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

----------RECENT MAJOR CHANGES----------
Dosage and Administration (2.4) 10/2014

---------- INDICATIONS AND USAGE----------
TAMIFLU is an influenza neuraminidase inhibitor indicated for:
- Treatment of acute, uncomplicated influenza in patients 2 weeks of age and older who have been symptomatic for no more than 2 days. (1.1)
- Prophylaxis of influenza in patients 1 year and older. (1.2)

Important Limitations of Use:
- Efficacy not established in patients who begin therapy after 48 hours of symptoms. (1.3)
- Not a substitute for annual influenza vaccination. (1.3)
- No evidence of efficacy for illness from agents other than influenza viruses types A and B. (1.3)
- Consider available information on influenza drug susceptibility patterns and treatment effects when deciding whether to use. (1.3)

----------DOSAGE AND ADMINISTRATION----------
Treatment of influenza (2.2)
- Adults and adolescents (13 years and older): 75 mg twice daily for 5 days
- Pediatric patients 1 to 12 years of age: Based on weight twice daily for 5 days
- Pediatric patients 2 weeks to less than 1 year of age: 3mg/kg twice daily for 5 days.
- Renally impaired adult patients (creatinine clearance >30-60 mL/min): Reduce to 30 mg twice daily for 5 days (2.4)
- Renally impaired adult patients (creatinine clearance >10-30 mL/min): Reduce to 30 mg once daily for 5 days (2.4)
- ESRD patients on hemodialysis: Reduce to 30 mg after every hemodialysis cycle. Treatment duration not to exceed 5 days (2.4)
- ESRD patients on CAPD: Reduce to a single 30 mg dose administered immediately after a dialysis exchange (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 to 12 years of age: Based on weight once daily for 10 days
  - Community outbreak: Based on weight once daily for up to 6 weeks
- Renally impaired adult patients (creatinine clearance >30-60 mL/min): Reduce to 30 mg once daily (2.4)
- Renally impaired adult patients (creatinine clearance >10-30 mL/min): Reduce to 30 mg once every other day (2.4)
- ESRD patients on hemodialysis: Reduce to 30 mg after alternate hemodialysis cycles for the recommended duration of prophylaxis (2.4)
- ESRD patients on CAPD: Reduce to 30 mg once weekly immediately after dialysis exchange for the recommended duration of prophylaxis (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 such as Stevens-Johnson Syndrome, toxic epidermal necrolysis and erythema multiforme: 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.

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

Revised: 11/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
- 1.1 Treatment of Influenza
- 1.2 Prophylaxis of Influenza
- 1.3 Limitations of Use

2 DOSAGE AND ADMINISTRATION
- 2.1 Dosing for Treatment and Prophylaxis of Influenza
- 2.2 Treatment of Influenza
- 2.3 Prophylaxis of Influenza
- 2.4 Renal Impairment
- 2.5 Hepatic Impairment
- 2.6 Geriatric Patients
- 2.7 Preparation of TAMIFLU for Oral Suspension
- 2.8 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
- 5.1 Serious Skin/Hypersensitivity Reactions
- 5.2 Neuropsychiatric Events
- 5.3 Bacterial Infections
- 5.4 Limitations of Populations Studied

6 ADVERSE REACTIONS
- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS
- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics
- 12.4 Microbiology

13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES
- 14.1 Treatment of Influenza
- 14.2 Prophylaxis of Influenza

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION
- 17.1 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 acute, uncomplicated illness due to influenza infection in patients 2 weeks of age 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 substitutions 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

Treatment with TAMIFLU should begin within 2 days of onset of symptoms of influenza or following close contact with an infected individual.

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.

For 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)]*.

2.2 Treatment of Influenza

<u>Adults and Adolescents (13 years of age and older)</u>

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. TAMIFLU for oral suspension may be used by patients who cannot swallow a capsule (12.5 mL of TAMIFLU for oral suspension [6 mg/mL] delivers 75 mg) *[see Dosage and Administration (2.1)]*.

<u>Pediatric Patients (2 weeks to 12 years of age)</u>

The recommended oral dose of TAMIFLU for treatment of influenza in pediatric patients 1 to 12 years of age is shown in Table 1.

