



TAMIFLU

(oseltamivir phosphate)

CAPSULES

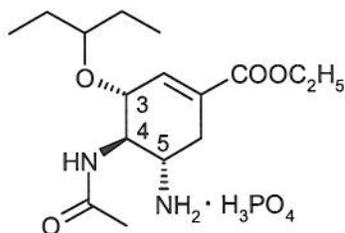
AND FOR ORAL SUSPENSION

R_x only

DESCRIPTION

TAMIFLU (oseltamivir phosphate) is available as capsules containing 30 mg, 45 mg, or 75 mg oseltamivir for oral use, in the form of oseltamivir phosphate, and as a powder for oral suspension, which when constituted with water as directed contains 12 mg/mL oseltamivir base. In addition to the active ingredient, each capsule contains pregelatinized starch, talc, povidone K 30, croscarmellose sodium, and sodium stearyl fumarate. The 30 mg capsule shell contains gelatin, titanium dioxide, yellow iron oxide, and red iron oxide. The 45 mg capsule shell contains gelatin, titanium dioxide, and black iron oxide. The 75 mg capsule shell contains gelatin, titanium dioxide, yellow iron oxide, black iron oxide, and red iron oxide. Each capsule is printed with blue ink, which includes FD&C Blue No. 2 as the colorant. In addition to the active ingredient, the powder for oral suspension contains sorbitol, monosodium citrate, xanthan gum, titanium dioxide, tutti-frutti flavoring, sodium benzoate, and saccharin sodium.

Oseltamivir phosphate is a white crystalline solid with the chemical name (3R,4R,5S)-4-acetylamino-5-amino-3(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid, ethyl ester, phosphate (1:1). The chemical formula is C₁₆H₂₈N₂O₄ (free base). The molecular weight is 312.4 for oseltamivir free base and 410.4 for oseltamivir phosphate salt. The structural formula is as follows:



MICROBIOLOGY

Mechanism of Action

Oseltamivir phosphate is an ethyl ester prodrug requiring ester hydrolysis for conversion to the active form, oseltamivir carboxylate. Oseltamivir carboxylate is an inhibitor of influenza virus neuraminidase affecting release of viral particles.

31 **Antiviral Activity**

32 The antiviral activity of oseltamivir carboxylate against laboratory strains and clinical
33 isolates of influenza virus was determined in cell culture assays. The concentrations of
34 oseltamivir carboxylate required for inhibition of influenza virus were highly variable
35 depending on the assay method used and the virus tested. The 50% and 90% effective
36 concentrations (EC₅₀ and EC₉₀) were in the range of 0.0008 μM to >35 μM and 0.004 μM
37 to >100 μM, respectively (1 μM=0.284 μg/mL). The relationship between the antiviral
38 activity in cell culture and the inhibition of influenza virus replication in humans has not
39 been established.

40 **Resistance**

41 Influenza A virus isolates with reduced susceptibility to oseltamivir carboxylate have
42 been recovered by serial passage of virus in cell culture in the presence of increasing
43 concentrations of oseltamivir carboxylate. Genetic analysis of these isolates showed that
44 reduced susceptibility to oseltamivir carboxylate is associated with mutations that result
45 in amino acid changes in the viral neuraminidase or viral hemagglutinin or both.
46 Resistance substitutions selected in cell culture in neuraminidase are I222T and H274Y in
47 influenza A N1 and I222T and R292K in influenza A N2. Substitutions E119V, R292K
48 and R305Q have been selected in avian influenza A neuraminidase N9. Substitutions
49 A28T and R124M have been selected in the hemagglutinin of influenza A H3N2 and
50 substitution H154Q in the hemagglutinin of a reassortant human/avian virus H1N9.

51 In clinical studies in the treatment of naturally acquired infection with influenza virus,
52 1.3% (4/301) of posttreatment isolates in adult patients and adolescents, and 8.6% (9/105)
53 in pediatric patients aged 1 to 12 years showed emergence of influenza variants with
54 decreased neuraminidase susceptibility in cell culture to oseltamivir carboxylate.
55 Substitutions in influenza A neuraminidase resulting in decreased susceptibility were
56 H274Y in neuraminidase N1 and E119V and R292K in neuraminidase N2. Insufficient
57 information is available to fully characterize the risk of emergence of TAMIFLU
58 resistance in clinical use.

59 In clinical studies of postexposure and seasonal prophylaxis, determination of resistance
60 by population nucleotide sequence analysis was limited by the low overall incidence rate
61 of influenza infection and prophylactic effect of TAMIFLU.

62 **Cross-resistance**

63 Cross-resistance between zanamivir-resistant influenza mutants and oseltamivir-resistant
64 influenza mutants has been observed in cell culture. Due to limitations in the assays
65 available to detect drug-induced shifts in virus susceptibility, an estimate of the incidence
66 of oseltamivir resistance and possible cross-resistance to zanamivir in clinical isolates
67 cannot be made. However, two of the three oseltamivir-induced substitutions (E119V,
68 H274Y and R292K) in the viral neuraminidase from clinical isolates occur at the same
69 amino acid residues as two of the three substitutions (E119G/A/D, R152K and R292K)
70 observed in zanamivir-resistant virus.

71 **Immune Response**

72 No influenza vaccine interaction study has been conducted. In studies of naturally
73 acquired and experimental influenza, treatment with TAMIFLU did not impair normal
74 humoral antibody response to infection.

75 **CLINICAL PHARMACOLOGY**

76 **Pharmacokinetics**

77 **Absorption and Bioavailability**

78 Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of
79 oseltamivir phosphate and is extensively converted predominantly by hepatic esterases to
80 oseltamivir carboxylate. At least 75% of an oral dose reaches the systemic circulation as
81 oseltamivir carboxylate. Exposure to oseltamivir is less than 5% of the total exposure
82 after oral dosing (see Table 1).

83 **Table 1 Mean (% CV) Pharmacokinetic Parameters of Oseltamivir**
84 **and Oseltamivir Carboxylate After a Multiple 75 mg Capsule**
85 **Twice Daily Oral Dose (n=20)**

Parameter	Oseltamivir	Oseltamivir Carboxylate
C _{max} (ng/mL)	65.2 (26)	348 (18)
AUC _{0-12h} (ng·h/mL)	112 (25)	2719 (20)

86 Plasma concentrations of oseltamivir carboxylate are proportional to doses up to 500 mg
87 given twice daily (see **DOSAGE AND ADMINISTRATION**).

88 Coadministration with food has no significant effect on the peak plasma concentration
89 (551 ng/mL under fasted conditions and 441 ng/mL under fed conditions) and the area
90 under the plasma concentration time curve (6218 ng·h/mL under fasted conditions and
91 6069 ng·h/mL under fed conditions) of oseltamivir carboxylate.

92 **Distribution**

93 The volume of distribution (V_{ss}) of oseltamivir carboxylate, following intravenous
94 administration in 24 subjects, ranged between 23 and 26 liters.

95 The binding of oseltamivir carboxylate to human plasma protein is low (3%). The
96 binding of oseltamivir to human plasma protein is 42%, which is insufficient to cause
97 significant displacement-based drug interactions.

98 **Metabolism**

99 Oseltamivir is extensively converted to oseltamivir carboxylate by esterases located
100 predominantly in the liver. Neither oseltamivir nor oseltamivir carboxylate is a substrate
101 for, or inhibitor of, cytochrome P450 isoforms.

102 **Elimination**

103 Absorbed oseltamivir is primarily (>90%) eliminated by conversion to oseltamivir
 104 carboxylate. Plasma concentrations of oseltamivir declined with a half-life of 1 to 3 hours
 105 in most subjects after oral administration. Oseltamivir carboxylate is not further
 106 metabolized and is eliminated in the urine. Plasma concentrations of oseltamivir
 107 carboxylate declined with a half-life of 6 to 10 hours in most subjects after oral
 108 administration. Oseltamivir carboxylate is eliminated entirely (>99%) by renal excretion.
 109 Renal clearance (18.8 L/h) exceeds glomerular filtration rate (7.5 L/h) indicating that
 110 tubular secretion occurs, in addition to glomerular filtration. Less than 20% of an oral
 111 radiolabeled dose is eliminated in feces.

112 **Special Populations**

113 **Renal Impairment**

114 Administration of 100 mg of oseltamivir phosphate twice daily for 5 days to patients with
 115 various degrees of renal impairment showed that exposure to oseltamivir carboxylate is
 116 inversely proportional to declining renal function. Oseltamivir carboxylate exposures in
 117 patients with normal and abnormal renal function administered various dose regimens of
 118 oseltamivir are described in **Table 2**.

119 **Table 2 Oseltamivir Carboxylate Exposures in Patients With Normal**
 120 **and Reduced Serum Creatinine Clearance**

Parameter	Normal Renal Function			Impaired Renal Function				
	75 mg qd	75 mg bid	150 mg bid	Creatinine Clearance <10 mL/min		Creatinine Clearance >10 and <30 mL/min		
				CAPD	Hemodialysis			
				30 mg weekly	30 mg alternate HD cycle	75 mg daily	75 mg alternate days	30 mg daily
C _{max}	259*	348*	705*	766	850	1638	1175	655
C _{min}	39*	138*	288*	62	48	864	209	346
AUC ₄₈	7476*	10876*	21864*	17381	12429	62636	21999	25054

121 *Observed values. All other values are predicted.

