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Subject: 1-year Post-Pediatric Exclusivity Post-Marketing Adverse Event  
Review

Drug Name(s): Eloxatin® (oxaliplatin for injection)

Submission Number: SE8-008

Application Type/Number: NDA 21-492

Applicant/sponsor: Sanofi-Aventis

OSE RCM #: 2007-174

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# CONTENTS

EXECUTIVE SUMMARY .....	2
1 Background .....	2
1.1 Introduction .....	2
1.2 Regulatory history .....	2
1.3 Product labeling .....	2
2 Methods and Materials .....	3
2.1 Introduction .....	3
2.2 Determining setting of care .....	3
2.3 Data sources used .....	3
3 Results .....	4
4 Discussion .....	6
5 Conclusions .....	6
APPENDIX A .....	7
REFERENCES .....	8

## **EXECUTIVE SUMMARY**

This consult examines drug use trends for Eloxatin® (oxaliplatin) in the pediatric population (i.e., ages 0 to 16 years), with a primary focus on patterns of use during three one-year periods from October 2004 through September 2007, two years before and one year after the granting of Pediatric Exclusivity for this product on September 27, 2006.

IMS Health, IMS National Sales Perspectives™ data were used to determine the settings in which oxaliplatin was sold. In the one-year period Post-exclusivity (i.e., October 2006 through September 2007), a projected 970,100 vials of oxaliplatin injection were sold in the U.S. Most (99%) oxaliplatin was purchased by non-retail facilities. Most oxaliplatin (75%) was sold to clinics and 20% to non-federal hospitals.

Hospital discharge data from the Premier™ network of approximately 590 acute care hospitals revealed that pediatric use accounted for 2 of 2,023 (<1%) oxaliplatin-associated discharges (unprojected) in the 6 months post-pediatric exclusivity (September 2006 through August 2007). Most discharges for oxaliplatin were directly associated with oncologic conditions.

Among the Premier™ network of 37 pediatric hospitals, the frequency distribution of Principle Diagnosis ICD-9 codes was the same as that of the full set of 590 Premier™ hospitals.

A major limitation of the analysis was that the data resources available to FDA do not capture use of oxaliplatin in the outpatient clinic setting, which represented approximately 75% of its use.

## **1 BACKGROUND**

### **1.1 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.

### **1.2 REGULATORY HISTORY**

Eloxatin® (oxaliplatin) was first approved in the U.S. in August 2002. A Pediatric Written Request Letter was issued to Sanofi Aventis on December 9, 2004. In response, two Phase I and two Phase II studies were conducted in 159 patients ages 7 months to 22 years old with advanced and/or refractory solid tumors<sup>1</sup>. Pediatric Exclusivity was granted on September 27, 2006. Effectiveness was not established in children as a result of these trials.

### **1.3 PRODUCT LABELING**

As a result of the pediatric Phase I and Phase II studies, revisions were made to the product labeling sections **CLINICAL PHARMACOLOGY**, **Pharmacokinetics in Special Populations**, **USE IN SPECIFIC POPULATIONS**, and **Pediatric Use**<sup>2</sup>.

## 2 METHODS AND MATERIALS

### 2.1 INTRODUCTION

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

### 2.2 DETERMINING SETTING OF USE

IMS Health, IMS National Sales Perspectives™ data were used to determine the settings in which oxaliplatin and two comparator products, carboplatin and cisplatin, were sold.<sup>3</sup> Sales of these products by number of vials sold from manufacturer to retail and non-retail channels of distribution were analyzed for three 12-month time periods from October 2004 through September 2007. Table 1 provides a summary of the number of vials (in thousands) of carboplatin, cisplatin, and oxaliplatin sold.

In the one-year period Post-exclusivity (i.e., October 2006 through September 2007), a projected 970,100 vials of oxaliplatin injection were sold in the U.S.