The recommended oral dose of TAMIFLU for treatment of influenza in pediatric patients 2 weeks to less than 1 year of age is 3 mg/kg twice daily for 5 days (shown in Table 1).

2.3 Prophylaxis of Influenza

Adults and Adolescents (13 years of age and older)

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. 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 (12.5 mL of TAMIFLU for oral suspension [6 mg/mL] delivers 75 mg).

Pediatric Patients (1 to 12 years of age)

The recommended oral dose of TAMIFLU for prophylaxis of influenza in pediatric patients 1 to 12 years of age based on body weight is shown in Table 1. Prophylaxis in pediatric patients following close contact with an infected individual is recommended for 10 days. For prophylaxis in pediatric patients during a community outbreak of influenza, dosing may be continued for up to 6 weeks.

The safety and efficacy of TAMIFLU for prophylaxis of influenza have not been established in infants less than 1 year of age.

Table 1 Treatment (twice daily dosing for 5 days) and Prophylaxis (once daily dosing for 10 days) Dosing of Oral TAMIFLU for Influenza in Pediatric Patients

Weight (kg)	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†
Patients from 2 Weeks to less than 1 Year of Age					
Any weight	3 mg/kg **twice** daily	Not applicable‡	0.5 mL/kg§	1 bottle	Not applicable
Patients 1 to 12 Years of Age Based on Body Weight					
15 kg or less	30 mg **twice** daily	30 mg **once** daily	5 mL	1 bottle	10 Capsules 30 mg
15.1 kg thru 23 kg	45 mg **twice** daily	45 mg **once** daily	7.5 mL	2 bottles	10 Capsules 45 mg
23.1 kg thru 40 kg	60 mg **twice** daily	60 mg **once** daily	10 mL	2 bottles	20 Capsules 30 mg
40.1 kg or more	75 mg **twice** daily	75 mg **once** daily	12.5 mL	3 bottles	10 Capsules 75 mg

* An oral dosing dispensing device that measures the appropriate volume in mL should be utilized with the oral suspension.
† Oral Suspension is the preferred formulation for patients who cannot swallow capsules.
‡ TAMIFLU is not approved for prophylaxis of patients less than 1 year of age.
§ For patients less than 1 year of age, provide an appropriate dosing device that can accurately measure and administer small volumes.

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 60 mL/min and patients with end-stage renal disease (ESRD) undergoing hemodialysis or continuous peritoneal dialysis receiving TAMIFLU for the treatment of influenza [*see Clinical Pharmacology (12.3)*]. TAMIFLU is not recommended for patients with ESRD not undergoing dialysis. The recommended doses are detailed in Table 2 below.

Table 2 Recommended Dose Adjustments for Treatment of Influenza in Adult Patients with Renal Impairment or End Stage Renal Disease (ESRD) on Dialysis

Renal Impairment/Creatinine Clearance	Recommended Treatment Regimen*
Mild Creatinine Clearance >60-90 mL/min	75 mg twice daily for 5 days
Moderate Creatinine Clearance >30-60 mL/min	30 mg twice daily for 5 days
Severe Creatinine Clearance >10-30 mL/min	30 mg once daily for 5 days
ESRD Patients on Hemodialysis Creatinine Clearance ≤10 mL/min	30 mg after every hemodialysis cycle. Treatment duration not to exceed 5 days†
ESRD Patients on Continuous Ambulatory Peritoneal Dialysis‡ Creatinine Clearance ≤10 mL/min	A single 30 mg dose administered immediately after a dialysis exchange

* Capsules or suspension can be used for 30 mg dosing.

† Assuming three hemodialysis sessions are performed in the 5-day period. Treatment can be initiated immediately if influenza symptoms develop during the 48 hours between hemodialysis sessions; however, the post-hemodialysis dose should still be administered independently of time of administration of the initial dose.

‡ Data derived from studies in continuous ambulatory peritoneal dialysis (CAPD) patients.

Prophylaxis of Influenza

For the prophylaxis of influenza, dose adjustment is recommended for adult patients with creatinine clearance between 10 and 60 mL/min and patients with end-stage renal disease (ESRD) undergoing hemodialysis or continuous peritoneal dialysis receiving TAMIFLU [*see Clinical Pharmacology (12.3)*]. The duration of prophylaxis is the same as recommended for patients with normal renal function. TAMIFLU is not recommended for patients with ESRD not undergoing dialysis. The recommended doses are detailed in

Table 3 below.

