

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		Form Approved: OMB No. 0910-0430 Expiration Date: April 30, 2009 See OMB Statement on page 2.
APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE <i>(Title 21, Code of Federal Regulations, Parts 314 & 601)</i>		FOR FDA USE ONLY
		APPLICATION NUMBER
APPLICANT INFORMATION		
NAME OF APPLICANT Hoffmann-La Roche Inc.		DATE OF SUBMISSION 10/03/2008
TELEPHONE NO. <i>(Include Area Code)</i> (973)235-5268		FACSIMILE (FAX) Number <i>(Include Area Code)</i> (973) 562-3700
APPLICANT ADDRESS <i>(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):</i> 340 Kingsland Street Nutley, New Jersey 07110		AUTHORIZED U.S. AGENT NAME & ADDRESS <i>(Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE</i>
PRODUCT DESCRIPTION		
NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER <i>(If previously issued)</i> NDA 21-087		
ESTABLISHED NAME <i>(e.g., Proper name, USP/USAN name)</i> oseltamivir phosphate		PROPRIETARY NAME <i>(trade name) IF ANY</i> Tamiflu®
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME <i>(If any)</i> (3R,4R,5S)-4-acetylamino-5-amino-3(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid, ethyl ester, phosphate (1:1)		CODE NAME <i>(If any)</i>
DOSAGE FORM: Capsules	STRENGTHS: 75 mg (free base equivalent)	ROUTE OF ADMINISTRATION: Oral
(PROPOSED) INDICATION(S) FOR USE: Treatment and Prophylaxis of Influenza		
APPLICATION DESCRIPTION		
APPLICATION TYPE <i>(check one)</i> <input checked="" type="checkbox"/> NEW DRUG APPLICATION (CDA, 21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)		
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)		
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug _____ Holder of Approved Application _____		
TYPE OF SUBMISSION <i>(check one)</i> <input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input checked="" type="checkbox"/> OTHER		
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____		
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)		
REASON FOR SUBMISSION TAMIFLU Briefing Package		
PROPOSED MARKETING STATUS <i>(check one)</i> <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)		
NUMBER OF VOLUMES SUBMITTED <u> 1 </u> THIS APPLICATION IS <input type="checkbox"/> PAPER <input checked="" type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC		
ESTABLISHMENT INFORMATION <i>(Full establishment information should be provided in the body of the Application.)</i> Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.		
Cross References <i>(list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)</i>		
IND 53,093 NDA 21-246		

This application contains the following items: (Check all that apply)		
<input checked="" type="checkbox"/>	1. Index	
<input type="checkbox"/>	2. Labeling (check one)	<input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))	
<input type="checkbox"/>	4. Chemistry section	
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)	
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)	
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)	
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)	
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))	
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)	
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)	
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)	
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)	
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)	
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))	
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))	
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)	
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))	
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))	
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)	
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)	
<input checked="" type="checkbox"/>	20. OTHER (Specify) GENERAL CORRESPONDENCE: TAMIFLU Briefing Package	
CERTIFICATION		
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:		
<ol style="list-style-type: none"> 1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820. 2. Biological establishment standards in 21 CFR Part 600. 3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809. 4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202. 5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12. 6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81. 7. Local, state and Federal environmental impact laws. 		
If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.		
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.		
Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.		
SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
	Angela Stephenson, Sr. Program Manager	10/03/2008
ADDRESS (Street, City, State, and ZIP Code)		Telephone Number
340 Kingsland Street, Nutley, New Jersey		(973) 235-5268
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Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Central Document Room 5901-B Ammendale Road Beltsville, MD 20705-1266	Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research (HFM-99) 1401 Rockville Pike Rockville, MD 20852-1448	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.



October 3, 2008

Paul T. Tran, RPh.
Advisors and Consultants Staff
FDA, CDER, OEP
HFD-21, Room 1093
5630 Fishers Lane
Rockville, MD 20857-1734

Re: NDA 21-087 - Tamiflu® (oseltamivir phosphate)
GENERAL CORRESPONDENCE: TAMIFLU Briefing Package for the October 29, 2008 Joint Antiviral Drugs Advisory Committee and Nonprescription Drugs Advisory Committee

Dear Mr. Tran:

Reference is made to the letter from Mr. Paul Tran, dated August 22, 2008, which provides details on the Sponsor and FDA's briefing package for the October 29, 2008 joint Antiviral Drugs Advisory Committee and Nonprescription Drugs Advisory Committee meeting which has been scheduled to discuss the pre-deployment of antiviral influenza drug "MedKits" in preparation for a possible pandemic. As requested in your letter, 40 electronic CD copies and 40 paper copies of the Sponsor's background package, available for public disclosure, are included in this submission.

The CD has been scanned with Symantec AntiVirus, Version 10/1/2008 rev. 3, and no viruses were found.

Should you have any questions concerning this submission, please do not hesitate to contact the undersigned.

Sincerely,

HOFFMANN-LA ROCHE, INC.


for

Angela Stephenson, Pharm.D.
Sr. Program Manager
Drug Regulatory Affairs
Telephone: (973)235-5268
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AS/sv
Attachment
HLR No.: N2008-02886

Desk Copy: NDA 21-087

**ANTIVIRAL DRUGS ADVISORY COMMITTEE
NONPRESCRIPTION DRUGS ADVISORY COMMITTEE
BRIEFING DOCUMENT FOR TAMIFLU**

HOFFMANN-LA ROCHE INC
Nutley, New Jersey

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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GLOSSARY OF ABBREVIATIONS

CDC	Centers for Disease Control and Prevention
ECDC	European Centre for Disease Control and Prevention
FDA	Food and Drug Administration
HHS	Health and Human Services
OTC	Over-the-counter
REALM	Rapid Estimate of Adult Literacy in Medicine
US	United States
WHO	World Health Organization

1. EXECUTIVE SUMMARY

Influenza pandemics are recurring events that have the potential to cause more death and illness than any other public health threat today. Since the timing and magnitude of the next pandemic cannot be predicted, preparedness planning for a severe pandemic is vital.

Vaccination will be the primary measure for minimizing the morbidity and mortality of pandemic influenza. However, there will be delays in the production of a pandemic vaccine since this can only start after a pandemic virus has been identified. During this period, influenza antiviral drugs will have a significant beneficial impact in reducing morbidity and mortality and limiting the local spread of disease by allowing for treatment of infected individuals and post-exposure prophylaxis of healthcare workers and other critical personnel. A key element in the Department of Health and Human Services (HHS) Pandemic Influenza Plan is the stockpiling of Tamiflu, an oral antiviral inhibitor of the neuraminidase enzyme of influenza virus types A and B [1]. The current United States (US) Strategic National Stockpile of Tamiflu is at 81 million regimens; these regimens are allocated for the treatment of acute influenza infection and would allow for 25% of the US population to be treated.

In March 2008, HHS initiated discussions with Roche on a proposed initiative for the home stockpiling of Tamiflu in a medical kit (ie, MedKit) as a way of supplementing the current government antiviral stockpile and thereby, enhancing its pandemic preparedness. Home stockpiling of antivirals, significantly in advance of a pandemic threat, could greatly expand the domestic supply available at the time of a pandemic and offers the additional benefits of: 1) a potential increased treatment benefit by shortening the time from symptom onset to treatment initiation, 2) decreased pandemic infection rates by reducing the need for infected individuals to leave the home to obtain treatment; and 3) decreased pandemic infection rates by allowing for post-exposure prophylaxis.

Recognizing the public health need and the need to provide a mechanism to allow for individuals to prepare for a pandemic, Roche is pursuing the development of a Tamiflu MedKit for pandemic influenza. The MedKit would provide one Tamiflu treatment course for one member of the household, to be used for the treatment or prophylaxis of pandemic influenza, and would be stored in the household until a regional or local pandemic outbreak occurs. Roche is proposing a new label and new packaging for the MedKit to clearly distinguish Tamiflu for use in pandemic influenza from Tamiflu for use in seasonal influenza.

The purpose of this document is to summarize Roche's proposal for a Tamiflu MedKit for pandemic influenza, including the MedKit components, the proposed studies to support marketing approval, plans for resistance monitoring and the prevention of resistance, plans for the collection and reporting of safety information, and the communication plan through which timely information on resistance, safety, and Tamiflu dosing will be communicated to health authorities, public health agencies, healthcare professionals, and the general public.

Roche welcomes the opportunity to discuss and collaborate with the Advisory Committee, public health agencies, and other groups on how to enhance pandemic

preparedness including how to maximize access to treatment options and how to provide guidance to the general public on the use of these treatments.

2. PANDEMIC INFLUENZA

2.1 Background

Influenza pandemics are recurring events that are associated with high morbidity and mortality, economic and social disruption, and sudden and sharp increases in the demand for health care. Influenza pandemics occur when a new influenza virus emerges for which people have little or no immunity and for which there is no vaccine. In past pandemics, the influenza virus spread worldwide within months, with the most severe pandemic (Spanish influenza, 1918-1919) resulting in 40-50 million deaths worldwide. Certain modern trends, such as an urbanized population, international travel, and an increasing number of elderly and those with chronic medical conditions, increase the potential for future pandemics to cause more illnesses and deaths than have been seen previously. For example, if an epidemic of a severity similar to the Spanish influenza occurred in the US today, there would be an estimated 1.9 million deaths and 10 million hospitalizations [1].

It is difficult to predict when the next pandemic will occur, however, several highly pathogenic, novel avian viruses (H5N1, H7N7, and H9N2) have emerged that represent a potential human pandemic threat. Human infections with these viruses have occurred and in the case of H5N1, the fatality rate has been high (61%). To date, there has been no sustained human-to-human transmission of infection, but these viruses could evolve into viruses capable of human-to-human transmission, leading to a potentially significant pandemic threat.

2.2 Vaccines and Antivirals

Vaccination will be the primary measure for minimizing the morbidity and mortality of pandemic influenza. However, during the early stages of a pandemic, vaccine supplies will be limited since vaccine production, which can take several months, can only start once a pandemic virus has been identified. Until a vaccine against pandemic influenza becomes available in sufficient quantities to have a significant protective impact, antiviral drugs will play an important public health role.

Tamiflu® (oseltamivir phosphate), an oral antiviral inhibitor of the neuraminidase enzyme of influenza virus types A and B, is approved in the US for the treatment and prophylaxis of influenza in patients 1 year and older. Tamiflu is currently being stockpiled by the US federal government, state governments, and select businesses and healthcare organizations as part of pandemic preparedness. The current US Strategic National Stockpile of Tamiflu is at 81 million regimens. These regimens are allocated for the treatment of acute influenza infection and would allow for 25% of the US population to be treated during a pandemic, according to priority recommendations approved by the National Vaccine Advisory Committee. However, as shown in [Table 1](#), it is predicted that significantly more deaths and hospitalizations in the US could be prevented during a pandemic if the current stockpile was increased to allow for both treatment and post-exposure prophylaxis.

Table 1 Estimated Health Impacts, Antiviral Drug Requirements, and Cost Effectiveness

Parameter	Treatment of Acute Influenza Infection Alone	Household Post-Exposure Prophylaxis Alone	Treatment and Post-Exposure Prophylaxis
No. of antiviral regimens	79.4 mil	106.4 mil	167.1 mil
No. of deaths prevented	144,000	155,000	288,000
No. of hospitalizations prevented	1.845 mil	838,000	2.427 mil
Cost per death prevented*	\$11,200	\$14,000	\$11,800
Cost per hospitalization prevented**	\$900	\$2,600	\$1,400

*Average cost per regimen based on federal contract price for oseltamivir and zanamavir, the relative proportions of each agent targeted for acquisition for the national stockpile rounded to the nearest \$100

**Estimates included are sensitive to the assumptions used in modeling

Source: HHS

2.3 MedKit for Pandemic Influenza

In 2005, a Center for Disease Control and Prevention’s (CDC) advisory group discussed the concept of a medical kit (ie, MedKit) that would: 1) provide families with critical prescription medicines needed during emergencies such as radiation sickness following a nuclear attack or accident, anthrax exposure, or an influenza pandemic and 2) be used only as directed in a declared public health emergency. The CDC advisory panel’s report cited the general benefits of a MedKit as “rapid availability of preventive therapy, avoidance of waiting in lines for dispensing, and prevention of excessive burden on the local public health systems during a crisis”.

