TAMIFLU® MedKit
for Pandemic Influenza

Hoffmann-La Roche Inc.

October 29, 2008
Presentation Outline

- Introduction/Overview
- TAMIFLU MedKit
  - Stakeholder Feedback
- Pandemic Planning
  - Resistance
  - Collection and Reporting of Safety Information
  - Communication Plan
- Proposed Studies
- Conclusions
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<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>William Blumentals, PhD</td>
<td>Medical Data Analytics</td>
</tr>
<tr>
<td>Ellen Carey, PharmD</td>
<td>Global Regulatory Leader</td>
</tr>
<tr>
<td>Brian Davies, PhD</td>
<td>Clinical Pharmacologist</td>
</tr>
<tr>
<td>Barbara Donner, MD</td>
<td>Safety Director</td>
</tr>
<tr>
<td>Regina Dutkowski, PhD</td>
<td>Clinical Science Leader</td>
</tr>
<tr>
<td>Dominick Iacuzio, PhD</td>
<td>Medical Director</td>
</tr>
<tr>
<td>Klaus Klumpp, PhD</td>
<td>Director, Virology</td>
</tr>
<tr>
<td>Michael McGuire, MBA</td>
<td>Vice President, TAMIFLU</td>
</tr>
<tr>
<td>David Reddy, PhD</td>
<td>Life Cycle Leader, TAMIFLU</td>
</tr>
<tr>
<td>Susan Sacks, PhD</td>
<td>Director, Epidemiology</td>
</tr>
<tr>
<td>Miklos Salgo, MD, PhD</td>
<td>Clinical Science Leader, HIV</td>
</tr>
<tr>
<td>James Smith, PhD</td>
<td>International Medical Leader</td>
</tr>
<tr>
<td>Duane Voss, BA</td>
<td>Program Director, Regulatory CMC</td>
</tr>
</tbody>
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### Experts Available

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
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</thead>
<tbody>
<tr>
<td>David Bradford, PhD</td>
<td>Sr. Vice President for OTC Switches</td>
</tr>
<tr>
<td></td>
<td>PEGUS Research</td>
</tr>
<tr>
<td>Donald Low, MD</td>
<td>Chief of Microbiology</td>
</tr>
<tr>
<td></td>
<td>Mt. Sinai Hospital and</td>
</tr>
<tr>
<td></td>
<td>Toronto Medical Laboratories</td>
</tr>
</tbody>
</table>
## TAMIFLU

### Indication and Usage

- Indicated for the treatment and prophylaxis of influenza in patients 1 year and older

### Dosage and Administration

<table>
<thead>
<tr>
<th></th>
<th>Treatment BID x 5d</th>
<th>Prophylaxis QD x 10 d</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adults and Adolescents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(≥ 13 years)</td>
<td>75 mg</td>
<td>75 mg</td>
</tr>
<tr>
<td><strong>Children</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1-12 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 33 lbs</td>
<td>30 mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>34-51 lbs</td>
<td>45 mg</td>
<td>45 mg</td>
</tr>
<tr>
<td>52-88 lbs</td>
<td>60 mg</td>
<td>60 mg</td>
</tr>
<tr>
<td>&gt; 88 lbs</td>
<td>75 mg</td>
<td>75 mg</td>
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</tbody>
</table>
TAMIFLU

Most Frequent Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Treatment</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PBO (N=716)</td>
<td>TAMIFLU (N=724)</td>
</tr>
<tr>
<td>Nausea</td>
<td>40 (6%)</td>
<td>72 (10%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21 (3%)</td>
<td>68 (9%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>70 (10%)</td>
<td>48 (7%)</td>
</tr>
</tbody>
</table>

Postmarketing Serious Adverse Events

- Rare reports of skin/hypersensitivity reactions
- Neuropsychiatric adverse events, sometimes leading to injury
  - Reported in influenza patients with or without TAMIFLU use
  - Contribution of TAMIFLU has not been established
TAMIFLU

Clinical Studies

Treatment of Influenza

- 849 influenza-infected adults and 452 influenza-infected pediatrics
- Primary endpoint
  - Adults: Time to improvement of all influenza-associated symptoms
    - 1.3 day reduction in median time to improvement compared to placebo
  - Pediatrics: Time to freedom from illness
    - 1.5 day reduction in total composite time to freedom from illness compared to placebo

