

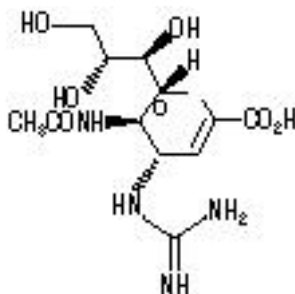
**PRESCRIBING INFORMATION**

**RELENZA<sup>®</sup>**  
**(zanamivir for inhalation)**

**For Oral Inhalation Only**  
**For Use with the DISKHALER<sup>®</sup> Inhalation Device**

**DESCRIPTION**

The active component of RELENZA is zanamivir. The chemical name of zanamivir is 5-(acetylamino)-4-[(aminoiminomethyl)-amino]-2,6-anhydro-3,4,5-trideoxy-D-glycero-D-galactonon-2-enonic acid. It has a molecular formula of C<sub>12</sub>H<sub>20</sub>N<sub>4</sub>O<sub>7</sub> and a molecular weight of 332.3. It has the following structural formula:



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

RELENZA is for administration to the respiratory tract by oral inhalation only. Each RELENZA ROTADISK<sup>®</sup> contains 4 regularly spaced double-foil blisters with each blister containing a powder mixture of 5 mg of zanamivir and 20 mg of lactose (which contains milk proteins). The contents of each blister are inhaled using a specially designed breath-activated plastic device for inhaling powder called the DISKHALER. After a RELENZA ROTADISK is loaded into the DISKHALER, a blister that contains medication is pierced and the zanamivir is dispersed into the air stream created when the patient inhales through the mouthpiece. The amount of drug delivered to the respiratory tract will depend on patient factors such as inspiratory flow. Under standardized in vitro testing, RELENZA ROTADISK delivers 4 mg of zanamivir from the DISKHALER device when tested at a pressure drop of 3 kPa (corresponding to a flow rate of about 62 to 65 L/min) for 3 seconds. In a study of 5 adult and 5 adolescent patients with obstructive airway diseases, the combined peak inspiratory flow rates (PIFR) ranged from 66 to 140 L/min. In a separate study of 16 pediatric patients, PIFR results were more variable; 4 did not achieve measurable flow rates, and PIFR for measurable inhalations by 12 children ranged from 30.5 to 122.4 L/min. Only 1 of 4 children under age 8 had a measurable flow rate (see CLINICAL PHARMACOLOGY: Pediatric Patients, INDICATIONS AND USAGE: Description of Clinical Studies, and PRECAUTIONS: Pediatric Use).

33 **MICROBIOLOGY**

34 **Mechanism of Action:** The mechanism of action of zanamivir is via inhibition of influenza  
35 virus neuraminidase with the possibility of alteration of virus particle aggregation and release.

36 **Antiviral Activity:** The antiviral activity of zanamivir against laboratory and clinical isolates of  
37 influenza virus was determined in cell culture assays. The concentrations of zanamivir required  
38 for inhibition of influenza virus were highly variable depending on the assay method used and  
39 virus isolate tested. The 50% and 90% effective concentrations (EC<sub>50</sub> and EC<sub>90</sub>) of zanamivir  
40 were in the range of 0.005 to 16.0 μM and 0.05 to >100 μM, respectively  
41 (1 μM = 0.33 mcg/mL). The relationship between the in vitro inhibition of influenza virus by  
42 zanamivir and the inhibition of influenza virus replication in humans has not been established.

43 **Resistance:** Influenza viruses with reduced susceptibility to zanamivir have been recovered  
44 in vitro by multiple passages of the virus in the presence of increasing concentrations of the drug.  
45 Genetic analysis of these viruses showed that the reduced susceptibility in vitro to zanamivir is  
46 associated with mutations that result in amino acid changes in the viral neuraminidase or viral  
47 hemagglutinin or both. Resistance mutations selected in vitro which result in neuraminidase  
48 amino acid substitutions include E119G/A/D and R292K. Mutations selected in vitro in  
49 hemagglutinin include: K68R, G75E, E114K, N145S, S165N, S186F, N199S, and K222T.

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

56 **Cross-Resistance:** Cross-resistance has been observed between some zanamivir-resistant and  
57 some oseltamivir-resistant influenza virus mutants generated in vitro. However, some of the  
58 in vitro zanamivir-induced resistance mutations, E119G/A/D and R292K, occurred at the same  
59 neuraminidase amino acid positions as in the clinical isolates resistant to oseltamivir, E119V and  
60 R292K. No studies have been performed to assess risk of emergence of cross-resistance during  
61 clinical use.