Table 3 Recommended Dose Adjustments for Prophylaxis of Influenza in Adult Patients with Renal Impairment or End Stage Renal Disease (ESRD) on Dialysis

Renal Impairment/Creatinine Clearance	Recommended Prophylaxis Regimen*
Mild Creatinine Clearance >60-90 mL/min	75 mg once daily
Moderate Creatinine Clearance >30-60 mL/min	30 mg once daily
Severe Creatinine Clearance >10-30 mL/min	30 mg every other day
ESRD Patients on Hemodialysis Creatinine Clearance ≤10 mL/min	30 mg after alternate hemodialysis cycles†
ESRD Patients on Continuous Ambulatory Peritoneal Dialysis‡ Creatinine Clearance ≤10 mL/min	30 mg once weekly immediately after dialysis exchange

* Capsules or suspension can be used for 30 mg dosing.
† An initial dose can be administered prior to the start of dialysis.
‡ Data derived from studies in continuous ambulatory peritoneal dialysis (CAPD) patients.

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 **55 mL** of water in a graduated cylinder.

c) Add the total amount of water for constitution to the bottle.

d) Close bottle with child-resistant cap tightly and shake the closed bottle well for 15 seconds.

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

The constituted TAMIFLU for oral suspension (6 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 should be dispensed to the patient. Pharmacists should ensure patients have an oral dosing dispenser that measures the

appropriate volume in milliliters. Pharmacists should counsel patients on how to utilize an oral dosing dispenser and correctly measure the oral suspension as prescribed (see Table 1).

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, determine the dose of TAMIFLU for the patients [*see Dosage and Administration (2)*] then determine total volume of an oral suspension needed to be compounded based on Table 4.

Table 4 Volume of an Oral Suspension (6 mg/mL) Needed to be Compounded Based Upon the Patient's TAMIFLU Dose

TAMIFLU Dose*	Total Volume to Compound per Patient (mL)
15 mg or less	37.5 mL
30 mg	75 mL
45 mg	100 mL
60 mg	125 mL
75 mg	150 mL

* If the TAMIFLU dose is between the doses listed, the total volume of oral suspension to compound should default to the next greater dose listed.

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 4: 37.5 mL, 75 mL, 100 mL, 125 mL, or 150 mL) of compounded oral suspension (6 mg/mL) (see Table 5).

Table 5 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	**37.5 mL**	**75 mL**	**100 mL**	**125 mL**	**150 mL**
Number of TAMIFLU 75 mg Capsules*	3 capsules (225 mg oseltamivir)	6 capsules (450 mg oseltamivir)	8 capsules (600 mg oseltamivir)	10 capsules (750 mg oseltamivir)	12 capsules (900 mg oseltamivir)
Amount of Water	2.5 mL	5 mL	7 mL	8 mL	10 mL
Volume of Vehicle Cherry Syrup (Humco®) **OR** Ora-Sweet® SF (Paddock Laboratories) **OR** simple syrup	34.5 mL	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 5).
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.
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.

<u>Storage of the Emergency Compounded Suspension</u>

- 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.

<u>Dosing of the Compounded Suspension (6 mg/mL)</u>

Refer to Dosage and Administration sections 2.2, 2.3, 2.4 and Table 1 for the proper dosing instructions for the pharmacy label.

3 DOSAGE FORMS AND STRENGTHS

Capsules: 30 mg, 45 mg, 75 mg

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

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

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Serious Skin/Hypersensitivity Reactions

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

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.

Safety and efficacy of TAMIFLU for treatment of influenza in pediatric patients less than 2 weeks of age have not been established. Safety and efficacy of TAMIFLU for prophylaxis of influenza have not been established for pediatric patients less than 1 year of age.

