

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PID#: D030547

DATE: December 2, 2004

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SUBJECT: One Year Post-Pediatric Exclusivity Post-Marketing Adverse Event Review:
Drug Use Data - Nelfinavir Mesylate
Viracept® 250mg Tablet (NDA 20-779), Viracept® 50mg/gm Powder (NDA 20-778), Viracept® 625mg Tablet (NDA 21-503)
Pediatric Exclusivity Grant Date: September 4, 2003

EXECUTIVE SUMMARY

This consult examines drug use for nelfinavir mesylate (Viracept®) in the pediatric population (0-16 years), with primary focus on patterns of use one year before and one year following the granting of Pediatric Exclusivity on September 4, 2003.

For all HIV protease inhibitors as a class, an estimated 1.9 million prescriptions were dispensed in the U.S. during the 12-month period from September 2003 through August 2004. This prescription volume represents a 20% increase when compared to an estimated 1.6 million prescriptions dispensed in the previous 12-month time period from September 2002 through August 2003. In contrast, the total number of dispensed prescriptions for the HIV protease inhibitors decreased by an estimated 1% in the 12 month time period from September 2002 through August 2003, compared to the previous 12-month time period from September 2001

through August 2002. This variation in market growth is likely due to the addition of atazanavir and fosamprenavir into the market in 2003. Total dispensed prescriptions for Viracept® appear to have decreased approximately 22% from roughly 398,379 dispensed prescriptions from September 2002 to August 2003, inclusive, to approximately 311,583 dispensed prescriptions in the 12 months from September 2003 to August 2004, inclusive.

Among an insured population in the Caremark system, the pediatric age group (1-16 years) accounted for roughly 3.2% of claims, from September 1, 2003 and August 31, 2004. Estimates of the number of prescriptions dispensed nationally to pediatric populations were not possible to generate from this data source, given that our data sources do not include dispensing from clinics, which represents a substantial proportion of product sales (~13%) and, therefore, product use.

Pediatricians were responsible for roughly 3% (~7,000 prescriptions) of all Viracept® prescriptions dispensed in the U.S. between September 1, 2003 and August 31, 2004.

INTRODUCTION

On January 3, 2001, 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 the drug in children during the one-year period following the date when the drug received marketing exclusivity. In support of this mandate, the FDA is required to provide a report to the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory 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.

Viracept® is an antiviral protease inhibitor available as an oral tablet containing either 250mg or 625mg of nelfinavir mesylate (NDA 20-779 and NDA 21-503), respectively). Viracept® is also available as an oral powder containing 50mg of nelfinavir base per gram (NDA 20-778). The 250mg oral tablet and the 50mg/gm oral powder were approved under NDA 20-779 and NDA 20-778, respectively, on March 14, 1997. The 625mg tablet was approved under NDA 21-503 on April 30, 2003. All three products, in combination with other antivirals, are indicated for the treatment of HIV infection. The recommended adult dose of Viracept® is 1250mg (five 250mg tablets or two 625mg tablets) given twice daily or 750mg (three 250mg tablets) given three times daily with food. The pediatric dose of Viracept® is 45-55mg/kg given twice daily or 25-35mg/kg given three times daily with food. In patients less than 2 years of age, Viracept® was found to be safe at doses studied; however, efficacy could not be established.

The Pediatric Exclusivity Board of the FDA granted pediatric exclusivity for Viracept® (NDAs 20-778, 20-779, and 21-503) on September 4, 2003. Other currently marketed protease inhibitors include; ritonavir, lopinavir, atazanavir, indinavir, saquinavir, fosamprenavir, and amprenavir.

We will use the term Viracept® to refer to all forms of nelfinavir mesylate unless otherwise specified. To date, there are no generic competitors of this product.

