



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

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

Drug Name: Eloxatin[®] (oxaliplatin for injection)

Pediatric Exclusivity
Approval Date: September 27, 2006

Application
Type/Numbers: NDA # 21-492

Applicant/sponsors: Sanofi Aventis

OSE RCM #: 2007-174

1. Executive Summary

The AERS database was searched for reports of adverse events (serious and non-serious) occurring with the use of oxaliplatin in pediatric patients. Up to the "data lock" date of 10/27/2007, AERS contained 5,484 reports for oxaliplatin (crude counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric reports represent approximately 0.27% of the total (15/5,484).

DDRE was asked to focus on the 1-year period following the approval of pediatric exclusivity, September 27, 2006 to September 27, 2007. We used an AERS data lock date of 10/27/2007 to allow time for reports received up to 9/27/2007 to be entered into AERS. During the first 13 months after pediatric exclusivity was granted, AERS received a total of 1,495 reports (crude counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric reports represent approximately 0.40% of the total (6/1,495). We will refer to this 13-month interval as the pediatric exclusivity period in the remainder of this review.

DDRE was also asked to focus on renal, gastrointestinal (pancreatitis), and hearing loss adverse events in the pediatric exclusivity period, and to consider looking for the signal since first marketing in the pediatric and possibly the adult population if the reports are few in number. In addition, DDRE was asked to assess if the adverse events in pediatrics are similar to or quantitatively different than the adult profile if the pediatric population is experiencing different or more frequent severe adverse events than adults.

Three pediatric cases were identified in AERS during the pediatric exclusivity period. Two of these describe labeled events, including sensory neuropathy syndrome and a case with a bleeding event; the third case reported an intussusception, which is unlabeled, that resolved the same day. During the time period from marketing approval to the start of pediatric exclusivity, there were five pediatric cases. These cases involved the labeled events of sensory neuropathy, allergic reaction, and the unlabeled events of seizure and increased lipase/amylase levels. There have been no subsequent pediatric reports of pancreatitis or elevated pancreatic enzymes. There are no pediatric reports of renal or hearing loss adverse events in AERS.

Based on the above findings, a comparison of pediatric adverse events with the adult profile is not indicated.

2. Products, Indications, Pediatric Labeling, and Pediatric Filing History

2.1 Products:

- NDA 21-492, Oxaliplatin for Injection (Sterile Lyophilized Powder), Approved 8/9/2002
- NDA 21-759, Oxaliplatin Injection (Sterile Aqueous Solution), Approved 1/31/2005

2.2 Indications:

ELOXATIN, used in combination with infusional 5-FU/LV, is indicated for adjuvant treatment of stage III colon cancer patients who have undergone complete resection of the

primary tumor. The indication is based on an improvement in disease-free survival, with no demonstrated benefit in overall survival after a median follow up of 4 years.

ELOXATIN, used in combination with infusional 5-FU/LV, is indicated for the treatment of advanced colorectal cancer.

2.3 Pediatric labeling:

USE IN SPECIFIC POPULATIONS

Pediatric Use

The effectiveness of oxaliplatin in children has not been established. Oxaliplatin has been tested in 2 Phase I and 2 Phase II trials in 159 patients ages 7 months to 22 years with solid tumors (see below) and no significant activity observed. In a Phase I/II study, oxaliplatin was administered as a 2-hour IV infusion on days 1, 8 and 15 every 4 weeks (1 cycle), for a maximum of 6 cycles, to 43 patients with refractory or relapsed malignant solid tumors, mainly neuroblastoma and osteosarcoma. Twenty eight pediatric patients in the Phase I study received oxaliplatin at 6 dose levels starting at 40 mg/m² with escalation to 110 mg/m². The dose limiting toxicity (DLT) was sensory neuropathy at the 110 mg/m² dose. Fifteen patients received oxaliplatin at a dose of 90 mg/m² IV in the Phase II portion of the study. At this dose, paresthesia (60%, G3/4: 7%), fever (40%, G3/4: 7%) and thrombocytopenia (40%, G3/4: 27%) were the main adverse events. No responses were observed.