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 and Adolescent Subjects (13 years of age and older)

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% or greater 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 and Adolescent Subjects (13 years of age and older)

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*	Treatment				Prophylaxis			
	Placebo N=716		TAMIFLU 75 mg twice daily N=724		Placebo/ No Prophylaxis† 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%)

* Adverse events included are all events reported in the treatment studies with frequency ≥1% in the TAMIFLU 75 mg twice daily group.
† 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 less than 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 (1 to 12 years of age)

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% or greater 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 (1 to 12 years of age)

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‡	Treatment Trials*				Household Prophylaxis Trial†			
	Placebo N=517		TAMIFLU 2 mg/kg twice daily N=515		No Prophylaxis§ N=87		Prophylaxis with TAMIFLU once daily§ 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%)	-		-	

* Pooled data from trials of TAMIFLU treatment of naturally acquired influenza.

† 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.

‡ 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.

§ Unit dose = age-based dosing of 30 mg, 45 mg, or 60 mg

Treatment Studies in Pediatric Subjects (2 weeks to less than 1 year of age)

Assessment of adverse reactions is based on two open label studies that included safety data on 135 influenza-infected subjects 2 weeks to less than 1 year of age (including premature infants at least 36 weeks post conceptional age) exposed to TAMIFLU at doses ranging from 2 to 3.5 mg/kg twice daily for 5 days. The safety profile was similar across the age range studied, with vomiting, diarrhea and diaper rash being the most frequently reported adverse reactions. The safety profile observed in subjects 2 weeks to less than 1 year of age was consistent with the established safety profile of adults and pediatric subjects older than 1 year of age.

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

Risk Summary

There are no adequate and well-controlled studies with TAMIFLU in pregnant women. Available published epidemiological data suggest that TAMIFLU, taken in any trimester, is not associated with an increased risk of birth defects. However, these studies individually are limited by small sample sizes, use of different comparison groups, and some lacked information on dose, which preclude a definitive assessment of the risk. In animal studies, there was a dose-dependent increase in the incidence rates of a variety of minor skeletal abnormalities and variants in offspring of rats and rabbits exposed at maternally toxic doses 100 and 50 times human exposures, respectively. TAMIFLU should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Pregnant women are at higher risk of severe complications from influenza, which may lead to adverse pregnancy and/or fetal outcomes including maternal death, still births, birth defects, preterm delivery, low birth weight and small for gestational age.

Data

Human Data – Published prospective and retrospective observational studies of approximately 1500 women exposed to oseltamivir during pregnancy including approximately 400 women exposed in the first trimester suggest that the observed rate of congenital malformations was not increased above the rate in the general comparison population, regardless of when therapy was administered during the gestational period. However, individually, none of these studies had adequate sample sizes and some lacked information on dose which preclude a definitive assessment of the risk.

Animal Data - 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, based on AUC. Pharmacokinetic studies indicated that there was fetal exposure 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. At the maternally toxic doses, statistically significant increases in the incidence rates of a variety of minor skeletal abnormalities and variants were observed in the exposed offspring. However, the individual incidence rate of each skeletal abnormality or variant remained within the background rates of occurrence in the species studied.

8.3 Nursing Mothers

Risk Summary

Based on limited published data, oseltamivir and oseltamivir carboxylate are present in human milk at low levels considered unlikely to lead to toxicity in the breastfed infant. Exercise caution when TAMIFLU is administered to a nursing woman.

8.4 Pediatric Use

Safety and efficacy of TAMIFLU for treatment of influenza in pediatric patients less than 2 weeks of age have not been established. Safety and efficacy of TAMIFLU for prophylaxis of influenza have not been established for pediatric patients less than 1 year of age.

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 subjects 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 60 mL/min and for patients with end-stage renal disease (ESRD) undergoing routine hemodialysis or continuous peritoneal dialysis treatment *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

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)]*.

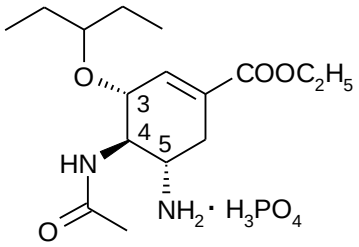
10 OVERDOSAGE

Reports of overdoses with TAMIFLU have been received from clinical trials and during postmarketing experience. In the majority of cases reporting overdose, no adverse events were reported. Adverse events reported following overdose were similar in nature to those observed with therapeutic doses of TAMIFLU *[see Adverse Reactions (6)]*.

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.

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 with activity against influenza virus *[see Microbiology (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_{max} (ng/mL)	65 (26)	348 (18)
$AUC_{0\text{-}12h}$ (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_{ss}) 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.