122 AUC normalized to 48 hours.

123 **Hepatic Impairment**

124 In clinical studies oseltamivir carboxylate exposure was not altered in patients with mild
 125 or moderate hepatic impairment (see **PRECAUTIONS: Hepatic Impairment** and
 126 **DOSAGE AND ADMINISTRATION**).

127 **Pediatric Patients**

128 The pharmacokinetics of oseltamivir and oseltamivir carboxylate have been evaluated in
 129 a single dose pharmacokinetic study in pediatric patients aged 5 to 16 years (n=18) and in
 130 a small number of pediatric patients aged 3 to 12 years (n=5) enrolled in a clinical trial.
 131 Younger pediatric patients cleared both the prodrug and the active metabolite faster than
 132 adult patients resulting in a lower exposure for a given mg/kg dose. For oseltamivir
 133 carboxylate, apparent total clearance decreases linearly with increasing age (up to 12

134 years). The pharmacokinetics of oseltamivir in pediatric patients over 12 years of age are
135 similar to those in adult patients.

136 Geriatric Patients

137 Exposure to oseltamivir carboxylate at steady-state was 25% to 35% higher in geriatric
138 patients (age range 65 to 78 years) compared to young adults given comparable doses of
139 oseltamivir. Half-lives observed in the geriatric patients were similar to those seen in
140 young adults. Based on drug exposure and tolerability, dose adjustments are not required
141 for geriatric patients for either treatment or prophylaxis (see **DOSAGE AND**
142 **ADMINISTRATION: Special Dosage Instructions**).

143 INDICATIONS AND USAGE

144 Treatment of Influenza

145 TAMIFLU is indicated for the treatment of uncomplicated acute illness due to influenza
146 infection in patients 1 year and older who have been symptomatic for no more than 2
147 days.

148 Prophylaxis of Influenza

149 TAMIFLU is indicated for the prophylaxis of influenza in patients 1 year and older.

150 The following points should be considered before initiating treatment or prophylaxis with
151 TAMIFLU:

- 152 • TAMIFLU is not a substitute for early vaccination on an annual basis as
153 recommended by the Centers for Disease Control and Prevention Advisory
154 Committee on Immunization Practices.
- 155 • Influenza viruses change over time. Emergence of resistance mutations could
156 decrease drug effectiveness. Other factors (for example, changes in viral virulence)
157 might also diminish clinical benefit of antiviral drugs. Prescribers should consider
158 available information on influenza drug susceptibility patterns and treatment effects
159 when deciding whether to use TAMIFLU.
160

161 Description of Clinical Studies: Studies in Naturally Occurring Influenza

162 Treatment of Influenza

163 Adult Patients

164 Two phase III placebo-controlled and double-blind clinical trials were conducted: one in
165 the USA and one outside the USA. Patients were eligible for these trials if they had fever
166 >100°F, accompanied by at least one respiratory symptom (cough, nasal symptoms or
167 sore throat) and at least one systemic symptom (myalgia, chills/sweats, malaise, fatigue
168 or headache) and influenza virus was known to be circulating in the community. In
169 addition, all patients enrolled in the trials were allowed to take fever-reducing
170 medications.

171 Of 1355 patients enrolled in these two trials, 849 (63%) patients were influenza-infected
172 (age range 18 to 65 years; median age 34 years; 52% male; 90% Caucasian; 31%
173 smokers). Of the 849 influenza-infected patients, 95% were infected with influenza A,
174 3% with influenza B, and 2% with influenza of unknown type.

175 TAMIFLU was started within 40 hours of onset of symptoms. Subjects participating in
176 the trials were required to self-assess the influenza-associated symptoms as “none”,
177 “mild”, “moderate” or “severe”. Time to improvement was calculated from the time of
178 treatment initiation to the time when all symptoms (nasal congestion, sore throat, cough,
179 aches, fatigue, headaches, and chills/sweats) were assessed as “none” or “mild”. In both
180 studies, at the recommended dose of TAMIFLU 75 mg twice daily for 5 days, there was a
181 1.3 day reduction in the median time to improvement in influenza-infected subjects
182 receiving TAMIFLU compared to subjects receiving placebo. Subgroup analyses of these
183 studies by gender showed no differences in the treatment effect of TAMIFLU in men and
184 women.

185 In the treatment of influenza, no increased efficacy was demonstrated in subjects
186 receiving treatment of 150 mg TAMIFLU twice daily for 5 days.

187 *Geriatric Patients*

188 Three double-blind placebo-controlled treatment trials were conducted in patients ≥ 65
189 years of age in three consecutive seasons. The enrollment criteria were similar to that of
190 adult trials with the exception of fever being defined as $>97.5^{\circ}\text{F}$. Of 741 patients
191 enrolled, 476 (65%) patients were influenza-infected. Of the 476 influenza-infected
192 patients, 95% were infected with influenza type A and 5% with influenza type B.

193 In the pooled analysis, at the recommended dose of TAMIFLU 75 mg twice daily for 5
194 days, there was a 1 day reduction in the median time to improvement in influenza-
195 infected subjects receiving TAMIFLU compared to those receiving placebo ($p=\text{NS}$).
196 However, the magnitude of treatment effect varied between studies.

197 *Pediatric Patients*

198 One double-blind placebo-controlled treatment trial was conducted in pediatric patients
199 aged 1 to 12 years (median age 5 years), who had fever ($>100^{\circ}\text{F}$) plus one respiratory
200 symptom (cough or coryza) when influenza virus was known to be circulating in the
201 community. Of 698 patients enrolled in this trial, 452 (65%) were influenza-infected
202 (50% male; 68% Caucasian). Of the 452 influenza-infected patients, 67% were infected
203 with influenza A and 33% with influenza B.

204 The primary endpoint in this study was the time to freedom from illness, a composite
205 endpoint which required 4 individual conditions to be met. These were: alleviation of
206 cough, alleviation of coryza, resolution of fever, and parental opinion of a return to
207 normal health and activity. TAMIFLU treatment of 2 mg/kg twice daily, started within 48
208 hours of onset of symptoms, significantly reduced the total composite time to freedom
209 from illness by 1.5 days compared to placebo. Subgroup analyses of this study by gender
210 showed no differences in the treatment effect of TAMIFLU in males and females.

211 Prophylaxis of Influenza

212 *Adult Patients*

213 The efficacy of TAMIFLU in preventing naturally occurring influenza illness has been
214 demonstrated in three seasonal prophylaxis studies and a postexposure prophylaxis study
215 in households. The primary efficacy parameter for all these studies was the incidence of
216 laboratory-confirmed clinical influenza. Laboratory-confirmed clinical influenza was
217 defined as oral temperature $\geq 99.0^{\circ}\text{F}/37.2^{\circ}\text{C}$ plus at least one respiratory symptom (cough,
218 sore throat, nasal congestion) and at least one constitutional symptom (aches and pain,
219 fatigue, headache, chills/sweats), all recorded within 24 hours, plus either a positive virus
220 isolation or a fourfold increase in virus antibody titers from baseline.

221 In a pooled analysis of two seasonal prophylaxis studies in healthy unvaccinated adults
222 (aged 13 to 65 years), TAMIFLU 75 mg once daily taken for 42 days during a
223 community outbreak reduced the incidence of laboratory-confirmed clinical influenza
224 from 4.8% (25/519) for the placebo group to 1.2% (6/520) for the TAMIFLU group.

225 In a seasonal prophylaxis study in elderly residents of skilled nursing homes, TAMIFLU
226 75 mg once daily taken for 42 days reduced the incidence of laboratory-confirmed
227 clinical influenza from 4.4% (12/272) for the placebo group to 0.4% (1/276) for the
228 TAMIFLU group. About 80% of this elderly population were vaccinated, 14% of
229 subjects had chronic airway obstructive disorders, and 43% had cardiac disorders.

230 In a study of postexposure prophylaxis in household contacts (aged ≥ 13 years) of an
231 index case, TAMIFLU 75 mg once daily administered within 2 days of onset of
232 symptoms in the index case and continued for 7 days reduced the incidence of laboratory-
233 confirmed clinical influenza from 12% (24/200) in the placebo group to 1% (2/205) for
234 the TAMIFLU group. Index cases did not receive TAMIFLU in the study.

235 *Pediatric Patients*

236 The efficacy of TAMIFLU in preventing naturally occurring influenza illness has been
237 demonstrated in a randomized, open-label, postexposure prophylaxis study in households
238 that included children aged 1 to 12 years, both as index cases and as family contacts. All
239 index cases in this study received treatment. The primary efficacy parameter for this
240 study was the incidence of laboratory-confirmed clinical influenza in the household.
241 Laboratory-confirmed clinical influenza was defined as oral temperature $\geq 100^{\circ}\text{F}/37.8^{\circ}\text{C}$
242 plus cough and/or coryza recorded within 48 hours, plus either a positive virus isolation
243 or a fourfold or greater increase in virus antibody titers from baseline or at illness visits.
244 Among household contacts 1 to 12 years of age not already shedding virus at baseline,
245 TAMIFLU for Oral Suspension 30 mg to 60 mg taken once daily for 10 days reduced the
246 incidence of laboratory-confirmed clinical influenza from 17% (18/106) in the group not
247 receiving prophylaxis to 3% (3/95) in the group receiving prophylaxis.

