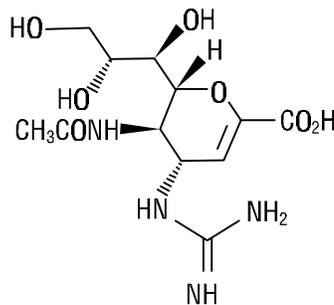


**RELENZA®****(zanamivir for inhalation)****For Oral Inhalation Only****For Use with the DISKHALER® Inhalation Device**

**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  $C_{12}H_{20}N_4O_7$  and a molecular weight of 332.3. It has the following structural formula:



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

RELENZA is for administration to the respiratory tract by oral inhalation only. Each RELENZA ROTADISK® contains 4 regularly spaced double-foil blisters with each blister containing a powder mixture of 5 mg of zanamivir and 20 mg of lactose. 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 ranged from 66 to 140 L/min.

**MICROBIOLOGY:**

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

**RELENZA®  
(zanamivir for inhalation)**

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

40 **Drug Resistance:** Influenza viruses with reduced susceptibility to zanamivir have been recovered in  
41 vitro by passage of the virus in the presence of increasing concentrations of the drug. Genetic  
42 analysis of these viruses showed that the reduced susceptibility in vitro to zanamivir is associated  
43 with mutations that result in amino acid changes in the viral neuraminidase or viral hemagglutinin or  
44 both.

45 In an immunocompromised patient infected with influenza B virus, a variant virus emerged after  
46 treatment with an investigational nebulized solution of zanamivir for 2 weeks. Analysis of this variant  
47 showed a hemagglutinin mutation (Thr 198 Ile) which resulted in a reduced affinity for human cell  
48 receptors, and a mutation in the neuraminidase active site (Arg 152 Lys) which reduced the  
49 enzyme's activity to zanamivir by 1000-fold.

50 Insufficient information is available to characterize the risk of emergence of zanamivir resistance  
51 in clinical use.

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

57 **Influenza Challenge Studies:** Antiviral activity of zanamivir was supported for influenza A, and to a  
58 more limited extent for influenza B, by Phase I studies in volunteers who received intranasal  
59 inoculations of challenge strains of influenza virus, and received an intranasal formulation of  
60 zanamivir or placebo starting before or shortly after viral inoculation.

61

62 **CLINICAL PHARMACOLOGY:**

63 **Pharmacokinetics: Absorption and Bioavailability:** Pharmacokinetic studies of orally inhaled  
64 zanamivir indicate that approximately 4% to 17% of the inhaled dose is systemically absorbed. The  
65 peak serum concentrations ranged from 17 to 142 ng/mL within 1 to 2 hours following a 10-mg dose.  
66 The area under the serum concentration versus time curve (AUC<sub>∞</sub>) ranged from 111 to  
67 1364 ng•h/mL.

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

**RELENZA®**  
**(zanamivir for inhalation)**

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

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

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

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

84       **Pediatric Patients:** The pharmacokinetics of zanamivir have not been studied in pediatric  
85 patients under 12 years of age with influenza (see PRECAUTIONS: Pediatric Use).

86       **Geriatric Patients:** The pharmacokinetics of zanamivir have not been studied in patients over  
87 65 years of age (see PRECAUTIONS: Geriatric Use).

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

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

96       Zanamivir is not a substrate nor does it affect cytochrome P450 (CYP) isoenzymes (CYP1A1/2,  
97 2A6, 2C9, 2C18, 2D6, 2E1, and 3A4) in human liver microsomes.

98

99       **INDICATIONS AND USAGE:** RELENZA is indicated for treatment of uncomplicated acute illness  
100 due to influenza virus in adults and adolescents 12 years and older who have been symptomatic for  
101 no more than 2 days. This indication is based on studies in which the predominant influenza  
102 infections were influenza A, and a limited number of patients with influenza B were also enrolled (see  
103 Description of Clinical Studies and PRECAUTIONS).

104       **Description of Clinical Studies:** The efficacy of RELENZA 10 mg inhaled twice daily for 5 days in  
105 the treatment of influenza has been evaluated in placebo-controlled studies conducted in North

**RELENZA®  
(zanamivir for inhalation)**

106 America, the Southern Hemisphere, and Europe during their respective influenza seasons. The  
107 magnitude of treatment effect varied between studies, with possible relationships to  
108 population-related factors including amount of symptomatic relief medication used.