One of the first MedKit initiatives was for the treatment of anthrax. CDC, in collaboration with FDA and the Missouri state health authority, conducted a MedKit pilot program in 2006 in 4,076 households in St. Louis to evaluate consumer’s acceptance and maintenance of MedKits for anthrax treatment. In this study, the majority (94%) of participants appropriately stored and retained the MedKit for use until directed by public health officials. Only 3% of households did not return their kits and 3% reported using them. In addition, a large proportion of study participants reported “they would like to have emergency MedKits in their homes and would be willing to purchase these MedKits”.

In March 2008, HHS initiated discussions with Roche on a proposed initiative for the home stockpiling of Tamiflu as a way of supplementing the current government antiviral stockpile and thereby, enhancing its preparedness activities for pandemic influenza. Home stockpiling of influenza antivirals in a MedKit, could greatly expand the domestic supply available at the time of a pandemic and offers the following additional benefits:

- A potential increased treatment benefit by shortening the time from symptom onset to treatment initiation
- Decreased pandemic infection rates by reducing the need for infected people to leave the home to obtain treatment
- Decreased pandemic infection rates by allowing for post-exposure prophylaxis

Recognizing the public health need and the need to provide a mechanism to allow for individuals to prepare for a pandemic, Roche is pursuing the development of a Tamiflu MedKit for pandemic influenza that would: 1) provide Tamiflu regimens for treatment and prophylaxis of pandemic influenza for all members of an individual household and 2) be stored in the household until a regional or a local pandemic outbreak occurs. Roche is proposing a new label and new packaging for the MedKit to clearly distinguish Tamiflu for use in pandemic influenza from Tamiflu for use in seasonal influenza.

The purpose of this document is to summarize Roche's proposal for a Tamiflu MedKit for pandemic influenza, including the MedKit components, the proposed studies to support marketing approval, plans for resistance monitoring and the prevention of resistance, plans for the collection and reporting of safety information, and plans for communications through which information on resistance, safety, and Tamiflu dosing will be communicated.

2.4 Regulatory Framework for MedKit Development and Approval

There are two regulatory pathways available for drug approval, either as a prescription product or an over-the-counter (OTC) product, both of which require distinct development programs. Proposed OTC drugs generally require two types of studies:

- A label comprehension study that demonstrates that the label clearly communicates the uses, directions, and warnings to a diverse population and enables consumers to make appropriate judgements about self-selection
- An actual use study that demonstrates that consumers can appropriately self-select or de-select a product for use, based on the product label and their unique medical histories, and can take a product safely using the directions provided in the product label without the intervention of a healthcare provider

As outlined in Section 6, FDA has requested and Roche has agreed to conduct an OTC-like development program for approval of the Tamiflu MedKit since the MedKit, similar to other OTC products, will be stored in the home and used by the patient according to directions provided in the product label. However, approval of the MedKit as an OTC product requires that the MedKit be distinguished in either indication, dose, or patient population, from prescription Tamiflu for seasonal influenza. Roche and FDA are currently in discussion about which approval pathway is the most appropriate for the MedKit. However, because there is currently no clear distinction between the Tamiflu MedKit and prescription Tamiflu for seasonal use with respect to indication (treatment and prophylaxis of influenza), dose (75 mg; Section 4.1), and patient population, Roche is constrained, under the current regulatory rules and legislation, to use the prescription drug approval route for the MedKit.

To minimize any potential or perceived barriers to obtaining the MedKit, it may be necessary for a unique Tamiflu access model, beyond the model of either prescription or OTC distribution, to be developed. This may require the creation of an alternative regulatory approval mechanism for a Tamiflu MedKit as the availability MedKit through an OTC-like mechanism would likely maximize access by:

- Allowing the MedKit to more easily be obtained for all household members since multiple prescriptions from different healthcare providers will not be necessary.
- Allowing the MedKit to be obtained by individuals who would not or could not see a healthcare provider for a MedKit prescription
- Eliminating any potential complications or confusion with state pharmacy dispensing laws related to product expiry (ie, 1 year) compared to the Tamiflu shelf-life expiration date (5 years)

3. TAMIFLU BACKGROUND

3.1 Description of Product

Tamiflu (oseltamivir phosphate) is an orally available, ethyl ester pro-drug of oseltamivir carboxylate, which is a potent, stable, and selective inhibitor of influenza A and B neuraminidase and which displays no activity against other viruses. Neuraminidase is a critical protein on the surface membrane of the influenza virus that enables replicated virus to bud from infected host cells and that helps the virus pass through mucus between cells in the entire respiratory tract. Inhibition of neuraminidase by oseltamivir carboxylate is effective for the treatment and prophylaxis of influenza A and B infections.

Tamiflu is dosed twice daily for 5 days for the treatment of influenza infection. Treatment should begin within 2 days of onset of the symptoms of influenza. Tamiflu is dosed once daily for 10 days for prophylaxis of influenza; therapy should begin within 2 days of exposure. The recommended Tamiflu doses for treatment and prophylaxis are shown in [Table 2](#).

Table 2 Tamiflu Dosage Chart for Treatment and Prophylaxis

Age and Weight	Dosage
Adults and children 13 years and older	1 dose = 75 mg
Children 1to 12 years ≤ 33 lbs (≤ 15 kg)	1 dose = 30 mg
> 33 lbs to 51 lbs (> 15 kg to 23 kg)	1 dose = 45 mg
> 51 lbs to 88 lbs (> 23 kg to 40 kg)	1 dose = 60 mg
> 88 lbs (> 40 kg)	1 dose = 75 mg

3.2 Registration History

Tamiflu has been approved in over 80 countries worldwide for both treatment and prophylaxis of influenza. The registration history of Tamiflu in the US is provided in [Table 3](#). In the US, Tamiflu was approved in 1999 for the treatment of uncomplicated acute illness due to influenza infection in adults and adolescents who have been symptomatic for no more than 2 days. Tamiflu was also approved for the treatment of influenza in children aged 1-12 years in 2000 and for prophylactic use in persons 13 years of age and older and for children > 1 year of age in 2000 and 2005, respectively. The current Tamiflu Package Insert and Patient Package Insert are provided on [page 26](#) and [page 49](#) , respectively.

Registration of Tamiflu for the treatment of influenza in children was based on double-blind, randomized, placebo-controlled treatment studies as well as a prophylaxis study in children. Pediatric exclusivity was granted in March 2004 on the basis of the pediatric registration studies and a Phase 3, randomized, open-label study of Tamiflu for the management of influenza in households in which children (aged 1-12 years) participated.

Table 3 Tamiflu US Registration History

Indication	Population	Approval Date
Treatment of influenza	Adults and adolescents	October 27, 1999
Prophylaxis of influenza	adults and adolescents \geq 13 years of age	November 17, 2000
Treatment of influenza	patients \geq 1 year of age	December 14, 2000
Pediatric exclusivity	-	March 22, 2004
Prophylaxis of influenza	patients \geq 1 year of age	December 21, 2005

3.3 Benefits of Tamiflu Treatment and Prophylaxis

The key benefits of Tamiflu in the treatment of influenza in adults are an earlier resolution of illness and an earlier return to normal health and activity. Increased benefit can be obtained by providing Tamiflu as soon as possible after the onset of symptoms [2].

The benefits of Tamiflu in the treatment of influenza in children are similar to those seen in adults including significant reductions in the median duration of illness, the time taken to return to normal activity, and the median duration of symptoms [3].

Prophylaxis studies of Tamiflu have been completed in a range of populations and settings and with differing durations of therapies. Post-exposure prophylaxis studies of Tamiflu in adults and adolescents show that a 75 mg dose of Tamiflu administered once daily for 7 days reduces the incidence of influenza by up to 92%, does not prevent an antibody response to influenza infection, and does not result in the development of Tamiflu resistance [4, 5, 6]. Post-exposure prophylaxis of children aged 1 to 12 years with Tamiflu reduced the incidence of influenza from 21% in the group not receiving prophylaxis to 4% in the group receiving prophylaxis [7].

Tamiflu has been used in some clinical cases of avian influenza in which there was reduced mortality; however, there are a limited number of clinical cases available for assessment [8, 9, 10].

3.4 Side Effects of Tamiflu Treatment and Prophylaxis

To date, Tamiflu has been administered to 2,620 subjects in prophylaxis studies and 5,376 subjects in treatment studies. In addition, based on prescription fill rates, 55 million patients worldwide are estimated to have received Tamiflu since 1999.

Tamiflu is generally well tolerated. In treatment studies in adult patients, the most frequently reported adverse events (incidence \geq 1%) were nausea and vomiting [11]. A similar adverse event profile was seen in prophylaxis studies in adult patients [11].

Gastrointestinal events were also the most frequently reported adverse events in treatment (vomiting) [12] and prophylaxis (nausea without vomiting; vomiting) studies of Tamiflu in children [7].

There have been post-marketing 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.

3.5 Tamiflu Resistance

As mentioned previously, Tamiflu is a specific inhibitor of influenza virus neuraminidase and displays no activity against other viruses. Thus, Tamiflu cannot induce resistance unless there is influenza virus present. For example, Tamiflu resistance cannot develop in an individual with a common cold who is prescribed Tamiflu inadvertently. Also, neuraminidase mutations generally lead to a functionally defective enzyme, that reduces the fitness of the virus and results in decreased infectivity. Multiple genetic changes are necessary to generate a replication competent, transmissible, Tamiflu-resistant virus and thus, there is a high genetic barrier and consequent low risk of drug-induced resistance selection during Tamiflu treatment.

Results obtained from global viral surveillance studies indicate that the prevalence of Tamiflu-resistant viruses was low (< 1%) between 1999 to 2007. A higher incidence (15%; range, 0% to 68% depending on the region) of Tamiflu-resistant influenza A H1N1 viruses was observed in the 2007-2008 influenza season. [13]. There was no apparent association between the detection of Tamiflu-resistant H1N1 viruses and Tamiflu use since the vast majority of patients with resistant virus had not received Tamiflu or been exposed to any patient who had. Multiple mutations that compensate for a replication defect have been identified in these strains [14]. These data suggest that the frequencies of resistant H1N1 viruses are not correlated with Tamiflu usage and provide insight into the emergence of naturally occurring resistance to Tamiflu [14].

4. TAMIFLU PANDEMIC MEDKIT COMPONENTS

The Tamiflu MedKit for pandemic use will consist of the following components (Figure 1):

- 75 mg capsule formulation of Tamiflu supplied as a blister carton that contains 10 Tamiflu capsules; this is enough doses for one treatment or one prophylaxis course for one person
- Instructions for use including:
 - Product information on the Tamiflu blister cartons
 - A Pandemic MedKit Educational Booklet that will be attached to the Tamiflu blister carton

Each of these components of the MedKit is designed to maximize compliance with: 1) use during a local outbreak of pandemic influenza as opposed to seasonal influenza, 2) use for treatment or post-exposure prophylaxis of pandemic flu as opposed to other respiratory illnesses during a local outbreak of pandemic influenza, 3) dosing instructions for different family members; and 4) appropriate storage conditions. Additional details about the MedKit are provided in Section 4.1 to Section 4.2.3.

Figure 1 Tamiflu Pandemic MedKit Components



4.1 Tamiflu Dosage

Roche's proposal is that the MedKit contain the 75 mg capsule formulation of Tamiflu as this can be used to dose all household members. The MedKit will provide one treatment course for one member of the household (10 x 75 mg capsules), to be used in either the treatment or prophylaxis setting, based on the current labeling and data on the use of Tamiflu for seasonal influenza. Therefore, the number of treatment days provided in the MedKit will be 5 days if Tamiflu is dosed twice daily for treatment of an acute infection or 10 days if dosed once daily for prophylaxis. Consumers will need to purchase as many treatment courses as needed to appropriately protect family members.

