



TAMIFLU®

(oseltamivir phosphate)

CAPSULES

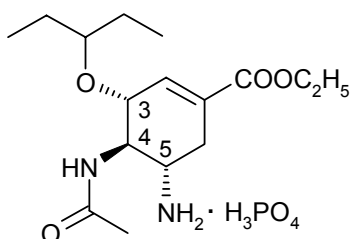
AND FOR ORAL SUSPENSION

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 C₁₆H₂₈N₂O₄ (free base). The molecular weight is 312.4 for oseltamivir free base and 410.4 for oseltamivir phosphate salt. The structural formula is as follows:



MICROBIOLOGY

Mechanism of Action

Oseltamivir 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 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 |

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 **Information for Patients**

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

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

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

277 **Drug Interactions**

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

280 Oseltamivir is extensively converted to oseltamivir carboxylate by esterases, located
281 predominantly in the liver. Drug interactions involving competition for esterases have not
282 been extensively reported in literature. Low protein binding of oseltamivir and
283 oseltamivir carboxylate suggests that the probability of drug displacement interactions is
284 low.

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

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

290 Clinically important drug interactions involving competition for renal tubular secretion
291 are unlikely due to the known safety margin for most of these drugs, the elimination
292 characteristics of oseltamivir carboxylate (glomerular filtration and anionic tubular
293 secretion) and the excretion capacity of these pathways. Coadministration of probenecid
294 results in an approximate twofold increase in exposure to oseltamivir carboxylate due to a
295 decrease in active anionic tubular secretion in the kidney. However, due to the safety
296 margin of oseltamivir carboxylate, no dose adjustments are required when
297 coadministering with probenecid.

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

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

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

303 Long-term carcinogenicity tests with oseltamivir are underway but have not been
304 completed. However, a 26-week dermal carcinogenicity study of oseltamivir carboxylate
305 in FVB/Tg.AC transgenic mice was negative. The animals were dosed at 40, 140, 400 or
306 780 mg/kg/day in two divided doses. The highest dose represents the maximum feasible
307 dose based on the solubility of the compound in the control vehicle. A positive control,
308 tetradecanoyl phorbol-13-acetate administered at 2.5 µg per dose three times per week
309 gave a positive response.

310 Oseltamivir was found to be non-mutagenic in the Ames test and the human lymphocyte
311 chromosome assay with and without enzymatic activation and negative in the mouse
312 micronucleus test. It was found to be positive in a Syrian Hamster Embryo (SHE) cell
313 transformation test. Oseltamivir carboxylate was non-mutagenic in the Ames test and the
314 L5178Y mouse lymphoma assay with and without enzymatic activation and negative in
315 the SHE cell transformation test.

316 In a fertility and early embryonic development study in rats, doses of oseltamivir at 50,
317 250, and 1500 mg/kg/day were administered to females for 2 weeks before mating,
318 during mating and until day 6 of pregnancy. Males were dosed for 4 weeks before
319 mating, during and for 2 weeks after mating. There were no effects on fertility, mating
320 performance or early embryonic development at any dose level. The highest dose was
321 approximately 100 times the human systemic exposure (AUC_{0-24h}) of oseltamivir
322 carboxylate.

323 **Pregnancy**

324 **Pregnancy Category C**

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

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

341 **Nursing Mothers**

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

346 **Geriatric Use**

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

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

357 **Pediatric Use**

358 The safety and efficacy of TAMIFLU in pediatric patients younger than 1 year of age
359 have not been studied. TAMIFLU is not indicated for either treatment or prophylaxis of
360 influenza in pediatric patients younger than 1 year of age because of uncertainties
361 regarding the rate of development of the human blood-brain barrier and the unknown

362 clinical significance of non-clinical animal toxicology data for human infants (see
363 **ANIMAL TOXICOLOGY**).

