

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

TAMIFLU® (oseltamivir phosphate) capsules
TAMIFLU® (oseltamivir phosphate) for oral suspension
Initial U.S. Approval: 1999

----- **RECENT MAJOR CHANGES** -----
Dosage and Administration (2.1, 2.2, 2.3, 2.7, 2.8) 3/2011

----- **INDICATIONS AND USAGE** -----

TAMIFLU is an influenza neuraminidase inhibitor indicated for:

- Treatment of influenza in patients 1 year and older who have been symptomatic for no more than 2 days. (1.1)
 - Prophylaxis of influenza in patients 1 year and older. (1.2)
- Important Limitations of Use:**
- Efficacy not established in patients who begin therapy after 48 hours of symptoms. (1.3)
 - Not a substitute for annual influenza vaccination. (1.3)
 - No evidence of efficacy for illness from agents other than influenza viruses types A and B. (1.3)
 - Consider available information on influenza drug susceptibility patterns and treatment effects when deciding whether to use. (1.3)

----- **DOSAGE AND ADMINISTRATION** -----

Treatment of influenza (2.2)

- Adults and adolescents (13 years and older): 75 mg twice daily for 5 days
- Pediatric patients (1 year and older): Based on weight twice daily for 5 days
- Renally impaired patients (creatinine clearance 10-30 mL/min): Reduce to 75 mg once daily for 5 days (2.4)

Prophylaxis of influenza (2.3)

- Adults and adolescents (13 years and older): 75 mg once daily for at least 10 days
 - Community outbreak: 75 mg once daily for up to 6 weeks
- Pediatric patients (1 year and older): Based on weight once daily for 10 days
 - Community outbreak: Based on weight once daily for up to 6 weeks
- Renally impaired patients (creatinine clearance 10-30 mL/min): Reduce to 75 mg once every other day or 30 mg once daily (2.4)

----- **DOSAGE FORMS AND STRENGTHS** -----

- Capsules: 30 mg, 45 mg, 75 mg (3)
- Powder for oral suspension: 360 mg oseltamivir base (constituted to a final concentration of 6 mg/mL) (3)

----- **CONTRAINDICATIONS** -----

Patients with known serious hypersensitivity to oseltamivir or any of the components of TAMIFLU (4)

----- **WARNINGS AND PRECAUTIONS** -----

- Serious skin/hypersensitivity reactions: Discontinue TAMIFLU and initiate appropriate treatment if allergic-like reactions occur or are suspected. (5.1)
- Neuropsychiatric events: Patients with influenza, including those receiving TAMIFLU, particularly pediatric patients, may be at an increased risk of confusion or abnormal behavior early in their illness. Monitor for signs of abnormal behavior. (5.2)

----- **ADVERSE REACTIONS** -----

Most common adverse reactions (>1% and more common than with placebo):

- Treatment studies – Nausea, vomiting (6.1)
- Prophylaxis studies – Nausea, vomiting, diarrhea, abdominal pain (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----- **DRUG INTERACTIONS** -----

Live attenuated influenza vaccine, intranasal (7):

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

----- **USE IN SPECIFIC POPULATIONS** -----

- Pregnancy: No data in pregnant women. Use only if clearly needed. (8.1)
- Nursing mothers: Caution should be exercised when administered to a nursing woman. (8.3).
- Pediatric use: Safety and efficacy not established in patients less than 1 year old. (8.4)

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

Revised: 03/2011

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1 **FULL PRESCRIBING INFORMATION**

2 **1 INDICATIONS AND USAGE**

3 **1.1 Treatment of Influenza**

4 TAMIFLU is indicated for the treatment of uncomplicated acute illness due to influenza infection in patients
5 1 year and older who have been symptomatic for no more than 2 days.

6 **1.2 Prophylaxis of Influenza**

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

8 **1.3 Limitations of Use**

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

- 10 • Efficacy of TAMIFLU in patients who begin treatment after 48 hours of symptoms has not been established.
11 • TAMIFLU is not a substitute for early influenza vaccination on an annual basis as recommended by the
12 Centers for Disease Control and Prevention Advisory Committee on Immunization Practices.
13 • There is no evidence for efficacy of TAMIFLU in any illness caused by agents other than influenza viruses
14 types A and B.
15 • Influenza viruses change over time. Emergence of resistance mutations could decrease drug effectiveness.
16 Other factors (for example, changes in viral virulence) might also diminish clinical benefit of antiviral
17 drugs. Prescribers should consider available information on influenza drug susceptibility patterns and
18 treatment effects when deciding whether to use TAMIFLU.

19 **2 DOSAGE AND ADMINISTRATION**

20 **2.1 Dosing for Treatment and Prophylaxis of Influenza**

21 TAMIFLU may be taken with or without food [see *Clinical Pharmacology (12.3)*]. However, when taken with
22 food, tolerability may be enhanced in some patients.

23 The recommended oral treatment and prophylaxis dose of TAMIFLU for patients 1 year of age and older is
24 shown in Table 1.

25 **Table 1 Treatment and Prophylaxis Dosing of Oral TAMIFLU for Influenza**
26 **For Patients 1 Year of Age and Older Based on Body Weight**

Weight (kg)	Weight (lbs)	Treatment Dosing for 5 days	Prophylaxis Dosing for 10 days	Volume of Oral Suspension (6 mg/mL) for each Dose*	Number of Bottles of Oral Suspension to Dispense	Number of Capsules and Strength to Dispense
15 kg or less	33 lbs or less	30 mg twice daily	30 mg once daily	5 mL	1 bottle	10 Capsules 30 mg
16 kg thru 23 kg	34 lbs thru 51 lbs	45 mg twice daily	45 mg once daily	7.5 mL	2 bottles	10 Capsules 45 mg
24 kg thru 40 kg	52 lbs thru 88 lbs	60 mg twice daily	60 mg once daily	10 mL	2 bottles	20 Capsules 30 mg
41 kg or more	89 lbs or more	75 mg twice daily	75 mg once daily	12.5 mL†	3 bottles	10 Capsules 75 mg

27 * A 10 mL oral dosing dispenser is provided with the oral suspension. In the event that the dispenser provided is lost or damaged,
28 another dosing dispenser may be used to deliver the volumes.
29

30 † Delivery of this TAMIFLU for Oral Suspension dose requires administering 10 mL followed by another 2.5 mL.