Tamiflu doses corresponding to the currently recommended seasonal dose were studied in animals infected with the avian influenza virus, H5N1, and were found to increase survival and reduce clinical symptoms in animals that are treated early in the course of infection. Higher doses were required in animals that were treated later in the course of infection. Limited published case study reports from humans infected with the avian

influenza virus, H5N1, have also demonstrated that early Tamiflu use improved survival [8, 9].

4.1.1 Pediatric Dosing

Since only the 75 mg capsule strength of Tamiflu will be included in the MedKit, instructions on how to prepare an oral suspension for pediatric patients who require different doses and for adults who cannot swallow capsules will be provided in the Tamiflu Pandemic MedKit Educational Booklet (Section 4.2).

The MedKit will not be recommended for use in children < 1 year of age since Tamiflu is currently not approved for use in this pediatric population; the MedKit will instruct consumers to consult a doctor for children under 1 year of age. However, there is currently an ongoing study that includes children under 1 year old that may allow for future Tamiflu dosing recommendations for this population.

4.2 Instructions for Use

Instructions for use of the MedKit have been developed to:

- Discourage use of the MedKit in seasonal influenza while encouraging use in pandemic influenza
- Encourage compliance with the dosing regimens for different household members
- Encourage proper storage

These instructions will be provided on the Tamiflu blister carton and in the MedKit educational booklet which will be attached to each blister carton. Samples of the proposed MedKit blister carton and the proposed educational booklet are provided on [page 54](#) , and [page 55](#) , respectively.

4.2.1 Use in Pandemic Influenza

To discourage the use of the MedKit for seasonal influenza while encouraging use in pandemic influenza, the MedKit blister carton has been designed to display the following prominent messages to allow consumers to easily distinguish the Tamiflu MedKit for pandemic influenza from Tamiflu for seasonal influenza:

- MedKit for pandemic flu
- Do not open unless a flu pandemic has been declared

The MedKit educational booklet will also state “you should take this medicine ONLY when your local health department says there is pandemic flu in your area” and that the Tamiflu in the MedKit should not be used to treat or prevent seasonal flu.

To allow consumers to determine when to initiate Tamiflu treatment or prophylaxis after a pandemic has been declared in their area, the CDC has developed an algorithm that allows an individual to determine if initiating treatment or post-exposure prophylaxis with Tamiflu is appropriate. This algorithm will identify those individuals who should immediately seek medical care or who should contact a healthcare provider before taking Tamiflu (eg, signs of severe illness present, has a medical condition affecting immunity, child < 1 year old, etc). These consumer groups will also be identified on the Tamiflu

blister carton and instructed to consult a doctor before taking Tamiflu. The algorithm will also allow individuals to determine if medical follow-up is necessary after the initiation of Tamiflu treatment.

4.2.2 Compliance with the Dosing Regimen

Dosing directions for the MedKit will be provided for all household members on both the blister carton and in the educational booklet. These directions will emphasize the need to strictly follow the indicated dosing regimen and to complete the full course of Tamiflu treatment to minimize the risk of suboptimal drug exposure and the development of drug-induced antiviral resistance. However, since dosing for children varies, the blister carton will refer consumers to the accompanying educational booklet which will provide directions, including accompanying diagrams, for mixing and administering oral doses of Tamiflu to children. The educational booklet will also provide directions on the preparation of an oral suspension of Tamiflu for children and adults who cannot swallow capsules.

4.2.3 Storage Instructions

To encourage proper storage of the MedKit, information on appropriate storage conditions will be provided on the MedKit blister carton; these instructions will be repeated in the educational booklet.

5. ADDITIONAL PANDEMIC PREPAREDNESS PLANS

Roche has established or is supporting a number of studies and programs for monitoring the resistance, efficacy, and safety profile of Tamiflu in the treatment of seasonal and avian influenza. These studies and programs will likely provide valuable information on the characteristics of an emerging pandemic virus and the response of this virus to Tamiflu treatment. Programs include the following:

- Resistance monitoring. Roche plans to begin enrollment in the upcoming influenza season in a global, prospective, seasonal influenza resistance study to examine the natural prevalence and/or emergence of resistance to all available influenza antivirals among influenza virus isolates and to better understand the clinical outcomes of influenza infection. This study will enroll approximately 1,200 patients per year over the next three influenza seasons and will be conducted in seven regions including the US.
- Participation in the Avian Influenza Registry, a global, multi-center, observational registry of patients with suspected or confirmed infection with avian H5N1. Data from this registry will provide information on the clinical course of patients infected with avian influenza as well as treatment course and dosing regimen used.
- Development of a H5N1 dose-prediction model. Since modification of the seasonal Tamiflu dosage regimen (eg, higher doses, longer duration of treatment) may be needed for an emerging pandemic strain, Roche is developing a dose prediction model that may provide insight into the Tamiflu dosage required to achieve an active drug concentration that suppresses pandemic viral replication.
- A study of Tamiflu in children between the ages of 0 to 23 months that may allow for Tamiflu dosing recommendations for children < 1 year of age.

Roche has also developed plans for safety monitoring during a pandemic and is open to collaborating with public health and government agencies on resistance monitoring; these plans are described in Section 5.1 and Section 5.2. Roche is also developing a pandemic communication plan; this plan is described in Section 5.3.

5.1 Resistance Monitoring

A key component to pandemic preparedness is resistance surveillance. In an effort to augment the standard resistance surveillance conducted each influenza season, Roche plans to begin enrollment in the upcoming influenza season in a global, prospective, seasonal influenza surveillance study to examine the natural prevalence and/or emergence of resistance to all available influenza antivirals among influenza virus isolates and to better understand the clinical outcomes of influenza infection. This study will enroll approximately 1,200 patients per year over the next three influenza seasons and will provide additional insights into the clinical outcome of patients with resistant virus.

Based on discussions with the WHO, Roche understands the WHO's view on antiviral resistance monitoring among influenza viruses as a basic and important public health risk assessment activity. Currently, resistance to antiviral drugs is monitored globally through the WHO Collaborating Centers as well as National Influenza Surveillance Centers including the US CDC and through the European Centre for Disease Control and Prevention's (ECDC) European Union surveillance initiative. WHO expects this monitoring of antiviral resistance to continue during both seasonal and pandemic periods. WHO has also indicated to Roche that it expects to continue working closely with all involved partners, including industry, to make sure that the assessment, communications, and response is as optimal as possible during pandemic and seasonal periods. Roche is keen to continue working with WHO and other partners around the interpretation and timely communication of such information, including during a pandemic.

5.2 Adverse Event Monitoring

Although the safety profile of Tamiflu after 55 million treatment courses is considered to be mature, Roche is prepared to closely monitor the safety profile of Tamiflu during a pandemic. To enable this, a plan for enhanced spontaneous adverse event reporting is being developed to collect information about adverse effects associated with the use of Tamiflu during a pandemic from either the MedKit, government or business stockpile, or by prescription.

During a pandemic, it is anticipated that adverse event reporting by consumers may increase due to shortages in professional healthcare support and that to capture these reports, it will be necessary to provide multiple reporting mechanisms for patients. The following options for reporting adverse events associated with the use of Tamiflu during a pandemic will be provided:

- A dedicated telephone number
- A dedicated web page that is available in case of a pandemic
- A patient adverse event form that will be provided in the MedKit and that can also be downloaded from the Roche homepage, completed, and then returned to Roche via mail or fax

Each of these reporting options will be highlighted in the MedKit Educational Booklet.

Consumers who receive Tamiflu from a source other than a MedKit (eg, government, corporate, or personal stockpile) must also be aware of the adverse event reporting options to ensure that all adverse events associated with the pandemic use of Tamiflu are captured. Roche is currently investigating options on how to ensure that these additional events are captured for processing and analysis. Roche proposes a close collaboration with FDA and HHS to provide updated safety information to patients who receive Tamiflu either from the government stockpile or other sources such as the MedKit.

Roche proposes to notify FDA and other health authorities of any safety-related issues associated with the pandemic use of Tamiflu in twice-monthly, Tamiflu safety reports that will be submitted once the WHO declares a pandemic alert period, Phase 5 (ie, the phase in which there is evidence of significant human-to-human transmission). This report will present an analysis of aggregate data with an emphasis on subpopulations of interest (eg, patients who lacked efficacy, pregnant and lactating women). New risks associated with the use of Tamiflu during a pandemic and possible risk mitigation measures will be communicated as described in Section 5.3.

5.3 Communication Plan

Roche is developing a communication plan for the Tamiflu MedKit that addresses the need to widely disseminate real-time updates on MedKit usage recommendations to healthcare professionals, public health officials, and the general public should a Tamiflu-resistant virus, the need for a different Tamiflu dosing regimen, or a new safety signal associated with the use of Tamiflu emerge during a pandemic.

To ensure that information on each of these topics is rapidly and consistently disseminated, Roche is proposing an active collaboration with CDC, FDA, HHS, and the WHO in the development and communication of this information through the use of public service announcements, websites, print media, and other modalities (eg, healthcare provider letters, press releases, etc). Roche is also proposing to coordinate the dissemination of information through medical and pharmacy societies.

5.4 Stakeholder Feedback

A number of concerns, including resistance, inappropriate use, timing of use, and the need to address the potential burden on healthcare providers, were highlighted in feedback Roche received on the Tamiflu MedKit from FDA and the HHS based on discussions held with medical societies, including the Infectious Disease Society of America, the American Academy of Pediatrics, the American Academy of Family Physicians, and the American Medical Association.

To address these concerns, Roche is organizing a Scientific Advisory Board whose primary objective will be to identify and suggest ways to address key issues and barriers to the use of the MedKit. This feedback will be used to help Roche develop a plan to address any additional MedKit development considerations. Three broad constituent groups will be included in this Scientific Advisory Board: the medical community, the public health community, and pharmacies. Individuals that have been contacted to participate include representatives from the American Academy of Pediatrics, the

American Medical Association, the American Public Health Association, the American Academy of Family Physicians, the Infectious Disease Society of America, the National Association of Chain Drugstores, and pharmacy benefits managers.

6. PROPOSED STUDIES

Based upon prior feedback from FDA, Roche is proposing to conduct the following studies to support the approval of a Tamiflu MedKit for home stockpiling for pandemic influenza:

- A labeling comprehension study
- A simulation and compliance study
- An oral dose preparation study

All of these studies will enroll lower literacy participants and participants from socio-economically diverse regions. Brief outlines of each of these studies are provided in Sections 6.1 to 6.3. A pilot of the label comprehension study has been completed. Results from the pilot are presented in Section 6.1.2.

6.1 Labeling Comprehension Study

6.1.1 Proposed Study

The objective of the labeling comprehension study is to assess comprehension of the proposed MedKit labeling components including the MedKit educational booklet and Tamiflu blister carton and to learn whether participants, including those at lower literacy levels, correctly understand the key messages.

A total of 500 study participants will be enrolled in the study from socio-economically diverse regions. Consumers will be excluded from participation if they are younger than 16 years of age, have been prescribed Tamiflu in the past 12 months, are unable to speak or understand English, cannot see well enough to read the information in the educational booklet, or if the consumer or household member works for a market research company, an advertising agency, a public relations firm, a pharmaceutical company, as a healthcare professional, or as part of a healthcare practice.

After providing demographic data, study participants will be provided with the labeling components and asked to read them. When participants finish reading, they will be interviewed using a standardized questionnaire. The questionnaire will include closed and open-ended questions and hypothetical scenarios to assess understanding. Participants will be free to refer to the labeling components throughout the administration of the questionnaire, but will neither be encouraged nor discouraged to do so. Following administration of the questionnaire, information regarding demographics and medical history relevant to influenza will be collected and the Rapid Estimate of Adult Literacy in Medicine (REALM) or teen REALM test will be administered to assess reading level.

Comprehension will be evaluated based on pre-specified correct and acceptable responses to questions in the survey and by computing point estimates and 95% confidence limits (calculated with binomial standard errors) for each interview question. Comparative statistics (t-test for continuous variables; chi square or Fisher's exact test for categorical

variables) will be used to compare responses from normal and low literacy participants or other subgroups where appropriate.

