

## 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

Indications and Usage (1.3)	2/2010
Dosage and Administration (2.3, 2.4, 2.7)	2/2010
Warnings and Precautions (5.3, 5.4)	2/2010

### 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): 75 mg twice daily for 5 days
- Pediatric patients (≥1 year): 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): 75 mg once daily for at least 10 days
  - Community outbreak: 75 mg once daily for up to 6 weeks
- Pediatric patients (≥1 year): 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: 300 mg oseltamivir base (constituted to a final concentration of 12 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](http://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: 02/2011

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## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

#### **1.1 Treatment of Influenza**

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

#### **1.2 Prophylaxis of Influenza**

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

#### **1.3 Limitations of Use**

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

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

### **2 DOSAGE AND ADMINISTRATION**

#### **2.1 Dosing Considerations**

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

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

##### Adults and Adolescents

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

##### Pediatric Patients

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

The recommended oral dose of TAMIFLU for pediatric patients 1 year and older is shown in Table 1. TAMIFLU for oral suspension may also be used by patients who cannot swallow a capsule. For pediatric patients who cannot swallow capsules, TAMIFLU for oral suspension is the preferred formulation. If the oral suspension product is not available, TAMIFLU capsules may be opened and mixed with sweetened liquids such as regular or sugar-free chocolate syrup.

**Table 1 Oral Dose of TAMIFLU for Treatment of Influenza in Pediatric Patients by Weight**

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

An oral dosing dispenser with 30 mg, 45 mg, and 60 mg graduations is provided with the oral suspension; the 75 mg dose can be measured using a combination of 30 mg and 45 mg. It is recommended that patients use this dispenser. In the event that the dispenser provided is lost or damaged, another dosing syringe or other device may be used to deliver the following volumes: 2.5 mL (1/2 tsp) for children ≤15 kg, 3.8 mL (3/4 tsp) for >15 to 23 kg, 5 mL (1 tsp) for >23 to 40 kg, and 6.2 mL (1 1/4 tsp) for >40 kg.

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

#### Adults and Adolescents

The recommended oral dose of TAMIFLU for prophylaxis of influenza in adults and adolescents 13 years and older following close contact with an infected individual is 75 mg once daily for at least 10 days. Therapy should begin within 2 days of exposure. The recommended dose for prophylaxis during a community outbreak of influenza is 75 mg once daily. Safety and efficacy have been demonstrated for up to 6 weeks in immunocompetent patients. Safety has been demonstrated for up to 12 weeks in immunocompromised patients. The duration of protection lasts for as long as dosing is continued.

#### Pediatric Patients

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

The recommended oral dose of TAMIFLU for pediatric patients 1 year and older following close contact with an infected individual is shown in Table 2. TAMIFLU for oral suspension may also be used by patients who cannot swallow a capsule. For pediatric patients who cannot swallow capsules, TAMIFLU for oral suspension is the preferred formulation. If the oral suspension product is not available, TAMIFLU capsules may be opened and mixed with sweetened liquids such as regular or sugar-free chocolate syrup.

**Table 2 Oral Dose of TAMIFLU for Prophylaxis of Influenza in Pediatric Patients by Weight**

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

An oral dosing dispenser with 30 mg, 45 mg, and 60 mg graduations is provided with the oral suspension; the 75 mg dose can be measured using a combination of 30 mg and 45 mg. It is recommended that patients use this dispenser. In the event that the dispenser provided is lost or damaged, another dosing syringe or other device may be used to deliver the following volumes: 2.5 mL (1/2 tsp) for children ≤15 kg, 3.8 mL (3/4 tsp) for >15 to 23 kg, 5 mL (1 tsp) for >23 to 40 kg, and 6.2 mL (1 1/4 tsp) for >40 kg.