109 **Populations Studied:** The principal phase 3 studies enrolled 1588 patients ages 12 years and  
110 older (median age 34 years, 49% male, 91% Caucasian), with uncomplicated influenza-like illness  
111 within 2 days of symptom onset. Influenza was confirmed by culture, hemagglutination inhibition  
112 antibodies, or investigational direct tests. Of 1164 patients with confirmed influenza, 89% had  
113 influenza A and 11% had influenza B. These studies served as the principal basis for efficacy  
114 evaluation, with more limited phase 2 studies providing supporting information where necessary.  
115 Following randomization to either zanamivir or placebo (inhaled lactose vehicle), all patients received  
116 instruction and supervision by a healthcare professional for the initial dose.

117 **Principal Results:** The definition of time to improvement in major symptoms of influenza included  
118 no fever and self-assessment of “none” or “mild” for headache, myalgia, cough, and sore throat. A  
119 phase 2 and a phase 3 study conducted in North America (total of over 600 influenza-positive  
120 patients) suggested up to one day of shortening of median time to this defined improvement in  
121 symptoms in patients receiving zanamivir compared to placebo, although statistical significance was  
122 not reached in either of these studies. In a study conducted in the Southern Hemisphere  
123 (321 influenza-positive patients), a 1.5-day difference in median time to symptom improvement was  
124 observed. Additional evidence of efficacy was provided by the European study.

125 **Other Findings:**

- 126 • There was no consistent difference in treatment effect in patients with influenza A compared to  
127 influenza B; however, these trials enrolled smaller numbers of patients with influenza B and thus  
128 provided less evidence in support of efficacy in influenza B (see PRECAUTIONS).
- 129 • In general, patients with lower temperature (e.g., 38.2°C or less) or investigator-rated as having  
130 less severe symptoms at entry derived less benefit from therapy.
- 131 • No consistent treatment effect was demonstrated in patients with underlying chronic medical  
132 conditions, including respiratory or cardiovascular disease (see PRECAUTIONS).
- 133 • No consistent differences in rate of development of complications were observed between  
134 treatment groups.
- 135 • Some fluctuation of symptoms was observed after the primary study endpoint in both treatment  
136 groups.

137

138 **CONTRAINDICATIONS:** RELENZA is contraindicated in patients with a known hypersensitivity to  
139 any component of the formulation.

140

141 **PRECAUTIONS:**

**RELENZA®  
(zanamivir for inhalation)**

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

146 There is no evidence for efficacy of zanamivir in any illness caused by agents other than influenza  
147 virus A and B. Data on treatment of influenza B are limited (see INDICATIONS AND USAGE:  
148 Description of Clinical Studies).

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

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

152 **Patients with Underlying Respiratory Disease:** Safety and efficacy have not been demonstrated  
153 in patients with underlying chronic pulmonary disease. In particular, this product has not been shown  
154 to be effective, and may carry risk, in patients with severe or decompensated chronic obstructive  
155 pulmonary disease or asthma. Bronchospasm was documented following administration of zanamivir  
156 in 1 of 13 patients with mild or moderate asthma (but without acute influenza-like illness) in a phase  
157 1 study. In interim results from an ongoing treatment study in patients with acute influenza-like illness  
158 superimposed on underlying asthma or chronic obstructive pulmonary disease, more patients on  
159 zanamivir than on placebo experienced greater than 20% decline in FEV<sub>1</sub> or peak expiratory flow  
160 rate. Some patients with underlying respiratory disease may experience bronchospasm and/or  
161 decline in lung function when treated with zanamivir. Any patient who develops bronchospasm or  
162 decline in lung function should stop the drug. Patients with underlying respiratory disease should be  
163 instructed to have a fast-acting inhaled bronchodilator available when treated with zanamivir.

164 **Prevention of Influenza:** Use of zanamivir should not affect the evaluation of individuals for annual  
165 influenza vaccination in accordance with guidelines of the Centers for Disease Control and  
166 Prevention Advisory Committee on Immunization Practices. Safety and efficacy of zanamivir have  
167 not been established for prophylactic use of zanamivir to prevent influenza.

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

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

175 For the proper use of RELENZA, the patient should read and follow carefully the accompanying  
176 Patient's Instructions for Use.

177 Patients should be advised to finish the entire 5-day course of treatment even if they start to feel  
178 better sooner.

**RELENZA®  
(zanamivir for inhalation)**

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

181 **Patients with asthma or chronic obstructive pulmonary disease should be advised of the**  
182 **potential risk of bronchospasm with zanamivir**, should have a fast-acting inhaled bronchodilator  
183 available, and should stop zanamivir and contact their physician promptly if they experience  
184 worsening respiratory symptoms. Patients scheduled to take inhaled bronchodilators at the same  
185 time as RELENZA should be advised to use their bronchodilators before taking RELENZA.