248 **CONTRAINDICATIONS**

249 TAMIFLU is contraindicated in patients with known hypersensitivity to any of the
250 components of the product.

251 **PRECAUTIONS**

252 **General**

253 There is no evidence for efficacy of TAMIFLU in any illness caused by agents other than
254 influenza viruses Types A and B.

255 Use of TAMIFLU should not affect the evaluation of individuals for annual influenza
256 vaccination in accordance with guidelines of the Centers for Disease Control and
257 Prevention Advisory Committee on Immunization Practices.

258 Efficacy of TAMIFLU in patients who begin treatment after 40 hours of symptoms has
259 not been established.

260 Efficacy of TAMIFLU in the treatment of subjects with chronic cardiac disease and/or
261 respiratory disease has not been established. No difference in the incidence of
262 complications was observed between the treatment and placebo groups in this population.
263 No information is available regarding treatment of influenza in patients with any medical
264 condition sufficiently severe or unstable to be considered at imminent risk of requiring
265 hospitalization.

266 Safety and efficacy of repeated treatment or prophylaxis courses have not been studied.

267 Efficacy of TAMIFLU for treatment or prophylaxis has not been established in
268 immunocompromised patients.

269 Serious bacterial infections may begin with influenza-like symptoms or may coexist with
270 or occur as complications during the course of influenza. TAMIFLU has not been shown
271 to prevent such complications.

272 **Hepatic Impairment**

273 The safety and pharmacokinetics in patients with severe hepatic impairment have not
274 been evaluated (see **DOSAGE AND ADMINISTRATION**).

275 **Renal Impairment**

276 Dose adjustment is recommended for patients with a serum creatinine clearance
277 <30 mL/min (see **DOSAGE AND ADMINISTRATION**).

278 **Serious Skin/Hypersensitivity Reactions**

279 Rare cases of anaphylaxis and serious skin reactions including toxic epidermal necrolysis,
280 Stevens-Johnson Syndrome, and erythema multiforme have been reported in post-
281 marketing experience with TAMIFLU. TAMIFLU should be stopped and appropriate
282 treatment instituted if an allergic-like reaction occurs or is suspected.

283 **Neuropsychiatric Events**

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

288 There have been postmarketing reports (mostly from Japan) of delirium and abnormal
289 behavior leading to injury, and in some cases resulting in fatal outcomes, in patients with
290 influenza who were receiving TAMIFLU. Because these events were reported voluntarily
291 during clinical practice, estimates of frequency cannot be made but they appear to be
292 uncommon based on TAMIFLU usage data. These events were reported primarily among
293 pediatric patients and often had an abrupt onset and rapid resolution. The contribution of
294 TAMIFLU to these events has not been established. Patients with influenza should be
295 closely monitored for signs of abnormal behavior. If neuropsychiatric symptoms occur,
296 the risks and benefits of continuing treatment should be evaluated for each patient.

297 **Information for Patients**

298 Patients should be instructed to begin treatment with TAMIFLU as soon as possible from
299 the first appearance of flu symptoms. Similarly, prevention should begin as soon as
300 possible after exposure, at the recommendation of a physician.

301 Patients should be instructed to take any missed doses as soon as they remember, except
302 if it is near the next scheduled dose (within 2 hours), and then continue to take
303 TAMIFLU at the usual times.

304 TAMIFLU is not a substitute for a flu vaccination. Patients should continue receiving an
305 annual flu vaccination according to guidelines on immunization practices.

306 A bottle of 13 g TAMIFLU for Oral Suspension contains approximately 11 g sorbitol.
307 One dose of 75 mg TAMIFLU for Oral Suspension delivers 2 g sorbitol. For patients
308 with hereditary fructose intolerance, this is above the daily maximum limit of sorbitol and
309 may cause dyspepsia and diarrhea.

310 **Drug Interactions**

311 The concurrent use of TAMIFLU with live attenuated influenza vaccine (LAIV)
312 intranasal has not been evaluated. However, because of the potential for interference
313 between these products, LAIV should not be administered within 2 weeks before or 48
314 hours after administration of TAMIFLU, unless medically indicated. The concern about
315 possible interference arises from the potential for antiviral drugs to inhibit replication of
316 live vaccine virus. Trivalent inactivated influenza vaccine can be administered at any
317 time relative to use of TAMIFLU.

318 Information derived from pharmacology and pharmacokinetic studies of oseltamivir
319 suggests that clinically significant drug interactions are unlikely.

320 Oseltamivir is extensively converted to oseltamivir carboxylate by esterases, located
321 predominantly in the liver. Drug interactions involving competition for esterases have not
322 been extensively reported in literature. Low protein binding of oseltamivir and
323 oseltamivir carboxylate suggests that the probability of drug displacement interactions is
324 low.

325 In vitro studies demonstrate that neither oseltamivir nor oseltamivir carboxylate is a good
326 substrate for P450 mixed-function oxidases or for glucuronyl transferases.

327 Clinically important drug interactions involving competition for renal tubular secretion
328 are unlikely due to the known safety margin for most of these drugs, the elimination
329 characteristics of oseltamivir carboxylate (glomerular filtration and anionic tubular
330 secretion) and the excretion capacity of these pathways. Coadministration of probenecid
331 results in an approximate twofold increase in exposure to oseltamivir carboxylate due to a
332 decrease in active anionic tubular secretion in the kidney. However, due to the safety
333 margin of oseltamivir carboxylate, no dose adjustments are required when
334 coadministering with probenecid.

335 No pharmacokinetic interactions have been observed when coadministering oseltamivir
336 with amoxicillin, acetaminophen, cimetidine or with antacids (magnesium and aluminum
337 hydroxides and calcium carbonates).

338 **Carcinogenesis, Mutagenesis, and Impairment of Fertility**

339 In 2-year carcinogenicity studies in mice and rats given daily oral doses of the pro-drug
340 oseltamivir phosphate up to 400 mg/kg and 500 mg/kg, respectively, the pro-drug
341 oseltamivir phosphate and the active form oseltamivir carboxylate induced no statistically
342 significant increases in tumors over controls. The mean maximum daily exposures to the
343 prodrug in mice and rats were approximately 130- and 320-fold, respectively, greater
344 than those in humans at the proposed clinical dose based on AUC comparisons. The
345 respective safety margins of the exposures to the active oseltamivir carboxylate were 15-
346 and 50-fold.

347 Oseltamivir was found to be non-mutagenic in the Ames test and the human lymphocyte
348 chromosome assay with and without enzymatic activation and negative in the mouse
349 micronucleus test. It was found to be positive in a Syrian Hamster Embryo (SHE) cell
350 transformation test. Oseltamivir carboxylate was non-mutagenic in the Ames test and the
351 L5178Y mouse lymphoma assay with and without enzymatic activation and negative in
352 the SHE cell transformation test.

353 In a fertility and early embryonic development study in rats, doses of oseltamivir at 50,
354 250, and 1500 mg/kg/day were administered to females for 2 weeks before mating,
355 during mating and until day 6 of pregnancy. Males were dosed for 4 weeks before
356 mating, during and for 2 weeks after mating. There were no effects on fertility, mating
357 performance or early embryonic development at any dose level. The highest dose was
358 approximately 100 times the human systemic exposure (AUC_{0-24h}) of oseltamivir
359 carboxylate.

360 **Pregnancy**

361 **Pregnancy Category C**

362 There are insufficient human data upon which to base an evaluation of risk of TAMIFLU
363 to the pregnant woman or developing fetus. Studies for effects on embryo-fetal
364 development were conducted in rats (50, 250, and 1500 mg/kg/day) and rabbits (50, 150,
365 and 500 mg/kg/day) by the oral route. Relative exposures at these doses were,
366 respectively, 2, 13, and 100 times human exposure in the rat and 4, 8, and 50 times
367 human exposure in the rabbit. Pharmacokinetic studies indicated that fetal exposure was

368 seen in both species. In the rat study, minimal maternal toxicity was reported in the 1500
369 mg/kg/day group. In the rabbit study, slight and marked maternal toxicities were
370 observed, respectively, in the 150 and 500 mg/kg/day groups. There was a dose-
371 dependent increase in the incidence rates of a variety of minor skeletal abnormalities and
372 variants in the exposed offspring in these studies. However, the individual incidence rate
373 of each skeletal abnormality or variant remained within the background rates of
374 occurrence in the species studied.

375 Because animal reproductive studies may not be predictive of human response and there
376 are no adequate and well-controlled studies in pregnant women, TAMIFLU should be
377 used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

378 **Nursing Mothers**

379 In lactating rats, oseltamivir and oseltamivir carboxylate are excreted in the milk. It is not
380 known whether oseltamivir or oseltamivir carboxylate is excreted in human milk.
381 TAMIFLU should, therefore, be used only if the potential benefit for the lactating mother
382 justifies the potential risk to the breast-fed infant.

383 **Geriatric Use**

384 The safety of TAMIFLU has been established in clinical studies which enrolled 741
385 subjects (374 received placebo and 362 received TAMIFLU). Some seasonal variability
386 was noted in the clinical efficacy outcomes (see **INDICATIONS AND USAGE:
387 Description of Clinical Studies: Studies in Naturally Occurring Influenza:
388 Treatment of Influenza: Geriatric Patients**).

