

**DIVISION OF ANTIVIRAL PRODUCTS
DIVISION OF NONPRESCRIPTION CLINICAL EVALUATION
FDA BRIEFING INFORMATION**

**MEDKITS CONTAINING INFLUENZA ANTIVIRALS FOR THE
TREATMENT OR PROPHYLAXIS OF INFLUENZA DURING A
PANDEMIC**

Joint Meeting of the Antiviral Drugs Advisory Committee and the Nonprescription
Drugs
Advisory Committee

October 29, 2008

TABLE OF CONTENTS

A.	PURPOSE OF MEETING.....	3
B.	QUESTIONS FOR THE COMMITTEE.....	5
C.	BACKGROUND INFORMATION ON INFLUENZA AND INFLUENZA ANTIVIRALS.....	7
C1.	Influenza: Virology/Epidemiology.....	7
C2.	Antiviral drugs approved for influenza.....	7
C3.	Resistance to Influenza Antivirals.....	9
D.	ROLE OF ANTIVIRAL DRUGS IN PANDEMIC PREPAREDNESS.....	11
D1.	Proposals for home stockpiling of antimicrobial products for emergency use.....	12
D2.	Influenza Diagnosis Issues and Influenza MedKits.....	12
D3.	MedKit Labeling and Instructions.....	13
D4.	Supply and expiry issues.....	13
D5.	OTC and BTC (behind-the counter) Considerations.....	14
E.	BACKGROUND ON NONPRESCRIPTION DRUG MARKETING AND CONSUMER STUDIES.....	16
E1.	Regulations that Guide the Prescription Drug to Nonprescription Drug Switch Process.....	16
E2.	Consumer Studies.....	18
E3.	Consumer Study Analysis.....	22
F.	APPROACH FOR INFLUENZA MEDKIT DEVELOPMENT.....	23
F1.	SELECTED ISSUES RELATED TO GSK's PROPOSAL FOR A RELENZA (ZANAMIVIR) MEDKIT.....	23
F2.	SELECTED ISSUES RELATED TO ROCHE PROPOSAL FOR TAMIFLU MEDKIT.....	26
G.	ENDNOTES AND CITATIONS.....	30

A. PURPOSE OF MEETING

The primary purpose of this combined meeting of the Antiviral Drugs and Nonprescription Drugs Advisory Committees is to elicit advice and discussion on proposals for influenza antiviral MedKits for home storage in preparation for potential occurrences of pandemic influenza. In response to requests from the Department of Health and Human Services (DHHS), two pharmaceutical sponsors (GlaxoSmithKline and Roche), are proposing development of MedKits consisting of an approved influenza antiviral drug and patient instructions supplied in special packaging. In the proposed MedKits, GlaxoSmithKline's (GSK) antiviral drug, zanamivir (Relenza), is administered via a hand held inhalation device, and Roche's antiviral drug, oseltamivir (Tamiflu), is administered as oral capsules. Each of the proposed MedKits will contain the amount of drug that could be used for either treatment (5-day course, twice daily) or prophylaxis (10-day course, once daily).

Although the primary focus of the meeting will be prescription MedKits for use during a pandemic, if time permits, we will also ask the committees to consider the potential risks and benefits of 1) nonprescription, "over-the-counter" (OTC), availability of Tamiflu or Relenza MedKits and 2) prescription MedKits for use during seasonal outbreaks of influenza

To date, FDA's preliminary advice for the development of a prescription MedKit intended to treat or prevent serious infections or illnesses of public health importance has roughly followed the types of studies that are conducted for nonprescription drug development. Nonprescription drug marketing is supported by consumer studies, (described in Section E of this document). FDA has relied on the nonprescription (OTC) development model because prescription MedKits and OTC drugs share similarities such as, reliance on patients to ultimately decide, without the direct supervision of a health care provider, when and how to use the drug and/or determine if they actually have the disease/condition for which the drug is indicated. Although an influenza antiviral MedKit would be prescribed in the context of some counseling by a learned health care professional, the actual use of a MedKit may not occur until months or perhaps years after the prescribing date. Therefore, time-of-use decisions about issues such as dosing, treatment initiation, duration dosing, and safety are similar to those expected during use of nonprescription products.

FDA acknowledges previous DHHS meetings held to discuss the value and feasibility of antiviral influenza MedKits. Previous meetings included discussions of important public health issues such as: the availability of sufficient product for public stockpiling of drugs vs. home stockpiling, the potential effects of home stockpiling on reducing the impact of a pandemic, and equity and affordability of personal MedKits. However, the focus of this FDA advisory committee on antiviral MedKits will follow the usual charge of the FDA, which is to give advice on the safety and efficacy (or risk-benefit) of a product for its intended use for individual patients. Since influenza MedKits are still in development, we will be asking advice on 1) the general concept of an antiviral influenza MedKit, 2)

the development program that could support potential approval of a MedKit. It should be noted that one could determine that a MedKit could be safe and effective for individuals without knowing whether home storage of MedKits was the “optimal” or most equitable public health intervention for limiting a pandemic. On the other hand, there are public health issues that are relevant to FDA risk-benefit determinations. One example is the potential for an increased incidence of resistance from possible inappropriate use of a MedKit. Development of resistance has implications for efficacy in an individual and those around that person who might become infected.

Section E of this document contains background information regarding the types of studies typically used to support OTC availability of drugs. Section F contains a summary of Roche and GSK’s proposals for MedKit development. After consideration of the background information in this document and in those documents provided by GSK and Roche for each of their respective products, the Committees will be asked to comment on the risk-benefit balance of prescription MedKits and advise on the types of studies and study designs that are important to assess safe and effective use of antiviral influenza MedKits.

During the advisory committee meeting invited speakers will also review and summarize important issues relating to influenza, influenza resistance, and nonprescription drug development. Roche and GSK will summarize their proposals for MedKit development. Finally, representatives from multiple professional health care organizations/societies will voice their opinions on the concept of antiviral influenza MedKit availability for home stockpiling. The committees will then be asked to address the issues/questions in Section B of this document. Please note that these questions may be updated, as FDA continues to have an open dialogue with GSK and Roche regarding MedKit development.

B. QUESTIONS FOR THE COMMITTEE

Primary Focus Questions

1. Please comment on the concept of a prescription influenza antiviral MedKit intended for use during a pandemic. Specifically address potential risks and benefits, for individual consumers and the U.S. population, if prescription MedKits were approved with the intention of home stockpiling.
2. Please comment on the use of a MedKits for treatment versus prophylaxis of influenza during a pandemic. Specifically, taking into account the characteristics of the drugs included in the proposed MedKits:
 - Are both treatment and prophylaxis indications appropriate for MedKits for both of the proposed products?
 - If both indications are appropriate, is it acceptable for the same MedKit to be used for both indications?
3. The Tamiflu MedKit proposal includes instructions for dosing children using the contents of the 75 mg adult capsules although Tamiflu is also available commercially as 30 mg and 45 mg capsules. What is the most appropriate formulation to be used for pediatric dosing in this setting?
4. Comment on specific elements of labeling, packaging, or instructions that are critical for safe and effective use of a MedKit.
5. Will the previously conducted phase 3 clinical trials and favorable results from the proposed “consumer use” studies (e.g., label comprehension, simulated use, and compliance studies) allow for safe and effective use of the MedKits by individuals who may not be under direct medical supervision at the time of antiviral drug use?
6. Please comment on additions or modifications to the proposed studies (e.g., label comprehension, simulated use, or additional studies) that would help to assess risks and benefits. Specifically:
 - Are there differences in the types of studies needed to support a “treatment” or “prophylaxis” indication?
 - What is a reasonable percentage of study subjects who should understand various components of the labeling and/or be able to refrain from using the product for seasonal influenza?

Additional Questions

7. Please comment on the type of availability that would best be suited to provide MedKits to the American public and state your reasons for your comments.
8. If availability without a prescription is considered an option, please describe any additional studies that would be needed to support a switch from prescription to nonprescription availability.

C. BACKGROUND INFORMATION ON INFLUENZA AND INFLUENZA ANTIVIRALS

C1. Influenza: Virology/Epidemiology

Influenza viruses causing acute influenza illness in humans generally belong to two types, influenza A and influenza B. Influenza A is divided into subtypes based on hemagglutinin (H) and neuraminidase (N) surface proteins, and affects many birds and mammals in addition to humans. Avian influenza strains are classed as highly pathogenic (HPAI) or not, based on molecular structure (primarily hemagglutinin) and virulence in birds, which does not necessarily correspond to ease or severity of infection for humans. Thus far, 16 hemagglutinin and 9 neuraminidase subtypes have been recognized in birds, but only a few have circulated extensively in humans. Influenza viruses undergo rapid error-prone replication with emergence of different strains or clades within subtypes. Influenza A(H3N2), influenza A(H1N1), and influenza B currently all circulate and may reach epidemic proportions during a typical influenza season. When gradual accumulation of mutations (antigenic drift) leads to changes in antigenicity, changes in annual vaccines are needed to optimize protection. Influenza A (but not influenza B) is also subject to occasional major changes known as antigenic shift, for example reassortment between mammalian and avian influenza or progressive mutation of an avian strain to increased pathogenicity and transmissibility in humans. Antigenic shift can result in a new dominant influenza A subtype to which humans have little or no immunity, and rapidly progressive worldwide outbreaks known as pandemics: examples in the twentieth century included the emergence of influenza A(H1N1) in 1918, H2N2 in 1957, and H3N2 in 1968. Recent outbreaks of highly pathogenic influenza A(H5N1) in avian hosts, together with sporadic cases and small clusters of human infection by H5N1 strains, have led to concern among many experts that this subtype could evolve to precipitate the next influenza pandemic. This concern has heightened government and public attention to pandemic preparedness¹.

C2. Antiviral drugs approved for influenza

Four antiviral drugs have been approved for treatment and prophylaxis of influenza (Table 1). These drugs fall into two classes: the adamantanes, or M2 blockers; and the more recently developed neuraminidase inhibitors. Treatment approvals have been based on symptom improvement in acute uncomplicated influenza illness, and prophylaxis on reduction in the frequency of laboratory-confirmed influenza illness when influenza is circulating in the community (outbreak or seasonal prophylaxis) or following exposure to an ill household member (post-exposure prophylaxis). Based on the available study data and information about influenza epidemiology, influenza antivirals have been approved and labeled for treatment of acute uncomplicated influenza caused by influenza A or by influenza A and B (see the package inserts for precise wording for each drug).

Table 1. Antiviral Drugs Approved for Influenza

	Amantadine	Rimantadine	Zanamivir	Oseltamivir
Influenza types inhibited	A	A	A and B	A and B
Route of administration	Oral (tablet, capsule, syrup)	Oral (tablet, syrup)	Inhalation	Oral (capsule, suspension)
Treatment approved (ages)	1 year or greater	Adults	7 years or greater	1 year or greater
Prophylaxis approved (ages)	1 year or greater	1 year or greater	5 years or greater	1 year or greater
Initial approval	1960's	9/17/93	7/26/99	10/27/99

Influenza Antiviral Drug Efficacy

Clinical trials of currently approved influenza antivirals² have reported decreases (by 1 to 1.5 days) in time to alleviation of symptoms in otherwise healthy patients with acute uncomplicated influenza illness. Most such studies enrolled participants with clinical diagnostic criteria while influenza was circulating in the community, and used laboratory confirmation for the primary analysis population. Across different influenza treatment trials, the clinical diagnostic criteria used during a community outbreak of influenza identified laboratory-confirmed influenza in about 60% of study participants. Clinical trials of prophylaxis have been carried out in community outbreak settings (4-6 week regimens) or after household exposure (7-10 day regimens).

Use of approved influenza antivirals for each successive new influenza strain emerging during interpandemic years or potentially during a pandemic has not been considered to be off-label, but claims of efficacy specifically against “pandemic influenza” have not been considered appropriate because the next pandemic strain cannot be predicted with certainty³ and would itself in the course of time evolve into “seasonal” influenza, then possibly superseded by another different pandemic strain. The labeling/claim issue is similar to other situations in which clinical trials are not expected to independently demonstrate robust efficacy in every subgroup of the population for whom the drug might be used, but a specific claim of clinical benefit in one of those subgroups lacking adequate data would not be acceptable. Because of the evolution of influenza and the potential for altered drug-responsiveness of different strains, whether associated with specific drug-resistance mutations or with changes in virulence properties, label changes have recently been requested to emphasize that prescribers should consider available information about susceptibility and treatment effects in their treatment decisions⁴.

Influenza Antiviral Safety

The package inserts for currently marketed neuraminidase inhibitors contain information about adverse events observed in clinical trials and in postmarketing reports⁵. For Tamiflu, the most prominent adverse events in clinical trials when active drug was

compared to placebo were nausea and vomiting. For Relenza, the adverse events of greatest concern were reports of bronchospasm with or without underlying airways disease. Most cases of bronchospasm were identified in the postmarketing period with causality difficult to assess. Consequently, the product is not recommended for persons with underlying airways disease. Both oseltamivir and zanamivir have some reports of allergic reactions including serious skin reactions and anaphylaxis.

Neuropsychiatric adverse events, sometimes leading to injury, were noted in a number of Japanese reports during a regularly scheduled Pediatric Advisory Committee review of Tamiflu adverse event reports following pediatric exclusivity determination. Neuropsychiatric adverse events for all four influenza drugs were discussed in greater detail at follow-up meetings of the Pediatric Advisory Committee⁶ and the difficulty of evaluating the relative causal contributions of the treatment and the treated illness was emphasized.

Other conditions including serious bacterial infections may begin with influenza-like symptoms or occur as complications of influenza. FDA received reports of bacterial infections that progressed during antiviral treatment, noted in a Public Health Advisory during the influenza season that followed approval of the two neuraminidase inhibitors⁷. Recent publications describing the contribution of bacterial pneumonia to mortality in the 1918 pandemic⁸ and recent emergence of community-acquired MRSA pneumonia⁹ have provided reminders of possible bacterial infections requiring specific treatment during treatment of influenza or influenza-like illness.

The potential for emergence of additional safety issues during more widespread use of a drug in diverse populations cannot be predicted with certainty. Because usual reporting and surveillance mechanisms may be severely stressed during a public health emergency, provisions for adequate monitoring should be considered during product development.

C3. Resistance to Influenza Antivirals

Emergence of resistant viral strains can be considered as affecting both efficacy and safety of a product. Concerns for antiviral resistance emergence may differ from those noted in discussions of inappropriate use of antibiotics, because of the narrower spectrum of the antivirals and lesser occurrence of asymptomatic infection and replication. Because there is no human reservoir for influenza, persons who take influenza antivirals but are not infected with influenza virus are not likely sources of resistant pathogens. Viruses do not exchange resistance plasmids as bacteria may; but possible effects of reassortment between drug-resistant and susceptible influenza strains are unknown¹⁰. Effects of inappropriate drug dosing or duration on emergence of resistant influenza virus variants have not been extensively studied¹¹.

Resistant variants can be isolated from influenza-infected patients treated with antivirals. Shedding of resistant virus is common during treatment with adamantanes. Adamantane resistant virus appears to have pathogenicity similar to wild-type, and emergence of widespread resistance has been anecdotally proposed as linked to adamantanes in over-

the-counter medications (in countries outside the U.S.) and/or in animal feed¹². Shedding of resistant virus during treatment has been less common with neuraminidase inhibitors and virulence and transmissibility of treatment-emergent resistant variants has appeared variable¹³. Children have been reported to have greater propensity to shed resistant virus than adults, possibly due to increased viral loads and/or limited immunity to previous circulating influenza strains compared to adults¹⁴.

Interpretation of influenza virus susceptibility testing is complicated by the use of different assays and substrates¹⁵, and the lack of established relationships between PK (or tissue distribution measurements) and clinical outcomes. Explorations of viral fitness are also limited by the difficulty of predicting compensatory mutations or reassortments that might increase replication competence or virulence if these are compromised by a single initial mutation. However, if viable viruses emerge with target sites changed such that inhibitory activity of an antiviral is greatly reduced, expectations of clinical benefit are correspondingly lowered.

For either drug class, after emergence of transmissible and pathogenic resistant variants, ongoing transmission appears possible even without selection pressure from ongoing drug use. Modeling exercises¹⁶ have suggested that when both susceptible and resistant strains are in circulation, increased antiviral use would favor greater spread of resistant variants, but exploration of control strategies suggests complex relationships to pandemic evolution that may be difficult to predict. Resistance does not appear to be an intrinsic property of specific subtypes (for example, the neuraminidase inhibitors are reported to inhibit all neuraminidase subtypes though with varying potency¹⁷), but subtypes may differ in specific mutations that arise. For example, in two Japanese pediatric studies, reported incidence of treatment-emergent oseltamivir resistance mutations in influenza A (H3N2) and A (H1N1) was similar between the two studies but the mutations identified were different between the two subtypes¹⁸. As another example, circulating strains of influenza A (H3N2) in the US have had much higher prevalence of adamantane resistance than observed for influenza A (H1N1), while recent reports of increasing oseltamivir resistance have been associated with influenza A (H1N1) but not with influenza A (H3N2)¹⁹. Specific types of resistance mutations may also have differing implications for cross-resistance: for example, amino acid substitutions at neuraminidase catalytic residues have been reported to confer resistance to both marketed neuraminidase inhibitors, and framework substitutions to be more specific to the selecting drug.²⁰

A recent publication²¹ has summarized analysis of influenza isolates received by the World Health Organization Collaborating Center for Surveillance, Epidemiology, and Control of Influenza at the Centers for Disease Control and Prevention, for several recent seasons and the initial part of the 2007-8 influenza season, using neuraminidase assay and genotypic analysis. In the US, the frequency of oseltamivir resistance in circulating H1N1 strains increased from 0.7% (4/588) in the 2006-7 influenza season to 7.1% in 2007-8 (50/706). Oseltamivir resistance was not found in 232 H3N2 US isolates and 181 influenza B isolates. Zanamivir resistance was not found in any of the US isolates. These frequencies may represent minimums as population based analyses of isolates amplified in cell culture were employed and the minimum shift in neuraminidase

susceptibility has not been associated with clinically identified resistance using a standardized assay. More recent updates are posted periodically on the CDC and WHO websites²².