Specific Populations

Renal Impairment

Administration of 100 mg of oseltamivir phosphate twice daily for 5 days to subjects with various degrees of renal impairment showed that exposure to oseltamivir carboxylate is inversely proportional to declining renal function.

Population-derived pharmacokinetic parameters were determined for patients with varying degrees of renal function including ESRD patients on hemodialysis. Median simulated exposures of oseltamivir carboxylate for recommended treatment and prophylaxis regimens are provided in Table 9. The pharmacokinetics of oseltamivir have not been studied in ESRD patients not undergoing dialysis [*see Dosage and Administration (2.4)*].

Table 9 Simulated Median Treatment Exposure Metrics of Oseltamivir Carboxylate in Normal, Renally Impaired and ESRD Patients on Hemodialysis

Renal Function/ Impairment	**Normal Creatinine Clearance 90-140 mL/min (n=57)**	**Mild Creatinine Clearance 60-90 mL/min (n=45)**	**Moderate Creatinine Clearance 30-60 mL/min (n=13)**	**Severe Creatinine Clearance 10-30 mL/min (n=11)**	**ESRD Creatinine Clearance <10 mL/min on Hemodialysis (n=24)**
Recommended Treatment Regimens					
PK exposure parameter	**75 mg twice daily**	**75 mg twice daily**	**30 mg twice daily**	**30 mg once daily**	**30 mg every HD cycle**
C_{min} (ng/mL)	145	253	180	219	221
C_{max} (ng/mL)	298	464	306	477	1170
AUC_{48} (ng·h/mL)*	11224	18476	12008	16818	23200
Recommended Prophylaxis Regimens					
PK exposure parameter	**75 mg once daily**	**75 mg once daily**	**30 mg once daily**	**30 mg every other day**	**30 mg alternate HD cycle**
C_{min} (ng/mL)	39	62	57	70	42
C_{max} (ng/mL)	213	311	209	377	903
AUC_{48} (ng·hr/mL)*	5294	8336	6262	9317	11200

*AUC normalized to 48 hours.

In continuous ambulatory peritoneal dialysis (CAPD) patients, the peak concentration of oseltamivir carboxylate following a single 30 mg dose of oseltamivir or once weekly oseltamivir was approximately 3-fold higher than in patients with normal renal function who received 75 mg twice daily. The plasma concentration of oseltamivir carboxylate on Day 5 (147 ng/mL) following a single 30 mg dose in CAPD patients is similar to the predicted C_{min} (160 ng/mL) in patients with normal renal function following 75 mg twice daily. Administration of 30 mg once weekly to CAPD patients resulted in plasma concentrations of oseltamivir carboxylate at the 168 hour blood sample of 63 ng/mL, which were comparable to the C_{min} in patients with normal renal function receiving the approved regimen of 75 mg once daily (40 ng/mL).

Hepatic Impairment

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

Pregnant Women

A pooled population pharmacokinetic analysis indicates that the TAMIFLU dosage regimen [*see Dosage and Administration (2)*] resulted in lower exposure to the active metabolite in pregnant women (n=59) compared to non-pregnant women (n=33). However, this predicted exposure is expected to have activity against susceptible influenza virus strains and there are insufficient pharmacokinetics and safety data to recommend a dose adjustment for pregnant women.

Pediatric Subjects (1 to 12 years of age)

The pharmacokinetics of oseltamivir and oseltamivir carboxylate have been evaluated in a single-dose pharmacokinetic study in pediatric subjects aged 5 to 16 years (n=18) and in a small number of pediatric subjects aged 3 to 12 years (n=5) enrolled in a clinical trial. Younger pediatric subjects cleared both the prodrug and the active metabolite faster than adult subjects 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 subjects over 12 years of age are similar to those in adult subjects.

Pediatric Subjects (2 weeks to less than 1 year of age)

The pharmacokinetics of oseltamivir and oseltamivir carboxylate have been evaluated in two open-label studies of pediatric subjects less than one year of age (n=122) infected with influenza. Apparent clearance of the active metabolite decreases with decreasing age in subjects less than 1 year of age; however the oseltamivir and oseltamivir carboxylate exposure following a 3 mg/kg dose in subjects under 1 year of age is expected to be within the observed exposures in adults and adolescents receiving 75 mg twice daily and 150 mg twice daily.