389 Safety and efficacy have been demonstrated in elderly residents of nursing homes who
390 took TAMIFLU for up to 42 days for the prevention of influenza. Many of these
391 individuals had cardiac and/or respiratory disease, and most had received vaccine that
392 season (see **INDICATIONS AND USAGE: Description of Clinical Studies: Studies
393 in Naturally Occurring Influenza: Prophylaxis of Influenza: Adult Patients**).

394 **Pediatric Use**

395 The safety and efficacy of TAMIFLU in pediatric patients younger than 1 year of age
396 have not been studied. TAMIFLU is not indicated for either treatment or prophylaxis of
397 influenza in pediatric patients younger than 1 year of age because of uncertainties
398 regarding the rate of development of the human blood-brain barrier and the unknown
399 clinical significance of non-clinical animal toxicology data for human infants (see
400 **ANIMAL TOXICOLOGY**).

401 **ANIMAL TOXICOLOGY**

402 In a 2-week study in unweaned rats, administration of a single dose of 1000 mg/kg
403 oseltamivir phosphate to 7-day-old rats resulted in deaths associated with unusually high
404 exposure to the prodrug. However, at 2000 mg/kg, there were no deaths or other
405 significant effects in 14-day-old unweaned rats. Further follow-up investigations of the
406 unexpected deaths of 7-day-old rats at 1000 mg/kg revealed that the concentrations of the
407 prodrug in the brains were approximately 1500-fold those of the brains of adult rats

408 administered the same oral dose of 1000 mg/kg, and those of the active metabolite were
409 approximately 3-fold higher. Plasma levels of the prodrug were 10-fold higher in 7-day-
410 old rats as compared with adult rats. These observations suggest that the levels of
411 oseltamivir in the brains of rats decrease with increasing age and most likely reflect the
412 maturation stage of the blood-brain barrier. No adverse effects occurred at 500 mg/kg/day
413 administered to 7- to 21-day-old rats. At this dosage, the exposure to prodrug was
414 approximately 800-fold the exposure expected in a 1-year-old child.

415 **ADVERSE REACTIONS**

416 **Treatment Studies in Adult Patients**

417 A total of 1171 patients who participated in adult phase III controlled clinical trials for
418 the treatment of influenza were treated with TAMIFLU. The most frequently reported
419 adverse events in these studies were nausea and vomiting. These events were generally of
420 mild to moderate degree and usually occurred on the first 2 days of administration. Less
421 than 1% of subjects discontinued prematurely from clinical trials due to nausea and
422 vomiting.

423 Adverse events that occurred with an incidence of $\geq 1\%$ in 1440 patients taking placebo or
424 TAMIFLU 75 mg twice daily in adult phase III treatment studies are shown in **Table 3**.
425 This summary includes 945 healthy young adults and 495 “at risk” patients (elderly
426 patients and patients with chronic cardiac or respiratory disease). Those events reported
427 numerically more frequently in patients taking TAMIFLU compared with placebo were
428 nausea, vomiting, bronchitis, insomnia, and vertigo.

429 **Prophylaxis Studies in Adult Patients**

430 A total of 4187 subjects (adolescents, healthy adults and elderly) participated in phase III
431 prophylaxis studies, of whom 1790 received the recommended dose of 75 mg once daily
432 for up to 6 weeks. Adverse events were qualitatively very similar to those seen in the
433 treatment studies, despite a longer duration of dosing (see **Table 3**). Events reported more
434 frequently in subjects receiving TAMIFLU compared to subjects receiving placebo in
435 prophylaxis studies, and more commonly than in treatment studies, were aches and pains,
436 rhinorrhea, dyspepsia and upper respiratory tract infections. However, the difference in
437 incidence between TAMIFLU and placebo for these events was less than 1%. There were
438 no clinically relevant differences in the safety profile of the 942 elderly subjects who
439 received TAMIFLU or placebo, compared with the younger population.

440 **Table 3** Most Frequent Adverse Events in Studies in Naturally
 441 Acquired Influenza in Patients 13 Years of Age and Older

Adverse Event	Treatment		Prophylaxis	
	Placebo N=716	Oseltamivir 75 mg bid N=724	Placebo/ No Prophylaxis ^a N=1688	Oseltamivir 75 mg qd N=1790
Nausea (without vomiting)	40 (6%)	72 (10%)	56 (3%)	129 (7%)
Vomiting	21 (3%)	68 (9%)	16 (1%)	39 (2%)
Diarrhea	70 (10%)	48 (7%)	40 (2%)	50 (3%)
Bronchitis	15 (2%)	17 (2%)	22 (1%)	15 (1%)
Abdominal pain	16 (2%)	16 (2%)	25 (1%)	37 (2%)
Dizziness	25 (3%)	15 (2%)	21 (1%)	24 (1%)
Headache	14 (2%)	13 (2%)	306 (18%)	326 (18%)
Cough	12 (2%)	9 (1%)	119 (7%)	94 (5%)
Insomnia	6 (1%)	8 (1%)	15 (1%)	22 (1%)
Vertigo	4 (1%)	7 (1%)	4 (<1%)	4 (<1%)
Fatigue	7 (1%)	7 (1%)	163 (10%)	139 (8%)

442 ^a The majority of subjects received placebo; 254 subjects from a randomized, open-label post exposure
 443 prophylaxis study in households did not receive placebo or prophylaxis therapy.

444 Adverse events included are: all events reported in the treatment studies with frequency
 445 $\geq 1\%$ in the oseltamivir 75 mg bid group.

446 Additional adverse events occurring in $<1\%$ of patients receiving TAMIFLU for
 447 treatment included unstable angina, anemia, pseudomembranous colitis, humerus
 448 fracture, pneumonia, pyrexia, and peritonsillar abscess.

449 Treatment Studies in Pediatric Patients

450 A total of 1032 pediatric patients aged 1 to 12 years (including 698 otherwise healthy
 451 pediatric patients aged 1 to 12 years and 334 asthmatic pediatric patients aged 6 to 12
 452 years) participated in phase III studies of TAMIFLU given for the treatment of influenza.
 453 A total of 515 pediatric patients received treatment with TAMIFLU for Oral Suspension.

454 Adverse events occurring in $\geq 1\%$ of pediatric patients receiving TAMIFLU treatment are
 455 listed in **Table 4**. The most frequently reported adverse event was vomiting. Other events
 456 reported more frequently by pediatric patients treated with TAMIFLU included
 457 abdominal pain, epistaxis, ear disorder, and conjunctivitis. These events generally
 458 occurred once and resolved despite continued dosing. They did not cause discontinuation
 459 of drug in the vast majority of cases.

460 The adverse event profile in adolescents is similar to that described for adult patients and
 461 pediatric patients aged 1 to 12 years.

462 **Prophylaxis in Pediatric Patients**

463 Pediatric patients aged 1 to 12 years participated in a postexposure prophylaxis study in
 464 households, both as index cases (134) and as contacts (222). Gastrointestinal events were
 465 the most frequent, particularly vomiting. The adverse events noted were consistent with
 466 those previously observed in pediatric treatment studies (see Table 4).

467 **Table 4 Most Frequent Adverse Events Occurring in Children Aged**
 468 **1 to 12 Years in Studies in Naturally Acquired Influenza**

Adverse Event	Treatment Trials ^a		Household Prophylaxis Trial ^b	
	Placebo N=517	Oseltamivir 2 mg/kg bid N=515	No Prophylaxis ^c N=87	Prophylaxis with Oseltamivir QD ^c N=99
Vomiting	48 (9%)	77 (15%)	2 (2%)	10 (10%)
Diarrhea	55 (11%)	49 (10%)	-	1 (1%)
Otitis media	58 (11%)	45 (9%)	2 (2%)	2 (2%)
Abdominal pain	20 (4%)	24 (5%)	-	3 (3%)
Asthma (including aggravated)	19 (4%)	18 (3%)	1 (1%)	1 (1%)
Nausea	22 (4%)	17 (3%)	1 (1%)	4 (4%)
Epistaxis	13 (3%)	16 (3%)	-	1 (1%)
Pneumonia	17 (3%)	10 (2%)	2 (2%)	-
Ear disorder	6 (1%)	9 (2%)	-	-
Sinusitis	13 (3%)	9 (2%)	-	-
Bronchitis	11 (2%)	8 (2%)	2 (2%)	-
Conjunctivitis	2 (<1%)	5 (1%)	-	-
Dermatitis	10 (2%)	5 (1%)	-	-
Lymphadenopathy	8 (2%)	5 (1%)	-	-
Tympanic membrane disorder	6 (1%)	5 (1%)	-	-

469 ^a Pooled data from Phase III trials of TAMIFLU treatment of naturally acquired influenza.

470 ^b A randomized, open-label study of household transmission in which household contacts received either
 471 prophylaxis or no prophylaxis but treatment if they became ill. Only contacts who received prophylaxis
 472 or who remained on no prophylaxis are included in this table.

473 ^c Unit dose = age-based dosing

Age	Prophylaxis (10 days)
1-2 years	30 mg QD
3-5 years	45 mg QD
6-12 years	60 mg QD

474

475 Adverse events included in Table 4 are: all events reported in the treatment studies with
 476 frequency $\geq 1\%$ in the oseltamivir 75 mg bid group.