6.1.2 Pilot Study Results

6.1.2.1 Study Methodology

A pilot labeling comprehension study was conducted to determine whether or not the MedKit could be labeled in a way that would allow consumers who possess it to use it correctly during an outbreak of pandemic influenza and not to use it for anything else.

Participants were identified at five US shopping malls and invited to participate in an interview to evaluate their comprehension of draft versions of the MedKit educational booklet and the MedKit blister carton label. Both the educational booklet and the blister carton label were printed and supplied to participants to read on standard letter size paper and not in the final configuration envisioned for the MedKit. When participants finished reading, they were interviewed using a questionnaire. Participants were free to refer to the educational booklet and the blister carton label throughout the interview. At the conclusion of the interview, the REALM test was administered.

6.1.2.2 Results

A total of 210 individuals agreed to participate in the study. Of these individuals, 204 (97.1%) completed the interview and 6 dropped out (5 who did not qualify and 1 who qualified, but subsequently declined to participate). The majority of participants (79.9%) were in the normal literacy category.

Participants demonstrated a high comprehension of the instructions for use provided on the Tamiflu blister carton label, as demonstrated by a high percentage of correct or acceptable responses to the interview questions. The majority of participants understood when they should start using Tamiflu for treatment (94%), how many capsules they should take at a time for treatment (99.0%) or prevention (99.0%), and how many days they should take the product for either treatment (86.3%) or prevention (88.2%). A lower percentage of participants were able to correctly identify the specific reasons for use of the MedKit (69.1%) or based upon their reading of the educational booklet, whether the Tamiflu in the MedKit should be used to treat seasonal flu (53.9%).

A lower percentage of correct responses was exhibited when participants were directed to specific pages of the educational booklet and then asked a question about a hypothetical situation.

These results will be used to improve the blister carton and the educational booklet prior to initiation of the proposed labeling comprehension study.

6.2 Simulation and Compliance Study

The primary objective of the simulation and compliance study is to demonstrate the subject's ability to make appropriate decisions about when to use the Tamiflu MedKit (only for the purpose of preventing or treating pandemic influenza). Co-primary objectives include: 1) to assess the number of MedKits returned that are intact relative to the total number of MedKits returned and 2) to evaluate the subject's intended actions based upon responses to pandemic scenarios.

Secondary objectives include the following:

- To demonstrate the subject's ability to appropriately retain and locate the MedKit containing all 10 doses of Tamiflu
- To conduct a separate analysis of the primary and co-primary endpoints for each cohort
- To assess the subject's ability to locate the Tamiflu MedKit
- To understand the reasons:
 - Why participants did not make the appropriate decision about when to use the Tamiflu MedKit
 - Why participants were unable to retain and locate the Tamiflu MedKit containing all 10 doses of Tamiflu
 - Why participants had intended actions based on verbal responses to a pandemic that were incorrect
- To assess if members of the household who should not have taken Tamiflu took Tamiflu and to find out the reasons why

Roche proposes that this study be conducted in an estimated 2,000 households over a 6-month period covering one flu season in five metropolitan locations in the US. Participants will be told that the purpose of the study is to evaluate the value of the placement of a medication in their homes that would be used in the event of an influenza pandemic. Participating households will be identified using multiple sources and directed to one of several designated large pharmacies within their geographic area to enroll in the study. Each adult household member will receive an explanation of the study and, if interested, will be enrolled into the program by signing a consent form. They will also be informed that they will be contacted within a few months for study follow-up. The MedKits, containing the appropriate amount of Tamiflu for each household, will be given to each participating household.

At the conclusion of the influenza season, participants will be contacted and asked to complete and return a follow-up questionnaire. The questionnaire will include questions regarding various scenarios that might be encountered in the event of a pandemic and the answers will ascertain how well the participants understand the purpose of the MedKit and the distinction between seasonal and pandemic influenza. In addition, the questionnaire will ask how and where the MedKit was stored and their compliance with the original instructions that they received regarding use of the MedKit. They will also be asked to return the MedKits. The returned MedKits will be visually inspected; missing capsules from the blister pack will constitute non-compliance.

This study will be initiated after completion of the labeling comprehension study and any necessary updates of the MedKit components.

6.3 Oral Dose Preparation Study

The Tamiflu MedKit will provide instructions within the MedKit educational booklet on how to prepare an oral suspension of Tamiflu for pediatric patients and for adult patients who cannot swallow capsules.

The mixing instructions will be tested in a dose preparation study to determine whether or not they are easy for the general public to understand and follow or whether adjustments are necessary for increased comprehension. This study will be conducted at three geographically dispersed facilities in the US with approximately 30 study participants. Study participants will be evaluated on their ability to prepare an oral suspension following the instructions provided within the educational booklet and will also be asked a series of questions to determine what is missing or confusing about the instructions.

7. PUBLIC HEALTH NEED AND ACCESS TO A TAMIFLU MEDKIT

The Tamiflu MedKit for pandemic influenza must be weighed against the morbidity, mortality, and economic and social disruption that such a treatment could mitigate.

A Tamiflu MedKit for pandemic influenza would allow for:

- Expansion of the existing domestic stockpile of antivirals for pandemic influenza, which would provide additional coverage for the US population at the time of a pandemic
- An increased treatment benefit by shortening the time from symptom onset to treatment initiation
- Decreased pandemic infection rates by reducing the need for infected people to leave the home to obtain treatment
- Decreased pandemic infection rates by allowing for post-exposure prophylaxis

Roche recognizes the potential issues associated with a Tamiflu MedKit including how to provide access to the MedKit, resistance and safety monitoring, and the need for a communication plan for MedKit usage recommendations that interfaces with public health systems and welcomes the opportunity to discuss and collaborate with others on how to address these issues.

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TAMIFLU

(oseltamivir phosphate)

CAPSULES

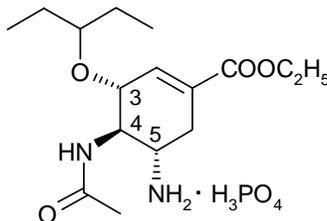
AND FOR ORAL SUSPENSION

R_x only

DESCRIPTION

TAMIFLU (oseltamivir phosphate) is available as capsules containing 30 mg, 45 mg, or 75 mg oseltamivir for oral use, in the form of oseltamivir phosphate, and as a powder for oral suspension, which when constituted with water as directed contains 12 mg/mL oseltamivir base. In addition to the active ingredient, each capsule contains pregelatinized starch, talc, povidone K 30, 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 C₁₆H₂₈N₂O₄ (free base). The molecular weight is 312.4 for oseltamivir free base and 410.4 for oseltamivir phosphate salt. The structural formula is as follows:



MICROBIOLOGY

Mechanism of Action

Oseltamivir 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.

31 **Antiviral Activity**

32 The antiviral activity of oseltamivir carboxylate against laboratory strains and clinical
33 isolates of influenza virus was determined in cell culture assays. The concentrations of
34 oseltamivir carboxylate required for inhibition of influenza virus were highly variable
35 depending on the assay method used and the virus tested. The 50% and 90% effective
36 concentrations (EC₅₀ and EC₉₀) were in the range of 0.0008 μM to >35 μM and 0.004 μM
37 to >100 μM, respectively (1 μM=0.284 μg/mL). The relationship between the antiviral
38 activity in cell culture and the inhibition of influenza virus replication in humans has not
39 been established.

40 **Resistance**

41 Influenza A virus isolates with reduced susceptibility to oseltamivir carboxylate have
42 been recovered by serial passage of virus in cell culture in the presence of increasing
43 concentrations of oseltamivir carboxylate. Genetic analysis of these isolates showed that
44 reduced susceptibility to oseltamivir carboxylate is associated with mutations that result
45 in amino acid changes in the viral neuraminidase or viral hemagglutinin or both.
46 Resistance substitutions selected in cell culture in neuraminidase are I222T and H274Y in
47 influenza A N1 and I222T and R292K in influenza A N2. Substitutions E119V, R292K
48 and R305Q have been selected in avian influenza A neuraminidase N9. Substitutions
49 A28T and R124M have been selected in the hemagglutinin of influenza A H3N2 and
50 substitution H154Q in the hemagglutinin of a reassortant human/avian virus H1N9.

51 In clinical studies in the treatment of naturally acquired infection with influenza virus,
52 1.3% (4/301) of posttreatment isolates in adult patients and adolescents, and 8.6% (9/105)
53 in pediatric patients aged 1 to 12 years showed emergence of influenza variants with
54 decreased neuraminidase susceptibility in cell culture to oseltamivir carboxylate.
55 Substitutions in influenza A neuraminidase resulting in decreased susceptibility were
56 H274Y in neuraminidase N1 and E119V and R292K in neuraminidase N2. Insufficient
57 information is available to fully characterize the risk of emergence of TAMIFLU
58 resistance in clinical use.

59 In clinical studies of postexposure and seasonal prophylaxis, determination of resistance
60 by population nucleotide sequence analysis was limited by the low overall incidence rate
61 of influenza infection and prophylactic effect of TAMIFLU.

62 **Cross-resistance**

63 Cross-resistance between zanamivir-resistant influenza mutants and oseltamivir-resistant
64 influenza mutants has been observed in cell culture. Due to limitations in the assays
65 available to detect drug-induced shifts in virus susceptibility, an estimate of the incidence
66 of oseltamivir resistance and possible cross-resistance to zanamivir in clinical isolates
67 cannot be made. However, two of the three oseltamivir-induced substitutions (E119V,
68 H274Y and R292K) in the viral neuraminidase from clinical isolates occur at the same
69 amino acid residues as two of the three substitutions (E119G/A/D, R152K and R292K)
70 observed in zanamivir-resistant virus.

71 **Immune Response**

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

75 **CLINICAL PHARMACOLOGY**

76 **Pharmacokinetics**

77 **Absorption and Bioavailability**

78 Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of
79 oseltamivir phosphate and is extensively converted predominantly by hepatic esterases to
80 oseltamivir carboxylate. At least 75% of an oral dose reaches the systemic circulation as
81 oseltamivir carboxylate. Exposure to oseltamivir is less than 5% of the total exposure
82 after oral dosing (see **Table 1**).

83 **Table 1** **Mean (% CV) Pharmacokinetic Parameters of Oseltamivir**
84 **and Oseltamivir Carboxylate After a Multiple 75 mg Capsule**
85 **Twice Daily Oral Dose (n=20)**

Parameter	Oseltamivir	Oseltamivir Carboxylate
C_{max} (ng/mL)	65.2 (26)	348 (18)
AUC_{0-12h} (ng·h/mL)	112 (25)	2719 (20)

86 Plasma concentrations of oseltamivir carboxylate are proportional to doses up to 500 mg
87 given twice daily (see **DOSAGE AND ADMINISTRATION**).

88 Coadministration with food has no significant effect on the peak plasma concentration
89 (551 ng/mL under fasted conditions and 441 ng/mL under fed conditions) and the area
90 under the plasma concentration time curve (6218 ng·h/mL under fasted conditions and
91 6069 ng·h/mL under fed conditions) of oseltamivir carboxylate.

92 **Distribution**

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

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

98 **Metabolism**

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

102 **Elimination**

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

112 **Special Populations**

113 **Renal Impairment**

114 Administration of 100 mg of oseltamivir phosphate twice daily for 5 days to patients with
115 various degrees of renal impairment showed that exposure to oseltamivir carboxylate is
116 inversely proportional to declining renal function. Oseltamivir carboxylate exposures in
117 patients with normal and abnormal renal function administered various dose regimens of
118 oseltamivir are described in **Table 2**.

119 **Table 2 Oseltamivir Carboxylate Exposures in Patients With Normal**
120 **and Reduced Serum Creatinine Clearance**

Parameter	Normal Renal Function			Impaired Renal Function				
	75 mg qd	75 mg bid	150 mg bid	Creatinine Clearance <10 mL/min		Creatinine Clearance >10 and <30 mL/min		
				CAPD 30 mg weekly	Hemodialysis 30 mg alternate HD cycle	75 mg daily	75 mg alternate days	30 mg daily
C _{max}	259*	348*	705*	766	850	1638	1175	655
C _{min}	39*	138*	288*	62	48	864	209	346
AUC ₄₈	7476*	10876*	21864*	17381	12429	62636	21999	25054

121 *Observed values. All other values are predicted.