31

32 **2.2 Standard Dosage – Treatment of Influenza**

33 Adults and Adolescents

34 The recommended oral dose of TAMIFLU for treatment of influenza in adults and adolescents 13 years and
35 older is 75 mg twice daily for 5 days. Treatment should begin within 2 days of onset of symptoms of influenza.
36 TAMIFLU for oral suspension may be used by patients who cannot swallow a capsule (see Table 1).

37 Pediatric Patients

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

39 The recommended oral dose of TAMIFLU for pediatric patients 1 year and older is shown in Table 1. For
40 pediatric patients who cannot swallow capsules, TAMIFLU for oral suspension is the preferred formulation. If
41 the oral suspension product is not available, TAMIFLU capsules may be opened and mixed with sweetened
42 liquids such as regular or sugar-free chocolate syrup, corn syrup, caramel topping, or light brown sugar
43 (dissolved in water). If the appropriate strengths of TAMIFLU capsules are not available to mix with sweetened
44 liquids and the oral suspension product is not available, then a pharmacist may compound an emergency supply
45 of oral suspension from TAMIFLU 75 mg capsules [see *Dosage and Administration (2.8)*].

46 **2.3 Standard Dosage – Prophylaxis of Influenza**

47 Adults and Adolescents

48 The recommended oral dose of TAMIFLU for prophylaxis of influenza in adults and adolescents 13 years and
49 older following close contact with an infected individual is 75 mg once daily for at least 10 days. Therapy
50 should begin within 2 days of exposure. The recommended dose for prophylaxis during a community outbreak
51 of influenza is 75 mg once daily. Safety and efficacy have been demonstrated for up to 6 weeks in
52 immunocompetent patients. The duration of protection lasts for as long as dosing is continued. Safety has been
53 demonstrated for up to 12 weeks in immunocompromised patients. TAMIFLU for oral suspension may also be
54 used by patients who cannot swallow a capsule (see Table 1).

55 Pediatric Patients

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

58 The recommended oral dose of TAMIFLU for pediatric patients 1 year and older following close contact with
59 an infected individual is shown in Table 1. For pediatric patients who cannot swallow capsules, TAMIFLU for
60 oral suspension is the preferred formulation. If the oral suspension product is not available, TAMIFLU capsules
61 may be opened and mixed with sweetened liquids such as regular or sugar-free chocolate syrup, corn syrup,
62 caramel topping, or light brown sugar (dissolved in water). If the appropriate strengths of TAMIFLU capsules
63 are not available to mix with sweetened liquids and the oral suspension product is not available, then a
64 pharmacist may compound an emergency supply of oral suspension from TAMIFLU 75 mg capsules [see
65 *Dosage and Administration (2.8)*].

66 Prophylaxis in pediatric patients following close contact with an infected individual is recommended for
67 10 days. Therapy should begin within 2 days of exposure. For prophylaxis in pediatric patients during a
68 community outbreak of influenza, dosing may be continued for up to 6 weeks.

69 **2.4 Renal Impairment**

70 Data are available on plasma concentrations of oseltamivir carboxylate following various dosing schedules in
71 patients with renal impairment [see *Clinical Pharmacology (12.3)*].

72 *Treatment of Influenza*

73 Dose adjustment is recommended for adult patients with creatinine clearance between 10 and 30 mL/min
74 receiving TAMIFLU for the treatment of influenza. In these patients it is recommended that the dose be reduced

75 to 75 mg of TAMIFLU once daily for 5 days. No recommended dosing regimens are available for patients with
76 end-stage renal disease undergoing routine hemodialysis or continuous peritoneal dialysis treatment.

77 *Prophylaxis of Influenza*

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

83 **2.5 Hepatic Impairment**

84 No dose adjustment is recommended for patients with mild or moderate hepatic impairment (Child-Pugh score
85 ≤ 9) [see *Clinical Pharmacology (12.3)*].

86 **2.6 Geriatric Patients**

87 No dose adjustment is required for geriatric patients [see *Use in Specific Populations (8.5) and Clinical*
88 *Pharmacology (12.3)*].

89 **2.7 Preparation of TAMIFLU for Oral Suspension**

90 It is recommended that TAMIFLU for oral suspension be constituted by the pharmacist prior to dispensing to
91 the patient:

- 92 a) Tap the closed bottle several times to loosen the powder.
- 93 b) Measure **55 mL** of water in a graduated cylinder.
- 94 c) Add the total amount of water for constitution to the bottle and shake the closed bottle well for 15 seconds.
- 95 d) Remove the child-resistant cap and push bottle adapter into the neck of the bottle.
- 96 e) Close bottle with child-resistant cap tightly. This will assure the proper seating of the bottle adapter in the
97 bottle and child-resistant status of the cap.

98 Label the bottle with instructions to Shake Well before each use.

99 The constituted TAMIFLU for oral suspension (6 mg/mL) should be used within 17 days of preparation when
100 stored under refrigeration or within 10 days if stored at controlled room temperature; the pharmacist should
101 write the date of expiration of the constituted suspension on a pharmacy label. The patient package insert and
102 oral dispenser should be dispensed to the patient.

103 **2.8 Emergency Compounding of an Oral Suspension from 75 mg TAMIFLU Capsules (Final** 104 **Concentration 6 mg/mL)**

105 The following directions are provided for use only during emergency situations. These directions are not
106 intended to be used if the FDA-approved, commercially manufactured TAMIFLU for oral suspension is readily
107 available from wholesalers or the manufacturer.

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

110 Commercially manufactured TAMIFLU for oral suspension (6 mg/mL) is the preferred product for pediatric and
111 adult patients who have difficulty swallowing capsules or where lower doses are needed. In the event that
112 TAMIFLU for oral suspension is not available, the pharmacist may compound a suspension (6 mg/mL) from
113 TAMIFLU capsules 75 mg using one of these vehicles: Cherry Syrup (Humco[®]), Ora-Sweet[®] SF (sugar-free)
114 (Paddock Laboratories), or simple syrup. Other vehicles have not been studied. **This compounded suspension**

115 should not be used for convenience or when the FDA-approved TAMIFLU for oral suspension is
116 commercially available.