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

#### **2.4 Renal Impairment**

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

##### *Treatment of Influenza*

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

##### *Prophylaxis of Influenza*

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

#### **2.5 Hepatic Impairment**

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

#### **2.6 Geriatric Patients**

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

## 2.7 Preparation of TAMIFLU for Oral Suspension

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

- a) Tap the closed bottle several times to loosen the powder.
- b) Measure **23 mL** of water in a graduated cylinder.
- c) Add the total amount of water for constitution to the bottle and shake the closed bottle well for 15 seconds.
- d) Remove the child-resistant cap and push bottle adapter into the neck of the bottle.
- e) Close bottle with child-resistant cap tightly. This will assure the proper seating of the bottle adapter in the bottle and child-resistant status of the cap.

Label the bottle with instructions to shake well before each use.

The constituted TAMIFLU for oral suspension (12 mg/mL) should be used within 17 days of preparation when stored under refrigeration or within 10 days if stored at controlled room temperature; the pharmacist should write the date of expiration of the constituted suspension on a pharmacy label. The patient package insert and oral dispenser should be dispensed to the patient.

## 2.8 Emergency Compounding of an Oral Suspension from TAMIFLU Capsules (Final Concentration 15 mg/mL)

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

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

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

First, calculate the total volume of an oral suspension needed to be compounded and dispensed for each patient. The total volume required is determined by the weight of the patient (see Table 3).

**Table 3** Volume of an Oral Suspension (15 mg/mL) Needed to be Compounded Based Upon the Patient's Weight

Body Weight (kg)	Body Weight (lbs)	Total Volume to Compound per Patient (mL)
≤15 kg	≤33 lbs	30 mL
>15 to 23 kg	>33 to 51 lbs	40 mL
>23 to 40 kg	>51 to 88 lbs	50 mL
>40 kg	>88 lbs	60 mL

Second, determine the number of capsules and the amount of vehicle (Cherry Syrup or Ora-Sweet<sup>®</sup> SF) that are needed to prepare the total volume (calculated from Table 3: 30 mL, 40 mL, 50 mL, or 60 mL) of compounded oral suspension (15 mg/mL) (see Table 4).

**Table 4**            **Number of TAMIFLU 75 mg Capsules and Amount of Vehicle (Cherry Syrup OR Ora-Sweet<sup>®</sup> SF) Needed to Prepare the Total Volume of a Compounded Oral Suspension (15 mg/mL)**

<b>Total Volume of Compounded Oral Suspension to be Prepared</b>	<b>30 mL</b>	<b>40 mL</b>	<b>50 mL</b>	<b>60 mL</b>
<b>Required Number of TAMIFLU 75 mg Capsules</b>	6 capsules (450 mg oseltamivir)	8 capsules (600 mg oseltamivir)	10 capsules (750 mg oseltamivir)	12 capsules (900 mg oseltamivir)
<b>Required Volume of Vehicle</b>  Cherry Syrup (Humco <sup>®</sup> ) <b>OR</b> Ora-Sweet <sup>®</sup> SF (Paddock Laboratories)	29 mL	38.5 mL	48 mL	57 mL

Third, follow the procedure below for compounding the oral suspension (15 mg/mL) from TAMIFLU capsules 75 mg:

- a) Carefully separate the capsule body and cap and transfer the contents of the required number of TAMIFLU 75 mg capsules into a clean mortar.
- b) Triturate the granules to a fine powder.
- c) Slowly add a small amount of vehicle (approximately 1 mL per 6 capsule contents) to the triturated TAMIFLU powder and levigate well with the pestle (approximately 2-3 minutes) to a smooth mass. Continue adding very slowly the remainder of one-third (1/3) of the total amount of vehicle in 3 small portions to the mortar while triturating with the pestle until a uniform suspension is achieved each time.
- d) Transfer the suspension to an amber glass or amber polyethyleneterephthalate (PET) bottle. A funnel may be used to eliminate any spillage.
- e) Add the second one-third (1/3) of the vehicle to the mortar, rinse the pestle and mortar by a triturating motion, and transfer the vehicle into the bottle.
- f) Repeat the rinsing with the remaining one-third (1/3) of the vehicle.
- g) Close the bottle using a child-resistant cap.
- h) Shake well to completely dissolve the active 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.)
- i) Put an ancillary label on the bottle indicating “Shake Gently Before Use.” (Note: This compounded suspension should be gently shaken prior to administration to minimize the tendency for air entrapment, particularly with the Ora-Sweet<sup>®</sup> SF preparation.)
- j) 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.
- k) Place an appropriate expiration date on the label according to storage conditions below.