D. ROLE OF ANTIVIRAL DRUGS IN PANDEMIC PREPAREDNESS

Development of specific vaccines is considered fundamental to control any new strain of influenza, but is not possible for a future novel pandemic strain until that strain is recognized and relevant antigens are incorporated into vaccines. Infection control interventions are also important both for seasonal epidemics and for pandemic preparedness.

Unlike vaccines based on hemagglutinin and neuraminidase antigens, antiviral drugs will not necessarily vary greatly in efficacy based strictly on influenza subtype if the molecular target of the drug is conserved. For example, limited data have been reported to suggest that studies of antivirals (adamantane only, as the neuraminidase inhibitors had not yet been developed) during the emergence of influenza A(H3N2) during the 1968 pandemic, or during the re-emergence of influenza A(H1N1) in 1977, showed effects that were considered to be clinically meaningful, although these could not be directly compared to studies of antiviral therapy for longer-circulating influenza strains considered to be “seasonal” influenza²³.

Because existing antiviral drugs for influenza are directed at molecular targets conserved across many different influenza strains and subtypes, pandemic preparedness efforts have included government stockpiling of antivirals, with an announced US goal of stockpiling treatment courses sufficient to treat 25% of the population²⁴. Because resistance emerges rapidly when adamantanes are used to treat influenza, stockpiling efforts have focused on the neuraminidase inhibitors.

Potential Limitations of Influenza Antivirals for Treatment during a Pandemic

Uncertainty remains regarding the effects of antivirals if used against more novel viral strains that might have different virulence properties and for which even partially cross-reactive immunity may be lacking in the population at risk. For example, WHO has suggested that higher doses or longer treatment regimens may need assessment for treatment of human infections with influenza A(H5N1)²⁵, based in part on animal studies suggesting that in vivo drug responses may be decreased. Such reports have not necessarily been linked to corresponding changes in susceptibility using neuraminidase assays²⁶; and neither neuraminidase assays nor pharmacokinetic (PK) parameters have been shown to be reliable predictors of the ability to demonstrate efficacy in clinical trials evaluating seasonal influenza. In general, relationships between in vitro susceptibility and degree of clinical effect remain uncertain. Data are limited regarding the ability of antivirals to treat influenza infections with systemic dissemination of virus, to prevent serious complications, or to prevent mortality. No controlled studies are available to

assess effectiveness of the approved antivirals in severe or life-threatening influenza illness requiring hospitalization.

D1. Proposals for home stockpiling of antimicrobial products for emergency use

The Department of Health and Human Services in the past few years has considered the possibility of drug supplies kept in the home in preparation for certain infectious disease emergencies, in usual prescription form or specially packaged “MedKits.” This concept has been considered both for antibacterial drugs that might be used for postexposure prophylaxis of inhalational anthrax if anthrax spores were released in a bioterrorist event, and for antivirals that might be used in the event of pandemic influenza.²⁷ A CDC study report²⁸ found that 97% of participants in a study group given a supply of specially packaged antibacterial drugs were able to return the package unopened after a period of months. This report also noted an expectation of further testing of comprehension of labeling and instructions in population groups of varying literacy, understanding of correct usage in a simulation setting, and ability to prepare and administer pediatric dosing.

Development of labeling and instructions for influenza-antiviral MedKit-type products should take into account the potential differences in usage conditions for influenza compared to anthrax²⁹, but would likewise be expected to involve “consumer studies”, such as testing of label comprehension, appropriate usage in actual-use scenarios or simulations, dose preparation for children and others who may not be able to use the provided formulation without assistance, and ability to retain the product and avoid inappropriate use. Because new packaging with new instructions and conditions for use of a previously approved drug normally requires submission of a supplement to the New Drug Application (sNDA), consumer studies contribute to the evidence base to be submitted in support of such an sNDA.

D2. Influenza Diagnosis Issues and Influenza MedKits

During typical seasonal outbreaks, influenza can present with a range of symptoms that overlaps with symptoms of other viral and bacterial illnesses. Rapid diagnostic tests have limited availability and limited sensitivity³⁰, so initial management decisions are often based on clinical evaluation. Availability and accuracy of diagnostic tests during a future pandemic cannot be predicted with certainty, especially if an unexpected subtype emerges in a pandemic or if anatomic distribution of the virus is different from typical circulating influenza. Attempts to develop clinical diagnosis algorithms have also met with limited success³¹ and generalizability to future novel influenza strains is unknown, especially if novel virulence properties or organ involvement lead to shifts in patterns of clinical presentation. Predictive values of any diagnostic approach depend not only on sensitivity and specificity of the diagnostic but also on prevalence of the disease: for

example, in communities where a pandemic wave is beginning or ending, a high proportion of “flu-like” illnesses may be caused by other pathogens relative to communities where the pandemic wave is at its peak.³² As noted in the Safety section above, several recent articles have reinforced that even in the presence of a true influenza diagnosis, bacterial infections may be major causes of morbidity and mortality, and assessment of the need for antibacterial as well as antiviral therapy may be important. Therefore, development and testing of instructions for a MedKit-type product for influenza should include consideration of: 1) how community presence of a pandemic would be recognized, 2) the ability to diagnose at the individual level, for institution of treatment if the product will be used to treat established illness 3) how an individual will recognize an exposure if it will be used for post-exposure prophylaxis, and 4) how users would determine when additional medical care (such as evaluation for bacterial superinfection) should be sought. Issues for testing include whether written instructions are understood, whether following the written instructions would lead to correct actions in an emergency setting, and how alternative directions might be developed and disseminated if warranted by the nature of the emergency event.

D3. MedKit Labeling and Instructions

The dosing and duration of influenza antiviral drug administration differ for treatment of established illness, post-exposure prophylaxis after household exposure, and outbreak-length prophylaxis in community outbreaks. Users of MedKit drugs would need adequate instructions for appropriate timing, dose, administration, and duration of use and instruction to help them differentiate the proposed pandemic use of the MedKit from use of antiviral drugs during a usual influenza season³³. If MedKit sponsors plan to rely on public service announcements during a pandemic to clarify uses of their product, putative content of such messages may be important to include in testing of instructions.

Dosing and administration for pediatric patients, elderly users, for or persons with underlying comorbidities or disabilities, and effects of viral resistance or systemic invasive properties of a viral strain on appropriate treatment selection, may also raise distinctive issues with each drug under consideration. Depending in part on whether a MedKit is intended to supply a household rather than an individual, possible changes in household composition during several years’ storage of the product might also affect its adequacy for household needs in a pandemic. Recommendations for households containing infants should take into account the lack of data and of approved indications for children under 1 year of age.

D4. Supply and expiry issues

Several years ago, a number of government and professional organizations recommended against personal stockpiling of influenza antivirals. Cited reasons included depletion of supply for seasonal epidemic use as well as potential for inappropriate use and resistance emergence³⁴. Total supplies and manufacturing capacity are reported to have increased

since that time. Discussions of antivirals for emergency situations have also cited the potential for misallocation, lack of equity, and variable levels of public health control for direction of available drugs to areas of greatest need³⁵. Prospects for the coordination of different sources of drug supply may be important considerations.

Influenza antivirals are dated for expiry a number of years after manufacture based on stability under usual storage conditions. Because some stockpiled products have undergone additional testing and have been stored under strictly controlled conditions it has been possible to extend the expiration date printed on the package. In other words, the original date has been replaced by a date 1-2 years in the future. However extending the expiration date of individually prescribed products may raise issues related to state pharmacy laws and variability in household storage (e.g., temperature or humidity). The potential release of drug into the environment has raised questions related to the possible effects of widespread intensive use, especially with regard to resistance development.³⁶ Provisions for disposal and replacement of expired drug may need further consideration.

D5. OTC and BTC (behind-the counter) Considerations

The proposals for MedKit labeling and packaging under discussion are for prescription products. Media reports have suggested some sources of comment favor over-the-counter influenza antivirals, though such proposals³⁷ more closely resemble restricted “behind-the-counter” (BTC) pharmacist dispensing to patients meeting special criteria. A general BTC category for drug approvals does not exist in the US (despite a few OTC approvals with labeling conditions that result in pharmacy verification of age or identity, rather than clinical criteria such as diagnosis or risk assessment), though potential criteria for establishing such a category were debated in an open meeting in November 2007³⁸. Australian regulatory authorities have recently turned down a proposal for BTC availability of oseltamivir (while noting that individual states and territories have the authority to allow nonphysician healthcare providers to prescribe or dispense prescription products in emergency situations)³⁹. While we have not located examples of unrestricted access to neuraminidase inhibitors in other countries, New Zealand authorities have allowed limited pharmacist dispensing of the prescription product that could be rescinded if concerns about resistance or supply and distribution arise, while concluding evidence was insufficient to proceed to broader availability⁴⁰. In the UK, website documents describe limited availability of Tamiflu under Patient Group Directions if a local Primary Care Trust determines it may be dispensed to patients meeting specified criteria⁴¹. We have not located any examples of detailed follow-up assessments of outcomes such as diagnostic accuracy or complications.

In proposals for OTC switches of prescription drugs in the US, usually sponsors submit supporting information and rationale, labeling and testing, for FDA review and advisory committee discussion. Rx-to-OTC switch applications for systemic antimicrobial drugs have raised concerns about self-diagnosis, consequences of misdiagnosis, and resistance selection, leading to non-approval in the past⁴². Even as prescription products, the proposed MedKit strategies raise issues that overlap with study types used to evaluate

prospective OTC products, in that persons receiving prescription MedKits would need to make decisions about diagnosis, treatment initiation, dosing and duration, and safety in circumstances remote from the initial prescription encounter⁴³. These plus other issues, for example concerning selection of products for individuals and household and avoidance of specific products by persons who may be at risk for adverse events or have difficulty with product administration, might be important to assess further if a MedKit-type product were proposed for OTC purchase without any initial prescription encounter.

E. BACKGROUND ON NONPRESCRIPTION DRUG MARKETING AND CONSUMER STUDIES

The purpose of this section is to familiarize the committees with:

- Regulations that provide for nonprescription drug marketing and nonprescription labeling
- Consumer studies commonly conducted to support the approval of nonprescription drugs: Label Comprehension Studies (LCS), Self-Selection (SS) and Actual Use Studies (AUS)

The sponsors have proposed to conduct consumer studies to support the in home stockpiling of antiviral drugs for use during an influenza pandemic. Although the studies proposed by the sponsors may differ somewhat in their specifics from the three types of studies broadly described in this memorandum, the themes are similar and reviewing this document will help to prepare the committee to better understand consumer research and the issues the in home stockpiling proposals raise.

Data from consumer studies provide information about how well an over-the-counter (OTC) product label can inform the nonprescription drug consumers about the drug and whether consumers can appropriately use the drug based upon the information on the label. Thus, these data play a major role in helping to determine whether a product should be marketed without a prescription. LCS, SS, and AUS have unique characteristics and this memorandum cannot address all of the nuances of consumer study design but will provide an overview. During the meeting, you will hear a presentation about these topics.

E1. Regulations that Guide the Prescription Drug to Nonprescription Drug Switch Process

The prescription to OTC switch process is guided by federal regulations. The Federal Food, Drug, and Cosmetic Act Section 201 [321] (g)(1) states that the term “drug” means articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease and intended to affect the structure or any function of the body of man. The Durham-Humphrey Amendment to the Federal Food, Drug, and Cosmetic Act draws a distinction between prescription and non-prescription drugs. This distinction is stated in the Code of Federal Regulations 21 CFR 310.200(b) as follows:

“Any drug limited to prescription use under section 503(b)(1)(C) of the act shall be exempted from prescription-dispensing requirements when the Commissioner finds such requirements are not necessary for the protection of the public health by reason of the drug’s toxicity or other potentiality for harmful effect, or the method of its use, or the

collateral measures necessary to its use, and he finds that the drug is safe and effective for use in self-medication as directed in proposed labeling.”

When a drug that has been previously available only by prescription is switched to OTC status, the healthcare provider no longer serves as a gatekeeper to drug access. Thus, to comply with 21 CFR 310.200(b), it is important to take the indication, the target population, the safety concerns, and the behaviors that proper use of the drug demands of the consumer into account when considering whether a drug would be an appropriate candidate for nonprescription sale.

The OTC Label:

The Code of Federal Regulations 21 CFR 201 Subpart C establishes labeling requirements for OTC drugs. It consists of many sections and addresses all aspects of the OTC label, but this memorandum will focus on 21 CFR 201.66, the regulation that “sets forth the content and format requirements for the *Drug Facts* labeling of all OTC drug products.”

The regulation describes the types of information that must be on the label (active ingredient, purpose, uses, warnings, directions, etc.) It standardizes the OTC label construct with the intent that consumers can become familiar with a standard label format so they can easily find the information they seek on any OTC label. The outside container or wrapper of the retail package, or the immediate container label (if there is no outside container or wrapper), must contain the “*Drug Facts*” title and specified headings, subheadings, and information.

The regulations are very specific about the design of the label. For example:

- The regulations require a minimum font size (six) but encourage even larger fonts so consumers can easily read the label information;
- The regulations require that the type be easy to read with no more than 39 characters per inch;
- The continuation of the required content and format onto multiple panels must retain the required order and flow of headings, subheadings, and information and a visual graphic (e.g., an arrow) is to be used to signal the continuation of the *Drug Facts* labeling to the next adjacent panel;
- The regulations describe how to use hairlines to separate subheadings.

To bring a new drug to the OTC market, the sponsor must comply with the CFR labeling rules.

Exemptions to the labeling regulations:

If a particular labeling requirement is inapplicable, impracticable, or contrary to public health or safety for a particular product the FDA can grant an exemption to the rule. Granting exemptions is precedent setting and can lead to inconsistency in labeling. There is also a significant regulatory hurdle that we must be able to explain that justifies the exemption. Therefore, it is important to consider the risk of the unforeseen consequences of granting an exemption at a given time to a given product and what an exemption for one product will mean for labeling on other products. Exemptions may possibly impact

consumer literacy with regard to OTC labeling. Thus, granting exemptions is not done often and consumer data is required to support the decision to grant an exemption. Examples of types of labeling modifications that would require an exemption are:

- Deviating from the mandated formatting or headings
- Pictograms

E2. Consumer Studies

Label Comprehension Studies

It is important to study whether consumers can understand the information on a product label, particularly when new OTC indications, directions for use, and new warnings are contained therein. LCS can help to develop labeling that communicates effectively.

The label comprehension study is a trial in which no drug is administered. The study is a critical element of the label development process for an OTC drug. If a study succeeds, it can at least assure that respondents understand the label that will accompany the product to market or that will be used in a Self-Selection, Actual Use, or other type of consumer study. If the results suggest that certain elements are not understood, the study can still be contributory as long as information is collected to help establish the reasons for the errors. The LCS results may not accurately predict consumer behavior, such as self-selection, purchase decisions, or adherence. The main data collection tool for a LCS is the consumer Questionnaire, which should be administered by a trained study investigator. More information about the design of LCS Questionnaires can be found below.

LCS should have a series of key communication objectives, (the information that it is important to convey to the consumer). LCS can test how well consumers comprehend the information displayed on the outside of drug carton, contained inside the package (inserts), and any other crucial informational material. It is important to point out that a given study participant may technically answer a label comprehension question incorrectly, but the unique characteristic of that participant may mean that the response is acceptable. Thus, the investigators should ascertain why participants who answer incorrectly, answer the way they do.

Label comprehension studies can be useful under many different circumstances some of which are:

- The drug is the first in its class to enter the OTC market;
- The drug targets a new OTC population;
- There is a new OTC indication;
- There is a substantive labeling change to an existing OTC product (e.g., a new warning);
- There is a product with a new active ingredient that uses a proprietary name associated with another active ingredient;
- The sponsor generates multiple proprietary names for products containing identical active ingredients.

Target Population:

We have often sought a LCS target population that is representative of the United States population of potential product users and nonusers. To attract this target population, tests have been administered in shopping malls and other purchase sites that are demographically diverse.

The general population is often enriched with subgroups of special interest, for example, those of a particular gender, age, race, sex, or those with a medical condition that would put them at high risk if they took the drug. The populations have included a low literacy cohort (which we have tended to define as those with less than a 9th grade reading level) whose literacy level is determined by a validated literacy testing instrument that is administered by a trained investigator.

Although we gather data on the low literacy population, how to assess the potential differences between low literate subjects and those of normal literacy is unclear. For example, we deliberate over an acceptable comprehension difference, whether the two groups should be studied separately or en masse, or whether there should be different acceptable comprehension score “cut offs” for the two groups. This issue is relevant to the consideration of home stockpiling of antiviral drug products.

Questionnaire:

The questionnaire used in a LCS should be designed to reflect the communication objectives of the study. The wording of the questionnaire, the order of questions, and the structure of the questions can affect the results of the study by not gathering the appropriate information, introducing respondent fatigue, or by introducing bias. As such, the questionnaire should:

- Be short and simple and use language that people of low literacy can understand;
- Address one objective per question;
- Address different levels of information processing;
- Contain questions of variable design;
- Allow the investigator to record verbatim responses from the respondent that can then be coded and analyzed.

