

Memorandum

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Center for Drug Evaluation and Research**

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SUBJECT: One Year Post-Pediatric Exclusivity Review: Drug Use Data
Invanz[®] (ertapenem sodium for injection): NDA 21-337
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 Invanz[®] (ertapenem) injection 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 determine the sales of Invanz[®] and comparator drug products into the various retail and non-retail channels of distribution. Since Invanz[®] was sold predominantly to the non-retail setting; we examined the utilization patterns for Invanz[®] focusing on the inpatient setting. Hospital-based inpatient 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.

Invanz[®]-associated discharges for patients of all ages in Premier network hospitals increased by 15% from 7,675 during the 6 months pre-exclusivity to 8,181 discharges during the 6 months post exclusivity. Invanz[®] associated discharges for pediatric patients age 0-16 years increased by 26% from 70 during the 6 months pre-exclusivity to 88 during the 6 months post-exclusivity. Invanz associated discharges for pediatric patients accounted for 1% or less of all Invanz use during each of the 6-month periods.

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.

Invanz[®] (ertapenem) 1 gram/vial, NDA 21-337, is a sterile, synthetic parenteral 1- β methyl carbapenem that is structurally related to the beta lactam antibiotics. Invanz[®] was approved on November 21, 2001, for the treatment of adult patients with moderate to severe infections (complicated intra-abdominal infection, complicated skin and skin structure infections, community acquired pneumonia, complicated urinary tract infections, and acute pelvic infections) caused by susceptible strains of designated organisms. There have been two significant changes to the labeling since approval. The Pediatric Exclusivity Board of the FDA granted pediatric exclusivity for Invanz[®] on February 11, 2005. On May 18, 2005, Invanz[®] received approval for use of the drug in the pediatric population aged 3 months to 17 years with specific dosing and administration information under supplemental NDA 21-337/S-018. On October 14, 2005, Invanz[®] received an additional indication for treatment of adult diabetic foot infection under supplemental NDA 21-337/S-019,

This review describes the product sales distribution and inpatient drug use patterns for Invanz[®] (ertapenem) in the pediatric and adult population in the years 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

Drug use of Invanz[®] was examined in the context of other injectable comparators, which are used for similar clinical conditions. We compared ertapenem (Invanz[®]) to meropenem (Merrem[®]), imipenem/cilastatin (Primaxin[®]), piperacillin/tazobactam (Zosyn[®]), and ticarcillin/clavulanate (Timentin[®]).

IMS Health, National Sales Perspectives™ data (see Appendix) were used to determine the setting in which Invanz® (ertapenem) 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 February 1, 2003 through January 31, 2006. Of the five products examined, Invanz® accounted for less than 3% of sales during each year examined (data not shown).¹

The data indicate that Invanz® is sold mainly to the non-retail setting, which accounted for over 98% of vials and bottles sold during each year examined in this analysis. We therefore examined the utilization patterns for Invanz® (ertapenem) focusing on the inpatient setting. 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

I. Inpatient Drug Usage and Patient Demographics

For adult and pediatric patients who were discharged from one of the ~350 reporting Premier network acute care hospitals, the total number of discharges associated with a charge for Invanz® (ertapenem) or the 4 comparators² increased from 138,891 in the pre-exclusivity period to 143,644 in the post-exclusivity period, a relative increase of approximately 3% (Table 1). For Invanz®, there were 7,675 actual discharges during the 6 months prior to the granting of exclusivity (August 2004 – January 2005) and 8,818 discharges in the 6 months following the granting of exclusivity (February 2005 – July 2005). This represents a 15% relative increase in Invanz® use. Against the other comparator products, Invanz® was associated with approximately 6% of the total discharges for all 5 products combined.

Pediatric patients aged 0 – 16 years accounted for 0.9% of discharges in the pre-exclusivity period (70 discharges) and 1% of discharges in the post-exclusivity period (88 discharges), a 26% relative increase. Within the pediatric population, the 12-16 year old subgroup accounted for most of the Invanz® related discharges (81%) during both the pre- and post-exclusivity periods.

¹ IMS Health, IMS National Sales Perspectives™ Combined, February 2003 – January 2006, Data Extracted March 2006. Source File: 0603ert1.qry

² Comparator drugs used in this analysis were: Merrem® (meropenem), Primaxin® (imipenem/cilastatin), Zosyn® (piperacillin/tazobactam), and Timentin® (ticarcillin/clavulanate).