477 **Observed During Clinical Practice**

478 The following adverse reactions have been identified during postmarketing use of
479 TAMIFLU. Because these reactions are reported voluntarily from a population of
480 uncertain size, it is not possible to reliably estimate their frequency or establish a causal
481 relationship to TAMIFLU exposure.

482 Body as a Whole: Swelling of the face or tongue, allergy, anaphylactic/anaphylactoid
483 reactions

484 Dermatologic: Dermatitis, rash, eczema, urticaria, erythema multiforme, Stevens-Johnson
485 Syndrome, toxic epidermal necrolysis (see **PRECAUTIONS**)

486 Digestive: Hepatitis, liver function tests abnormal

487 Cardiac: Arrhythmia

488 Gastrointestinal disorders: Gastrointestinal bleeding, hemorrhagic colitis

489 Neurologic: Seizure

490 Metabolic: Aggravation of diabetes

491 Psychiatric: Delirium, including symptoms such as altered level of consciousness,
492 confusion, abnormal behavior, delusions, hallucinations, agitation, anxiety, nightmares
493 (see **PRECAUTIONS**)

494 **OVERDOSAGE**

495 At present, there has been no experience with overdose. Single doses of up to 1000 mg of
496 TAMIFLU have been associated with nausea and/or vomiting.

497 **DOSAGE AND ADMINISTRATION**

498 TAMIFLU may be taken with or without food (see **CLINICAL PHARMACOLOGY:**
499 **Pharmacokinetics**). However, when taken with food, tolerability may be enhanced in
500 some patients.

501 **Standard Dosage – Treatment of Influenza**

502 **Adults and Adolescents**

503 The recommended oral dose of TAMIFLU for treatment of influenza in adults and
504 adolescents 13 years and older is 75 mg twice daily for 5 days. Treatment should begin
505 within 2 days of onset of symptoms of influenza.

506 **Pediatric Patients**

507 TAMIFLU is not indicated for treatment of influenza in pediatric patients younger than
508 1 year.

509 The recommended oral dose of TAMIFLU for pediatric patients 1 year and older is
510 shown in **Table 5**. TAMIFLU for Oral Suspension may also be used by patients who
511 cannot swallow a capsule. For pediatric patients who cannot swallow capsules,

512 TAMIFLU for Oral Suspension is the preferred formulation. If the for Oral Suspension
 513 product is not available, TAMIFLU Capsules may be opened and mixed with sweetened
 514 liquids such as regular or sugar-free chocolate syrup.

515 **Table 5 Oral Dose of TAMIFLU for Treatment of Influenza in Pediatric**
 516 **Patients by Weight**

Body Weight (kg)	Body Weight (lbs)	Recommended Dose for 5 Days	Number of Bottles of TAMIFLU for Oral Suspension Needed to Obtain the Recommended Doses for a 5 Day Regimen	Number of TAMIFLU Capsules Needed to Obtain the Recommended Doses for a 5 Day Regimen
≤15 kg	≤33 lbs	30 mg twice daily	1	10 TAMIFLU Capsules (30 mg)
>15 kg to 23 kg	>33 lbs to 51 lbs	45 mg twice daily	2	10 TAMIFLU Capsules (45 mg)
>23 kg to 40 kg	>51 lbs to 88 lbs	60 mg twice daily	2	20 TAMIFLU Capsules (30 mg)
>40 kg	>88 lbs	75 mg twice daily	3	10 TAMIFLU Capsules (75 mg)

517 An oral dosing dispenser with 30 mg, 45 mg, and 60 mg graduations is provided with the
 518 oral suspension; the 75 mg dose can be measured using a combination of 30 mg and
 519 45 mg. It is recommended that patients use this dispenser. In the event that the dispenser
 520 provided is lost or damaged, another dosing syringe or other device may be used to
 521 deliver the following volumes: 2.5 mL (1/2 tsp) for children ≤15 kg, 3.8 mL (3/4 tsp) for
 522 >15 to 23 kg, 5.0 mL (1 tsp) for >23 to 40 kg, and 6.2 mL (1 1/4 tsp) for >40 kg.

523 **Standard Dosage – Prophylaxis of Influenza**

524 **Adults and Adolescents**

525 The recommended oral dose of TAMIFLU for prophylaxis of influenza in adults and
 526 adolescents 13 years and older following close contact with an infected individual is
 527 75 mg once daily for at least 10 days. Therapy should begin within 2 days of exposure.
 528 The recommended dose for prophylaxis during a community outbreak of influenza is
 529 75 mg once daily. Safety and efficacy have been demonstrated for up to 6 weeks. The
 530 duration of protection lasts for as long as dosing is continued.

531 **Pediatric Patients**

532 The safety and efficacy of TAMIFLU for prophylaxis of influenza in pediatric patients
 533 younger than 1 year of age have not been established.

534 The recommended oral dose of TAMIFLU for pediatric patients 1 year and older
 535 following close contact with an infected individual is shown in **Table 6**. TAMIFLU for
 536 Oral Suspension may also be used by patients who cannot swallow a capsule. For
 537 pediatric patients who cannot swallow capsules, TAMIFLU for Oral Suspension is the
 538 preferred formulation. If the for Oral Suspension product is not available, TAMIFLU
 539 Capsules may be opened and mixed with sweetened liquids such as regular or sugar-free
 540 chocolate syrup.

541 **Table 6 Oral Dose of TAMIFLU for Prophylaxis of Influenza in**
 542 **Pediatric Patients by Weight**

Body Weight (kg)	Body Weight (lbs)	Recommended Dose for 10 Days	Number of Bottles of TAMIFLU for Oral Suspension Needed to Obtain the Recommended Doses for a 10 Day Regimen	Number of TAMIFLU Capsules Needed to Obtain the Recommended Doses for a 10 Day Regimen
≤15 kg	≤33 lbs	30 mg once daily	1	10 TAMIFLU Capsules (30 mg)
>15 kg to 23 kg	>33 lbs to 51 lbs	45 mg once daily	2	10 TAMIFLU Capsules (45 mg)
>23 kg to 40 kg	>51 lbs to 88 lbs	60 mg once daily	2	20 TAMIFLU Capsules (30 mg)
>40 kg	>88 lbs	75 mg once daily	3	10 TAMIFLU Capsules (75 mg)

543 An oral dosing dispenser with 30 mg, 45 mg, and 60 mg graduations is provided with the
 544 oral suspension; the 75 mg dose can be measured using a combination of 30 mg and
 545 45 mg. It is recommended that patients use this dispenser. In the event that the dispenser
 546 provided is lost or damaged, another dosing syringe or other device may be used to
 547 deliver the following volumes: 2.5 mL (1/2 tsp) for children ≤15 kg, 3.8 mL (3/4 tsp) for
 548 >15 to 23 kg, 5.0 mL (1 tsp) for >23 to 40 kg, and 6.2 mL (1 1/4 tsp) for >40 kg.

549 Prophylaxis in pediatric patients following close contact with an infected individual is
 550 recommended for 10 days. Prophylaxis in patients 1 to 12 years of age has not been
 551 evaluated for longer than 10 days duration. Therapy should begin within 2 days of
 552 exposure.

553 **Special Dosage Instructions**

554 **Hepatic Impairment**

555 No dose adjustment is recommended for patients with mild or moderate hepatic
 556 impairment (Child-Pugh score ≤9) (see **CLINICAL PHARMACOLOGY:**
 557 **Pharmacokinetics: Special Populations**).

558 Renal Impairment

559 For plasma concentrations of oseltamivir carboxylate predicted to occur following
560 various dosing schedules in patients with renal impairment, see **CLINICAL**
561 **PHARMACOLOGY: Pharmacokinetics: Special Populations.**

562 *Treatment of Influenza*

563 Dose adjustment is recommended for patients with creatinine clearance between 10 and
564 30 mL/min receiving TAMIFLU for the treatment of influenza. In these patients it is
565 recommended that the dose be reduced to 75 mg of TAMIFLU once daily for 5 days. No
566 recommended dosing regimens are available for patients undergoing routine
567 hemodialysis and continuous peritoneal dialysis treatment with end-stage renal disease.

568 *Prophylaxis of Influenza*

569 For the prophylaxis of influenza, dose adjustment is recommended for patients with
570 creatinine clearance between 10 and 30 mL/min receiving TAMIFLU. In these patients it
571 is recommended that the dose be reduced to 75 mg of TAMIFLU every other day or
572 30 mg TAMIFLU every day. No recommended dosing regimens are available for patients
573 undergoing routine hemodialysis and continuous peritoneal dialysis treatment with end-
574 stage renal disease.

575 Geriatric Patients

576 No dose adjustment is required for geriatric patients (see **CLINICAL**
577 **PHARMACOLOGY: Pharmacokinetics: Special Populations** and **PRECAUTIONS**).

578 **Preparation of TAMIFLU for Oral Suspension**

579 It is recommended that TAMIFLU for Oral Suspension be constituted by the pharmacist
580 prior to dispensing to the patient:

- 581 1. Tap the closed bottle several times to loosen the powder.
- 582 2. Measure **23 mL** of water in a graduated cylinder.
- 583 3. Add the total amount of water for constitution to the bottle and shake the closed bottle
584 well for 15 seconds.
- 585 4. Remove the child-resistant cap and push bottle adapter into the neck of the bottle.
- 586 5. Close bottle with child-resistant cap tightly. This will assure the proper seating of the
587 bottle adapter in the bottle and child-resistant status of the cap.

