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Subject: Tamiflu<sup>®</sup> BPCA update

Drug Name(s): Oseltamivir (Tamiflu<sup>®</sup>)

Application Type/Number: NDA 21-087 and NDA 21-246

Applicant/sponsor: Roche

OSE RCM #: 2007-1169

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## EXECUTIVE SUMMARY

This consult provides an update of Tamiflu<sup>®</sup> utilization trends with a focus on the pediatric population for the two-year time period from April 1, 2005 – March 31, 2007. According to IMS Health, IMS National Sales Perspectives™ (data not provided), from April 2006 through March 2007, approximately 73% of Tamiflu<sup>®</sup> (oseltamivir) sales were for the capsule dosage form and approximately 28% as the oral suspension. However, during this time period, non-federal hospitals accounted for approximately 66% of the capsule dosage form sales, which represented 8% of Tamiflu<sup>®</sup> sales in the previous 12-month time period from April 2005 to March 2006. The retail setting (chain stores, independent stores, mail-order pharmacies and food stores) accounted for the majority of oral suspension sales (~95%). Thus, this consult examines inpatient and outpatient drug utilization data. As comparators, the drug use patterns of other anti-influenza products [NDA 21-036 Relenza<sup>®</sup> (zanamivir); NDA 17-118 and NDA 18-101 Symmetrel<sup>®</sup> (amantadine); NDA 19-649 and NDA 19-650 Flumadine<sup>®</sup> (rimantadine)] are examined.

- Since approval of the capsule dosage form in 1999, over 10 million Tamiflu<sup>®</sup> prescriptions have been dispensed from U.S. retail pharmacies. Overall outpatient dispensed prescriptions decreased by less than 2% during this 2-year analysis, and Tamiflu<sup>®</sup> continues to be the most commonly prescribed antiviral anti-influenza product, accounting for close to 99% of prescriptions dispensed when compared to zanamivir, amantadine, and rimantadine.
- Approximately 1.8 million patients received a prescription for Tamiflu<sup>®</sup> each 12-month period during this 2-year analysis.
- During this 2-year analysis, 21-35% of overall Tamiflu<sup>®</sup> prescriptions were dispensed to patients aged 0-12 years and 12-14% of overall Tamiflu<sup>®</sup> prescriptions were dispensed to patients aged 13-21 years.
- The capsule dosage form represents 84% of Tamiflu<sup>®</sup> prescriptions dispensed since approval, the majority of which are dispensed to adults aged 22 years or older.
- The suspension dosage form represents close to 16% of Tamiflu<sup>®</sup> prescriptions dispensed since approval. Over 95% of Tamiflu<sup>®</sup> Suspension prescriptions are dispensed to children aged 0-12 years.
- General Practice was the most common prescribing specialty for Tamiflu<sup>®</sup> Capsules and Pediatrics was the most common prescribing specialty for Tamiflu<sup>®</sup> Suspension.
- The most common diagnosis associated with a mention of Tamiflu<sup>®</sup> in both the pediatric patients (aged 0-12 years and 13-21 years) and adults (age 22 and over) in office based physician-patient encounters was “Influenza with other Respiratory Manifestations” (ICD-9 487.1) which accounted for 70-85% of mentions for pediatric patients aged 0-12 years, 89-97% of mentions for pediatric patients aged 13-21 years, and 83-85% of mentions for adults (aged 22+ years) in each of the 2 years from April 2005 – March 2007.
- In the hospital inpatient setting, approximately 5,687 patient discharges had Tamiflu<sup>®</sup> reported on their billing records from April 2005 through March 2006. Patients aged 0-12 years represented approximately 8% and patients aged 13-21 years represented less than 3%.

# **1 BACKGROUND**

Trends in the pediatric utilization of oseltamivir (Tamiflu<sup>®</sup>) were previously examined in September, 2005 (PID# D040278) for a three-year period from April 1, 2002 – March 31, 2005.

## **1.1 INTRODUCTION**

On January 4, 2002, Congress enacted the Best Pharmaceuticals for Children Act (BPCA) to improve the safety and efficacy of pharmaceuticals for children. Section 17 of that Act requires the review of adverse events associated with the use of a drug in children during the one year following the date on which the drug received marketing exclusivity. In support of this mandate, the FDA is required to provide a report to the Pediatric Advisory Committee on the drug utilization patterns and adverse events associated with the use of the drug soon after the one-year anniversary of granting exclusivity. This review is in addition to the routine post-marketing safety surveillance activities the FDA performs for all marketed drugs.

## **1.2 REGULATORY HISTORY**

Tamiflu<sup>®</sup> (oseltamivir), available as a 75 mg capsule and 12 mg/ml powder for oral suspension, is an antiviral agent that inhibits influenza virus neuraminidase. Tamiflu<sup>®</sup> 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. Tamiflu<sup>®</sup> is indicated for the prophylaxis of influenza in patients 1 year and older. The capsule dosage form of Tamiflu<sup>®</sup> (oseltamivir) was approved on December 27, 1999 under NDA 21-087. The oral suspension dosage form was approved on December 14, 2000 under NDA 21-246 and Pediatric Exclusivity for the suspension was granted on March 22, 2004.

