

Memorandum

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SUBJECT: One Year Post-Pediatric Exclusivity Post-marketing Adverse Event Review: Drug Use Data oseltamivir (Tamiflu[®]) Oral Suspension: NDA 21-246

****This document contains proprietary data from IMS Health and Verispan, LLC which cannot be shared outside of FDA without clearance from the data vendors obtained through the Office of Drug Safety.****

EXECUTIVE SUMMARY

This consult examines drug utilization trends for oseltamivir (Tamiflu[®]) in the pediatric population (ages 0-16 years). Sales and outpatient drug utilization data were examined for the three-year period from April 1, 2002 – March 31, 2005 with a primary focus on patterns 12 months before and 12 months following the granting of Pediatric Exclusivity for Tamiflu[®] oral suspension on March 22, 2004. As comparators, the sales and outpatient drug use patterns of the three other commercially available anti-influenza products (amantadine, rimantadine, and zanamivir) were examined. Since over 90% of all oseltamivir sales are into the retail channels, only outpatient drug utilization patterns were examined.

Outpatient prescriptions of all oral anti-influenza products combined increased by 82% over the three year period of April 2002 – March 2005. Compared to the other anti-influenza products, by the final year of this analysis (April 2004 - March 2005) oseltamivir had become the most commonly prescribed oral anti-influenza product, accounting for 58% of prescriptions dispensed.

Prescriptions for all oseltamivir products combined increased by 183% over the three 1-year periods of this analysis with 637,000 prescriptions dispensed during April 2002 - March 2003,

1.5 million prescriptions dispensed during the pre-exclusivity year (April 2003 - March 2004), and 1.8 million prescriptions dispensed during the post-exclusivity period (April 2004 - March 2005). The suspension dose form accounted for 18% of oseltamivir prescriptions dispensed during April 2002 – March 2003, decreased to 14% in April 2003 - March 2004, then rose to 16% of prescriptions in April 2004 - March 2005, exhibiting a 3 year overall increase of 152%.

The top specialties prescribing oral oseltamivir capsules from April 2002 through March 2005 were general practitioners¹, which accounted for 42% of dispensing both pre-exclusivity (April 2003 – March 2004) and post-exclusivity (April 2004 – March 2005); pediatricians were ranked 3rd in each of these years. For oseltamivir suspension prescriptions, pediatricians were the top prescribers in each of the three years examined between April 2002 – March 2005. Pediatricians accounted for 51% of dispensing during April 2002 – March 2003, 43% of dispensing in the year pre-exclusivity (April 2003 – March 2004) and 52% of dispensing in the year post-exclusivity (April 2004 – March 2005). In general, prescribing patterns for oral oseltamivir suspension dispensed in outpatient retail pharmacy settings showed no substantial change across provider specialties during the 36-month study period.

Although the total number of oseltamivir prescriptions dispensed to pediatric patients ages 0-16 years old increased by a relative 80% during the three years of this analysis, the yearly percentage of prescriptions for pediatric patients age 0-16 years decreased. The proportion of prescriptions dispensed for patients age 0-16 declined from 39.9% of prescriptions dispensed during April 2002 – March 2003, 28.1% of prescriptions dispensed during April 2003 – March 2004 to 25.3% of prescriptions dispensed during April 2004 – March 2005. Although use in patients less than 1 year old has not been approved, this pediatric subgroup accounted for 2-6% of the yearly total of oseltamivir prescriptions dispensed to patients ages 0-16 years.

The most common diagnosis associated with a mention of oseltamivir in both the pediatric patients (ages 0-16 years) and adults (age 17 and over) in office based physician-patient encounters was “Influenza with other Respiratory Manifestations” (ICD-9 487.1) which accounted for 95-99% of mentions for pediatric patients and 86-92% of mentions for adults in each of the 3 years from April 2002 – March 2005.

In summary, use of oral oseltamivir in pediatric patients ages 0-16 years is substantial, accounting for possibly as high as 25% of overall outpatient prescriptions in the post-exclusivity period. The number of pediatric outpatient prescriptions increased by 5.6% from the pre to post exclusivity years, while prescriptions for adults increased by 22.3% over the same two-year period.

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 the BPCA requires the reporting of adverse events associated with the use of a drug in children during the one-year period following the date on which the drug received pediatric marketing exclusivity. In support of this mandate, the FDA is required to provide a report to the Pediatric Advisory

¹ The general practitioner category includes general practice, family practice, and osteopathic physicians.

