

Memorandum

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

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SUBJECT: One Year Post-Pediatric Exclusivity Review: Drug Use Data
Zyvox[®] (linezolid) Tablets: NDA 21-130/S-008
Zyvox[®] (linezolid) Injection: NDA 21-131/S-010
Zyvox[®] (linezolid) Oral Suspension: NDA 21-132/S-009
Pediatric Exclusivity Grant Date: February 11, 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 inpatient drug utilization trends for Zyvox[®] (linezolid) in the pediatric population (aged 0-16 years), with primary focus on patterns of use one year before and one year following the granting of Pediatric Exclusivity on February 11, 2005. Proprietary drug use databases licensed by the Agency were used to conduct this analysis. The IMS National Sales Perspective[™] was used to characterize the sales of Zyvox[®] and comparator drug products into the various retail and non-retail channels of distribution. Since Zyvox[®] was sold predominantly to

the non-retail setting, we focused our study on the utilization patterns for Zyvox® in the inpatient setting. Hospital-based inpatient drug usage data were derived from Premier Rx Market Advisor™ and were examined for two six-month time periods: August 2004-January 2005 and February – July 2005.

Overall, there were 12,603 actual discharges associated with a charge for linezolid in Premier network hospitals during the 6 months prior to the granting of exclusivity (August 2004 – January 2005) and 15,267 discharges in the 6 months following the granting of exclusivity (February 2005 – July 2005). This represented a 21% relative increase in linezolid use in all age groups. Pediatric patients aged 0 – 16 years accounted for 141 discharges (1.1%) in the pre-exclusivity period and 184 discharges (1.2%) in the post-exclusivity period, a 30% relative increase. Infants (age 0-1) accounted for approximately 24.1% - 26.1% of use among the pediatric population for the pre- and post-exclusivity periods, respectively.

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.

Linezolid is a synthetic antibiotic agent of the oxazolidinone class. Zyvox® (linezolid) Tablet (NDA 21-130), Injection (NDA 21-131), and Oral Suspension (NDA 21-132), were approved on April 18, 2000, for the treatment of infections (vancomycin-resistant *Enterococcus faecium* infections; nosocomial pneumonia; complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis; uncomplicated skin and skin structure infections; and community-acquired pneumonia) caused by susceptible strains of gram positive bacteria. On May 12, 2005, labeling changes were made to include use in the pediatric population. Indications for pediatric patients ranging in age from birth through 11 years include the following¹:

- nosocomial pneumonia
- complicated skin and skin structure infections
- community-acquired pneumonia (also supported by evidence from an uncontrolled study in patients ranging in age from 8 months through 12 years)
- vancomycin-resistant *Enterococcus faecium* infections

¹ PDR® Electronic Library™, accessed April 2006

Zyvox has also been found to be safe and effective for the following indication in pediatric patients ranging in age from 5 through 17 years:

- uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible strains only) or *Streptococcus pyogenes*

The Pediatric Exclusivity Board of the FDA granted pediatric exclusivity for Zyvox[®] (NDA 21-130, NDA 21-131, NDA 21-132) on February 11, 2005. This review describes the product sales distribution and inpatient drug use patterns for Zyvox[®] in the pediatric and adult population in time periods before and after granting the pediatric exclusivity. Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

METHODS

Setting of Use

Inpatient utilization of Zyvox[®] (linezolid) was examined in the context of other systemic comparators, which are used for similar clinical conditions. We compared Zyvox[®] (linezolid) to vancomycin and Synercid[®] (quinupristin/dalfopristin).

IMS Health, National Sales Perspectives[™] data (see Appendix) were used to determine the setting in which Zyvox[®] was sold. Sales of this product by number of vials sold from the manufacturer to various retail and non-retail channels of distribution were analyzed for the three 12-month time periods from March 1, 2003 through February 28, 2006. The data indicate that Zyvox[®] is sold mainly to the non-retail setting, which accounted for over 92% of vials and bottles sold during each twelve-month period examined in this analysis.² We therefore focused on the inpatient setting to examine the utilization patterns for Zyvox[®].

Inpatient drug use data were derived from Premier's Rx Market Advisor[™] (see Appendix). Premier's inpatient data were examined for the two six-month time periods: the pre-exclusivity period, defined as August 2004-January 2005, and the post exclusivity period, defined as February – July 2005. Throughout our analysis, we used the agency's cut-off age definition of a pediatric patient (age 0-16 years).

RESULTS

Of the three products examined, vancomycin accounted for the majority of sales with 87.8% of the market share, followed by Zyvox[®] with approximately 11.4%, and Synercid[®] with less than 1% of sales during each year examined (data not shown).³

² IMS Health, IMS National Sales Perspectives[™] Combined, March 2003 – February 2006, Data Extracted April 2006, Source File: 0604zyvo.dvr

³ IMS Health, IMS National Sales Perspectives[™] Combined, March 2003 – February 2006, Data Extracted April 2006. Source File: 0604zyv1.dvr

I. Inpatient Drug Usage and Patient Demographics

Utilizing Premier's database of approximately 450 reporting acute care hospitals, the total number of discharges associated with a charge for linezolid or the 2 comparators increased 5% from 183,390 in the pre-exclusivity period to 193,385 in the post-exclusivity period. For linezolid, there were 12,603 actual discharges during the 6 months prior to the granting of exclusivity (August 2004 – January 2005) and 15,267 discharges in the 6 months following the granting of exclusivity (February 2005 – July 2005) (Table 1). This represents a 21% relative increase in linezolid use in all age groups. Of the three drugs (vancomycin, linezolid and quinopristin/dalfopristin) examined, linezolid accounted for approximately 7% – 8% of total discharges during the time period examined. Pediatric patients aged 0 – 16 years accounted for 141 discharges (1.1%) in the pre-exclusivity period and 184 discharges (1.2%) in the post-exclusivity period, a 30% relative increase. Infants (age 0-1) accounted for approximately 24.1% - 26.1% of linezolid use among the pediatric population for both pre- and post-exclusivity periods, respectively.