117 First, calculate the total volume of an oral suspension needed to be compounded and dispensed for each patient.
118 The total volume required is determined by the weight of the patient (see Table 2).

119 **Table 2 Volume of an Oral Suspension (6 mg/mL) Needed to be Compounded Based Upon the**
120 **Patient's Body Weight**

Weight (kg)	Weight (lbs)	Total Volume to Compound per Patient (mL)
15 kg or less	33 lbs or less	75 mL
16 thru 23 kg	34 thru 51 lbs	100 mL
24 thru 40 kg	52 thru 88 lbs	125 mL
41 kg or more	89 lbs or more	150 mL

121

122 Second, determine the number of capsules and the amount of water and vehicle (Cherry Syrup, Ora-Sweet[®] SF,
123 or simple syrup) that are needed to prepare the total volume (determined from Table 2: 75 mL, 100 mL,
124 125 mL, or 150 mL) of compounded oral suspension (6 mg/mL) (see Table 3).

125 **Table 3 Number of TAMIFLU 75 mg Capsules and Amount of Vehicle (Cherry Syrup,**
126 **Ora-Sweet[®] SF, or Simple Syrup) Needed to Prepare the Total Volume of a**
127 **Compounded Oral Suspension (6 mg/mL)**

Total Volume of Compounded Oral Suspension to be Prepared	75 mL	100 mL	125 mL	150 mL
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)
Amount of Water	5 mL	7 mL	8 mL	10 mL
Volume of Vehicle				
Cherry Syrup (Humco [®]) OR Ora-Sweet [®] SF (Paddock Laboratories) OR simple syrup	69 mL	91 mL	115 mL	137 mL

128 *Includes overage to ensure all doses can be delivered

129 Third, follow the procedure below for compounding the oral suspension (6 mg/mL) from TAMIFLU capsules
130 75 mg:

- 131 1. Place the specified amount of water into a polyethyleneterephthalate (PET) or glass bottle (see Table 3).
- 132 2. Carefully separate the capsule body and cap and pour the contents of the required number of TAMIFLU
- 133 75 mg capsules into the PET or glass bottle.
- 134 3. Gently swirl the suspension to ensure adequate wetting of the TAMIFLU powder for at least 2 minutes.
- 135 4. Slowly add the specified amount of vehicle to the bottle.
- 136 5. Close the bottle using a child-resistant cap and shake well for 30 seconds to completely dissolve the active
- 137 drug and to ensure homogeneous distribution of the dissolved drug in the resulting suspension. (Note: The

active drug, oseltamivir phosphate, readily dissolves in the specified vehicles. The suspension is caused by inert ingredients of TAMIFLU capsules which are insoluble in these vehicles.)

6. Put an ancillary label on the bottle indicating “Shake Well Before Use.”
7. Instruct the parent or caregiver that any unused suspension remaining in the bottle following completion of therapy must be discarded by either affixing an ancillary label to the bottle or adding a statement to the pharmacy label instructions.
8. Place an appropriate expiration date on the label according to storage conditions below.

Storage of the Emergency Compounded Suspension

- Refrigeration: Stable for 5 weeks (35 days) when stored in a refrigerator at 2° to 8°C (36° to 46°F).
- Room Temperature: Stable for five days (5 days) when stored at room temperature, 25°C (77°F).

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

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

Dosing of the Compounded Suspension (6 mg/mL)

Refer to Table 1 for the proper dosing instructions for the pharmacy label.

3 DOSAGE FORMS AND STRENGTHS

Capsules: 30 mg, 45 mg, 75 mg

- 30-mg capsules (30 mg free base equivalent of the phosphate salt): light yellow hard gelatin capsules. “ROCHE” is printed in blue ink on the light yellow body and “30 mg” is printed in blue ink on the light yellow cap.
- 45-mg capsules (45 mg free base equivalent of the phosphate salt): grey hard gelatin capsules. “ROCHE” is printed in blue ink on the grey body and “45 mg” is printed in blue ink on the grey cap.
- 75-mg capsules (75 mg free base equivalent of the phosphate salt): grey/light yellow hard gelatin capsules. “ROCHE” is printed in blue ink on the grey body and “75 mg” is printed in blue ink on the light yellow cap.

For Oral Suspension: 6 mg/mL (final concentration when constituted)

- White powder blend for constitution to a white tutti-frutti–flavored suspension. After constitution, each bottle delivers a usable volume of 60 mL of oral suspension equivalent to 360 mg oseltamivir base (6 mg/mL).

4 CONTRAINDICATIONS

TAMIFLU is contraindicated in patients with known serious hypersensitivity to oseltamivir or any component of the product. Severe allergic reactions have included anaphylaxis and serious skin reactions including toxic epidermal necrolysis, Stevens-Johnson Syndrome, and erythema multiforme [see *Warnings and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Serious Skin/Hypersensitivity Reactions

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

Reference ID: 2921316

179 **5.2 Neuropsychiatric Events**

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

183 There have been postmarketing reports (mostly from Japan) of delirium and abnormal behavior leading to
184 injury, and in some cases resulting in fatal outcomes, in patients with influenza who were receiving TAMIFLU.
185 Because these events were reported voluntarily during clinical practice, estimates of frequency cannot be made
186 but they appear to be uncommon based on TAMIFLU usage data. These events were reported primarily among
187 pediatric patients and often had an abrupt onset and rapid resolution. The contribution of TAMIFLU to these
188 events has not been established. Closely monitor patients with influenza for signs of abnormal behavior. If
189 neuropsychiatric symptoms occur, evaluate the risks and benefits of continuing treatment for each patient.

190 **5.3 Bacterial Infections**

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

193 **5.4 Limitations of Populations Studied**

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

199 Efficacy of TAMIFLU for treatment or prophylaxis of influenza has not been established in
200 immunocompromised patients.