Committee on the drug utilization patterns and adverse events associated with the use of the drug on a quarterly basis. This review is in addition to the routine post-marketing safety surveillance activities the FDA performs for all marketed drugs.

Oseltamivir (Tamiflu[®]) is an oral antiviral agent active against laboratory and clinical isolates of influenza virus. It is available as 75mg capsules for oral administration (NDA 21-087), and as a powder for oral suspension 12mg/ml (NDA 21-246). Oseltamivir suspension was approved on December 14, 2000, for the prophylaxis of influenza in patients age 13 and older and for the treatment of influenza in patients 1 year of age and older.

For influenza prophylaxis, the recommended oral dose of oseltamivir in adults and adolescents 13 years of age and older following close contact with an infected individual is 75 mg once daily for at least 7 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.

For the treatment of influenza in patients age 13 years of age and older, the recommended oral dose of oseltamivir is 75mg twice daily for 5 days while for patients age 1-12 years, dosing is weight based. Treatment should begin within 2 days of symptom onset.

The Pediatric Exclusivity Board of the FDA granted pediatric exclusivity for Tamiflu[®] Oral Suspension (NDA 21-246) on March 22, 2004.

This review describes outpatient drug usage of oseltamivir (Tamiflu[®]) oral capsules and suspension in the pediatric population as compared to the adult population. Use of Tamiflu[®] is provided in the context of other drug products routinely used in the treatment of influenza. These products include amantadine, rimantadine, and zanamivir. Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

DATA SOURCES

This review describes the annual sales and drug use patterns of oseltamivir (Tamiflu[®]) oral suspension in the pediatric population as compared to the adult population in two years before and one year after the granting of pediatric exclusivity. Proprietary drug use databases licensed by the Agency were used to conduct this analysis. The data sources for this analysis are described in detail below.

IMS Health, National Sales Perspectives[™]

IMS Health National Sales Perspectives[™] measures the volume of drug products (both prescription and over-the-counter) and selected diagnostic products moving from manufacturers into retail and non-retail markets. The volume of drug products transferred to these markets is expressed in terms of sales dollars, vials, and market share. 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. These data are based on national projections.

For this analysis, the sales trend of oral influenza antivirals was examined yearly from April 1, 2002 – March 31, 2005 inclusive.

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 and the patient's age and gender are available from these prescription data.

The number of dispensed prescriptions is obtained from a sample of virtually all retail pharmacies throughout the U.S and represents approximately half of the retail prescriptions dispensed nationwide. The Verispan sample consists of all prescriptions from approximately one-third of the stores and an average of 30% of prescriptions from the remaining stores.

In the Vector One™ database, prescription activity from a variety of sources including national retail chains, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups is integrated and then projected to make national estimates of dispensed prescriptions. These projections are based on 1.8 billion prescription claims per year entering the database.

Data for this analysis included all oral influenza antiviral prescriptions dispensed yearly from April 1, 2002 – March 31, 2005 inclusive.

IMS Health, National Disease And Therapeutic Index™ (NDTI™)

The National Disease and Therapeutic Index™ (NDTI™) is an ongoing survey designed and conducted by IMS Health to provide descriptive information on the patterns and treatment of disease encountered in office-based practices in the continental U.S. The data are collected from a panel of approximately 3,000 office-based physicians who complete and submit a survey of their practice patterns to IMS Health for two consecutive days per quarter. These data may include profiles and trends of diagnoses, patients, drug products mentioned, and treatment patterns. These data are projected nationally to reflect national prescribing patterns.

NDTI™ uses the term drug uses for 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.

For this analysis, we examined annual mentions of oseltamivir oral products during office-based physician visits yearly during the time period from April 1, 2002 – March 31, 2005 inclusive.

Outpatient Drug Usage

Sales and Distribution Channels

Sales of oral anti-influenza products were examined yearly from April 1, 2002 – March 31, 2003 (Table 1). Retail channels are the largest purchasers of oseltamivir, representing at least 92% of the bottles of capsules and at least 98% of the bottles of suspension sold in each of the three one-year periods of this analysis.

