



TAMIFLU

(oseltamivir phosphate)

CAPSULES

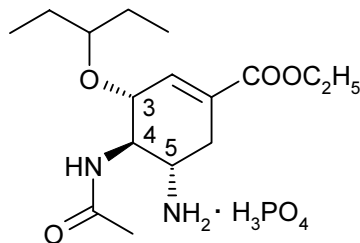
AND FOR ORAL SUSPENSION

R_x only

DESCRIPTION

TAMIFLU (oseltamivir phosphate) is available as a capsule containing 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 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 xanthan gum, monosodium citrate, sodium benzoate, sorbitol, saccharin sodium, titanium dioxide, and tutti-frutti flavoring.

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 is an ethyl ester prodrug requiring ester hydrolysis for conversion to the active form, oseltamivir carboxylate. The proposed mechanism of action of oseltamivir is inhibition of influenza virus neuraminidase with the possibility of alteration of virus particle aggregation and release.

30 **Antiviral Activity In Vitro**

31 The antiviral activity of oseltamivir carboxylate against laboratory strains and clinical
32 isolates of influenza virus was determined in cell culture assays. The concentrations of
33 oseltamivir carboxylate required for inhibition of influenza virus were highly variable
34 depending on the assay method used and the virus tested. The 50% and 90% inhibitory
35 concentrations (IC₅₀ and IC₉₀) were in the range of 0.0008 μM to >35 μM and 0.004 μM
36 to >100 μM, respectively (1 μM=0.284 μg/mL). The relationship between the in vitro
37 antiviral activity in cell culture and the inhibition of influenza virus replication in humans
38 has not been established.

39 **Resistance**

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

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

57 In clinical studies of postexposure and seasonal prophylaxis, determination of resistance
58 was limited by the low overall incidence rate of influenza infection and prophylactic
59 effect of TAMIFLU.

60 **Cross-resistance**

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

69 **Immune Response**

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

73 **CLINICAL PHARMACOLOGY**

74 **Pharmacokinetics**

75 **Absorption and Bioavailability**

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

81 **Table 1 Mean (% CV) Pharmacokinetic Parameters of Oseltamivir**
82 **and Oseltamivir Carboxylate After a Multiple 75 mg Capsule**
83 **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)

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

86 Coadministration with food has no significant effect on the peak plasma concentration
87 (551 ng/mL under fasted conditions and 441 ng/mL under fed conditions) and the area
88 under the plasma concentration time curve (6218 ng·h/mL under fasted conditions and
89 6069 ng·h/mL under fed conditions) of oseltamivir carboxylate.

90 **Distribution**

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

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

96 **Metabolism**

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

100 **Elimination**

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

110 **Special Populations**

111 **Renal Impairment**

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

117 **Table 2 Oseltamivir Carboxylate Exposures in Patients With Normal**
118 **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	75 mg daily	75 mg alternate days	30 mg daily
				30 mg weekly	30 mg alternate HD cycle			
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

119 *Observed values. All other values are predicted.

120 AUC normalized to 48 hours.

121 **Pediatric Patients**

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

130 **Geriatric Patients**

131 Exposure to oseltamivir carboxylate at steady-state was 25% to 35% higher in geriatric
132 patients (age range 65 to 78 years) compared to young adults given comparable doses of

133 oseltamivir. Half-lives observed in the geriatric patients were similar to those seen in
134 young adults. Based on drug exposure and tolerability, dose adjustments are not required
135 for geriatric patients for either treatment or prophylaxis (see **DOSAGE AND**
136 **ADMINISTRATION: Special Dosage Instructions**).

137 **INDICATIONS AND USAGE**

138 **Treatment of Influenza**

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

142 **Prophylaxis of Influenza**

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

144 TAMIFLU is not a substitute for early vaccination on an annual basis as recommended
145 by the Centers for Disease Control’s Immunization Practices Advisory Committee.

146 **Description of Clinical Studies: Studies in Naturally Occurring Influenza**

147 **Treatment of Influenza**

148 *Adult Patients*

149 Two phase III placebo-controlled and double-blind clinical trials were conducted: one in
150 the USA and one outside the USA. Patients were eligible for these trials if they had fever
151 >100°F, accompanied by at least one respiratory symptom (cough, nasal symptoms or
152 sore throat) and at least one systemic symptom (myalgia, chills/sweats, malaise, fatigue
153 or headache) and influenza virus was known to be circulating in the community. In
154 addition, all patients enrolled in the trials were allowed to take fever-reducing
155 medications.

