Prophylaxis Studies: Adverse events
186 that occurred with an incidence of $\geq 1.5\%$ in the 2 prophylaxis studies are listed in Table 3. This
187 table shows adverse events occurring in patients aged ≥ 5 years receiving RELENZA 10 mg
188 inhaled once daily for 10 days.

189

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

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%

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

195
196 *Community Prophylaxis Studies:* Adverse events that occurred with an incidence of
197 $\geq 1.5\%$ in 2 prophylaxis studies are listed in Table 4. This table shows adverse events occurring
198 in patients aged ≥ 5 years receiving RELENZA 10 mg inhaled once daily for 28 days.

199

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

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%

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

205

206 **6.2 Postmarketing Experience**

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

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

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

217 **Cardiac:** Arrhythmias, syncope.

218 **Neurologic:** Seizures. Vasovagal-like episodes have been reported shortly following
219 inhalation of zanamivir.

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

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

224 **7 DRUG INTERACTIONS**

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

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

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

236 **8 USE IN SPECIFIC POPULATIONS**

237 **8.1 Pregnancy**

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

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

249 An additional embryo/fetal study, in a different strain of rat, was conducted using
250 subcutaneous administration of zanamivir, 3 times daily, at doses of 1, 9, or 80 mg/kg during
251 days 7 to 17 of pregnancy. There was an increase in the incidence rates of a variety of minor
252 skeleton alterations and variants in the exposed offspring in this study. Based on AUC

253 measurements, the 80 mg/kg dose produced an exposure greater than 1,000 times the human
254 exposure at the proposed clinical dose. However, in most instances, the individual incidence rate
255 of each skeletal alteration or variant remained within the background rates of the historical
256 occurrence in the strain studied.

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

260 **8.3 Nursing Mothers**

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

265 **8.4 Pediatric Use**

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

273 In a Phase I study of 16 children aged 6 to 12 years with signs and symptoms of
274 respiratory disease, 4 did not produce a measurable peak inspiratory flow rate (PIFR) through the
275 DISKHALER (3 with no adequate inhalation on request, 1 with missing data), 9 had measurable
276 PIFR on each of 2 inhalations, and 3 achieved measurable PIFR on only 1 of 2 inhalations.
277 Neither of two 6-year-olds and one of two 7-year-olds produced measurable PIFR. Overall, 8 of
278 the 16 children (including all those younger than 8 years) either did not produce measurable
279 inspiratory flow through the DISKHALER or produced peak inspiratory flow rates below the
280 60 L/min considered optimal for the device under standardized in vitro testing; lack of
281 measurable flow rate was related to low or undetectable serum concentrations [see *Clinical*
282 *Pharmacology (12.3)*, *Clinical Studies (14.1)*]. Prescribers should carefully evaluate the ability
283 of young children to use the delivery system if prescription of RELENZA is considered.

284 Prophylaxis of Influenza: The safety and effectiveness of RELENZA for prophylaxis of
285 influenza have been studied in 4 Phase III studies where 273 children aged 5 to 11 years and
286 239 adolescents aged 12 to 16 years received RELENZA. No differences in safety and
287 effectiveness were observed between pediatric and adult subjects [see *Clinical Studies (14.2)*].

288 **8.5 Geriatric Use**

289 Of the total number of patients in 6 clinical studies of RELENZA for treatment of
290 influenza, 59 patients were aged 65 years and older, while 24 patients were aged 75 years and
291 older. Of the total number of patients in 4 clinical studies of RELENZA for prophylaxis of
292 influenza in households and community settings, 954 patients were aged 65 years and older,

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

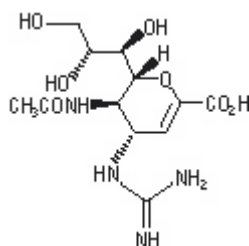
298 In 2 additional studies of RELENZA for prophylaxis of influenza in the nursing home
299 setting, efficacy was not demonstrated [see *Indications and Usage (1.3)*].

