

Memorandum

**Department of Health and Human Services
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Center for Drug Evaluation and Research**

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SUBJECT: One Year Post-Pediatric Exclusivity Post-marketing Adverse Event Review: Drug Use Data
Carboplatin for Injection (Paraplatin®): NDA 19-880
Pediatric Exclusivity Grant Date: April 30, 2004

****This document contains proprietary data from IMS Health and Premier which cannot be shared outside of FDA without clearance from IMS Health and Premier obtained through the Office of Drug Safety.****

EXECUTIVE SUMMARY

This consult examines drug utilization trends for Paraplatin® (carboplatin) 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 for Paraplatin® on April 30, 2004. The IMS Health, National Sales Perspective™ was used to determine the various retail and non-retail channels of distribution. Total sales by channel of distribution showed that carboplatin was mostly sold in the non-retail sector (~97%), predominantly to clinics and non-federal hospitals, which accounted for approximately 60.2% and 31.6%, respectively, of all vials sold during the 12-month period from May 2004 to April 2005, inclusive. Generic carboplatin became available for sale in the U.S. in October, 2004.

There were approximately 1,492,600 vials of carboplatin sold in the U. S. from May 2002 through April 2003. An estimated 1,573,200 vials were sold during the 12-month time period from May 2003 through April 2004. While generic carboplatin became available in the fall of 2004, total carboplatin sales decreased almost 18% with an estimated 1,292,400 vials sold during the 12-month post-pediatric exclusivity period from May 2004 through April 2005.

Actual hospital discharge data from Premier's™ network of approximately 450 acute care hospitals revealed that pediatric (0-16 years) use of carboplatin accounted for approximately 2.9% of actual discharges in which carboplatin was billed between July through December 2004 in the U.S. Data from a subgroup of Premier's 37 freestanding pediatric hospitals showed that 98 distinct discharges for pediatric patients (0-16 years) were associated with carboplatin use from January 2004 through December 2004.

“Malignant neoplasm kidney” (ICD-9 code: 189), “malignant neoplasm of retina” (ICD-9 code 190.5), and “chemotherapy” (ICD-9 code: V58.1) were the only three principal diagnoses appearing in the pediatric population in the Premier database during July through December 2004.

A major limitation of the current analysis is that the data resources available to the agency do not capture use of carboplatin in the outpatient clinic setting, which represents approximately 60% of its use.

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 that Act requires the reporting of adverse events associated with the use of the 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.

Carboplatin for injection (Paraplatin®, NDA 19-880) was approved on March 31, 1989, for the initial treatment of advanced ovarian carcinoma in established combination with other approved chemotherapeutic agents. Carboplatin is also indicated for the palliative treatment of patients with ovarian cancer recurrent after prior chemotherapy, including patients who have been previously treated with cisplatin. At this time, there are no approved pediatric indications and no labeling for use in patients under the age of 16 years. Paraplatin® is supplied as a sterile, lyophilized white powder available in single dose vials containing 50 mg, 150mg, or 450mg containing equal parts of carboplatin and mannitol ready for reconstitution. Paraplatin® is also available in ready to use infusion bags. The first generic carboplatin product was approved in October, 2004.

The Pediatric Exclusivity Board of the FDA granted pediatric exclusivity for Paraplatin® for Injection (NDA 20-038) on April 30, 2004. No changes to the product labeling have been made since this exclusivity was granted. This review describes sales trends and inpatient drug use patterns for Paraplatin® in the pediatric population as compared to the adult population. Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

This review describes only inpatient drug use patterns for carboplatin in the pediatric and adult population approximately six months before and after the granting of pediatric exclusivity. Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

METHODS

Determining Setting of Use

IMS Health, National Sales Perspectives™ data were used to determine the setting in which the product was sold.¹ 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 May 2002 through April 2005. It was clear from these data that the majority of this product was sold into non-retail settings; 97.4% of all vials sold were to non-retail pharmacies during the 12-month period from May 2004 through April 2005, of which approximately 60% were sold to clinics. Since the Agency does not have access to data describing the use of drug products in clinics, we could only examine the utilization patterns for carboplatin focusing on the inpatient setting. Inpatient use was assessed from hospital billing data provided by Premier™. *It should be noted, however, that the inpatient use described in the current study likely reflects only approximately one third of the total use of carboplatin.* Detailed descriptions of all data resources used in this consult are included in Appendix B.

RESULTS

A. Acute Care, Short-stay Hospitals

Actual hospital discharge data from Premier's™ network of approximately 450 acute care hospitals revealed that pediatric (0-16 years) use of Paraplatin® accounted for approximately 4% of actual discharges in which carboplatin was billed between January through June 2004 (100 of 2,482 actual discharges) and 2.9% of discharges from July through December 2004 (68 of 2,348 discharges) in the U.S. (Table 1). Between July and December 2004, “malignant neoplasm of kidney” (ICD-9 code: 189), “malignant neoplasm of retina” (ICD-9 code: 190.5), and “chemotherapy” (ICD-9 code: V58.1) were the three principal diagnoses appearing in the pediatric population.

