Tamiflu (oseltamivir)

NDA 21,087 and NDA 21,246

Pediatric Advisory Committee Meeting

November 18, 2005

Tamiflu US Registration History

Indication	Population	Approval Date
Treatment of influenza	Adults	October 27, 1999
Prophylaxis of influenza	Adults and adolescents ≥ 13 years	November 17, 2000
Treatment of influenza	Patients ≥1 year old	December 14, 2000
Pediatric Exclusivity	--	March 22, 2004
Prophylaxis of influenza	Patients ≥1 year old	Pending

Roche Experts Available for Q & A

• Clinical Science	• Regina Dutkowski, Ph.D.
• US Medical Affairs	• Dominick Iacuzio, Ph.D.
• Drug Safety	• Paul Dolin, Ph.D.
• Product Team Leader	• David Reddy, Ph.D.
• Pre-Clinical	• Gerhard Hoffmann, Ph.D.
• Clinical Pharmacology	• Craig Rayner, PharmD

Pediatric Post-Marketing Safety Review

Joseph Hoffman, MD, Vice President
Pharma Development

Objectives

- Provide an overview of the pediatric safety experience with Tamiflu since FDA approval in December 2000
- Respond to FDA request for review of neuropsychiatric SAEs and deaths
- Compare global experience with that of Japan

Overview of Tamiflu Experience

- Tamiflu shown to be safe and effective in registration program (age ≥ 1 year)
- Roche Drug Safety Database (ADVENT) of post-approval use supports current product labeling; proposal submitted to FDA to update US Package Insert with information on skin events
- Increased reporting in Japan secondary to several factors including burden of disease, number of courses dispensed, clinical use patterns, and safety reporting practices

Global Tamiflu Prescriptions

Use in Japan exceeds US and ROW

- Japan: 24.5 million
- USA 6.5 million
- RoW 1.0 million

Total	32.0 million

* Japan IMS Quarterly Rx Data => until June 2005
** USA IMS weekly prescriptions =>until September 2005
*** RoW IMS MIDAS Quarterly Retail Data (France, Germany, UK, Brazil, Canada, Argentina)

Tamiflu Use in U.S. and Japan
Pediatric Experience

	Japan	USA
Total Prescriptions (Millions)	24.5	6.5
Adults	12.9	5.2
Children (0-16 years)	11.6	1.3

Roche Drug Safety (ADVENT) Database SAEs – Children ≤16 years of age

Country	Male	Female	Unknown	Total
Japan	162	111	2	275
USA	15	9	1	25
ROW	12	12	1	25
All countries	189	132	4	325

- ~ 13 million pediatric prescriptions to date
- ~ 10 times more pediatric prescriptions written in Japan vs. US
- ~ 10 times the number of SAEs reported in Japan vs. US

Roche Drug Safety (ADVENT) Database SAEs – Children ≤16 years of age

325 SAEs reported*

System Organ Class (SOC)	Global %
Nervous System Disorders	20
Gastrointestinal Disorders	15
Skin & Subcutaneous Disorders	14
Psychiatric Disorders	13

*based on 13 million pediatric prescriptions through June 2005

Neuropsychiatric Events* in ADVENT Database: Children (≤16 years of age)

- 59 patients (67 events)
  - Japan 57; USA 1; Germany 1
  - Convulsion / encephalitis / encephalopathy – 19; depressed consciousness – 15; hallucination / delusion – 13; delirium – 10; abnormal behaviors / other – 10
- Assessment –
  - 51 cases with a possible alternative explanation
  - 6 cases had insufficient information
  - 2 cases, no alternative explanation
    - 8 y.o. male with abnormal behavior
    - 8 y.o. male with abnormal behavior and disturbed consciousness

* **FDA defined neuropsychiatric events**

Neuropsychiatric Events in ADVENT Database Children (≤16 years of age)

Complicating Factors and Considerations in 51 cases with possible alternative explanations

- Influenza and secondary complication of influenza (26 cases)
- High fever (18 cases)
- Dehydration (5 cases)
- Concomitant medications – e.g., levofloxacin, cyproheptadine, theophylline infusion (3 cases)
- Orthostatic hypotension (2 cases)
- Long latency (> 5 days) after last dose of oseltamivir (2 cases)

Mortality in ADVENT Database (≤ 16 years of age)

13 fatalities reported between January 2000 and June 2005

13,000,000 pediatric prescriptions written

- All cases from Japan
  - < 1 years — 1 (8 months)
  - 1 – 5 years — 10
  - > 5 years — 2 (9 years, 14 years)
- 8 Cases: Alternative possible explanations
  - Major complications of influenza present (pneumonia, pulmonary edema, myocarditis, pancreatitis/acidosis)
  - Pre-existing disease present (asthma, renal impairment, congenital CNS disease)
- 5 Cases: Insufficient information available (4 cases described in a newspaper article)

Signal Detection
Data Review

- Pediatric Registration Data
- United HealthCare Claims Database
- Prospective Japanese Pediatric Study

Safety Profile of Tamiflu Treated Children in Registration Studies (ex-Japan)

- N = 1180; placebo=567, Tamiflu=613
- Ages 1-2 (N=173), 3-5 (N=226), 6-12 (N=633), 13-17 (N=148)
- Most frequent adverse events (> 3%): GI disorders, infections, and respiratory disorders