There are many types of questions that have been used and each has advantages. Open-ended questions allow the respondent to give an unrestricted answer that can be recorded verbatim. Closed-ended questions offer the opportunity for the respondent to choose from among a restricted answer set as in a multiple choice question. Scenarios are questions that require the respondent to apply information from the label to respond correctly. The question consists of a brief description of a medical situation. The respondent responds to a question about whether, in this situation, the product would be appropriate to use. Scenario questions can provide very informative data and may offer a window into the ability of respondents to use the product properly. They are used commonly in LCS because they require not just the comprehension of information, but the ability to process it.

Information from one question should not influence the responses to subsequent questions. It is important that multiple choice questions be mutually exclusive and that they not contain language that participants may interpret as a “safe” answer. They should not contain a default answer such as “ask a doctor” unless asking a doctor is the correct answer according to the label.

Trained investigators should administer the questionnaire using scripted interactions with the respondent. Generally respondents have been given unrestricted time to read the label and can refer back to it during the testing. This methodology presents a dilemma since it may tend to favorably bias the study results; respondents are probably studying the label more intensely than they would in “real life” or in an actual use study (see below). On the other hand, it does not seem realistic to put respondents in a position where they need to essentially memorize the label to participate in the testing. However, we have noted that how well respondents perform in the LCS does not necessarily predict their behavior in the Actual Use Study. There are many factors that may influence behavior aside from comprehension alone.

Self-Selection Studies:

Self-selection data is collected to determine if a consumer can, after reading the product label, make a correct decision about whether or not the product is appropriate for him/her to use based upon the indications and warnings. SS should assess the ability of a consumer to correctly self-diagnose the condition for which a product is indicated and determine whether the product is appropriate for them to use. Sometimes the self-selection question has been included in the LCS or the AUS and sometimes it has been the focus of a stand alone study. This has occurred in the situation where we have concerns about the consumers’ ability to self-diagnose a condition or about the impact of a new warning on the ability to properly choose whether to use the product but are not concerned about the ability to follow the directions for product use. The language used to pose a self-selection question can influence how people may respond to it. Generally, the study participant reads the product label and then answers the question as to whether it is or is not okay for them to use the product.

The target population of the SS should be potential users of the product some of whom could use the product and some of whom should not use the product. Clearly, it is important to understand why consumers self-select incorrectly so study investigators ask study participants why they answered the self-selection question the way they did and also take a medical history on the study participants.

The acceptability of the success rate for pivotal issues related to self-selection for an OTC product and the acceptability of the failure rate is the topic of much debate. It can be difficult to determine when the majority who could benefit from access to an OTC drug should be denied that access because of self-selection errors made by a small subpopulation that could be at risk for using the drug.

Actual Use Studies:

Unlike a LCS, in an actual use study participants actually take the study drug home and ingest it. This is a clinical trial. The purpose of an actual use study is to simulate the OTC use of a product. Hopefully, the AUS can provide meaningful consumer data so we can attempt to predict if a drug will be used properly, safely, and effectively in the OTC setting. Examples of things an actual use study can assess are:

- Adherence (taking the drug and performing any monitoring for efficacy and safety in accordance with the drug label);
- Safety (adverse events that occur during the study);
- Efficacy (whether the clinical benefit in the prescription setting is reproduced in the OTC setting). This seldom has been done.

AUS can evaluate the relationship between a self-selection decision and the decision to actually purchase the drug. They can assess the ability of the consumer to use the product for the indicated purpose (self-treat) and can also assess whether consumers abuse or misuse the study drug. Studies that test the ability of consumers to properly measure or self-administer a drug, such as they would need to do for Tamiflu or Relenza, are variations on actual use studies.

Some issues that might trigger the need for an actual use study include:

- New OTC indication;
- New method of use for an OTC drug;
- New OTC warnings;
- New OTC medical follow-up requirements or recommendations;
- Specific concerns about self-selection or de-selection.

Study Design:

The design of an AUS can vary. It makes sense that the label used in the AUS should be one that tests well in a LCS. Nevertheless, it is important to note that we have seen very well comprehended labels that do not lead to successful outcomes in SS or AUS.

Often AUS have been single-arm, multi-center, uncontrolled, open-label studies. However, it is possible that we should be considering other designs such as those where multiple arms compare different methods of communication and consumer education (e.g. additional educational material versus none) or the inclusion of a control group. The goal of the study is to provide a venue that simulates, as closely as possible, the true OTC environment. However, it is clear that a truly “naturalistic” environment cannot be perfectly achieved; data needs to be collected. Study elements that limit the naturalistic setting are the informed consent form, data collection tools like diaries which can serve as memory prompts to the study participant, and any other educational tools that may not be carried over into the true OTC setting. When study elements that limit the naturalistic setting are used in the AUS we cannot be certain that the same level of safety and efficacy will be achieved if the consumer uses the product without these additional elements. This issue is always considered when we provide comments to a sponsor about their AUS study design.

Ideally, all consumers who have an interest in the product should be the target of recruitment efforts. It is reasonable to attract people with a certain symptom or condition. Although we do not have the data to support this supposition, it appears that people generally enter a pharmacy because they have a specific medical need and are looking for a product to take care of that need. They are not just “window shopping” for an OTC medication.

It is also reasonable to recruit targeted subgroups of interest (e.g., low literacy, specific demographics, and medical conditions). These subgroups can provide more information about the potential safety (or efficacy) concerns. As with the LCS and SS, sometimes it has been difficult to determine how to factor the low literacy data and data from other subpopulations into the decision about drug approval. This is certainly the case with these influenza drugs as we grapple with how close the low literate and general population cohorts’ scores need to be to make these MedKits available.

E3. Consumer Study Analysis

It is important to note that “adequate” label communication, self-selection, or actual use is an issue of clinical judgment and varies depending upon the medical significance of a particular objective. Different healthcare professionals may have different thresholds for adequacy and thus this often has become a matter of discussion. It is always debatable what a realistic expectation of consumer comprehension, self-selection or actual use should be but, despite this, we pre-specify the target success rates for each objective.

F. APPROACH FOR INFLUENZA MEDKIT DEVELOPMENT

Roche (sponsor of Tamiflu) and GlaxoSmithKline (sponsor of Relenza) are proposing to conduct studies to ensure safe and effective use of their products in a home MedKit without the availability of learned intermediary at the time of use. Both sponsors propose a Label Comprehension Study and a Compliance Study. The Label Comprehension studies test comprehension of the written materials that describe: 1) when and how to use the products, 2) warnings regarding adverse events, and 3) when to seek medical care. The Compliance studies test appropriate non-use of the product during a routine flu season as well as the ability to locate the MedKit after it has been stored for a specific time period.

Appropriate selection to take the treatment dosing regimen verses the prophylaxis dosing regimen will be addressed in the label comprehension study using hypothetical scenarios. Instructions regarding when to begin treatment or prophylaxis will be based on an algorithm developed by consultants from HHS, the CDC, professional societies, and the sponsors. The ability to appropriately self-select to use the product based on medical history will not be addressed because the MedKit as proposed will be initially distributed by a prescriber who will screen for contraindications.

Roche and GSK will also be conducting additional studies that pertain to the specific use of their respective drugs. The sponsors' proposed studies are summarized in the sections below. However, the committee should also refer to the individual background documents prepared by Roche and GSK for more details. It should be noted that FDA and the two pharmaceutical sponsors are having ongoing discussions regarding the designs of these "consumer studies". Sponsor proposals at the advisory committee may change from what is described in this document.

F1. SELECTED ISSUES RELATED TO GSK'S PROPOSAL FOR A RELENZA (ZANAMIVIR) MEDKIT

This section summarizes GSK's Relenza MedKit proposal and highlights important issues. Committee members should refer to the GSK background document for additional details regarding the proposal.

GSK's development program proposes the following studies:

- Labeling Comprehension Study
- Human Factors Study
- Compliance Studies (Retention and Avoidance of Inappropriate Usage)

The current proposed contents of the MedKit are summarized in Table 2.

Table 2. Contents of RELENZA MedKit

Component	Description
Outer Carton	Carton labeling provides: (1) List of contents of the MedKit (2) Basic instructions on when to open and use the MedKit (3) All of the current carton information for Relenza, including storage conditions
Pandemic Patient Brochure	Provides information about pandemic influenza, why the MedKit is needed, how to use the practice inhaler (i.e., “Practice-Haler”), and when to take Relenza
Diskhaler Instructions	Step-by-step instruction guide on how to use the Relenza Diskhaler and Rotadisks
Reminder Card	Reference guide in the event of pandemic influenza
Practice-Haler (will not contain Relenza)	Used to familiarize consumers with the Diskhaler
Relenza Diskhaler and Rotadisks	Inhalational device and antiviral drug

Labeling Comprehension Study

GSK states that the proper use of a Relenza MedKit in the event of pandemic influenza will rely heavily on the individual, who may be making decisions at a time and place far removed from the initial interaction with the prescriber. GSK’s proposed label comprehension study would evaluate at least 350 subjects, evenly distributed between normal and low literacy as defined by the Rapid Estimate of Adult Literacy in Medicine test. However, GSK acknowledges that the proposed label comprehension study would not be able to evaluate actual consumer behavior in the event of a pandemic influenza outbreak. Therefore, GSK also proposes to perform the Human Factors Study, which would evaluate ability to follow the Relenza delivery system directions for use while relying only on the enclosed patient instructions for guidance.

Human Factors Study

This study is intended to evaluate the ability to complete the steps outlined in the patient instruction sheet regarding use of the Diskhaler inhalational device for successful administration of the drug. Similar to the label comprehension study, this study would evaluate the instruction sheet in both normal and low literacy populations. As proper administration of Relenza requires the correct performance of all nine steps listed in the Diskhaler directions, one concern has been whether the primary study endpoint should be the successful completion of all nine steps. Secondary objectives could include assessments of how well study participants performed individual steps of the Diskhaler instructions in order to determine the need for revisions to the instructions. Additionally, characterizing patient subpopulations that have difficulty completing all steps correctly

may contribute to the overall risk-benefit assessment of the proposed MedKit configuration.

Compliance Studies

GSK has proposed to conduct two compliance studies. These studies are intended to determine the ability of households to appropriately store and use the Relenza MedKit.

The first study would be conducted over 12 weeks in approximately 10-20 clinical research sites across the United States. It is intended to evaluate the study participant's ability to retain the MedKit at home, avoid inappropriate use during an influenza season, and to make appropriate decisions during a pandemic scenario.

Instructions regarding the use of the Relenza MedKit would be provided and a baseline survey of understanding performed. The participant would then be given an opportunity to become aware of the MedKit concept and to be evaluated by a healthcare professional in order to determine if s/he is an appropriate candidate for the MedKit. Participants would be instructed to store their MedKit until they return for follow-up in approximately 12 weeks. During the 12-week period, participants would not be contacted by study staff, except to schedule the second visit (Study Day 85). At this visit, participants would be assigned to one of the following pandemic scenarios and asked to describe the actions they would take:

1. Pandemic flu in the U.S.
2. Pandemic flu confirmed/communicated in their local area

Participants would verbalize their intended actions based on their judgment and the product labeling. The study staff will subsequently conduct follow-up questioning to further understand the reasons behind any incorrect or incomplete responses.

The second proposed compliance study includes a 15-month, at-home product retention evaluation to evaluate consumer behavior related to product retention or use during at least two influenza seasons. Of note, pandemic scenarios would not be tested during this study.

One area of concern has been that it is unclear how much instruction will be provided by investigators at the study enrollment sites (i.e., a greater intensity of instruction than would occur during actual practice could bias the study findings). Also, because the amount of information that will be available to patients at the time of a pandemic is unknown, the materials contained in the packaging should be able to stand alone in providing the necessary information for appropriate use of the device.

F2. SELECTED ISSUES RELATED TO ROCHE PROPOSAL FOR TAMIFLU MEDKIT

Roche has submitted a proposal to develop a Tamiflu MedKit, also intended for use during an influenza pandemic. Their developmental program contains many of the same elements proposed by GSK but must also evaluate strategies for pediatric dosing based on age or weight. Their proposed program includes the following studies for which draft protocols or concept sheets were submitted (for detailed descriptions of the studies refer to the Roche background document for this AC):

- A labeling comprehension study
- A MedKit simulation study
- A compliance study
- A mixing and dosing study (of pediatric dosing)

Table 3. Contents of Tamiflu MedKit

Component	Description
Outer Carton	Carton labeling provides: (1) Product name (2) Instructions not to open the MedKit unless a pandemic has been declared (3) Appropriate storage conditions (4) Each carton will contain one blister carton for each member of the household.
Blister Carton (one or more to be packaged inside the Outer Carton)	(1) Product name, strength, number of capsules (2) Instructions not to open the MedKit unless a pandemic has been declared and not to open until consumer has read the Educational Booklet (3) OTC-style product description including: uses, warnings, adverse event information, when to talk to a health care provider, dose recommendations, and list of inactive ingredients (4) Each blister carton will contain 10 75mg capsules of Tamiflu
Educational Booklet	Provides information about pandemic influenza, why the MedKit is needed, how to dose Tamiflu for children according to age, when to take Tamiflu, and how to report adverse drug reactions; this information has not been finalized.
Treatment Algorithm	Provides an algorithm (HHS/CDC draft document) to be used for diagnosis of influenza during a pandemic and to guide use of the antiviral drug in the MedKit; this has not been finalized.

Labeling Comprehension Study

It is anticipated that the MedKit will be prescribed for and purchased by consumers, stored for some undetermined length of time, and then used at a later time with very little input from health care providers. The labeling comprehension study proposed by Roche is intended to assess comprehension of the proposed labeling components including the Educational Booklet, blister carton packaging, and outer carton packaging, and determine whether participants correctly understand the key messages conveyed. In this study, participants will be provided with the labeling components, asked to read them, and then will complete a standardized interview. Participants will have access to all of the materials during the interview and can refer back to the MedKit components but will not be instructed to do so. The sponsor proposes that comprehension will be evaluated based on pre-specified correct or acceptable responses to the survey questions. However, the proportion of participants answering correctly needed for the study to be considered successful has not been decided.

Simulation Study

The simulation study proposed by Roche is intended to determine whether individuals correctly understand key messages from the labeling components well enough to apply their learning to situations that might or might not lead to use of the MedKit. Study methodology and analysis is similar to that proposed for the labeling comprehension study. However, from our perspective, the purpose of this study is not clear. As described, it appears that there is considerable overlap between the labeling comprehension study and the proposed MedKit simulation study. In this case, a simulation study should evaluate whether or not individuals are able to make correct decisions regarding when to use the product and then appropriately dose the product for all members of the household.

Compliance Study

The proposed compliance study is intended to determine the rate of household compliance with storage and use of the Tamiflu MedKit. This study is proposed as an observational epidemiologic study planned for 5 metropolitan locations scattered across the U.S. Participating households will be recruited from multiple sources and will be directed to a designated pharmacy in their area for enrollment. During enrollment, the Tamiflu MedKit will be provided and a baseline survey of understanding will be performed. Participants will be instructed to store their MedKit until they are contacted for follow-up. The sponsor proposes to ship the MedKit to each household after enrollment. At some time after the influenza season, households will be contacted and asked to complete a follow-up questionnaire and return their MedKit using a pre-paid mailer. Those households not returning the MedKit will be visited in person. In this study, the primary measure of compliance is proposed to be the proportion of households with Tamiflu MedKits intact out of all those who returned their MedKits. The sponsor

notes that their criteria for success for the proportion who return their MedKits will be 70% and, of those, 80% of MedKits will be intact.

There are several concerns regarding the proposal for the compliance study. Overall, the study should simulate “real-life” conditions. Because there are no guarantees that information made available to healthcare providers will be provided to patients in the “real-world” setting of a pandemic, the materials contained in the packaging should essentially be able to stand alone in providing the necessary information for safe, effective and appropriate use. The secondary packaging will contain the Tamiflu blisters cartons for each member of the household. Roche proposes to define success as: 1) return of 70% of these kits and 2) 80% of the blister packages within the kits returned will not have missing capsules. This definition of success allows for an overall high failure rate. Finally, the compliance study proposed provides only information on which households can successfully store the MedKit and avoid using it during seasonal influenza. It does not test whether a household can react appropriately to instructions advising them to open their MedKits and dose all household members correctly.

Mixing and Dosing Study (for pediatric dosing)

The sponsor has provided very little detail regarding a proposed “mixing and dosing study” intended to test whether consumers can adequately understand instructions on how to prepare a liquid preparation from opened Tamiflu capsule contents and then give the appropriate dose to children. The Educational Booklet included in the MedKit provides directions on how to open capsules and mix the contents of the capsules with water and another product that provides taste-masking (e.g., chocolate syrup, corn syrup, sugar).

In response to concern that not all households will have access to a weight scale, Roche has presented a proposal to dose the Tamiflu in MedKits according to age. They have also proposed that only 75 mg capsules will be provided in the MedKits, although 30 mg and 45 mg capsules are commercially available. This approach does allow dosing flexibility for all ages and allows the product to be useful over a longer period of time if the household includes children. However, the directions needed for this approach are clearly more complicated and will inevitably lead to more dosing errors than using the more age-specific capsules. Since pediatric patients generally have high viral burden and shed influenza virus for a longer period, the consequences of incorrect/under dosing may be significant.

Areas of Uncertainty

There remain significant areas of uncertainty in relation to how the Tamiflu MedKit would be distributed and packaged so that educational information is available to a wide segment of the population. We remain concerned that the Educational Booklet and treatment algorithm do not clearly identify when a consumer should use the drug contained in the MedKit for either prophylaxis or treatment, although we recognize that these components are not finalized at the time of writing this document. We are also not certain that demonstrating that households can retain and locate a MedKit a few months

after acquisition is a good predictor that they will be able to use the drug in the appropriate circumstances or be able to appropriately dose everyone in the household.