156 Of 1355 patients enrolled in these two trials, 849 (63%) patients were influenza-infected
157 (age range 18 to 65 years; median age 34 years; 52% male; 90% Caucasian; 31%
158 smokers). Of the 849 influenza-infected patients, 95% were infected with influenza A,
159 3% with influenza B, and 2% with influenza of unknown type.

160 TAMIFLU was started within 40 hours of onset of symptoms. Subjects participating in
161 the trials were required to self-assess the influenza-associated symptoms as “none”,
162 “mild”, “moderate” or “severe”. Time to improvement was calculated from the time of
163 treatment initiation to the time when all symptoms (nasal congestion, sore throat, cough,
164 aches, fatigue, headaches, and chills/sweats) were assessed as “none” or “mild”. In both
165 studies, at the recommended dose of TAMIFLU 75 mg twice daily for 5 days, there was a
166 1.3 day reduction in the median time to improvement in influenza-infected subjects
167 receiving TAMIFLU compared to subjects receiving placebo. Subgroup analyses of these
168 studies by gender showed no differences in the treatment effect of TAMIFLU in men and
169 women.

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

172 *Geriatric Patients*

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

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

182 *Pediatric Patients*

183 One double-blind placebo-controlled treatment trial was conducted in pediatric patients
184 aged 1 to 12 years (median age 5 years), who had fever ($>100^{\circ}\text{F}$) plus one respiratory
185 symptom (cough or coryza) when influenza virus was known to be circulating in the
186 community. Of 698 patients enrolled in this trial, 452 (65%) were influenza-infected
187 (50% male; 68% Caucasian). Of the 452 influenza-infected patients, 67% were infected
188 with influenza A and 33% with influenza B.

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

196 **Prophylaxis of Influenza**

197 *Adult Patients*

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

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

210 In a seasonal prophylaxis study in elderly residents of skilled nursing homes, TAMIFLU
211 75 mg once daily taken for 42 days reduced the incidence of laboratory-confirmed
212 clinical influenza from 4.4% (12/272) for the placebo group to 0.4% (1/276) for the
213 TAMIFLU group. About 80% of this elderly population were vaccinated, 14% of
214 subjects had chronic airway obstructive disorders, and 43% had cardiac disorders.

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

220 *Pediatric Patients*

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

233 **CONTRAINDICATIONS**

234 TAMIFLU is contraindicated in patients with known hypersensitivity to any of the
235 components of the product.

236 **PRECAUTIONS**

237 **General**

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

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

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

245 Efficacy of TAMIFLU in the treatment of subjects with chronic cardiac disease and/or
246 respiratory disease has not been established. No difference in the incidence of
247 complications was observed between the treatment and placebo groups in this population.
248 No information is available regarding treatment of influenza in patients with any medical

249 condition sufficiently severe or unstable to be considered at imminent risk of requiring
250 hospitalization.

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

252 Efficacy of TAMIFLU for treatment or prophylaxis has not been established in
253 immunocompromised patients.

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

257 **Hepatic Impairment**

258 The safety and pharmacokinetics in patients with hepatic impairment have not been
259 evaluated.

260 **Renal Impairment**

261 Dose adjustment is recommended for patients with a serum creatinine clearance
262 <30 mL/min (see **DOSAGE AND ADMINISTRATION**).

263 **Serious Skin/Hypersensitivity Reactions**

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

268 **Neuropsychiatric Events**

269 There have been postmarketing reports (mostly from Japan) of self-injury and delirium
270 with the use of TAMIFLU in patients with influenza. The reports were primarily among
271 pediatric patients. The relative contribution of the drug to these events is not known.
272 Patients with influenza should be closely monitored for signs of abnormal behavior
273 throughout the treatment period.

274 **Information for Patients**

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

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

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

283 **Drug Interactions**

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

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

293 Oseltamivir is extensively converted to oseltamivir carboxylate by esterases, located
294 predominantly in the liver. Drug interactions involving competition for esterases have not
295 been extensively reported in literature. Low protein binding of oseltamivir and
296 oseltamivir carboxylate suggests that the probability of drug displacement interactions is
297 low.

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

300 Cimetidine, a non-specific inhibitor of cytochrome P450 isoforms and competitor for
301 renal tubular secretion of basic or cationic drugs, has no effect on plasma levels of
302 oseltamivir or oseltamivir carboxylate.