Table 1. Premier Network Acute Care Hospital Discharges Associated with a Charge for Invanz[®] (ertapenem) or a Comparator Drug for the 6 Months Before and After the Granting of Pediatric Exclusivity, Premier (August 2004-July 2005)

	August 2004 - January 2005		February - July 2005	
	Number of Patient Discharges			
	N [†]	%	N [†]	%
Total	138,891	100.0	143,644	100.0
Pipercillin/Tazo	99,999	72.0	104,486	72.7
Imipenem/Cila	20,059	14.4	21,394	14.9
Ertapenem	7,675	5.5	8,818	6.1
<i>Age 0-16</i>	<i>70</i>	<i>0.9</i>	<i>88</i>	<i>1.0</i>
Age 0-1	2	2.9	0	0.0
Age 2-11	11	15.7	17	19.3
Age 12-16	57	81.4	71	80.7
<i>Age 17+</i>	<i>7605</i>	<i>99.1</i>	<i>8730</i>	<i>99.0</i>
Ticarcillin/Clav	5,428	3.9	4,644	3.2
Meropenem	5,730	4.1	4,302	3.0

Source: Premier Informatics Data Extracted 3-22-206

File: Ertapenem All Hosp by Age.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 Invanz[®] (ertapenem) for patients aged 0-16 years increased from 5 discharges during the 6 months prior to the pediatric exclusivity (August 2004 – January 2005) to 14 discharges during the 6 months after granting the exclusivity (February 2005 – July 2005) (Table 2). Against the other comparator products, Invanz[®] was associated with less than 1% of the total discharges for all 5 products combined.

Table 2 . Premier Network Pediatric Care Center Discharges Associated with a Charge for Invanz[®] or a Comparator Drug 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	1,817	100	1,842	100
Piperacillin/Tazo	881	48.5	949	51.5
Imipenem/Cila	234	12.9	297	16.1
Meropenem	376	20.7	291	15.8
Ticarcillin/Clav	321	17.7	291	15.8
Ertapenem	5	0.3	14	0.8

Source: Premier Informatics Extracted 3-23-2006
File: Ertapenem bpca peds hosp.xls
[†]Subtotals may not sum correctly due to rounding error

DISCUSSION

Based on the databases used for this consult, the use of Invanz[®] (ertapenem) increased slightly from the pre- exclusivity period (August 2004 – January 2005) to the post-exclusivity period (February 2005 – July 2005). The use of Invanz[®] in the pediatric population aged 0-16 years increased at a higher rate as compared to adults; however, this rate increase in the pediatric population should be interpreted with caution due to the comparatively low usage. Adult patients accounted for nearly all of Invanz[®]-related discharges.

Newer-generation carbapenems, such as ertapenem, the active ingredient in Invanz[®], are characterized by a broad-spectrum of antimicrobial activity. The pharmacological properties of ertapenem allow it to be given once daily with more rapid bactericidal activity and less likelihood for development of resistance. These properties make the drug more appealing for use. However, because of their proven activity against highly resistant organisms, such antibacterial agents should be reserved only for life-threatening situations or when resistant pathogens are suspected.³ Rational antimicrobial use is crucial for preventing the emergence of drug-resistance.

Findings from this consult should be interpreted in the context of the known limitations of the databases used. We estimated that the use of Invanz[®] was mostly in non-retail settings based on sales reported by the IMS National Sales PerspectivesTM. 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 hospital 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. Databases to which the agency

³ Raghavan M, Linden PK. Newer treatment options for skin and soft tissue infections. *Drugs*. 2004;64(15):1621-42

has access cannot be used to evaluate the use of drug products within these channels. In addition, further analysis for discharges associated with Invanz[®] in the pediatric patient and interpretation is infeasible, given the low number of discharges reported.

CONCLUSION

In summary, Invanz[®] is primarily sold into non-retail channels of distribution. The use of Invanz[®] in inpatient hospitals for both pediatric and adult patients has increased over the past three years. Invanz[®]-associated discharges for patients of all ages in Premier network hospitals increased by 15% from 7,675 during the 6 months pre-exclusivity to 8,181 discharges during the 6 months post exclusivity. Invanz[®] associated discharges for pediatric patients age 0-16 years increased by 26% from 70 during the 6 months pre-exclusivity to 88 during the 6 months post-exclusivity. Use of Invanz[®] in pediatric patients is low, accounting for approximately 1% of the combined adult and pediatric Invanz[®] associated discharges.

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 Invanz® and comparator products were examined for the three one year periods from February 2003 through January 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

For this analysis, we examined inpatient usage of Invanz® 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 Invanz[®] 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.

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