G. ENDNOTES AND CITATIONS

-
- ¹ Information on US government pandemic preparedness efforts is available at www.pandemicflu.gov.
- ² Package inserts. Drugs@FDA website (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)
- ³ For example, in addition to current concerns about the potential for strains of subtype H5N1 avian influenza A to infect humans and possibly evolve into a form more readily transmissible between humans, recent reports have suggested that some influenza strains with hemagglutinin subtypes H7 or H9 could also be cause for concern (Wan H et al., “Replication and transmission of H9N2 influenza viruses in ferrets: evaluation of pandemic potential,” *PLoS ONE* 2008;3:e2923; Belser JA et al., “Contemporary North American influenza H7 viruses possess human receptor specificity: implications for virus transmissibility,” *PNAS* 2008;105:7558-63).
- ⁴ Package inserts are being changed to include the following language in locations appropriate to each label format: “Influenza viruses change over time. Emergence of resistance mutations could decrease drug effectiveness. Other factors (for example, changes in viral virulence) might also diminish clinical benefit of antiviral drugs. Prescribers should consider available information on influenza drug susceptibility patterns and treatment effects when deciding whether to use [name of drug].”
- ⁵ See package inserts for individual products available from manufacturers or through Drugs@FDA website (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>) or FDA/CDER “Influenza (Flu) Antiviral Drugs and Related Information” website
- ⁶ See transcripts and additional information from November Pediatric Advisory Committee meetings in 2005, 2006, and 2007, available through <http://www.fda.gov/oc/advisory/OCPEdSACpg.html>.
- ⁷ See discussion in Public Health Advisory at <http://www.fda.gov/cder/drug/advisory/influenza.htm>. Package inserts were revised to include the following precautionary language: “Serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza. [name of drug] has not been shown to prevent such complications.”
- ⁸ See for example Brundage JF and Shanks GD, “Deaths from bacterial pneumonia during 1918-19 influenza pandemic,” *Emerg Infect Dis* 2008;14:1193-9 (which also raises questions about the common description of a typically fulminant clinical course); Morens DM, Taubenberger JK, Fauci AS, “Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness,” *JID* 2008;198:962-70; McCullers JA, “Planning for an influenza pandemic: thinking beyond the virus,” *JID* 2008;198:945-7.
- ⁹ See for example discussion in Kallen AJ et al., “Staphylococcus aureus community-acquired pneumonia during the 2006 to 2007 influenza season,” *Ann Emerg Med* [e-pub before print, doi:10.1016/j.annemergmed.2008.04.027] at [http://www.annemergmed.com/article/S0196-0644\(08\)00773-7/abstract](http://www.annemergmed.com/article/S0196-0644(08)00773-7/abstract)
- ¹⁰ Some recent studies (e.g. Nelson MI et al., “Multiple reassortment events in the evolutionary history of H1N1 influenza A virus since 1918,” *PLoS Pathogens* 2008;(8):e1000012; Nelson MI et al., “Molecular epidemiology of A/H3N2 and A/H1N1 influenza virus during a single epidemic season in the United States,” *PLoS Pathogens* 2008;4(8):e1000133) suggest that reassortment may be more common among circulating influenza strains than historically recognized.
- ¹¹ Some authors have suggested that higher levels of oseltamivir resistance recognized in a few small pediatric studies, compared to other clinical trial data, may have been a consequence of a dosing regimen leading to lower drug exposure as well as other factors such as more intensive monitoring (see Kiso et al., “Resistant influenza A viruses in children treated with oseltamivir: descriptive study,” *Lancet* 2004;364:759-65; Ward P et al., “Oseltamivir (Tamiflu®) and its potential for use in the event of an influenza pandemic,” *J Antimicrob Chemother* 2005;55(Suppl. S1):i5-i21; Aoki FY, Boivin G, Roberts N, “Influenza virus susceptibility and resistance to oseltamivir,” *Antivir Ther* 2007;12:603-16). Others have suggested that the differences in exposure associated with mis-dosing are unlikely to be large enough to affect the rate of resistance emergence, but that the magnitude of use of a product when a mixture of resistant and susceptible strains is circulating could affect the balance of strains to be further transmitted.
- ¹² See for example Bright RA et al., “Incidence of adamantane resistance among influenza A (H3N2) viruses isolated worldwide from 1994 to 2005: a cause for concern,” *Lancet* 2005;366:1175-81; Cyranoski, “China’s chicken farmers under fire for antiviral abuse,” *Nature* 2005;435:1009.

-
- ¹³ See package inserts, also Herlocher JL et al, "Influenza viruses resistant to the antiviral drug oseltamivir: transmission studies in ferrets," *JID* 2004;190:1627-30; Yen HL et al., "Neuraminidase inhibitor-resistant recombinant A/Vietnam/1203/04 (H5N1) influenza viruses retain their replication efficiency and pathogenicity in vitro and in vivo," *J Virol* 2007;81:12418-26; Sheu TG et al., "Surveillance for neuraminidase inhibitor resistance among human influenza A and B viruses circulating worldwide from 2004 to 2008," *Antimicrob Agents Chemother* 2008;52:3284-92.
- ¹⁴ See for example comparative numbers for adult and pediatric studies in Tamiflu package insert; and discussions in review articles cited earlier, including discussion of potential relevance of pediatric study results to immunologically naïve populations in Hayden FG and Pavia AT, "Antiviral management of seasonal and pandemic influenza," *JID* 2006;194(Suppl2):S119-26.
- ¹⁵ See discussion in Sheu et al., cited above.
- ¹⁶ See for example Lipsitch M et al., "Antiviral resistance and the control of pandemic influenza," *PLoS Medicine* 2007;4:e15; Moghadas SM et al., "Population-wide emergence of antiviral resistance during pandemic influenza," *PLoS ONE* 2008;3:e1839; McCaw JM et al., "Impact of emerging antiviral drug resistance on influenza containment and spread: influence of subclinical infection and strategic use of a stockpile containing one or two drugs," *PLoS ONE* 2008;3:e2362.
- ¹⁷ Ferraris O, Lina B, "Mutations of neuraminidase implicated in neuraminidase inhibitors resistance," *J Clin Virol* 2008;41:13-19.
- ¹⁸ See Kiso et al. and Ward et al. articles cited above.
- ¹⁹ See Bright et al. and Sheu et al. articles cited above; also WHO summaries at http://www.who.int/csr/disease/influenza/oseltamivir_summary/en/index.html and http://www.who.int/csr/disease/influenza/h1n1_table/en/index.html.
- ²⁰ See Ferraris and Lina, cited above.
- ²¹ Sheu et al., 2008, cited above.
- ²² See CDC surveillance reports at <http://www.cdc.gov/flu/weekly/fluactivity.htm> and WHO reports at <http://www.who.int/csr/disease/influenza/en/>.
- ²³ See for example discussion and citations in Hayden FG and Pavia AT, cited above.
- ²⁴ See March 1, 2006, news release, "HHS Buys Additional Antiviral Medication As Preparations for Potential Influenza Pandemic Continue," at <http://www.hhs.gov/news/press/2006pres/20060301.html>.
- ²⁵ See discussion in WHO, "Clinical management of human infection with avian influenza A(H5N1) virus," at http://www.who.int/csr/disease/avian_influenza/guidelines/ClinicalManagement07.pdf.
- ²⁶ In reports of need for increased oseltamivir dosing to protect animals infected with more virulent viral strains, decreased drug responsiveness has not been associated with corresponding changes in drug susceptibility results in vitro: see for example Govorkova et al., "Comparison of efficacies of RWJ-270201, zanamivir, and oseltamivir against H5N1, H9N2, and other avian influenza viruses," *Antimicrob Agents Chemother* 2001;45:2723-32; Yen et al., "Virulence may determine the necessary duration and dosage of oseltamivir therapy for highly pathogenic A/Vietnam/1203/04 influenza virus in mice," *JID* 2005;192:665-72; Govorkova et al., "Efficacy of oseltamivir therapy in ferrets inoculated with different clades of H5N1 influenza virus," *Antimicrob Agents Chemother* 2007;51:1414-24.
- ²⁷ See for example discussions in the meeting summaries from June 18 and August 11, 2008, at <http://www.hhs.gov/aspr/omsph/nbsb/meetings/index.html> and in the workshop materials at <http://www.hhs.gov/aspr/barda/phemce/workshop/2008/2008workshop.html>.
- ²⁸ See report from CDC Coordinating Office for Terrorism Prevention and Emergency Response, "CDC's Division of Strategic National Stockpile Emergency MedKit Evaluation Study Summary Background, Key Results, and Next Steps(as of November 15, 2007)," at <http://emergency.cdc.gov/agent/anthrax/prep/pdf/medkit-evaluation-summary-2007.pdf>.
- ²⁹ For example, descriptions of anthrax-directed MedKit projects in a recent meeting (<http://www.hhs.gov/aspr/barda/phemce/workshop/2008/2008workshop.html>) focused on a projected intent to ensure administration of antibiotics to as much of the population as possible within 48 hours after a single anthrax-dispersal attack. Because an influenza pandemic involves person-to-person spread estimated as occurring over a period of weeks rather than a single-source dispersal event exposing a population over a period of hours, simultaneous initiation of medications by everyone in a geographic area would be much less appropriate for influenza and might be harmful, in that many persons would use their drug when not exposed and have no drug available when exposed at a later time. Other discussions at the same meeting

addressed the potential effect of emergency settings on the ability to communicate and process information and instructions.

³⁰ See FDA Center for Devices and Radiologic Health “Cautions in using rapid tests for detecting influenza A virus” at <http://www.fda.gov/cdrh/oivd/tips/rapidflu.html>; World Health Organization, “WHO recommendations on the use of rapid testing for influenza diagnosis” at http://www.who.int/csr/disease/avian_influenza/guidelines/RapidTestInfluenza_web.pdf; and Writing Committee of the Second World Health Organization Consultation on Clinical Aspects of Human Infection with Avian Influenza A (H5N1) Virus, “Update on avian influenza A (H5N1) virus infections in humans,” *NEJM* 2008;358:261-73. Depending on tests and specimen types, sensitivity and specificity and confidence intervals vary widely.

³¹ See examples of study entry based on clinical criteria and rate of laboratory confirmation from package inserts; also Govaert T et al., “The predictive value of influenza symptomatology in elderly people,” *Family Practice* 1998;15:16-22; Monto A et al., “Clinical signs and symptoms predicting influenza infection,” *Arch Intern Med* 2000;160:3243-7; van Elden L et al., “Clinical diagnosis of influenza virus infection: evaluation of diagnostic tools in general practice,” *Br J General Practice* 2001;51:630-4; Peltola V et al., “Accuracy of clinical diagnosis of influenza in outpatient children,” *CID* 2005;41:1198-200; Hoeven A et al., “Lack of discriminating signs and symptoms in clinical diagnosis of influenza of patients admitted to the hospital,” *Infection* 2007;35:65-8; and WHO testing recommendations cited immediately above. Positive predictive values have varied from below 20% to over 80% depending on different study populations and circumstances; comparisons among different algorithms and laboratory tests and physician’s subjective judgment have not revealed a consistent best strategy; no comparisons between any of these strategies and patient’s subjective judgment were recovered in literature search. These analyses have usually focused on discussion of the ability of certain signs and symptoms to predict the presence of influenza infection, not on any independent validation of the ability of algorithm users to accurately detect the presence of those signs and symptoms; presumably both factors would have the potential to affect outcomes. In addition, the overall usefulness of a test or algorithm, and the consequences of individual false positive or negative results, might vary for different intended uses (for example, epidemiologic surveillance or individual case management).

³² Some experts have also suggested that increased attention to symptoms during a period of pandemic awareness could lead to lower positive predictive values at the same time that rising prevalence of influenza could lead to higher positive predictive values. See for example discussions at <http://www.dhsspsni.gov.uk/pandemicclinicalguidelines-03.pdf> and http://books.nap.edu/openbook.php?record_id=12170&page=55; and experiences reported during the 2001 anthrax events (e.g. M’ikanatha NM et al., “Patients’ request for and emergency physicians’ prescription of antimicrobial prophylaxis for anthrax during the 2001 bioterrorism-related outbreak,” *BMC Public Health* 2005;5:2).

³³ The distinction between uses of a drug approved for influenza in a product configuration intended to be held for availability in the event of a pandemic, versus use of the same drug in a product configuration not so specified, may raise additional questions about the interpretation of label comprehension studies. For example, if a patient issued a MedKit takes the influenza drug because of flu-like symptoms in the absence of a pandemic, the patient has not accurately followed the MedKit instructions for pandemic use and does not have the intended drug supply if a pandemic occurs subsequently. Information may or may not be available to determine whether the patient had an illness that would have resulted in a prescription for the same antiviral in its usual commercial configuration had the MedKit not been present in the home. Whether MedKits should be designed to cover potential uses during annual epidemics as well as potential future pandemics – and if so, how instructions and testing thereof should be modified – is an issue that may not be fully addressable within the bounds of the proposals currently under discussion, but may be important to overall public health and medical strategies.

³⁴ See for example http://www.mass.gov/Eeohhs2/docs/dph/cdc/immunization/alerts_antiviral_stockpiling_recommendations.pdf, <http://aapnews.aapublications.org/cgi/content/full/e2005187v1>, <http://www.dhss.mo.gov/PandemicInfluenza/StockpilingFluAntiviralMeds.pdf>, <http://www.nyc.gov/html/doh/downloads/pdf/cd/cd-hcp-h5n1-stockantiretro.pdf>.

³⁵ See for example issues discussed by the National Association of County and City Health Officials (NACCHO) at <http://www.naccho.org/advocacy/positions/upload/08-04antiviral-pan-flu.pdf>.

³⁶ See for example Singer AC et al., “Potential risks associated with the proposed widespread use of Tamiflu,” *Environ Health Perspect* 2007;115:102-106; Fick J et al., “Antiviral oseltamivir is not removed or degraded in normal sewage water treatment: implications for development of resistance by influenza A virus,” *PLoS ONE* 2007;2(10):e96.

³⁷ See for example Kimery AL, “Prophylactic use of Tamiflu bad idea, leading virologist says,” *Homeland Security Today* June 10, 2008, at <http://hstoday.us> <http://www.hstoday.us/content/view/3741/150/1/1/>.

³⁸ “Behind the Counter Availability of Certain Drugs Public Meeting” November 14, 2007, <http://www.fda.gov/oc/op/btc>.

³⁹ See discussion on pages 155-176 at <http://www.tga.gov.au/ndpsc/record/rr200806b.pdf>.

⁴⁰ See discussions in meeting minutes at <http://www.medsafe.govt.nz/profs/class/minutes.asp>.

⁴¹ See documents at <http://www.portal.nelm.nhs.uk/pgd/navigate.aspx?categoryid=3992>.

⁴² See for example draft guidance for industry “OTC treatment of herpes labialis with antiviral agents” at <http://www.fda.gov/cder/guidance/3571dft.htm> and advisory committee transcript at <http://www.fda.gov/ohrms/dockets/ac/98/transcpt/3477t1.pdf>, which addressed similar issues though in the context of a topical product proposal. See also Sande MA et al., “Perspectives on switching oral acyclovir from prescription to over-the-counter status: report of a consensus panel,” *CID* 1998;26:659-63, which alludes to some of the issues raised in an earlier Advisory Committee discussion.

⁴³ Measurement of label understanding by diverse populations (such as different languages of origin, or households in which children may serve as language interpreters) is also not as well standardized and could have different implications for a product intended for management of a communicable disease, compared with precedents for other types of user-selected drugs that might be evaluated for OTC use.



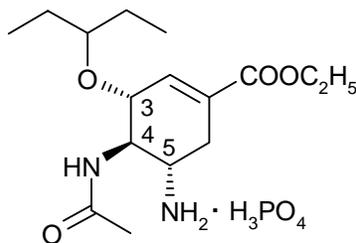
TAMIFLU®
(oseltamivir phosphate)
CAPSULES
AND FOR ORAL SUSPENSION

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.

Antiviral Activity

The antiviral activity of oseltamivir carboxylate against laboratory strains and clinical isolates of influenza virus was determined in cell culture assays. The concentrations of oseltamivir carboxylate required for inhibition of influenza virus were highly variable depending on the assay method used and the virus tested. The 50% and 90% effective concentrations (EC_{50} and EC_{90}) were in the range of 0.0008 μ M to >35 μ M and 0.004 μ M to >100 μ M, respectively (1 μ M=0.284 μ g/mL). The relationship between the antiviral activity in cell culture and the inhibition of influenza virus replication in humans has not been established.

Resistance

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

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

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

Cross-resistance

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

Immune Response

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

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption and Bioavailability

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

Table 1 Mean (% CV) Pharmacokinetic Parameters of Oseltamivir and Oseltamivir Carboxylate After a Multiple 75 mg Capsule 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)

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

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

Distribution

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

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

Metabolism

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

Elimination

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

Special Populations

Renal Impairment

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

Table 2 Oseltamivir Carboxylate Exposures in Patients With Normal 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

*Observed values. All other values are predicted.

AUC normalized to 48 hours.

Hepatic Impairment

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

Pediatric Patients

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

Geriatric Patients

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

INDICATIONS AND USAGE

Treatment of Influenza

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

Prophylaxis of Influenza

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

TAMIFLU is not a substitute for early vaccination on an annual basis as recommended by the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices.

Description of Clinical Studies: Studies in Naturally Occurring Influenza

Treatment of Influenza

Adult Patients

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

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

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

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

Geriatric Patients

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

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

Pediatric Patients

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

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

Prophylaxis of Influenza

Adult Patients

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

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

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

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

Pediatric Patients

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

CONTRAINDICATIONS

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

PRECAUTIONS

General

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

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

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

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

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

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

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

Hepatic Impairment

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

Renal Impairment

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

Serious Skin/Hypersensitivity Reactions

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

Neuropsychiatric Events

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

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

Information for Patients

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

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

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

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

Drug Interactions

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

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

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

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

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

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility

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

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

non-mutagenic in the Ames test and the L5178Y mouse lymphoma assay with and without enzymatic activation and negative in the SHE cell transformation test.