122 AUC normalized to 48 hours.

123 **Hepatic Impairment**

124 In clinical studies oseltamivir carboxylate exposure was not altered in patients with mild
125 or moderate hepatic impairment (see **PRECAUTIONS: Hepatic Impairment** and
126 **DOSAGE AND ADMINISTRATION**).

127 **Pediatric Patients**

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

134 years). The pharmacokinetics of oseltamivir in pediatric patients over 12 years of age are
135 similar to those in adult patients.

136 Geriatric Patients

137 Exposure to oseltamivir carboxylate at steady-state was 25% to 35% higher in geriatric
138 patients (age range 65 to 78 years) compared to young adults given comparable doses of
139 oseltamivir. Half-lives observed in the geriatric patients were similar to those seen in
140 young adults. Based on drug exposure and tolerability, dose adjustments are not required
141 for geriatric patients for either treatment or prophylaxis (see **DOSAGE AND**
142 **ADMINISTRATION: Special Dosage Instructions**).

143 INDICATIONS AND USAGE

144 Treatment of Influenza

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

148 Prophylaxis of Influenza

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

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

- 152 • TAMIFLU is not a substitute for early vaccination on an annual basis as
153 recommended by the Centers for Disease Control and Prevention Advisory
154 Committee on Immunization Practices.
- 155 • Influenza viruses change over time. Emergence of resistance mutations could
156 decrease drug effectiveness. Other factors (for example, changes in viral virulence)
157 might also diminish clinical benefit of antiviral drugs. Prescribers should consider
158 available information on influenza drug susceptibility patterns and treatment effects
159 when deciding whether to use TAMIFLU.
160

161 Description of Clinical Studies: Studies in Naturally Occurring Influenza

162 Treatment of Influenza

163 *Adult Patients*

164 Two phase III placebo-controlled and double-blind clinical trials were conducted: one in
165 the USA and one outside the USA. Patients were eligible for these trials if they had fever
166 >100°F, accompanied by at least one respiratory symptom (cough, nasal symptoms or
167 sore throat) and at least one systemic symptom (myalgia, chills/sweats, malaise, fatigue
168 or headache) and influenza virus was known to be circulating in the community. In
169 addition, all patients enrolled in the trials were allowed to take fever-reducing
170 medications.

171 Of 1355 patients enrolled in these two trials, 849 (63%) patients were influenza-infected
172 (age range 18 to 65 years; median age 34 years; 52% male; 90% Caucasian; 31%
173 smokers). Of the 849 influenza-infected patients, 95% were infected with influenza A,
174 3% with influenza B, and 2% with influenza of unknown type.

175 TAMIFLU was started within 40 hours of onset of symptoms. Subjects participating in
176 the trials were required to self-assess the influenza-associated symptoms as “none”,
177 “mild”, “moderate” or “severe”. Time to improvement was calculated from the time of
178 treatment initiation to the time when all symptoms (nasal congestion, sore throat, cough,
179 aches, fatigue, headaches, and chills/sweats) were assessed as “none” or “mild”. In both
180 studies, at the recommended dose of TAMIFLU 75 mg twice daily for 5 days, there was a
181 1.3 day reduction in the median time to improvement in influenza-infected subjects
182 receiving TAMIFLU compared to subjects receiving placebo. Subgroup analyses of these
183 studies by gender showed no differences in the treatment effect of TAMIFLU in men and
184 women.

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

187 *Geriatric Patients*

188 Three double-blind placebo-controlled treatment trials were conducted in patients ≥65
189 years of age in three consecutive seasons. The enrollment criteria were similar to that of
190 adult trials with the exception of fever being defined as >97.5°F. Of 741 patients
191 enrolled, 476 (65%) patients were influenza-infected. Of the 476 influenza-infected
192 patients, 95% were infected with influenza type A and 5% with influenza type B.

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

197 *Pediatric Patients*

198 One double-blind placebo-controlled treatment trial was conducted in pediatric patients
199 aged 1 to 12 years (median age 5 years), who had fever (>100°F) plus one respiratory
200 symptom (cough or coryza) when influenza virus was known to be circulating in the
201 community. Of 698 patients enrolled in this trial, 452 (65%) were influenza-infected
202 (50% male; 68% Caucasian). Of the 452 influenza-infected patients, 67% were infected
203 with influenza A and 33% with influenza B.

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

211 Prophylaxis of Influenza

212 *Adult Patients*

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

221 In a pooled analysis of two seasonal prophylaxis studies in healthy unvaccinated adults
222 (aged 13 to 65 years), TAMIFLU 75 mg once daily taken for 42 days during a
223 community outbreak reduced the incidence of laboratory-confirmed clinical influenza
224 from 4.8% (25/519) for the placebo group to 1.2% (6/520) for the TAMIFLU group.

225 In a seasonal prophylaxis study in elderly residents of skilled nursing homes, TAMIFLU
226 75 mg once daily taken for 42 days reduced the incidence of laboratory-confirmed
227 clinical influenza from 4.4% (12/272) for the placebo group to 0.4% (1/276) for the
228 TAMIFLU group. About 80% of this elderly population were vaccinated, 14% of
229 subjects had chronic airway obstructive disorders, and 43% had cardiac disorders.

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

235 *Pediatric Patients*

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

248 **CONTRAINDICATIONS**

249 TAMIFLU is contraindicated in patients with known hypersensitivity to any of the
250 components of the product.

251 **PRECAUTIONS**

252 **General**

253 There is no evidence for efficacy of TAMIFLU in any illness caused by agents other than
254 influenza viruses Types A and B.

255 Use of TAMIFLU should not affect the evaluation of individuals for annual influenza
256 vaccination in accordance with guidelines of the Centers for Disease Control and
257 Prevention Advisory Committee on Immunization Practices.

258 Efficacy of TAMIFLU in patients who begin treatment after 40 hours of symptoms has
259 not been established.

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

266 Safety and efficacy of repeated treatment or prophylaxis courses have not been studied.

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

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

272 **Hepatic Impairment**

273 The safety and pharmacokinetics in patients with severe hepatic impairment have not
274 been evaluated (see **DOSAGE AND ADMINISTRATION**).

275 **Renal Impairment**

276 Dose adjustment is recommended for patients with a serum creatinine clearance
277 <30 mL/min (see **DOSAGE AND ADMINISTRATION**).

278 **Serious Skin/Hypersensitivity Reactions**

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

283 **Neuropsychiatric Events**

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

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

297 **Information for Patients**

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

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

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

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

310 **Drug Interactions**

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

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

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

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

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

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

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

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

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

353 In a fertility and early embryonic development study in rats, doses of oseltamivir at 50,
354 250, and 1500 mg/kg/day were administered to females for 2 weeks before mating,
355 during mating and until day 6 of pregnancy. Males were dosed for 4 weeks before
356 mating, during and for 2 weeks after mating. There were no effects on fertility, mating
357 performance or early embryonic development at any dose level. The highest dose was
358 approximately 100 times the human systemic exposure (AUC_{0-24h}) of oseltamivir
359 carboxylate.

360 **Pregnancy**

361 **Pregnancy Category C**

362 There are insufficient human data upon which to base an evaluation of risk of TAMIFLU
363 to the pregnant woman or developing fetus. Studies for effects on embryo-fetal
364 development were conducted in rats (50, 250, and 1500 mg/kg/day) and rabbits (50, 150,
365 and 500 mg/kg/day) by the oral route. Relative exposures at these doses were,
366 respectively, 2, 13, and 100 times human exposure in the rat and 4, 8, and 50 times
367 human exposure in the rabbit. Pharmacokinetic studies indicated that fetal exposure was

368 seen in both species. In the rat study, minimal maternal toxicity was reported in the 1500
369 mg/kg/day group. In the rabbit study, slight and marked maternal toxicities were
370 observed, respectively, in the 150 and 500 mg/kg/day groups. There was a dose-
371 dependent increase in the incidence rates of a variety of minor skeletal abnormalities and
372 variants in the exposed offspring in these studies. However, the individual incidence rate
373 of each skeletal abnormality or variant remained within the background rates of
374 occurrence in the species studied.

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

378 **Nursing Mothers**

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

383 **Geriatric Use**

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

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

394 **Pediatric Use**

395 The safety and efficacy of TAMIFLU in pediatric patients younger than 1 year of age
396 have not been studied. TAMIFLU is not indicated for either treatment or prophylaxis of
397 influenza in pediatric patients younger than 1 year of age because of uncertainties
398 regarding the rate of development of the human blood-brain barrier and the unknown
399 clinical significance of non-clinical animal toxicology data for human infants (see
400 **ANIMAL TOXICOLOGY**).

401 **ANIMAL TOXICOLOGY**

402 In a 2-week study in unweaned rats, administration of a single dose of 1000 mg/kg
403 oseltamivir phosphate to 7-day-old rats resulted in deaths associated with unusually high
404 exposure to the prodrug. However, at 2000 mg/kg, there were no deaths or other
405 significant effects in 14-day-old unweaned rats. Further follow-up investigations of the
406 unexpected deaths of 7-day-old rats at 1000 mg/kg revealed that the concentrations of the
407 prodrug in the brains were approximately 1500-fold those of the brains of adult rats

408 administered the same oral dose of 1000 mg/kg, and those of the active metabolite were
409 approximately 3-fold higher. Plasma levels of the prodrug were 10-fold higher in 7-day-
410 old rats as compared with adult rats. These observations suggest that the levels of
411 oseltamivir in the brains of rats decrease with increasing age and most likely reflect the
412 maturation stage of the blood-brain barrier. No adverse effects occurred at 500 mg/kg/day
413 administered to 7- to 21-day-old rats. At this dosage, the exposure to prodrug was
414 approximately 800-fold the exposure expected in a 1-year-old child.

415 **ADVERSE REACTIONS**

416 **Treatment Studies in Adult Patients**

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

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

429 **Prophylaxis Studies in Adult Patients**

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

440
441

Table 3 Most Frequent Adverse Events in Studies in Naturally Acquired Influenza in Patients 13 Years of Age and Older

Adverse Event	Treatment		Prophylaxis	
	Placebo N=716	Oseltamivir 75 mg bid N=724	Placebo/ No Prophylaxis ^a N=1688	Oseltamivir 75 mg qd N=1790
Nausea (without vomiting)	40 (6%)	72 (10%)	56 (3%)	129 (7%)
Vomiting	21 (3%)	68 (9%)	16 (1%)	39 (2%)
Diarrhea	70 (10%)	48 (7%)	40 (2%)	50 (3%)
Bronchitis	15 (2%)	17 (2%)	22 (1%)	15 (1%)
Abdominal pain	16 (2%)	16 (2%)	25 (1%)	37 (2%)
Dizziness	25 (3%)	15 (2%)	21 (1%)	24 (1%)
Headache	14 (2%)	13 (2%)	306 (18%)	326 (18%)
Cough	12 (2%)	9 (1%)	119 (7%)	94 (5%)
Insomnia	6 (1%)	8 (1%)	15 (1%)	22 (1%)
Vertigo	4 (1%)	7 (1%)	4 (<1%)	4 (<1%)
Fatigue	7 (1%)	7 (1%)	163 (10%)	139 (8%)

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

444 Adverse events included are: all events reported in the treatment studies with frequency
445 $\geq 1\%$ in the oseltamivir 75 mg bid group.

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

449 Treatment Studies in Pediatric Patients

450 A total of 1032 pediatric patients aged 1 to 12 years (including 698 otherwise healthy
451 pediatric patients aged 1 to 12 years and 334 asthmatic pediatric patients aged 6 to 12
452 years) participated in phase III studies of TAMIFLU given for the treatment of influenza.
453 A total of 515 pediatric patients received treatment with TAMIFLU for Oral Suspension.