### Storage of the 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 amber glass and amber 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 (15 mg/mL)

Refer to Table 5 for the proper dosing instructions for the pharmacy label.

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

**Table 5**                    **Dosing Chart for Pharmacy-Compounded Suspension from TAMIFLU Capsules 75 mg**

<b>Body Weight (kg)</b>	<b>Body Weight (lbs)</b>	<b>Dose (mg)</b>	<b>Volume per Dose (15 mg/mL)</b>	<b>Treatment Dose (for 5 days)</b>	<b>Prophylaxis Dose (for 10 days)</b>
≤15 kg	≤33 lbs	30 mg	2 mL	2 mL two times a day	2 mL once daily
>15 to 23 kg	>33 to 51 lbs	45 mg	3 mL	3 mL two times a day	3 mL once daily
>23 to 40 kg	>51 to 88 lbs	60 mg	4 mL	4 mL two times a day	4 mL once daily
>40 kg	>88 lbs	75 mg	5 mL	5 mL two times a day	5 mL once daily

Note: 1 teaspoon = 5 mL

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

### **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: 12 mg/mL (final concentration)

- White powder blend for constitution to a white tutti-frutti–flavored suspension. Each bottle delivers 25 mL of suspension equivalent to 300 mg oseltamivir base.

#### **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.

##### **5.2 Neuropsychiatric Events**

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

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

##### **5.3 Bacterial Infections**

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

##### **5.4 Limitations of Populations Studied**

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

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

#### **6 ADVERSE REACTIONS**

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

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

The most common adverse reactions are nausea and vomiting.

## 6.1 Clinical Trials Experience

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

### Treatment Studies in Adult Subjects

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

Adverse events that occurred with an incidence of  $\geq 1\%$  in 1440 subjects taking placebo or TAMIFLU 75 mg twice daily in adult treatment studies are shown in Table 6. This summary includes 945 healthy young adults and 495 “at risk” subjects (elderly patients and patients with chronic cardiac or respiratory disease). Those events reported numerically more frequently in subjects taking TAMIFLU compared with placebo were nausea, vomiting, bronchitis, insomnia, and vertigo.

### Prophylaxis Studies in Adult Subjects

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

**Table 6 Most Frequent Adverse Events in Studies in Naturally Acquired Influenza in Subjects 13 Years of Age and Older**

Adverse Event <sup>a</sup>	Treatment				Prophylaxis			
	Placebo N=716		TAMIFLU 75 mg twice daily N=724		Placebo/ No Prophylaxis <sup>b</sup> 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%)

<sup>a</sup> Adverse events included are all events reported in the treatment studies with frequency  $\geq 1\%$  in the TAMIFLU 75 mg twice daily group.

<sup>b</sup> The majority of subjects received placebo; 254 subjects from a randomized, open-label postexposure prophylaxis study in households did not receive placebo or prophylaxis therapy.

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

### Treatment Studies in Pediatric Subjects

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

Adverse events occurring in ≥1% of pediatric subjects receiving TAMIFLU treatment are listed in Table 7. The most frequently reported adverse event was vomiting. Other events reported more frequently by pediatric subjects treated with TAMIFLU included abdominal pain, epistaxis, ear disorder, and conjunctivitis. These events generally occurred once and resolved despite continued dosing resulting in discontinuation of drug in 8 out of 515 (2%) cases.

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

### Prophylaxis Studies in Pediatric Subjects

Pediatric subjects aged 1 to 12 years participated in a postexposure prophylaxis study in households, both as index cases (n=134) and as contacts (n=222). Gastrointestinal events were the most frequent, particularly vomiting. In a separate 6-week, uncontrolled, pediatric seasonal prophylaxis study (n=49), the adverse events noted were consistent with those previously observed (see Table 7).

**Table 7 Most Frequent Adverse Events Occurring in Children Aged 1 to 12 Years in Studies in Naturally Acquired Influenza**

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

<sup>a</sup> Adverse events included in Table 7 are all events reported in the treatment studies with frequency ≥1% in the TAMIFLU 75 mg twice daily group.