Geriatric Patients

Exposure to oseltamivir carboxylate at steady-state was 25% to 35% higher in geriatric subjects (age range 65 to 78 years) compared to young adults given comparable doses of oseltamivir. Half-lives observed in the geriatric subjects 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. The median IC_{50} 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.

Antiviral Activity

The antiviral activity of oseltamivir carboxylate against laboratory strains and clinical isolates of influenza virus was determined in cell culture. 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_{50} and EC_{90}) 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 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

Cell culture studies: 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. 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.

Clinical studies: Reduced susceptibility isolates have been obtained during treatment with oseltamivir and from sampling during community surveillance studies. Changes in the viral neuraminidase that have been associated with reduced susceptibility to oseltamivir carboxylate are summarized in Table 10. The clinical impact of this

reduced susceptibility is unknown. 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 Associated with Reduced Susceptibility to Oseltamivir

Amino Acid Substitution*	Source
Influenza A N1 (N1 numbering in brackets)	
I117V (I117V)	Publication
E119V (E119V)	Publication
R152K (R152K)	Publication
Y155H (Y155H)	Publication
F173V (F174V)	Publication
D198G/N (D199G/N)	Roche clinical trial, publication
I222K/R/T/V (I223K/R/T/V)	Publication
S246N (S247N)	Publication
G248R+I266V (G249R+I267V)	Publication
H274Y (H275Y)	Roche clinical trial, publication
N294S (N295S)	Publication
Q312R+I427T (Q313R+I427T)	Publication
N325K (N325K)	Publication
R371K (R368K)	Publication
Influenza A N2	
E41G	Publication
E119I/V	Roche clinical trial, publication
D151V	Publication
I222L/V	Publication
Q226H	Publication
SASG245-248 deletion	Roche clinical trial, publication
S247P	Publication
R292K	Roche clinical trials, publication
N294S	Publication
Influenza B (B numbering in brackets)	
E119A (E117A)	Publication
P141S (P139S)	Publication
G142R (G140R)	Publication
R152K (R150K)	Publication
D198E/N/Y (D197E/N/Y)	Publication
I222L/T/V (I221L/T/V)	Publication
A246D/S/T (A245D/S/T)	Roche clinical trial, publication
H274Y (H273Y)	Publication
N294S (N294S)	Publication
R371K (R374K)	Publication
G402S (G407S)	Publication

* All numbering is N2, except where indicated

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 virus isolates. The 2009 H1N1 influenza virus ("swine flu") was almost uniformly susceptible to oseltamivir. Prescribers should consider available information from the CDC on influenza virus 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 virus neuraminidase, 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 virus neuraminidase, confer reduced susceptibility to both oseltamivir and zanamivir. These examples do not represent an exhaustive list of cross resistance-associated substitutions and prescribers should consider available information from the CDC on influenza drug susceptibility patterns and treatment effects when deciding whether to use TAMIFLU.

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 ≥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 and Adolescent Subjects (13 years of age and older)

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 >100ºF, 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 ≥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°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 (1 to 12 years of age)

One double-blind placebo-controlled treatment trial was conducted in pediatric subjects aged 1 to 12 years (median age 5 years), who had fever (>100ºF) 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.

Pediatric Subjects (2 weeks to less than 1 year of age)

Two open label trials evaluated the safety and pharmacokinetics of oseltamivir and oseltamivir carboxylate in influenza-infected pediatric subjects 2 weeks to less than 1 year of age (including premature infants at least 36 weeks post conceptional age). Subjects received TAMIFLU at doses ranging from 2 to 3.5 mg/kg twice daily for 5 days depending on subject age. These clinical trials were not designed to evaluate clinical efficacy or virologic response.

Of the 136 subjects under the age of 1 year enrolled and dosed in the trials, the majority of the subjects were male (55%), white (79%), non-Hispanic (74%), full term (76%) and infected with influenza A (80%). Pharmacokinetic data indicated that a dose of 3 mg/kg twice daily in pediatric subjects 2 weeks to less than 1 year of age provided TAMIFLU concentrations similar to or higher than those observed in older pediatric subjects and adults receiving the approved dose and, by extrapolation, is expected to provide similar efficacy. The trials provided adequate safety data to support this dose selection *[see Adverse Reactions (6.1)*].