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

Pregnancy

Pregnancy Category C

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

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

Nursing Mothers

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

Geriatric Use

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

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

Description of Clinical Studies: Studies in Naturally Occurring Influenza: Prophylaxis of Influenza: Adult Patients).

Pediatric Use

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

ANIMAL TOXICOLOGY

In a 2-week study in unweaned rats, administration of a single dose of 1000 mg/kg oseltamivir phosphate to 7-day-old rats resulted in deaths associated with unusually high exposure to the prodrug. However, at 2000 mg/kg, there were no deaths or other significant effects in 14-day-old unweaned rats. Further follow-up investigations of the unexpected deaths of 7-day-old rats at 1000 mg/kg revealed that the concentrations of the prodrug in the brains were approximately 1500-fold those of the brains of adult rats administered the same oral dose of 1000 mg/kg, and those of the active metabolite were approximately 3-fold higher. Plasma levels of the prodrug were 10-fold higher in 7-day-old rats as compared with adult rats. These observations suggest that the levels of oseltamivir in the brains of rats decrease with increasing age and most likely reflect the maturation stage of the blood-brain barrier. No adverse effects occurred at 500 mg/kg/day administered to 7- to 21-day-old rats. At this dosage, the exposure to prodrug was approximately 800-fold the exposure expected in a 1-year-old child.

ADVERSE REACTIONS

Treatment Studies in Adult Patients

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

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

Prophylaxis Studies in Adult Patients

A total of 4187 subjects (adolescents, healthy adults and elderly) participated in phase III prophylaxis studies, of whom 1790 received the recommended dose of 75 mg once daily for up to 6 weeks. Adverse events were qualitatively very similar to those seen in the treatment studies, despite a longer duration of dosing (see **Table 3**). Events reported more frequently in subjects receiving TAMIFLU compared to subjects receiving placebo in prophylaxis studies, and more commonly than in treatment studies, were aches and pains, rhinorrhea, dyspepsia and upper respiratory tract infections. However, the difference in incidence between TAMIFLU and placebo for these events was less than 1%. There

were no clinically relevant differences in the safety profile of the 942 elderly subjects who received TAMIFLU or placebo, compared with the younger population.

Table 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%)

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

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

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

Treatment Studies in Pediatric Patients

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

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

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

Prophylaxis in Pediatric Patients

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

Table 4 Most Frequent Adverse Events Occurring in Children Aged 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%)	-	-

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

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

^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

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

Observed During Clinical Practice

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

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

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

Digestive: Hepatitis, liver function tests abnormal

Cardiac: Arrhythmia

Gastrointestinal disorders: Gastrointestinal bleeding, hemorrhagic colitis

Neurologic: Seizure

Metabolic: Aggravation of diabetes

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

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

Standard Dosage – Treatment of Influenza

Adults and Adolescents

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

Pediatric Patients

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

The recommended oral dose of TAMIFLU for pediatric patients 1 year and older is shown in **Table 5**. TAMIFLU for Oral Suspension may also be used by patients who cannot swallow a capsule. For pediatric patients who cannot swallow capsules, TAMIFLU for Oral Suspension is the preferred formulation. If the for Oral Suspension product is not available, TAMIFLU Capsules may be opened and mixed with sweetened liquids such as regular or sugar-free chocolate syrup.

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

Body Weight (kg)	Body Weight (lbs)	Recommended Dose for 5 Days	Number of Bottles of TAMIFLU for Oral Suspension 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)

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

Standard Dosage – Prophylaxis of Influenza

Adults and Adolescents

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

Pediatric Patients

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

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

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

Body Weight (kg)	Body Weight (lbs)	Recommended Dose for 10 Days	Number of Bottles of TAMIFLU for Oral Suspension 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)

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

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

Special Dosage Instructions

Hepatic Impairment

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

Renal Impairment

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

Treatment of Influenza

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

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

Prophylaxis of Influenza

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

Geriatric Patients

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

Preparation of TAMIFLU for Oral Suspension

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

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

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

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

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

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

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

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

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

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

Body Weight (kg)	Body Weight (lbs)	Total Volume to Compound per patient (mL)
≤15 kg	≤33 lbs	30 mL
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

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

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

Total Volume of Compounded Oral Suspension needed to be Prepared	30 mL	40 mL	50 mL	60 mL
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	29 mL	38.5 mL	48 mL	57 mL

Laboratories)				
---------------	--	--	--	--

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

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

STORAGE OF THE PHARMACY-COMPOUNDED SUSPENSION:

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

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

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

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

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

Table 9 Dosing Chart for Pharmacy-Compounded Suspension from 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

Note: 1 teaspoon = 5 mL

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

HOW SUPPLIED

TAMIFLU Capsules

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

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

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

Storage

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

TAMIFLU for Oral Suspension

Supplied as a white powder blend for constitution to a white tutti-frutti-flavored suspension. Available in glass bottles containing approximately 33 mL of suspension after constitution. Each bottle delivers

NDA 21-087/S-042
NDA 21-246/S-030
January 17, 2008
Page 23

25 mL of suspension equivalent to 300 mg oseltamivir base. Each bottle is supplied with a bottle adapter and 1 oral dispenser (NDC 0004-0810-95).

Storage

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

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

Humco® is a registered trademark of Humco Holding Group, Inc.
Ora-Sweet® SF is a registered trademark of Paddock Laboratories

Distributed by:



Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Licensors:

Gilead Sciences, Inc.
Foster City, California 94404

xxxxxxxx

Rev. January, 2008

Copyright © 1999-200x by Roche Laboratories Inc. All rights reserved.



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.

Who should not take TAMIFLU?

Do not take TAMIFLU if you are allergic to the main ingredient, oseltamivir phosphate, or to any other ingredients of TAMIFLU. Before starting treatment, make sure your healthcare professional knows if you take any other medicines, or are pregnant, planning to become pregnant, or breastfeeding. TAMIFLU is normally not recommended for use during pregnancy or nursing, as the effects on the

unborn child or nursing infant are unknown. TAMIFLU is not recommended for use in children younger than 1 year of age.

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

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

How should I take TAMIFLU?

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

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

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

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

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

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

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

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

What are the possible side effects of TAMIFLU?

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

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

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

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

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

How and where should I store TAMIFLU?

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

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

General advice about prescription medicines:

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

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

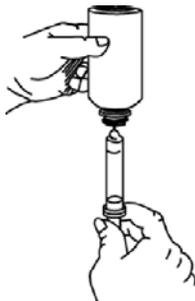
DOSING INSTRUCTIONS FOR PATIENTS:

How Do I Prepare TAMIFLU for Oral Suspension?

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



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



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

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

Please follow instructions carefully to ensure proper dosing.

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

NDA 21-087/S-042
NDA 21-246/S-030
January 17, 2008
Page 28

Distributed by:



Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Licensors:

Gilead Sciences, Inc.
Foster City, California 94404

Rev. January, 2008

Copyright © 1999-200x by Roche Laboratories Inc. All rights reserved.

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

RELENZA® (zanamivir) Inhalation Powder, for oral inhalation
Initial U.S. Approval: 1999

RECENT MAJOR CHANGES

Warnings and Precautions
Neuropsychiatric Events (5.3) February 2008

INDICATIONS AND USAGE

RELENZA, an influenza neuraminidase inhibitor, is indicated for:
Treatment of influenza in patients 7 years of age and older who have been symptomatic for no more than 2 days. (1.1)

Prophylaxis of influenza in patients 5 years of age and older. (1.2)

Important Limitations on Use of RELENZA:

Not recommended for treatment or prophylaxis of influenza in:

- Individuals with underlying airways disease. (5.1)

Not proven effective for:

- Treatment in individuals with underlying airways disease. (1.3)
- Prophylaxis in nursing home residents. (1.3)

Not a substitute for annual influenza vaccination. (1.3)

DOSAGE AND ADMINISTRATION

Indication	Dose
Treatment of Influenza (2.2)	10 mg twice daily for 5 days
Prophylaxis: (2.3)	
Household Setting	10 mg once daily for 10 days
Community Outbreaks	10 mg once daily for 28 days

Note: The 10 mg dose is provided by 2 inhalations (one 5 mg blister per inhalation). (2.1)

DOSAGE FORMS AND STRENGTHS

Four 5 mg blisters of powder on a ROTADISK® for oral inhalation via DISKHALER®. Packaged in carton containing 5 ROTADISKS (total of 10 doses) and 1 DISKHALER inhalation device. (3)

CONTRAINDICATIONS

Do not use in patients with history of allergic reaction to any ingredient of RELENZA, including lactose (which contains milk proteins). (4)

WARNINGS AND PRECAUTIONS

- **Bronchospasm:** Serious, sometimes fatal, cases have occurred. Not recommended in individuals with underlying airways disease. Discontinue RELENZA if bronchospasm or decline in respiratory function develops. (5.1)
- **Allergic Reactions:** Discontinue RELENZA and initiate appropriate treatment if an allergic reaction occurs or is suspected. (5.2)
- **Neuropsychiatric Events:** Patients with influenza, particularly pediatric patients, may be at an increased risk of seizures, confusion, or abnormal behavior early in their illness. Monitor for signs of abnormal behavior. (5.3)
- **High-risk underlying medical conditions:** Safety and effectiveness have not been demonstrated in these patients. (5.4)

ADVERSE REACTIONS

The most common adverse events reported in >1.5% of patients treated with RELENZA and more commonly than in patients treated with placebo are:

- Treatment Studies – sinusitis, dizziness.
- Prophylaxis studies – fever and/or chills, arthralgia and articular rheumatism. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Live attenuated influenza vaccine, intranasal (7):

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

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

Revised: February 2008
RLZ:3PI

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Treatment of Influenza
- 1.2 Prophylaxis of Influenza
- 1.3 Important Limitations on Use of RELENZA

2 DOSAGE AND ADMINISTRATION

- 2.1 Dosing Considerations
- 2.2 Treatment of Influenza
- 2.3 Prophylaxis of Influenza

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Bronchospasm
- 5.2 Allergic Reactions
- 5.3 Neuropsychiatric Events
- 5.4 Limitations of Populations Studied
- 5.5 Bacterial Infections
- 5.6 Importance of Proper Use of DISKHALER

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers

- 8.4 Pediatric Use
- 8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics
- 12.4 Microbiology

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Treatment of Influenza
- 14.2 Prophylaxis of Influenza

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

- 17.1 Bronchospasm
- 17.2 Concomitant Bronchodilator Use
- 17.3 Neuropsychiatric Events
- 17.4 Instructions for Use
- 17.5 Risk of Influenza Transmission to Others
- 17.6 FDA-Approved Patient Labeling and Instructions for Use

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

1

2 **FULL PRESCRIBING INFORMATION**

3 **1 INDICATIONS AND USAGE**

4 **1.1 Treatment of Influenza**

5 RELENZA is indicated for treatment of uncomplicated acute illness due to influenza A
6 and B virus in adults and pediatric patients 7 years of age and older who have been symptomatic
7 for no more than 2 days.

8 **1.2 Prophylaxis of Influenza**

9 RELENZA is indicated for prophylaxis of influenza in adults and pediatric patients
10 5 years of age and older.

11 **1.3 Important Limitations on Use of RELENZA**

- 12 • RELENZA is not recommended for treatment or prophylaxis of influenza in individuals with
13 underlying airways disease (such as asthma or chronic obstructive pulmonary disease) due to
14 risk of serious bronchospasm [*see Warnings and Precautions (5.1)*].
- 15 • RELENZA has not been proven effective for treatment of influenza in individuals with
16 underlying airways disease.
- 17 • RELENZA has not been proven effective for prophylaxis of influenza in the nursing home
18 setting.
- 19 • RELENZA is not a substitute for early influenza vaccination on an annual basis as
20 recommended by the Centers for Disease Control's Immunization Practices Advisory
21 Committee.
- 22 • There is no evidence for efficacy of zanamivir in any illness caused by agents other than
23 influenza virus A and B.
- 24 • Patients should be advised that the use of RELENZA for treatment of influenza has not been
25 shown to reduce the risk of transmission of influenza to others.

26 **2 DOSAGE AND ADMINISTRATION**

27 **2.1 Dosing Considerations**

- 28 • RELENZA is for administration to the respiratory tract by oral inhalation only, using the
29 DISKHALER device provided.
- 30 • The 10 mg dose is provided by 2 inhalations (one 5 mg blister per inhalation).
- 31 • Patients should be instructed in the use of the delivery system. Instructions should include a
32 demonstration whenever possible. If RELENZA is prescribed for children, it should be used
33 only under adult supervision and instruction, and the supervising adult should first be
34 instructed by a healthcare professional [*see Patient Counseling Information (17.3)*].
- 35 • Patients scheduled to use an inhaled bronchodilator at the same time as RELENZA should
36 use their bronchodilator before taking RELENZA [*see Patient Counseling Information*
37 (*17.2*)].

38 **2.2 Treatment of Influenza**

- 39 • The recommended dose of RELENZA for treatment of influenza in adults and pediatric
40 patients ages 7 years of age and older is 10 mg twice daily (approximately 12 hours apart) for
41 5 days.
- 42 • Two doses should be taken on the first day of treatment whenever possible provided there is
43 at least 2 hours between doses.
- 44 • On subsequent days, doses should be about 12 hours apart (e.g., morning and evening) at
45 approximately the same time each day.
- 46 • The safety and efficacy of repeated treatment courses have not been studied.

47 **2.3 Prophylaxis of Influenza**

48 Household Setting:

- 49 • The recommended dose of RELENZA for prophylaxis of influenza in adults and pediatric
50 patients 5 years of age and older in a household setting is 10 mg once daily for 10 days.
- 51 • The dose should be administered at approximately the same time each day.
- 52 • There are no data on the effectiveness of prophylaxis with RELENZA in a household setting
53 when initiated more than 1.5 days after the onset of signs or symptoms in the index case.

54 Community Outbreaks:

- 55 • The recommended dose of RELENZA for prophylaxis of influenza in adults and adolescents
56 in a community setting is 10 mg once daily for 28 days.
- 57 • The dose should be administered at approximately the same time each day.
- 58 • There are no data on the effectiveness of prophylaxis with RELENZA in a community
59 outbreak when initiated more than 5 days after the outbreak was identified in the community.
- 60 • The safety and effectiveness of prophylaxis with RELENZA have not been evaluated for
61 longer than 28 days' duration.

62 **3 DOSAGE FORMS AND STRENGTHS**

63 Four 5 mg blisters of powder on a ROTADISK for oral inhalation via DISKHALER.
64 Packaged in carton containing 5 ROTADISKS (total of 10 doses) and 1 DISKHALER inhalation
65 device [see *How Supplied/Storage and Handling (16)*].

66 **4 CONTRAINDICATIONS**

67 Do not use in patients with history of allergic reaction to any ingredient of RELENZA
68 including lactose (which contains milk proteins) [see *Warnings and Precautions (5.2)*,
69 *Description (11)*].

70 **5 WARNINGS AND PRECAUTIONS**

71 **5.1 Bronchospasm**

72 RELENZA is not recommended for treatment or prophylaxis of influenza in individuals
73 with underlying airways disease (such as asthma or chronic obstructive pulmonary disease).

74 Serious cases of bronchospasm, including fatalities, have been reported during treatment
75 with RELENZA in patients with and without underlying airways disease. Many of these cases
76 were reported during postmarketing and causality was difficult to assess.

77 RELENZA should be discontinued in any patient who develops bronchospasm or decline
78 in respiratory function; immediate treatment and hospitalization may be required.

79 Some patients without prior pulmonary disease may also have respiratory abnormalities
80 from acute respiratory infection that could resemble adverse drug reactions or increase patient
81 vulnerability to adverse drug reactions.

82 Bronchospasm was documented following administration of zanamivir in 1 of 13 patients
83 with mild or moderate asthma (but without acute influenza-like illness) in a Phase I study. In a
84 Phase III study in patients with acute influenza-like illness superimposed on underlying asthma
85 or chronic obstructive pulmonary disease, 10% (24 of 244) of patients on zanamivir and 9% (22
86 of 237) on placebo experienced a greater than 20% decline in FEV₁ following treatment for
87 5 days.

88 If use of RELENZA is considered for a patient with underlying airways disease, the
89 potential risks and benefits should be carefully weighed. If a decision is made to prescribe
90 RELENZA for such a patient, this should be done only under conditions of careful monitoring of
91 respiratory function, close observation, and appropriate supportive care including availability of
92 fast-acting bronchodilators.

93 **5.2 Allergic Reactions**

94 Allergic-like reactions, including oropharyngeal edema, serious skin rashes, and
95 anaphylaxis have been reported in postmarketing experience with RELENZA. RELENZA
96 should be stopped and appropriate treatment instituted if an allergic reaction occurs or is
97 suspected.

98 **5.3 Neuropsychiatric Events**

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

103 There have been postmarketing reports (mostly from Japan) of delirium and abnormal
104 behavior leading to injury in patients with influenza who were receiving neuraminidase
105 inhibitors, including RELENZA. Because these events were reported voluntarily during clinical
106 practice, estimates of frequency cannot be made, but they appear to be uncommon based on
107 usage data for RELENZA. These events were reported primarily among pediatric patients and
108 often had an abrupt onset and rapid resolution. The contribution of RELENZA to these events
109 has not been established. Patients with influenza should be closely monitored for signs of
110 abnormal behavior. If neuropsychiatric symptoms occur, the risks and benefits of continuing
111 treatment should be evaluated for each patient.

112 **5.4 Limitations of Populations Studied**

113 Safety and efficacy have not been demonstrated in patients with high-risk underlying
114 medical conditions. No information is available regarding treatment of influenza in patients with
115 any medical condition sufficiently severe or unstable to be considered at imminent risk of
116 requiring inpatient management.