201 **6 ADVERSE REACTIONS**

202 The following serious adverse reactions are discussed below and elsewhere in the labeling:

- 203 • Serious skin and hypersensitivity reactions [*see Warnings and Precautions (5.1)*]
- 204 • Neuropsychiatric events [*see Warnings and Precautions (5.2)*]

205
206 The most common adverse reactions are nausea and vomiting.

207 **6.1 Clinical Trials Experience**

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

211 Treatment Studies in Adult Subjects

212 A total of 1171 subjects who participated in adult controlled clinical trials for the treatment of influenza were
213 treated with TAMIFLU. The most frequently reported adverse events in these studies were nausea and
214 vomiting. These events were generally of mild to moderate severity and usually occurred on the first 2 days of
215 administration. Less than 1% of subjects discontinued prematurely from clinical trials due to nausea and
216 vomiting.

217 Adverse events that occurred with an incidence of $\geq 1\%$ in 1440 subjects taking placebo or TAMIFLU 75 mg
218 twice daily in adult treatment studies are shown in Table 4. This summary includes 945 healthy young adults
219 and 495 “at risk” subjects (elderly patients and patients with chronic cardiac or respiratory disease). Those
220 events reported numerically more frequently in subjects taking TAMIFLU compared with placebo were nausea,
221 vomiting, bronchitis, insomnia, and vertigo.

222 Prophylaxis Studies in Adult Subjects

223 A total of 4187 subjects (adolescents, healthy adults, and elderly) participated in prophylaxis studies, of whom
224 1790 received the recommended dose of 75 mg once daily for up to 6 weeks. Adverse events were qualitatively
225 very similar to those seen in the treatment studies, despite a longer duration of dosing (see Table 4). Events
226 reported more frequently in subjects receiving TAMIFLU compared to subjects receiving placebo in
227 prophylaxis studies, and more commonly than in treatment studies, were aches and pains, rhinorrhea, dyspepsia
228 and upper respiratory tract infections. However, the difference in incidence between TAMIFLU and placebo for
229 these events was less than 1%. There were no clinically relevant differences in the safety profile of the 942
230 elderly subjects who received TAMIFLU or placebo, compared with the younger population.

231 **Table 4 Most Frequent Adverse Events in Studies in Naturally Acquired**
232 **Influenza in Subjects 13 Years of Age and Older**

Adverse Event ^a	Treatment		Prophylaxis	
	Placebo N=716	TAMIFLU 75 mg twice daily N=724	Placebo/ No Prophylaxis ^b N=1688	TAMIFLU 75 mg once daily 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%)

233 ^a Adverse events included are all events reported in the treatment studies with frequency ≥1% in the TAMIFLU 75 mg twice daily
234 group.

235 ^b The majority of subjects received placebo; 254 subjects from a randomized, open-label postexposure prophylaxis study in
236 households did not receive placebo or prophylaxis therapy.

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

240 Treatment Studies in Pediatric Subjects

241 A total of 1032 pediatric subjects aged 1 to 12 years (including 698 otherwise healthy pediatric subjects aged 1
242 to 12 years and 334 asthmatic pediatric subjects aged 6 to 12 years) participated in controlled clinical trials of
243 TAMIFLU given for the treatment of influenza. A total of 515 pediatric subjects received treatment with
244 TAMIFLU for oral suspension.

245 Adverse events occurring in ≥1% of pediatric subjects receiving TAMIFLU treatment are listed in Table 5. The
246 most frequently reported adverse event was vomiting. Other events reported more frequently by pediatric
247 subjects treated with TAMIFLU included abdominal pain, epistaxis, ear disorder, and conjunctivitis. These
248 events generally occurred once and resolved despite continued dosing resulting in discontinuation of drug in 8
249 out of 515 (2%) cases.

250 The adverse event profile in adolescents is similar to that described for adult subjects and pediatric subjects
251 aged 1 to 12 years.

252 Prophylaxis Studies in Pediatric Subjects

253 Pediatric subjects aged 1 to 12 years participated in a postexposure prophylaxis study in households, both as
254 index cases (n=134) and as contacts (n=222). Gastrointestinal events were the most frequent, particularly
255 vomiting. In a separate 6-week, uncontrolled, pediatric seasonal prophylaxis study (n=49), the adverse events
256 noted were consistent with those previously observed (see Table 5).

257 **Table 5 Most Frequent Adverse Events Occurring in Children Aged**
258 **1 to 12 Years in Studies in Naturally Acquired Influenza**

Adverse Event ^a	Treatment Trials ^b		Household Prophylaxis Trial ^c	
	Placebo N=517	TAMIFLU 2 mg/kg twice daily N=515	No Prophylaxis ^d N=87	Prophylaxis with TAMIFLU once daily ^d 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%)	-	-

259 ^a Adverse events included in Table 5 are all events reported in the treatment studies with frequency ≥1% in the TAMIFLU 75 mg
260 twice daily group.

261 ^b Pooled data from trials of TAMIFLU treatment of naturally acquired influenza.

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

265 ^d Unit dose = age-based dosing of 30 mg, 45 mg, or 60 mg
266

267 Prophylaxis Study in Immunocompromised Subjects

268 In a 12-week seasonal prophylaxis study in 475 immunocompromised subjects, including 18 pediatric subjects
269 1 to 12 years of age, the safety profile in the 238 subjects receiving TAMIFLU was consistent with that
270 previously observed in other TAMIFLU prophylaxis clinical trials.

271 **6.2 Postmarketing Experience**

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

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

276 Dermatologic: Rash, dermatitis, urticaria, eczema, toxic epidermal necrolysis, Stevens-Johnson Syndrome,
277 erythema multiforme [see Warnings and Precautions (5.1)]

278 Digestive: Hepatitis, liver function tests abnormal

279 Cardiac: Arrhythmia

280 Gastrointestinal disorders: Gastrointestinal bleeding, hemorrhagic colitis

281 Neurologic: Seizure

282 Metabolic: Aggravation of diabetes

283 Psychiatric: Abnormal behavior, delirium, including symptoms such as hallucinations, agitation, anxiety, altered
284 level of consciousness, confusion, nightmares, delusions [see Warnings and Precautions (5.2)]

285 **7 DRUG INTERACTIONS**

286 Influenza Vaccines

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

293 Overall Drug Interaction Profile for Oseltamivir

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

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

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

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

308 No pharmacokinetic interactions have been observed when coadministering oseltamivir with amoxicillin,
309 acetaminophen, aspirin, cimetidine, antacids (magnesium and aluminum hydroxides and calcium carbonates), or
310 warfarin.