303 Clinically important drug interactions involving competition for renal tubular secretion
304 are unlikely due to the known safety margin for most of these drugs, the elimination
305 characteristics of oseltamivir carboxylate (glomerular filtration and anionic tubular
306 secretion) and the excretion capacity of these pathways. Coadministration of probenecid
307 results in an approximate twofold increase in exposure to oseltamivir carboxylate due to a
308 decrease in active anionic tubular secretion in the kidney. However, due to the safety
309 margin of oseltamivir carboxylate, no dose adjustments are required when
310 coadministering with probenecid.

311 Coadministration with amoxicillin does not alter plasma levels of either compound,
312 indicating that competition for the anionic secretion pathway is weak.

313 In six subjects, multiple doses of oseltamivir did not affect the single-dose
314 pharmacokinetics of acetaminophen.

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

316 Long-term carcinogenicity tests with oseltamivir are underway but have not been
317 completed. However, a 26-week dermal carcinogenicity study of oseltamivir carboxylate
318 in FVB/Tg.AC transgenic mice was negative. The animals were dosed at 40, 140, 400 or
319 780 mg/kg/day in two divided doses. The highest dose represents the maximum feasible
320 dose based on the solubility of the compound in the control vehicle. A positive control,
321 tetradecanoyl phorbol-13-acetate administered at 2.5 µg per dose three times per week
322 gave a positive response.

323 Oseltamivir was found to be non-mutagenic in the Ames test and the human lymphocyte
324 chromosome assay with and without enzymatic activation and negative in the mouse
325 micronucleus test. It was found to be positive in a Syrian Hamster Embryo (SHE) cell
326 transformation test. Oseltamivir carboxylate was non-mutagenic in the Ames test and the
327 L5178Y mouse lymphoma assay with and without enzymatic activation and negative in
328 the SHE cell transformation test.

329 In a fertility and early embryonic development study in rats, doses of oseltamivir at 50,
330 250, and 1500 mg/kg/day were administered to females for 2 weeks before mating,
331 during mating and until day 6 of pregnancy. Males were dosed for 4 weeks before
332 mating, during and for 2 weeks after mating. There were no effects on fertility, mating
333 performance or early embryonic development at any dose level. The highest dose was
334 approximately 100 times the human systemic exposure (AUC_{0-24h}) of oseltamivir
335 carboxylate.

336 **Pregnancy**

337 **Pregnancy Category C**

338 There are insufficient human data upon which to base an evaluation of risk of TAMIFLU
339 to the pregnant woman or developing fetus. Studies for effects on embryo-fetal
340 development were conducted in rats (50, 250, and 1500 mg/kg/day) and rabbits (50, 150,
341 and 500 mg/kg/day) by the oral route. Relative exposures at these doses were,
342 respectively, 2, 13, and 100 times human exposure in the rat and 4, 8, and 50 times
343 human exposure in the rabbit. Pharmacokinetic studies indicated that fetal exposure was
344 seen in both species. In the rat study, minimal maternal toxicity was reported in the 1500
345 mg/kg/day group. In the rabbit study, slight and marked maternal toxicities were
346 observed, respectively, in the 150 and 500 mg/kg/day groups. There was a dose-
347 dependent increase in the incidence rates of a variety of minor skeletal abnormalities and
348 variants in the exposed offspring in these studies. However, the individual incidence rate
349 of each skeletal abnormality or variant remained within the background rates of
350 occurrence in the species studied.

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

354 **Nursing Mothers**

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

359 **Geriatric Use**

360 The safety of TAMIFLU has been established in clinical studies which enrolled 741
361 subjects (374 received placebo and 362 received TAMIFLU). Some seasonal variability
362 was noted in the clinical efficacy outcomes (see **INDICATIONS AND USAGE:**

363 **Description of Clinical Studies: Studies in Naturally Occurring Influenza:**
364 **Treatment of Influenza: Geriatric Patients).**

