

MEMORANDUM

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

PID#: A060087

DATE: April 20, 2006

FROM: Carol A. Pamer, R.Ph., Pharmacist/Drug Use Specialist
Sigal Kaplan, Ph.D., B.Pharm., Pharmacoepidemiologist
Division of Surveillance, Research and Communication Support, HFD-410

THROUGH: Toni Piazza-Hepp, Pharm.D., Acting Director
Division of Surveillance, Research and Communication Support, HFD-410

TO: M. Dianne Murphy, M.D.
Director, Office of Pediatric Therapeutics (OPT), OIASI
Office of the Commissioner

Solomon Iyasu, M.D., M.P.H.
Division of Pediatric Drug Development, HFD-960
Office of Counter-Terrorism and Pediatric Drug Development

SUBJECT: One Year Post-Pediatric Exclusivity Post-marketing Adverse Event Review:
Drug Use Data for Gemcitabine (Gemzar[®]): NDA 20-509
Pediatric Exclusivity Grant Date: January 27, 2005

****This document contains copyrighted, proprietary data from IMS Health[™] and Premier[™] that cannot be shared with non-FDA staff without permission from IMS Health[™] and Premier[™]. Permission must be obtained through the FDA Office of Drug Safety.****

EXECUTIVE SUMMARY

This consult examines drug utilization trends for Gemzar[®] (gemcitabine) in the pediatric population (ages 0-16 years), with a primary focus on patterns of use one year before and one year following the granting of Pediatric Exclusivity for Gemzar[®] on January 27, 2005.

IMS Health, National Sales Perspective[™] data were used to determine the retail and non-retail channels of distribution. Total sales by channel of distribution showed that gemcitabine was mostly sold in the non-retail sector (about 98%), predominantly to clinics and non-federal

hospitals. These two types of facilities accounted for approximately 74.8% and 20.8%, respectively, of all vials sold during the 12-month period from February 2005 to January 2006, inclusive.

Hospital discharge data from the Premier™ network of approximately 450 acute care hospitals revealed that discharges associated with gemcitabine use for pediatric patients (0-16 years) accounted for approximately 0.4% of the total discharges in which gemcitabine was billed in the 6-month period from January through June 2005. Data from a subgroup of the Premier™ 37 freestanding pediatric hospitals showed that 9 hospital discharges for pediatric patients (0-16 years) were associated with gemcitabine use in a one-year period, from July 2004 through June 2005.

“Chemotherapy” (ICD-9 code: V58.1) was the only principal diagnosis code appearing in the pediatric discharges in the Premier™ data from July 2004 through June 2005.

A major limitation of the current analysis is that the data resources available to FDA do not capture use of gemcitabine in the outpatient clinic setting, which represents approximately 75% of its use.

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 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.

Gemzar® (gemcitabine) NDA 20-509 is a nucleoside analogue that exhibits antitumor activity. The product was first approved in the U.S. on May 15, 1996. It is supplied as a sterile, lyophilized white powder in 200 mg and 1 gram single use vials.

The FDA-approved indications for Gemzar® (gemcitabine) include the following:¹

- Breast cancer: Combination therapy with paclitaxel for first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy (unless anthracyclines were contraindicated).
- Non-small cell lung cancer: Combination therapy with cisplatin for first-line treatment of patients with inoperable, locally advanced (Stage IIIA or IIIB), or metastatic (Stage IV) non-small cell lung cancer.
- Pancreatic cancer: First-line treatment for patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. Indicated for patients previously treated with 5-FU (fluorouracil).

At this time, there are no approved pediatric indications for gemcitabine.

The FDA Pediatric Exclusivity Board granted pediatric exclusivity for Gemzar[®] for Injection (NDA 20-509) on January 27, 2005. Based upon the studies completed for pediatric exclusivity, the following language was added to the product labeling in the PRECAUTIONS section, under the Pediatric Patients subsection:

“The effectiveness of Gemzar in pediatric patients has not been demonstrated. Gemzar was evaluated in a Phase 1 trial in pediatric patients with refractory leukemia and determined that the maximum tolerated dose was 10mg/m²/min for 360 minutes three times weekly followed by a one week rest period. Gemzar was also evaluated in a Phase 2 trial in patients with relapsed acute lymphoblastic leukemia (22 patients) and acute myelogenous leukemia (10 patients) using 10mg/m²/min for 360 minutes three times weekly followed by a one week rest period. Toxicities observed included bone marrow suppression, febrile neutropenia, elevation of serum transaminases, nausea, and rash/desquamation, which were similar to those reported in adults. No meaningful clinical activity was observed in this Phase 2 trial.”