Table 1. Total Number of Bottles (capsules, suspension) of Oseltamivir Sold into U.S. Distribution Channels During April 2002 – March 2005 (in thousands)

	April 2002 - March 2003		April 2003 - March 2004		April 2004 - March 2005	
	N (000)		N (000)		N (000)	
Total Oral Anti-Influenza Market	2,052	100%	4,006	100%	5,723	100%
Oseltamivir	988	48%	2,310	58%	3,272	57%
Capsules	680	69%	1,848	80%	2,518	77%
Retail	651	96%	1,696	92%	2,348	93%
Non-Retail	29	4%	152	8%	170	7%
Suspension	308	31%	462	20%	754	23%
Retail	304	99%	451	98%	741	98%
Non-Retail	4	1%	11	2%	13	2%
Amantadine	982	48%	1,565	39%	2,333	41%
Rimantadine	58	3%	114	3%	100	2%
Zanamivir	24	1%	17	0%	17	0%

IMS Health, National Sales Perspectives™ Combined, April 2002 – March 2005, Data Extracted 07-2005 (File:0507tam2.dvr)
 *Retail includes chain, independent, mail order, food store pharmacies
 ** Non-retail includes Non-federal hospitals, federal facilities, long term care, clinics, HMOs, home health care, prisons, universities, and other
 †Subtotals may not sum exactly due to rounding error

Dispensed Prescriptions

Outpatient prescriptions for the selected oral anti-influenza agents combined increased by approximately 82% over the 3 years from April 2002 – March 2005, rising from 1.7 million prescriptions dispensed in the 12-month period from April 2002 - March 2003 to 3.2 million prescriptions in the 12-month period from April 2003 - March 2004 then declining to 3.1 million prescriptions dispensed in April 2004 - March 2005 (Table 2). During April 2002 - March 2003, oseltamivir accounted for 37% (637,000 prescriptions) of the combined oral anti-influenza prescriptions and amantadine accounted for 51% (874,000 prescriptions). In the final year of this analysis (April 2004 – March 2005), oseltamivir prescriptions accounted for 58% (1.8 million prescriptions) of the market and amantadine accounted for 34% (1.0 million prescriptions). During April 2004 - March 2005, rimantadine accounted for 9% of the market (266,000 prescriptions) and zanamivir accounted for 0.2% (7,000 prescriptions).

Prescriptions for all oseltamivir products combined increased by 183% over the three 1-year periods of this analysis with 637,000 prescriptions dispensed during April 2002 - March 2003, 1.5 million prescriptions dispensed during the pre-exclusivity year (April 2003 - March 2004), and 1.8 million prescriptions dispensed during the post-exclusivity year (April 2004 - March 2005). The suspension dosage form accounted for 18% (115,000) of oseltamivir prescriptions dispensed in April 2002 – March 2003; 14% (212,000) in April 2003 - March 2004, and 16% (290,000) of prescriptions in April 2004 - March 2005, and exhibited an overall increase of 152% over the 3 years of this analysis.

Table 2: Total Number of Prescriptions Dispensed (in thousands) in Retail Pharmacies* Nationwide for Anti-influenza Products During April 2002 – March 2005

	April 2002 - March 2003		April 2003 - March 2004		April 2004 - March 2005	
	N (000)		N (000)		N (000)	
Anti-Influenza Market	1,717	100.0%	3,223	100.0%	3,118	100.0%
Oseltamivir	637	37.1%	1,535	47.6%	1,801	57.8%
Capsules	521	81.9%	1,322	86.2%	1,511	83.9%
Suspension	115	18.1%	212	13.8%	290	16.1%
Amantadine	874	50.9%	1,337	41.5%	1,044	33.5%
Rimantadine	189	11.0%	343	10.7%	266	8.5%
Zanamivir	18	1.0%	8	0.2%	7	0.2%

Verispan, LLC, April 2002 – March 2005, Data Extracted 8-2005 (File: D040278 BPCA Tamiflu.qry)

† Subtotals may not sum exactly due to rounding error

* Does not include mail order or long-term care

Prescriber Specialty

The top prescriber specialties prescribing oral oseltamivir capsules from April 2002 through March 2005 were general practitioners², which accounted for 44% of dispensing during April 2002 – March 2003, and 42% of dispensing in both the year pre-exclusivity (April 2003 – March 2004) and the year post-exclusivity (April 2004 – March 2005) (Table 3). Of all specialties, pediatricians were ranked 3rd in prescribing oral oseltamivir capsules during both the pre-exclusivity and post-exclusivity years. For oseltamivir suspension prescriptions, pediatricians were the top prescribers in each of the 3 years examined. Pediatricians accounted for 51% of suspension prescriptions during April 2002 – March 2003, 43% of suspension prescriptions in the year pre-exclusivity (April 2003 – March 2004) and 52% of prescriptions in the year post-exclusivity (April 2004 – March 2005). In general, prescribing patterns for oral oseltamivir suspension dispensed in outpatient retail pharmacy settings showed no substantial change across provider specialties during the 36-month study period.