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

370 **Pediatric Use**

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

377 **ANIMAL TOXICOLOGY**

378 In a 2-week study in unweaned rats, administration of a single dose of 1000 mg/kg
379 oseltamivir phosphate to 7-day-old rats resulted in deaths associated with unusually high
380 exposure to the prodrug. However, at 2000 mg/kg, there were no deaths or other
381 significant effects in 14-day-old unweaned rats. Further follow-up investigations of the
382 unexpected deaths of 7-day-old rats at 1000 mg/kg revealed that the concentrations of the
383 prodrug in the brains were approximately 1500-fold those of the brains of adult rats
384 administered the same oral dose of 1000 mg/kg, and those of the active metabolite were
385 approximately 3-fold higher. Plasma levels of the prodrug were 10-fold higher in 7-day-
386 old rats as compared with adult rats. These observations suggest that the levels of
387 oseltamivir in the brains of rats decrease with increasing age and most likely reflect the
388 maturation stage of the blood-brain barrier. No adverse effects occurred at 500 mg/kg/day
389 administered to 7- to 21-day-old rats. At this dosage, the exposure to prodrug was
390 approximately 800-fold the exposure expected in a 1-year-old child.

391 **ADVERSE REACTIONS**

392 **Treatment Studies in Adult Patients**

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

399 Adverse events that occurred with an incidence of $\geq 1\%$ in 1440 patients taking placebo or
400 TAMIFLU 75 mg twice daily in adult phase III treatment studies are shown in **Table 3**.
401 This summary includes 945 healthy young adults and 495 “at risk” patients (elderly
402 patients and patients with chronic cardiac or respiratory disease). Those events reported

403 numerically more frequently in patients taking TAMIFLU compared with placebo were
 404 nausea, vomiting, bronchitis, insomnia, and vertigo.

405 **Prophylaxis Studies in Adult Patients**

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

416 **Table 3 Most Frequent Adverse Events in Studies in Naturally**
 417 **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%)

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

420 Adverse events included are: all events reported in the treatment studies with frequency
 421 ≥1% in the oseltamivir 75 mg bid group.

422 Additional adverse events occurring in <1% of patients receiving TAMIFLU for
 423 treatment included unstable angina, anemia, pseudomembranous colitis, humerus
 424 fracture, pneumonia, pyrexia, and peritonsillar abscess.

425 **Treatment Studies in Pediatric Patients**

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

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

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

438 **Prophylaxis in Pediatric Patients**

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

443 **Table 4 Most Frequent Adverse Events Occurring in Children Aged**
 444 **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%)	-	-

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

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

449 ^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

450

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

453 **Observed During Clinical Practice**

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

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

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

462 Digestive: Hepatitis, liver function tests abnormal

463 Cardiac: Arrhythmia

464 Neurologic: Seizure, confusion

465 Metabolic: Aggravation of diabetes

466 **OVERDOSAGE**

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

469 **DOSAGE AND ADMINISTRATION**

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

473 **Standard Dosage – Treatment of Influenza:**

474 **Adults and Adolescents**

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

478 **Pediatric Patients**

479 TAMIFLU is not indicated for treatment of influenza in pediatric patients younger than
480 1 year.

481 The recommended oral dose of TAMIFLU Oral Suspension for pediatric patients 1 year
482 and older or adult patients who cannot swallow a capsule is:

Body Weight in kg	Body Weight in lbs	Recommended Dose for 5 Days	Number of Bottles Needed to Obtain the Recommended Dose
≤15 kg	≤33 lbs	30 mg twice daily	1
>15 kg to 23 kg	>33 lbs to 51 lbs	45 mg twice daily	2
>23 kg to 40 kg	>51 lbs to 88 lbs	60 mg twice daily	2
>40 kg	>88 lbs	75 mg twice daily	3

483 An oral dosing dispenser with 30 mg, 45 mg, and 60 mg graduations is provided with the
484 oral suspension; the 75 mg dose can be measured using a combination of 30 mg and
485 45 mg. It is recommended that patients use this dispenser. In the event that the dispenser
486 provided is lost or damaged, another dosing syringe or other device may be used to
487 deliver the following volumes: 2.5 mL (1/2 tsp) for children ≤15 kg, 3.8 mL (3/4 tsp) for
488 >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.

489 **Standard Dosage – Prophylaxis of Influenza:**

490 **Adults and Adolescents**

491 The recommended oral dose of TAMIFLU for prophylaxis of influenza in adults and
492 adolescents 13 years and older following close contact with an infected individual is
493 75 mg once daily for at least 10 days. Therapy should begin within 2 days of exposure.
494 The recommended dose for prophylaxis during a community outbreak of influenza is
495 75 mg once daily. Safety and efficacy have been demonstrated for up to 6 weeks. The
496 duration of protection lasts for as long as dosing is continued.