The results of these two studies have also been reported in the medical literature.^{2,3}

This review describes sales trends and inpatient drug use patterns for Gemzar[®] (gemcitabine) in the pediatric population as compared with the adult population. Proprietary drug use databases licensed by FDA were used to conduct this analysis.

METHODS

Determining Setting of Use

IMS Health, IMS National Sales PerspectivesTM data were used to determine the setting in which the product was sold.⁴ Sales of this product by number of vials sold from the manufacturer to various retail and non-retail channels of distribution were analyzed for three 12-month time periods from February 2003 through January 2006. Review of these data revealed that the majority of Gemzar was sold to non-retail facilities; 98.4% of all vials sold were to non-retail pharmacies during the 12-month period from February 2005 through January 2006. Most of those vials (74.8%) were sold to clinics and approximately 20.8% of these vials were sold to non-federal hospitals.

FDA does not have access to data describing the use of drug products in clinics. Therefore, we could only examine the utilization patterns for gemcitabine, focusing on the inpatient setting. This likely only reflects approximately 21% of the current total use of gemcitabine. Inpatient drug use data were derived from Premier's Rx Market Advisor and were examined for two six-month time periods: July – December 2004 and January – June 2005. Detailed descriptions of all data resources used in this consult are included in Appendix A.

RESULTS

A. Acute Care, Short-stay Hospitals

Hospital discharge data from Premier's™ network of approximately 450 acute care hospitals revealed that pediatric (0-16 years) use of gemcitabine accounted for approximately 0.5% of the total number of discharges in which gemcitabine was billed in the 6 months preceding the pediatric exclusivity approval date (July through December 2004) and 0.4% of the total number of discharges in the 6 months following the exclusivity approval (January through June 2005) in the U.S. (Table 1).

During this time period, "Chemotherapy" (ICD-9 code: V58.1) was the only principal diagnosis recorded for the pediatric population in the Premier™ network of acute care hospitals.

Table 1: Total Number of Discharges (Unprojected) Associated with Gemcitabine by Age Groups in Premier Hospitals, July 2004 through June 2005, Rx Market Advisor™

			July – December 2004	January – June 2005
Age Groups	ICD-9	Principal Diagnosis	Total No. Discharges (Unprojected)	
Total			936	905
0-16 years			5	4
	V58.1	Chemotherapy	5	4
17+ years			931	901
	V58.1	Chemotherapy	113	132
	140 – 195	Malignant Neoplasms, Primary (except heme/lymphatic sites)	252	237
	196 – 198	Malignant Neoplasms, Secondary, spec. sites	233	210
	199	Malignant Neoplasms, without spec. of site	4	8
	200 – 208	Malignant Neoplasms, Primary (hematopoietic, lymphatic tissue)	24	18
	210 – 229	Benign neoplasms	0	0
	230 – 234	Carcinoma in situ	0	0
	235 – 239	Neoplasms, uncertain behav. or unspec.nature	1	1
	Other	All other ICD-9 codes	304	295
Premier Rx Market Advisor, data extracted March 2006.				

B. Pediatric Hospitals

Among a subset of Premier's™ 37 pediatric hospitals, there were a total of 9 discharges associated with billing of gemcitabine in the pediatric population (ages 0-16) during the one-year time period. Five of the pediatric discharges occurred during the 6-month period from July 2004 through December 2004 and 4 discharges occurred during the 6-month period from January 2005 through June 2005.

The only principle discharge diagnosis mentioned for patients aged 0-16 years was "Chemotherapy" (ICD-9 code: V58.1). The cancer diagnosis associated with administration of the chemotherapy was not provided.

DISCUSSION

The IMS Health, IMS 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. These data do not include demographic information for the patients receiving these products. 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.

Currently, much of the chemotherapy administration in the U.S. occurs in outpatient hospital clinics. A major limitation of the current analysis is that the data resources available to FDA do not capture use in the outpatient hospital clinic setting. Sales data from IMS Health, National Sales Perspective™ do suggest that gemcitabine is most often administered in clinics and non-federal hospitals. The number of chemotherapy treatment centers, nationally, is unknown.