300 **10 OVERDOSAGE**

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

302 **11 DESCRIPTION**

303 The active component of RELENZA is zanamivir. The chemical name of zanamivir is 5-
304 (acetylamino)-4-[(aminoiminomethyl)-amino]-2,6-anhydro-3,4,5-trideoxy-D-glycero-D-galacto-
305 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
306 has the following structural formula:



308
309 Zanamivir is a white to off-white powder for oral inhalation with a solubility of
310 approximately 18 mg/mL in water at 20°C.

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

322 **12 CLINICAL PHARMACOLOGY**

323 **12.1 Mechanism of Action**

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

325 **12.3 Pharmacokinetics**

326 **Absorption and Bioavailability:** Pharmacokinetic studies of orally inhaled zanamivir
327 indicate that approximately 4% to 17% of the inhaled dose is systemically absorbed. The peak
328 serum concentrations ranged from 17 to 142 ng/mL within 1 to 2 hours following a 10 mg dose.
329 The area under the serum concentration versus time curve (AUC_{∞}) ranged from 111 to
330 1,364 ng•hr/mL.

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

332 **Metabolism:** Zanamivir is renally excreted as unchanged drug. No metabolites have
333 been detected in humans.

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

338 **Impaired Hepatic Function:** The pharmacokinetics of zanamivir have not been studied
339 in patients with impaired hepatic function.

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

349 **Pediatric Patients:** The pharmacokinetics of zanamivir were evaluated in pediatric
350 patients with signs and symptoms of respiratory illness. Sixteen patients, aged 6 to 12 years ,
351 received a single dose of 10 mg zanamivir dry powder via DISKHALER. Five patients had either
352 undetectable zanamivir serum concentrations or had low drug concentrations (8.32 to
353 10.38 ng/mL) that were not detectable after 1.5 hours. Eleven patients had C_{max} median values of
354 43 ng/mL (range: 15 to 74) and AUC_{∞} median values of 167 ng•hr/mL (range: 58 to 279). Low
355 or undetectable serum concentrations were related to lack of measurable PIFR in individual
356 patients [see *Use in Specific Populations (8.4), Clinical Studies (14.1)*].

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

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

366 **12.4 Microbiology**

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

369 Antiviral Activity: The antiviral activity of zanamivir against laboratory and clinical
370 isolates of influenza virus was determined in cell culture assays. The concentrations of zanamivir
371 required for inhibition of influenza virus were highly variable depending on the assay method
372 used and virus isolate tested. The 50% and 90% effective concentrations (EC₅₀ and EC₉₀) of
373 zanamivir were in the range of 0.005 to 16.0 μM and 0.05 to >100 μM, respectively
374 (1 μM = 0.33 mcg/mL). The relationship between the cell culture inhibition of influenza virus by
375 zanamivir and the inhibition of influenza virus replication in humans has not been established.

376 Resistance: Influenza viruses with reduced susceptibility to zanamivir have been
377 selected in cell culture by multiple passages of the virus in the presence of increasing
378 concentrations of the drug. Genetic analysis of these viruses showed that the reduced
379 susceptibility in cell culture to zanamivir is associated with mutations that result in amino acid
380 changes in the viral neuraminidase or viral hemagglutinin or both. Resistance mutations selected
381 in cell culture which result in neuraminidase amino acid substitutions include E119G/A/D and
382 R292K. Mutations selected in cell culture in hemagglutinin include: K68R, G75E, E114K,
383 N145S, S165N, S186F, N199S, and K222T.

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

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

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

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

406 **13 NONCLINICAL TOXICOLOGY**

407 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

417 Impairment of Fertility: The effects of zanamivir on fertility and general reproductive
418 performance were investigated in male (dosed for 10 weeks prior to mating, and throughout
419 mating, gestation/lactation, and shortly after weaning) and female rats (dosed for 3 weeks prior
420 to mating through Day 19 of pregnancy, or Day 21 post partum) at IV doses 1, 9, and
421 90 mg/kg/day. Zanamivir did not impair mating or fertility of male or female rats, and did not
422 affect the sperm of treated male rats. The reproductive performance of the F1 generation born to
423 female rats given zanamivir was not affected. Based on a subchronic study in rats at a
424 90 mg/kg/day IV dose, AUC values ranged between 142 and 199 mcg•hr/mL (>300 times the
425 human exposure at the proposed clinical dose).