The following describes the regulatory history covering the review period for this consult, the two-year time period from April 1, 2005 – March 31, 2007. On August 16, 2005, a “Changes Being Effected” supplemental NDA 21-087/S-026 provided for a new bottle label and prophylaxis stickers for the unit-of-use bottles of 10 count specific for stockpiling by the Department of Defense. On October 27, 2005, supplemental NDA 21-087/S-025 provided for a new bottle label for the previously approved 10-count bottle of Tamiflu<sup>®</sup> capsules for stockpiling by state government, state government agencies, groups acting on behalf of state governments, and Federal entities. Supplemental NDA 21-087/S-030 and NDA 21-246/S-017 dated December 21, 2005, provided for the use of Tamiflu<sup>®</sup> (oseltamivir phosphate) Oral Suspension and Capsules for prophylaxis of influenza for patients between ages 1-12 years. On November 13, 2006, supplemental NDA 21-087/S-033 and NDA 21-246/S-021 provided language in the PRECAUTIONS section of the package insert and in the patient package insert, explaining that patients with influenza should be closely monitored for signs of abnormal behavior while taking Tamiflu<sup>®</sup> as a result of post-marketing reports of neuropsychiatric events in children. This supplemental application also provided language in the DRUG INTERACTIONS section of the package insert and patient package insert regarding concurrent use of Tamiflu<sup>®</sup> with live attenuated influenza vaccine intranasal. Additionally, the supplemental NDA provided instructions for pharmacists for the preparation of a suspension using the contents of Tamiflu<sup>®</sup> Capsules in an emergency setting, when the commercially manufactured oral suspension is not available. Lastly, the supplemental NDA provided clarification regarding the volume declaration for Tamiflu<sup>®</sup> Oral Suspension in the HOW SUPPLIED section of the package insert.

## 1.3 PRODUCT LABELING

### INDICATIONS AND USAGE<sup>1</sup>

#### 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's Immunization Practices Advisory Committee.

## 2 METHODS AND MATERIALS

### 2.1 INTRODUCTION

Using the currently available data resources, this review describes outpatient and inpatient drug use patterns for Tamiflu<sup>®</sup> in the pediatric population as well as in the adult population and includes data two-12 month periods starting one year subsequent to the granting of pediatric exclusivity on March 22, 2004. Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

### 2.2 DETERMINING SETTINGS OF CARE

IMS Health, IMS National Sales Perspectives<sup>™</sup> data (*see Appendix*) were used to determine the setting in which Tamiflu<sup>®</sup> is sold. Sales of this product by number of capsules and number of milliliters (mL) of suspension sold from the manufacturer into the various retail and non-retail channels of distribution were analyzed for two 12-month periods from April 2005 through March 2007.<sup>2</sup> Overall sales of Tamiflu<sup>®</sup> increased by 152% during the two 12-month periods of this review. Examination of sales by dosage form revealed a 217% increase in number of overall oral capsule sales and a 63% increase in number of overall oral suspension (in mL) sales. However, there was a shift in the overall proportion of sales in terms of dosage forms during these two 12-month periods, April 2005 – March 2006 to April 2006 - March 2007. From April 2006 to March 2007, approximately 72% of Tamiflu<sup>®</sup> sales were for the capsule dosage form and approximately 28% as the oral suspension. This represents an increase from close to 58% to 72% in the proportion of Tamiflu<sup>®</sup> Capsules sold and a decrease from 43% to 28% in Tamiflu<sup>®</sup> Suspension sold since the previous 12 months (*Graph 1; see Appendix 2*).

Also, these data showed a shift in the distribution for the capsule dosage form from the outpatient retail channels (chain, independent, and food store) to mail-order pharmacies and inpatient (non-federal hospitals) settings of care during April 2005 – March 2006 to April 2006 - March 2007 (*Graph 2; see Appendix 2*). The pattern of distribution for the oral capsule dosage form into mail order pharmacies accounted for approximately 15% of sales during April 2006 to March 2007,

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<sup>1</sup> PDR<sup>®</sup> Electronic Library<sup>™</sup>, accessed June 2007.

<sup>2</sup> IMS Health, IMS Nationals Sales Perspectives<sup>™</sup>, Data extracted 6-6-2007, Source file: 0706tam2.DVR

increasing from 1.5% of sales during the previous 12-month period. Non-federal hospital purchases accounted for close to 66% of sales for the capsule dosage form, which was 8% during the previous 12-month period from April 2005 to March 2006. Distribution into the outpatient retail channels (excluding mail order) accounted for close to 16.5% of all sales for the capsule dosage form, which was approximately 75% during the previous 12-month period from April 2005 to March 2006.

The pattern of distribution for the oral suspension dosage form remained relatively consistent over the reviewed time period. The retail setting (chain stores, independent stores, and food stores) accounted for the majority of oral suspension sales (~95%). Thus, this consult examines inpatient and outpatient drug utilization data.