497 **Pediatric Patients**

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

500 The recommended oral dose of TAMIFLU Oral Suspension for pediatric patients 1 year
501 and older following close contact with an infected individual is:

Body Weight in kg	Body Weight in lbs	Recommended Dose for 10 Days	Number of Bottles Needed to Obtain the Recommended Dose
≤15 kg	≤33 lbs	30 mg once daily	1
>15 kg to 23 kg	>33 lbs to 51 lbs	45 mg once daily	2
>23 kg to 40 kg	>51 lbs to 88 lbs	60 mg once daily	2
>40 kg	>88 lbs	75 mg once daily	3

502 An oral dosing dispenser with 30 mg, 45 mg, and 60 mg graduations is provided with the
503 oral suspension; the 75 mg dose can be measured using a combination of 30 mg and
504 45 mg. It is recommended that patients use this dispenser. In the event that the dispenser
505 provided is lost or damaged, another dosing syringe or other device may be used to
506 deliver the following volumes: 2.5 mL (1/2 tsp) for children ≤15 kg, 3.8 mL (3/4 tsp) for
507 >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.

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

512 **Special Dosage Instructions**

513 **Hepatic Impairment**

514 The safety and pharmacokinetics in patients with hepatic impairment have not been
515 evaluated.

516 **Renal Impairment**

517 For plasma concentrations of oseltamivir carboxylate predicted to occur following
518 various dosing schedules in patients with renal impairment (see **CLINICAL**
519 **PHARMACOLOGY: Pharmacokinetics: Special Populations**).

520 *Treatment of Influenza*

521 Dose adjustment is recommended for patients with creatinine clearance between 10 and
522 30 mL/min receiving TAMIFLU for the treatment of influenza. In these patients it is
523 recommended that the dose be reduced to 75 mg of TAMIFLU once daily for 5 days. No
524 recommended dosing regimens are available for patients undergoing routine
525 hemodialysis and continuous peritoneal dialysis treatment with end-stage renal disease.

526 *Prophylaxis of Influenza*

527 For the prophylaxis of influenza, dose adjustment is recommended for patients with
528 creatinine clearance between 10 and 30 mL/min receiving TAMIFLU. In these patients it
529 is recommended that the dose be reduced to 75 mg of TAMIFLU every other day or
530 30 mg TAMIFLU Oral Suspension every day. No recommended dosing regimens are
531 available for patients undergoing routine hemodialysis and continuous peritoneal dialysis
532 treatment with end-stage renal disease.

533 **Geriatric Patients**

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

536 **Preparation of TAMIFLU Oral Suspension**

537 It is recommended that TAMIFLU Oral Suspension be constituted by the pharmacist
538 prior to dispensing to the patient:

- 539 1. Tap the closed bottle several times to loosen the powder.
- 540 2. Measure **23 mL** of water in a graduated cylinder.
- 541 3. Add the total amount of water for constitution to the bottle and shake the closed bottle
542 well for 15 seconds.
- 543 4. Remove the child-resistant cap and push bottle adapter into the neck of the bottle.
- 544 5. Close bottle with child-resistant cap tightly. This will assure the proper seating of the
545 bottle adapter in the bottle and child-resistant status of the cap.

546 NOTE: SHAKE THE TAMIFLU ORAL SUSPENSION WELL BEFORE EACH USE.

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

551 **Emergency Compounding of an Oral Suspension from TAMIFLU**
552 **Capsules**

553 **(Final Concentration 15 mg/mL)**

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

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

559 Commercially manufactured TAMIFLU Oral Suspension (12 mg/mL) is the preferred
560 product for pediatric and adult patients who have difficulty swallowing capsules or where
561 lower doses are needed. In the event that TAMIFLU Oral Suspension is not available, the

562 pharmacist may compound a suspension (15 mg/mL) from TAMIFLU (oseltamivir
 563 phosphate) Capsules 75 mg using either of two vehicles: Cherry Syrup (Humco®) or
 564 Ora-Sweet SF (sugar-free) (Paddock Laboratories). Other vehicles have not been
 565 studied. **This compounded suspension should not be used for convenience or when**
 566 **the FDA-approved TAMIFLU Oral Suspension is commercially available.**

567 First, calculate the Total Volume of an oral suspension needed to be compounded and
 568 dispensed for each patient. The Total Volume required is determined by the weight of
 569 each patient. Refer to **Table 5**.