62 **Influenza Vaccine Interaction Study:** An interaction study (n = 138) was conducted to  
63 evaluate the effects of zanamivir (10 mg once daily) on the serological response to a single dose  
64 of trivalent inactivated influenza vaccine, as measured by hemagglutination inhibition titers.  
65 There was no clear difference in hemagglutination inhibition antibody titers at 2 weeks and  
66 4 weeks after vaccine administration between zanamivir and placebo recipients.

67 **Influenza Challenge Studies:** Antiviral activity of zanamivir was supported for infection  
68 with influenza A virus, and to a more limited extent for infection with influenza B virus, by  
69 Phase 1 studies in volunteers who received intranasal inoculations of challenge strains of  
70 influenza virus, and received an intranasal formulation of zanamivir or placebo starting before or  
71 shortly after viral inoculation.

72 **CLINICAL PHARMACOLOGY**

73 **Pharmacokinetics: Absorption and Bioavailability:** Pharmacokinetic studies of orally  
74 inhaled zanamivir indicate that approximately 4% to 17% of the inhaled dose is systemically  
75 absorbed. The peak serum concentrations ranged from 17 to 142 ng/mL within 1 to 2 hours  
76 following a 10-mg dose. The area under the serum concentration versus time curve (AUC<sub>∞</sub>)  
77 ranged from 111 to 1,364 ng•hr/mL.

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

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

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

85 **Special Populations: Impaired Hepatic Function:** The pharmacokinetics of zanamivir  
86 have not been studied in patients with impaired hepatic function.

87 **Impaired Renal Function:** Systemic exposure is limited after inhalation (see Absorption  
88 and Bioavailability). After a single intravenous dose of 4 mg or 2 mg of zanamivir in volunteers  
89 with mild/moderate or severe renal impairment, respectively, significant decreases in renal  
90 clearance (and hence total clearance: normals 5.3 L/hr, mild/moderate 2.7 L/hr, and severe  
91 0.8 L/hr; median values) and significant increases in half-life (normals 3.1 hr, mild/moderate  
92 4.7 hr, and severe 18.5 hr; median values) and systemic exposure were observed. Safety and  
93 efficacy have not been documented in the presence of severe renal insufficiency.

94 **Pediatric Patients:** The pharmacokinetics of zanamivir were evaluated in pediatric  
95 patients with signs and symptoms of respiratory illness. Sixteen patients, 6 to 12 years of age,  
96 received a single dose of 10-mg zanamivir dry powder via DISKHALER. Five patients had  
97 either undetectable zanamivir serum concentrations or had low drug concentrations (8.32 to  
98 10.38 ng/mL) that were not detectable after 1.5 hours. Eleven patients had C<sub>max</sub> median values of  
99 43 ng/mL (range 15 to 74) and AUC<sub>∞</sub> median values of 167 ng•hr/mL (range 58 to 279). Low or  
100 undetectable serum concentrations were related to lack of measurable PIFR in individual patients  
101 (see DESCRIPTION, INDICATIONS AND USAGE: Description of Clinical Studies, and  
102 PRECAUTIONS: Pediatric Use).

103 **Geriatric Patients:** The pharmacokinetics of zanamivir have not been studied in patients  
104 over 65 years of age (see PRECAUTIONS: Geriatric Use).

105 **Gender, Race, and Weight:** In a population pharmacokinetic analysis in patient studies,  
106 no clinically significant differences in serum concentrations and/or pharmacokinetic parameters  
107 (V/F, CL/F, ka, AUC<sub>0-3</sub>, C<sub>max</sub>, T<sub>max</sub>, CLr, and % excreted in urine) were observed when  
108 demographic variables (gender, age, race, and weight) and indices of infection (laboratory  
109 evidence of infection, overall symptoms, symptoms of upper respiratory illness, and viral titers)  
110 were considered. There were no significant correlations between measures of systemic exposure  
111 and safety parameters.

112 **Drug Interactions:** No clinically significant pharmacokinetic drug interactions are predicted  
113 based on data from in vitro studies.

114 Zanamivir is not a substrate nor does it affect cytochrome P450 (CYP) isoenzymes  
115 (CYP1A1/2, 2A6, 2C9, 2C18, 2D6, 2E1, and 3A4) in human liver microsomes.