## **2.3 DATA SOURCES USED**

### **2.3.1 Outpatient data**

Outpatient use and patient demographics were measured with two data sources from Verispan, LLC: Vector One®: National (VONA) and Total Patient Tracker (TPT) (*see Appendix*). From these two sources, nationally projected estimates of the number of prescriptions dispensed by retail pharmacies and the number of patients who received a dispensed prescription for Tamiflu® were obtained. Indications for use were obtained from the Verispan, Physician Drug and Diagnosis Audit (PDDA) (*see Appendix*). Outpatient drug utilization patterns were examined for two twelve-month periods from April 1, 2005 through March 31, 2007.

### **2.3.2 Inpatient data**

Hospital use was measured using the Premier RxMarket Advisor™ tool from Premier Perspective™ data source (*see Appendix*). From this data source, we examined the number of *UNPROJECTED* patient discharges from a select sample of U.S. hospitals. These data do not include outpatient treatment in hospital clinics or emergency departments unless the patient is admitted. Inpatient drug utilization patterns were examined for one twelve-month period from April 2005 to March 2006 and one 9-month period from April 2006 to December 2006. Data for the year 2007 is unavailable due to the six month lag time of data availability.

## **2.4 PRODUCTS INCLUDED**

In addition to examining outpatient and inpatient drug utilization patterns for Tamiflu®, we examined outpatient prescription dispensing patterns for other anti-influenza products. These products were selected based on previous and ongoing post marketing surveillance. Comparator products were analyzed at the molecule level and include zanamivir, amantadine, and rimantadine.

## **3 RESULTS**

### **3.1 OUTPATIENT DATA**

### 3.1.1 Dispensed Prescriptions

#### 3.1.1.1 Tamiflu® capsule and suspension prescriptions

Over 10 million prescriptions have been dispensed from U.S. retail pharmacies for Tamiflu® since approval of the capsules in December 1999 until May 2007 (*Table 1*). The capsule dosage form represents 84% of the overall Tamiflu® market.

*Table 1.*

<i>Total Number of Prescriptions (TRx) Dispensed (in thousands) by Retail Pharmacies for Tamiflu® (oseltamivir phosphate) Oral Suspension and Capsules from December 1999 to May 2007</i>		
	<b>December 1999 - May 2007</b>	
	TRxs (000)	Share (%)
<b>Oseltamivir phosphate</b>	<b>10,134</b>	<b>100.0%</b>
<b>Capsule</b>	<b>8,531</b>	<b>84.2%</b>
<b>Suspension</b>	<b>1,602</b>	<b>15.8%</b>

*Verispan, LLC: Vector One®: National (VONA) Data extracted 6-20-2007  
Source file: 2007-1169 VONA 6-20-07 tamiflu cumm BPCA.qry*

#### 3.1.1.2 Prescriptions for Select Antiviral Influenza Drugs

Tamiflu® accounts for over 98% of the select anti-influenza antiviral market (*Table 2*). The majority of prescriptions dispensed from retail pharmacies for Tamiflu® are for the capsule dosage form. However, prescriptions dispensed for Tamiflu® suspension increased by approximately 75% and prescriptions for the capsule decreased by approximately 18% during this 2-year analysis.

*Table 2.*

<i>Total Number of Prescriptions (TRx) Dispensed (in thousands) by Retail Pharmacies for Select Anti-Influenza Antiviral Drugs</i>				
	<b>April 2005 - March 2006</b>		<b>April 2006 - March 2007</b>	
	TRxs (000)	Share (%)	TRxs (000)	Share (%)
<b>Anti-Influenza Antiviral Market</b>	<b>1,935</b>	<b>100.0%</b>	<b>1,890</b>	<b>100.0%</b>
<b>Oseltamivir phosphate</b>	<b>1,907</b>	<b>98.5%</b>	<b>1,876</b>	<b>99.3%</b>
<b>Capsule</b>	<b>1,572</b>	<b>82.5%</b>	<b>1,288</b>	<b>68.7%</b>
<b>Suspension</b>	<b>335</b>	<b>17.5%</b>	<b>588</b>	<b>31.3%</b>
<b>Rimantadine HCL</b>	<b>16</b>	<b>0.8%</b>	<b>9</b>	<b>0.5%</b>
<b>Syrup</b>	<b>11</b>	<b>69.0%</b>	<b>7</b>	<b>74.9%</b>
<b>Tablet</b>	<b>5</b>	<b>31.0%</b>	<b>2</b>	<b>25.1%</b>
<b>Zanamivir</b>	<b>8</b>	<b>0.4%</b>	<b>3</b>	<b>0.1%</b>
<b>Inhalant, Other</b>	<b>8</b>	<b>100.0%</b>	<b>3</b>	<b>100.0%</b>
<b>Amantadine HCL</b>	<b>4</b>	<b>0.2%</b>	<b>2</b>	<b>0.1%</b>
<b>Tablet</b>	<b>4</b>	<b>99.3%</b>	<b>2</b>	<b>99.4%</b>
<b>Capsule</b>	<b>--</b>	<b>--</b>	<b>0</b>	<b>0.5%</b>
<b>Syrup</b>	<b>0</b>	<b>0.7%</b>	<b>0</b>	<b>0.1%</b>