426 **14 CLINICAL STUDIES**

427 **14.1 Treatment of Influenza**

428 Adults and Adolescents: The efficacy of RELENZA 10 mg inhaled twice daily for
429 5 days in the treatment of influenza has been evaluated in placebo-controlled studies conducted
430 in North America, the Southern Hemisphere, and Europe during their respective influenza
431 seasons. The magnitude of treatment effect varied between studies, with possible relationships to
432 population-related factors including amount of symptomatic relief medication used.

433 Populations Studied: The principal Phase III studies enrolled 1,588 patients aged
434 12 years and older (median age 34 years, 49% male, 91% Caucasian), with uncomplicated
435 influenza-like illness within 2 days of symptom onset. Influenza was confirmed by culture,
436 hemagglutination inhibition antibodies, or investigational direct tests. Of 1,164 patients with
437 confirmed influenza, 89% had influenza A and 11% had influenza B. These studies served as the
438 principal basis for efficacy evaluation, with more limited Phase II studies providing supporting
439 information where necessary. Following randomization to either zanamivir or placebo (inhaled
440 lactose vehicle), all patients received instruction and supervision by a healthcare professional for
441 the initial dose.

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

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

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

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

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

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

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

463 **Pediatric Patients:** The efficacy of RELENZA 10 mg inhaled twice daily for 5 days in
464 the treatment of influenza in pediatric patients has been evaluated in a placebo-controlled study
465 conducted in North America and Europe, enrolling 471 patients, aged 5 to 12 years (55% male,
466 90% Caucasian), within 36 hours of symptom onset. Of 346 patients with confirmed influenza,
467 65% had influenza A and 35% had influenza B. The definition of time to improvement included
468 no fever and parental assessment of no or mild cough and absent/minimal muscle and joint aches
469 or pains, sore throat, chills/feverishness, and headache. Median time to symptom improvement
470 was 1 day shorter in patients receiving zanamivir compared with placebo. No consistent
471 differences in rate of development of complications were observed between treatment groups.
472 Some fluctuation of symptoms was observed after the primary study endpoint in both treatment
473 groups.

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

479 **14.2 Prophylaxis of Influenza**

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

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

488 **Household Prophylaxis Studies:** Two studies assessed post-exposure prophylaxis in
489 household contacts of an index case. Within 1.5 days of onset of symptoms in an index case,
490 each household (including all family members aged ≥ 5 years) was randomized to RELENZA
491 10 mg inhaled once daily or placebo inhaled once daily for 10 days. In the first study only, each
492 index case was randomized to RELENZA 10 mg inhaled twice daily for 5 days or inhaled
493 placebo twice daily for 5 days. In this study, the proportion of households with at least 1 new
494 case of symptomatic laboratory-confirmed influenza was reduced from 19.0% (32 of
495 168 households) for the placebo group to 4.1% (7 of 169 households) for the group receiving
496 RELENZA.

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

500 **Seasonal Prophylaxis Studies:** Two seasonal prophylaxis studies assessed RELENZA
501 10 mg inhaled once daily versus placebo inhaled once daily for 28 days during community
502 outbreaks. The first study enrolled subjects aged 18 years or older (mean age 29 years) from 2
503 university communities. The majority of subjects were unvaccinated (86%). In this study, the
504 incidence of symptomatic laboratory-confirmed influenza was reduced from 6.1% (34 of 554)
505 for the placebo group to 2.0% (11 of 553) for the group receiving RELENZA.

506 The second seasonal prophylaxis study enrolled subjects aged 12 to 94 years (mean age
507 60 years) with 56% of them older than 65 years. Sixty-seven percent of the subjects were
508 vaccinated. In this study, the incidence of symptomatic laboratory-confirmed influenza was
509 reduced from 1.4% (23 of 1,685) for the placebo group to 0.2% (4 of 1,678) for the group
510 receiving RELENZA.