454 Adverse events occurring in $\geq 1\%$ of pediatric patients receiving TAMIFLU treatment are
455 listed in [Table 4](#). The most frequently reported adverse event was vomiting. Other events
456 reported more frequently by pediatric patients treated with TAMIFLU included
457 abdominal pain, epistaxis, ear disorder, and conjunctivitis. These events generally
458 occurred once and resolved despite continued dosing. They did not cause discontinuation
459 of drug in the vast majority of cases.

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

462 **Prophylaxis in Pediatric Patients**

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

467 **Table 4 Most Frequent Adverse Events Occurring in Children Aged**
 468 **1 to 12 Years in Studies in Naturally Acquired Influenza**

Adverse Event	Treatment Trials ^a		Household Prophylaxis Trial ^b	
	Placebo N=517	Oseltamivir 2 mg/kg bid N=515	No Prophylaxis ^c N=87	Prophylaxis with Oseltamivir QD ^c N=99
Vomiting	48 (9%)	77 (15%)	2 (2%)	10 (10%)
Diarrhea	55 (11%)	49 (10%)	-	1 (1%)
Otitis media	58 (11%)	45 (9%)	2 (2%)	2 (2%)
Abdominal pain	20 (4%)	24 (5%)	-	3 (3%)
Asthma (including aggravated)	19 (4%)	18 (3%)	1 (1%)	1 (1%)
Nausea	22 (4%)	17 (3%)	1 (1%)	4 (4%)
Epistaxis	13 (3%)	16 (3%)	-	1 (1%)
Pneumonia	17 (3%)	10 (2%)	2 (2%)	-
Ear disorder	6 (1%)	9 (2%)	-	-
Sinusitis	13 (3%)	9 (2%)	-	-
Bronchitis	11 (2%)	8 (2%)	2 (2%)	-
Conjunctivitis	2 (<1%)	5 (1%)	-	-
Dermatitis	10 (2%)	5 (1%)	-	-
Lymphadenopathy	8 (2%)	5 (1%)	-	-
Tympanic membrane disorder	6 (1%)	5 (1%)	-	-

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

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

473 ^c Unit dose = age-based dosing

Age	Prophylaxis (10 days)
1-2 years	30 mg QD
3-5 years	45 mg QD
6-12 years	60 mg QD

474

475 Adverse events included in Table 4 are: all events reported in the treatment studies with
 476 frequency ≥1% in the oseltamivir 75 mg bid group.

477 **Observed During Clinical Practice**

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

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

484 Dermatologic: Dermatitis, rash, eczema, urticaria, erythema multiforme, Stevens-Johnson
485 Syndrome, toxic epidermal necrolysis (see **PRECAUTIONS**)

486 Digestive: Hepatitis, liver function tests abnormal

487 Cardiac: Arrhythmia

488 Gastrointestinal disorders: Gastrointestinal bleeding, hemorrhagic colitis

489 Neurologic: Seizure

490 Metabolic: Aggravation of diabetes

491 Psychiatric: Delirium, including symptoms such as altered level of consciousness,
492 confusion, abnormal behavior, delusions, hallucinations, agitation, anxiety, nightmares
493 (see **PRECAUTIONS**)

494 **OVERDOSAGE**

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

497 **DOSAGE AND ADMINISTRATION**

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

501 **Standard Dosage – Treatment of Influenza**

502 **Adults and Adolescents**

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

506 **Pediatric Patients**

507 TAMIFLU is not indicated for treatment of influenza in pediatric patients younger than
508 1 year.

509 The recommended oral dose of TAMIFLU for pediatric patients 1 year and older is
510 shown in **Table 5**. TAMIFLU for Oral Suspension may also be used by patients who
511 cannot swallow a capsule. For pediatric patients who cannot swallow capsules,

512 TAMIFLU for Oral Suspension is the preferred formulation. If the for Oral Suspension
 513 product is not available, TAMIFLU Capsules may be opened and mixed with sweetened
 514 liquids such as regular or sugar-free chocolate syrup.

515 **Table 5 Oral Dose of TAMIFLU for Treatment of Influenza in Pediatric**
 516 **Patients by Weight**

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

517 An oral dosing dispenser with 30 mg, 45 mg, and 60 mg graduations is provided with the
 518 oral suspension; the 75 mg dose can be measured using a combination of 30 mg and
 519 45 mg. It is recommended that patients use this dispenser. In the event that the dispenser
 520 provided is lost or damaged, another dosing syringe or other device may be used to
 521 deliver the following volumes: 2.5 mL (1/2 tsp) for children ≤15 kg, 3.8 mL (3/4 tsp) for
 522 >15 to 23 kg, 5.0 mL (1 tsp) for >23 to 40 kg, and 6.2 mL (1 1/4 tsp) for >40 kg.

523 **Standard Dosage – Prophylaxis of Influenza**

524 **Adults and Adolescents**

525 The recommended oral dose of TAMIFLU for prophylaxis of influenza in adults and
 526 adolescents 13 years and older following close contact with an infected individual is
 527 75 mg once daily for at least 10 days. Therapy should begin within 2 days of exposure.
 528 The recommended dose for prophylaxis during a community outbreak of influenza is
 529 75 mg once daily. Safety and efficacy have been demonstrated for up to 6 weeks. The
 530 duration of protection lasts for as long as dosing is continued.

531 **Pediatric Patients**

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

534 The recommended oral dose of TAMIFLU for pediatric patients 1 year and older
 535 following close contact with an infected individual is shown in **Table 6**. TAMIFLU for
 536 Oral Suspension may also be used by patients who cannot swallow a capsule. For
 537 pediatric patients who cannot swallow capsules, TAMIFLU for Oral Suspension is the
 538 preferred formulation. If the for Oral Suspension product is not available, TAMIFLU
 539 Capsules may be opened and mixed with sweetened liquids such as regular or sugar-free
 540 chocolate syrup.

541 **Table 6 Oral Dose of TAMIFLU for Prophylaxis of Influenza in**
 542 **Pediatric Patients by Weight**

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

543 An oral dosing dispenser with 30 mg, 45 mg, and 60 mg graduations is provided with the
 544 oral suspension; the 75 mg dose can be measured using a combination of 30 mg and
 545 45 mg. It is recommended that patients use this dispenser. In the event that the dispenser
 546 provided is lost or damaged, another dosing syringe or other device may be used to
 547 deliver the following volumes: 2.5 mL (1/2 tsp) for children ≤15 kg, 3.8 mL (3/4 tsp) for
 548 >15 to 23 kg, 5.0 mL (1 tsp) for >23 to 40 kg, and 6.2 mL (1 1/4 tsp) for >40 kg.

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

553 **Special Dosage Instructions**

554 **Hepatic Impairment**

555 No dose adjustment is recommended for patients with mild or moderate hepatic
 556 impairment (Child-Pugh score ≤9) (see **CLINICAL PHARMACOLOGY:**
 557 **Pharmacokinetics: Special Populations**).

558 **Renal Impairment**

559 For plasma concentrations of oseltamivir carboxylate predicted to occur following
560 various dosing schedules in patients with renal impairment, see **CLINICAL**
561 **PHARMACOLOGY: Pharmacokinetics: Special Populations**.

562 *Treatment of Influenza*

563 Dose adjustment is recommended for patients with creatinine clearance between 10 and
564 30 mL/min receiving TAMIFLU for the treatment of influenza. In these patients it is
565 recommended that the dose be reduced to 75 mg of TAMIFLU once daily for 5 days. No
566 recommended dosing regimens are available for patients undergoing routine
567 hemodialysis and continuous peritoneal dialysis treatment with end-stage renal disease.

568 *Prophylaxis of Influenza*

569 For the prophylaxis of influenza, dose adjustment is recommended for patients with
570 creatinine clearance between 10 and 30 mL/min receiving TAMIFLU. In these patients it
571 is recommended that the dose be reduced to 75 mg of TAMIFLU every other day or
572 30 mg TAMIFLU every day. No recommended dosing regimens are available for patients
573 undergoing routine hemodialysis and continuous peritoneal dialysis treatment with end-
574 stage renal disease.

575 **Geriatric Patients**

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

578 **Preparation of TAMIFLU for Oral Suspension**

579 It is recommended that TAMIFLU for Oral Suspension be constituted by the pharmacist
580 prior to dispensing to the patient:

- 581 1. Tap the closed bottle several times to loosen the powder.
- 582 2. Measure **23 mL** of water in a graduated cylinder.
- 583 3. Add the total amount of water for constitution to the bottle and shake the closed bottle
584 well for 15 seconds.
- 585 4. Remove the child-resistant cap and push bottle adapter into the neck of the bottle.
- 586 5. Close bottle with child-resistant cap tightly. This will assure the proper seating of the
587 bottle adapter in the bottle and child-resistant status of the cap.

588 **NOTE: SHAKE THE TAMIFLU FOR ORAL SUSPENSION WELL BEFORE EACH**
589 **USE.**

590 The constituted TAMIFLU for Oral Suspension (12 mg/mL) should be used within 10
591 days of preparation; the pharmacist should write the date of expiration of the constituted
592 suspension on a pharmacy label. The patient package insert and oral dispenser should be
593 dispensed to the patient.

594 **Emergency Compounding of an Oral Suspension from TAMIFLU Capsules**
 595 **(Final Concentration 15 mg/mL)**

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

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

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

610 First, calculate the Total Volume of an oral suspension needed to be compounded and
 611 dispensed for each patient. The Total Volume required is determined by the weight of
 612 each patient. Refer to **Table 7**.

613 **Table 7 Volume of an Oral Suspension (15 mg/mL) Needed to be**
 614 **Compounded Based Upon the Patient’s Weight**

Body Weight (kg)	Body Weight (lbs)	Total Volume to Compound per patient (mL)
≤15 kg	≤33 lbs	30 mL
16 to 23 kg	34 to 51 lbs	40 mL
24 to 40 kg	52 to 88 lbs	50 mL
≥41 kg	≥89 lbs	60 mL

615

616 Second, determine the number of capsules and the amount of vehicle (Cherry Syrup or
 617 Ora-Sweet SF) that are needed to prepare the Total Volume (calculated from Table 7:
 618 30 mL, 40 mL, 50 mL, or 60 mL) of compounded oral suspension (15 mg/mL). Refer to
 619 **Table 8**.

620 **Table 8 Number of TAMIFLU 75 mg Capsules and Amount of Vehicle**
 621 **(Cherry Syrup OR Ora-Sweet SF) Needed to Prepare the**
 622 **Total Volume of a Compounded Oral Suspension (15 mg/mL)**

Total Volume of Compounded Oral	30 mL	40 mL	50 mL	60 mL

Suspension needed to be Prepared				
Required number of TAMIFLU 75 mg Capsules	6 capsules (450 mg oseltamivir)	8 capsules (600 mg oseltamivir)	10 capsules (750 mg oseltamivir)	12 capsules (900 mg oseltamivir)
Required volume of vehicle Cherry Syrup (Humco) OR Ora-Sweet SF (Paddock Laboratories)	29 mL	38.5 mL	48 mL	57 mL

623

624 Third, follow the procedure below for compounding the oral suspension (15 mg/mL)
625 from TAMIFLU Capsules 75 mg

- 626 1. Carefully separate the capsule body and cap and transfer the contents of the required
627 number of TAMIFLU 75 mg Capsules into a clean mortar.
- 628 2. Triturate the granules to a fine powder.
- 629 3. Add one-third (1/3) of the specified amount of vehicle and triturate the powder until a
630 uniform suspension is achieved.
- 631 4. Transfer the suspension to an amber glass or amber polyethyleneterephthalate (PET)
632 bottle. A funnel may be used to eliminate any spillage.
- 633 5. Add another one-third (1/3) of the vehicle to the mortar, rinse the pestle and mortar
634 by a triturating motion and transfer the vehicle into the bottle.
- 635 6. Repeat the rinsing (Step 5) with the remainder of the vehicle.
- 636 7. Close the bottle using a child-resistant cap.
- 637 8. Shake well to completely dissolve the active drug and to ensure homogeneous
638 distribution of the dissolved drug in the resulting suspension. (Note: The active drug,
639 oseltamivir phosphate, readily dissolves in the specified vehicles. The suspension is
640 caused by some of the inert ingredients of TAMIFLU Capsules which are insoluble in
641 these vehicles.)
- 642 9. Put an ancillary label on the bottle indicating "Shake Gently Before Use". [This
643 compounded suspension should be gently shaken prior to administration to minimize
644 the tendency for air entrapment, particularly with the Ora-Sweet SF preparation.]
- 645 10. Instruct the parent or guardian that any remaining material following completion of
646 therapy must be discarded by either affixing an ancillary label to the bottle or adding
647 a statement to the pharmacy label instructions.
- 648 11. Place an appropriate expiration date label according to storage condition (see below).
649

20

650 STORAGE OF THE PHARMACY-COMPOUNDED SUSPENSION:

651 **Refrigeration:** Stable for 5 weeks (35 days) when stored in a refrigerator at 2° to 8°C
652 (36° to 46°F).