*Verispan, LLC: Vector One®: National (VONA) Data extracted 6-6-2007  
Source file: 2007-1169 VONA 6-6-07 antiviral flu drugs BPCA.qry*

### 3.1.2 Patient Demographics

#### 3.1.2.1 Prescriptions by age

The majority of Tamiflu<sup>®</sup> prescriptions for the capsule dosage form are dispensed to adults aged 22 years or older (**Table 3**). However, Tamiflu<sup>®</sup> prescriptions for the capsule dosage form dispensed to children aged 0-12 years increased by approximately 30% and to children aged 13-21 years by approximately 11% during this 2-year analysis. Tamiflu<sup>®</sup> capsule dosage form prescriptions dispensed to adults aged 22 years or older has decreased by approximately 26%.

From April 2005 to March 2007, over 95% of Tamiflu<sup>®</sup> prescriptions for the suspension dosage form are dispensed to children aged 0-12 years. Tamiflu<sup>®</sup> suspension dosage form prescriptions for children aged 0-12 years increased by close to 78% and for children aged 13-21 years increased by 46% during this 2-year analysis.

The increase in Tamiflu<sup>®</sup> prescriptions stratified by dosage form over the two-year period of this analysis coincides with the overall trend of increased total dispensed Tamiflu<sup>®</sup> prescriptions for pediatrics patients (aged 0-16 years) over time as shown in **Graph 3** (*see Appendix 2*).

**Table 3.**

**Total Number of Prescriptions Dispensed (TRx) by Retail Pharmacies for Tamiflu<sup>®</sup> (oseltamivir phosphate) Oral Suspension and Capsules stratified by age**

	April 2005 - March 2006		April 2006 - March 2007	
	TRxs	Share (%)	TRxs	Share (%)
<b>Oseltamivir phosphate</b>	<b>1,906,700</b>	<b>100.0%</b>	<b>1,876,331</b>	<b>100.0%</b>
<b>Capsule</b>	<b>1,572,122</b>	<b>82.5%</b>	<b>1,288,293</b>	<b>68.7%</b>
<b>0-12 years</b>	<b>77,278</b>	<b>4.9%</b>	<b>100,356</b>	<b>7.8%</b>
0-1 years	792	0.1%	547	0.0%
2-5 years	3,091	0.2%	1,561	0.1%
6-12 years	73,395	4.7%	98,248	7.6%
<b>13-21 years</b>	<b>218,913</b>	<b>13.9%</b>	<b>243,845</b>	<b>18.9%</b>
<b>22+ years</b>	<b>1,262,989</b>	<b>80.3%</b>	<b>937,968</b>	<b>72.8%</b>
<b>unspecified age</b>	<b>12,942</b>	<b>0.8%</b>	<b>6,124</b>	<b>0.5%</b>
<b>Suspension</b>	<b>334,578</b>	<b>17.5%</b>	<b>588,038</b>	<b>31.3%</b>
<b>0-12 years</b>	<b>318,110</b>	<b>95.1%</b>	<b>565,573</b>	<b>96.2%</b>
0-1 years	21,829	6.5%	26,760	4.6%
2-5 years	133,128	39.8%	218,764	37.2%
6-12 years	163,153	48.8%	320,049	54.4%
<b>13-21 years</b>	<b>7,916</b>	<b>2.4%</b>	<b>11,591</b>	<b>2.0%</b>
<b>22+ years</b>	<b>4,479</b>	<b>1.3%</b>	<b>4,365</b>	<b>0.7%</b>
<b>unspecified age</b>	<b>4,073</b>	<b>1.2%</b>	<b>6,509</b>	<b>1.1%</b>

Verispan, LLC: Vector One<sup>®</sup>: National (VONA) Data extracted 6-21-2007 and 7-13-07  
 Source file: 2007-1169 VONA 6-21-07 tamiflu form age BPCA.qry and 2007-1169 VONA 7-13-07 tamiflu form age bkdown BPCA.qry

#### 3.1.2.2 Patients by Age

Approximately 1.8 million patients received a prescription for Tamiflu<sup>®</sup> each 12-month period covered by this review (**Table 4**). Similar to the pattern of dispensed prescriptions during this 2-year analysis, the number of patients aged 0-12 years who received a prescription for Tamiflu<sup>®</sup>

increased by approximately 66%. The number of patients aged 13-21 years who received a prescription for Tamiflu® increased by approximately 13%. Additionally, the number of patients aged 22-85 years who received a prescription for Tamiflu® decreased by approximately 24%.