364 **ANIMAL TOXICOLOGY**

365 In a 2-week study in unweaned rats, administration of a single dose of 1000 mg/kg
366 oseltamivir phosphate to 7-day-old rats resulted in deaths associated with unusually high
367 exposure to the prodrug. However, at 2000 mg/kg, there were no deaths or other
368 significant effects in 14-day-old unweaned rats. Further follow-up investigations of the
369 unexpected deaths of 7-day-old rats at 1000 mg/kg revealed that the concentrations of the
370 prodrug in the brains were approximately 1500-fold those of the brains of adult rats
371 administered the same oral dose of 1000 mg/kg, and those of the active metabolite were
372 approximately 3-fold higher. Plasma levels of the prodrug were 10-fold higher in 7-day-
373 old rats as compared with adult rats. These observations suggest that the levels of
374 oseltamivir in the brains of rats decrease with increasing age and most likely reflect the
375 maturation stage of the blood-brain barrier. No adverse effects occurred at 500 mg/kg/day
376 administered to 7- to 21-day-old rats. At this dosage, the exposure to prodrug was
377 approximately 800-fold the exposure expected in a 1-year-old child.

378 **ADVERSE REACTIONS**

379 **Treatment Studies in Adult Patients**

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

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

392 **Prophylaxis Studies in Adult Patients**

393 A total of 4187 subjects (adolescents, healthy adults and elderly) participated in phase
394 III prophylaxis studies, of whom 1790 received the recommended dose of 75 mg once
395 daily for up to 6 weeks. Adverse events were qualitatively very similar to those seen in
396 the treatment studies, despite a longer duration of dosing (see **Table 3**). Events reported
397 more frequently in subjects receiving TAMIFLU compared to subjects receiving placebo
398 in prophylaxis studies, and more commonly than in treatment studies, were aches and
399 pains, rhinorrhea, dyspepsia and upper respiratory tract infections. However, the
400 difference in incidence between TAMIFLU and placebo for these events was less than
401 1%. There were no clinically relevant differences in the safety profile of the 942 elderly
402 subjects who received TAMIFLU or placebo, compared with the younger population.

403

404 **Table 3** Most Frequent Adverse Events in Studies in Naturally
 405 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%) |

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

408 Adverse events included are: all events reported in the treatment studies with frequency
 409 $\geq 1\%$ in the oseltamivir 75 mg bid group.

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

413 **Treatment Studies in Pediatric Patients**

414 A total of 1032 pediatric patients aged 1 to 12 years (including 698 otherwise healthy
 415 pediatric patients aged 1 to 12 years and 334 asthmatic pediatric patients aged 6 to 12
 416 years) participated in phase III studies of TAMIFLU given for the treatment of influenza.
 417 A total of 515 pediatric patients received treatment with TAMIFLU oral suspension.

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

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

426 **Prophylaxis in Pediatric Patients**

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

431

432 **Table 4 Most Frequent Adverse Events Occurring in Children Aged**
 433 **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%) | - | - |

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

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

438 ^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 |

439

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

442 **Observed During Clinical Practice**

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

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

449 Dermatologic: Dermatitis, rash, eczema, urticaria, erythema multiforme, Stevens-
450 Johnson-Syndrome, toxic epidermal necrolysis (see PRECAUTIONS).

451 Digestive: Hepatitis, liver function tests abnormal

452 Cardiac: Arrhythmia

453 Neurologic: Seizure, confusion

454 Metabolic: Aggravation of diabetes

455 **OVERDOSAGE**

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

458 **DOSAGE AND ADMINISTRATION**

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

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

463 **Adults and Adolescents**

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

467 **Pediatric Patients**

468 TAMIFLU is not indicated for treatment of influenza in pediatric patients younger than
469 1 year.

470 The recommended oral dose of TAMIFLU oral suspension for pediatric patients 1 year
471 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 |

472 An oral dosing dispenser with 30 mg, 45 mg, and 60 mg graduations is provided with the
473 oral suspension; the 75 mg dose can be measured using a combination of 30 mg and
474 45 mg. It is recommended that patients use this dispenser. In the event that the dispenser
475 provided is lost or damaged, another dosing syringe or other device may be used to
476 deliver the following volumes: 2.5 mL (1/2 tsp) for children ≤15 kg, 3.8 mL (3/4 tsp) for
477 >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.