In a second Phase I study, oxaliplatin was administered to 26 pediatric patients as a 2-hour IV infusion on day 1 every 3 weeks (1 cycle) at 5 dose levels starting at 100 mg/m² with escalation to 160 mg/m², for a maximum of 6 cycles. In a separate cohort, oxaliplatin 85 mg/m² was administered on day 1 every 2 weeks, for a maximum of 9 doses. Patients had metastatic or unresectable solid tumors mainly neuroblastoma and ganglioneuroblastoma. No responses were observed. The DLT was sensory neuropathy at the 160 mg/m² dose. Based on these studies, oxaliplatin 130 mg/m² as a 2-hour IV infusion on day 1 every 3 weeks (1 cycle) was used in subsequent Phase II studies. A dose of 85 mg/m² on day 1 every 2 weeks was also found to be tolerable.

In one Phase II study, 43 pediatric patients with recurrent or refractory embryonal CNS tumors received oxaliplatin 130 mg/m² every 3 weeks for a maximum of 12 months in absence of progressive disease or unacceptable toxicity. In patients < 10 kg the oxaliplatin dose used was 4.3 mg/kg. The most common adverse events reported were leukopenia (67%, G3/4: 12%), anemia (65%, G3/4: 5%), thrombocytopenia (65%, G3/4: 26%), vomiting (65%, G3/4: 7%), neutropenia (58%, G3/4: 16%) and sensory neuropathy (40%, G3/4: 5%). One partial response was observed.

In a second Phase II study, 47 pediatric patients with recurrent solid tumors, including Ewing sarcoma or peripheral PNET, osteosarcoma, rhabdomyosarcoma and neuroblastoma, received oxaliplatin 130 mg/m² every 3 weeks for a maximum of 12 months or 17 cycles. In patients < 12 months old the oxaliplatin dose used was 4.3 mg/kg. The most common adverse events reported were sensory neuropathy (53%, G3/4: 15%), thrombocytopenia (40%, G3/4: 26%), anemia (40%, G3/4: 15%), vomiting (32%, G3/4: 0%), nausea (30%, G3/4: 2%) and AST increased (26%, G3/4: 4%). No responses were observed.

The pharmacokinetic parameters of ultrafiltrable platinum have been evaluated in 105 pediatric patients during the first cycle. The mean clearance in pediatric patients estimated by the population pharmacokinetic analysis was 4.7 L/h/m². The inter-patient variability of platinum clearance in pediatric cancer patients was 41%. Mean platinum pharmacokinetic parameters in ultrafiltrate were C_{max} of 0.75 ± 0.24 mcg/mL, AUC₀₋₄₈ of 7.52 ± 5.07 mcg·h/mL and AUC_{inf} of 8.83 ± 1.57 mcg·h/mL at 85 mg/m² of oxaliplatin and C_{max} of 1.10 ± 0.43 mcg/mL, AUC₀₋₄₈ of 9.74 ± 2.52 mcg·h/mL and AUC_{inf} of 17.3 ± 5.34 mcg·h/mL at 130 mg/m² of oxaliplatin.

2.4 Pediatric Filing History:

A formal Written Request (WR) for pediatric studies of oxaliplatin was issued to Sanofi-Synthelabo, Inc. on December 9, 2004. An amendment to the WR was approved on March 4, 2005. The supplemental new drug application was approved on January 10, 2007 and pediatric exclusivity was granted on September 27, 2006.