Premier™ data are derived from hospital billing data, and therefore, may not reflect exactly which drugs are administered to patients. Also, there is no direct linkage between the drugs billed and the discharge diagnosis and procedure, so indications for use cannot be determined from this database. Finally, we are not able to use Premier™ data to make reliable national estimates of drug use for the subpopulation of pediatric inpatients at this time. Although Premier™ network hospitals appear representative of all U.S. acute short-stay hospitals in general, it is not clear whether they are representative of pediatric inpatient care in the U.S.

CONCLUSIONS

Drug use data suggest that most of Gemzar® (gemcitabine) vials (~75%) were sold to clinics. About 21% of the vials were sold to non-federal hospitals, such as those which appear in the Premier™ data. Since the data resources available to FDA do not capture use of gemcitabine in the outpatient clinic setting, we only examined utilization patterns of gemcitabine in the inpatient setting. This likely reflects only one-fifth of the total use of gemcitabine.

An analysis of hospital discharge billing data in the period from January through June 2005 from a sample of 450 acute care hospitals revealed that a very low percentage of discharge data for gemcitabine (~0.4%) was associated with pediatric (0-16 years) discharges. “Chemotherapy” (ICD-9 code: V58.1) was the only principal diagnosis code appearing in the pediatric population in the Premier database.

Carol A. Pamer, R.Ph.
Pharmacist/Drug Utilization Data Specialist
Division of Surveillance, Research, and
Communication Support (DSRCS)

Sigal Kaplan, P.h.D., B.Pharm.
Pharmacoepidemiologist
Division of Surveillance, Research, and
Communication Support (DSRCS)

Toni Piazza-Hepp, Pharm.D.
Acting Director
Division of Surveillance, Research and
Communication Support

*The authors wish to acknowledge the contributions of Lawrence Krebs, Pharm.D. candidate at the University of Maryland School of Pharmacy, for his review of the medical literature concerning gemcitabine use in children.

APPENDIX A

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.

PREMIER™

Premier maintains a large hospital drug utilization and financial database which contains billing information from over 450 acute care facilities and includes approximately 14 million inpatient records. Roughly one out of every seven inpatient discharges in the United States is represented in Premier's database.⁵ Data are available from January 2000 through the present, but have a lag time of approximately 6 months.

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, number of beds, population served, payers, 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.⁶ Based upon these analyses, we believe that overall estimates of national inpatient drug use using Premier data appear to be reasonable, but strongly recommend making this determination on a drug-specific and population-specific basis. We used only actual samples for gemcitabine, since we cannot use Premier data at this time to make reliable national estimates of drug use for the subpopulation of pediatric inpatients.

PREMIER PEDIATRIC™

Premier's pediatric database is a subset of the larger database described above. Information is available from 37 pediatric hospitals. Data are also available from January 2000 through the present, but have a lag time of approximately six months.

¹ Eli Lilly and Company. Gemzar® for Injection complete prescribing information. Version PV4064AMP. Revision date April 26, 2005.

² Angiolillo AL, Whitlock J, Chen Z, Krailo M, Reaman G. Phase II study of gemcitabine in children with relapsed acute lymphoblastic leukemia or acute myelogenous leukemia (ADVL0022): a Children's Oncology Group Report. *Pediatr Blood Cancer* 2006; 46:193-7.

³ Steinherz PG, Seibel NL, Ames MM, Avramis VI, Krailo MD, Liu-Mares W, Reid JM, Safgren SL, Reaman GH. Phase I study of gemcitabine (difluorodeoxycytidine) in children with relapsed or refractory leukemia (CCG-0955): a report from the Children's Cancer Group. *Leuk Lymphoma* 2002; 43(10):1945-50.

⁴ IMS Health, IMS National Sales Perspective™, Moving Annual Totals, February 2004-January 2006, Data extracted March 2006. Original File: 0603gem3.dvr

⁵ National Center of Health Statistics. *Health United States*, 2003

⁶ Staffa JA, Gutierrez B, Kornegay C, et al. Outcome-based evaluation of a method for obtaining U.S. national estimates of inpatient drug utilization. *Pharmacoepidemiology Drug Safety* 2003;12: S173

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Carol Pamer
4/20/2006 04:41:33 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
4/21/2006 08:42:22 AM
DRUG SAFETY OFFICE REVIEWER