Prophylaxis of Influenza

- 1992 adults and 201 pediatrics enrolled in seasonal or post-exposure prophylaxis studies
- Primary endpoint: incidence of laboratory-confirmed clinical influenza
  - Seasonal in adults: 76%-92% protective efficacy
  - PEP in adults: 68%-89% and in pediatrics: 80% protective efficacy
Rationale for MedKit

- While government pandemic preparations are ongoing, individual action and responsibility are necessary

- Pandemic preparations have been ongoing:
  - Federal/State government antiviral stockpile at 81 million treatments
  - Corporate guidelines issued by HHS/CDC in 2007 to protect employees and maintain business continuity

- Pandemic MedKit allows households to prepare
  - Immediate access to antivirals when first symptoms appear
  - Reduce barriers to obtain and utilize antivirals
WHO Guidance on the Role of Antivirals in the Management of Avian and Pandemic Influenza Infection

**Human Infection with H5N1 Avian Influenza**

- “Oseltamivir … remains the primary antiviral agent of choice for the treatment of A(H5N1) virus infections.”
- “Limited observational evidence suggests that early oseltamivir administration may be associated with reduced mortality in patients”

**Pandemic Influenza**

- “Pending the availability of vaccines, antiviral drugs will be the principal medical intervention for reducing morbidity and mortality”
- Stockpiling ensures sufficient supplies of antivirals

Survival in H5N1 Case Studies

Case Series from Egypt and Indonesia

**Egypt**

- Days from Onset until Admission and Treatment:
  - 1 day: 14/15, 93%
  - 2 days: 4/5, 80%
  - 3 days: 5/7, 71%
  - 4 or More: 1/12

**Indonesia**

- Time from Symptom Onset to Oseltamivir Treatment (Days):
  - 0-2: 1/1, 100%
  - 2-4: 4/11, 36%
  - 5-6: 6/16, 38%
  - 7 or More: 10/54

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1. Adapted from Abdel-Ghafar. *Working On the Front Line with H5N1*. Perspectives in Interpandemic Influenza, Madrid, Spain 2007
Regulatory Framework for TAMIFLU MedKit

- Current pathways for drug approval:
  - Prescription
  - Over-the-Counter (OTC)

- OTC pathway requires differentiation of MedKit from seasonal TAMIFLU
  - By indication, dose or patient population

- Roche constrained to prescription pathway
  - No differentiation between the MedKit and seasonal TAMIFLU identified

- OTC-like mechanism would likely maximize access to the MedKit
  - For individuals who would not or could not see a healthcare provider

- Creation of alternative regulatory approval mechanism may be appropriate for MedKit
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TAMIFLU MedKit Contents

Designed to Maximize the Likelihood of Compliance and Proper Use of TAMIFLU
Dosage Strength for TAMIFLU MedKit

- One dosage strength (75 mg capsules) included in TAMIFLU MedKit
  - Ability to adjust dose for growing children
  - Less confusion for households with children (e.g., selection of wrong dosage strength)
  - Simplifies dispensing of kits for household members of different ages

- Mixing studies have been conducted to support the mixing of capsule content in different foods
  - Stability
  - Palatability
  - Preservative efficacy
CDC Pandemic Influenza Diagnostic Algorithm

- CDC algorithm designed for appropriate use of antivirals in a pandemic
  - Included in TAMIFLU MedKit Educational Booklet

- Developed by CDC for diagnosis of influenza outside of healthcare setting during a pandemic
  - Refers patients with underlying medical conditions to their healthcare professional

- To be applied only:
  - After a health department declaration of pandemic
  - For individuals with new onset of flu symptoms and their household members
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Stakeholder Feedback on TAMIFLU MedKit

- HHS Meeting with medical and pharmacy societies identified challenges
  - Need to address burden on HCP
  - Inappropriate use
  - Timing of use
  - Resistance
  - Adverse events

- Roche planning Scientific Advisory Board
  - Will invite representatives from: AAP, AMA, APhA, AAFP, IDSA, NACDS, PBMs
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Ongoing Pre-Pandemic Preparedness Activities

Avian Flu Registry

- Global, multi-center, observational registry of patients with H5N1 infection
- To collect information on:
  - Clinical course and outcome of H5N1 infection
  - Treatments and dosing regimen used