## 116 **INDICATIONS AND USAGE**

117 **Treatment of Influenza:** RELENZA is indicated for treatment of uncomplicated acute illness  
118 due to influenza A and B virus in adults and pediatric patients 7 years of age and older who have  
119 been symptomatic for no more than 2 days (see Description of Clinical Studies and  
120 PRECAUTIONS).

121 **Prophylaxis of Influenza:** RELENZA is indicated in adults and pediatric patients 5 years of  
122 age and older for prophylaxis of influenza.

### 123 **Important Information on Use of RELENZA:**

- 124 • RELENZA is not recommended for treatment or prophylaxis of influenza in individuals with  
125 underlying airways disease (such as asthma or chronic obstructive pulmonary disease [see  
126 WARNINGS]) due to risk of serious bronchospasm.
- 127 • RELENZA has not been proven effective for treatment of influenza in individuals with  
128 underlying airways disease.
- 129 • RELENZA has not been proven effective for prophylaxis of influenza in the nursing home  
130 setting.
- 131 • RELENZA is not a substitute for early vaccination on an annual basis as recommended by the  
132 Centers for Disease Control's Immunization Practices Advisory Committee.

### 133 **Description of Clinical Studies: *Treatment of Influenza: Adults and Adolescents:***

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

139 ***Populations Studied:*** The principal Phase 3 studies enrolled 1,588 patients ages  
140 12 years and older (median age 34 years, 49% male, 91% Caucasian), with uncomplicated  
141 influenza-like illness within 2 days of symptom onset. Influenza was confirmed by culture,  
142 hemagglutination inhibition antibodies, or investigational direct tests. Of 1,164 patients with  
143 confirmed influenza, 89% had influenza A and 11% had influenza B. These studies served as the  
144 principal basis for efficacy evaluation, with more limited Phase 2 studies providing supporting  
145 information where necessary. Following randomization to either zanamivir or placebo (inhaled  
146 lactose vehicle), all patients received instruction and supervision by a healthcare professional for  
147 the initial dose.

148 ***Principal Results:*** The definition of time to improvement in major symptoms of  
149 influenza included no fever and self-assessment of “none” or “mild” for headache, myalgia,  
150 cough, and sore throat. A Phase 2 and a Phase 3 study conducted in North America (total of over

151 600 influenza-positive patients) suggested up to one day of shortening of median time to this  
152 defined improvement in symptoms in patients receiving zanamivir compared to placebo,  
153 although statistical significance was not reached in either of these studies. In a study conducted  
154 in the Southern Hemisphere (321 influenza-positive patients), a 1.5-day difference in median  
155 time to symptom improvement was observed. Additional evidence of efficacy was provided by  
156 the European study.

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

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

162 No consistent treatment effect was demonstrated in patients with underlying chronic medical  
163 conditions, including respiratory or cardiovascular disease (see WARNINGS and  
164 PRECAUTIONS).

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

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

169 **Pediatric Patients:** The efficacy of RELENZA 10 mg inhaled twice daily for 5 days in  
170 the treatment of influenza in pediatric patients has been evaluated in a placebo-controlled study  
171 conducted in North America and Europe, enrolling 471 patients, ages 5 to 12 years (55% male,  
172 90% Caucasian), within 36 hours of symptom onset. Of 346 patients with confirmed influenza,  
173 65% had influenza A and 35% had influenza B. The definition of time to improvement included  
174 no fever and parental assessment of no or mild cough and absent/minimal muscle and joint aches  
175 or pains, sore throat, chills/feverishness, and headache. Median time to symptom improvement  
176 was one day shorter in patients receiving zanamivir compared with placebo. No consistent  
177 differences in rate of development of complications were observed between treatment groups.  
178 Some fluctuation of symptoms was observed after the primary study endpoint in both treatment  
179 groups.

180 Although this study was designed to enroll children ages 5 to 12 years, the product is  
181 indicated only for children 7 years of age and older. This evaluation is based on the combination  
182 of lower estimates of treatment effect in 5- and 6-year-olds compared with the overall study  
183 population, and evidence of inadequate inhalation through the DISKHALER in a  
184 pharmacokinetic study (see DESCRIPTION, CLINICAL PHARMACOLOGY: Pediatric  
185 Patients, and PRECAUTIONS: Pediatric Use).