117 **5.5 Bacterial Infections**

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

121 **5.6 Importance of Proper Use of DISKHALER**

122 Effective and safe use of RELENZA requires proper use of the DISKHALER to inhale
123 the drug. Prescribers should carefully evaluate the ability of young children to use the delivery
124 system if use of RELENZA is considered [*see Use in Specific Populations (8.4)*].

125 **6 ADVERSE REACTIONS**

126 See Warnings and Precautions for information about risk of serious adverse events such
127 as bronchospasm (5.1) and allergic-like reactions (5.2), and for safety information in patients
128 with underlying airways disease (5.1).

129 **6.1 Clinical Trials Experience**

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

133 The placebo used in clinical studies consisted of inhaled lactose powder, which is also the
134 vehicle for the active drug; therefore, some adverse events occurring at similar frequencies in
135 different treatment groups could be related to lactose vehicle inhalation.

136 Treatment of Influenza: Clinical Trials in Adults and Adolescents: Adverse events
137 that occurred with an incidence $\geq 1.5\%$ in treatment studies are listed in Table 1. This table shows
138 adverse events occurring in patients ≥ 12 years of age receiving RELENZA 10 mg inhaled twice
139 daily, RELENZA in all inhalation regimens, and placebo inhaled twice daily (where placebo
140 consisted of the same lactose vehicle used in RELENZA).

141

142 **Table 1. Summary of Adverse Events $\geq 1.5\%$ Incidence During Treatment in Adults and**
 143 **Adolescents**

Adverse Event	RELENZA		Placebo (Lactose Vehicle) (n = 1,520)
	10 mg b.i.d. Inhaled (n = 1,132)	All Dosing Regimens* (n = 2,289)	
Body as a whole			
Headaches	2%	2%	3%
Digestive			
Diarrhea	3%	3%	4%
Nausea	3%	3%	3%
Vomiting	1%	1%	2%
Respiratory			
Nasal signs and symptoms	2%	3%	3%
Bronchitis	2%	2%	3%
Cough	2%	2%	3%
Sinusitis	3%	2%	2%
Ear, nose, and throat infections	2%	1%	2%
Nervous system			
Dizziness	2%	1%	<1%

144 * Includes studies where RELENZA was administered intranasally (6.4 mg 2 to 4 times per day
 145 in addition to inhaled preparation) and/or inhaled more frequently (q.i.d.) than the currently
 146 recommended dose.

147
 148 Additional adverse reactions occurring in less than 1.5% of patients receiving RELENZA
 149 included malaise, fatigue, fever, abdominal pain, myalgia, arthralgia, and urticaria.

150 The most frequent laboratory abnormalities in Phase III treatment studies included elevations
 151 of liver enzymes and CPK, lymphopenia, and neutropenia. These were reported in similar
 152 proportions of zanamivir and lactose vehicle placebo recipients with acute influenza-like illness.

153 *Clinical Trials in Pediatric Patients:* Adverse events that occurred with an incidence
 154 $\geq 1.5\%$ in children receiving treatment doses of RELENZA in 2 Phase III studies are listed in
 155 Table 2. This table shows adverse events occurring in pediatric patients 5 to 12 years old
 156 receiving RELENZA 10 mg inhaled twice daily and placebo inhaled twice daily (where placebo
 157 consisted of the same lactose vehicle used in RELENZA).

158

159 **Table 2. Summary of Adverse Events $\geq 1.5\%$ Incidence During Treatment in Pediatric**
 160 **Patients***

Adverse Event	RELENZA 10 mg b.i.d. Inhaled (n = 291)	Placebo (Lactose Vehicle) (n = 318)
Respiratory		
Ear, nose, and throat infections	5%	5%
Ear, nose, and throat hemorrhage	<1%	2%
Asthma	<1%	2%
Cough	<1%	2%
Digestive		
Vomiting	2%	3%
Diarrhea	2%	2%
Nausea	<1%	2%

161 * Includes a subset of patients receiving RELENZA for treatment of influenza in a prophylaxis
 162 study.

163
 164 In 1 of the 2 studies described in Table 2, some additional information is available from
 165 children (5 to 12 years old) without acute influenza-like illness who received an investigational
 166 prophylaxis regimen of RELENZA; 132 children received RELENZA and 145 children received
 167 placebo. Among these children, nasal signs and symptoms (zanamivir 20%, placebo 9%), cough
 168 (zanamivir 16%, placebo 8%), and throat/tonsil discomfort and pain (zanamivir 11%, placebo
 169 6%) were reported more frequently with RELENZA than placebo. In a subset with chronic
 170 pulmonary disease, lower respiratory adverse events (described as asthma, cough, or viral
 171 respiratory infections which could include influenza-like symptoms) were reported in 7 of 7
 172 zanamivir recipients and 5 of 12 placebo recipients.

173 Prophylaxis of Influenza: Family/Household Prophylaxis Studies: Adverse events
 174 that occurred with an incidence of $\geq 1.5\%$ in the 2 prophylaxis studies are listed in Table 3. This
 175 table shows adverse events occurring in patients ≥ 5 years of age receiving RELENZA 10 mg
 176 inhaled once daily for 10 days.

177

178 **Table 3. Summary of Adverse Events $\geq 1.5\%$ Incidence During 10-Day Prophylaxis Studies**
 179 **in Adults, Adolescents, and Children***

Adverse Event	Contact Cases	
	RELENZA (n = 1,068)	Placebo (n = 1,059)
Lower respiratory		
Viral respiratory infections	13%	19%
Cough	7%	9%
Neurologic		
Headaches	13%	14%
Ear, nose, and throat		
Nasal signs and symptoms	12%	12%
Throat and tonsil discomfort and pain	8%	9%
Nasal inflammation	1%	2%
Musculoskeletal		
Muscle pain	3%	3%
Endocrine and metabolic		
Feeding problems (decreased or increased appetite and anorexia)	2%	2%
Gastrointestinal		
Nausea and vomiting	1%	2%
Non-site specific		
Malaise and fatigue	5%	5%
Temperature regulation disturbances (fever and/or chills)	5%	4%

180 * In prophylaxis studies, symptoms associated with influenza-like illness were captured as
 181 adverse events; subjects were enrolled during a winter respiratory season during which time
 182 any symptoms that occurred were captured as adverse events.

183
 184 *Community Prophylaxis Studies:* Adverse events that occurred with an incidence of
 185 $\geq 1.5\%$ in 2 prophylaxis studies are listed in Table 4. This table shows adverse events occurring
 186 in patients ≥ 5 years of age receiving RELENZA 10 mg inhaled once daily for 28 days.

187
188
189

Table 4. Summary of Adverse Events ≥1.5% Incidence During 28-Day Prophylaxis Studies in Adults, Adolescents, and Children*

Adverse Event	RELENZA (n = 2,231)	Placebo (n = 2,239)
Neurologic		
Headaches	24%	26%
Ear, nose, and throat		
Throat and tonsil discomfort and pain	19%	20%
Nasal signs and symptoms	12%	13%
Ear, nose, and throat infections	2%	2%
Lower respiratory		
Cough	17%	18%
Viral respiratory infections	3%	4%
Musculoskeletal		
Muscle pain	8%	8%
Musculoskeletal pain	6%	6%
Arthralgia and articular rheumatism	2%	<1%
Endocrine and metabolic		
Feeding problems (decreased or increased appetite and anorexia)	4%	4%
Gastrointestinal		
Nausea and vomiting	2%	3%
Diarrhea	2%	2%
Non-site specific		
Temperature regulation disturbances (fever and/or chills)	9%	10%
Malaise & fatigue	8%	8%

190 * In prophylaxis studies, symptoms associated with influenza-like illness were captured as
191 adverse events; subjects were enrolled during a winter respiratory season during which time
192 any symptoms that occurred were captured as adverse events.

193

194 **6.2 Postmarketing Experience**

195 In addition to adverse events reported from clinical trials, the following events have been
196 identified during postmarketing use of zanamivir (RELENZA). Because they are reported
197 voluntarily from a population of unknown size, estimates of frequency cannot be made. These
198 events have been chosen for inclusion due to a combination of their seriousness, frequency of
199 reporting, or potential causal connection to zanamivir (RELENZA).

200 Allergic Reactions: Allergic or allergic-like reaction, including oropharyngeal edema
201 [see *Warnings and Precautions* (5.2)].

202 **Psychiatric:** Delirium, including symptoms such as altered level of consciousness,
203 confusion, abnormal behavior, delusions, hallucinations, agitation, anxiety, nightmares [*see*
204 *Warnings and Precautions (5.3)*].

205 **Cardiac:** Arrhythmias, syncope.

206 **Neurologic:** Seizures.

207 **Respiratory:** Bronchospasm, dyspnea [*see Warnings and Precautions (5.1)*].

208 **Skin:** Facial edema; rash, including serious cutaneous reactions; urticaria [*see Warnings*
209 *and Precautions (5.2)*].

210 **7 DRUG INTERACTIONS**

211 Zanamivir is not a substrate nor does it affect cytochrome P450 (CYP) isoenzymes
212 (CYP1A1/2, 2A6, 2C9, 2C18, 2D6, 2E1, and 3A4) in human liver microsomes. No clinically
213 significant pharmacokinetic drug interactions are predicted based on data from in vitro studies.

214 The concurrent use of RELENZA with live attenuated influenza vaccine (LAIV)
215 intranasal has not been evaluated. However, because of potential interference between these
216 products, LAIV should not be administered within 2 weeks before or 48 hours after
217 administration of RELENZA, unless medically indicated. The concern about possible
218 interference arises from the potential for antiviral drugs to inhibit replication of live vaccine
219 virus.

220 Trivalent inactivated influenza vaccine can be administered at any time relative to use of
221 RELENZA [*see Clinical Pharmacology (12.4)*].

222 **8 USE IN SPECIFIC POPULATIONS**

223 **8.1 Pregnancy**

224 Pregnancy Category C. There are no adequate and well-controlled studies of zanamivir in
225 pregnant women. Zanamivir should be used during pregnancy only if the potential benefit
226 justifies the potential risk to the fetus.

227 Embryo/fetal development studies were conducted in rats (dosed from days 6 to 15 of
228 pregnancy) and rabbits (dosed from days 7 to 19 of pregnancy) using the same IV doses (1, 9,
229 and 90 mg/kg/day). Pre- and post-natal developmental studies were performed in rats (dosed
230 from day 16 of pregnancy until litter day 21 to 23). No malformations, maternal toxicity, or
231 embryotoxicity were observed in pregnant rats or rabbits and their fetuses. Because of
232 insufficient blood sampling timepoints in rat and rabbit reproductive toxicity studies, AUC
233 values were not available. In a subchronic study in rats at the 90 mg/kg/day IV dose, the AUC
234 values were greater than 300 times the human exposure at the proposed clinical dose.

235 An additional embryo/fetal study, in a different strain of rat, was conducted using
236 subcutaneous administration of zanamivir, 3 times daily, at doses of 1, 9, or 80 mg/kg during
237 days 7 to 17 of pregnancy. There was an increase in the incidence rates of a variety of minor
238 skeleton alterations and variants in the exposed offspring in this study. Based on AUC
239 measurements, the 80 mg/kg dose produced an exposure greater than 1,000 times the human
240 exposure at the proposed clinical dose. However, in most instances, the individual incidence rate

241 of each skeletal alteration or variant remained within the background rates of the historical
242 occurrence in the strain studied.

243 Zanamivir has been shown to cross the placenta in rats and rabbits. In these animals, fetal
244 blood concentrations of zanamivir were significantly lower than zanamivir concentrations in the
245 maternal blood.

246 **8.3 Nursing Mothers**

247 Studies in rats have demonstrated that zanamivir is excreted in milk. However, nursing
248 mothers should be instructed that it is not known whether zanamivir is excreted in human milk.
249 Because many drugs are excreted in human milk, caution should be exercised when RELENZA
250 is administered to a nursing mother.

251 **8.4 Pediatric Use**

252 Treatment of Influenza: Safety and effectiveness of RELENZA for treatment of
253 influenza have not been assessed in pediatric patients less than 7 years of age, but were studied in
254 a Phase III treatment study in pediatric patients, where 471 children 5 to 12 years of age received
255 zanamivir or placebo [*see Clinical Studies 14.1*]. Adolescents were included in the three
256 principal Phase III adult treatment studies. In these studies, 67 patients were 12 to 16 years of
257 age. No definite differences in safety and efficacy were observed between these adolescent
258 patients and young adults.

259 In a Phase I study of 16 children ages 6 to 12 years with signs and symptoms of
260 respiratory disease, 4 did not produce a measurable peak inspiratory flow rate (PIFR) through the
261 DISKHALER (3 with no adequate inhalation on request, 1 with missing data), 9 had measurable
262 PIFR on each of 2 inhalations, and 3 achieved measurable PIFR on only 1 of 2 inhalations.
263 Neither of two 6-year-olds and one of two 7-year-olds produced measurable PIFR. Overall, 8 of
264 the 16 children (including all those under 8 years old) either did not produce measurable
265 inspiratory flow through the DISKHALER or produced peak inspiratory flow rates below the
266 60 L/min considered optimal for the device under standardized in vitro testing; lack of
267 measurable flow rate was related to low or undetectable serum concentrations [*see Clinical*
268 *Pharmacology (12.3), Clinical Studies (14.1)*]. Prescribers should carefully evaluate the ability
269 of young children to use the delivery system if prescription of RELENZA is considered.

270 Prophylaxis of Influenza: The safety and effectiveness of RELENZA for prophylaxis of
271 influenza have been studied in 4 Phase III studies where 273 children 5 to 11 years of age and
272 239 adolescents 12 to 16 years of age received RELENZA. No differences in safety and
273 effectiveness were observed between pediatric and adult subjects [*see Clinical Studies (14.2)*].

274 **8.5 Geriatric Use**

275 Of the total number of patients in 6 clinical studies of RELENZA for treatment of
276 influenza, 59 patients were 65 years of age and older, while 24 patients were 75 years of age and
277 older. Of the total number of patients in 4 clinical studies of RELENZA for prophylaxis of
278 influenza in households and community settings, 954 patients were 65 years of age and older,
279 while 347 patients were 75 years of age and older. No overall differences in safety or
280 effectiveness were observed between these patients and younger patients, and other reported

281 clinical experience has not identified differences in responses between the elderly and younger
282 patients, but greater sensitivity of some older individuals cannot be ruled out. Elderly patients
283 may need assistance with use of the device.

284 In 2 additional studies of RELENZA for prophylaxis of influenza in the nursing home
285 setting, efficacy was not demonstrated [see *Indications and Usage (1.3)*].

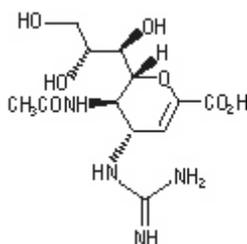
286 10 OVERDOSAGE

287 There have been no reports of overdose from administration of RELENZA.

288 11 DESCRIPTION

289 The active component of RELENZA is zanamivir. The chemical name of zanamivir is 5-
290 (acetylamino)-4-[(aminoiminomethyl)-amino]-2,6-anhydro-3,4,5-trideoxy-D-glycero-D-galacto-
291 non-2-enonic acid. It has a molecular formula of $C_{12}H_{20}N_4O_7$ and a molecular weight of 332.3. It
292 has the following structural formula:

293



294

295 Zanamivir is a white to off-white powder for oral inhalation with a solubility of
296 approximately 18 mg/mL in water at 20°C.

297 RELENZA is for administration to the respiratory tract by oral inhalation only. Each
298 RELENZA ROTADISK contains 4 regularly spaced double-foil blisters with each blister
299 containing a powder mixture of 5 mg of zanamivir and 20 mg of lactose (which contains milk
300 proteins). The contents of each blister are inhaled using a specially designed breath-activated
301 plastic device for inhaling powder called the DISKHALER. After a RELENZA ROTADISK is
302 loaded into the DISKHALER, a blister that contains medication is pierced and the zanamivir is
303 dispersed into the air stream created when the patient inhales through the mouthpiece. The
304 amount of drug delivered to the respiratory tract will depend on patient factors such as
305 inspiratory flow. Under standardized in vitro testing, RELENZA ROTADISK delivers 4 mg of
306 zanamivir from the DISKHALER device when tested at a pressure drop of 3 kPa (corresponding
307 to a flow rate of about 62 to 65 L/min) for 3 seconds.

308 12 CLINICAL PHARMACOLOGY

309 12.1 Mechanism of Action

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

311 12.3 Pharmacokinetics

312 Absorption and Bioavailability: Pharmacokinetic studies of orally inhaled zanamivir
313 indicate that approximately 4% to 17% of the inhaled dose is systemically absorbed. The peak

314 serum concentrations ranged from 17 to 142 ng/mL within 1 to 2 hours following a 10 mg dose.
315 The area under the serum concentration versus time curve (AUC_{∞}) ranged from 111 to
316 1,364 ng•hr/mL.

317 Distribution: Zanamivir has limited plasma protein binding (<10%).

318 Metabolism: Zanamivir is renally excreted as unchanged drug. No metabolites have
319 been detected in humans.

320 Elimination: The serum half-life of zanamivir following administration by oral inhalation
321 ranges from 2.5 to 5.1 hours. It is excreted unchanged in the urine with excretion of a single dose
322 completed within 24 hours. Total clearance ranges from 2.5 to 10.9 L/hr. Unabsorbed drug is
323 excreted in the feces.

324 Impaired Hepatic Function: The pharmacokinetics of zanamivir have not been studied
325 in patients with impaired hepatic function.

