

MEMORANDUM

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

PID#: A060094-D050372

DATE: September 14, 2006

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SUBJECT: Norvir[®] (ritonavir, NDA 20-659/SE5-034)
One Year Post-Pediatric Exclusivity Post-marketing Adverse Event Review:
Drug Utilization Data
Pediatric Exclusivity Grant Date: June 14, 2005

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

EXECUTIVE SUMMARY

This consult examines the drug utilization patterns for Norvir[®] in the pediatric population (ages 0-16 years), with primary focus on patterns of use one year before and one year following the granting of Pediatric Exclusivity on June 14, 2005. Norvir[®] (ritonavir) is a protease inhibitor used in combination with other antiretroviral agents for the treatment of HIV infection.

Proprietary drug use databases licensed by FDA were used to conduct this analysis. The IMS Health, IMS National Sales Perspectives[™] was used to determine the various retail and non-retail channels of distribution. Indications for outpatient use were measured by Verispan's Physician Drug and Diagnosis Audit, while retail prescriptions, patient counts and demographics were measured by Verispan's Vector One[®]: National (VONA) and Total Patient Tracker (TPT). We examined outpatient drug use patterns for Norvir[®], as well as for the other protease inhibitors, including Kaletra[®] (lopinavir/ritonavir), for the three 1-year periods from July 1, 2003 through June 30, 2006.

The examination of wholesale sales data indicates that 53-55% of Norvir[®] distribution is into retail pharmacies. Mail order pharmacies and Clinics combined accounted for approximately 30% of the total distribution and at this time are not captured by the Verispan databases which were used to measure outpatient dispensing.

The number of dispensed prescriptions for Norvir[®] increased by 23% from 426,000 prescriptions in the pre-exclusivity period (July 2004 through June 2005) to approximately 524,000 prescriptions in the post-exclusivity period (July 2005 through June 2006). Pediatric patients age 0-16 years accounted for approximately 0.8% of dispensed prescriptions in the post-exclusivity period.

Overall, there was a 20% increase in the number of adult patients and a 31% decrease in the number of pediatric patients receiving a Norvir[®] prescription from the pre- to post-exclusivity years. During the post-exclusivity year, there were 765 pediatric patients who received a Norvir[®] prescription, and over 94,000 adult patients.

Infectious Disease Physicians were the most frequent prescribers of Norvir[®] and accounted for 32% of dispensed prescriptions in the post-exclusivity year. The indication for use most frequently linked to Norvir[®] for both adults and children was “HIV & Specific Infection” (ICD-9 042.0).

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 reporting 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 on a quarterly basis. This review is in addition to the routine post-marketing safety surveillance activities the FDA performs for all marketed drugs.

Ritonavir is an inhibitor of both the HIV-1 and HIV-2 proteases. Inhibition of HIV protease renders the enzyme incapable of processing the polyprotein precursor, which leads to production of non-infectious immature HIV particles.

Norvir[®] (ritonavir) soft gelatin 100mg capsule was approved on June 29, 1999, for the treatment of HIV-infection under NDA 20-945. The 80mg/mL oral solution was approved on March 1, 1996, under NDA 20-659.

Ritonavir should be used in combination with other antiretroviral agents. It may also be used as a pharmacokinetic “booster” for other protease inhibitors.¹ The recommended adult dosage of ritonavir is 600mg twice daily by mouth. Use of a dose titration schedule may help to reduce treatment-emergent adverse events while maintaining appropriate ritonavir plasma levels. Ritonavir should be started at no less than 300mg twice daily and increased at 2 to 3 day intervals by 100mg twice daily.²

The Pediatric Exclusivity Board of the FDA granted pediatric exclusivity for Norvir[®] (ritonavir) on June 14, 2005.

¹ PDR[®] Electronic Library™

² Norvir[®] product labeling dated November 14, 2005.