186 **Prophylaxis of Influenza:** The efficacy of RELENZA in preventing naturally occurring  
187 influenza illness has been demonstrated in 2 post-exposure prophylaxis studies in households and  
188 2 seasonal prophylaxis studies during community outbreaks of influenza. The primary efficacy  
189 endpoint in these studies was the incidence of symptomatic, laboratory-confirmed influenza,  
190 defined as the presence of 2 or more of the following symptoms: oral temperature

191  $\geq 100^{\circ}\text{F}/37.8^{\circ}\text{C}$  or feverishness, cough, headache, sore throat, and myalgia; and laboratory  
192 confirmation of influenza A or B by culture, PCR, or seroconversion (defined as a 4-fold  
193 increase in convalescent antibody titer from baseline).

194 Two studies assessed post-exposure prophylaxis in household contacts of an index case.  
195 Within 1.5 days of onset of symptoms in an index case, each household (including all family  
196 members  $\geq 5$  years of age) was randomized to RELENZA 10 mg inhaled once daily or placebo  
197 inhaled once daily for 10 days. In the first study only, each index case was randomized to  
198 RELENZA 10 mg inhaled twice daily for 5 days or inhaled placebo twice daily for 5 days. In  
199 this study, the proportion of households with at least 1 new case of symptomatic  
200 laboratory-confirmed influenza was reduced from 19.0% (32 of 168 households) for the placebo  
201 group to 4.1% (7 of 169 households) for the group receiving RELENZA.

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

205 Two seasonal prophylaxis studies assessed RELENZA 10 mg inhaled once daily versus  
206 placebo inhaled once daily for 28 days during community outbreaks. The first study enrolled  
207 subjects 18 years of age or greater (mean age 29 years) from two university communities. The  
208 majority of subjects were unvaccinated (86%). In this study, the incidence of symptomatic  
209 laboratory-confirmed influenza was reduced from 6.1% (34 of 554) for the placebo group to  
210 2.0% (11 of 553) for the group receiving RELENZA.

211 The second seasonal prophylaxis study enrolled subjects 12 to 94 years of age (mean age  
212 60 years) with 56% of them older than 65 years of age. Sixty-seven percent of the subjects were  
213 vaccinated. In this study, the incidence of symptomatic laboratory-confirmed influenza was  
214 reduced from 1.4% (23 of 1,685) for the placebo group to 0.2% (4 of 1,678) for the group  
215 receiving RELENZA.

## 216 **CONTRAINDICATIONS**

217 RELENZA is contraindicated in patients with a known hypersensitivity to any component of  
218 the formulation (see DESCRIPTION).

## 219 **WARNINGS**

220 **RELENZA IS NOT RECOMMENDED FOR TREATMENT OR PROPHYLAXIS OF**  
221 **INFLUENZA IN INDIVIDUALS WITH UNDERLYING AIRWAYS DISEASE (SUCH AS**  
222 **ASTHMA OR CHRONIC OBSTRUCTIVE PULMONARY DISEASE) (see**  
223 **INDICATIONS AND USAGE).**

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

227 **RELENZA SHOULD BE DISCONTINUED IN ANY PATIENT WHO DEVELOPS**  
228 **BRONCHOSPASM OR DECLINE IN RESPIRATORY FUNCTION; immediate**  
229 **treatment and hospitalization may be required.** Some patients without prior pulmonary

230 disease may also have respiratory abnormalities from acute respiratory infection that could  
231 resemble adverse drug reactions or increase patient vulnerability to adverse drug reactions.

232 Bronchospasm was documented following administration of zanamivir in 1 of 13 patients  
233 with mild or moderate asthma (but without acute influenza-like illness) in a Phase 1 study. In  
234 interim results from an ongoing treatment study in patients with acute influenza-like illness  
235 superimposed on underlying asthma or chronic obstructive pulmonary disease, more patients on  
236 zanamivir than on placebo experienced greater than 20% decline in FEV<sub>1</sub> or peak expiratory  
237 flow rate.

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

## 243 **PRECAUTIONS**

244 **General:** Patients should be instructed in the use of the delivery system. Instructions  
245 should include a demonstration whenever possible. Patients should read and follow carefully  
246 the Patient Instructions for Use accompanying the product. Effective and safe use of RELENZA  
247 requires proper use of the DISKHALER to inhale the drug.

248 There is no evidence for efficacy of zanamivir in any illness caused by agents other than  
249 influenza virus A and B.

250 No data are available to support safety or efficacy in patients who begin treatment after  
251 48 hours of symptoms.

252 Safety and efficacy of repeated treatment courses have not been studied.

253 **Allergic Reactions:** Allergic-like reactions, including oropharyngeal edema, serious skin  
254 rashes, and anaphylaxis have been reported in post-marketing experience with RELENZA.  
255 RELENZA should be stopped and appropriate treatment instituted if an allergic reaction occurs  
256 or is suspected.