14.2 Prophylaxis of Influenza

Adult and Adolescent Subjects (13 years of age and older)

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 ≥99.0ºF/37.2ºC 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% (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 (1 to 12 years of age)

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 pediatric subjects 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 ≥100°F/37.8°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°F/37.2°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 infection. Among subjects who were not already shedding virus at baseline, the incidence of RT-PCR-confirmed clinical influenza infection 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 25ºC (77ºF); excursions permitted to 15º to 30ºC (59º to 86ºF) [See USP Controlled Room Temperature].

TAMIFLU for Oral Suspension

Supplied as a white powder blend in a glass bottle. After constitution, the powder blend produces a white tutti-frutti–flavored oral suspension. After constitution with 55 mL of water, each bottle delivers a usable volume of 60 mL of oral suspension equivalent to 360 mg oseltamivir base (6 mg/mL). (NDC 0004-0822-05).

Storage

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

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient Labeling (Patient Information and Instructions for Use)

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 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.

Tamiflu® (oseltamivir phosphate)

Distributed by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
©2014 Genentech, Inc. All rights reserved

Licensor:
Gilead Sciences, Inc.
Foster City, California 94404

PATIENT INFORMATION

TAMIFLU® (TAM-ih-flew)
(oseltamivir phosphate)
capsules, for oral use

TAMIFLU® (TAM-ih-flew)
(oseltamivir phosphate)
for oral suspension

What is TAMIFLU?

TAMIFLU is a prescription medicine used to:

- treat the flu (influenza) in people 2 weeks of age and older who have had flu symptoms for no more than two days.
- prevent the flu in people who are 1 year of age and older.

It is not known if TAMIFLU is:

- effective in people who start treatment after 2 days of developing flu symptoms.
- effective for the treatment of the flu in people with long-time (chronic) heart problems or breathing problems.
- effective for the treatment or prevention of flu in people who have weakened immune systems (immunocompromised).
- safe and effective for the treatment of the flu in children less than 2 weeks of age.
- safe and effective in the prevention of the flu in children less than 1 year of age.

TAMIFLU does not treat or prevent illness that is caused by infections other than the influenza virus.

TAMIFLU does not prevent bacterial infections that may happen with the flu.

TAMIFLU does not take the place of receiving a flu vaccination. Talk to your healthcare provider about when you should receive an annual flu vaccination.

Who should not take TAMIFLU?

Do not take TAMIFLU if you are allergic to oseltamivir phosphate or any of the ingredients in TAMIFLU. **See the end of this leaflet for a complete list of ingredients in TAMIFLU.**

What should I tell my healthcare provider before taking TAMIFLU?

Before you take TAMIFLU, tell your healthcare provider if you:

- have problems swallowing TAMIFLU capsules.
- have kidney problems
- have a history of fructose (fruit sugar) intolerance. TAMIFLU contains sorbitol and may cause stomach upset and diarrhea in people who are fructose intolerant.

- have any other medical conditions
- are pregnant or plan to become pregnant. Available information indicate that TAMIFLU does not increase the risk of birth defects.
- are breastfeeding or plan to breastfeed. TAMIFLU can pass into breast milk in small amounts.

Tell your healthcare provider about all the medicines you take, including prescription or over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take TAMIFLU?

- Take TAMIFLU exactly as your healthcare provider tells you to.
- Take TAMIFLU with food or without food. There is less chance of stomach upset if you take TAMIFLU with food.
- If you miss a dose of TAMIFLU, take it as soon as you remember. If it is 2 hours or less before your next dose, do not take the missed dose. Take your next dose of TAMIFLU at your scheduled time. Do not take 2 doses at the same time.
- If TAMIFLU for oral suspension is not available or you cannot swallow TAMIFLU capsules, your healthcare provider may instruct you to open TAMIFLU capsules and mix the capsules contents with sweetened liquids such as chocolate syrup (regular or sugar-free), corn syrup, caramel topping, or light brown sugar (dissolved in water).
- **If your healthcare provider has instructed you to take TAMIFLU oral suspension or open your TAMIFLU capsules, read the detailed Instructions for Use at the end of this leaflet. Ask your pharmacist if you have any questions.**

What are the possible side effects of TAMIFLU?