This review describes outpatient drug usage of Viracept® in the pediatric population as compared to the adult population. Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

DATA SOURCES

Sales data reflecting the number of bottles and tablets sold by the manufacturer to various retail and non-retail channels of distribution were analyzed using IMS Health's, National Sales Perspectives™ database. Because greater than 67% of sales of these products occurred in the outpatient setting and because only an estimated 6% of sales were purchased by non-federal hospitals from September 2003 through August 2004, we only examined the outpatient drug utilization of these products (Table 1). Although clinics represented a significant proportion of sales (~13.4%), the data resources currently available to the Agency do not capture drug use in outpatient clinics, hence limiting our analysis. Outpatient Viracept® dispensed prescriptions were estimated by using 2 databases in concert: IMS Health's National Prescription Audit Plus™ (NPA Plus™) and Caremark (Dimension Rx™).

Table 1: Sales of Bottles (Eaches) and Tablets (Extended Units) Sold Through Retail and Non-Retail Channels of Distribution During September 2003 – August 2004 in IMS Health, National Sales Perspectives™					
September 2003 – August 2004					
NELFINAVIR		Bottles (000's)	%	Tablets (000's)	%
All Nelfinavir		438	(100%)	123,148	(100%)
All tablets (250mg & 625mg)					
	Total	430.2	(98.2%)	122,067	(99.1%)
	Retail	288.5	(67%)	82,264	(67.4%)
	*Non-Retail	141.9	**(33%)	39,804	(32.6%)
Powder for Suspension (50mg/gm)				milligrams	
	Total	7.5	(1.7%)	1,081	(0.9%)
	Retail	4.9	(65.3%)	709	(65.6%)
	Non-Retail	2.4	(32%)	372	(34.4%)
				Tablets	
	***HIV PEP Kit	0.3	(0.1%)	0	(0%)

*Non-retail channels include non-federal hospitals, federal facilities, long term care, home health care, clinics, HMO's, and miscellaneous-prison, universities, and other
 **Non-Federal hospital sales (~6%), Clinics over (13%)
 ***HIV PEP Kit contains nelfinavir, lamivudine, zidovudine and channel of distribution is @100% Non-Federal Hospitals
 IMS Health, IMS National Sales Perspectives™, Moving Annual Totals: Sept 2001 – August 2004, Data Extracted October 2004
 Original File: 0410nel3.dvr

I. OUTPATIENT DRUG USE

IMS HEALTH, NATIONAL PRESCRIPTION AUDIT PLUS™ (NPA PLUS™)

NPA Plus™ measures the retail dispensing of prescriptions, or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions.

These retail pharmacies include chain, independent, food store, mail order, discount houses, and mass merchandiser pharmacies, as well as nursing home (long-term care) pharmacy providers. Information on the specialty of the prescribing physician can also be collected, except for in the long-term care and mail order pharmacy settings.

The number of dispensed prescriptions is obtained from a sample of approximately 22,000 pharmacies throughout the U.S. and projected nationally. The pharmacies in the database account for approximately 40% of all pharmacy stores and represent approximately 45% of prescription coverage in the U.S.

Data for this analysis included all prescriptions dispensed from September 1, 2001 to August 31, 2004, inclusive.

Caremark DIMENSION RX™

Caremark is one of the largest pharmacy benefit manager (PBM) companies in the US, currently covering over 75 million patient lives, and processing over 450 million prescription claims annually. Patients whose claims are processed by Caremark are covered under various types of insurance plans, including health maintenance organizations (HMOs), employers' self-insured health plans, selected managed care plans, and other selected traditional health insurers. Caremark represents patients from all 50 states and includes special populations such as the elderly, children, and women of childbearing age. The representativeness of those included in the Caremark system to all persons receiving dispensed prescriptions in the U.S. is not known however.

For this analysis, prescription claims in the Caremark system were examined from September 1, 2002 to August 31, 2004, inclusive.

RESULTS

I. Dispensed Prescriptions

Viracept® accounted for approximately 16% of the estimated 1.9 million prescriptions dispensed for the HIV-Protease Inhibitor class (USC5 82120) in the U.S. from September 1, 2003 to August 31, 2004 (Table 2). Dispensed prescriptions for nelfinavir appear to have decreased approximately 22% from 398,379 dispensed prescriptions from September 2002 through August 2003, inclusive, to 311,583 prescriptions dispensed in the 12-month period from September 2003 to August 2004, inclusive (Table 2). During the most recent 12-month time period (Sep03 – Aug04), the 250mg tablet accounted for approximately 93% of all nelfinavir dispensed, followed by the 625mg tablet (~6%) and the 50mg/gm oral powder (~0.5%), respectively.