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

479 **Adults and Adolescents**

480 The recommended oral dose of TAMIFLU for prophylaxis of influenza in adults and
481 adolescents 13 years and older following close contact with an infected individual is
482 75 mg once daily for at least 10 days. Therapy should begin within 2 days of exposure.
483 The recommended dose for prophylaxis during a community outbreak of influenza is
484 75 mg once daily. Safety and efficacy have been demonstrated for up to 6 weeks. The
485 duration of protection lasts for as long as dosing is continued.

486 **Pediatric Patients**

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

489 The recommended oral dose of TAMIFLU oral suspension for pediatric patients 1 year
490 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 |

491 An oral dosing dispenser with 30 mg, 45 mg, and 60 mg graduations is provided with the
492 oral suspension; the 75 mg dose can be measured using a combination of 30 mg and
493 45 mg. It is recommended that patients use this dispenser. In the event that the dispenser
494 provided is lost or damaged, another dosing syringe or other device may be used to
495 deliver the following volumes: 2.5 mL (1/2 tsp) for children ≤15 kg, 3.8 mL (3/4 tsp) for
496 >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.

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

501 **Special Dosage Instructions**

502 **Hepatic Impairment**

503 The safety and pharmacokinetics in patients with hepatic impairment have not been
504 evaluated.

505 **Renal Impairment**

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

509 *Treatment of Influenza*

510 Dose adjustment is recommended for patients with creatinine clearance between 10 and
511 30 mL/min receiving TAMIFLU for the treatment of influenza. In these patients it is
512 recommended that the dose be reduced to 75 mg of TAMIFLU once daily for 5 days. No
513 recommended dosing regimens are available for patients undergoing routine
514 hemodialysis and continuous peritoneal dialysis treatment with end-stage renal disease.

515 *Prophylaxis of Influenza*

516 For the prophylaxis of influenza, dose adjustment is recommended for patients with
517 creatinine clearance between 10 and 30 mL/min receiving TAMIFLU. In these patients it
518 is recommended that the dose be reduced to 75 mg of TAMIFLU every other day or
519 30 mg TAMIFLU oral suspension every day. No recommended dosing regimens are
520 available for patients undergoing routine hemodialysis and continuous peritoneal dialysis
521 treatment with end-stage renal disease.

522 **Geriatric Patients**

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

525 **Preparation of TAMIFLU Oral Suspension**

526 It is recommended that TAMIFLU oral suspension be constituted by the pharmacist prior
527 to dispensing to the patient:

- 528 1. Tap the closed bottle several times to loosen the powder.
- 529 2. Measure **23 mL** of water in a graduated cylinder.
- 530 3. Add the total amount of water for constitution to the bottle and shake the closed bottle
531 well for 15 seconds.
- 532 4. Remove the child-resistant cap and push bottle adapter into the neck of the bottle.
- 533 5. Close bottle with child-resistant cap tightly. This will assure the proper seating of the
534 bottle adapter in the bottle and child-resistant status of the cap.

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

536 The constituted oral suspension should be used within 10 days of preparation; the
537 pharmacist should write the date of expiration of the constituted suspension on a
538 pharmacy label. The patient package insert and oral dispenser should be dispensed to the
539 patient.

540 **HOW SUPPLIED**

541 **TAMIFLU Capsules**

542 Supplied as 75-mg (75 mg free base equivalent of the phosphate salt) grey/light yellow
543 hard gelatin capsules. "ROCHE" is printed in blue ink on the grey body and "75 mg" is
544 printed in blue ink on the light yellow cap. Available in blister packages of 10 (NDC
545 0004-0800-85).

546 **Storage**

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

549 **TAMIFLU for Oral Suspension**

550 Supplied as a white powder blend for constitution to a white tutti-frutti-flavored
551 suspension. Available in glass bottles containing 25 mL of suspension after constitution
552 equivalent to 300 mg oseltamivir base. Each bottle is supplied with a bottle adapter and
553 1 oral dispenser (NDC 0004-0810-95).

554 **Storage**

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

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

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