

# New Emergency Compounding Instructions for Pharmacists for Oral Suspension of TAMIFLU (oseltamivir phosphate)



**Tamiflu**<sup>®</sup>  
oseltamivir phosphate  
*treat. prevent. protect.*

**NEW STRENGTH**

## Rx only

(Directions are included in the Prescribing Information)

Emergency Compounding of an Oral Suspension from TAMIFLU 75 mg Capsules (Final Concentration 6 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 (6 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 (6 mg/mL) from TAMIFLU 75 mg capsules using one of these vehicles: Cherry Syrup (Humco®), Ora-Sweet® SF (sugar-free) (Paddock Laboratories), or simple syrup. 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 2 in Prescribing Information).

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

### New Strength for Tamiflu for Oral Suspension 6 mg/mL Now Available

- 6mg/mL harmonizes concentration for both emergency compounding and pre-manufactured concentration
- FDA has approved simplified steps for emergency compounding
- Simple syrup has been added as an additional vehicle option

*The new oral suspension will help simplify prescribing, dosing and administration.*

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

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

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

Table 3 in Prescribing Information

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

\*Includes overage to ensure all doses can be delivered



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

1. Place the specified amount of water into a polyethyleneterephthalate (PET) or glass bottle (see Table 3 in PI).
2. Carefully separate the capsule body and cap and pour the contents of the required number of TAMIFLU 75 mg capsules into the PET or glass bottle. Weighing paper may also be used to hold capsule contents for transfer into bottle.
3. Gently swirl the suspension to ensure adequate wetting of the TAMIFLU powder for at least 2 minutes.
4. Slowly add the specified amount of vehicle to the bottle.
5. Close the bottle using a child-resistant cap and shake well for 30 seconds 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.)
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.

## Oral Dosing Device

Consider dispensing the suspension with an oral dosing device (a graduated oral syringe or spoon) suitable for measuring the suspension. If possible, mark or highlight the graduation corresponding to the appropriate dose (5 mL, 7.5 mL, 10 mL, or 12.5 mL) on the oral syringe or spoon for each patient.

For further information, please visit <http://www.Tamiflu.com/HCP> or refer to the Pharmaceutical Insert.

## Indications and Limitations of Use

TAMIFLU is indicated in patients 1 year and older for the treatment of uncomplicated influenza caused by viruses types A and B who have been symptomatic for no more than 2 days and for the prophylaxis of influenza.

Efficacy of TAMIFLU in patients who begin treatment after 48 hours of symptoms has not been established.

TAMIFLU is not a substitute for early and annual vaccination as recommended by the Centers for Disease Control's Advisory Committee on Immunization Practices (ACIP).

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 benefits of antiviral drugs. Consider available information on influenza drug susceptibility patterns and treatment effects when deciding whether to use TAMIFLU.

## Table 1 Below from Prescribing Information for Dosing of the Compounded Suspension by Indication

**Treatment and Prophylaxis Dosing of Oral TAMIFLU for Influenza for Patients 1 Year of Age and Older Based on Body Weight<sup>†</sup>**  
Table 1 in Prescribing Information

Weight (kg)	Weight (lbs)	Treatment Dosing for 5 days	Prophylaxis Dosing for 10 days <sup>‡</sup>	Volume of Oral Suspension (6 mg/mL) for each Dose
15 kg or less	33 lbs or less	30 mg <b>twice</b> daily	30 mg <b>once</b> daily	5 mL
16 kg thru 23 kg	34 lbs thru 51 lbs	45 mg <b>twice</b> daily	45 mg <b>once</b> daily	7.5 mL
24 kg thru 40 kg	52 lbs thru 88 lbs	60 mg <b>twice</b> daily	60 mg <b>once</b> daily	10 mL
41 kg or more	89 lbs or more	75 mg <b>twice</b> daily	75 mg <b>once</b> daily	12.5 mL

<sup>†</sup> Treatment should begin within 2 days of onset of symptoms and prophylaxis should begin within 2 days of exposure to an infected individual. Please see the Prescribing Information for dosing in patients with renal impairment.