588 **NOTE: SHAKE THE TAMIFLU FOR ORAL SUSPENSION WELL BEFORE EACH**
589 **USE.**

590 The constituted TAMIFLU for Oral Suspension (12 mg/mL) should be used within 10
591 days of preparation; the pharmacist should write the date of expiration of the constituted
592 suspension on a pharmacy label. The patient package insert and oral dispenser should be
593 dispensed to the patient.

594 **Emergency Compounding of an Oral Suspension from TAMIFLU Capsules**
 595 **(Final Concentration 15 mg/mL)**

596 The following directions are provided for use only during emergency situations. These
 597 directions are not intended to be used if the FDA-approved, commercially manufactured
 598 TAMIFLU for Oral Suspension is readily available from wholesalers or the
 599 manufacturer.

600 Compounding an oral suspension with this procedure will provide one patient with
 601 enough medication for a 5-day course of treatment or a 10-day course of prophylaxis.

602 Commercially manufactured TAMIFLU for Oral Suspension (12 mg/mL) is the preferred
 603 product for pediatric and adult patients who have difficulty swallowing capsules or where
 604 lower doses are needed. In the event that TAMIFLU for Oral Suspension is not available,
 605 the pharmacist may compound a suspension (15 mg/mL) from TAMIFLU (oseltamivir
 606 phosphate) Capsules 75 mg using either of two vehicles: Cherry Syrup (Humco®) or
 607 Ora-Sweet SF (sugar-free) (Paddock Laboratories). Other vehicles have not been
 608 studied. **This compounded suspension should not be used for convenience or when**
 609 **the FDA-approved TAMIFLU for Oral Suspension is commercially available.**

610 First, calculate the Total Volume of an oral suspension needed to be compounded and
 611 dispensed for each patient. The Total Volume required is determined by the weight of
 612 each patient. Refer to **Table 7**.

613 **Table 7 Volume of an Oral Suspension (15 mg/mL) Needed to be**
 614 **Compounded Based Upon the Patient's Weight**

Body Weight (kg)	Body Weight (lbs)	Total Volume to Compound per patient (mL)
≤15 kg	≤33 lbs	30 mL
16 to 23 kg	34 to 51 lbs	40 mL
24 to 40 kg	52 to 88 lbs	50 mL
≥41 kg	≥89 lbs	60 mL

615

616 Second, determine the number of capsules and the amount of vehicle (Cherry Syrup or
 617 Ora-Sweet SF) that are needed to prepare the Total Volume (calculated from Table 7:
 618 30 mL, 40 mL, 50 mL, or 60 mL) of compounded oral suspension (15 mg/mL). Refer to
 619 **Table 8**.

620 **Table 8 Number of TAMIFLU 75 mg Capsules and Amount of Vehicle**
 621 **(Cherry Syrup OR Ora-Sweet SF) Needed to Prepare the**
 622 **Total Volume of a Compounded Oral Suspension (15 mg/mL)**

Total Volume of Compounded Oral	30 mL	40 mL	50 mL	60 mL

Suspension needed to be Prepared				
Required number of TAMIFLU 75 mg Capsules	6 capsules (450 mg oseltamivir)	8 capsules (600 mg oseltamivir)	10 capsules (750 mg oseltamivir)	12 capsules (900 mg oseltamivir)
Required volume of vehicle Cherry Syrup (Humco) OR Ora-Sweet SF (Paddock Laboratories)	29 mL	38.5 mL	48 mL	57 mL

623

624 Third, follow the procedure below for compounding the oral suspension (15 mg/mL)
625 from TAMIFLU Capsules 75 mg

- 626 1. Carefully separate the capsule body and cap and transfer the contents of the required
627 number of TAMIFLU 75 mg Capsules into a clean mortar.
- 628 2. Triturate the granules to a fine powder.
- 629 3. Add one-third (1/3) of the specified amount of vehicle and triturate the powder until a
630 uniform suspension is achieved.
- 631 4. Transfer the suspension to an amber glass or amber polyethyleneterephthalate (PET)
632 bottle. A funnel may be used to eliminate any spillage.
- 633 5. Add another one-third (1/3) of the vehicle to the mortar, rinse the pestle and mortar
634 by a triturating motion and transfer the vehicle into the bottle.
- 635 6. Repeat the rinsing (Step 5) with the remainder of the vehicle.
- 636 7. Close the bottle using a child-resistant cap.
- 637 8. Shake well to completely dissolve the active drug and to ensure homogeneous
638 distribution of the dissolved drug in the resulting suspension. (Note: The active drug,
639 oseltamivir phosphate, readily dissolves in the specified vehicles. The suspension is
640 caused by some of the inert ingredients of TAMIFLU Capsules which are insoluble in
641 these vehicles.)
- 642 9. Put an ancillary label on the bottle indicating "Shake Gently Before Use". [This
643 compounded suspension should be gently shaken prior to administration to minimize
644 the tendency for air entrapment, particularly with the Ora-Sweet SF preparation.]
- 645 10. Instruct the parent or guardian that any remaining material following completion of
646 therapy must be discarded by either affixing an ancillary label to the bottle or adding
647 a statement to the pharmacy label instructions.
- 648 11. Place an appropriate expiration date label according to storage condition (see below).
649

650

STORAGE OF THE PHARMACY-COMPOUNDED SUSPENSION:

651

Refrigeration: Stable for 5 weeks (35 days) when stored in a refrigerator at 2° to 8°C (36° to 46°F).

652

653

Room Temperature: Stable for five days (5 days) when stored at room temperature, 25°C (77°F).

654

655

Note: The storage conditions are based on stability studies of compounded oral suspensions, using the above mentioned vehicles, which were placed in amber glass and amber polyethyleneterephthalate (PET) bottles. Stability studies have not been conducted with other vehicles or bottle types.

656

657

658

659

Place a pharmacy label on the bottle that includes the patient’s name, dosing instructions, and drug name and any other required information to be in compliance with all State and Federal Pharmacy Regulations. Refer to Table 9 for the proper dosing instructions.

660

661

662

Note: This compounding procedure results in a 15 mg/mL suspension, which is different from the commercially available TAMIFLU for Oral Suspension, which has a concentration of 12 mg/mL.

663

664

665

Table 9 Dosing Chart for Pharmacy-Compounded Suspension from TAMIFLU Capsules 75 mg

666

Body Weight (kg)	Body Weight (lbs)	Dose (mg)	Volume per Dose 15 mg/mL	Treatment Dose (for 5 days)	Prophylaxis Dose (for 10 days)
≤15 kg	≤33 lbs	30 mg	2 mL	2 mL two times a day	2 mL once daily
16 to 23 kg	34 to 51 lbs	45 mg	3 mL	3 mL two times a day	3 mL once daily
24 to 40 kg	52 to 88 lbs	60 mg	4 mL	4 mL two times a day	4 mL once daily
≥41 kg	≥89 lbs	75 mg	5 mL	5 mL two times a day	5 mL once daily

667

Note: 1 teaspoon = 5 mL

668

Consider dispensing the suspension with a graduated oral syringe for measuring small amounts of suspension. If possible, mark or highlight the graduation corresponding to the appropriate dose (2 mL, 3 mL, 4 mL, or 5 mL) on the oral syringe for each patient. The dosing device dispensed with the commercially available TAMIFLU for Oral Suspension should NOT be used with the compounded suspension since they have different concentrations.

669

670

671

672

673

674 **HOW SUPPLIED**

675 **TAMIFLU Capsules**

676 30-mg capsules (30 mg free base equivalent of the phosphate salt): light yellow hard
677 gelatin capsules. "ROCHE" is printed in blue ink on the light yellow body and "30 mg" is
678 printed in blue ink on the light yellow cap. Available in blister packages of 10 (NDC
679 0004-0802-85).

680 45-mg capsules (45 mg free base equivalent of the phosphate salt): grey hard gelatin
681 capsules. "ROCHE" is printed in blue ink on the grey body and "45 mg" is printed in blue
682 ink on the grey cap. Available in blister packages of 10 (NDC 0004-0801-85).

683 75-mg capsules (75 mg free base equivalent of the phosphate salt): grey/light yellow hard
684 gelatin capsules. "ROCHE" is printed in blue ink on the grey body and "75 mg" is printed
685 in blue ink on the light yellow cap. Available in blister packages of 10 (NDC 0004-0800-
686 85).

687 **Storage**

688 Store the capsules at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See
689 USP Controlled Room Temperature]

690 **TAMIFLU for Oral Suspension**

691 Supplied as a white powder blend for constitution to a white tutti-frutti-flavored
692 suspension. Available in glass bottles containing approximately 33 mL of suspension
693 after constitution. Each bottle delivers 25 mL of suspension equivalent to 300 mg
694 oseltamivir base. Each bottle is supplied with a bottle adapter and 1 oral dispenser (NDC
695 0004-0810-95).

696 **Storage**

697 Store dry powder at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See
698 USP Controlled Room Temperature]

699 Store constituted suspension under refrigeration at 2° to 8°C (36° to 46°F). Do not freeze.

700

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702 Ora-Sweet® SF is a registered trademark of Paddock Laboratories

703

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1
2 **Patient Information**

3 **TAMIFLU**

4 **(oseltamivir phosphate)**

5 **R_x only**

6 This leaflet contains important information about TAMIFLU (TAM-ih-flew). Read it
7 well before you begin treatment. This information does not take the place of talking with
8 your healthcare professional about your medical condition or your treatment. This leaflet
9 does not list all the benefits and risks of TAMIFLU. If you have any questions about
10 TAMIFLU, ask your healthcare professional. Only your healthcare professional can
11 determine if TAMIFLU is right for you.