On October 6, 2005, Norvir® (ritonavir) oral solution and soft gelatin capsules were approved under NDAs 20-945/S-017 and 20-659/S-034, respectively, in combination with other antiretroviral agents, for the treatment of HIV-infection in pediatric patients from age one month to two years of age. The major revisions to the Dosage and Administration section for Pediatric Patients in the package insert reads as follows:

Ritonavir should be used in combination with other antiretroviral agents (see General Dosing Guidelines). The recommended dosage of ritonavir in children > 1 month is 350 to 400 mg/m² twice daily by mouth and should not exceed 600 mg twice daily. Ritonavir should be started at 250 mg/m² and increased at 2 to 3 day intervals by 50 mg/m² twice daily. If patients do not tolerate 400 mg/m² twice daily due to adverse events, the highest tolerated dose may be used for maintenance therapy in combination with other antiretroviral agents, however, alternative therapy should be considered. When possible, dose should be administered using a calibrated dosing syringe.³

This review describes outpatient drug use patterns for Norvir® compared with other protease inhibitors during the three 1-year time periods from July 1, 2003 through June 30, 2006. Proprietary drug use databases licensed by the FDA were used to conduct this analysis.

METHODS

IMS Health, IMS National Sales Perspectives™ data (see Appendix) were used to determine the setting in which Norvir® is sold. Sales of this product by number of extended units (capsules/milliliters of solution) sold from the manufacturer into the various retail and non-retail channels of distribution were analyzed for three 12-month periods from July 2003 through June 2006 (Table 1). From these data, it was clear that this product is sold primarily to retail outlets (chain, independent, and food stores), which accounted for 53-55% of the total number of extended units sold in each of the three 1-year periods in this analysis. The second most common distribution channel was non-retail outlets, which accounted for 17-18% of the overall wholesale sales during the same time period.

³ Norvir® product labeling dated November 14, 2005.

Table 1. Total Number of Capsules/Milliliters of Solution of Ritonavir Sold into U.S. Distribution Channels During July 2003 – June 2006 (in thousands)

	July 1 2003 - June 30 2004		July 1 2004 - June 30 2005		July 1 2005 - June 30 2006	
	N (000)	%	N (000)	%	N (000)	%
Total Ritonavir	187,924	100.0%	192,970	100.0%	177,151	100.0%
Retail*	104,195	55.4%	104,644	54.2%	93,940	53.0%
Capsule	99,383	95.4%	99,359	94.9%	88,952	94.7%
Oral Solution	4,811	4.6%	5,284	5.0%	4,988	5.3%
Non-Retail**	34,325	18.1%	33,098	17.0%	31,597	17.8%
Clinics	25,992	13.8%	28,872	15.0%	26,352	14.9%
Mail Service	23,413	12.5%	26,355	13.7%	25,262	14.3%

IMS Health, IMS National Sales Perspectives™ Combined, July 2003 – June 2006, Data Extracted 8-2006
(File: 0608rito.dvr)

*Retail includes chain, independent, and food store pharmacies

** Non-retail includes Non-federal hospitals, federal facilities, long term care, HMOs, home health care, prisons, universities, and other

†Subtotals may not sum exactly due to rounding

Because the majority of drug product sales of Norvir® for this time period were to retail settings, we examined the utilization patterns for Norvir® along with the other protease inhibitors by focusing on the outpatient setting only.

Outpatient use and patient demographics were measured with the following data sources from Verispan, LLC: Vector One®: National (VONA), Total Patient Tracker (TPT) and indications for use were obtained from the Physician's Drug and Diagnosis Audit (see Appendix). Estimates of the number of drug mentions by office-based physicians, the number of dispensed prescriptions by retail pharmacies and the number of patients⁴ who received a dispensed Norvir® retail prescription were obtained. Outpatient drug utilization patterns were examined for the 3-year period from July 1, 2003 through June 30, 2006.

RESULTS

I. Dispensed Prescriptions

There was a slight increase in the volume of prescriptions dispensed for protease inhibitors over the 3 years of this analysis (Table 2).

During the pre-exclusivity period (July 2004 through June 2005), an estimated 1.8 million prescriptions (95% CI 1.832– 1.838 million) were dispensed by retail pharmacies in the U.S. for the protease inhibitors combined. During the post-exclusivity period (July 2005 to June 2006), approximately 1.9 million prescriptions (95% CI 1.956 – 1.962 million) were dispensed. Norvir® accounted for approximately 27% of the market share during the post-exclusivity period. The combination ritonavir/lopinavir product, Kaletra®, had the highest market share among protease inhibitors during the pre-exclusivity years, but its market share declined over the 3 years of this analysis from 32% in the year ending June 2004 to 25% for the year ending June 2006. Atazanavir (Reyataz®) prescriptions accounted for 23% of the protease inhibitor market during the post-exclusivity period.