<sup>‡</sup> Prophylaxis for adults following close contact with an infected individual for at least 10 days. Duration of prophylaxis in both adults and pediatric patients during a community outbreak is up to 6 weeks in immunocompetent patients.

Please see accompanying Full Prescribing Information.

Please see next page for Important Safety Information.

## Important Safety Information

TAMIFLU is contraindicated in patients who have had severe allergic reactions such as anaphylaxis or serious skin reactions such as toxic epidermal necrolysis, Stevens-Johnson syndrome, or erythema multiforme to any component of TAMIFLU. Cases of these events 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.

There have been postmarketing reports of delirium and abnormal behavior leading to injury, and in some cases resulting in fatal outcomes, in patients with influenza who were receiving TAMIFLU. 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. Patients with influenza should be closely monitored for signs of abnormal behavior. If neuropsychiatric symptoms occur, the risks and benefits of continuing treatment should be evaluated for each patient.

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

Efficacy in subjects with chronic cardiac and/or respiratory disease or in immunocompromised patients has not been established. No information is available regarding treatment of influenza in patients at imminent risk of requiring hospitalization.

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.

Adverse events that occurred more frequently in patients treated with TAMIFLU than in patients taking placebo and occurred in  $\geq 2\%$  of patients were (TAMIFLU%, placebo %):

- Treatment in adults – nausea (10%, 6%), vomiting (9%, 3%), bronchitis (2%, 2%)
- Treatment in pediatrics – vomiting (15%, 9%), abdominal pain (5%, 4%), epistaxis (3%, 3%), ear disorder (2%, 1%)
- Prophylaxis of adults – headache (18%, 18%), nausea (7%, 3%), diarrhea (3%, 2%), vomiting (2%, 1%), abdominal pain (2%, 1%)
- Prophylaxis of pediatrics – vomiting (10%, 2%), abdominal pain (3%, 0%), nausea (4%, 1%)

## TAMIFLU® (oseltamivir phosphate) capsules

## TAMIFLU® (oseltamivir phosphate) for oral suspension

### 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**

<b>RECENT MAJOR CHANGES</b>	
Dosage and Administration (2.1, 2.2, 2.3, 2.7, 2.8)	3/2011

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|--|
| <b>INDICATIONS AND USAGE</b>   |
| TAMIFLU is an influenza neuraminidase inhibitor indicated for: <ul style="list-style-type: none"><li>Treatment of influenza in patients 1 year and older who have been symptomatic for no more than 2 days. (1.1)</li> <li>Prophylaxis of influenza in patients 1 year and older. (1.2)</li></ul>  |
| <b>Important Limitations of Use:</b> <ul style="list-style-type: none"><li>Efficacy not established in patients who begin therapy after 48 hours of symptoms. (1.2)</li> <li>Not a substitute for annual influenza vaccination. (1.3)</li> <li>No evidence of efficacy for illness from agents other than influenza viruses types A and B. (1.3)</li></ul> |
| <ul style="list-style-type: none"><li>Consider available information on influenza drug susceptibility patterns and treatment effects when deciding whether to use. (1.3)</li></ul>   |

#### 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**

### FULL PRESCRIBING INFORMATION: CONTENTS\*

#### 1 INDICATIONS AND USAGE

- Treatment of Influenza
- Prophylaxis of Influenza
- Limitations of Use

#### 2 DOSAGE AND ADMINISTRATION

- Dosing for Treatment and Prophylaxis of Influenza
- Standard Dosage – Treatment of Influenza
- Standard Dosage – Prophylaxis of Influenza
- Renal Impairment
- Hepatic Impairment
- Geriatric Patients
- Preparation of TAMIFLU for Oral Suspension
- Emergency Compounding of an Oral Suspension from 75 mg TAMIFLU Capsules (Final Concentration 6 mg/mL)

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

- Serious Skin/Hypersensitivity Reactions
- Neuropsychiatric Events
- Bacterial Infections
- Limitations of Populations Studied

#### 6 ADVERSE REACTIONS

- Clinical Trials Experience
- Postmarketing Experience

#### 7 DRUG INTERACTIONS

#### 8 USE IN SPECIFIC POPULATIONS

- Pregnancy
- Nursing Mothers
- Pediatric Use
- Geriatric Use
- Renal Impairment
- Hepatic Impairment