12 **What is TAMIFLU?**

13 TAMIFLU attacks the influenza virus and stops it from spreading inside your body.
14 TAMIFLU treats flu at its source, by attacking the virus that causes the flu, rather than
15 simply masking symptoms.

16 TAMIFLU is for treating adults and children age 1 and older with the flu whose flu
17 symptoms started within the last day or two. TAMIFLU can also reduce the chance of
18 getting the flu in people age 1 and older who have a higher chance of getting the flu
19 because they spend time with someone who has the flu. TAMIFLU can also reduce the
20 chance of getting the flu if there is a flu outbreak in the community.

21 **What is "Flu"?**

22 "The flu" is an infection caused by the influenza virus. Flu symptoms include fever
23 (usually 100°F to 103°F in adults, and sometimes higher in children) and problems such
24 as cough, sore throat, runny or stuffy nose, headaches, muscle aches, fever, and extreme
25 tiredness. Many people use the term "flu" to mean any combination of these symptoms,
26 such as the common cold, but true influenza infection is often worse and may last longer
27 than a cold.

28 Flu outbreaks happen about once a year, usually in the winter, when the influenza virus
29 spreads widely in the community. Outside of those outbreaks, only a very tiny number of
30 respiratory infections are caused by the influenza virus.

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

32 TAMIFLU is not a substitute for a flu vaccination. You should continue to get a flu
33 vaccination every year, according to your healthcare professional's advice.

34 **Who should not take TAMIFLU?**

35 Do not take TAMIFLU if you are allergic to the main ingredient, oseltamivir phosphate,
36 or to any other ingredients of TAMIFLU. Before starting treatment, make sure your
37 healthcare professional knows if you take any other medicines, or are pregnant, planning
38 to become pregnant, or breastfeeding. TAMIFLU is normally not recommended for use
39 during pregnancy or nursing, as the effects on the unborn child or nursing infant are
40 unknown. TAMIFLU is not recommended for use in children younger than 1 year of age.

41 Tell your healthcare professional if you have any type of kidney disease, heart disease,
42 respiratory disease, or any serious health condition.

43 TAMIFLU for Oral Suspension contains sorbitol. Sorbitol may cause upset stomach and
44 diarrhea in patients with a family history of fructose intolerance.

45 **How should I take TAMIFLU?**

46 It is important that you begin your treatment with TAMIFLU as soon as possible from the
47 first appearance of your flu symptoms or soon after you are exposed to the flu. If you feel
48 worse or develop new symptoms during treatment with TAMIFLU, or if your flu
49 symptoms do not start to get better, you should contact your healthcare professional.

50 If you have the flu: Take TAMIFLU twice a day for 5 days, once in the morning and
51 once in the evening. You should complete the entire treatment of 10 doses (capsules or
52 suspension), even if you feel better.

53 To prevent the flu: If someone in your home has the flu, take TAMIFLU once a day for
54 10 days or for as long as prescribed. You can take TAMIFLU for up to 6 weeks if you are
55 exposed to the flu because of an outbreak in your community. Follow your healthcare
56 professional's advice on how long to take TAMIFLU.

57 TAMIFLU has not been studied in children 1 to 12 years of age for preventing flu during
58 an outbreak in your community or for use for more than 10 days.

59 You can take TAMIFLU with food or without food. There is less chance of stomach
60 upset if you take it with a light snack, milk, or a meal.

61 If you are taking TAMIFLU for Oral Suspension, your pharmacist will give you a dosing
62 dispenser marked with three possible doses. Follow your healthcare professional's
63 instructions on which dose to take or how to combine them for the proper dose for you. In
64 order to be sure you receive the proper dose, it is important that you use the dispenser
65 provided. Review the instructions below on how to use the dispenser and ask your
66 pharmacist if you have any questions. If you lose or damage the dispenser and cannot use
67 it, contact your healthcare professional or pharmacist for advice on the proper dose.

68 If TAMIFLU for Oral Suspension is not available, your healthcare provider may instruct
69 you to open TAMIFLU Capsules and mix the contents with sweetened liquids such as
70 regular or sugar-free chocolate syrup. Please follow the dosing instructions below.

71 If you forget to take your medicine, take the missed dose as soon as you remember,
72 except if it is 2 hours or less before your next dose. Then continue to take TAMIFLU at

73 the usual times. Do not take 2 doses at a time to make up for a missed dose. If you miss
74 several doses, tell your healthcare professional and follow the advice given to you.

75 **What are the possible side effects of TAMIFLU?**

76 The most common side effects of TAMIFLU are nausea and vomiting. These are usually
77 mild to moderate. They usually happen in the first 2 days of treatment. Taking TAMIFLU
78 with food may reduce the chance of getting these side effects.

79 If you develop an allergic reaction or severe rash, stop taking TAMIFLU and contact
80 your healthcare professional.

81 People with the flu, particularly children and adolescents, may be at an increased risk of
82 seizures, confusion, or abnormal behavior early during their illness. These events may
83 occur shortly after beginning TAMIFLU or may occur when flu is not treated. These
84 events are uncommon but may result in accidental injury to the patient. Therefore,
85 patients should be observed for signs of unusual behavior and a healthcare professional
86 should be contacted immediately if the patient shows any signs of unusual behavior.

87 Before taking TAMIFLU, please let your healthcare provider know if you have received
88 nasally administered influenza virus vaccine during the past two weeks.

89 If you notice any side effects not mentioned in this leaflet, or if you have any concerns
90 about the side effects you get, tell your healthcare professional.

91 **How and where should I store TAMIFLU?**

92 TAMIFLU Capsules should be stored at room temperature, 77°F (25°C) and kept in a dry
93 place. Keep this medication out of reach of children.

94 TAMIFLU for Oral Suspension should be stored under refrigeration at 36° to 46°F (2° to
95 8°C). Do not freeze.

96 **General advice about prescription medicines:**

97 Medicines are sometimes prescribed for conditions that are not mentioned in patient
98 information leaflets. Do not use TAMIFLU for a condition for which it was not
99 prescribed. Do not give TAMIFLU to other people, even if they have the same symptoms
100 you have. It may not be right for them.

101 This leaflet summarizes the most important information about TAMIFLU. If you would
102 like more information, talk with your healthcare professional. You can ask your
103 pharmacist or healthcare professional for information about TAMIFLU that is written for
104 health professionals.

105

106 **DOSING INSTRUCTIONS FOR PATIENTS:**

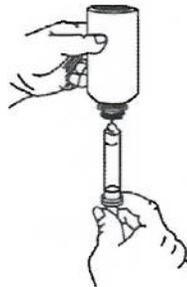
107 **How Do I Prepare TAMIFLU for Oral Suspension?**

108 **Please follow instructions carefully to ensure proper dosing of the oral suspension.**



109

- 110 • Shake closed bottle well for about 5 seconds before each use.
- 111 • Remove child-resistant cap.
- 112 • Before inserting the tip of the oral dispenser into bottle adapter, push the plunger completely down toward the tip of the oral dispenser. Insert tip firmly into opening of the bottle adapter.
- 113
- 114
- 115 • Turn the entire unit (bottle and oral dispenser) upside down.
- 116 • Pull the plunger out slowly until the desired amount of medication is withdrawn into the oral dispenser (see figure). The 75 mg dose is obtained by filling the dispenser twice, once to the 30 mg graduation, and a second fill to the 45 mg graduation.
- 117
- 118



119

- 120 • Turn the entire unit right side up and remove the oral dispenser slowly from the bottle.
- 121
- 122 • Dispense directly into mouth. Do not mix with any liquid prior to dispensing.
- 123 • Close bottle with child-resistant cap after each use.
- 124 • Disassemble oral dispenser, rinse under running tap water and air dry prior to next use.
- 125

126 **If Directed by My Healthcare Provider, How Do I Mix the Contents of TAMIFLU**
 127 **Capsules with Sweetened Liquids?**

128 **Please follow instructions carefully to ensure proper dosing.**

- 129 • Holding one capsule over a small bowl, carefully pull the capsule open and pour the complete contents of the capsule into the bowl.
- 130
- 131 • Add a small amount of a sweetened liquid such as chocolate syrup (regular or sugar-free) that the child will consume completely.
- 132

133 • Stir the mixture and give the entire dose to the child.

134

135 Distributed by:



Pharmaceuticals

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340 Kingsland Street
Nutley, New Jersey 07110-1199

136

137 Licensor:

138 Gilead Sciences, Inc.

139 Foster City, California 94404

140 27899468

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HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

RECENT MAJOR CHANGES

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

INDICATIONS AND USAGE

RELENZA, an influenza neuraminidase inhibitor, is indicated for:
Treatment of influenza in patients 7 years of age and older who have been symptomatic for no more than 2 days. (1.1)
Prophylaxis of influenza in patients 5 years of age and older. (1.2)

Important Limitations on Use of RELENZA:

Not recommended for treatment or prophylaxis of influenza in:

- Individuals with underlying airways disease. (5.1)

Not proven effective for:

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

Not a substitute for annual influenza vaccination. (1.3)

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

DOSAGE AND ADMINISTRATION

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

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

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

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

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

DRUG INTERACTIONS

Live attenuated influenza vaccine, intranasal (7):

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

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

Revised: October 2008
RLZ:5PI

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Influenza

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

1.2 Prophylaxis of Influenza

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

1.3 Important Limitations on Use of RELENZA

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Considerations

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

only under adult supervision and instruction, and the supervising adult should first be instructed by a healthcare professional [see *Patient Counseling Information (17.4)*].