**Table 4.**

***Total Number of Patients Receiving Prescriptions Through Retail Pharmacies for Tamiflu® (oseltamivir phosphate) by Patient Age***

Age Group	MAT Ending March 2006		MAT Ending March 2007	
	Projected Patient Count	Total Patient Share	Projected Patient Count	Total Patient Share
<b>Grand Total</b>	<b>1,802,018</b>	<b>100.0%</b>	<b>1,798,218</b>	<b>100.0%</b>
<b>0 – 12 years</b>	<b>384,138</b>	<b>21.3%</b>	<b>638,309</b>	<b>35.5%</b>
0-1 years	25,682	1.43	31,064	1.73
2-5 years	130,604	7.25	211,137	11.74
6-12 years	228,042	12.65	396,922	22.07
<b>13 – 21 years</b>	<b>221,658</b>	<b>12.3%</b>	<b>249,948</b>	<b>13.9%</b>
<b>22 – 85 years</b>	<b>1,175,403</b>	<b>65.2%</b>	<b>895,397</b>	<b>49.9%</b>
<b>Unknown Age</b>	<b>20,602</b>	<b>1.1%</b>	<b>14,561</b>	<b>0.8%</b>

\*Subtotals may not sum exactly due to rounding. Because of patients aging during the study period (“the cohort effect”), patients may be counted more than once in the individual age categories. For this reason, summing across age bands is not advisable and will result in overestimates of patient counts.

Verispan, Total Patient Tracker, data extracted 6-25-07 and 7-31-07

Source File: 2007-1169 TPT 6-25-07 antiviral flu drugs age BPCA.XLS and 2007-1169 TPT 7-31-07 tamiflu age BPCA4-02to3-07.XLS

### **3.1.3 Prescriber Specialty (Top 5)**

General Practice specialty was the most common prescribing specialty for Tamiflu® capsules followed by Internal Medicine (**Table 5**). Pediatric specialty was the most common prescribing specialty for Tamiflu® suspension followed by General Practice.

**Table 5.**

**Total Number of Retail Prescriptions (TRx) Dispensed (in thousands) for Tamiflu® (oseltamivir phosphate) Capsules and Suspension by Prescriber Specialty (Top 5)**

	April 2005 - March 2006		April 2006 - March 2007	
	TRxs (000)	Share (%)	TRxs (000)	Share (%)
<b>Oseltamivir phosphate</b>	<b>1,907</b>	<b>100.0%</b>	<b>1,876</b>	<b>100.0%</b>
<b>Capsule</b>	<b>1,572</b>	<b>82.5%</b>	<b>1,288</b>	<b>68.7%</b>
GP/FM/DO	581	36.9%	551	42.8%
Internal medicine	322	20.5%	199	15.5%
Pediatrics	152	9.7%	189	14.7%
Unspecified	102	6.5%	71	5.5%
Nurse Practitioner	46	2.9%	56	4.3%
All Others	369	23.5%	222	17.3%
<b>Suspension</b>	<b>335</b>	<b>17.5%</b>	<b>588</b>	<b>31.3%</b>
Pediatrics	178	53.1%	320	54.4%
GP/FM/DO	65	19.5%	123	20.9%
Unspecified	33	9.9%	52	8.9%
Nurse Practitioner	11	3.2%	24	4.0%
Physician Assistant	8	2.4%	17	3.0%
All Others	40	11.9%	52	8.9%

Verispan, LLC: Vector One®: National (VONA) Data extracted 6-21-2007

Source file: 2007-1169 VONA 6-21-07 tamiflu specialty BPCA.gry

GP/FM/DO = General Practice, Family Medicine, Doctors of Osteopathy

**3.1.4 Indication for Use (Top 5)**

According to office-based physician practices in the U.S., “influenza with other respiratory manifestations” (ICD-9 487.1) was the number one diagnosis code associated with the use of Tamiflu® for all ages (**Table 6**). For patients aged 0-12 years and 13-21 years, “other diseases of nasal cavity and sinuses” (ICD-9 478.1) was the second leading diagnosis code associated with the use of Tamiflu®. The second leading diagnosis code associated with Tamiflu® for patients aged 22 years or older was “unspecified viral and chlamydial infections” (ICD-9 079.9).

**Table 6.**

***Top 5 Projected Uses\* (in thousands) of Tamiflu® (oseltamivir phosphate) Capsules and Suspension in Association with a Diagnosis During an Office-based Patient Visit by 4-digit ICD-9 code***