TAMIFLU® (oseltamivir phosphate) capsules  
TAMIFLU® (oseltamivir phosphate) for oral suspension

#### 10 OVERDOSAGE

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

- Mechanism of Action
- Pharmacokinetics
- Microbiology

#### 13 NONCLINICAL TOXICOLOGY

- Carcinogenesis, Mutagenesis, Impairment of Fertility
- Animal Toxicology and/or Pharmacology

#### 14 CLINICAL STUDIES

- Treatment of Influenza
- Prophylaxis of Influenza

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

- Information for Patients

\*Sections or subsections omitted from the full prescribing information are not listed.

### 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 for Treatment and Prophylaxis of Influenza

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.

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

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 <b>twice</b> daily	30 mg <b>once</b> daily	5 mL <sup>†</sup>	1 bottle	10 Capsules 30 mg
16 kg thru 23 kg	34 lbs thru 51 lbs	45 mg <b>twice</b> daily	45 mg <b>once</b> daily	7.5 mL	2 bottles	10 Capsules 45 mg
24 kg thru 40 kg	52 lbs thru 88 lbs	60 mg <b>twice</b> daily	60 mg <b>once</b> daily	10 mL	2 bottles	20 Capsules 30 mg
41 kg or more	89 lbs or more	75 mg <b>twice</b> daily	75 mg <b>once</b> daily	12.5 mL <sup>†</sup>	3 bottles	10 Capsules 75 mg

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

<sup>†</sup> Delivery of this TAMIFLU for Oral Suspension dose requires administering 10 mL followed by another 2.5 mL.

##### 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. TAMIFLU for oral suspension may be used by patients who cannot swallow a capsule (see Table 1).

##### 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. 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, corn syrup, caramel topping, or light brown sugar (dissolved in water). If the appropriate strengths of TAMIFLU capsules are not available to mix with sweetened liquids and the oral suspension product is not available, then a pharmacist may compound an emergency supply of oral suspension from TAMIFLU 75 mg capsules *[see Dosage and Administration (2.8)]*.

##### 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. The duration of protection lasts for as long as dosing is continued. Safety has been demonstrated for up to 12 weeks in immunocompromised patients. TAMIFLU for oral suspension may also be used by patients who cannot swallow a capsule (see Table 1).

##### 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.

TAMIFLU® (oseltamivir phosphate) capsules  
TAMIFLU® (oseltamivir phosphate) for oral suspension

The recommended oral dose of TAMIFLU for pediatric patients 1 year and older following close contact with an infected individual is shown in Table 1. 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, corn syrup, caramel topping, or light brown sugar (dissolved in water). If the appropriate strengths of TAMIFLU capsules are not available to mix with sweetened liquids and the oral suspension product is not available, then a pharmacist may compound an emergency supply of oral suspension from TAMIFLU 75 mg capsules *[see Dosage and Administration (2.8)]*.

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:

- Tap the closed bottle several times to loosen the powder.
- Measure 55 mL of water in a graduated cylinder.
- Add the total amount of water for constitution to the bottle and shake the closed bottle well for 15 seconds.
- Remove the child-resistant cap and push bottle adapter into the neck of the bottle.
- 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 (6 mg/mL) should be used within 14 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 75 mg TAMIFLU Capsules (Final Concentration 6 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 (6 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 (6 mg/mL) from TAMIFLU capsules 75 mg using one of these vehicles: Cherry Syrup (Humco®), Ora-Sweet® SF (sugar-free) (Paddock Laboratories), or simple syrup. 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 2).

##### Table 2 Volume of an Oral Suspension (6 mg/mL) Needed to be Compounded Based Upon the 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

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

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

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

\*Includes overage to ensure all doses can be delivered

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

- Place the specified amount of water into a polyethyleneterephthalate (PET) or glass bottle (see Table 3).
- Carefully separate the capsule body and cap and pour the contents of the required number of TAMIFLU 75 mg capsules into the PET or glass bottle.
- Gently swirl the suspension to ensure adequate wetting of the TAMIFLU powder for at least 2 minutes.
- Slowly add the specified amount of vehicle to the bottle.
- Close the bottle using a child-resistant cap and shake well for 30 seconds 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.)