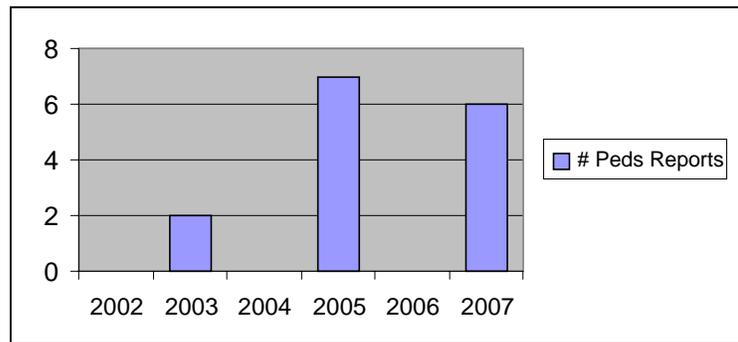
3. AERS Search Results: Oxaliplatin

3.1 Count of Reports: AERS Search including all sources – U.S. & foreign from marketing approval date (Table 1).

Table 1: Crude counts¹ of AERS Reports for All Sources from Marketing Approval Date (8/9/2002) through 10/27/2007 (US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Adults (≥ 17 yrs.)	4,693 (2,313)	4,456 (2,143)	953 (345)
Pediatrics (0-16 yrs.)	15 (8)	15 (8)	2 (2)
Age unknown (Null values)	776 (382)	428 (261)	82 (35)
Total	5,484 (2,703)	4,899 (2,412)	1,037 (382)

¹ May include duplicates
² Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life-threatening, hospitalization (initial or prolonged), disability, and congenital anomaly.

Figure 1: Reporting trend for pediatric reports from approval date



3.2 Count of Reports: AERS Search including all sources - U.S. & foreign from Pediatric Exclusivity approval date (Table 2)

Table 2: Crude counts¹ of AERS Reports for All Sources from date Pediatric Exclusivity was Granted (9/27/2006) through 10/27/2007 (US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Adults (≥ 17 yrs.)	1,387 (634)	1,359 (609)	320 (118)
Pediatrics (0-16 yrs)	6 (1)	6 (1)	1 (1)
Age unknown (Null Values)	102 (53)	102 (53)	20 (10)
Total	1,495(688)	1,467 (663)	341 (129)
¹ May include duplicates			
² Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life-threatening, hospitalization (initial or prolonged), disability, and congenital anomaly.			

4. Postmarketing Review of All Pediatric Adverse Event Reports received during the one-year after a drug receives pediatric market exclusivity

During the first 13 months after pediatric exclusivity was granted, AERS received a total of 6 reports for oxaliplatin (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). One of these reports involved the miscoding of age for a 60 year old female and two other reports were duplicates. The remaining three pediatric cases were reported from the same Phase 2 clinical study and are described below. Unlabeled events are underlined.

4.1. ISR #5346387, United Kingdom, Clinical Study Report

A 10 year-old female with a history of autistic spectrum disorder and medulloblastoma was enrolled in a single-arm study of gemcitabine in combination with oxaliplatin for the treatment of refractory and relapsed pediatric solid tumors. The patient received two courses of gemcitabine 1000 mg/m² and oxaliplatin 100 mg/m². Thirty minutes after the end of the second oxaliplatin infusion, she experienced laryngopharyngeal dysesthesia, slurred speech, abnormal eye movements (twitching), and generalized weakness. No specific treatment was necessary and the patient fully recovered. The investigator thought the causal relationship between the events and oxaliplatin treatment was likely.¹ Concomitant treatments included paracetamol and ondansetron.

4.2. ISR #5483986, United Kingdom, Clinical Study Report

A 12 year-old male with recurrent supratentorial neuroectodermal tumor was enrolled in a single-arm study of gemcitabine in combination with oxaliplatin for the treatment of refractory and relapsed pediatric solid tumors. Relevant medical history included previous hemorrhage on the right side. There were no concurrent conditions or factors such as hemostatic disorders, arterial aneurysm, recent head injury or radiation therapy. About three weeks after receiving the seventh cycle of study treatment, the patient experienced increasing tiredness and confusion and was hospitalized. CT showed a large left frontal cerebral hemorrhage. The platelet count was 51,000/mm³. He was treated with platelet transfusion

¹ The symptoms of this patient, including pharyngolaryngeal dysesthesia, closely resemble the acute, reversible sensory neuropathy syndrome described in the Warnings and Precautions section of the oxaliplatin labeling.

and IV fluids. The outcome at the time of the report was listed as not recovered. The investigator's assessment of the causal relationship with study drugs was reported as dubious, but not excluded.²