	April 2005 - March 2006		April 2006 - March 2007	
	Uses (000)	Share (%)	Uses (000)	Share (%)
<b>Oseltamivir phosphate</b>	<b>1,478</b>	<b>100.0%</b>	<b>1,529</b>	<b>100.0%</b>
<b>0-12 years</b>	<b>320</b>	<b>21.7%</b>	<b>538</b>	<b>35.2%</b>
4871 Flu W Resp Manifest Nec	226	70.4%	459	85.4%
4781 Nasal & Sinus Dis Nec	--	--	22	4.0%
7806 Pyrexia Unknown Origin	5	1.5%	20	3.7%
V048 Vaccin For Oth Viral Dis	18	5.6%	14	2.6%
V679 Follow-Up Exam Nos	25	7.8%	8	1.5%
All Others	47	14.7%	15	2.8%
<b>13-21 years</b>	<b>290</b>	<b>19.6%</b>	<b>232</b>	<b>15.2%</b>
4871 Flu W Resp Manifest Nec	258	88.9%	225	96.9%
4781 Nasal & Sinus Dis Nec	--	--	7	3.1%
7806 Pyrexia Unknown Origin	6	2.1%	--	--
4620 Acute Pharyngitis	8	2.6%	--	--
5140 Pulm Congest/Hypostasis	6	2.1%	--	--
All Others	12	4.2%	--	--
<b>22+ years</b>	<b>802</b>	<b>54.3%</b>	<b>734</b>	<b>48.0%</b>
4871 Flu W Resp Manifest Nec	664	82.7%	620	84.5%
0799 Viral Infection Nos	--	--	41	5.5%
7806 Pyrexia Unknown Origin	20	2.5%	20	2.8%
4659 Acute Uri Nos	24	3.0%	16	2.2%
9949 Effect External Caus Nec	--	--	10	1.3%
All Others	94	11.8%	27	3.7%
<b>Unspecified Age</b>	<b>66</b>	<b>4.5%</b>	<b>25</b>	<b>1.6%</b>
4871 Flu W Resp Manifest Nec	38	57.7%	15	59.7%
9919 Effect Reduced Temp Nos	--	--	10	40.3%
4781 Nasal & Sinus Dis Nec	8	12.0%	--	--
4620 Acute Pharyngitis	8	12.0%	--	--
7862 Cough	8	12.0%	--	--
All Others	4	6.2%	--	--

\*Number of times Tamiflu® has been reported for treatment of a particular disease during an office-based patient visit Verispan, Physician Drug and Diagnosis Audit (PDDA) Data extracted 6-20-2007

Source file: 2007-1169 PDDA 6-20-07 tamiflu 4ddx BPCA.qry

Diagnosis codes beginning with the letter “V” are codes used for supplementary classification to deal with occasions when circumstances other than a disease or injury classifiable to categories 001-999 are recorded as diagnoses or problems and are not for use in primary, single cause tabulations.<sup>3</sup> Thus, this analysis does not attempt to discern between diagnoses that are treatment versus prevention.

<sup>3</sup> <http://icd9cm.chrisendres.com/2007/index.php?action+child&recordid=10083>. Accessed 6/18/07

## 3.2 INPATIENT DATA

### 3.2.1 Patient Discharges from a Select Sample of Hospitals

From April 2005 through March 2006, 5,687 patient discharges had Tamiflu<sup>®</sup> reported on their billing records from a select sample of U.S. hospitals (*Table 7*). Patients aged 0-12 years represented approximately 8% and patients aged 13-21 years represented less than 3% of this unprojected number.

*Table 7.*

<b><i>Total Number of Unprojected Patient Discharges* stratified by age for Tamiflu<sup>®</sup> (oseltamivir phosphate) Dispensed by Hospitals in the Premier Hospital Network</i></b>				
	<b>Patient Age</b>	<b>April 2005 - March 2006 (12 months) Patient Discharges</b>	<b>April 2006 - December 2006 (9 months) Patient Discharges</b>	<b>April 2005 - December 2006 (Total: 21 months) Total Patient Discharges</b>
<b>Total</b>		<b>5,687</b>	<b>1,609</b>	<b>7,296</b>
Oseltamivir	0-12 years	456	241	<b>697</b>
	13-21 years	154	51	<b>205</b>
	22+ years	5,077	1,317	<b>6,394</b>

*Premier RxMarket Advisor<sup>™</sup>, Data extracted June 21, 2007*

*Source file: 2007-1169 Premier 6-21-07 tamiflu age discharges.xls*

*Premier Perspective<sup>™</sup> contains data from approximately 450 hospitals from January 2000 through present with a lag time of 6 months*

*These data do not include out-patient treatment in hospital clinics nor emergency departments unless the patient is admitted.*

*\*Unprojected Patient Discharges represent use in a sample of hospitals.*

## 4 DISCUSSION

Tamiflu<sup>®</sup> is indicated for the treatment and prophylaxis of influenza. For the past decade, the world has increasingly recognized the threat of pandemic flu caused by the highly pathogenic avian influenza virus of the subtype H5N1. Globally, influenza pandemic preparedness plans have incorporated stockpiling of Tamiflu<sup>®</sup>. In 2005, U.S. state and local governments began to establish Tamiflu<sup>®</sup> stockpiles in concert with healthcare facilities. During the two 12-month periods of this review, April 2005 – March 2006 to April 2006 - March 2007, overall sales of Tamiflu<sup>®</sup> increased by 152%. Further examination of sales by distribution channels for Tamiflu<sup>®</sup> using IMS Health, IMS National Sales Perspectives<sup>™</sup>, data revealed a shift in proportions of dosage form sales. From April 2006 to March 2007, Tamiflu<sup>®</sup> Capsules are being sold more into non-retail channels than in the previous 12-month period. There was also a shift of Tamiflu<sup>®</sup> Capsule sales into mail order pharmacies and non-federal hospital distribution channels from the previous 12-month time period. Whereas, the pattern of distribution for the suspension dosage form had not change substantially during the two year period of this review. One possible explanation for the shift in capsule sales into non-federal hospital channels is the establishment of institutional stockpiling by healthcare facilities. Limitations of the database used to examine hospital drug utilization patterns for Tamiflu<sup>®</sup> include incomplete 2007 data and the absolute patient counts for the 12-month time period of April 2005 to March 2006.

