



TAMIFLU®

(oseltamivir phosphate)

CAPSULES

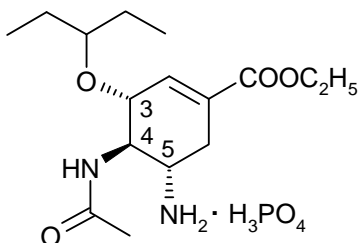
AND FOR ORAL SUSPENSION

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 $C_{16}H_{28}N_2O_4$ (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 30 mg weekly	Hemodialysis 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
441

Table 3 Most Frequent Adverse Events in Studies in Naturally 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 ≥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 ≥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 ≥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: Pharmacokinetics: Special Populations**).
557

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
652 (36° to 46°F).

653 **Room Temperature:** Stable for five days (5 days) when stored at room temperature,
654 25°C (77°F).

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

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

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

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

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

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]

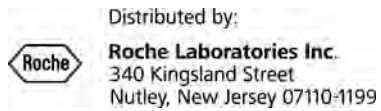
699 Store constituted suspension under refrigeration at 2° to 8°C (36° to 46°F). Do not freeze.

700

701 Humco® is a registered trademark of Humco Holding Group, Inc.

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

703



704

705 Licensor:

706 Gilead Sciences, Inc.

707 Foster City, California 94404

708 27899527

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Patient Information
TAMIFLU®
(oseltamivir phosphate)

R_X ONLY

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

What is TAMIFLU?

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

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

What is “Flu”?

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

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

Should I get a flu shot?

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

Who should not take TAMIFLU?

Do not take TAMIFLU if you are allergic to the main ingredient, oseltamivir phosphate, or to any other ingredients of TAMIFLU. Before starting treatment, make sure your healthcare professional knows if you take any other medicines, or are pregnant, planning to become pregnant, or breastfeeding. TAMIFLU is normally not recommended for use during pregnancy or nursing, as the effects on the

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unborn child or nursing infant are unknown. TAMIFLU is not recommended for use in children younger than 1 year of age.

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

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

How should I take TAMIFLU?

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

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

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

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

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

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

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

If you forget to take your medicine, take the missed dose as soon as you remember, except if it is 2 hours or less before your next dose. Then continue to take TAMIFLU at the usual times. Do not take 2 doses at a time to make up for a missed dose. If you miss several doses, tell your healthcare professional and follow the advice given to you.

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What are the possible side effects of TAMIFLU?

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

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

People with the flu, particularly children and adolescents, may be at an increased risk of seizures, confusion, or abnormal behavior early during their illness. These events may occur shortly after beginning TAMIFLU 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.

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

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

How and where should I store TAMIFLU?

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

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

General advice about prescription medicines:

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

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

DOSING INSTRUCTIONS FOR PATIENTS:

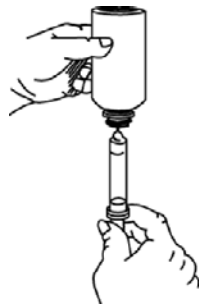
How Do I Prepare TAMIFLU for Oral Suspension?

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

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- Shake closed bottle well for about 5 seconds before each use.
- Remove child-resistant cap.
- 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.
- Turn the entire unit (bottle and oral dispenser) upside down.
- 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.



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

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

Please follow instructions carefully to ensure proper dosing.

- Holding one capsule over a small bowl, carefully pull the capsule open and pour the complete contents of the capsule into the bowl.
- Add a small amount of a sweetened liquid such as chocolate syrup (regular or sugar-free) that the child will consume completely.
- Stir the mixture and give the entire dose to the child.

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/s/

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