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

260 **Prevention of Influenza:** Use of zanamivir should not affect the evaluation of individuals for  
261 annual influenza vaccination in accordance with guidelines of the Centers for Disease Control  
262 and Prevention Advisory Committee on Immunization Practices.

263 **Limitations of Populations Studied:** Safety and efficacy have not been demonstrated in  
264 patients with high-risk underlying medical conditions (see INDICATIONS AND USAGE:  
265 Description of Clinical Studies, and WARNINGS). No information is available regarding  
266 treatment of influenza in patients with any medical condition sufficiently severe or unstable  
267 to be considered at imminent risk of requiring inpatient management.

268 **Information for Patients:** Patients should be instructed in use of the delivery system.  
269 Instructions should include a demonstration whenever possible.

270 For the proper use of RELENZA, the patient should read and follow carefully the  
271 accompanying Patient Instructions for Use.

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

274 **Patients should be advised of the risk of bronchospasm, especially in the setting of**  
275 **underlying airways disease, and should stop RELENZA and contact their physician if they**  
276 **experience increased respiratory symptoms during treatment such as worsening wheezing,**  
277 **shortness of breath, or other signs or symptoms of bronchospasm (see WARNINGS). If a**  
278 **decision is made to prescribe RELENZA for a patient with asthma or chronic obstructive**  
279 **pulmonary disease, the patient should be made aware of the risks and should have a**  
280 **fast-acting bronchodilator available.** Patients scheduled to take inhaled bronchodilators at the  
281 same time as RELENZA should be advised to use their bronchodilators before taking  
282 RELENZA.

283 **Drug Interactions:** No clinically significant pharmacokinetic drug interactions are predicted  
284 based on data from in vitro studies.

285 **Carcinogenesis, Mutagenesis, and Impairment of Fertility: *Carcinogenesis:*** In  
286 2-year carcinogenicity studies conducted in rats and mice using a powder formulation  
287 administered through inhalation, zanamivir induced no statistically significant increases in  
288 tumors over controls. The maximum daily exposures in rats and mice were approximately 23 to  
289 25 and 20 to 22 times, respectively, greater than those in humans at the proposed clinical dose  
290 based on AUC comparisons.

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

295 ***Impairment of Fertility:*** The effects of zanamivir on fertility and general reproductive  
296 performance were investigated in male (dosed for 10 weeks prior to mating, and throughout  
297 mating, gestation/lactation, and shortly after weaning) and female rats (dosed for 3 weeks prior  
298 to mating through day 19 of pregnancy, or day 21 post partum) at IV doses 1, 9, and  
299 90 mg/kg/day. Zanamivir did not impair mating or fertility of male or female rats, and did not  
300 affect the sperm of treated male rats. The reproductive performance of the F1 generation born to  
301 female rats given zanamivir was not affected. Based on a subchronic study in rats at a  
302 90-mg/kg/day IV dose, AUC values ranged between 142 and 199 mcg•hr/mL (>300 times the  
303 human exposure at the proposed clinical dose).

304 **Pregnancy:** Pregnancy Category C. Embryo/fetal development studies were conducted in rats  
305 (dosed from days 6 to 15 of pregnancy) and rabbits (dosed from days 7 to 19 of pregnancy) using  
306 the same IV doses. Pre- and post-natal developmental studies were performed in rats (dosed from  
307 day 16 of pregnancy until litter day 21 to 23). In all studies, intravenous (1, 9, and 90 mg/kg/day)

308 instead of the inhalational route of drug administration was used. No malformations, maternal  
309 toxicity, or embryotoxicity were observed in pregnant rats or rabbits and their fetuses. Because  
310 of insufficient blood sampling timepoints in both rat and rabbit reproductive toxicity studies,  
311 AUC values were not available. However, in a subchronic study in rats at the 90-mg/kg/day IV  
312 dose, the AUC values were greater than 300 times the human exposure at the proposed clinical  
313 dose.

314 An additional embryo/fetal study, in a different strain of rat, was conducted using  
315 subcutaneous administration of zanamivir, 3 times daily, at doses of 1, 9, or 80 mg/kg during  
316 days 7 to 17 of pregnancy. There was an increase in the incidence rates of a variety of minor  
317 skeleton alterations and variants in the exposed offspring in this study. Based on AUC  
318 measurements, the high dose in the study produced an exposure greater than 1,000 times the  
319 human exposure at the proposed clinical dose. However, the individual incidence rate of each  
320 skeletal alteration or variant, in most instances, remained within the background rates of the  
321 historical occurrence in the strain studied.