Verispan, LLC: Physician Drug and Diagnosis Audit (PDDA) data provide estimates of patient demographics and indications for use of medicinal products in the U.S. Due to sampling and data collection methodologies, the small sample size can make these data unstable, particularly if use is not common in the pediatric population. Verispan recommends caution interpreting projected annual uses or mentions below 100,000 as the sample size is very small with correspondingly large confidence intervals and trending variability. Additionally, when interpreting diagnoses data, one must take into consideration that while the supplementary “V code” (V04.8) “need for prophylactic vaccination and inoculation against other viral diseases” is present in the top 5 diagnoses for children aged 0-12 years, it is not definitively indicative of the number of prophylactic uses for Tamiflu®.

The inpatient data presented in this review are all based on **unprojected patient** counts and any observed changes in absolute patient counts do not necessarily represent national trends and should be interpreted with caution. Other limitations for the inpatient analysis include the 6 month lag time of the database and the unavailability of complete data for January 2007 through March 2007.

## **5 CONCLUSION**

Outpatient prescription data indicate that use of Tamiflu® in the pediatric population is substantial and increasing over time. Outpatient diagnoses data indicate that “influenza with other respiratory manifestations” (ICD-9 487.1) was the number one diagnosis code associated with the use of Tamiflu® for all ages. Inpatient pediatric utilization patterns should be interpreted with caution.

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## APPENDICES

### APPENDIX 1: Database Descriptions

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#### *IMS Health, IMS National Sales Perspective, Retail, Non-Retail or Combined*

The IMS Health, IMS National Sales Perspective measures the volume of drug products (both prescription and over-the-counter) and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. IMS National Sales Perspectives™ measures the volume of drug products moving from manufacturer into retail and non-retail settings in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections.

#### *Verispan, LLC: Vector One®: National (VONA)*

Verispan's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 1.5 billion prescription claims per year, representing over 100 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. Verispan receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

#### *Verispan, LLC: Vector One®: Total Patient Tracker (TPT)*

Verispan's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems. Vector One® receives over 1.5 billion prescription claims per year, representing over 100 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

#### *Premier*

Premier's database is a large hospital drug utilization and financial database. Information is available from over 450 acute care and pediatric facilities and includes approximately 16 million

inpatient records. On an annual basis, this constitutes roughly one out of every seven inpatient discharges in the United States. Data are available from January 2000 through the present, but have a lag time of approximately six months. Premier's primary mission is to assist health care institutions improve clinical and operating performance in three strategic areas: group purchasing, supply chain and healthcare informatics. To that end, the Premier Informatics group developed this database in part to analyze utilization of resources to improve clinical efficiency.

The hospitals that contribute information to this database are a select sample of both Premier and U.S. institutions, and do not necessarily represent all hospitals in the U.S. Data are collected from this sample of participating hospitals with diverse characteristics based upon geographic location, bed size, population served, payors and teaching status. The data collected include demographic and pharmacy-billing information, as well as all diagnoses and procedures for every patient discharge. Preliminary comparisons between participating Premier hospital and patient characteristics and those of the probability sample of hospitals and patients selected for the National Hospital Discharge Survey (NHDS) proved to be very similar with regard to patient age, gender, length of stay, mortality, primary discharge diagnosis and primary procedure groups. Based upon these analyses, FDA believes that most estimates of national inpatient drug use based on Premier data appear to be reasonable, but strongly recommends making this determination on a drug-specific basis.

#### ***Verispan, LLC: Physician Drug & Diagnosis Audit (PDDA)***

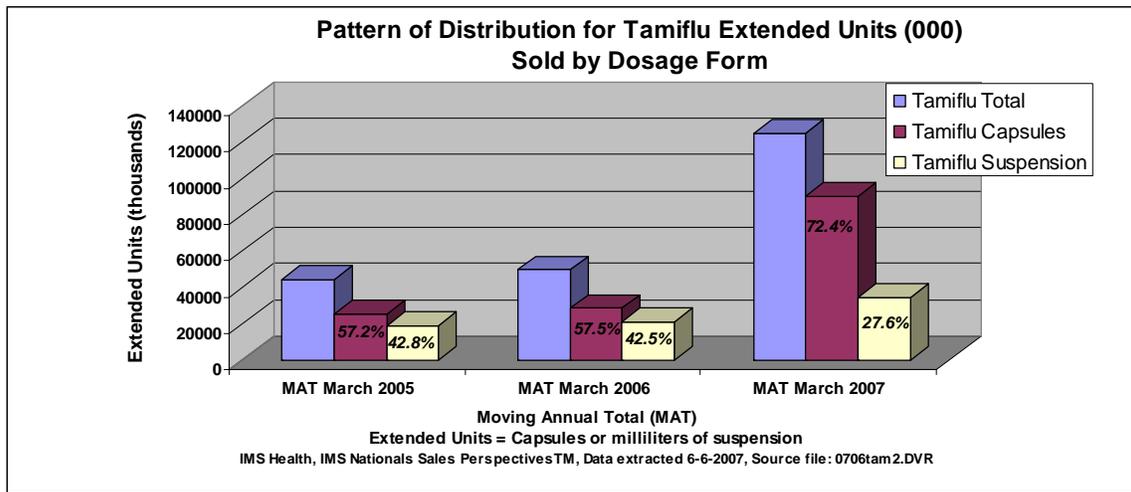
Verispan's Physician Drug & Diagnosis Audit (PDDA) is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from approximately 3,100 office-based physicians representing 29 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