⁴ Note that data concerning the total number of patients based on Verispan's Total Patient Tracker may not be summed due to aging of patients during the study period.

Norvir[®] was the most commonly dispensed protease inhibitor during the post-exclusivity period (Table 2). The total number of prescriptions for Norvir[®] rose from 260,000 prescriptions (95% CI: 259,000 – 261,000) dispensed during July 2003 – June 2004, to 426,000 prescriptions (95% CI: 425,000 – 427,000) dispensed during the pre-exclusivity period (July 2004 – June 2005), to 524,000 prescriptions (95% CI: 522,000 – 526,000) dispensed during the post-exclusivity period (July 2005 – June 2006). Prescriptions dispensed for Norvir[®] increased by 102% from July 2003 through June 2006, and increased by 23% during the pre to post-exclusivity years. Capsules were the most commonly dispensed formulation of Norvir[®] and accounted for 99% of dispensing during the post-exclusivity year.

Table 2: Total Number of Prescriptions Dispensed (in Thousands) by Retail Pharmacies for Protease Inhibitors during July 1, 2003 through June 30, 2006 (mail order pharmacies not included)

	July 1 2003 - June 30 2004		July 1 2004 - June 30 2005		July 1 2005 - June 30 2006	
	TRxs	Share	TRxs	Share	TRxs	Share
	(000)	%	(000)	%	(000)	%
Total Market	1,516	100.0%	1,835	100.0%	1,959	100.0%
Ritonavir (Norvir[®])	260	17.2%	426	23.2%	524	26.8%
Regular Cap	256	98.2%	422	99.1%	521	99.3%
Solution	5	1.8%	4	0.9%	3	0.7%
Ritonavir/Lopinavir (Kaletra[®])	487	32.1%	497	27.1%	484	24.7%
Regular Cap	474	97.4%	481	96.7%	238	49.3%
Regular Tab	---	---	---	---	230	47.5%
Solution	13	2.6%	16	3.3%	16	3.2%
Atazanavir Sulfate (Reyataz[®])	202	13.3%	385	21.0%	449	22.9%
Nelfinavir Mesylate	265	17.5%	216	11.8%	175	8.9%
Fosamprenavir Calcium	35	2.3%	131	7.2%	164	8.4%
Saquinavir	101	6.7%	82	4.5%	75	3.9%
Indinavir Sulfate	119	7.9%	85	4.6%	59	3.0%
Taprinavir	---	---	---	---	28	1.4%
Amprenavir/Vitamin E	46	3.0%	13	0.7%	1	0.0%
Darunavir	---	---	---	---	0	0.0%

Verispan, LLC. Vector One National (VONA) Data extracted 8-8-2006 File: A060094 8-8-06 ritonavir USC.qry

II. Patient Demographics

Retail prescriptions for Norvir[®] dispensed to the pediatric population (ages 0 – 16 years) decreased 2% from approximately 4,617 prescriptions (95% CI: 4,467-4,767) dispensed during the pre-exclusivity period (July 2004 - June 2005) to approximately 4,504 prescriptions (95% CI: 4,355-4,653) dispensed during the post-exclusivity period (July 2005 – June 2006) (Table 3). The percent decrease for pediatrics was in opposition to the 24% increase seen for adult patients over the same period.

Prescriptions for Kaletra[®] dispensed to the pediatric population decreased 7%, from an estimated 15,773 prescriptions (95% CI: 15,493 – 16,053) to 14,713 prescriptions (95% CI: 14,443 – 14,983) during the same time period. There was a 2% decrease seen for adult patients over the same period.

Norvir[®] and Kaletra[®] prescriptions dispensed to the pediatric population aged 0-16 years old accounted for 0.8% and 3.1%, respectively, of the total dispensed Norvir[®] and Kaletra[®] prescriptions during the post-exclusivity period.

