

MedKits for Influenza: Discussion of a Personal Stockpiling Proposal



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

**Debra B. Birnkrant, M.D.
Director, Division of Antiviral Products**

**October 29, 2008
Rockville, Maryland**

What is an Influenza MedKit?

- A specially designed package with new labeling containing an approved antiviral drug for prophylaxis and/or treatment of influenza for use during a pandemic
- Proposed prescription product
- For home stockpiling, for use during a pandemic

What is an Influenza MedKit? (cont.)

- Submitted as a supplemental NDA to existing NDAs for Tamiflu and Relenza
 - Relies on previous safety and efficacy data that supported approval
 - Need additional evaluation of use in the intended population for new proposed use and to evaluate additional labeling
- Follows non-prescription drug development model for communication aspects
 - Reliance on patients to decide when and how to use the MedKit
 - Determine if they have the condition for which the drug is indicated
 - Projected use without a health care professional intermediary at time of use
 - Supplemental NDA would also include: labeling comprehension studies and actual use studies

Background

- HHS has asked Tamiflu (Roche) and Relenza (GSK) manufacturers to propose studies and development plans for a “home MedKit” containing flu antiviral for individual or family purchase to keep for use in an influenza pandemic
- HHS has asked FDA to outline information needs for approval of a “home MedKit” NDA for pandemic flu
 - Issues build on discussions of potential antibiotic “MedKit” development for anthrax defense, federal/state flu drug stockpiling and pandemic-use advice
- FDA provided general comments on study types to sponsors

Purpose of Meeting

- Obtain advice and generate discussion about proposals for influenza antiviral MedKits to assess risk/benefit regarding:
 - the concept of a MedKit, appropriate supportive studies and other issues such as resistance, etc.
- FDA responsibility is to assess safety and efficacy of proposed product for its intended use with the available instructions, based on review of submitted data
- Previous meetings discussed the potential effects of MedKits on reducing the impact of a pandemic, equity and affordability

Antiviral Drugs for Influenza

Background

- Four drugs in two classes (amantadine, rimantadine, oseltamivir (Tamiflu), zanamivir (Relenza)) approved for treatment and prophylaxis of influenza
- Widespread resistance limits usefulness of older class of M2 inhibitors, amantadine and rimantadine

Antiviral Drugs 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)
Ages for which treatment is approved	≥ 1 year	adults	≥ 7 years	≥ 1 year
Ages for which prophylaxis is approved	≥ 1 year	≥ 1 year	≥ 5 years	≥ 1 years
Original Approval Dates	1960's	9/17/93	7/26/99	10/27/99

Considerations in MedKit Design and Study

- How much of which product(s), formulation(s), dosage strengths?
 - Dosing for individual or household? Age groups?
 - For treatment, post-exposure prophylaxis, outbreak prophylaxis? Pandemic only, or flu epidemic use?
- Expected mechanisms for prescribing, dispensing, instructing, and tracking usage
- Provisions for monitoring (and preventing, to the extent possible) resistance emergence and adverse events
- Expectation of Advisory Committee discussions as part of development and NDA review process once all information is available from studies

Potential Study Types for MedKit NDA

- Design of written materials to convey accurate understanding of risk/benefit and usage options
- Formal label comprehension studies
 - When and how to use (evaluation of exposure and illness, individual triggers for starting or withholding more complex than for anthrax)
 - Algorithm to guide decisions is under development but subject to change; raises two separate questions
 - Can the algorithm identify the appropriate target population?
 - Can users follow the algorithm as translated to labeling?
 - Determination of appropriate dose/duration based on diagnosis and age group
- Actual use (compliance studies)
 - Ability to retain drug through at least one flu season
 - Will drug be used for non-pandemic influenza, flu-like illness?
 - Flu pandemic scenario questions

Potential Study Types for MedKit NDA

- Dosing/administration
 - Home preparation Mixing Study: Can user make/dose liquid preparation from Tamiflu capsules? Adjust for changes in child's size/dose?
 - Human Factor Study: Can user follow Relenza device instructions without hands-on demonstration?

What might be learned from recommended studies?

- Listed studies may show
 - Which parts of proposed instructions are understood by a range of potential users
 - Elements of instructions that could be clarified and re-tested
 - Whether study subjects can keep drug unused at home through a flu season

Examples of what might not be learned from recommended studies

- Listed studies cannot address
 - Accuracy of diagnosis, administration, and physician/patient communication in actual emergency
 - Effect on viral resistance emergence, recognition and management of bacterial complications, adverse event occurrence and monitoring
- Additional studies may be needed

Examples of issues related to resistance emergence

- Influenza undergoes frequent mutations; variants resistant to older drugs (M2 inhibitors) arise rapidly during treatment, are transmissible and pathogenic
 - No longer recommended by CDC for circulating influenza
- Oseltamivir registrational trials: some patients (especially children) shed virus with resistance mutations after treatment initiation
 - Not clear if these post-treatment variants could spread to others and cause disease
- Recent multi-country reports of oseltamivir-resistant H1N1 virus in untreated persons with influenza illness
 - 2007-2008 reports provide new information on ability of some resistant strains to circulate in association with flu-like illness

MedKit Development

Current Options

- Both NIs are available by prescription
 - Patient generally evaluated by prescriber at time of intended use
- Labeling for influenza, but not specific for pandemic situation
 - *it is not possible to determine what strain of influenza will emerge as the next pandemic strain*
 - *uncertainty about antiviral effects against novel strains*

MedKit

- New uses and instructions not previously tested
- Utilize IND mechanism
 - Develop new labeling to convey evidence base and risk/benefit for all components
 - Develop and initiate studies
 - Labeling comprehension, actual use, etc.
- Pursue NDA supplement pathway
 - Current AC to provide advice regarding development process
 - Present results to future AC

Agenda

Opening Remarks – D. Birnkrant, FDA

Influenza MedKit Initiative – J. Tegeris , BARDA

Epidemiology of Seasonal and Pandemic Influenza – T. Uyeki, CDC

Overview of Influenza, Treatment and Prophylaxis – F.Hayden, UVA

Influenza Resistance – A. Klimov, CDC

Studies to Support a MedKit – L.Shay, FDA

Break

Company Presentations – GSK, Roche

Presentations from Associations – IDSA, AAP, AAFP, AMA, ASHP,
NACCHO, APhA, ASTHO

Lunch

Open Public Hearing

AC Discussion

Questions for Committee Discussion

- 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. Will the phase 3 clinical trials that supported approvals and favorable results from the proposed “consumer use” studies (e.g., label comprehension, simulated use, etc.) 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? [voting question]. YES/NO/ABSTAIN
 - If no, what additional studies are needed?

Questions for Committee Discussion

- 3. Please comment on the use of a MedKit 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?

Questions for Committee Discussion

- 4. 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 as well as an oral suspension. What is the most appropriate formulation to be used for pediatric dosing in this setting?
- 5. Comment on specific elements of labeling, packaging, or instructions that are critical for safe and effective use of a MedKit.

Questions for Committee Discussion

- 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. For example:
 - 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?
 - What types of additional studies would be helpful to assess how users would behave in a real-life situation?

Questions for Committee Discussion

- 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. 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.