326 Impaired Renal Function: After a single intravenous dose of 4 mg or 2 mg of zanamivir
327 in volunteers with mild/moderate or severe renal impairment, respectively, significant decreases
328 in renal clearance (and hence total clearance: normals 5.3 L/hr, mild/moderate 2.7 L/hr, and
329 severe 0.8 L/hr; median values) and significant increases in half-life (normals 3.1 hr,
330 mild/moderate 4.7 hr, and severe 18.5 hr; median values) and systemic exposure were observed.
331 Safety and efficacy have not been documented in the presence of severe renal insufficiency. Due
332 to the low systemic bioavailability of zanamivir following oral inhalation, no dosage adjustments
333 are necessary in patients with renal impairment. However, the potential for drug accumulation
334 should be considered.

335 Pediatric Patients: The pharmacokinetics of zanamivir were evaluated in pediatric
336 patients with signs and symptoms of respiratory illness. Sixteen patients, 6 to 12 years of age,
337 received a single dose of 10 mg zanamivir dry powder via DISKHALER. Five patients had either
338 undetectable zanamivir serum concentrations or had low drug concentrations (8.32 to
339 10.38 ng/mL) that were not detectable after 1.5 hours. Eleven patients had C_{max} median values of
340 43 ng/mL (range 15 to 74) and AUC_{∞} median values of 167 ng•hr/mL (range 58 to 279). Low or
341 undetectable serum concentrations were related to lack of measurable PIFR in individual patients
342 [see *Use in Specific Populations (8.4), Clinical Studies (14.1)*].

343 Geriatric Patients: The pharmacokinetics of zanamivir have not been studied in patients
344 over 65 years of age [see *Use in Specific Populations (8.5)*].

345 Gender, Race, and Weight: In a population pharmacokinetic analysis in patient
346 studies, no clinically significant differences in serum concentrations and/or pharmacokinetic
347 parameters (V/F , CL/F , k_a , AUC_{0-3} , C_{max} , T_{max} , CL_r , and % excreted in urine) were observed
348 when demographic variables (gender, age, race, and weight) and indices of infection (laboratory
349 evidence of infection, overall symptoms, symptoms of upper respiratory illness, and viral titers)
350 were considered. There were no significant correlations between measures of systemic exposure
351 and safety parameters.

352 **12.4 Microbiology**

353 Mechanism of Action: Zanamivir is an inhibitor of influenza virus neuraminidase
354 affecting release of viral particles.

355 Antiviral Activity: The antiviral activity of zanamivir against laboratory and clinical
356 isolates of influenza virus was determined in cell culture assays. The concentrations of zanamivir
357 required for inhibition of influenza virus were highly variable depending on the assay method
358 used and virus isolate tested. The 50% and 90% effective concentrations (EC₅₀ and EC₉₀) of
359 zanamivir were in the range of 0.005 to 16.0 μM and 0.05 to >100 μM, respectively
360 (1 μM = 0.33 mcg/mL). The relationship between the cell culture inhibition of influenza virus by
361 zanamivir and the inhibition of influenza virus replication in humans has not been established.

362 Resistance: Influenza viruses with reduced susceptibility to zanamivir have been
363 selected in cell culture by multiple passages of the virus in the presence of increasing
364 concentrations of the drug. Genetic analysis of these viruses showed that the reduced
365 susceptibility in cell culture to zanamivir is associated with mutations that result in amino acid
366 changes in the viral neuraminidase or viral hemagglutinin or both. Resistance mutations selected
367 in cell culture which result in neuraminidase amino acid substitutions include E119G/A/D and
368 R292K. Mutations selected in cell culture in hemagglutinin include: K68R, G75E, E114K,
369 N145S, S165N, S186F, N199S, and K222T.

370 In an immunocompromised patient infected with influenza B virus, a variant virus
371 emerged after treatment with an investigational nebulized solution of zanamivir for 2 weeks.
372 Analysis of this variant showed a hemagglutinin substitution (T198I) which resulted in a reduced
373 affinity for human cell receptors, and a substitution in the neuraminidase active site (R152K)
374 which reduced the enzyme's activity to zanamivir by 1,000-fold. Insufficient information is
375 available to characterize the risk of emergence of zanamivir resistance in clinical use.

376 Cross-Resistance: Cross-resistance has been observed between some
377 zanamivir-resistant and some oseltamivir-resistant influenza virus mutants generated in cell
378 culture. However, some of the in cell culture zanamivir-induced resistance mutations,
379 E119G/A/D and R292K, occurred at the same neuraminidase amino acid positions as in the
380 clinical isolates resistant to oseltamivir, E119V and R292K. No studies have been performed to
381 assess risk of emergence of cross-resistance during clinical use.

382 Influenza Vaccine Interaction Study: An interaction study (n = 138) was conducted to
383 evaluate the effects of zanamivir (10 mg once daily) on the serological response to a single dose
384 of trivalent inactivated influenza vaccine, as measured by hemagglutination inhibition titers.
385 There was no difference in hemagglutination inhibition antibody titers at 2 weeks and 4 weeks
386 after vaccine administration between zanamivir and placebo recipients.

387 Influenza Challenge Studies: Antiviral activity of zanamivir was supported for
388 infection with influenza A virus, and to a more limited extent for infection with influenza B
389 virus, by Phase I studies in volunteers who received intranasal inoculations of challenge strains
390 of influenza virus, and received an intranasal formulation of zanamivir or placebo starting before
391 or shortly after viral inoculation.

392 **13 NONCLINICAL TOXICOLOGY**

393 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

394 Carcinogenesis: In 2-year carcinogenicity studies conducted in rats and mice using a
395 powder formulation administered through inhalation, zanamivir induced no statistically
396 significant increases in tumors over controls. The maximum daily exposures in rats and mice
397 were approximately 23 to 25 and 20 to 22 times, respectively, greater than those in humans at the
398 proposed clinical dose based on AUC comparisons.

399 Mutagenesis: Zanamivir was not mutagenic in in vitro and in vivo genotoxicity assays
400 which included bacterial mutation assays in *S. typhimurium* and *E. coli*, mammalian mutation
401 assays in mouse lymphoma, chromosomal aberration assays in human peripheral blood
402 lymphocytes, and the in vivo mouse bone marrow micronucleus assay.

403 Impairment of Fertility: The effects of zanamivir on fertility and general reproductive
404 performance were investigated in male (dosed for 10 weeks prior to mating, and throughout
405 mating, gestation/lactation, and shortly after weaning) and female rats (dosed for 3 weeks prior
406 to mating through Day 19 of pregnancy, or Day 21 post partum) at IV doses 1, 9, and
407 90 mg/kg/day. Zanamivir did not impair mating or fertility of male or female rats, and did not
408 affect the sperm of treated male rats. The reproductive performance of the F1 generation born to
409 female rats given zanamivir was not affected. Based on a subchronic study in rats at a
410 90 mg/kg/day IV dose, AUC values ranged between 142 and 199 mcg•hr/mL (>300 times the
411 human exposure at the proposed clinical dose).

412 **14 CLINICAL STUDIES**

413 **14.1 Treatment of Influenza**

414 Adults and Adolescents: The efficacy of RELENZA 10 mg inhaled twice daily for
415 5 days in the treatment of influenza has been evaluated in placebo-controlled studies conducted
416 in North America, the Southern Hemisphere, and Europe during their respective influenza
417 seasons. The magnitude of treatment effect varied between studies, with possible relationships to
418 population-related factors including amount of symptomatic relief medication used.

419 Populations Studied: The principal Phase III studies enrolled 1,588 patients ages
420 12 years and older (median age 34 years, 49% male, 91% Caucasian), with uncomplicated
421 influenza-like illness within 2 days of symptom onset. Influenza was confirmed by culture,
422 hemagglutination inhibition antibodies, or investigational direct tests. Of 1,164 patients with
423 confirmed influenza, 89% had influenza A and 11% had influenza B. These studies served as the
424 principal basis for efficacy evaluation, with more limited Phase II studies providing supporting
425 information where necessary. Following randomization to either zanamivir or placebo (inhaled
426 lactose vehicle), all patients received instruction and supervision by a healthcare professional for
427 the initial dose.

428 Principal Results: The definition of time to improvement in major symptoms of
429 influenza included no fever and self-assessment of “none” or “mild” for headache, myalgia,
430 cough, and sore throat. A Phase II and a Phase III study conducted in North America (total of

431 over 600 influenza-positive patients) suggested up to 1 day of shortening of median time to this
432 defined improvement in symptoms in patients receiving zanamivir compared with placebo,
433 although statistical significance was not reached in either of these studies. In a study conducted
434 in the Southern Hemisphere (321 influenza-positive patients), a 1.5-day difference in median
435 time to symptom improvement was observed. Additional evidence of efficacy was provided by
436 the European study.

437 **Other Findings:** There was no consistent difference in treatment effect in patients
438 with influenza A compared with influenza B; however, these trials enrolled smaller numbers of
439 patients with influenza B and thus provided less evidence in support of efficacy in influenza B.

440 In general, patients with lower temperature (e.g., 38.2°C or less) or investigator-rated as
441 having less severe symptoms at entry derived less benefit from therapy.

442 No consistent treatment effect was demonstrated in patients with underlying chronic
443 medical conditions, including respiratory or cardiovascular disease [*see Warnings and*
444 *Precautions (5.3)*].

445 No consistent differences in rate of development of complications were observed
446 between treatment groups.

447 Some fluctuation of symptoms was observed after the primary study endpoint in both
448 treatment groups.

449 **Pediatric Patients:** The efficacy of RELENZA 10 mg inhaled twice daily for 5 days in
450 the treatment of influenza in pediatric patients has been evaluated in a placebo-controlled study
451 conducted in North America and Europe, enrolling 471 patients, ages 5 to 12 years (55% male,
452 90% Caucasian), within 36 hours of symptom onset. Of 346 patients with confirmed influenza,
453 65% had influenza A and 35% had influenza B. The definition of time to improvement included
454 no fever and parental assessment of no or mild cough and absent/minimal muscle and joint aches
455 or pains, sore throat, chills/feverishness, and headache. Median time to symptom improvement
456 was 1 day shorter in patients receiving zanamivir compared with placebo. No consistent
457 differences in rate of development of complications were observed between treatment groups.
458 Some fluctuation of symptoms was observed after the primary study endpoint in both treatment
459 groups.

460 Although this study was designed to enroll children ages 5 to 12 years, the product is
461 indicated only for children 7 years of age and older. This evaluation is based on the combination
462 of lower estimates of treatment effect in 5- and 6-year-olds compared with the overall study
463 population, and evidence of inadequate inhalation through the DISKHALER in a
464 pharmacokinetic study [*see Use in Specific Populations (8.4), Clinical Pharmacology (12.3)*].

465 **14.2 Prophylaxis of Influenza**

466 The efficacy of RELENZA in preventing naturally occurring influenza illness has been
467 demonstrated in 2 post-exposure prophylaxis studies in households and 2 seasonal prophylaxis
468 studies during community outbreaks of influenza. The primary efficacy endpoint in these studies
469 was the incidence of symptomatic, laboratory-confirmed influenza, defined as the presence of 2
470 or more of the following symptoms: oral temperature $\geq 100^{\circ}\text{F}/37.8^{\circ}\text{C}$ or feverishness, cough,

471 headache, sore throat, and myalgia; and laboratory confirmation of influenza A or B by culture,
472 PCR, or seroconversion (defined as a 4-fold increase in convalescent antibody titer from
473 baseline).

474 **Household Prophylaxis Studies:** Two studies assessed post-exposure prophylaxis in
475 household contacts of an index case. Within 1.5 days of onset of symptoms in an index case,
476 each household (including all family members ≥ 5 years of age) was randomized to RELENZA
477 10 mg inhaled once daily or placebo inhaled once daily for 10 days. In the first study only, each
478 index case was randomized to RELENZA 10 mg inhaled twice daily for 5 days or inhaled
479 placebo twice daily for 5 days. In this study, the proportion of households with at least 1 new
480 case of symptomatic laboratory-confirmed influenza was reduced from 19.0% (32 of
481 168 households) for the placebo group to 4.1% (7 of 169 households) for the group receiving
482 RELENZA.

483 In the second study, index cases were not treated. The incidence of symptomatic
484 laboratory-confirmed influenza was reduced from 19.0% (46 of 242 households) for the placebo
485 group to 4.1% (10 of 245 households) for the group receiving RELENZA.

486 **Seasonal Prophylaxis Studies:** Two seasonal prophylaxis studies assessed RELENZA
487 10 mg inhaled once daily versus placebo inhaled once daily for 28 days during community
488 outbreaks. The first study enrolled subjects 18 years of age or greater (mean age 29 years) from 2
489 university communities. The majority of subjects were unvaccinated (86%). In this study, the
490 incidence of symptomatic laboratory-confirmed influenza was reduced from 6.1% (34 of 554)
491 for the placebo group to 2.0% (11 of 553) for the group receiving RELENZA.

492 The second seasonal prophylaxis study enrolled subjects 12 to 94 years of age (mean age
493 60 years) with 56% of them older than 65 years of age. Sixty-seven percent of the subjects were
494 vaccinated. In this study, the incidence of symptomatic laboratory-confirmed influenza was
495 reduced from 1.4% (23 of 1,685) for the placebo group to 0.2% (4 of 1,678) for the group
496 receiving RELENZA.

497 **16 HOW SUPPLIED/STORAGE AND HANDLING**

498 RELENZA is supplied in a circular double-foil pack (a ROTADISK) containing 4 blisters
499 of the drug. Five ROTADISKS are packaged in a white polypropylene tube. The tube is
500 packaged in a carton with 1 blue and gray DISKHALER inhalation device (NDC 0173-0681-01).

501 **Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP**
502 **Controlled Room Temperature).** Keep out of reach of children. Do not puncture any
503 RELENZA ROTADISK blister until taking a dose using the DISKHALER.

504 **17 PATIENT COUNSELING INFORMATION**

505 *See FDA-Approved Patient Labeling (17.6).*

506 **17.1 Bronchospasm**

507 **Patients should be advised of the risk of bronchospasm, especially in the setting of**
508 **underlying airways disease, and should stop RELENZA and contact their physician if they**
509 **experience increased respiratory symptoms during treatment such as worsening wheezing,**

510 shortness of breath, or other signs or symptoms of bronchospasm [see Warnings and
511 Precautions (5.1)]. If a decision is made to prescribe RELENZA for a patient with asthma
512 or chronic obstructive pulmonary disease, the patient should be made aware of the risks
513 and should have a fast-acting bronchodilator available.

514 **17.2 Concomitant Bronchodilator Use**

515 Patients scheduled to take inhaled bronchodilators at the same time as RELENZA should
516 be advised to use their bronchodilators before taking RELENZA.

517 **17.3 Neuropsychiatric Events**

518 Patients with influenza (the flu), particularly children and adolescents, may be at an
519 increased risk of seizures, confusion, or abnormal behavior early in their illness. These events
520 may occur after beginning RELENZA or may occur when flu is not treated. These events are
521 uncommon but may result in accidental injury to the patient. Therefore, patients should be
522 observed for signs of unusual behavior and a healthcare professional should be contacted
523 immediately if the patient shows any signs of unusual behavior [see Warnings and Precautions
524 (5.3)].

525 **17.4 Instructions for Use**

526 Patients should be instructed in use of the delivery system. Instructions should include a
527 demonstration whenever possible. For the proper use of RELENZA, the patient should read and
528 follow carefully the accompanying Patient Instructions for Use.

529 **If RELENZA is prescribed for children, it should be used only under adult**
530 **supervision and instruction, and the supervising adult should first be instructed by a**
531 **healthcare professional [see Dosage and Administration (2.1)].**

532 **17.5 Risk of Influenza Transmission to Others**

533 Patients should be advised that the use of RELENZA for treatment of influenza has not
534 been shown to reduce the risk of transmission of influenza to others.

535 **17.6 FDA-Approved Patient Labeling and Instructions for Use**

536 See separate leaflet.

537
538 RELENZA, DISKHALER, and ROTADISK are registered trademarks of GlaxoSmithKline.
539



541
542 GlaxoSmithKline
543 Research Triangle Park, NC 27709
544

545 ©2008, GlaxoSmithKline. All rights reserved.
546

1 **Patient Labeling**

2
3 **RELENZA® (zanamivir) Inhalation Powder**

4
5 This leaflet contains important patient information about RELENZA (zanamivir)
6 Inhalation Powder, and should be read completely before beginning treatment. It does not,
7 however, take the place of discussions with your healthcare provider about your medical
8 condition or your treatment. This summary does not list all benefits and risks of RELENZA. The
9 medication described here can only be prescribed and dispensed by a licensed healthcare
10 provider, who has information about your medical condition and more information about the
11 drug, including how to take it, what to expect, and potential side effects. If you have any
12 questions about RELENZA, talk with your healthcare provider.

13
14 **What is RELENZA?**

15 RELENZA (ruh-LENS-uh) is a medicine for the treatment of influenza (flu, infection
16 caused by influenza virus) and for reducing the chance of getting the flu in community and
17 household settings. It belongs to a group of medicines called neuraminidase inhibitors. These
18 medications attack the influenza virus and prevent it from spreading inside your body.
19 RELENZA treats the cause of influenza at its source, rather than simply masking the symptoms.

20
21 **Important Safety Information About RELENZA**

22 Some patients have had bronchospasm (wheezing) or serious breathing problems when
23 they used RELENZA. Many but not all of these patients had previous asthma or chronic
24 obstructive pulmonary disease. RELENZA has not been shown to shorten the duration of
25 influenza in people with these diseases. Because of the risk of side effects and because it has not
26 been shown to help them, RELENZA is not recommended for people with chronic respiratory
27 disease such as asthma or chronic obstructive pulmonary disease.

28 If you develop worsening respiratory symptoms such as wheezing or shortness of breath,
29 stop using RELENZA and contact your healthcare provider right away.