Table 3: Total Number of Retail Prescriptions Dispensed for Norvir[®] and Kaletra[®] by Patient Age, During July 1, 2003 through June 30, 2006 (mail order pharmacies not included)

	July 1 2003 - June 30 2004		July 1 2004 - June 30 2005		July 1 2005 - June 30 2006	
	TRxs*	Share*	TRxs*	Share*	TRxs*	Share*
		%		%		%
Ritonavir (Norvir[®])	260,497	34.9%	425,548	46.1%	524,472	52.0%
0-16 Years	4,769	1.8%	4,617	1.0%	4,504	0.8%
0-1 Years	99	0.0%	132	0.0%	108	0.0%
2-11 Years	2,461	1.0%	1,602	0.3%	1,146	0.2%
12-16 Years	2,209	0.8%	2,883	0.7%	3,250	0.6%
17+ Years	254,069	97.5%	417,155	98.0%	516,276	98.4%
Unspecified	1,659	0.6%	3,776	0.9%	3,692	0.7%
Ritonavir/Lopinavir (Kaletra[®])	486,854	65.1%	496,969	53.9%	483,954	48.0%
0-16 Years	14,923	3.1%	15,773	3.2%	14,713	3.1%
0-1 Years	338	0.1%	360	0.1%	363	0.1%
2-11 Years	8,899	1.8%	9,167	1.8%	7,643	1.6%
12-16 Years	5,686	1.2%	6,246	1.3%	6,707	1.4%
17+ Years	468,364	96.2%	476,064	95.8%	466,215	96.3%
Unspecified	3,567	0.7%	5,132	1.0%	3,026	0.6%

Verispan, LLC, Vector One National (VONA) Data extracted 8-8-2006 File: A060094 8-8-06 ritonavir age.qry
 *Subtotals may not sum exactly, due to rounding error.

The projected number of patients of all ages who received a dispensed retail prescription for Norvir[®] during this 3-year period increased from approximately 58,012 (95% CI: 57,471 – 58,552) patients from July 2003 – June 2004, to 80,241 (95% CI 79,605 – 80,878) in the pre-exclusivity period (July 2004 – June 2005), and 95,780 (95% CI: 95,084 – 96,477) in the post-exclusivity period (July 2005 – June 2006) (Table 4). This represented an increase of approximately 65% over the entire 3 years and an increase of 19% from the pre to post-exclusivity periods.

For Kaletra[®], the projected number of patients of all ages who received a dispensed retail prescription during this 3-year period decreased from approximately 93,673 (95% CI: 92,984 – 94,362) patients from July 2003 – June 2004, to 87,401 (95% CI: 86,736 – 88,066) in the pre-exclusivity period (July 2004 – June 2005), and increased to 89,661 (95% CI: 88,988 – 90,335) in the post-exclusivity period (July 2005 – June 2006) (Table 4). This represented a net decrease of approximately 4% over 3 years and an increase of 3% from the pre to post-exclusivity periods.

The number of adult patients age 17 years and older receiving a Norvir[®] retail prescription increased by 20% from 78,452 (95% CI 77,822 – 79,082) in the pre-exclusivity period to 94,359 (95% CI: 93,668 – 95,050) in the post-exclusivity period (Table 4). The projected number of unique pediatric patients (aged 0 through 16 years) who received a dispensed prescription for Norvir[®] decreased by 31% from 1,116 (95% CI: 1,043 – 1,189) in the pre-exclusivity year to 765 (95% CI: 704 - 826) in the post-exclusivity year. Similar to dispensed prescription data, the number of pediatric patients receiving a prescription for Norvir[®] accounted for less than 1% of all patients during the post-exclusivity period.

The number of adult patients age 17 years and older receiving a Kaletra[®] retail prescription increased by 3% from 83,908 (95% CI 83,257 – 84,559) in the pre-exclusivity period to 86,765 (95% CI 86,103 – 87,427) in the post-exclusivity period. The projected number of unique pediatric patients (aged 0 through 16 years) who received a dispensed prescription for Kaletra[®] decreased by 8% from 2,600 (95% CI 2,487 – 2,713) in the pre-exclusivity year to 2,383 (95% CI 2,275 - 2,491) in the post-exclusivity year. Similar to dispensed prescription data, the number of pediatric patients receiving a prescription for Kaletra[®] accounted for less than 1% of all patients during the post-exclusivity period.

For patients who received a dispensed prescription for Norvir[®], relative decreases were noted during the pre- to post-exclusivity periods for each of the pediatric age subgroups, with the age 0-1 year old group decreasing by 36%, the 2-11 year old group by 49%, and 12-16 year old group decreasing by 15% each.