Table 1. Premier Network Acute Care Hospital Discharges Associated with a Charge for Linezolid and Comparators for the 6 Months Before and After the Granting of Pediatric Exclusivity, Premier (August 2004-July 2005)

	August 2004 - January 2005		February - July 2005	
	N [†]	%	N [†]	%
Total (all ages)	183,390	100.0	193,385	100.0
Vancomycin	170,542	93.0	177,851	92.0
Linezolid	12,603	6.9	15,267	7.9
Age 0-16	141	1.1	184	1.2
Age 0-1	34	24.1	48	26.1
Age 2-5	18	12.8	38	20.7
Age 6-11	33	23.4	41	22.3
Age 12-16	56	39.7	57	31.0
Age 17+	12,462	98.9	15,083	98.8
Quinupristin/Dalfopristin	245	0.1	267	0.1

Source: Premier Informatics Data Extracted 5-1-2006

File: Premier All Hosp Zyvox 5-1-06.xls

†Subtotals may not sum correctly due to rounding error

In a subset of 37 Premier Network **pediatric hospitals and care centers**, the number of discharges associated with a charge for linezolid for patients aged 0-16 years increased from 172 discharges (2.4%) during the 6 months prior to the pediatric exclusivity (August 2004 – January 2005) to 210 discharges (3.0%) during the 6 months after granting the exclusivity (February

2005 – July 2005) (Table 2). This represented a 22% increase in linezolid use from the pre-exclusivity to the post-exclusivity period.

Table 2 . Premier Network Pediatric Care Center Discharges Associated with a Charge for Linezolid and Comparators for the 6 Months Before and After the Granting of Pediatric Exclusivity

	August 2004 - January 2005		February - July 2005	
	Number of Patient Discharges			
	N †	%	N †	%
Total	7,115	100	7,069	100
Vancomycin	6,942	97.6	6,858	97.0
Linezolid	172	2.4	210	3.0
Quinupristin/Dalfopristin	1	0.01	1	0.01

Source: Premier Informatics Extracted 5-1-2006
File: Premier Zyvox Peds Hosp 5-1-06.xls
†Subtotals may not sum correctly due to rounding error

DISCUSSION

Based on the databases used for this consult, the use of linezolid increased from the pre-exclusivity period (August 2004 – January 2005) to the post-exclusivity period (February 2005 – July 2005). The use of Zyvox[®] in the pediatric population aged 0-16 years increased at a higher rate compared to adults, however, adult patients accounted for the majority of linezolid-related discharges.

Findings from this consult should be interpreted in the context of the known limitations of the databases used. We determined that the use of Zyvox[®] was largely in the non-retail settings, based on sales reported by the IMS Health, IMS National Sales Perspectives[™]. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer to 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 that facilities purchase drugs in quantities reflective of actual patient use. Sales into the non-federal hospitals accounted for the largest proportion of sales. However, a substantial amount of product was sold into the home health care, outpatient clinic, and long term care channels, and the Agency does not have access to databases that would permit us to evaluate the use of drug products within these channels.

CONCLUSION

In summary, Zyvox[®] usage in the pediatric and adult population has increased over the past three years. Zyvox[®] is primarily sold into non-retail channels of distribution. Overall, Zyvox[®]-related discharges from Premier network hospitals increased by 21% in all ages from the pre- to post-exclusivity period, while Zyvox[®]-related discharges in the pediatric patients increased by 30% over the same period.

APPENDIX

IMS HEALTH, IMS 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 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, 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.

For this analysis, the sales trends of linezolid and comparator products were examined for the three twelve-month periods from March 2003 through February 2006, inclusive.

PREMIER (RX MARKET ADVISOR™)

Premier's database is a large hospital drug utilization and financial database. Information is available from over 450 acute care facilities and includes approximately 18 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.

For this analysis, we examined inpatient usage of Zyvox® during the two six-month time periods from August 2004 – July 2005, inclusive.

PREMIER PEDIATRIC™

Premier's pediatric database represents a subset of information from 37 pediatric hospitals. In addition, Premier maintains data on all pediatric discharges from the larger sample of approximately 450 acute care facilities. Overall, the pediatric population in Premier's pediatric database includes greater than 3 million inpatient records. Data are available from January 2000 through the present but have a lag time of approximately six months.

For this analysis, the total number of distinct discharges associated with linezolid use within these 37 tertiary care pediatric hospitals was examined for the 6 months before and after the granting of exclusivity, a one-year time period from August 2004 – July 2005, inclusive.

Concurrence:

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