30 If you have chronic respiratory disease such as asthma and chronic obstructive pulmonary
31 disease and your healthcare provider has prescribed RELENZA, you should have a fast-acting,
32 inhaled bronchodilator available for your use. If you are scheduled to use an inhaled
33 bronchodilator at the same time as RELENZA, use the inhaled bronchodilator **before** using
34 RELENZA.

35 Read the rest of this leaflet for more information about side effects and risks.

36 Other kinds of infections can appear like influenza or occur along with influenza, and
37 need different kinds of treatment. Contact your healthcare provider if you feel worse or develop
38 new symptoms during or after treatment, or if your influenza symptoms do not start to get better.

39
40 **Who should not take RELENZA?**

41 RELENZA is not recommended for people who have chronic lung disease such as
42 asthma or chronic obstructive pulmonary disease. RELENZA has not been shown to shorten the
43 duration of influenza in people with these diseases, and some people have had serious side
44 effects of bronchospasm and worsening lung function. (See the section of this Patient
45 Information entitled “**Important Safety Information About RELENZA.**”)

46 You should not take RELENZA if you are allergic to zanamivir or any other ingredient of
47 RELENZA. Also tell your healthcare provider if you have any type of chronic condition
48 including lung or heart disease, if you are allergic to any other medicines or food products, or if
49 you are pregnant.

50 RELENZA was not effective in reducing the chance of getting the flu in 2 studies in
51 nursing home patients.

52 RELENZA does not treat flu-like illness that is not caused by influenza virus.

53

54 **Who should consider taking RELENZA?**

55 Adult and pediatric patients at least 7 years of age who have influenza symptoms that
56 appeared within the previous day or two. Typical symptoms of influenza include sudden onset of
57 fever, cough, headache, fatigue, muscular weakness, and sore throat.

58 RELENZA can also help reduce the chance of getting the flu in adults and children at
59 least 5 years of age who have a higher chance of getting the flu because they spend time with
60 someone who has the flu. RELENZA can also reduce the chance of getting the flu if there is a flu
61 outbreak in the community.

62 The use of RELENZA for the treatment of flu has not been shown to reduce the risk of
63 spreading the virus to others.

64

65 **Can I take other medications with RELENZA?**

66 RELENZA has been shown to have an acceptable safety profile when used as labeled,
67 with minimal risk of drug interactions. Your healthcare provider may recommend taking other
68 medications, including over-the-counter medications, to reduce fever or other symptoms while
69 you are taking RELENZA. Before starting treatment, make sure that your healthcare provider
70 knows if you are taking other medicines. If you are scheduled to use an inhaled bronchodilator at
71 the same time as RELENZA, you should use the inhaled bronchodilator **before** using
72 RELENZA.

73 Before taking RELENZA, please let your healthcare provider know if you received live
74 attenuated influenza vaccine (FLUMIST[®]) intranasal in the past 2 weeks.

75

76 **How and when should I take RELENZA?**

77 RELENZA is packaged in medicine disks called ROTADISKS[®] and is inhaled by mouth
78 using a delivery device called a DISKHALER[®]. Each ROTADISK contains 4 blisters. Each
79 blister contains 5 mg of active drug and 20 mg of lactose powder (which contains milk proteins).

80 You should receive a demonstration on how to use RELENZA in the DISKHALER from
81 a healthcare provider. Before taking RELENZA, read the “Patient Instructions for Use.” Make
82 sure that you understand these instructions and talk to your healthcare provider if you have any
83 questions. Children who use RELENZA should always be supervised by an adult who
84 understands how to use RELENZA. Proper use of the DISKHALER to inhale the drug is
85 necessary for safe and effective use of RELENZA.

86 If you have the flu the usual dose for treatment is 2 inhalations of RELENZA (1 blister
87 per inhalation) twice daily (in the morning and evening) for 5 days. It is important that you begin
88 your treatment with RELENZA as soon as possible from the first appearance of your flu
89 symptoms. Take 2 doses on the first day of treatment whenever possible if there are at least
90 2 hours between doses.

91 To reduce the chance of getting the flu, the usual dose is 2 inhalations of RELENZA
92 (1 blister per inhalation) once daily for 10 or 28 days as prescribed by your healthcare provider.

93 Never share RELENZA with anyone, even if they have the same symptoms. If you feel
94 worse or develop new symptoms during treatment with RELENZA, or if your flu symptoms do
95 not start to get better, stop using the medicine and contact your healthcare provider.

96

97 **What if I miss a dose?**

98 If you forget to take your medicine at any time, take the missed dose as soon as you
99 remember, except if it is near the next dose (within 2 hours). Then continue to take RELENZA at
100 the usual times. You do not need to take a double dose. If you have missed several doses, inform
101 your healthcare provider and follow the advice given to you.

102

103 **What are important or common possible side effects of taking RELENZA?**

104 Some patients have had breathing problems while taking RELENZA. This can be very
105 serious and need treatment right away. Most of the patients who had this problem had asthma or
106 chronic obstructive pulmonary disease, but some did not. If you have trouble breathing or have
107 wheezing after your dose of RELENZA, stop taking RELENZA and get medical attention.

108 In studies, the most common side effects with RELENZA have been headaches; diarrhea;
109 nausea; vomiting; nasal irritation; bronchitis; cough; sinusitis; ear, nose, and throat infections;
110 and dizziness. Other side effects that have been reported, but were not as common, include
111 rashes and allergic reactions, some of which were severe.

112 People with influenza (the flu), particularly children and adolescents, may be at an
113 increased risk of seizures, confusion, or abnormal behavior early in their illness. These events
114 may occur after beginning RELENZA or may occur when flu is not treated. These events are
115 uncommon but may result in accidental injury to the patient. Therefore, patients should be
116 observed for signs of unusual behavior and a healthcare professional should be contacted
117 immediately if the patient shows any signs of unusual behavior.

118 This list of side effects is not complete. Your healthcare provider or pharmacist can
119 discuss with you a more complete list of possible side effects with RELENZA. Talk to your
120 healthcare provider promptly about any side effects you have.

121 Please refer to the section entitled "**Important Safety Information About RELENZA**"
122 for additional information.

123

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

125 RELENZA is not a substitute for a flu shot. You should receive an annual flu shot
126 according to guidelines on immunization practices that your healthcare provider can share with
127 you.

128

129 **What if I am pregnant or nursing?**

130 If you are pregnant or planning to become pregnant while taking RELENZA, talk to your
131 healthcare provider before taking this medication. RELENZA is normally not recommended for
132 use during pregnancy or nursing, as the effects on the unborn child or nursing infant are
133 unknown.

134

135 **How and where should I store RELENZA?**

136 RELENZA should be stored at room temperature below 77°F (25°C). RELENZA is not
137 in a childproof container. Keep RELENZA out of the reach of children. Discard the
138 DISKHALER after finishing your treatment.

139

140

PATIENT INSTRUCTIONS FOR USE



141

142

**IMPORTANT: Read Step-by-Step Instructions
before using the DISKHALER®.**

143

144

145

Be sure to take the dose your healthcare provider has prescribed.

146

147

BEFORE YOU START:

148

149

Please read the entire Patient Labeling for important information about the effects of RELENZA including the section “Important Safety Information About RELENZA” for information about the risk of breathing difficulties.

150

151

152

153

If RELENZA is prescribed for a child, dosing should be supervised by an adult who understands how to use RELENZA and has been instructed in its use by a healthcare provider.

154

155

Parts of the DISKHALER:

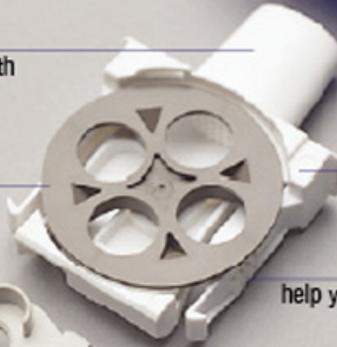
COVER

keeps the DISKHALER clean and free of foreign matter; replace cover when not in use



WHITE MOUTHPIECE

where the medicine is inhaled by mouth



DARK BROWN WHEEL

rotates to the next plister of medicine



WHITE TRAY

pulls in and out of DISKHALER body

RAISED RIDGES

help you pull out the tray for loading

NEEDLE

punctures the plister to release medicine

DISKHALER BODY

HALF-CIRCLE FLAP

lifts up and down to operate plastic needle



SILVER MEDICINE DISK

contains 4 plisters of medicine; the disk fits into the dark brown wheel inside the DISKHALER



156 **Step-by-step instructions for using the DISKHALER®**

157

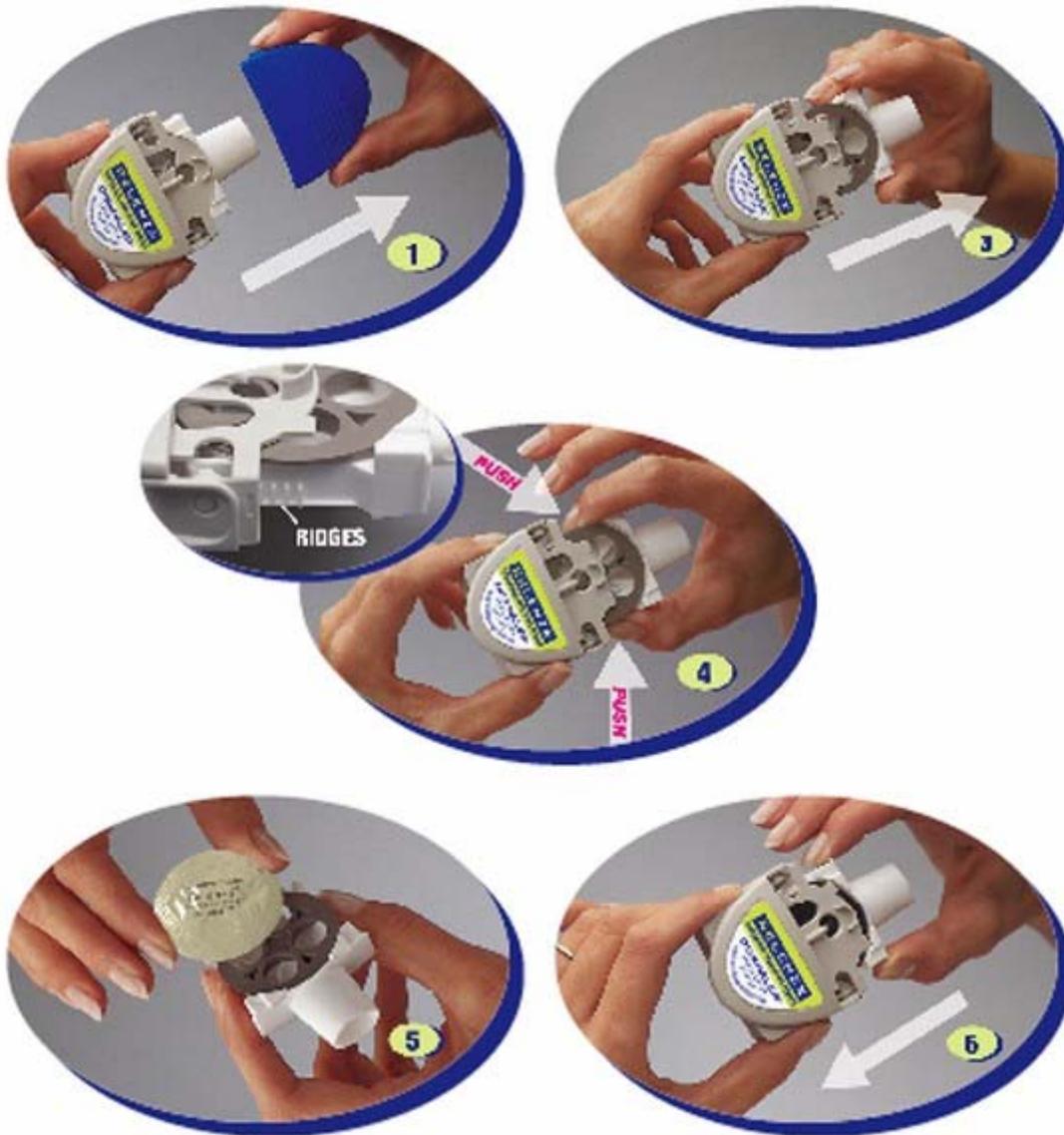
158 **Step A: Load the medicine into the DISKHALER**

159

160 1. Start by pulling off the blue cover.

161

- 162 2. **Always check inside the mouthpiece to make sure it is clear before each use. If foreign**
163 **objects are in the mouthpiece, they could be inhaled and cause serious harm.**
164
- 165 3. Pull the white mouthpiece by the edges to extend the white tray all the way.
166
- 167 4. Once the white tray is extended all the way, find the raised ridges on each side of it. Press in
168 these ridges, both sides at the same time, and **pull the whole white tray out of the**
169 **DISKHALER body.**
170
- 171 5. Place one silver medicine disk onto the dark brown wheel, flat side up. The four silver
172 blisters on the underside of the medicine disk will drop neatly into the four holes in the
173 wheel.
174
- 175 6. Push in the white tray as far as it will go. Now the DISKHALER is loaded with medicine.
176



177
178 **Step B: Puncture the blister**

179
180 **Be sure to keep the DISKHALER level.**

181
182 **The DISKHALER punctures one blister of medicine at a time so you can inhale the right**
183 **amount. It does not matter which blister you start with. Check to make sure that the silver**
184 **foil is unbroken.**

- 185
186 1. Be sure to keep the DISKHALER level so the medicine does not spill out.
187
188 2. Locate the half-circle flap with the name “RELENZA” on top of the DISKHALER.

189
190
191
192
193

3. Lift this flap from the outer edge until it cannot go any farther. Flap must be **straight up** for the plastic needle to puncture both the **top** and **bottom** of the silver medicine disk inside.
4. Keeping the DISKHALER level, click the flap down into place.



194
195
196
197
198
199

Step C: Inhale

1. Before putting the white mouthpiece into your mouth, breathe all the way out (exhale).

200 **Then put the white mouthpiece into your mouth. Be sure to keep the DISKHALER level so**
201 **the medicine does not spill out.**

202
203
204
205

2. Close your lips firmly around the mouthpiece. Be sure not to cover the small holes on either side of it.

3. Breathe in through your mouth steadily and as deeply as you can. Your breath pulls the medicine into your airways and lungs.

208

4. Hold your breath for a few seconds to help RELENZA stay in your lungs where it can work.

210

To take another inhalation, move to the next blister by following Step D below.

212

Once you've inhaled the number of blisters prescribed by your healthcare provider, replace the cover until your next dose.

214



215
216

Step D: Move the medicine disk to the next blister

218

219
220

1. **Pull** the mouthpiece to extend the white tray, without removing it.

221
222

2. Then **push** it back until it clicks. This pull-push motion rotates the medicine disk to the next blister.

223

224
225

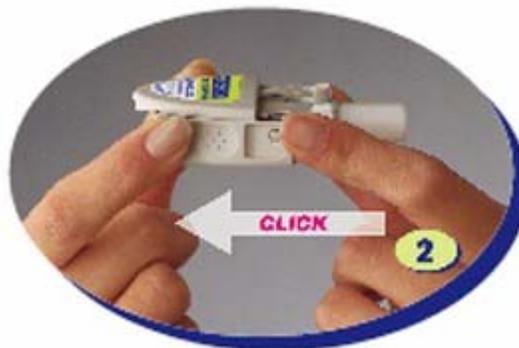
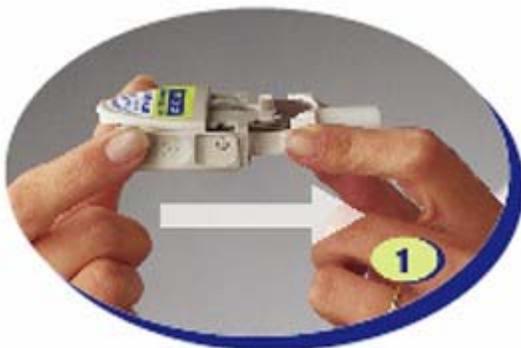
3. To take your next inhalation, repeat Steps B and C.

226

If all four blisters in the medicine disk have been used, you are ready to start a new medicine disk (see Step A). Check to make sure that the silver foil is unbroken each time you are ready to puncture the next blister.

227

228



229

IMPORTANT INSTRUCTIONS
Read this entire leaflet before using RELENZA. Even if you have had a previous prescription for RELENZA, read this leaflet to see if any information has changed.
If you have the flu, the usual dose is 2 inhalations twice daily. To reduce the chance of getting the flu, the usual dose is 2 inhalations once daily. However, you must take the

number of inhalations your healthcare provider has prescribed.

If you feel worse or develop new symptoms during or after treatment, or if your flu symptoms do not start to improve, stop using the medicine and contact your healthcare provider.

Keep out of reach of children.

Always check inside the mouthpiece to make sure it is clear before each use. If foreign objects are in the mouthpiece, they could be inhaled and cause serious harm.

Always replace the cover after each use.

Throw away the DISKHALER after treatment is completed.

This DISKHALER is for use only with RELENZA. Do not use the RELENZA DISKHALER device with FLOVENT[®] (fluticasone propionate) and do not use RELENZA with the FLOVENT DISKHALER device.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP Controlled Room Temperature).

REMEMBER: This medicine has been prescribed for you by your healthcare provider. **DO NOT** give this medicine to anyone else.

230
231
232
233
234
235

RELENZA, FLOVENT, ROTADISK, and DISKHALER are registered trademarks of GlaxoSmithKline.
FLUMIST is a registered trademark of MedImmune, Inc.



236
237
238
239
240
241
242
243

GlaxoSmithKline
Research Triangle Park, NC 27709
©2008, GlaxoSmithKline. All rights reserved.
February 2008
RLZ:3PIL