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

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

328 **Nursing Mothers:** Studies in rats have demonstrated that zanamivir is excreted in milk.  
329 However, nursing mothers should be instructed that it is not known whether zanamivir is  
330 excreted in human milk. Because many drugs are excreted in human milk, caution should be  
331 exercised when RELENZA is administered to a nursing mother.

332 **Pediatric Use:** Safety and effectiveness of RELENZA for treatment of influenza have not been  
333 assessed in pediatric patients less than 7 years of age.

334 The safety and effectiveness of RELENZA have been studied in a Phase 3 treatment study in  
335 pediatric patients, where 471 children 5 to 12 years of age received zanamivir or placebo (see  
336 INDICATIONS AND USAGE: Description of Clinical Studies, ADVERSE REACTIONS, and  
337 DOSAGE AND ADMINISTRATION). In a Phase 1 study of 16 children ages 6 to 12 years with  
338 signs and symptoms of respiratory disease, 4 did not produce a measurable peak inspiratory flow  
339 rate (PIFR) through the DISKHALER (3 with no adequate inhalation on request, 1 with missing  
340 data), 9 had measurable PIFR on each of 2 inhalations, and 3 achieved measurable PIFR on only  
341 1 of 2 inhalations. Neither of two 6-year-olds and one of two 7-year-olds produced measurable  
342 PIFR. Overall, 8 of the 16 children (including all those under 8 years old) either did not produce  
343 measurable inspiratory flow through the DISKHALER or produced peak inspiratory flow rates  
344 below the 60 L/min considered optimal for the device under standardized in vitro testing; lack of  
345 measurable flow rate was related to low or undetectable serum concentrations (see  
346 DESCRIPTION, CLINICAL PHARMACOLOGY: Pediatric Patients, and INDICATIONS AND  
347 USAGE: Description of Clinical Studies). Prescribers should carefully evaluate the ability of

348 young children to use the delivery system if prescription of RELENZA is considered. When  
349 RELENZA is prescribed for children, it should be used only under adult supervision and with  
350 attention to proper use of the delivery system.

351 Adolescents were included in the three principal Phase 3 adult treatment studies. In these  
352 studies, 67 patients were 12 to 16 years of age. No definite differences in safety and efficacy  
353 were observed between these adolescent patients and young adults.

354 In addition, the safety and effectiveness of RELENZA for prophylaxis of influenza have been  
355 studied in four Phase 3 studies where 273 children 5 to 11 years of age and 239 adolescents 12 to  
356 16 years of age received RELENZA. No differences in safety and effectiveness were observed  
357 between pediatric and adult subjects.

358 **Geriatric Use:** Of the total number of patients in 6 clinical studies of RELENZA for treatment  
359 of influenza, 59 were 65 and over, while 24 were 75 and over. Of the total number of patients in  
360 4 clinical studies of RELENZA for prophylaxis of influenza in households and community  
361 settings, 954 were 65 and over, while 347 were 75 and over. No overall differences in safety or  
362 effectiveness were observed between these subjects and younger patients, and other reported  
363 clinical experience has not identified differences in responses between the elderly and younger  
364 patients, but greater sensitivity of some older individuals cannot be ruled out.

365 In 2 additional studies of RELENZA for prophylaxis of influenza in the nursing home setting,  
366 efficacy was not demonstrated (see INDICATIONS AND USAGE). Elderly subjects may need  
367 assistance with use of the device.

## 368 **ADVERSE REACTIONS**

369 See **WARNINGS and PRECAUTIONS for information about risk of serious adverse**  
370 **events such as bronchospasm and allergic-like reactions, and for safety information in**  
371 **patients with underlying airways disease.**

372 Because the placebo consisted of inhaled lactose powder, which is also the vehicle for the  
373 active drug, some adverse events occurring at similar frequencies in different treatment groups  
374 could be related to lactose vehicle inhalation.

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

380

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

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

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

386

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

389 The most frequent laboratory abnormalities in Phase 3 treatment studies included elevations  
390 of liver enzymes and CPK, lymphopenia, and neutropenia. These were reported in similar  
391 proportions of zanamivir and lactose vehicle placebo recipients with acute influenza-like illness.