For patients who received a dispensed prescription for Kaletra[®], relative decreases were noted during the pre to post-exclusivity periods for each of the pediatric age subgroups, with the exception of the 0-1 year old group, which increased by 34%.

Table 4: Total Number of Patients Receiving Prescriptions Through Retail Pharmacies for Norvir[®] and Kaletra[®] by Patient Age, During July 1, 2003 through June 30, 2006 (mail order pharmacies not included)**

	July 1 2003 - June 30 2004		July 1 2004 - June 30 2005		July 1 2005 - June 30 2006	
	Projected Patient Count	Total Patient Share	Projected Patient Count	Total Patient Share	Projected Patient Count	Total Patient Share
Grand Total	141,940	100.0%	158,712	100.0%	176,958	100.0%
Ritonavir (Norvir[®])	58,012	40.87%	80,241	50.56%	95,780	54.13%
0-16	1,147	1.98%	1,116	1.39%	765	0.80%
0 - 1	33	2.88%	53	4.75%	34	4.44%
2 - 11	653	56.93%	482	43.19%	245	32.03%
12 - 16	483	42.11%	625	56.00%	533	69.67%
17+	56,486	97.37%	78,452	97.77%	94,359	98.52%
Unknown	1,708	2.94%	1,921	2.39%	1,885	1.97%
Ritonavir/Lopinavir (Kaletra[®])	93,673	65.99%	87,401	55.07%	89,661	50.67%
0-16	2,869	3.06%	2,600	2.97%	2,383	2.66%
0 - 1	167	5.82%	79	3.04%	106	4.45%
2 - 11	1,613	56.22%	1,490	57.31%	1,245	52.25%
12 - 16	1,322	46.08%	1,183	45.50%	1,153	48.38%
17+	90,122	96.21%	83,908	96.00%	86,765	96.77%
Unknown	1,496	1.60%	5,344	6.11%	1,050	1.17%

Verispan, LLC, Total Patient Tracker (TPT). Data extracted 8-22-2006

Files: TPT BPCA Ritonavir A060094.xls

**Subtotals may not sum exactly, due to rounding error. Due to aging of patients 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.

III. Prescriber Specialty

Infectious Disease Physicians were the most frequent prescribers of Norvir[®] and Kaletra[®] combined in each of the three (3) 1-year periods of observation, accounting for 30% of retail prescriptions (279,000,

95% CI: 278,000-280,000) in the pre-exclusivity period and 32% of prescriptions (321,000, 95% CI: 320,000-322,000) in the post-exclusivity period (Table 5). Pediatricians were the seventh most frequent prescribers during each year, with 1.3% of prescriptions (12,000, 95% CI: 11,800-12,200) for the pre-exclusivity period and 1.6% of prescriptions (17,000 thousand, 95% CI: 16,700-17,300) during the post-exclusivity year.

Table 5: Total Number of Retail Prescriptions Dispensed (in thousands) for Norvir[®] and Kaletra[®] by Prescriber Specialty, During July 1, 2003 through June 30, 2006 (mail order pharmacies not included)

	July 1 2003 - June 30 2004		July 1 2004 - June 30 2005		July 1 2005 - June 30 2006	
	TRxs	Share [†]	TRxs	Share [†]	TRxs	Share [†]
	(000)	%	(000)	%	(000)	%
Ritonavir (Norvir[®]) and Lopinavir/Ritonavir (Kaletra[®])	747	100.0%	922	100.0%	1,008	100.0%
Infectious Disease	225	30.1%	279	30.2%	321	31.8%
Internal Med	191	25.5%	227	24.6%	256	25.4%
Unspecified	152	20.3%	199	21.6%	167	16.5%
General Practice*	59	7.9%	72	7.8%	93	9.2%
Nurse Practitioner	27	3.6%	34	3.7%	47	4.6%
Hospital	31	4.1%	38	4.1%	44	4.3%
Pediatrics	10	1.3%	12	1.3%	17	1.6%
PA	7	0.9%	9	1.0%	13	1.3%
Total Others	47	6.2%	51	5.5%	52	5.2%

*General Practice includes General Practice, Family Medicine, and Doctors of Osteopathy

[†]Numbers may not sum exactly, due to rounding

Verispan, LLC, Vector One National (VONA) Data extracted 8-22-2006

File: A060094 8-22-06 ritonavir MD.qry

IV. Indication for Use

The most common indication for use for Norvir[®] and Kaletra[®] in all patients was “HIV & Specific Infection” (ICD-9 042.0), which accounted for nearly all (97% for Kaletra, 100% for Norvir) diagnosis mentions for each product in the post-exclusivity period (data not shown)⁵. No visit was recorded for pediatric patients in which Norvir[®] was mentioned during the entire three-year time period.