653 **Room Temperature:** Stable for five days (5 days) when stored at room temperature,
654 25°C (77°F).

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

659 Place a pharmacy label on the bottle that includes the patient's name, dosing instructions,
660 and drug name and any other required information to be in compliance with all State and
661 Federal Pharmacy Regulations. **Refer to Table 9 for the proper dosing instructions.**

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

665 **Table 9 Dosing Chart for Pharmacy-Compounded Suspension from**
666 **TAMIFLU Capsules 75 mg**

Body Weight (kg)	Body Weight (lbs)	Dose (mg)	Volume per Dose 15 mg/mL	Treatment Dose (for 5 days)	Prophylaxis Dose (for 10 days)
≤15 kg	≤33 lbs	30 mg	2 mL	2 mL two times a day	2 mL once daily
16 to 23 kg	34 to 51 lbs	45 mg	3 mL	3 mL two times a day	3 mL once daily
24 to 40 kg	52 to 88 lbs	60 mg	4 mL	4 mL two times a day	4 mL once daily
≥41 kg	≥89 lbs	75 mg	5 mL	5 mL two times a day	5 mL once daily

667 *Note: 1 teaspoon = 5 mL*

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

674 **HOW SUPPLIED**

675 **TAMIFLU Capsules**

676 30-mg capsules (30 mg free base equivalent of the phosphate salt): light yellow hard
677 gelatin capsules. "ROCHE" is printed in blue ink on the light yellow body and "30 mg" is
678 printed in blue ink on the light yellow cap. Available in blister packages of 10 (NDC
679 0004-0802-85).

680 45-mg capsules (45 mg free base equivalent of the phosphate salt): grey hard gelatin
681 capsules. "ROCHE" is printed in blue ink on the grey body and "45 mg" is printed in blue
682 ink on the grey cap. Available in blister packages of 10 (NDC 0004-0801-85).

683 75-mg capsules (75 mg free base equivalent of the phosphate salt): grey/light yellow hard
684 gelatin capsules. "ROCHE" is printed in blue ink on the grey body and "75 mg" is printed
685 in blue ink on the light yellow cap. Available in blister packages of 10 (NDC 0004-0800-
686 85).

687 **Storage**

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

690 **TAMIFLU for Oral Suspension**

691 Supplied as a white powder blend for constitution to a white tutti-frutti-flavored
692 suspension. Available in glass bottles containing approximately 33 mL of suspension
693 after constitution. Each bottle delivers 25 mL of suspension equivalent to 300 mg
694 oseltamivir base. Each bottle is supplied with a bottle adapter and 1 oral dispenser (NDC
695 0004-0810-95).

696 **Storage**

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

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

700

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702 Ora-Sweet® SF is a registered trademark of Paddock Laboratories

703

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707 Foster City, California 94404

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Patient Information

TAMIFLU

(oseltamivir phosphate)

R_x only

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

What is TAMIFLU?

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

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

What is “Flu”?

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

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

Should I get a flu shot?

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

34 **Who should not take TAMIFLU?**

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

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

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

45 **How should I take TAMIFLU?**

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

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

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

57 TAMIFLU has not been studied in children 1 to 12 years of age for preventing flu during
58 an outbreak in your community or for use for more than 10 days.

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

61 If you are taking TAMIFLU for Oral Suspension, your pharmacist will give you a dosing
62 dispenser marked with three possible doses. Follow your healthcare professional's
63 instructions on which dose to take or how to combine them for the proper dose for you. In
64 order to be sure you receive the proper dose, it is important that you use the dispenser
65 provided. Review the instructions below on how to use the dispenser and ask your
66 pharmacist if you have any questions. If you lose or damage the dispenser and cannot use
67 it, contact your healthcare professional or pharmacist for advice on the proper dose.

68 If TAMIFLU for Oral Suspension is not available, your healthcare provider may instruct
69 you to open TAMIFLU Capsules and mix the contents with sweetened liquids such as
70 regular or sugar-free chocolate syrup. Please follow the dosing instructions below.

71 If you forget to take your medicine, take the missed dose as soon as you remember,
72 except if it is 2 hours or less before your next dose. Then continue to take TAMIFLU at

73 the usual times. Do not take 2 doses at a time to make up for a missed dose. If you miss
74 several doses, tell your healthcare professional and follow the advice given to you.

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

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

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

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

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

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

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

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

94 TAMIFLU for Oral Suspension should be stored under refrigeration at 36° to 46°F (2° to
95 8°C). Do not freeze.

96 **General advice about prescription medicines:**

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

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

105

106 **DOSING INSTRUCTIONS FOR PATIENTS:**

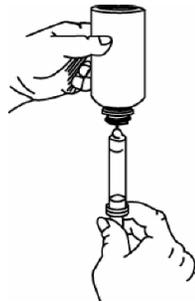
107 **How Do I Prepare TAMIFLU for Oral Suspension?**

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



109

- 110 • Shake closed bottle well for about 5 seconds before each use.
- 111 • Remove child-resistant cap.
- 112 • Before inserting the tip of the oral dispenser into bottle adapter, push the plunger completely down toward the tip of the oral dispenser. Insert tip firmly into opening of the bottle adapter.
- 113
- 114
- 115 • Turn the entire unit (bottle and oral dispenser) upside down.
- 116 • Pull the plunger out slowly until the desired amount of medication is withdrawn into the oral dispenser (see figure). The 75 mg dose is obtained by filling the dispenser twice, once to the 30 mg graduation, and a second fill to the 45 mg graduation.
- 117
- 118



119

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

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

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

- 129 • Holding one capsule over a small bowl, carefully pull the capsule open and pour the complete contents of the capsule into the bowl.
- 130
- 131 • Add a small amount of a sweetened liquid such as chocolate syrup (regular or sugar-free) that the child will consume completely.
- 132

133 • Stir the mixture and give the entire dose to the child.

134

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MEDKIT FOR PANDEMIC FLU

75 mg
10 Capsules

Important Product Information

Active ingredient (in each capsule)
Oseltamivir phosphate 75 mg

Purpose
Anti-influenza

Uses • Treatment of pandemic flu in patients 1 year and older • Prevention of pandemic flu in patients 1 year and older

Warnings Do not use • If you have ever had an allergic reaction to this product or any of its ingredients

Ask a doctor before use if you have • Had flu symptoms for more than 2 days
• Heart disease, respiratory disease or any other serious health condition
• Kidney disease • Heart disease, confusion or abnormal behavior

Ask a doctor or pharmacist before use if you have had a nasal spray flu vaccine in the last two weeks

When using this product the following may occur • Nausea, vomiting, and stomach pain • Seizures, confusion or abnormal behavior

Stop use and ask a doctor if • An allergic reaction or severe rash occurs.

if pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions
• For treatment. Use as soon as possible and within 2 days of start of flu symptoms.
• Find right dose on chart below. If possible, use weight to dose; otherwise use age.

Weight (lb)	Age (yr)	Treatment of Pandemic Flu	Prevention of Pandemic Flu
Adults and children 13 years of age and older		Take 1 capsule every 12 hours for 5 days	Take 1 capsule once a day for 10 days
88 lbs or more	10-12	Take 1 capsule every 12 hours for 5 days	Take 1 capsule once a day for 10 days
Up to 88 lbs	1-9	See attached Educational Booklet for dosing instructions (pp. 14-16)	Ask a doctor
Children under 1 year of age			

Other Information
• Patients with the flu should be watched for abnormal behavior including self-injury; talk to your health professional if this occurs or if flu symptoms worsen
• Store between 15° and 30°C (59° and 86°F)
• Protect from excessive moisture

Inactive Ingredients black iron oxide, croscarmellose sodium, FD&C Blue No. 2, gelatin, povidone K30, pregelatinized starch, red iron oxide, sodium stearyl fumarate, talc, titanium dioxide, yellow iron oxide

Questions? 1-877-78-ROCHE

27899509

75 mg
10 Capsules

MEDKIT FOR PANDEMIC FLU



MEDKIT – DO NOT OPEN UNLESS A FLU PANDEMIC HAS BEEN DECLARED



STOP: DO NOT USE UNTIL YOU READ THE ACCOMPANYING EDUCATIONAL BOOKLET.

MEDKIT FOR PANDEMIC FLU

75 mg

Each capsule contains 75 mg oseltamivir phosphate.

10 Capsules

Distributed by:
Roche Laboratories Inc.
Nutley, New Jersey 07110

LOT
EXP.

HOW TO USE THE



Tamiflu[®]
oseltamivir phosphate
**MEDKIT FOR
PANDEMIC FLU**

STOP! Before you use the TAMIFLU in this MEDKIT:

WAIT *until your local or state health department says that pandemic flu is in your area.*

READ this booklet to learn how to recognize pandemic flu symptoms.

*For the latest pandemic flu information, visit www.pandemicflu.gov,
or call **1-800-CDC-INFO (1-800-232-4636)**.*

Please see Important Safety Information inside.

Contents

The **blue** pages have general information about pandemic flu and the MEDKIT, plus **YES** and **NO** questions that will help you identify pandemic flu and decide what type of medical care is needed.

Pandemic flu is different from seasonal flu4

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Identifying people at risk for pandemic flu6

Recognizing a medical emergency7

Knowing if people with health concerns need medical care.....8

Identifying pandemic flu 10

Taking steps to feel better..... 11

If TAMIFLU is needed to treat or help prevent the flu, the **white** pages have directions on how to take TAMIFLU.

Start treatment or prevention of pandemic flu with TAMIFLU..... 12

TAMIFLU dosing information..... 13

Dosing instructions for children 1 to 9 years of age..... 14

FAQs about taking TAMIFLU..... 17

Important safety information..... 18

Seek medical care if you don't get better..... 19



4

Pandemic flu is different from seasonal flu

Seasonal flu is a common viral illness of the respiratory system with symptoms that include fever, cough, and extreme tiredness. Each year, people catch it and spread it to others, so it's smart to get a flu shot every year.

Pandemic flu is a brand-new type of flu that can be deadly. Because it's new, our bodies have little or no defense against it. It can cause serious illness and easily spread from person to person. It can even spread around the world. Like seasonal flu, pandemic flu spreads when a person with the flu coughs or sneezes, and tiny droplets land on the mouth or nose of others. Or if people touch these droplets on an object and then touch their mouth, they can get the flu. That's why it's important to wash your hands often.

People with pandemic flu can spread it for several days (possibly up to a week or longer) after they get sick, even when taking medicine. During this time, help prevent the spread of flu in your family by making a "sick room" at home and having one family member care for the sick person. To limit the spread of flu in the community, the sick person should stay home. If the person has to go out, he or she should wear a hospital mask. Other family members should also stay home because they may have the flu, even if they don't feel sick.

Visit www.pandemicflu.gov or call **1-800-CDC-INFO (1-800-232-4636)** to learn more about pandemic flu.

5

The TAMIFLU MEDKIT is only for pandemic flu

The TAMIFLU MEDKIT is specially made to be kept at home and used ONLY in an emergency due to pandemic flu. DO NOT use the TAMIFLU capsules in this MEDKIT for seasonal flu. If you have or a family member has flu symptoms but there is no pandemic, see your doctor for treatment.