311 **8 USE IN SPECIFIC POPULATIONS**

312 **8.1 Pregnancy**

313 Pregnancy Category C

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

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

The safety and efficacy of TAMIFLU in pediatric patients younger than 1 year of age have not been studied. TAMIFLU is not indicated for either treatment or prophylaxis of influenza in pediatric patients younger than 1 year of age because of the unknown clinical significance of nonclinical animal toxicology data for human infants [see *Nonclinical Toxicology (13.2)*].

8.5 Geriatric Use

Of the total number of subjects in clinical studies of TAMIFLU for the treatment of influenza, 19% were 65 and over, while 7% were 75 and over. Of the total number of patients in clinical studies of TAMIFLU for the prophylaxis of influenza, 25% were 65 and over, while 18% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

The safety of TAMIFLU in geriatric subjects has been established in clinical studies that enrolled 741 subjects (374 received placebo and 362 received TAMIFLU). Some seasonal variability was noted in the clinical efficacy outcomes [see *Clinical Studies (14.1)*].

Safety and efficacy have been demonstrated in elderly residents of nursing homes who took TAMIFLU for up to 42 days for the prevention of influenza. Many of these individuals had cardiac and/or respiratory disease, and most had received vaccine that season [see *Clinical Studies (14.2)*].

8.6 Renal Impairment

Dose adjustment is recommended for patients with a serum creatinine clearance between 10 and 30 mL/min [see *Dosage and Administration (2.4)* and *Clinical Pharmacology (12.3)*]. No recommended dosing regimens are available for patients with end-stage renal disease undergoing routine hemodialysis or continuous peritoneal dialysis treatment.

8.7 Hepatic Impairment

No dosage adjustment is required in patients with mild to moderate hepatic impairment. The safety and pharmacokinetics in patients with severe hepatic impairment have not been evaluated [see *Dosage and Administration (2.5)* and *Clinical Pharmacology (12.3)*].

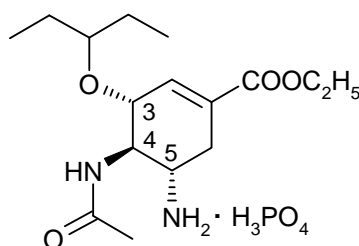
10 OVERDOSAGE

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

360 **11 DESCRIPTION**

361 TAMIFLU (oseltamivir phosphate) is available as capsules containing 30 mg, 45 mg, or 75 mg oseltamivir for
362 oral use, in the form of oseltamivir phosphate, and as a powder for oral suspension, which when constituted
363 with water as directed contains 6 mg/mL oseltamivir base. In addition to the active ingredient, each capsule
364 contains pregelatinized starch, talc, povidone K30, croscarmellose sodium, and sodium stearyl fumarate. The
365 30 mg capsule shell contains gelatin, titanium dioxide, yellow iron oxide, and red iron oxide. The 45 mg capsule
366 shell contains gelatin, titanium dioxide, and black iron oxide. The 75 mg capsule shell contains gelatin, titanium
367 dioxide, yellow iron oxide, black iron oxide, and red iron oxide. Each capsule is printed with blue ink, which
368 includes FD&C Blue No. 2 as the colorant. In addition to the active ingredient, the powder for oral suspension
369 contains sorbitol, monosodium citrate, xanthan gum, titanium dioxide, tutti-frutti flavoring, sodium benzoate,
370 and saccharin sodium.

371 Oseltamivir phosphate is a white crystalline solid with the chemical name (3R,4R,5S)-4-acetylamino-5-amino-
372 3(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid, ethyl ester, phosphate (1:1). The chemical formula is
373 C₁₆H₂₈N₂O₄ (free base). The molecular weight is 312.4 for oseltamivir free base and 410.4 for oseltamivir
374 phosphate salt. The structural formula is as follows:



375

376 **12 CLINICAL PHARMACOLOGY**

377 **12.1 Mechanism of Action**

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

379 **12.3 Pharmacokinetics**

380 Absorption and Bioavailability

381 Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate
382 and is extensively converted predominantly by hepatic esterases to oseltamivir carboxylate. At least 75% of an
383 oral dose reaches the systemic circulation as oseltamivir carboxylate. Exposure to oseltamivir is less than 5% of
384 the total exposure after oral dosing (see Table 6).

385 **Table 6 Mean (% CV) Pharmacokinetic Parameters of Oseltamivir and**
386 **Oseltamivir Carboxylate Following Multiple Dosing of 75 mg Capsules**
387 **Twice Daily (n=20)**

Parameter	Oseltamivir	Oseltamivir Carboxylate
C _{max} (ng/mL)	65 (26)	348 (18)
AUC _{0-12h} (ng·h/mL)	112 (25)	2719 (20)

388 Plasma concentrations of oseltamivir carboxylate are proportional to doses up to 500 mg given twice daily.

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

392 Distribution

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

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

397 Metabolism

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

400 Elimination

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

408 Special Populations

409 *Renal Impairment*

410 Administration of 100 mg of oseltamivir phosphate twice daily for 5 days to patients with various degrees of
411 renal impairment showed that exposure to oseltamivir carboxylate is inversely proportional to declining renal
412 function. Oseltamivir carboxylate exposures in patients with normal and impaired renal function administered
413 various dose regimens of oseltamivir are described in Table 7.

414 **Table 7 Oseltamivir Carboxylate Exposures in Patients With Normal and**
415 **Reduced Serum Creatinine Clearance**

Parameter	Normal Renal Function			Impaired Renal Function				
	75 mg once daily	75 mg twice daily	150 mg twice daily	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}^{\dagger}	7476*	10876*	21864*	17381	12429	62636	21999	25054

416 *Observed values. All other values are predicted.