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

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

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

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

207 **Pregnancy:** Pregnancy Category B. Embryo/fetal development studies were conducted in rats  
208 (dosed from days 6 to 15 of pregnancy) and rabbits (dosed from days 7 to 19 of pregnancy) using  
209 the same IV doses. Pre- and post-natal developmental studies were performed in rats (dosed from  
210 day 16 of pregnancy until litter day 21 to 23). In all studies, intravenous (1, 9, and 90 mg/kg per day)  
211 instead of the inhalational route of drug administration was used. No malformations, maternal  
212 toxicity, or embryotoxicity were observed in pregnant rats or rabbits and their fetuses. Because of  
213 insufficient blood sampling timepoints in both rat and rabbit reproductive toxicity studies, AUC values  
214 were not available. However, in a subchronic study in rats at the 90-mg/kg per day IV dose, the AUC  
215 values were greater than 300 times the human exposure at the proposed clinical dose.

**RELENZA®  
(zanamivir for inhalation)**

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

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

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

225 **Pediatric Use:** Safety and effectiveness in pediatric patients below 12 years of age have not been  
226 established. In the three principal phase 3 treatment studies, 67 patients were 12 to 16 years of age.  
227 No definite differences in safety and efficacy were observed between these adolescent patients and  
228 young adults.

229 **Geriatric Use:** Of the total number of patients in 6 clinical treatment studies of RELENZA, 59 were  
230 65 and over, while 24 were 75 and over. No overall differences in safety or effectiveness were  
231 observed between these subjects and younger patients, and other reported clinical experience has  
232 not identified differences in responses between the elderly and younger patients, but greater  
233 sensitivity of some older individuals cannot be ruled out.

234

235 **ADVERSE REACTIONS:** Adverse events that occurred with an incidence 1.5% in treatment  
236 studies are listed in Table 1. This table shows adverse events occurring in patients receiving  
237 RELENZA 10 mg inhaled twice daily, RELENZA in all inhalation regimens, and placebo inhaled twice  
238 daily (where placebo consisted of the same lactose vehicle used in RELENZA).

239

240 **Table 1: Summary of Adverse Events 1.5% Incidence During Treatment**

Adverse Event	RELENZA		Placebo (Lactose Vehicle†) (n = 1520)
	10 mg b.i.d. Inhaled (n = 1132)	All Dosing Regimens* (n = 2289)	

**RELENZA®  
(zanamivir for inhalation)**

<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, & throat infections	2%	1%	2%
<b>Nervous system</b>			
Dizziness	2%	1%	<1%

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

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

247

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

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

253 See PRECAUTIONS for safety information in patients with underlying respiratory disease.

254

255 **OVERDOSAGE:** There have been no reports of overdosage from administration of RELENZA.

256 Doses of zanamivir up to 64 mg/day have been administered by nebulizer. Additionally, doses of up  
257 to 1200 mg/day for 5 days have been administered intravenously. Adverse effects were similar to  
258 those seen in clinical studies at the recommended dose.

259

260 **DOSAGE AND ADMINISTRATION:** RELENZA is for administration to the respiratory tract by oral  
261 inhalation only, using the DISKHALER device provided. **Patients should be instructed in the use**  
262 **of the delivery system. Instructions should include a demonstration whenever possible.**

**RELENZA®  
(zanamivir for inhalation)**

263 The recommended dose of RELENZA for treatment of influenza in patients ≥12 years of age is  
264 2 inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) twice daily (approximately  
265 12 hours apart) for 5 days. Two doses should be taken on the first day of treatment whenever  
266 possible provided there is at least 2 hours between doses. On subsequent days, doses should be  
267 about 12 hours apart (e.g., morning and evening) at approximately the same time each day. There  
268 are no data on the effectiveness of treatment with RELENZA when initiated more than 2 days after  
269 the onset of signs or symptoms.

270 Patients scheduled to use an inhaled bronchodilator at the same time as RELENZA should use  
271 their bronchodilator before taking RELENZA. (See PRECAUTIONS regarding patients with chronic  
272 respiratory disease and other medical conditions.)

273

274 **HOW SUPPLIED:** RELENZA is supplied in a circular double-foil pack (a ROTADISK) containing  
275 4 blisters of the drug. Five ROTADISKS are packaged in a white polypropylene tube. The tube is  
276 packaged in a carton with 1 blue and gray DISKHALER inhalation device (NDC 0173-0681-01).

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

280

281

282 **GlaxoWellcome**

283 Glaxo Wellcome Inc.

284 Research Triangle Park, NC 27709

285

286 US Patent Nos. 4,627,432; 4,778,054; 4,811,731; 5,360,817; 5,648,379; 5,035,237; Des. 379,506

287

288 ©Copyright 1999, Glaxo Wellcome Inc. All rights reserved.

289

290 Date of Issue

RL no.

291