DISCUSSION

Based on the databases used in this analysis, there has been an increase in the number of adult patients receiving Norvir[®] over the three years studied. Since Norvir[®] is also used as a pharmacokinetic booster in antiretroviral therapy, we are unable to differentiate in the analysis exactly what role a dispensed prescription for Norvir[®] plays in the management of this disease.

⁵ Verispan, LLC. Physician’s Drug and Diagnosis Audit (PDDA) Data extracted 7-2006. File: A060092 7-06 PDDA Novolog Diag-age.xls

The findings from this consult should be interpreted in the context of the known limitations of the databases used. We estimated that Norvir[®] was distributed primarily in outpatient settings based on the IMS Health, IMS National Sales Perspectives[™] and determined that Clinics and Mail order pharmacies are the third and fourth most common retail distribution channel and collectively account for up to 30% of wholesale sales. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

While we conducted a comprehensive analysis of the use of this product in the outpatient settings, in which the majority of use occurred, a significant proportion of wholesale sales of Norvir[®] is to mail order pharmacies and clinics, which are distribution channels not currently captured by Verispan's retail prescription audits.

With Verispan's Total Patient Tracker (TPT) data, patients may be counted more than once in the individual age categories due to aging of patients during the study period ("the cohort effect"); if a patient has a birthday within a given time period, the patient will be counted twice. For this reason, summing across age bands is not advisable and will result in overestimates of patient counts.

Verispan's Physician Drug & Diagnosis Audit (PDDA) 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 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.

CONCLUSION

In summary, the prescriptions dispensed for all protease inhibitors combined increased during each of the three years examined. The number of prescriptions for Norvir[®] and the number of patients receiving a prescription for Norvir[®] has increased during each year.

Pediatric patients accounted for approximately 0.8% of Norvir[®] prescriptions. The number of patients receiving Norvir[®] over the pre to post-exclusivity years increased 20% for adults and decreased 31% for pediatric patients aged 0-16 years. In the post exclusivity year, an estimated 765 pediatric patients and over 94,000 adult patients received a Norvir[®] prescription.

Infectious Disease Physicians were the most frequent prescribers of Norvir[®] and accounted for 32% of dispensed prescriptions in the post-exclusivity year. The indication for use most frequently linked to Norvir[®] for both adults and children was "HIV & Specific Infection" (ICD-9 042.0).

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APPENDIX

IMS HEALTH

IMS National Sales Perspectives™

IMS Health, IMS National Sales Perspectives™ 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 Health, IMS National Sales Perspectives™ measures the volume of drug products moving from manufacturer into retail and non-retail settings in terms of sales dollars, vials, and market share. These data are based on national projections.

Data for this analysis include prescriptions dispensed for Norvir® from July 1, 2003 through June 30, 2006, inclusive.

VERISPAN, LLC

Vector One®: National (VONA)

Verispan's VONA is a nationally projected database which 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. 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, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2 billion prescription claims, representing over 160 million unique patients.

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. Verispan receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores. Mail order prescriptions are not included in the sample at this time.

Data for this analysis include prescriptions dispensed for Norvir® and other protease inhibitors from July 1, 2003 through June 30, 2006, inclusive.

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.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, pharmacy benefits managers

and their data systems, physician offices and hospitals. Vector One[®] receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

Data for this analysis include patients who were dispensed a prescription for Norvir[®] and Kaletra[®] from July 1, 2003 through June 30, 2006, inclusive.

VERISPAN, LLC

Physician Drug & Diagnosis Audit (PDDA)

Verispan's Physician Drug & Diagnosis Audit (PDDA) is a monthly survey that monitors disease states and the physician intended prescribing habits on a national-level. The survey is designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The audit is composed of 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.

The term drug uses refers 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.

Data for this analysis include physician mentions for Norvir[®] and Kaletra[®] from July 1, 2003 through June 30, 2006, inclusive.

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/s/

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10/6/2006 01:37:33 PM
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