511 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

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

518 **17 PATIENT COUNSELING INFORMATION**

519 *See FDA-Approved Patient Labeling.*

520 **17.1 Bronchospasm**

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

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

528 **17.2 Concomitant Bronchodilator Use**

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

531 **17.3 Neuropsychiatric Events**

532 Patients with influenza (the flu), particularly children and adolescents, may be at an
533 increased risk of seizures, confusion, or abnormal behavior early in their illness. These events
534 may occur after beginning RELENZA or may occur when flu is not treated. These events are
535 uncommon but may result in accidental injury to the patient. Therefore, patients should be
536 observed for signs of unusual behavior and a healthcare professional should be contacted
537 immediately if the patient shows any signs of unusual behavior [see Warnings and Precautions
538 (5.3)].

539 **17.4 Instructions for Use**

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

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

546 **17.5 Risk of Influenza Transmission to Others**

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

549
550 RELENZA, DISKHALER, and ROTADISK are registered trademarks of GlaxoSmithKline.

551
552



553
554 GlaxoSmithKline
555 Research Triangle Park, NC 27709

556
557 ©2010, GlaxoSmithKline. All rights reserved.

558
559 RLZ:8PI

560
561

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[®]) intranasal in the past 2 weeks.

75

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

77 RELENZA is packaged in medicine disks called ROTADISKS[®] and is inhaled by mouth
78 using a delivery device called a DISKHALER[®]. 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 If you are not feeling well when you take RELENZA, you may faint or become
119 lightheaded after inhaling RELENZA. You should sit down in a relaxed position before inhaling

120 the dose of RELENZA, and you should only hold your breath for as long as is comfortable after
121 inhaling the dose.

122 If you are not feeling well, you are advised to have someone with you while you are
123 inhaling the dose of RELENZA.

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

127 Please refer to the section entitled “**Important Safety Information About RELENZA**”
128 for additional information.

129

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

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

134

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

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

140

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

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

145

146

PATIENT INSTRUCTIONS FOR USE



147

148

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

149

150

151

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

152

153

BEFORE YOU START:

154

155

**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.**

156

157

158

159

**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.**

160

161



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

163

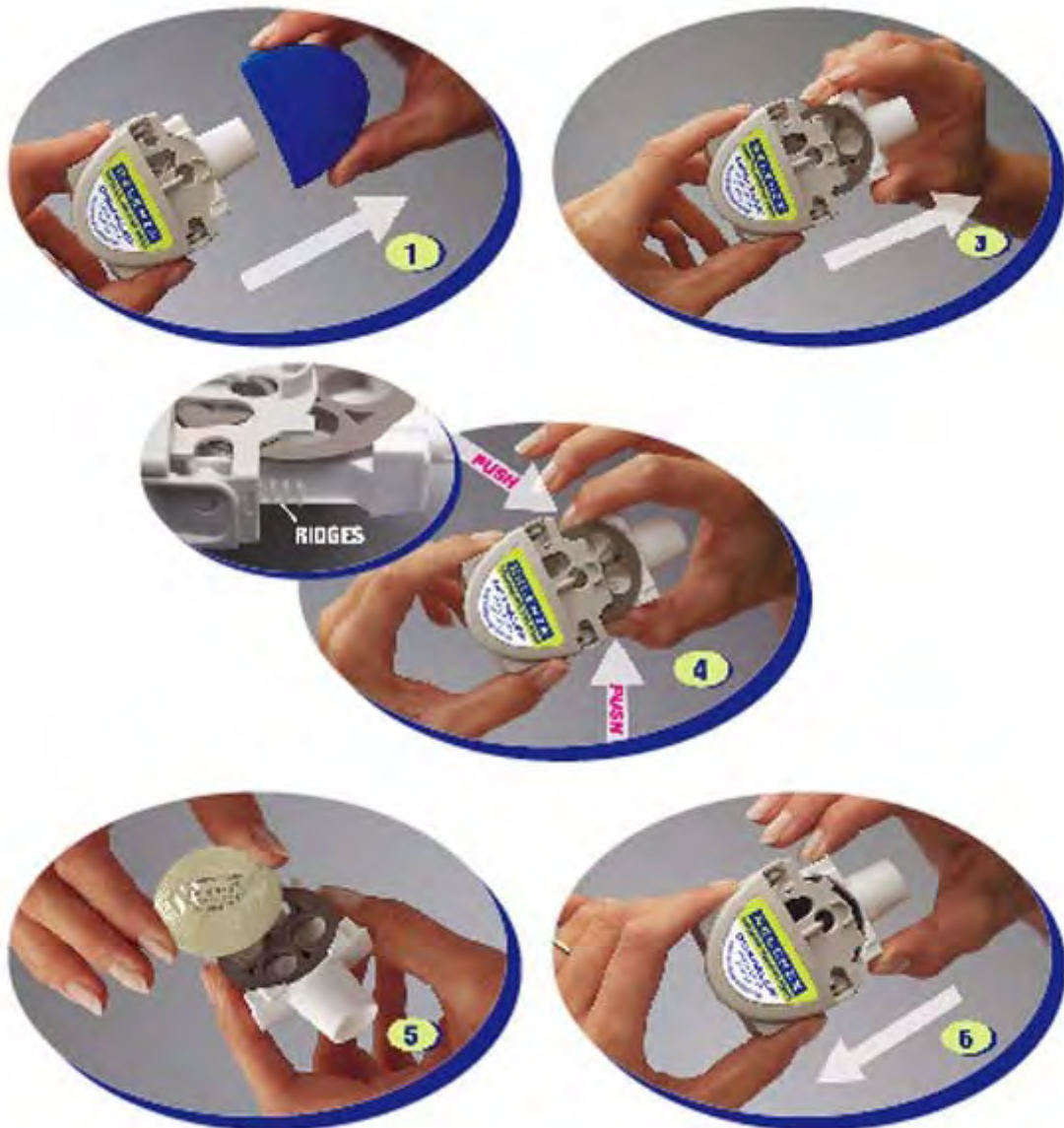
164 **Step A: Load the medicine into the DISKHALER**