	Placebo	Tamiflu
Neurologic	2.3%	1.0%
Psychiatric	0.6%	0.8%
Skin	3.3%	2.7%

Safety Profile of Tamiflu Treated Children in Registration Studies (ex-Japan)

- SAEs
  - 15 serious adverse events (5 on placebo, 10 on Tamiflu)
  - 0 / 15 considered related to study treatment by investigators
  - 1 neuropsychiatric event: viral encephalitis in patient on placebo
- Withdrawals
  - 16 patients withdrew: 8 from each treatment arm (no neuropsychiatric events)
  - Most common reason: vomiting
- No deaths reported in registration program

Japanese Pediatric Registration Study

- Open-label study in 70 children aged 1-12 (median age 4 yrs)
- Adverse events profile similar to registration studies outside of Japan
- Most frequently reported events were gastrointestinal
  - Vomiting (31%) and diarrhea (27%) most common
  - Severity was mild in most cases
  - Duration of events limited to a single day in most cases
- No deaths and no neuropsychiatric events reported

United HealthCare Insurance Claims Database Analyses

- Database includes information on over 20 million individuals
- Two large, retrospective cohort studies conducted in the US
  - Morbidity Study in Children (N= 63,261)
  - Mortality Outcome Study - all ages (N=176,001)
- Examined diagnoses/deaths reported in patients with a diagnosis of influenza via claims analysis
  - Influenza with Tamiflu prescription
  - Influenza without Tamiflu prescription
- Thirty (30) day risk for a number of outcomes, including nervous system and psychiatric events, and deaths were determined

United HealthCare Database: Morbidity Study in Children

- Study period Nov. 1, 1999 – Mar. 31, 2004
- Children 1 – 12 years diagnosed with influenza (1-2 years: 22%; 3-5 years: 29%; 6 – 12 years: 49%)
- Influenza with Tamiflu N = 8,875
- Influenza without Tamiflu N = 54,386
- Most common diagnoses were infections, and respiratory, ear, and general disorders
- Psychiatric diagnoses (No Tamiflu 0.6%, Tamiflu 0.6%)
- Nervous system diagnoses (No Tamiflu 0.3%, Tamiflu 0.2%)

United HealthCare Database: Mortality Outcome Study – All Ages

- **Study period Nov. 1, 1999 – Mar. 31, 2004**
- **Diagnosis of influenza**

	Tamiflu	No Tamiflu
	N = 39,202	**N = 136,799**
No. of Deaths	1	58
(%)	(0.003%)	(0.042%)

United HealthCare Database: Mortality Outcome Study Pediatric Subgroup

- Study period Nov. 1, 1999 – Mar. 31, 2004
- Diagnosis of influenza
- Total of 68,317 children

	1-5 years N=27,940		6-10 years N=19,754		11-15 years N=20,623	
	Tamiflu N=3,279	No Tamiflu N=24,661	Tamiflu N=2,789	No Tamiflu N=16,965	Tamiflu N=4,598	No Tamiflu N=16,025
No. of Deaths	0	3	0	1	0	0

Prospective Study in <1 Year Olds in Japan - Preliminary Data

- Conducted by “The Society of Ambulatory and General Pediatrics of Japan” and “The Japanese Society of Pediatric Infectious Disease” Jan to Sept 05
- Collection of adverse events in patients <1 y.o. with or without Tamiflu treatment
- Total patients 1771
- No deaths reported
- The final report is planned for the end of 2005

Japan Prospective Cohort Study (<1 y.o.)
Preliminary Data

Neuropsychiatric	No Tamiflu	Tamiflu
	N = 382 No. [%]	N = 1323 No. [%]
Febrile convulsion	3 [0.79%]	5 [0.38%]
Convulsion	--	3 [0.23%]
Encephalitis	1 [0.26%]	--
Lethargy	--	1 [0.08%]
Tremor	--	1 [0.08%]
Excitability	--	1 [0.08%]
TOTAL	4 [1.05%]	11 [0.86%]

Possible Reasons for Differences: Japanese vs. US Data

Burden of influenza

Population

- Japan – 127 million
- USA – 300 million

Country	2000/2001	2001/2002	2002/2003	2003/2004	2004/2005
Japan	3.5 M	7.7 M	14.8 M	9.8 M	18.0 M
USA	11.5 M	10.5 M	6.7 M	10.6 M*	9.4 M

* Note: Early season, most influenza cases in year 2003

Possible Reasons for Differences: Japanese vs. US Data

- High volume of usage of Tamiflu (10 times higher in children compared to US)
- Pediatric use patterns – exposure differences
  - Dose
  - Duration
  - Administration
- Differences in reporting practices
- Historic awareness (pre-Tamiflu) of influenza-related neuropsychiatric events in Japan

Conclusions

- Registration studies showed Tamiflu to be safe and effective in children
- No new safety signals related to mortality or neuropsychiatric events post-approval
- Proposed label modifications regarding skin reactions submitted by Roche to FDA
- Increased safety reporting in Japan mainly attributable to influenza incidence, number of Tamiflu prescriptions, clinical use patterns, and safety reporting practices
- The risk-benefit ratio for Tamiflu is unchanged and remains positive

Tamiflu Pharmacovigilance: Next Steps

Roche Drug Safety:

- Weekly review of new SAEs
- Monthly review of literature
- Quarterly ADVENT analyses for potential new signals
- Annual analysis of United HealthCare
  - Mortality
  - Neuropsychiatric events
  - Other events of interest