**Table 1: Carboplatin, Cisplatin, and Oxaliplatin Sales of Number of Vials (in Thousands), for three 12-month Periods—October 2004 through September 2007<sup>3</sup>**

	October 2004 – September 2005	Percent of Total	October 2005 – September 2006	Percent of Total	October 2006 – September 2007	Percent of Total
	Total vials, in thousands (add 000s)	(%)	Total vials, in thousands (add 000s)	(%)	Total vials, in thousands (add 000s)	(%)
<b>30910 PLATINUM COMPOUNDS</b>	<b>2438.5</b>	<b>100.0</b>	<b>2610.3</b>	<b>100.0</b>	<b>2600.6</b>	<b>100.0</b>
CISPLATIN	422.8	17.3	464.3	17.8	482.6	18.6
CARBOPLATIN	1225.6	50.3	1232.7	47.2	1147.8	44.1
OXALIPLATIN	790.1	32.4	913.2	35.0	970.1	37.3

Analysis of the data revealed that the majority (99%) of oxaliplatin vials were sold to non-retail facilities (i.e., clinics, federal and non-federal hospitals, home health care, long-term care, HMOs, universities, prisons, and other sites). Most oxaliplatin (75%) was sold to clinics and 20% to non-federal hospitals, such as those in the Premier® database currently licensed by FDA.

Currently FDA does not have access to data describing the use of drug products in clinics. Therefore, we could only examine the utilization patterns for oxaliplatin focusing on the non-federal hospital inpatient setting. This likely only reflects between 19% and 20% of the current use of Eloxatin for this three-year time period.

### 2.3 DATA SOURCES USED

Inpatient drug use data were derived from Premier's Rx Market Advisor. We examined data for three 12-month time periods from October 2004 through September 2007 before and after granting of pediatric exclusivity on September 27, 2006. Detailed descriptions of the data resources used are provided in Appendix A.

### 3 RESULTS

#### *A. Acute Care, Short-stay Hospitals*

Hospital discharge data from the Premier™ network of approximately 590 acute care hospitals revealed that pediatric use of oxaliplatin accounted for 2 of 2,027 (less than 1%) of the unprojected discharges in which oxaliplatin was billed in the 12 months post-pediatric exclusivity (October 2006 through September 2007)<sup>4</sup>. Table 2 provides a summary of the number of discharges (unprojected) for carboplatin, cisplatin, and oxaliplatin.

**Table 2: Total Number of Unprojected Discharges Associated with Platinum Compounds by Age Group from October 2004 through September 2007**

Source: Premier Rx Market Advisor™<sup>4</sup>

Drug Name	Baseline Year 10/2004 to 9/2005		Pre-Exclusivity 10/2005 to 9/2006		Post-Exclusivity 10/2006 to 9/2007		TOTAL 10/2004 to 9/2007
	Total Discharges (unprojected)						
	Age 0 to 16	Age 17 and older	Age 0 to 16	Age 17 and older	Age 0 to 16	Age 17 and older	All Ages
<b>Total</b>	<b>664</b>	<b>13,689</b>	<b>732</b>	<b>15,399</b>	<b>717</b>	<b>14,238</b>	<b>45,439</b>
<b>CARBOPLATIN</b>	260	5,494	281	6,318	291	6,095	<b>18,739</b>
<b>CISPLATIN</b>	401	5,842	435	6,416	424	6,118	<b>19,636</b>
<b>OXALIPLATIN</b>	<b>3</b>	<b>2,353</b>	<b>16</b>	<b>2,665</b>	<b>2</b>	<b>2,025</b>	<b>7,064</b>

When examined by Principle Diagnosis ICD-9 codes, oxaliplatin was associated with 2,023 total inpatient hospital discharges (unprojected) in the Premier hospital reporting network during the post-exclusivity year of study<sup>5</sup>. Most of these discharges were directly associated with oncologic conditions. In Table 3, all principal discharge diagnosis ICD-9 codes are displayed for children. For adults, ICD-9 codes associated with at least 20 total discharges during the three year period are displayed.

**Table 3: Total Number of Unprojected Discharges Associated with Oxaliplatin by Age Group and Principal Discharge Diagnosis ICD-9 Code October 2004 through September 2007**