TAMIFLU is a medicine proven to treat or help prevent different types of flu. Because there has not been a pandemic since TAMIFLU has been available, TAMIFLU has not been studied in pandemic flu and has been studied only in seasonal flu. Laboratory tests suggest that TAMIFLU may work in treating pandemic flu. Experts at the Centers for Disease Control (CDC) and World Health Organization (WHO) recommend TAMIFLU to treat and help prevent infection with pandemic flu.

Do not share TAMIFLU with others. If you share TAMIFLU, there may not be enough capsules left for you and your family to take the correct dosage (amount of medicine) for the correct number of days. If TAMIFLU is not taken as instructed, it may not work as well as it should.

Read this booklet before you open the boxes of TAMIFLU or take any of the capsules. Like any medicine, TAMIFLU works best when it is taken correctly.



6

Identifying people at risk for pandemic flu

Has the local or state health department said that pandemic flu has been detected in your area?

YES NO

Have you or any member of your household very recently developed one or more of these symptoms?

<input type="checkbox"/> Fever	<input type="checkbox"/> Runny nose	<input type="checkbox"/> Muscle aches
<input type="checkbox"/> Chills	<input type="checkbox"/> Sore throat	<input type="checkbox"/> Extreme tiredness
<input type="checkbox"/> Cough	<input type="checkbox"/> Shortness of breath	<input type="checkbox"/> Headache

YES NO

If you have checked ANY of the NO boxes, you don't need the MEDKIT now. Stay alert for pandemic flu announcements and flu symptoms.
If you have checked BOTH of the YES boxes above, go to page 

7

Recognizing a medical emergency

Does the person with symptoms show ANY of these signs?

<input type="checkbox"/> Difficulty talking, due to breathlessness
<input type="checkbox"/> For babies only, not eating or nursing, due to breathlessness
<input type="checkbox"/> Blue or gray skin color around the mouth
<input type="checkbox"/> Chest pain
<input type="checkbox"/> Being less awake or responsive than expected
<input type="checkbox"/> Not able to recognize family or friends
<input type="checkbox"/> Appears confused or disoriented

YES NO

If you checked the YES box, call 911 or take the person to the nearest Emergency Room.
If you checked the NO box, go to page 

8

Knowing if people with health concerns need medical care

Does the person with symptoms have ANY of the following?

- Shortness of breath (fast or difficult breathing)
- Severe vomiting
- Medical condition affecting the immune system, such as:
 - Recent bone marrow transplant
 - Leukemia or lymphoma
 - HIV infection or AIDS
 - Chemotherapy within the last month
 - Taking oral steroids for more than 1 week
- Aged less than 2 years or 70 years and older

YES NO

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Has the person with symptoms had to see a doctor

1) In the past month for ONE of these health conditions?

OR

2) In the last 6 months for TWO of these health conditions?

- Heart disease
- Kidney disease
- Lung disease (such as asthma or emphysema)
- Liver disease
- Diabetes

YES NO

If you checked ANY of the YES boxes, or if you think medical care is needed, contact a doctor or go to an Emergency Room.

If you checked BOTH the NO boxes, go to page 

10

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Identifying pandemic flu

Does the person have **BOTH** of these symptoms?

For people 5 years of age and older

- Fever of 100.4°F (38°C) or higher within the past day
- Cough

For children age 2 to 5 years of age

- Fever of 100.4°F (38°C) or higher within the past day
- Cough or runny nose or congestion

YES **NO**

If you checked the **NO** box, go to page **11** 

If you checked the **YES** box, go to page **12** 

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Taking steps to feel better

Treat symptoms with nonprescription medicines and/or take other steps to feel better

Make sure the person rests and drinks plenty of fluids. Follow the directions on the product label if nonprescription medicines are taken.

Watch the person to see if symptoms get worse over the next 48 hours

- **If cough AND fever of 100.4°F or higher develop**, follow the instructions on page 10
- **Contact a doctor or seek medical care at the Emergency Room** if the person shows ANY of these signs:
 - Continued fever after 48 hours of treatment with nonprescription medicines
 - Severe vomiting (throwing up) or signs of dehydration (sunken eyes, leathery skin, dizziness when sitting up or standing, infrequent or dark urine)
 - Worsening of or inability to care for an existing health condition (diabetes, asthma, etc)
- **Call 911 or take the person to the nearest Emergency Room** if you think that urgent medical care is needed, or if the person has signs of severe illness. The person could have a serious health condition that is not caused by the flu

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Start treatment or prevention of pandemic flu with TAMIFLU

Before taking TAMIFLU—when to talk to a doctor

Go over this health checklist before any family member starts to take TAMIFLU, either to treat or help prevent the flu. Talk to a doctor if any family member who is planning to take TAMIFLU:

- Has gotten pregnant, is planning to get pregnant, or is breastfeeding
- Is now taking any new prescription or nonprescription medicines
- Has ever had an allergic reaction to TAMIFLU or any of its ingredients
- Now has any type of kidney disease, heart disease, lung disease, or any serious health condition
- Has received flu vaccine as a mist that is sprayed into the nose in the past two weeks



Questions? Call 1-877-78-ROCHE (1-877-787-6243)

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TAMIFLU dosing information

Take TAMIFLU for treatment if you have had flu symptoms for fewer than 2 days. Start TAMIFLU as soon as possible.

Take TAMIFLU for prevention if someone in your home is sick with flu. If fever or cough develops, switch to the dosing for TREATMENT and seek medical care. Once you stop taking TAMIFLU, you are not protected from the flu.

Dosing instructions: Follow the chart below. If possible, use weight to find the right dose; if not, use age.

WEIGHT (LBS)	AGE (YRS)	TREATMENT OF PANDEMIC FLU	PREVENTION OF PANDEMIC FLU
Adults and children 13 years of age and older		Take one capsule every 12 hours for 5 days	Take one capsule once a day for 10 days
88 lbs or more	10-12		
Up to 88 lbs	1-9	See pages 14-16 of this booklet for dosing instructions	
Children under 1 year of age		Ask a doctor	

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Dosing instructions for children 1 to 9 years of age

To make doses of TAMIFLU for these children, you will need to mix the powder inside a TAMIFLU capsule with food. Then you can give the right amount of TAMIFLU mixed with food (the TAMIFLU mixture) to your child. Follow these instructions.

Gather the supplies you will need

1. One TAMIFLU capsule
2. A metal teaspoon
3. A small bowl
4. Water
5. One of these foods to hide the bitter taste of the TAMIFLU powder:
 - Sugar (light brown sugar or white table sugar)
 - Corn syrup (Karo)
 - Chocolate syrup (regular or sugar-free)
 - Dessert toppings like caramel or fudge sauce

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Make the TAMIFLU mixture

1. Hold one capsule over the small bowl. Carefully pull the capsule open and pour all the powder in the capsule into the bowl. Handle the powder carefully, because it may be irritating to the skin and eyes
2. Crush the powder carefully with the back of the metal teaspoon
3. Add two teaspoons of water to the bowl and mix it with the powder for 2 minutes
4. Add three teaspoons of one of the foods listed (sugar, corn syrup, chocolate syrup, or dessert topping) to hide the bitter taste of the TAMIFLU powder
5. Stir the TAMIFLU mixture well before giving the dose
(see page 16 to measure the dose for your child)



Unused TAMIFLU mixture should be stored in the refrigerator in a covered container. Remove the TAMIFLU mixture from the refrigerator before using and allow it to come to room temperature. The TAMIFLU mixture may be used for up to 2 days. Throw out any unused TAMIFLU mixture after 2 days.

Questions?  Call 1-877-78-ROCHE (1-877-787-6243)

Tamiflu
oseltamivir phosphate

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Measure the TAMIFLU dose for your child

To find the right dose, weigh your child. Find your child's weight on the left side of the chart below. Then, look across at the right side of the chart to see the amount (number of teaspoons) of TAMIFLU to give your child. This is the amount to give your child for ONE dose.

If you do not know your child's weight and cannot weigh your child, find your child's age in center of the chart. Then, use the right side of chart to see the number of teaspoons of TAMIFLU to give your child for one dose.

WEIGHT (LBS)	AGE (YRS)	TEASPOON DOSE
≤33	1-2	2 teaspoons = 1 dose 
34-51	3-5	3 teaspoons = 1 dose 
52-88	6-9	4 teaspoons = 1 dose 

Dosing the TAMIFLU mixture

- To TREAT pandemic flu, give your child one dose every 12 hours for 5 days
- To PREVENT pandemic flu, give your child one dose once a day for 10 days

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FAQs about taking TAMIFLU

Do I have to take TAMIFLU with food?

You can take TAMIFLU with or without food. If you take TAMIFLU with a light snack, milk, or a meal, you may have less of a chance of getting an upset stomach.

What should I do if I miss a dose of TAMIFLU?

If you miss a dose of TAMIFLU, take the missed dose as soon as you remember unless it is within 2 hours of the next scheduled dose. Do not take 2 doses at a time to make up for a missed dose. You can then continue to take TAMIFLU at the usual times.

How can adults who can't swallow pills take TAMIFLU?

Adults and children 10 years of age and older who cannot swallow capsules can still take TAMIFLU. Follow these instructions. Hold one capsule over a small bowl, and carefully pull it open, pouring all the powder in the capsule into the bowl. Handle the powder carefully, because it may be irritating to the skin and eyes. Add a small amount of sweetened liquid, such as chocolate syrup (regular or sugar-free). Stir the mixture and give all of it to the person.

Questions?  Call 1-877-78-ROCHE (1-877-787-6243)



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Important safety information

TAMIFLU is for treating adults and children aged 1 and older with seasonal flu whose flu symptoms started within the last day or two. TAMIFLU can also reduce the chance of getting the flu in patients aged 1 and older. TAMIFLU is not a substitute for an annual flu vaccination.

If you develop an allergic reaction or severe rash, stop taking TAMIFLU and contact your healthcare professional immediately, as it may be very serious. People with the flu, particularly children, may be at an increased risk of self-injury and confusion shortly after taking TAMIFLU and should be closely monitored for signs of unusual behavior. A healthcare professional should be contacted immediately if the patient taking TAMIFLU shows any signs of unusual behavior.

The most common side effects are mild to moderate nausea and vomiting.

If you experience any side effects not mentioned in this booklet or if you have any concerns about side effects you get, call your doctor right away for advice.

To report possible side effects of TAMIFLU, contact Roche or the FDA. Call Roche at 1-XXX-XXX-XXXX (1-XXX-XXX-XXXX). Contact the FDA at www.fda.gov/medwatch or call 1-800-FDA-1088 (1-800-332-1088).

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Seek medical care if you don't get better

You should start feeling better in the first few days after you start taking TAMIFLU. If you don't get better when you are taking TAMIFLU, you should seek medical attention.

- **Contact a doctor or seek medical care at the Emergency Room** if the person shows ANY of these signs:
 - Continued fever after 48 hours of treatment with nonprescription medicines
 - Severe vomiting (throwing up) or signs of dehydration (sunken eyes, leathery skin, dizziness when sitting up or standing, infrequent or dark urine)
 - Worsening or inability to care for an existing health condition (diabetes, asthma, etc)
- **Call 911 or take the person to the nearest Emergency Room** if you think that urgent medical care is needed, or if the person has signs of severe illness. The person could have a serious health condition that is not caused by the flu

If you don't get better, it is possible that you do not have the flu and need to be treated for another illness. Or, you may have a type of flu that cannot be treated by TAMIFLU. Only a medical professional can tell you.



What's inside your TAMIFLU MEDKIT

Your MEDKIT contains ten 75-mg capsules of TAMIFLU to be used ONLY for the treatment or prevention of pandemic flu.



Each box has 10 capsules.

The use-by date is stamped on the side of the box. After this date, do not take the TAMIFLU in the box.

Keep your TAMIFLU boxes in a cool, dry place, where the temperature does not get higher than 86°F (30°C).

Questions?  Call 1-877-78-ROCHE (1-877-787-6243)



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Tamiflu[®]
oseltamivir phosphate