Dose Prediction Model

- Model will predict TAMIFLU dosage required to suppress viral replication
- Model combines nonclinical and seasonal clinical data
  - H5N1 data to be incorporated
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Drug-Induced Resistance

- Low incidence of resistance during treatment with TAMIFLU\textsuperscript{1} in large clinical studies
  - Adults 0.32%
  - Children 4.1%

- No resistance observed in any of the prophylaxis clinical studies

- Low fitness and transmissibility

- High barrier to resistance

1. Aoki et al Antiviral Ther. 12;603-616:2007
Incidence of Resistance to Oseltamivir from Community Surveillance Samples\(^1,2\)

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td><strong>US</strong></td>
<td>N/A</td>
<td>0/370 (0%)</td>
<td>0/647 (0%)</td>
<td>5/584 (0.9%)</td>
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<tr>
<td><strong>Japan</strong></td>
<td>3/1180 (0.3%)</td>
<td>0/618 (0%)</td>
<td>4/429 (1%)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Low incidence of resistance in countries with high use of TAMIFLU

- Prescriptions for corresponding period:
  - Over 8 million in US
  - Over 29 million in Japan

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Naturally Occurring Resistance

- Naturally occurring resistance to any drug may arise and disappear spontaneously
  - Appears to be driven by antigenic drift and not by antiviral use
- Increased incidence of resistance to oseltamivir observed in 2007/08 season in H1N1 seasonal viruses
  - Associated with H274Y* and additional mutations
  - No apparent relationship to oseltamivir use or exposure

Prevalence of H1N1 Resistance

<table>
<thead>
<tr>
<th>Region</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>Global</td>
<td>15%</td>
</tr>
<tr>
<td>Europe</td>
<td>25%, Range 0-67%</td>
</tr>
<tr>
<td>US</td>
<td>11%</td>
</tr>
<tr>
<td>Japan</td>
<td>3%</td>
</tr>
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</table>

On-going Surveillance is Crucial

*Some scientists use N1 numbering (275Y) and some use N2 numbering (274Y) for same mutation in N1
Roche Plan for Resistance Monitoring

**Seasonal Influenza:**
- Roche convened expert panel for guidance on resistance data generation, analysis and communication
- Roche initiating large, global Influenza study (IRIS)
  - 1,200 patients per influenza season (2008-2011)
  - To evaluate clinical course and monitor naturally occurring and treatment-induced resistance to all anti-influenza drugs

**Pandemic Influenza:**
- WHO/CDC currently have extensive surveillance system, expected to continue during a pandemic
- Roche open to discuss opportunities to augment WHO/CDC activities, such as a variant of the IRIS study currently ongoing
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Pharmacovigilance Plan for Pandemic

- Roche anticipates increased Adverse Event Reports for TAMIFLU

- Roche will request HCP and consumer AE reporting via:
  - TAMIFLU MedKit educational booklet
  - Roche website
  - Radio, newspaper, and TV

- Enhanced HCP and consumer adverse event reporting mechanisms:
  - Telephone
  - Electronic (web page, e-mail)
  - Paper (mail, fax)
  - Consumer AE reporting form included in TAMIFLU MedKit
Pharmacovigilance Communications

Process Defined and Established for:

- **Continual** reporting to Health Authorities
  - Biweekly TAMIFLU reports once WHO declares pandemic, Phase V
  - Analysis of aggregate data with emphasis on populations of special interest (pregnant and lactating women)
  - Identification of new safety information possibly impacting public health

- **Urgent** communication of safety information impacting patient or public health
  - To patients, public, HCPs and other stakeholders
  - In collaboration with FDA, WHO, CDC
  - Process for rapid distribution of safety information established
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Roche Pandemic Communication Plan

- Roche will collaborate with CDC, FDA, HHS, and WHO to disseminate consistent information

- Communications may address:
  - Resistance
  - Safety
  - Dosing

- Various media channels will be used
  - TV – Public Service Announcement (PSA)
  - Web-based
  - Print

- Communications will also be coordinated through medical/pharmacy societies
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**TAMIFLU MedKit Development Plan**

<table>
<thead>
<tr>
<th></th>
<th>2008</th>
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<tr>
<td></td>
<td>Mar-Jun</td>
<td>Jul</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HHS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Approached Roche Initial Meeting with FDA</td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continued Dialogue and Meetings with HHS</td>
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</table>
Label Comprehension Study Design