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

2.2 Treatment of Influenza

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

2.3 Prophylaxis of Influenza

Household Setting:

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

Community Outbreaks:

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Bronchospasm

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

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

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

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

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

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

5.2 Allergic Reactions

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

5.3 Neuropsychiatric Events

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

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

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

5.4 Limitations of Populations Studied

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

5.5 Bacterial Infections

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

5.6 Importance of Proper Use of DISKHALER

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

6 ADVERSE REACTIONS

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

6.1 Clinical Trials Experience

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

* 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.

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

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

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

* 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.

6.2 Postmarketing Experience

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

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

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

Cardiac: Arrhythmias, syncope.

Neurologic: Seizures.

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

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

7 DRUG INTERACTIONS

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

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

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

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

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

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

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

8.5 Geriatric Use

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

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

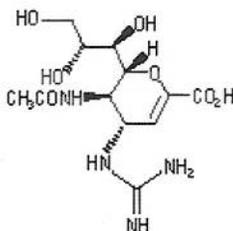
In 2 additional studies of RELENZA for prophylaxis of influenza in the nursing home setting, efficacy was not demonstrated [see *Indications and Usage (1.3)*].

10 OVERDOSAGE

There have been no reports of overdose from administration of RELENZA.

11 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 for oral inhalation 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 (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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

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

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

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

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

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

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

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

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

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

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

12.4 Microbiology

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

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

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

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

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

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

14 CLINICAL STUDIES

14.1 Treatment of Influenza

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

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

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

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

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

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

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

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

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

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

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

14.2 Prophylaxis of Influenza

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

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

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

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

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.6).

17.1 Bronchospasm

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

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

17.2 Concomitant Bronchodilator Use

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

17.3 Neuropsychiatric Events

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

17.4 Instructions for Use

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

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

17.5 Risk of Influenza Transmission to Others

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

17.6 FDA-Approved Patient Labeling and Instructions for Use

See separate leaflet.

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Research Triangle Park, NC 27709

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Patient Labeling

RELENZA[®] (zanamivir) Inhalation Powder

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

What is RELENZA?

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

Important Safety Information About RELENZA

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

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

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

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

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

Who should not take RELENZA?

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

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

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

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

Who should consider taking RELENZA?

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

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

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

Can I take other medications with RELENZA?

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

Before taking RELENZA, please let your healthcare provider know if you received live attenuated influenza vaccine (FLUMIST[®]) intranasal in the past 2 weeks.

How and when should I take RELENZA?

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

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

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

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

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

What if I miss a dose?

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

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

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

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

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

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

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

Should I get a flu shot?

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

What if I am pregnant or nursing?

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

How and where should I store RELENZA?

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

PATIENT INSTRUCTIONS FOR USE



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

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

BEFORE YOU START:

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.

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.

Parts of the DISKHALER:

COVER

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

WHITE MOUTHPIECE

where the medicine is inhaled by mouth

DARK BROWN WHEEL

rotates to the next blister of medicine

WHITE TRAY

pulls in and out of DISKHALER body

RAISED RIDGES

help you pull out the tray for loading

NEEDLE

punctures the blister to release medicine

DISKHALER BODY

HALF-CIRCLE FLAP

lifts up and down to operate plastic needle

SILVER MEDICINE DISK

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

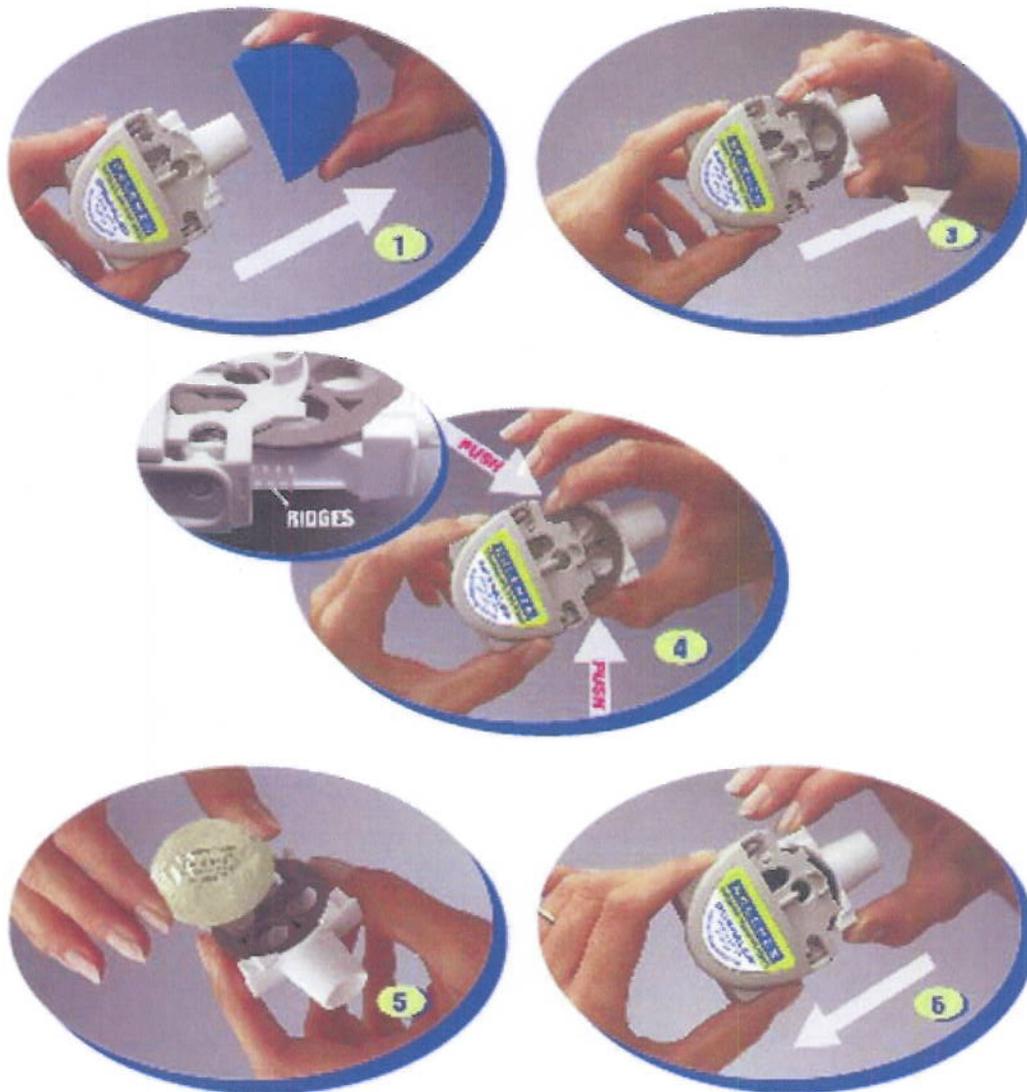


Step-by-step instructions for using the DISKHALER®

Step A: Load the medicine into the DISKHALER

1. Start by pulling off the blue cover.

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.**
3. Pull the white mouthpiece by the edges to extend the white tray all the way.
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.**
5. Place one silver medicine disk onto the dark brown wheel, flat side up. The four silver blisters on the underside of the medicine disk will drop neatly into the four holes in the wheel.
6. Push in the white tray as far as it will go. Now the DISKHALER is loaded with medicine.



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.

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

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



Step C: Inhale

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

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

2. Close your lips firmly around the mouthpiece. Be sure not to cover the small holes on either side of it.
3. Breathe in through your mouth steadily and as deeply as you can. Your breath pulls the medicine into your airways and lungs.
4. Hold your breath for a few seconds to help RELENZA stay in your lungs where it can work.

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

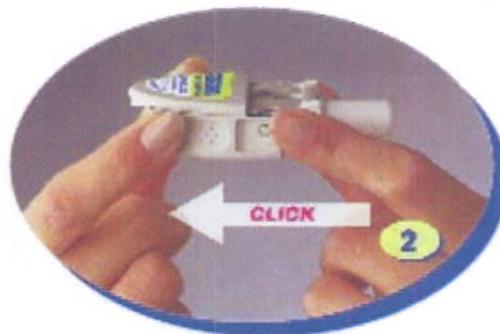
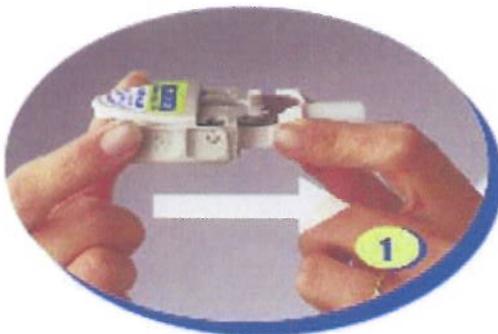
Once you've inhaled the number of blisters prescribed by your healthcare provider, replace the cover until your next dose.



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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