417 †AUC normalized to 48 hours.

418 *Hepatic Impairment*

419 In clinical studies oseltamivir carboxylate exposure was not altered in patients with mild or moderate hepatic
420 impairment [see *Dosage and Administration (2.5) and Use in Specific Populations (8.7)*].

421 *Pediatric Patients*

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

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428 *Geriatric Patients*

429 Exposure to oseltamivir carboxylate at steady-state was 25% to 35% higher in geriatric patients (age range 65 to
430 78 years) compared to young adults given comparable doses of oseltamivir. Half-lives observed in the geriatric
431 patients were similar to those seen in young adults. Based on drug exposure and tolerability, dose adjustments
432 are not required for geriatric patients for either treatment or prophylaxis [*see Dosage and Administration (2.6)*].

433 **12.4 Microbiology**

434 Mechanism of Action

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

438 Antiviral Activity

439 The antiviral activity and neuraminidase inhibitory activity of oseltamivir carboxylate against laboratory strains
440 and clinical isolates of influenza virus was determined in cell culture and biochemical assays. The
441 concentrations of oseltamivir carboxylate required for inhibition of influenza virus in cell culture were highly
442 variable depending on the assay method used and the virus tested. The 50% and 90% effective concentrations
443 (EC₅₀ and EC₉₀) were in the range of 0.0008 μM to >35 μM and 0.004 μM to >100 μM, respectively (1
444 μM=0.284 μg/mL). The median IC₅₀ values of oseltamivir against influenza A/H1N1, influenza A/H3N2, and
445 influenza B clinical isolates were 2.5 nM (range 0.93-4.16 nM, N=74), 0.96 nM (range 0.13-7.95 nM, N=774),
446 and 60 nM (20-285 nM, N=256), respectively, in a neuraminidase assay with a fluorescently labeled MUNANA
447 substrate. The relationship between the antiviral activity in cell culture, inhibitory activity in the neuraminidase
448 assay, and the inhibition of influenza virus replication in humans has not been established.

449 Resistance

450 Influenza A virus isolates with reduced susceptibility to oseltamivir carboxylate have been recovered by serial
451 passage of virus in cell culture in the presence of increasing concentrations of oseltamivir carboxylate, from
452 clinical isolates collected during treatment with oseltamivir, and from viral isolates sampled during community
453 surveillance studies. Reduced susceptibility of influenza virus to inhibition by oseltamivir carboxylate may be
454 conferred by amino acid substitutions in the viral neuraminidase and/or hemagglutinin proteins. Changes in the
455 viral neuraminidase that have been associated with reduced susceptibility to oseltamivir carboxylate are
456 summarized in Table 8. Hemagglutinin substitutions associated with oseltamivir resistance include A28T and
457 R124M in influenza A H3N2 and H154Q in H1N9, a reassortant human/avian virus.

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Table 8 Neuraminidase Amino Acid Substitutions Observed in Oseltamivir Treatment Studies or Community Surveillance

Amino Acid Substitution	Influenza Type/ Sub-type	Source
Catalytic Residues		
R292K	A N2	Roche clinical trials, publication, surveillance ^a
Framework Residues		
H275Y	A N1	Roche clinical trials, publication, surveillance ^a
N294S	A N1, N2	Publications
E119V	A N2	Roche clinical trials, publication, surveillance ^a
SASG245-248 deletion	A N2	Roche clinical trial
I222V	A N2	Publication
I222T	B	Publication
D198N	B	Publication, surveillance ^a
D198E	B	Surveillance ^a
R371K	B	Surveillance ^a
G402S	B	Publication

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^a Substitutions identified by surveillance data only; population and use of TAMIFLU are unknown

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Selection of influenza A viruses resistant to oseltamivir can occur at higher frequencies in children. The incidence of oseltamivir treatment-associated resistance in pediatric treatment studies has been detected at rates of 27% to 37% and 3% to 18% (3/11 to 7/19 and 1/34 to 9/50 post-treatment isolates, respectively) for influenza A/H1N1 and influenza A/H3N2, respectively. The frequency of resistance selection to oseltamivir and the prevalence of such resistant virus vary seasonally and geographically.

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Circulating seasonal influenza strains expressing neuraminidase resistance-associated substitutions have been observed in individuals who have not received oseltamivir treatment. The oseltamivir resistance-associated substitution H275Y was found in >99% of US circulating 2008 H1N1 influenza isolates. The 2009 H1N1 influenza (“swine flu”) was almost uniformly susceptible to oseltamivir. Prescribers should consider available information from the CDC on influenza drug susceptibility patterns and treatment effects when deciding whether to use TAMIFLU.

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Cross-resistance

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Cross-resistance between oseltamivir and zanamivir has been observed in neuraminidase biochemical assays. The H275Y (N1 numbering) or N294S (N2 numbering) oseltamivir resistance-associated substitutions observed in the N1 neuraminidase subtype, and the E119V or N294S oseltamivir resistance-associated substitutions observed in the N2 subtype (N2 numbering), are associated with reduced susceptibility to oseltamivir but not zanamivir. The Q136K and K150T zanamivir resistance-associated substitutions observed in N1 neuraminidase, or the S250G zanamivir resistance-associated substitutions observed in influenza B, confer reduced susceptibility to zanamivir but not oseltamivir. The R292K oseltamivir resistance-associated substitution observed in N2, and the I222T, D198E/N, R371K, or G402S oseltamivir resistance-associated substitutions observed in influenza B neuraminidase, confer reduced susceptibility to both oseltamivir and zanamivir. In general, amino acid substitutions at neuraminidase catalytic residues confer cross-resistance to other neuraminidase inhibitors while substitutions at framework residues may or may not confer cross-resistance.

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No single amino acid substitution has been identified that could confer cross-resistance between the neuraminidase inhibitor class (oseltamivir, zanamivir) and the M2 ion channel inhibitor class (amantadine, rimantadine). However, a virus may carry a neuraminidase inhibitor associated substitution in neuraminidase

488 and an M2 ion channel inhibitor associated substitution in M2 and may therefore be resistant to both classes of
489 inhibitors. The clinical relevance of phenotypic cross-resistance evaluations has not been established.