392 **Clinical Trials in Pediatric Patients:** Adverse events that occurred with an incidence  
393  $\geq 1.5\%$  in children receiving treatment doses of RELENZA in two Phase 3 studies are listed in  
394 Table 2. This table shows adverse events occurring in pediatric patients 5 to 12 years old  
395 receiving RELENZA 10 mg inhaled twice daily, and placebo inhaled twice daily (where placebo  
396 consisted of the same lactose vehicle used in RELENZA).

397

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

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

400 \* Includes a subset of patients receiving RELENZA for treatment of influenza in a prophylaxis  
401 study.

402

403 In 1 of the 2 studies described in Table 2, some additional information is available from  
404 children (5 to 12 years old) without acute influenza-like illness who received an investigational  
405 prophylaxis regimen of RELENZA; 132 children received RELENZA and 145 children received  
406 placebo. Among these children, nasal signs and symptoms (zanamivir 20%, placebo 9%), cough  
407 (zanamivir 16%, placebo 8%), and throat/tonsil discomfort and pain (zanamivir 11%, placebo  
408 6%) were reported more frequently with RELENZA than placebo. In a subset with chronic  
409 pulmonary disease, lower respiratory adverse events (described as asthma, cough, or viral  
410 respiratory infections which could include influenza-like symptoms) were reported in 7 of 7  
411 zanamivir recipients and 5 of 12 placebo recipients.

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

416

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

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

419 \* In prophylaxis studies symptoms associated with influenza-like illness were captured as  
420 adverse events; subjects were enrolled during a winter respiratory season during which time  
421 any symptoms that occurred were captured as adverse events.  
422

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

426

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

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

429

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

432

433 **Observed During Clinical Practice:** In addition to adverse events reported from clinical  
434 trials, the following events have been identified during post-marketing use of zanamivir  
435 (RELENZA). Because they are reported voluntarily from a population of unknown size,  
436 estimates of frequency cannot be made. These events have been chosen for inclusion due to a  
437 combination of their seriousness, frequency of reporting, or potential causal connection to  
438 zanamivir (RELENZA).

439

**General:** Allergic or allergic-like reaction, including oropharyngeal edema (see  
440 PRECAUTIONS).

- 441 **Cardiac:** Arrhythmias, syncope.  
442 **Neurologic:** Seizures.  
443 **Respiratory:** Bronchospasm, dyspnea (see WARNINGS and PRECAUTIONS).  
444 **Skin:** Facial edema; rash, including serious cutaneous reactions (see PRECAUTIONS).

#### 445 **OVERDOSAGE**

446 There have been no reports of overdose from administration of RELENZA. Doses of  
447 zanamivir up to 64 mg/day have been administered by nebulizer. Additionally, doses of up to  
448 1,200 mg/day for 5 days have been administered intravenously. Adverse effects were similar to  
449 those seen in clinical studies at the recommended dose.

#### 450 **DOSAGE AND ADMINISTRATION**

451 RELENZA is for administration to the respiratory tract by oral inhalation only, using the  
452 DISKHALER device provided. **Patients should be instructed in the use of the delivery**  
453 **system. Instructions should include a demonstration whenever possible. If RELENZA is**  
454 **prescribed for children, it should be used only under adult supervision and instruction, and**  
455 **the supervising adult should first be instructed by a healthcare professional (see**  
456 **PRECAUTIONS).**

457 Patients scheduled to use an inhaled bronchodilator at the same time as RELENZA should use  
458 their bronchodilator before taking RELENZA (see WARNINGS and PRECAUTIONS regarding  
459 patients with underlying airways disease and other medical conditions).

460 **Treatment:** The recommended dose of RELENZA for treatment of influenza in adults and  
461 pediatric patients ages 7 years of age and older is 2 inhalations (one 5-mg blister per inhalation  
462 for a total dose of 10 mg) twice daily (approximately 12 hours apart) for 5 days. Two doses  
463 should be taken on the first day of treatment whenever possible provided there is at least 2 hours  
464 between doses. On subsequent days, doses should be about 12 hours apart (e.g., morning and  
465 evening) at approximately the same time each day. There are no data on the effectiveness of  
466 treatment with RELENZA when initiated more than 2 days after the onset of signs or symptoms.

467 **Prophylaxis: Household Setting:** The recommended dose of RELENZA for prophylaxis of  
468 influenza in adults and pediatric patients 5 years of age and older in a household setting is 10 mg  
469 once daily for 10 days. The 10-mg dose is provided by 2 inhalations (one 5-mg blister per  
470 inhalation). The dose should be administered at approximately the same time each day. There are  
471 no data on the effectiveness of prophylaxis with RELENZA in a household setting when initiated  
472 more than 1.5 days after the onset of signs or symptoms in the index case.