¹ IMS Health, IMS National Sales Perspective™, Moving Annual Totals, May 2002-April 2005, Data extracted June 2005. Original File: 0506par2.dvr

Table 1: Total Number of Actual Discharges Associated with Carboplatin by Age Groups in Premier Hospitals, January 2004 through December 2004 (Rx Market Advisor™)

Patient Age Custom Groups	ICD-9	Principal Diagnosis	January – June 2004	July - December 2004
			Actual Discharges	Actual Discharges
Total			2,482	2,348
Patient Age 0-16	Total		100	68
	V58.1	Chemotherapy	85	62
	190.5	Malignant neoplasm of retina	9	3
	189	Malignant neoplasm of kidney	3	3
	194	Malignant neoplasm of adrenal	3	
Patient Age 17+	Total		2,382	2,280
	V58.1	Chemotherapy	838	781
	141-191.2	Malignant Neoplasms	759	831
	196-198.89	Secondary Malig. Neoplasms	397	380
		All other ICD-9 (8)	388	288

Premier Rx Market Advisor, data extracted June 2005.

B. Pediatric Hospitals

In the subset of 37 pediatric hospitals, there was a total of 98 discharges associated with billing of carboplatin in the pediatric population (ages 0-16) during the one-year time period (Table 2).

Table 2: Total Number of Actual Discharges Associated with Carboplatin by Age in Premier Pediatric Hospitals, January 2004 through December 2004 (Rx Market Advisor™)

				January – June 2004	July – December 2004
	Age (years)	ICD-9	Principal Diagnosis	Discharges	Discharges
Carboplatin				58	40
	<1	190.5	Malignant neoplasm of retina	3	0
		V58.1	Chemotherapy	8	10
	1	190.5	Malignant neoplasm of retina	3	0
		V58.1	Chemotherapy	15	11
	2	V58.1	Chemotherapy	12	0
	3	V58.1	Chemotherapy	3	4
	4	V58.1	Chemotherapy	3	0
	6	V58.1	Chemotherapy	3	0
	7	V58.1	Chemotherapy	0	3
	10	V58.1	Chemotherapy	0	4
	11	V58.1	Chemotherapy	0	3
	12	V58.1	Chemotherapy	3	0
	13	V58.1	Chemotherapy	0	5
	16	V58.1	Chemotherapy	5	0

Premier Pediatric Rx Market Advisor, data extracted June 2005.

The most common principle discharge diagnosis mentioned for patients aged 0-16 years, was “Chemotherapy encounter” (ICD-9 code: V58.1), accounting for 52 discharges (90%) during January 2004 through June 2004, and 40 discharges (100%) during July 2004 through December 2004. The reason for “Chemotherapy encounter” (ICD-9 code: V58.1) is not further defined. The next most frequently mentioned diagnosis was “Malignant neoplasm of Retina” (ICD- code: 190.5). Overall, this diagnosis accounted for 6 discharges (10%) during January 2004 through June 2004, and 0 discharges (0%) during July 2004 through December 2004 in the pediatric population.

DISCUSSION

The IMS Health, 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. It does not include complete historical demographic information for the patients receiving these products. The amount of products 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 chemotherapy treatment in the U.S. is provided in outpatient hospital clinics. A major limitation of the current analysis is that the data resources available to the Agency do not capture use in the outpatient hospital clinic setting. The sales data from the IMS Health, National Sales Perspective™ do suggest that carboplatin is most often administered in clinics, 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 what drugs are administered to patients. Also, there is no direct linkage between drugs billed and discharge diagnosis and procedure, so indications for use cannot be determined. Finally, we are not able use Premier data to make reliable national estimates of drug use for the subpopulation of pediatric inpatients at this time. Although Premier 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

An estimated 1,292,400 vials of carboplatin were sold during the 12-month post-pediatric period from May 2004 through April 2005, representing an 18% decrease from the prior year, despite the introduction of generic carboplatin in the fall of 2004. Approximately 30% of these vials were sold to hospitals. An analysis of a sample of 450 acute care hospitals revealed that a very low percentage of billing for carboplatin (~3%) were associated with pediatric (0-16 years) discharges. “Malignant neoplasm kidney” (ICD-9 code: 189), “malignant neoplasm of retina (ICD-9 code 190.5), and “chemotherapy” (ICD-9 code: V58.1) were the only three principal diagnoses appearing in the pediatric population in the Premier database during July through December 2004. A major limitation of the current analysis is that the data resources available to the agency do not capture use of carboplatin in the outpatient clinic setting, which represents approximately 60% of its use.

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.² 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, 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.³ 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 carboplatin, 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.

² National Center of Health Statistics. Health United States, 2003

³ 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

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