165

166 1. Start by pulling off the blue cover.

167

- 168 2. **Always check inside the mouthpiece to make sure it is clear before each use. If foreign**
169 **objects are in the mouthpiece, they could be inhaled and cause serious harm.**
170
- 171 3. Pull the white mouthpiece by the edges to extend the white tray all the way.
172
- 173 4. Once the white tray is extended all the way, find the raised ridges on each side of it. Press in
174 these ridges, both sides at the same time, and **pull the whole white tray out of the**
175 **DISKHALER body.**
176
- 177 5. Place one silver medicine disk onto the dark brown wheel, flat side up. The four silver
178 blisters on the underside of the medicine disk will drop neatly into the four holes in the
179 wheel.
180
- 181 6. Push in the white tray as far as it will go. Now the DISKHALER is loaded with medicine.
182



183
184
185
186
187
188
189
190
191

Step B: Puncture the blister

Be sure to keep the DISKHALER level.

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

- 192 1. Be sure to keep the DISKHALER level so the medicine does not spill out.
193
194 2. Locate the half-circle flap with the name “RELENZA” on top of the DISKHALER.

195

196 3. Lift this flap from the outer edge until it cannot go any farther. Flap must be **straight up** for
197 the plastic needle to puncture both the **top** and **bottom** of the silver medicine disk inside.

198

199 4. Keeping the DISKHALER level, click the flap down into place.



200

201

202 **Step C: Inhale**

203

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

205

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

208

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

211

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

214

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

216

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

218

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



221
222
223
224
225
226
227
228
229
230
231
232
233
234

Step D: Move the medicine disk to the next blister

1. **Pull** the mouthpiece to extend the white tray, without removing it.
2. Then **push** it back until it clicks. This pull-push motion rotates the medicine disk to the next blister.
3. To take your next inhalation, repeat Steps B and C.

If all 4 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.



235

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[®] (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.

236

237

RELENZA, FLOVENT, ROTADISK, and DISKHALER are registered trademarks of GlaxoSmithKline.

238

239

FLUMIST is a registered trademark of MedImmune, Inc.

240

241



242

243

GlaxoSmithKline

244

Research Triangle Park, NC 27709

245

246

©2010, GlaxoSmithKline. All rights reserved.

247

248

December 2010

249

RLZ:4PIL