Table 2: Total Number of Prescriptions Dispensed in Retail Pharmacies Nationwide for HIV-Protease Inhibitor Products (USC5 82120)

	Total Number of Dispensed Prescriptions					
	Sep 2001-Aug 2002		Sep 2002-Aug 2003		Sep 2003-Aug 2004	
	N	(%)	N	(%)	N	(%)
All HIV-Protease Inhibitors	1,602,516	100.0%	1,582,905	100.0%	1,899,047	100.0%
Ritonavir (*Kaletra, Norvir®)	230,716	(14.4%)	200,085	(12.5%)	341,108	(18%)
Lopinavir (*Kaletra®)	378,117	(23.6%)	535,018	(33.8%)	592,993	(31.2%)
Nelfinavir (Viracept®)	463,035	(28.9%)	398,379	(25.2%)	311,583	(16.4%)
250mg Tablet	461,057	(99.6%)	396,924	(99.6%)	291,287	(93.5%)
625mg Tablet					18,749	(6%)
50mg/gm Powder	1,978	(0.4%)	1,455	(0.4%)	1,957	(0.5%)
Atazanavir (Reyataz®)			14,113	(0.9%)	284,625	(15%)
Idinavir (Crixivan®)	277,016	(17.3%)	206,688	(13.1%)	144,133	(7.6%)
Saquinavir (Invirase®, Fortovase®)	143,010	(8.9%)	138,968	(8.8%)	114,339	(6%)
Fosamprenavir (Lexiva®)					62,141	(3.3%)
Amprenavir (Agenerase®)	110,577	(6.9%)	89,654	(5.7%)	48,125	(2.5%)

*Kaletra is a combination product containing both ritonavir and lopinavir: Kaletra Rx's counted under molecule lopinavir not ritonavir.
IMS Health, National Prescription Audit *Plus*™, Moving Annual Total: September-August 2001-2004, Data Extracted Oct 2004.
Original file: 0410nel2.dvr

The top two prescriber specialties for nelfinavir from September 2003 through August 2004 were infectious disease and internal medicine, with pediatricians accounting for roughly 3% of dispensed prescriptions (Table 3). There appears to have been no substantial change in prescriber specialty for nelfinavir during the 36-month study period.

Table 3: Total Number of Prescriptions Dispensed by Physician Specialty Nationwide for Nelfinavir* (excludes Long Term Care and Mail Order Channels)

	Number of Total Dispensed Prescriptions					
	Sep 2001-Aug 2002		Sep 2002-Aug 2003		Sep 2003-Aug 2004	
	N (000's)	(%)	N (000's)	(%)	N (000's)	(%)
*NELFINAVIR BY PHYSICIAN SPECIALTY	394	100.0%	341	100.0%	257	100.0%
Infectious Disease	130	(32.9%)	114	(33.3%)	84	(32.9%)
Internal Medicine	108	(27.4%)	93	(27.1%)	69	(26.7%)
Unknown	46	(11.7%)	40	(11.7%)	27	(10.6%)
Family Practice	27	(6.9%)	26	(7.5%)	21	(8%)
Nurse Practitioner	12	(3%)	13	(3.1%)	11	(4.1%)
Osteopathic Medicine	15	(3.8%)	13	(3.7%)	10	(4%)
Pediatrics	10	(2.6%)	9	(2.6%)	7	(2.9%)
Total Others (62)	42	(11.7%)	35	(11%)	25	(10.8%)

*Nelfinavir includes 250mg, 625mg, 50mg/gm powder
IMS Health, National Prescription Audit *Plus*™, Moving Annual Totals: September 2001-August 2004, Data Extracted October 2004.
Original file: 0410nel1.dvr

II. Patient Demographics

Among a large, insured patient population managed by Caremark, approximately 3.2% of processed claims for Viracept® were for persons aged 1-16 years from September 2003 through August 2004 (calculated from Table 4).