- Standard mall-intercept screening and recruitment
- 667 Respondents: 400 > 8\textsuperscript{th} grade reading level and 267 ≤ 8\textsuperscript{th} grade reading level
- Structured and scenario questions evaluating:
  - Drug Facts-like label
  - TAMIFLU MedKit booklet
- Screening and demographic questions
Simulation/Compliance Study

- Study in approximately 2,000 households

- Key objectives:
  - To evaluate the subject’s intended actions based on responses to pandemic scenarios
  - To assess the number of intact TAMIFLU MedKits returned relative to the total number returned

- Methods
  - Questionnaire with various scenarios that might be encountered in the event of a pandemic
  - TAMIFLU MedKits will be placed in homes for a 6-month period covering one influenza season
  - Return of TAMIFLU MedKit at end of influenza season with follow-up questionnaire
  - “Non-compliance” defined as missing capsules at the end of the study
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Potential Risks and Mitigation Strategies with TAMIFLU MedKit for Home Stockpiling

Adverse Events
- Safety profile well established with > 55 million prescriptions filled since 1999
- Comprehensive strategy for collecting adverse event reports during a pandemic

Viral Resistance
- Resistance patterns to antivirals monitored as part of worldwide surveillance

Dose
- Roche Dose Prediction Model will include data on emerging pandemic strains

Incorrect Diagnosis or Concomitant Secondary Bacterial Infections
- Complications of influenza decreased with treatment
- CDC Algorithm identifies patients requiring medical evaluation or not improving on treatment
Benefits of TAMIFLU MedKit for Home Stockpiling

- Increased availability for more widespread early treatment and household prophylaxis
  - Decreased burden on health care system and providers
  - Access prior to pandemic facilitates social distancing
  - Empowers individual and households to prepare for pandemic as part of individual protective measures
- Individual protection pending availability of a vaccine
Benefits of TAMIFLU MedKit for Home Stockpiling

- HHS Modeling for government and household stockpiling
- Suggests significant improvements in mortality and morbidity with treatment and prophylaxis*
  - Number of antiviral regimens: 167.1 mil.
  - Deaths prevented: 288,000
  - Hospitalizations prevented: 2.427 mil.

H5N1 Mortality Outcome with and without TAMIFLU

<table>
<thead>
<tr>
<th>Country</th>
<th>Clade</th>
<th>Survivors/ Treated (%)</th>
<th>Survivors/ Untreated (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vietnam</td>
<td>1</td>
<td>42/72 (58)</td>
<td>4/13 (31)</td>
</tr>
<tr>
<td>Thailand</td>
<td>1</td>
<td>3/10 (30)</td>
<td>2/7 (29)</td>
</tr>
<tr>
<td>Cambodia</td>
<td>1</td>
<td>–</td>
<td>0/6 (0)</td>
</tr>
<tr>
<td>Turkey</td>
<td>2.2</td>
<td>4/7 (57)</td>
<td>0/1 (0)</td>
</tr>
<tr>
<td>Egypt</td>
<td>2.2</td>
<td>20/34 (59)</td>
<td>–</td>
</tr>
<tr>
<td>Indonesia</td>
<td>2.1</td>
<td>19/65 (29)</td>
<td>1/29 (3)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td><strong>88/188 (47)</strong></td>
<td><strong>7/56 (12)</strong></td>
</tr>
</tbody>
</table>

\[p<0.001\]

“Observational Data on Treatment with Oseltamivir in the Early Stages of the Disease Suggest Its Usefulness in Reducing A(H5N1) Virus Infection-associated Mortality”

~ World Health Organization 2007′

Table: Writing Committee of the WHO. N Engl J Med 2008;358:261–73
Conclusions

- TAMIFLU MedKit addresses currently unmet public health needs
- Roche supports identification of optimal regulatory mechanism to maximize access to TAMIFLU MedKit
- Collaboration with HHS, CDC and FDA to implement the appropriate development program
- Pandemic Planning
  - IRIS: study to evaluate clinical course and monitor resistance
  - Plans for enhanced AE collection and communication with Health Authorities and the public
  - Collaboration with CDC, FDA, HHS, and WHO to disseminate consistent information
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