TAMIFLU may cause serious side effects, including:

- **Serious skin and allergic reactions**. TAMIFLU can cause serious skin and allergic reactions. Stop taking TAMIFLU and get medical help right away if you get any of the following symptoms:
  - skin rash or hives
  - your skin blisters and peels
  - blisters or sores in your mouth
  - itching
  - swelling of your face, eyes, lips, tongue, or throat
  - trouble breathing
  - chest pain or tightness

- **Change in behavior.** People, especially children, who have the flu can develop nervous system problems and abnormal behavior that can lead to death. During treatment with TAMIFLU, tell your healthcare provider right away if you or your child have confusion, speech problems, shaky movements, seizures, or start hearing voices or seeing things that are not really there (hallucinations).

The most common side effects of TAMIFLU when used for treatment of the flu include nausea and vomiting.

The most common side effect of TAMIFLU when used for prevention of the flu include nausea, vomiting, diarrhea, and stomach (abdomen) pain.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of TAMIFLU.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TAMIFLU?

- Store TAMIFLU capsules at room temperature between 68°F to 77°F (20°C to 25°C).
- Store TAMIFLU for oral suspension in the refrigerator for up to 17 days between 36ºF to 46ºF (2ºC to 8ºC)
- Store TAMIFLU for oral suspension for up to 10 days at room temperature between 68°F to 77°F (20°C to 25°C).
- Safely throw away any unused TAMIFLU that is out of date or no longer needed.

Keep TAMIFLU and all medicines out of the reach of children.

General information about the safe and effective use of TAMIFLU.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. 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 harm them.

If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about TAMIFLU that is written for health professionals.

For more information, go to www.tamiflu.com.

What are the ingredients in TAMIFLU?

Active ingredient: oseltamivir phosphate

Inactive ingredients:

TAMIFLU capsules: pregelatinized starch, talc, povidone K30, croscarmellose sodium, and sodium stearyl fumarate

30mg capsule shell: gelatin, titanium dioxide, yellow iron oxide, and red iron oxide

45mg capsules shell: gelatin, titanium dioxide, and black iron oxide

75mg capsules shell: gelatin, titanium dioxide, yellow iron oxide, black iron oxide, and red iron oxide

TAMIFLU for oral suspension: sorbitol, monosodium citrate, xanthan gum, titanium dioxide, tutti-frutti flavoring, sodium benzoate, saccharin sodium and water.

Instructions For Use
TAMIFLU® (TAM-ih-flew)
(oseltamivir phosphate)
capsules, for oral use

TAMIFLU® (TAM-ih-flew)
(oseltamivir phosphate)
for oral suspension

How do I prepare a dose of TAMIFLU for oral suspension?

- Step 1. Shake the TAMIFLU for oral suspension bottle well before each use.
- Step 2. Open the bottle by pushing downward on the child resistant bottle cap and twisting it in the direction of the arrow.
- Step 3. Measure the oral suspension with an appropriate oral dosing dispenser to be sure you get the correct dose. Contact your pharmacist if you do not have an appropriate oral dosing dispenser.
- Step 4. Dispense full contents of oral dosing dispenser directly into the mouth.
- Step 5. Close the bottle with the child-resistant bottle cap after each use.
- Step 6. Rinse oral dosing dispenser under running tap water and allow to air dry after each use.

How do I mix the contents of TAMIFLU capsules with sweetened liquids, if directed by my healthcare provider?

You will need:

- the prescribed dose of TAMIFLU capsules
- a small bowl
- sweetened liquid, such as chocolate syrup (regular or sugar-free), corn syrup, caramel topping, or light brown sugar (dissolved in water)

- Step 1. Open the contents of the prescribed dose of TAMIFLU capsules into a small bowl.
- Step 2. Add a small amount of the sweetened liquid to the capsule contents.
- Step 3. Stir the mixture and give the entire dose of TAMIFLU.

This Patient Information and Instructions for Use have been approved by the U.S. Food and Drug Administration.

Tamiflu® (oseltamivir phosphate)

Distributed by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

Licensor:
Gilead Sciences, Inc.
Foster City, California 94404

©2013 Genentech, Inc. All rights reserved
Rev. November 2014