² The general practitioner category includes general practice, family practice, and osteopathic physicians.

Table 3: Total Number of Prescriptions Dispensed (in thousands) for Oseltamivir Oral Suspension Nationwide by Physician Specialty During April 2002 – March 2005

	April 2002 - March 2003		April 2003 - March 2004		April 2004 - March 2005	
	N (000)		N (000)		N (000)	
Oseltamivir	637	100.0%	1,535	100.0%	1,801	100.0%
Oral Capsules	521	81.9%	1,322	86.2%	1,511	83.9%
GP, FM, & DO*	230	44.2%	555	42.0%	635	42.0%
Internal Medicine	77	14.8%	242	18.3%	312	20.6%
Pediatricians	79	15.2%	131	9.9%	134	8.9%
All Others	135	25.9%	394	29.8%	431	28.5%
Oral Suspension	115	18.1%	212	13.8%	290	16.1%
Pediatricians	59	51.4%	91	42.9%	150	51.6%
GP, FM, & DO*	27	23.8%	49	22.9%	57	19.6%
Unspecified	16	13.5%	38	17.7%	42	14.6%
All Others	13	11.2%	35	16.5%	41	14.1%

Verispan, LLC, April 2002 – March 2005, Data Extracted 8-2005 (File: D040278 BPCA Tamiflu MDs.qry)

* General Practice, Family Medicine & Osteopathic physicians

† Subtotals may not sum exactly due to rounding error

Patient Demographics: Prescription-based analysis (VONA)

While the total number of oseltamivir prescriptions dispensed to pediatric patients ages 0-16 years old increased during the three years of this analysis, the overall percentage of prescriptions for pediatric patients age 0-16 years declined (Table 4). Prescriptions dispensed for patients age 0-16 rose from 254,000 (39.9% of total prescriptions) during April 2002 – March 2003, to 432,000 (28.1%) during April 2003 – March 2004 and 456,000 prescriptions (25.3%) during April 2004 – March 2005.

Although oseltamivir use in patients less than 1 year old has not been approved, this pediatric subgroup appeared to account for 2-6% of the yearly total of oseltamivir prescriptions dispensed to patients ages 0-16 years, with the peak percent of use occurring in the year pre exclusivity (April 2003 – March 2004). Patients in the 2-11 year old subgroup accounted for 58-65% of yearly prescriptions, and patients in the 12-16 year old subgroup accounted for 31-41 % of yearly oseltamivir prescriptions for patients aged 0-16 years.

Table 4. Number and percentage of Oseltamivir Capsules and Suspension Prescriptions Dispensed (in thousands) to Adult and Pediatric Patients by Retail Pharmacies* in the U.S. During April 2002 – March 2005.

	April 2002 - March 2003		April 2003 - March 2004		April 2004 - March 2005	
	N [†] (000)		N [†] (000)		N [†] (000)	
Oseltamivir	637	100.0%	1,535	100.0%	1,801	100.0%
Age 0-16	254	39.9%	432	28.1%	456	25.3%
0-1	6	2.4%	27	6.3%	19	4.2%
2-11	145	57.1%	250	57.9%	296	64.9%
12-16	103	40.6%	155	35.9%	141	30.9%
Age 17+	383	60.2%	1,090	71.0%	1,333	74.0%
Age Unspecified	0		14	0.9%	13	0.7%

Verispan, LLC, VONA Vector One April 2002 – March 2005, Data Extracted 8-2005 (File: D040278 BPCA Tamiflu Age.qry)
[†]Subtotals may not sum exactly due to rounding error, a zero means less than 500 prescriptions
*Does not include mail order or long-term care

Indication for Use

The most common diagnosis for pediatric patients ages 0-16 years associated with a mention of oseltamivir capsules and suspension combined in office-based physician-patient encounters was “Influenza with other Respiratory Manifestations” (ICD-9 487.1) which accounted for 99% of mentions during the pre-exclusivity period (April 2003 - March 2004) and 95% of mentions during the post-exclusivity (April 2004 - March 2005) period (Table 5). Results for adult patients ages 17 years and older were similar.