4.3. ISR #5488571, Germany, Clinical Study Report

A 4 year-old female with an unspecified malignancy and hepatic metastases was enrolled in a single-arm study of gemcitabine in combination with oxaliplatin for the treatment of refractory and relapsed pediatric solid tumors. The patient initiated treatment with gemcitabine 1000 mg/m² and oxaliplatin 100 mg/m² and was hospitalized two days later with fever and abdominal pain. Ultrasound revealed an ileo-ileal intussusception,³ which resolved the same day. The event was considered possibly related to study drugs. Six days later, the patient experienced a right-sided pleural effusion with dyspnea. The outcome at the time of the report was reported as ongoing. The investigator's causal assessment noted the events were related to study medications, disease progression, and concomitant treatments, which also included Cotrim and allopurinol.

5. Postmarketing Review of Pediatric Adverse Event Reports received prior to the pediatric exclusivity period

During the time period from marketing approval to the start of the pediatric exclusivity period, AERS received a total of 9 reports for oxaliplatin (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Three of these reports involved age miscoding for adult patients and one other report was a duplicate. The remaining five pediatric cases are described below.

5.1. A 14 year-old male with refractory or relapsed solid tumor experienced dyspnea, confusion, sweating, and laryngeal symptoms associated with cold exposure and an acute sensory neuropathy reaction.

5.2. A 10 year-old child with megaloblastoma and a history of seizure activity experienced tremors, seizure, altered mental status, and peripheral neuropathy.

5.3. A 12 year-old female with hepatoblastoma experienced fever, chills, and vomiting with infusion of drug, and experienced chest pains during a subsequent infusion.

5.4. A 16 year-old female with metastatic Ewing's sarcoma was hospitalized with vomiting, severe diarrhea, and mild abdominal tenderness. She experienced an increased lipase level and increased amylase level of 1,368 U/L and 185 U/L, respectively. She was treated with IV fluids and octreotide and recovered.⁴

5.5. A 15 year-old female with metastatic renal cell carcinoma was hospitalized after developing diarrhea, nausea, vomiting, abdominal pain, and a grade 4 elevation in lipase.⁵

² Hematologic changes, including thrombocytopenia and bleeding events are described in the Adverse Reactions section of the oxaliplatin labeling.

³ There are no additional pediatric or adult cases of intussusception in the AERS database.

⁴ Pancreatitis is labeled under the Adverse Reactions, Postmarketing Experience section.

⁵ Grade 4 lipase elevation is defined as > 5.0 times the upper limit of normal, per the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0.

She was treated with IV fluids, octreotide, and other supportive care including pain management and recovered.

Cases 5.4 and 5.5 were two of three pediatric cases (one of the cases was reported to the IND but not to AERS) of pancreatitis or elevated pancreatic enzymes previously discussed in a postmarketing safety review completed in November 2005. The patients were treated for metastatic renal cell carcinoma or Ewing's sarcoma with a protocol involving the use of oxaliplatin and irinotecan. Two of the cases listed additional chemotherapy agents in use around the time of protocol initiation. The patients experienced pancreatitis or elevated pancreatic enzymes within the first 2-3 weeks after starting treatment, were withdrawn from the protocol, and recovered following hospitalization. There have been no subsequent pediatric reports of these events.

6. Summary/Recommendations

A review of AERS data during the pediatric exclusivity period found only three pediatric cases reported from a foreign Phase 2 single-arm study. The syndrome and events described in cases 4.1 and 4.2 are considered labeled. Unlabeled events reported in case 4.3 include intussusception and pleural effusion. Although a temporal relationship was in evidence for these two events, attribution to oxaliplatin therapy is difficult due to concomitant treatments and the potential for a causal relationship with underlying disease.

Nearly all of the pediatric adverse events since first marketing, but prior to the pediatric exclusivity period, are labeled or seem consistent with the context of a labeled event(s). Unlabeled events reported in case 5.2 are plausibly related to disease or another pre-existing condition.

This review does not reveal any new safety concerns for the use of oxaliplatin in pediatric patients. We will continue routine monitoring of adverse events in pediatric patients.

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Concur:

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/s/

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