<sup>b</sup> Pooled data from trials of TAMIFLU treatment of naturally acquired influenza.

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

<sup>d</sup> Unit dose = age-based dosing of 30 mg, 45 mg, or 60 mg

### Prophylaxis Study in Immunocompromised Subjects

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

## **6.2 Postmarketing Experience**

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

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

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

Digestive: Hepatitis, liver function tests abnormal

Cardiac: Arrhythmia

Gastrointestinal disorders: Gastrointestinal bleeding, hemorrhagic colitis

Neurologic: Seizure

Metabolic: Aggravation of diabetes

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

## **7 DRUG INTERACTIONS**

### Influenza Vaccines

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

### Overall Drug Interaction Profile for Oseltamivir

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

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

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

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

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

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Pregnancy Category C

There are insufficient human data upon which to base an evaluation of risk of TAMIFLU to the pregnant woman or developing fetus. Studies for effects on embryo-fetal development were conducted in rats (50, 250, and 1500 mg/kg/day) and rabbits (50, 150, and 500 mg/kg/day) by the oral route. Relative exposures at these 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)*].

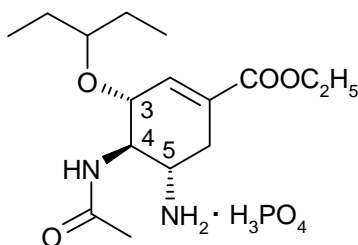
## 10 OVERDOSAGE

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.

## 11 DESCRIPTION

TAMIFLU (oseltamivir phosphate) is available as capsules containing 30 mg, 45 mg, or 75 mg oseltamivir for oral use, in the form of oseltamivir phosphate, and as a powder for oral suspension, which when constituted with water as directed contains 12 mg/mL oseltamivir base. In addition to the active ingredient, each capsule contains pregelatinized starch, talc, povidone K30, croscarmellose sodium, and sodium stearyl fumarate. The 30 mg capsule shell contains gelatin, titanium dioxide, yellow iron oxide, and red iron oxide. The 45 mg capsule shell contains gelatin, titanium dioxide, and black iron oxide. The 75 mg capsule shell contains gelatin, titanium dioxide, yellow iron oxide, black iron oxide, and red iron oxide. Each capsule is printed with blue ink, which includes FD&C Blue No. 2 as the colorant. In addition to the active ingredient, the powder for oral suspension contains sorbitol, monosodium citrate, xanthan gum, titanium dioxide, tutti-frutti flavoring, sodium benzoate, and saccharin sodium.

Oseltamivir phosphate is a white crystalline solid with the chemical name (3R,4R,5S)-4-acetylamino-5-amino-3(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid, ethyl ester, phosphate (1:1). The chemical formula is  $C_{16}H_{28}N_2O_4$  (free base). The molecular weight is 312.4 for oseltamivir free base and 410.4 for oseltamivir phosphate salt. The structural formula is as follows:



## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

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

### 12.3 Pharmacokinetics

#### Absorption and Bioavailability

Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate and is extensively converted predominantly by hepatic esterases to oseltamivir carboxylate. At least 75% of an

oral dose reaches the systemic circulation as oseltamivir carboxylate. Exposure to oseltamivir is less than 5% of the total exposure after oral dosing (see Table 8).

**Table 8 Mean (% CV) Pharmacokinetic Parameters of Oseltamivir and Oseltamivir Carboxylate Following Multiple Dosing of 75 mg Capsules Twice Daily (n=20)**

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

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

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

#### Distribution

The volume of distribution (V<sub>ss</sub>) of oseltamivir carboxylate, following intravenous administration in 24 subjects, ranged between 23 and 26 liters.

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

#### Metabolism

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

#### Elimination

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

#### Special Populations

##### *Renal Impairment*

Administration of 100 mg of oseltamivir phosphate twice daily for 5 days to patients with various degrees of renal impairment showed that exposure to oseltamivir carboxylate is inversely proportional to declining renal function. Oseltamivir carboxylate exposures in patients with normal and impaired renal function administered various dose regimens of oseltamivir are described in Table 9.