Source: Premier Rx Market Advisor™<sup>5</sup>

Age Group	Principal Dx ICD9		Baseline Year 10/2004 to 9/2005	Pre- Exclusivity 10/2005 to 9/2006	Post- Exclusivity 10/2006 to 9/2007	TOTAL 10/2004 to 9/2007
			Total Discharges (unprojected)			
<b>Total</b>			<b>2,354</b>	<b>2,678</b>	<b>2,023</b>	<b>7,055</b>
<b>Age 0 to 16</b>		<b>Total</b>	<b>3</b>	<b>16</b>	<b>2</b>	<b>21</b>
	V58.11	ENCOUNTER FOR ANTINEOPLASTIC C		14	1	15
	008.8	INTESTINAL INFECTION DUE TO OT			1	1
	153.8	MALIG NEOPLASM OTHER SPEC SITE	1			1
	194.0	MALIGNANT NEOPLASM OF ADRENAL	1			1
	453.41	VENUS EMBO&THROMB DP PROX LW E		1		1
	564.00	UNSPECIFIED CONSTIPATION		1		1
	V58.1	CHEMOTHERAPY	1			1
<b>Age 17 and older</b>		<b>Total</b>	<b>2,351</b>	<b>2,662</b>	<b>2,021</b>	<b>7,034</b>
	V58.11	ENCOUNTER FOR ANTINEOPLASTIC C		2,045	1,438	3,483
	V58.1	CHEMOTHERAPY	1,808			1,808
	197.7	SECONDARY MALIGNANT NEOPLASM O	31	54	47	132
	153.9	MALIGNANT NEOPLASM OF COLON UN	42	37	29	108
	197.6	SEC MALIG NEOPLASM RETROPERITO	41	27	40	108
	154.1	MALIGNANT NEOPLASM OF RECTUM	27	31	22	80
	154.0	MALIGNANT NEOPLASM OF RECTOSIG	24	16	22	62
	197.0	SECONDARY MALIGNANT NEOPLASM O	11	16	22	49
	153.3	MALIGNANT NEOPLASM OF SIGMOID	21	15	10	46
	415.19	OTHER PULMONARY EMBOLISM AND I	7	12	16	35
	276.51	DEHYDRATION		14	18	32
	996.62	INF&INFLAM REACT TO VASC DEVIC	7	13	8	28
	153.8	MALIG NEOPLASM OTHER SPEC SITE	13	7	7	27
	153.4	MALIGNANT NEOPLASM OF CECUM	6	7	12	25
	197.2	SECONDARY MALIGNANT NEOPLASM O	6	9	10	25
	198.5	SEC MALIGNANT NEOPLASM OF BONE	7	10	8	25
	153.6	MALIGNANT NEOPLASM OF ASCENDIN	6	13	5	24
	276.5	VOLUME DEPLETION	23			23
	198.89	SEC MALIGNANT NEOPLASM OF OTHE	13	5	3	21
	157.9	MALIGNANT NEOPLASM OF PANCREAS	3	8	9	20
<b>Age 17 and older</b>		<b>All Other ICD-9 Codes</b>	<b>255</b>	<b>323</b>	<b>295</b>	<b>873</b>

***B. Pediatric Hospitals***

Among a subset of Premier's™ 37 pediatric hospitals, there were a total of 21 unprojected hospital discharges associated with billing of oxaliplatin in the pediatric population (ages 0 to 16 years) during the three-year time period<sup>6</sup>. As with the full set of 590 Premier™ hospitals, 16 of these discharges occurred during the one-year pre-exclusivity period and 2 occurred during the one-year post-exclusivity period. The frequency distribution of the cases by Principle Diagnosis ICD-9 codes was the same as that of the full set of 590 Premier™ hospitals.

## **4 DISCUSSION**

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, IMS National Sales Perspective™ suggest that most oxaliplatin (75%) was sold to clinics during our study period. Only 20% of oxaliplatin was sold to non-federal hospitals such as those in the Premier® database used to conduct this analysis.

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.

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. Although Premier™ network hospitals appear to be 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.

## **5 CONCLUSIONS**

Drug use data suggest that most oxaliplatin (75%) was sold to clinics and approximately only 20% to inpatient hospitals such as those in the Premier™ database. Thus, this review likely reflects a small part of all oxaliplatin use, as FDA does not have access to data describing the use of drug products in clinics.

An analysis of the Premier™ hospital discharge billing data in the one-year post-exclusivity study period (i.e., October 2006 through September 2007) from a sample of 590 acute care hospitals revealed that less than 1% of inpatient discharges in which patients were billed for oxaliplatin were associated with pediatric (0-16 years) discharges. Most of these discharges were directly associated with the treatment of oncologic conditions.

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## APPENDIX A

### *IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail*

The 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. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. 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.

### *Premier RxMarket Advisor™*

Premier's database is a large hospital drug utilization and financial database. Information is available from over 590 acute care and pediatric facilities and includes approximately 38 million inpatient records. On an annual basis, this constitutes roughly one out of every six inpatient discharges in the United States.<sup>7</sup> Data are available from January 2000 through the present, but have a lag time of approximately 75 days. 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.<sup>8</sup> 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.

## REFERENCES

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