Verispan uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

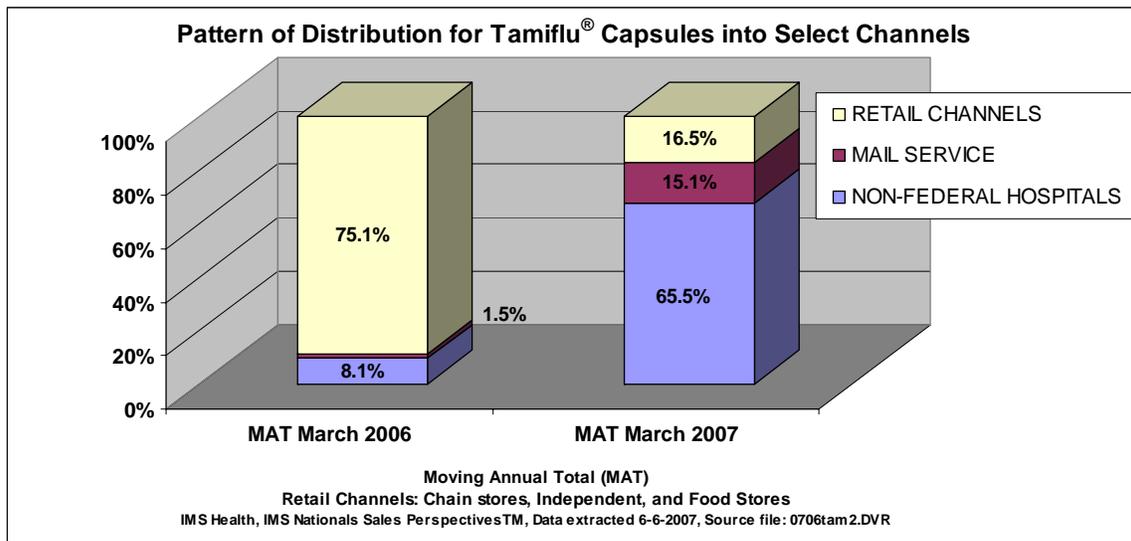
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APPENDIX 2: Tables and Figures

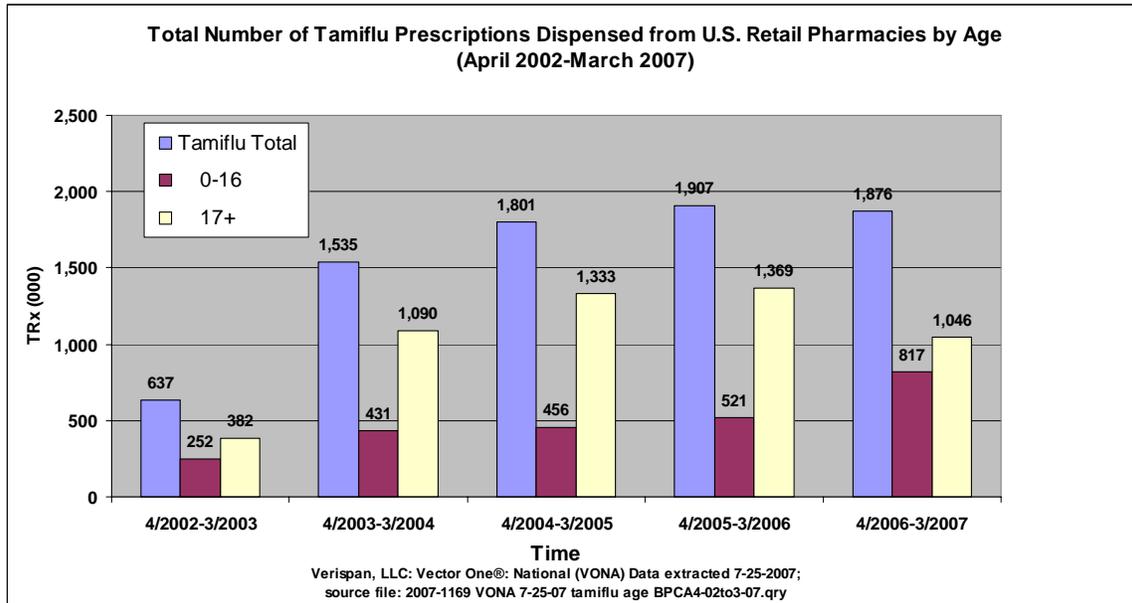
Graph 1.



Graph 2.



Graph 3.



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