**Table 9 Oseltamivir Carboxylate Exposures in Patients With Normal and 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	Hemodialysis			
				30 mg weekly	30 mg alternate HD cycle	75 mg daily	75 mg alternate days	30 mg daily
C <sub>max</sub>	259*	348*	705*	766	850	1638	1175	655
C <sub>min</sub>	39*	138*	288*	62	48	864	209	346
AUC <sub>48</sub> †	7476*	10876*	21864*	17381	12429	62636	21999	25054

\*Observed values. All other values are predicted.

†AUC normalized to 48 hours.

### Hepatic Impairment

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

### Pediatric Patients

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

### Geriatric Patients

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

## 12.4 Microbiology

### Mechanism of Action

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

### Antiviral Activity

The antiviral activity and neuraminidase inhibitory activity of oseltamivir carboxylate against laboratory strains and clinical isolates of influenza virus was determined in cell culture and biochemical assays. The concentrations of oseltamivir carboxylate required for inhibition of influenza virus in cell culture were highly variable depending on the assay method used and the virus tested. The 50% and 90% effective concentrations (EC<sub>50</sub> and EC<sub>90</sub>) were in the range of 0.0008 μM to >35 μM and 0.004 μM to >100 μM, respectively (1 μM=0.284 μg/mL). The median IC<sub>50</sub> values of oseltamivir against influenza A/H1N1, influenza A/H3N2, and 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), and 60 nM (20-285 nM, N=256), respectively, in a neuraminidase assay with a fluorescently labeled MUNANA substrate. The relationship between the antiviral activity in cell culture, inhibitory activity in the neuraminidase assay, and the inhibition of influenza virus replication in humans has not been established.



## Resistance

Influenza A virus isolates with reduced susceptibility to oseltamivir carboxylate have been recovered by serial passage of virus in cell culture in the presence of increasing concentrations of oseltamivir carboxylate, from clinical isolates collected during treatment with oseltamivir, and from viral isolates sampled during community surveillance studies. Reduced susceptibility of influenza virus to inhibition by oseltamivir carboxylate may be conferred by amino acid substitutions in the viral neuraminidase and/or hemagglutinin proteins. Changes in the viral neuraminidase that have been associated with reduced susceptibility to oseltamivir carboxylate are summarized in Table 10. Hemagglutinin substitutions associated with oseltamivir resistance include A28T and R124M in influenza A H3N2 and H154Q in H1N9, a reassortant human/avian virus.

**Table 10**      **Neuraminidase Amino Acid Substitutions Observed in Oseltamivir Treatment Studies or Community Surveillance**

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

<sup>a</sup> Substitutions identified by surveillance data only; population and use of TAMIFLU are unknown

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.

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.

## Cross-resistance

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.

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

### Immune Response

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

## **13 NONCLINICAL TOXICOLOGY**

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

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

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

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

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

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

## **14 CLINICAL STUDIES**

### **14.1 Treatment of Influenza**

#### Adult Subjects

Two placebo-controlled double-blind clinical trials were conducted: one in the U.S. and one outside the U.S. Subjects were eligible for these trials if they had fever  $>100^{\circ}\text{F}$ , accompanied by at least one respiratory symptom (cough, nasal symptoms, or sore throat) and at least one systemic symptom (myalgia, chills/sweats,

malaise, fatigue, or headache) and influenza virus was known to be circulating in the community. In addition, all subjects enrolled in the trials were allowed to take fever-reducing medications.

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

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

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

### Geriatric Subjects

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

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

### Pediatric Subjects

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

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

## 14.2 Prophylaxis of Influenza

### Adult Subjects

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

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

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

In a study of postexposure prophylaxis in household contacts (aged  $\geq 13$  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].

### TAMIFLU for Oral Suspension

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

#### *Storage*

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

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

## **17 PATIENT COUNSELING INFORMATION**

*See FDA-approved Patient Labeling.*

### **17.1 Information for Patients**

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

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

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

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

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

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

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