490 Immune Response

491 No influenza vaccine/oseltamivir interaction study has been conducted. In studies of naturally acquired and
492 experimental influenza, treatment with TAMIFLU did not impair normal humoral antibody response to
493 infection.

494 **13 NONCLINICAL TOXICOLOGY**

495 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

502 Oseltamivir was found to be non-mutagenic in the Ames test and the human lymphocyte chromosome assay
503 with and without enzymatic activation and negative in the mouse micronucleus test. It was found to be positive
504 in a Syrian Hamster Embryo (SHE) cell transformation test. Oseltamivir carboxylate was non-mutagenic in the
505 Ames test and the L5178Y mouse lymphoma assay with and without enzymatic activation and negative in the
506 SHE cell transformation test.

507 In a fertility and early embryonic development study in rats, doses of oseltamivir at 50, 250, and
508 1500 mg/kg/day were administered to females for 2 weeks before mating, during mating and until day 6 of
509 pregnancy. Males were dosed for 4 weeks before mating, during mating, and for 2 weeks after mating. There
510 were no effects on fertility, mating performance or early embryonic development at any dose level. The highest
511 dose was approximately 100 times the human systemic exposure (AUC_{0-24h}) of oseltamivir carboxylate.

512 **13.2 Animal Toxicology and/or Pharmacology**

513 Single, oral administration of ≥ 657 mg/kg oseltamivir resulted in toxicity, including death, in juvenile 7 day old
514 rats, but had no effect on adult rats. No toxicity was observed after repeated administration of up to 500 mg/kg
515 oseltamivir to developing juvenile rats 7 to 21 days old. This 500 mg/kg dose was approximately 280 and 14
516 times the human systemic exposure (AUC_{0-24h}) of oseltamivir and oseltamivir carboxylate, respectively. Clinical
517 relevance of the juvenile rat study finding for young infants is unknown.

518 **14 CLINICAL STUDIES**

519 **14.1 Treatment of Influenza**

520 Adult Subjects

521 Two placebo-controlled double-blind clinical trials were conducted: one in the U.S. and one outside the U.S.
522 Subjects were eligible for these trials if they had fever $>100^{\circ}\text{F}$, accompanied by at least one respiratory
523 symptom (cough, nasal symptoms, or sore throat) and at least one systemic symptom (myalgia, chills/sweats,
524 malaise, fatigue, or headache) and influenza virus was known to be circulating in the community. In addition,
525 all subjects enrolled in the trials were allowed to take fever-reducing medications.

526 Of 1355 subjects enrolled in these two trials, 849 (63%) subjects were influenza-infected (age range 18 to
527 65 years; median age 34 years; 52% male; 90% Caucasian; 31% smokers). Of the 849 influenza-infected
528 subjects, 95% were infected with influenza A, 3% with influenza B, and 2% with influenza of unknown type.

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

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

539 Geriatric Subjects

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

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

547 Pediatric Subjects

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

553 The primary endpoint in this study was the time to freedom from illness, a composite endpoint that required 4
554 individual conditions to be met. These were: alleviation of cough, alleviation of coryza, resolution of fever, and
555 parental opinion of a return to normal health and activity. TAMIFLU treatment of 2 mg/kg twice daily, started
556 within 48 hours of onset of symptoms, significantly reduced the total composite time to freedom from illness by
557 1.5 days compared to placebo. Subgroup analyses of this study by gender showed no differences in the
558 treatment effect of TAMIFLU in male and female pediatric subjects.

559 **14.2 Prophylaxis of Influenza**

560 Adult Subjects

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

568 In a pooled analysis of two seasonal prophylaxis studies in healthy unvaccinated adults (aged 13 to 65 years),
569 TAMIFLU 75 mg once daily taken for 42 days during a community outbreak reduced the incidence of
570 laboratory-confirmed clinical influenza from 5% (25/519) for the placebo group to 1% (6/520) for the
571 TAMIFLU group.

572 In a seasonal prophylaxis study in elderly residents of skilled nursing homes, TAMIFLU 75 mg once daily
573 taken for 42 days reduced the incidence of laboratory-confirmed clinical influenza from 4% (12/272) for the
574 placebo group to $<1\%$ (1/276) for the TAMIFLU group. About 80% of this elderly population were vaccinated,
575 14% of subjects had chronic airway obstructive disorders, and 43% had cardiac disorders.

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

Pediatric Subjects

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

Immunocompromised Subjects

A double-blind, placebo-controlled study was conducted for seasonal prophylaxis of influenza in 475 immunocompromised subjects (including 18 pediatric subjects 1 to 12 years of age) who had received solid organ (n=388; liver, kidney, liver and kidney) or hematopoietic stem cell transplants (n=87). Median time since transplant for solid organ transplant recipients was 1105 days for the placebo group and 1379 days for the oseltamivir group. Median time since transplant for hematopoietic stem cell transplant recipients was 424 days for the placebo group and 367 days for the oseltamivir group. Approximately 40% of subjects received influenza vaccine prior to entering the study. The primary efficacy endpoint for this study was the incidence of confirmed, clinical influenza, defined as oral temperature $>99.0^{\circ}\text{F}/37.2^{\circ}\text{C}$ plus cough and/or coryza, all recorded within 24 hours, plus either a positive virus culture or a four-fold increase in virus antibody titers from baseline. The incidence of confirmed clinical influenza was 3% (7/238) in the group not receiving TAMIFLU compared with 2% (5/237) in the group receiving TAMIFLU; this difference was not statistically significant. A secondary analysis was performed using the same clinical symptoms and RT-PCR for laboratory confirmation of influenza. Among subjects who were not already shedding virus at baseline, the incidence of RT-PCR-confirmed clinical influenza was 3% (7/231) in the group not receiving TAMIFLU and $<1\%$ (1/232) in the group receiving TAMIFLU.