Table 5. Top Diagnoses Associated with Mentions of Oseltamivir Capsules and Suspension Combined in Visits to Office-based Physicians During April 2002 - March 2005

IMS Reported ICD-9 Code	April 2002 - March 2003		April 2003 - March 2004		April 2004 - March 2005	
	N (000)		N (000)		N (000)	
Total All Patients	598	100.0%	1,178	100.0%	906	100.0%
Age 0 - 16	238	39.8%	497	42.2%	289	31.9%
4871 Influenza w/ other Resp Manifestations	232	97.3%	491	98.8%	276	95.3%
4659 Acute Resp Infection Unspecified Site	---	---	---	---	8	2.7%
0799 Unspecified viral and Chlamydia infections	---	---	---	---	6	2.0%
V048 Prophylactic Vaccination for Influenza	---	---	6	1.2%	---	---
5188 Other diseases of lung	6	2.7%	---	---	---	---
Total Others (0)	---	---	---	---	---	---
Age 17 +	339	56.7%	629	53.4%	598	66.0%
4871 Influenza w/ other Resp Manifestations	306	90.0%	538	85.5%	553	92.3%
0799 Unspecified viral and chlamydial infections	10	3.0%	19	3.1%	22	3.7%
4659 Acute Resp Infection Unspecified Site	10	2.8%	10	1.6%	12	1.9%
4660 Acute Bronchitis	---	---	---	---	6	.9%
4870 Influenza with Pneumonia	---	---	25	4.0%	5	.8%
Total Others (8)	14	4.2%	37	5.9%	2	.3%
Age Unspecified	21	3.5%	51	4.4%	19	2.0%

IMS National Disease and Therapeutic Index™, MAT 3yr Apr 2002 - Mar 2004. Data extracted 3-2005
(File: NDTI Tamiflu Diagnosis by Age Band D040223.xls)

DISCUSSION

Sales data

The IMS Health, National Sales Perspectives™ does not provide a direct estimate of use but does provide a national estimate of units sold from the manufacturer to various channels of distribution. It does not include demographic information for the patients ultimately receiving these products, such as age and gender. The amount of products purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume that facilities purchase drugs in quantities reflective of actual patient purchase and use.

Outpatient use data

Sales and prescription data for other antivirals are included as comparators for oseltamivir, however, these drugs also have indications other than treating or preventing influenza. In particular, amantadine is approved for influenza A prophylaxis and treatment, treatment of Parkinson's disease and treatment of drug-induced extra-pyramidal symptoms. In a survey of office-based physicians during the pre-exclusivity year, influenza related diagnoses accounted for 65% of amantadine mentions and 60% of mentions in the post-exclusivity year³. The exact proportions of amantadine prescriptions dispensed for influenza related diagnoses are unknown.

³ IMS Health, National Disease and Therapeutic Index™, MAT 4/2002 – 3/2005 file: NDTI Amantadine diagnoses.dvf

NDTI™ data provide estimates of patient demographics and indications for use of medicinal products in the U.S. Due to the sampling and data collection methodologies, the small sample size can make these data unstable, particularly when use is not prevalent, as in the case of oseltamivir suspension in the adult population. While a CPT code exists for prophylactic vaccination against influenza, there is not an equivalent code for influenza prophylaxis with an oral agent. We are unable to determine the extent of use of oseltamivir for prophylaxis.

VONA national prescription data currently do not include prescriptions obtained through mail order or long-term care settings. It is unlikely that pediatric patients would receive prescriptions for oseltamivir through these channels, however, it is very likely that elderly adults would receive oseltamivir, as well as other products, through these channels. Although the actual counts of pediatric prescriptions would not be affected by this omission, the estimated percentage of pediatric use of oseltamivir may be overestimated if a substantial number of prescriptions for elderly adults are not included in this product. Therefore, our estimates of the percentage of prescriptions of oseltamivir dispensed to children may be slightly high. The estimated numbers of prescriptions dispensed to children aged 0-1 year are very small, and therefore likely to be unstable – caution should be used when interpreting these estimates.

CONCLUSION

In summary, the use of oral oseltamivir is concentrated in adult patients, with 0-16 year olds accounting for possibly as high as 25% of overall outpatient prescriptions in the post-exclusivity year. Pediatric outpatient prescriptions increased by 5.6% from the pre to post exclusivity years, while prescriptions for adults increased by 22.3% over the same 2-year period.

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