473 **Community Outbreaks:** The recommended dose of RELENZA for prophylaxis of  
474 influenza in adults and adolescents in a community setting is 10 mg once daily for 28 days. The  
475 10-mg dose is provided by 2 inhalations (one 5-mg blister per inhalation). The dose should be  
476 administered at approximately the same time each day. There are no data on the effectiveness of  
477 prophylaxis with RELENZA in a community outbreak when initiated more than 5 days after the  
478 outbreak was identified in the community. The safety and effectiveness of prophylaxis with  
479 RELENZA have not been evaluated for longer than 28 days duration.

480 **HOW SUPPLIED**

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

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

487

488



489

490 GlaxoSmithKline

491 Research Triangle Park, NC 27709

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1 **PATIENT INFORMATION ABOUT:**

2 **RELENZA<sup>®</sup>**

3 **(zanamivir for inhalation)**

4  
5 This leaflet contains important patient information about RELENZA (zanamivir for inhalation),  
6 and should be read completely before beginning treatment. It does not, however, take the place  
7 of discussions with your healthcare provider about your medical condition or your treatment.

8 This summary does not list all benefits and risks of RELENZA. The medication described here  
9 can only be prescribed and dispensed by a licensed healthcare provider, who has information  
10 about your medical condition and more information about the drug, including how to take it,  
11 what to expect, and potential side effects. If you have any questions about RELENZA, talk with  
12 your healthcare provider.

13  
14 **What is RELENZA?**

15 RELENZA (ruh-LENS-uh) is a medicine for the treatment of influenza (flu, infection caused by  
16 influenza virus) and for reducing the chance of getting the flu in community and household  
17 settings. It belongs to a group of medicines called neuraminidase inhibitors. These medications  
18 attack the influenza virus and prevent it from spreading inside your body. RELENZA treats the  
19 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 they used  
23 RELENZA. Many but not all of these patients had previous asthma or chronic obstructive  
24 pulmonary disease. RELENZA has not been shown to shorten the duration of influenza in people  
25 with these diseases. Because of the risk of side effects and because it has not been shown to help  
26 them, RELENZA is not recommended for people with chronic respiratory disease such as asthma  
27 or chronic obstructive pulmonary disease.

28 If you develop worsening respiratory symptoms such as wheezing or shortness of breath, stop  
29 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 need  
37 different kinds of treatment. Contact your healthcare provider if you feel worse or develop new  
38 symptoms during or after treatment, or if your influenza symptoms do not start to get better.

39 **Who should not take RELENZA?**

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

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

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

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

52  
53 **Who should consider taking RELENZA?**

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

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

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

63  
64 **Can I take other medications with RELENZA?**

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

72  
73 **How and when should I take RELENZA?**

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

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

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

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

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

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

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

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

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

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

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

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

#### 112 **Should I get a flu shot?**

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

#### 115 **What if I am pregnant or nursing?**

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

#### 120 **How and where should I store RELENZA?**

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

129

130

**PATIENT INSTRUCTIONS FOR USE**

131

**RELENZA<sup>®</sup>**

132

**(zanamivir for inhalation)**

133

134

135

**IMPORTANT: Read Step-by-Step Instructions  
before using the DISKHALER<sup>®</sup>.**

136

137

138

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

139

140

**BEFORE YOU START:**

141

142

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

143

144

145

146

**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.**

147

148

149

Parts of the DISKHALER:

150

**Step-by-step instructions for using the DISKHALER<sup>®</sup>**

151

152

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

153

154

1. Start by pulling off the blue cover.

155

156

2. **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.**

157

158

159

3. Pull the white mouthpiece by the edges to extend the white tray all the way.

160

161

4. Once the white tray is extended all the way, find the raised ridges on each side of it. Press in these ridges, both sides at the same time, and **pull the whole white tray out of the DISKHALER body.**

162

163

164

165 5. Place one silver medicine disk onto the dark brown wheel, flat side up. The four silver  
166 blisters on the underside of the medicine disk will drop neatly into the four holes in the  
167 wheel.

168

169 6. Push in the white tray as far as it will go. Now the DISKHALER is loaded with medicine.

170

171

172 **Step B: Puncture the blister**

173

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

175

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

179

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

181

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

183

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

186

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

188

189

190 **Step C: Inhale**

191

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

193

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

196

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

199

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

202

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

204

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

206  
207  
208  
209  
210  
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212  
213  
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215  
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217  
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219  
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222  
223

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

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

**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.

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