Total Viracept® claims decreased ~30% (from 28,551 to 20,084 claims) between the two 12-month time periods, September 2002 – August 2004. Pediatric claims for all Viracept® decreased roughly 50%, from 1,267 to 636 claims, during the same two 12-month time periods (calculated from Table 4).

**Table 4: Total Number of Paid Prescription Claims for Viracept®
From Caremark Pharmacy Benefit Manager Database.**

# CLAIMS BY PRODUCT	Number of Paid Claims					
	Sep 2001-Aug 2002		Sep 2002-Aug 2003		Sep 2003-Aug 2004	
	N	(%)	N	(%)	N	(%)
All Viracept (Total)	34,083	(100)	28,551	(100)	20,084	(100)
Peds (1-16 yrs)	1,196	(3.5%)	1,267	(4.4%)	636	(3.2%)
Adults (17+ yrs)	32,887	(96.5%)	27,284	(95.6%)	19,448	(96.8%)
Viracept 250mg	33,976	(99.7%)	28,457	(99.7%)	18,961	(94.4%)
Peds (1-16 yrs)	1,092	(3.2%)	1,183	(4.2%)	589	(3.1%)
Adults (17+ yrs)	32,884	(96.8%)	27,274	(95.8%)	18,372	(96.9%)
Viracept 625mg					1,078	(5.4%)
Peds (1-16 yrs)					16	(1.5%)
Adults (17+ yrs)					1,062	(98.5%)
Viracept 50mg/gm	107	(0.3)	94	(0.3)	45	(0.2%)
Peds (1-16 yrs)	104	(97.2 %)	84	(89.4%)	31	(68.9%)
Adults (17+ yrs)	3	(2.8%)	10	(10.6%)	14	(31.1%)

Caremark Dimension Rx: Extracted October 14, 2004.

LIMITATIONS

NPA Plus™ data provide an estimate of the total number of prescriptions dispensed in the U.S. However, NPA Plus™ does not include complete historical demographic information, such as age and gender. The inclusion of prescriber specialty data in this report does not include mail order and long-term care channels. This may be significant as mail order (~13%) and long-term care (~7%) contributed substantially to total sales of nelfinavir in the U.S. (Data not shown).

NDTI™ data provide estimates of patient demographics and indications for use of medicinal products in the U.S. The absence of pediatric nelfinavir use in NDTI™ office-based physician

encounters is reflective of the low market share (less than 5%) observed in the HIV protease inhibitor market. Furthermore, due to the sampling and data collection methodologies, the small sample size can make these data unstable.

Caremark data cannot be projected to make national level estimates of use, but its large sample size can provide use estimates for even less commonly used products. Although the data from Caremark may not be nationally representative, they provide a useful description of prescription drug use in the U.S. for a large proportion of the population with prescription drug coverage. This is probably not representative of the HIV population, especially the pediatric HIV population because a larger proportion of these patients may be uninsured and/or receive their medications in clinics. Reliable information for patients less than the age of 1 year is not available from this data source. Estimates of the number of prescriptions dispensed nationally to pediatric populations were not possible to generate, given that our data sources do not include dispensing from clinics, which represents a substantial proportion of product sales (13%) and, therefore, product use.

CONCLUSION

For all HIV protease inhibitors as a class, an estimated 1.9 million prescriptions were dispensed in the U.S. during the 12-month period from September 2003 through August 2004. This prescription volume represents a 20% increase when compared to the previous 12-month time period from September 2002 through August 2003. In contrast, the total number of dispensed prescriptions for the HIV protease inhibitors decreased by an estimated 1% in the 12 month time period from September 2002 through August 2003, compared to the previous 12-month time period from September 2001 through August 2002. This variation in market growth is likely due to the addition of atazanavir and fosamprenavir into the market in 2003. Total dispensed prescriptions for Viracept® appear to have decreased approximately 22% from roughly 398,379 dispensed prescriptions from September 2002 to August 2003, inclusive, to approximately 311,583 dispensed prescriptions in the 12 months from September 2003 to August 2004, inclusive

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Pediatricians were responsible for roughly 3% (~7,000 prescriptions) of all Viracept® prescriptions dispensed in the U.S. between September 1, 2001 and August 31, 2004.

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