570 **Table 5 Volume of an Oral Suspension (15 mg/mL) needed to be**
 571 **compounded based upon the patient's weight**

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

572

573 Second, determine the number of capsules and the amount of vehicle (Cherry Syrup or
 574 Ora-Sweet SF) that are needed to prepare the Total Volume (calculated from Table 5: 30
 575 mL, 40 mL, 50 mL, or 60 mL) of compounded oral suspension (15 mg/mL). Refer to
 576 **Table 6**.

577 **Table 6 Number of TAMIFLU 75 mg Capsules and Amount of Vehicle**
 578 **(Cherry Syrup OR Ora-Sweet SF) Needed to Prepare the**
 579 **Total Volume of a Compounded Oral Suspension (15 mg/mL)**

Total Volume of Compounded Oral Suspension needed to be Prepared	30 mL	40 mL	50 mL	60 mL
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	29 mL	38.5 mL	48 mL	57 mL

Laboratories				
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580

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

- 583 1. Carefully separate the capsule body and cap and transfer the contents of the required
584 number of TAMIFLU 75 mg Capsules into a clean mortar.
- 585 2. Triturate the granules to a fine powder.
- 586 3. Add one-third (1/3) of the specified amount of vehicle and triturate the powder until a
587 uniform suspension is achieved.
- 588 4. Transfer the suspension to an amber glass or amber polyethyleneterephthalate (PET)
589 bottle. A funnel may be used to eliminate any spillage.
- 590 5. Add another one-third (1/3) of the vehicle to the mortar, rinse the pestle and mortar
591 by a triturating motion and transfer the vehicle into the bottle.
- 592 6. Repeat the rinsing (Step 5) with the remainder of the vehicle.
- 593 7. Close the bottle using a child-resistant cap.
- 594 8. Shake well to completely dissolve the active drug and to insure homogeneous
595 distribution of the dissolved drug in the resulting suspension. (Note: The active drug,
596 oseltamivir phosphate, readily dissolves in the specified vehicles. The suspension is
597 caused by some of the inert ingredients of TAMIFLU Capsules which are insoluble in
598 these vehicles.)
- 599 9. Put an ancillary label on the bottle indicating “Shake Gently Before Use”. [This
600 compounded suspension should be gently shaken prior to administration to minimize
601 the tendency for air entrapment, particularly with the Ora-Sweet SF preparation.]
- 602 10. Instruct the parent or guardian that any remaining material following completion of
603 therapy must be discarded by either affixing an ancillary label to the bottle or adding
604 a statement to the pharmacy label instructions.
- 605 11. Place an appropriate expiration date label according to storage condition (see below).
606

607 **STORAGE OF THE PHARMACY-COMPOUNDED SUSPENSION:**

608 **Refrigeration:** Stable for 5 weeks (35 days) when stored in a refrigerator at 2° to 8°C
609 (36° to 46°F).

610 **Room Temperature:** Stable for five days (5 days) when stored at room temperature,
611 25°C (77°F).

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

616 Place a pharmacy label on the bottle that includes the patient’s name, dosing instructions,
617 and drug name and any other required information to be in compliance with all State and
618 Federal Pharmacy Regulations. **Refer to Table 7 for the proper dosing instructions.**

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

622 **Table 7** Dosing Chart for Pharmacy-Compounded Suspension from
623 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 or less	33 lbs or less	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 or more	89 lbs or more	75 mg	5 mL	5 mL two times a day	5 mL once daily

624 *Note: 1 teaspoon = 5 mL*

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

631 **HOW SUPPLIED**

632 **TAMIFLU Capsules**

633 Supplied as 75-mg (75 mg free base equivalent of the phosphate salt) grey/light yellow
634 hard gelatin capsules. "ROCHE" is printed in blue ink on the grey body and "75 mg" is
635 printed in blue ink on the light yellow cap. Available in blister packages of 10 (NDC
636 0004-0800-85).

637 **Storage**

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

640 **TAMIFLU for Oral Suspension**

641 Supplied as a white powder blend for constitution to a white tutti-frutti-flavored
642 suspension. Available in glass bottles containing approximately 33 mL of suspension
643 after constitution. Each bottle delivers 25 mL of suspension equivalent to 300 mg

644 oseltamivir base. Each bottle is supplied with a bottle adapter and 1 oral dispenser (NDC
645 0004-0810-95).

646 **Storage**

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

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

650

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653

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