- Put an ancillary label on the bottle indicating “Shake Well Before Use.”
- 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.
- 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.
- 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.

##### 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 obviously 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 influenza 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 ≥1% in 1440 subjects taking placebo or TAMIFLU 75 mg twice daily in adult treatment studies are shown in Table 4. This summary includes 945 healthy young adults and 495 “at risk” subjects (elderly patients and patients with chronic cardiac or respiratory disease). These 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 4). 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

TAMIFLU® (oseltamivir phosphate) capsules  
TAMIFLU® (oseltamivir phosphate) for oral suspension

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.

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%)

**TAMIFLU® (oseltamivir phosphate)**

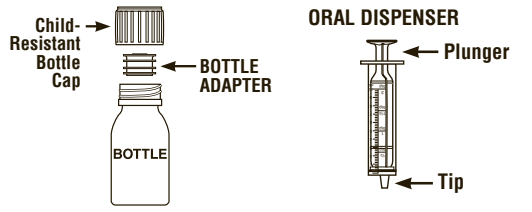
**General advice about prescription medicines:** Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use TAMIFLU for a condition for which it was not prescribed. Do not give TAMIFLU to other people, even if they have the same symptoms you have.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

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

## DOSING INSTRUCTIONS FOR PATIENTS:

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

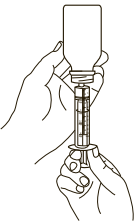
**Please follow instructions carefully to ensure proper dosing of the oral suspension.**



- Shake closed bottle well for about 5 seconds before each use.
- Remove child-resistant cap.
- Before inserting the tip of the oral dispenser into bottle adapter, push the plunger completely down toward the tip of the bottle adapter.
- Turn the entire unit (bottle and oral dispenser) upside down.

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- Pull the plunger out slowly until the desired amount of medication is withdrawn into the oral dispenser (see figure). The 12.5 mL (75 mg) dose is obtained by filling the dispenser twice, once to the 10 mL graduation, and a second fill to the 2.5 mL graduation.



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

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

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

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

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**TAMIFLU® (oseltamivir phosphate) for oral suspension**

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 carbonate), 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 *Non-clinical Toxicology* (13.2)].

### 8.5 Geriatric Use

Of the total number of subjects in clinical studies of TAMIFLU for the treatment of influenza, 13% 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.

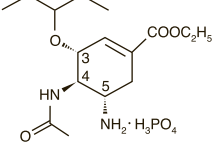
## 11 DESCRIPTION

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 6 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.

**TAMIFLU® (oseltamivir phosphate) capsules**

**TAMIFLU® (oseltamivir phosphate) for oral suspension**

Oseltamivir phosphate is a white crystalline solid with the chemical name (3R,4R,5S)-4-acetylamino-6-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid, ethyl ester, phosphate (1:1). The chemical formula is C<sub>21</sub>H<sub>35</sub>N<sub>3</sub>O<sub>6</sub> (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 6).

**Table 6 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>0-24h</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>d</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 7.

**Table 7 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	Creatinine Clearance <10 mL/min	Creatinine Clearance >10 and <30 mL/min				
			CAPD	Hemodialysis				
			30 mg alternate HD cycle	75 mg alternate days	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>0-8</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), 0.95 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 8. Hemagglutinin substitutions associated with oseltamivir resistance include A28T and R124M in influenza A H3N2 and H154Q in H1N9, a reassortant human/avian virus.

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

Amino Acid Substitution	Influenza Type/ Sub-type	Source
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 zanamivir 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 S250C 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

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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<sub>0-24h</sub>) of oseltamivir carboxylate.

### 13.2 Animal Toxicology and/or Pharmacology

Single, oral administration of >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<sub>0-24h</sub>) 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°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 stratified by self-assessed 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 ≥65 years of age in three consecutive seasons. The enrollment criteria were similar to that of adult patients with the exception of fever being defined as >97.5°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<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°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 household contacts. 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 >99.0°F/37.2°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 ≥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% (4/200) in the placebo group to