16 HOW SUPPLIED/STORAGE AND HANDLING

TAMIFLU Capsules

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

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

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

Storage

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

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621 TAMIFLU for Oral Suspension

622 Supplied as a white powder blend in a glass bottle. After constitution, the powder blend produces a white tutti-
623 frutti-flavored oral suspension. After constitution with 55 mL of water, each bottle delivers a usable volume of
624 60 mL of oral suspension equivalent to 360 mg oseltamivir base (6 mg/mL). Each bottle is supplied with a
625 bottle adapter and a 10 mL oral dispenser (NDC 0004-0820-09).

626 *Storage*

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

629 Store constituted suspension under refrigeration for up to 17 days at 2° to 8°C (36° to 46°F). Do not freeze.
630 Alternatively, store constituted suspension for up to 10 days at 25°C (77°F); excursions permitted to 15° to 30°C
631 (59° to 86°F) [See USP Controlled Room Temperature].

632 **17 PATIENT COUNSELING INFORMATION**

633 See FDA-approved Patient Labeling (Patient Information)

634 **17.1 Information for Patients**

635 Patients and/or caregivers should be advised of the risk of severe allergic reactions (including anaphylaxis) or
636 serious skin reactions and should stop TAMIFLU and seek immediate medical attention if an allergic-like
637 reaction occurs or is suspected.

638 Patients and/or caregivers should be advised of the risk of neuropsychiatric events in patients with influenza and
639 should contact their physician if they experience signs of abnormal behavior while receiving TAMIFLU. Their
640 physician will determine if TAMIFLU treatment should be continued.

641 Instruct patients to begin treatment with TAMIFLU as soon as possible from the first appearance of flu
642 symptoms. Similarly, prevention should begin as soon as possible after exposure, at the recommendation of a
643 physician.

644 Instruct patients to take any missed doses as soon as they remember, except if it is near the next scheduled dose
645 (within 2 hours), and then continue to take TAMIFLU at the usual times.

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

648 A bottle of TAMIFLU for oral suspension contains approximately 11 g sorbitol. One dose of 75 mg TAMIFLU
649 for oral suspension delivers 2 g sorbitol. For patients with hereditary fructose intolerance, this is above the daily
650 maximum limit of sorbitol and may cause dyspepsia and diarrhea.

651

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1 **Patient Information**

2 **TAMIFLU®**

3 **(oseltamivir phosphate)**

4 **R_x only**

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

11 **What is TAMIFLU?**

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

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

20 **What is “Flu”?**

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

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

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

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

33 **Who should not take TAMIFLU?**

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

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

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

44 **How should I take TAMIFLU?**

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

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

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

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

58 If you are taking TAMIFLU for Oral Suspension, your pharmacist will give you a dosing
59 dispenser to measure the proper amount of Oral Suspension for your dose. Follow your
60 healthcare professional's instructions on how to measure the proper dose for you. Review
61 the instructions below on how to use the dispenser and ask your pharmacist if you have
62 any questions. If you lose or damage the dispenser and cannot use it, contact your
63 healthcare professional or pharmacist for advice on the proper dose.

64 If TAMIFLU for Oral Suspension is not available, your healthcare provider may instruct
65 you to open TAMIFLU Capsules and mix the contents with sweetened liquids such as
66 regular or sugar-free chocolate syrup, corn syrup, caramel topping, or light brown sugar
67 (dissolved in water). Please follow the dosing instructions below.

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

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

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

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

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

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

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

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

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

91 TAMIFLU for Oral Suspension should be stored under refrigeration for up to 17 days at
92 36° to 46°F (2° to 8°C). Do not freeze. Alternatively, store at room temperature for up to
93 10 days. Discard any unused portion when you are finished with your prescribed dosing
94 of TAMIFLU.

95 **General advice about prescription medicines:**

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

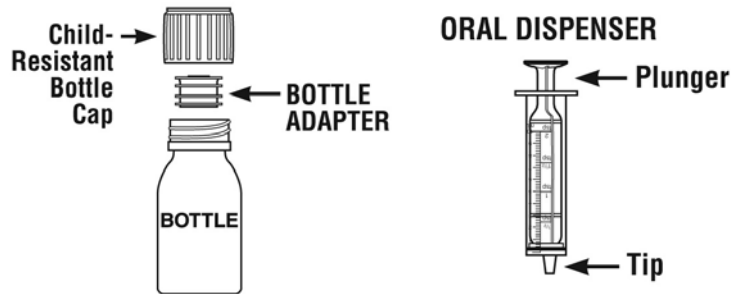
100 This leaflet summarizes the most important information about TAMIFLU. If you would
101 like more information, talk with your healthcare professional. You can ask your
102 pharmacist or healthcare professional for information about TAMIFLU that is written for
103 health professionals.

104

105 **DOSING INSTRUCTIONS FOR PATIENTS:**

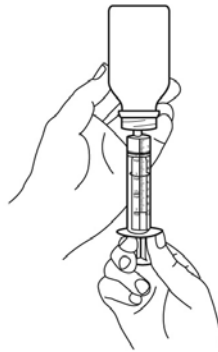
106 **How Do I Prepare a Dose of TAMIFLU for Oral Suspension?**

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



108

- 109 • Shake closed bottle well for about 5 seconds before each use.
- 110 • Remove child-resistant cap.
- 111 • Before inserting the tip of the oral dispenser into bottle adapter, push the plunger
112 completely down toward the tip of the oral dispenser. Insert tip firmly into opening of
113 the bottle adapter.
- 114 • Turn the entire unit (bottle and oral dispenser) upside down.
- 115 • Pull the plunger out slowly until the desired amount of medication is withdrawn into
116 the oral dispenser (see figure). The 12.5 mL (75 mg) dose is obtained by filling the
117 dispenser twice, once to the 10 mL graduation, and a second fill to the 2.5 mL
118 graduation.



119

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

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

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

- 129 • Holding one capsule over a small bowl, carefully pull the capsule open and pour the
130 complete contents of the capsule into the bowl.
- 131 • Add to the capsule contents a small amount of a sweetened liquid such as chocolate
132 syrup (regular or sugar-free), corn syrup, caramel topping, or light brown sugar
133 (dissolved in water) that the child will consume completely.
- 134 • Stir the mixture and give the entire dose to the child.

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