

One Year Post-Exclusivity Adverse Event Review: Oxaliplatin

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Background Drug Information

Drug: Eloxatin[®] (oxaliplatin)

Therapeutic Category: Anti-cancer agent

Sponsor: Sanofi-Aventis

Original Market Approval: August 9, 2002

Pediatric Exclusivity Granted: September 27, 2006

Background Drug Information

Indications

Use in combination with infusional 5-FU/LV [fluorouracil/leucovorin] for

- Adjuvant treatment of stage III colon cancer in patients who have undergone complete resection of the primary tumor (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)
- Treatment of advanced colorectal cancer

Drug Use Trends

- A projected 970,100 oxaliplatin vials were sold in the US for all age groups during the 12 month post-exclusivity period.
 - 75% was sold to clinics
 - 20% was sold to non-Federal hospitals

Drug Use Trends

- An unprojected 7,064 discharges from acute care, non-Federal hospitals were associated with oxaliplatin for all age groups from October 2004 to September 2007.
- **Pediatric Use**
 - 0.4% during the 24 month pre-exclusivity period
 - 0.1% during the 12 month post-exclusivity period
 - Most of the pediatric discharges were associated with the treatment of oncologic conditions.

Pediatric Exclusivity Studies: Overview

- **Indication**
 - Refractory or relapsed pediatric solid tumors
- **Study Types**
 - Two Phase 1 dose finding and safety studies
 - Two Phase 2 activity and safety studies
- **Study Design**
 - Open-label, non-comparative, non-randomized
- **Dosing**
 - 2 hour IV infusions at doses ranging from 40 to 160 mg/m²
- **Number and Ages of Pediatric Patients**
 - 159 pediatric patients, 7 months to 22 years old

Pediatric Exclusivity Studies: Dose Finding and Safety Study

Study ARD5531 (Phase 1)

43 pediatric patients, 6 months to 21 years old, with refractory or relapsed malignant solid tumors (mainly neuroblastoma and osteosarcoma) with a life expectancy of more than 6 weeks

- Oxaliplatin administered on days 1,8, and 15 every 4 weeks (1 cycle) for a maximum of 6 cycles

Pediatric Exclusivity Studies: Dose Finding and Safety Study

Study ARD5531 (continued)

- Cohort 1
 - 28 patients received 6 oxaliplatin dose levels of 40 to 110 mg/m²
 - Dose limiting toxicity (DLT) was sensory neuropathy at 110 mg/m²
 - Recommended dose (RD) was 90 mg/m²
- RD Cohort
 - 15 patients received oxaliplatin 90 mg/m²

Pediatric Exclusivity Studies: Dose Finding and Safety Study

Study DFI7434 (Phase 1)

26 pediatric patients, < 21 years old, with metastatic or unresectable solid tumors (mainly neuroblastoma and ganglioneuroblastoma) for which standard treatment did not exist or was no longer effective

- Oxaliplatin administered on day 1 of each cycle

Pediatric Exclusivity Studies: Dose Finding and Safety Study

Study DFI7434 (continued)

- 5 dose levels evaluated
 - Oxaliplatin 100, 130, and 160 mg/m² every 3 weeks (1 cycle) x 6 cycles
 - Oxaliplatin 160 mg/m² and carbamazepine every 3 weeks (1 cycle) x 6 cycles
 - Oxaliplatin 85 mg/m² every 2 weeks (1 cycle) x 9 doses
- DLT for oxaliplatin monotherapy was sensory neuropathy at 160 mg/m²
- RD was 130 mg/m² every 3 weeks
 - 85 mg/m² every 2 weeks was also tolerable

Pediatric Exclusivity Studies: Activity and Safety Study

Study ARD5021 (Phase 2)

43 pediatric patients, ≤ 21 years old, with recurrent or refractory embryonal CNS tumors (medulloblastoma, supratentorial primitive neuroectodermal tumor (PNET) or atypical teratoid rhabdoid tumor (ATRT))

- Oxaliplatin 130 mg/m² administered on day 1 every 3 weeks (1 cycle) for a maximum of 12 months if no disease progression or unacceptable toxicity
 - Patients < 10 kg received oxaliplatin 4.3 mg/kg

Pediatric Exclusivity Studies: Activity and Safety Study

Study ARD5530 (Phase 2)

47 pediatric patients, ≤ 21 years old, with recurrent solid tumors (Ewing sarcoma, osteosarcoma, rhabdomyosarcoma and neuroblastoma)

- Oxaliplatin 130 mg/m² administered on day 1 every 3 weeks (1 cycle) for a maximum of 12 months or 17 cycles
 - Patients ≤ 12 months old received oxaliplatin 4.3 mg/kg

Pediatric Exclusivity Studies: Pharmacokinetic Analysis (n=105)

Results and Conclusions

- Inter-patient variability of oxaliplatin clearance was 41%.
- Pharmacokinetic (PK) parameters in pediatric patients were similar to those seen in adults.

Pediatric Exclusivity Studies: Activity Analysis (n=159)

Activity Endpoint

Objective response rate (complete response plus partial response) in patients treated for 2 to 17 courses per year

Results and Conclusions

- Only 1 partial response was observed (Study ARD5021) resulting in a response rate of 0.25%.
- Oxaliplatin is ineffective in the regimens tested in children with refractory solid tumors.

Pediatric Exclusivity Studies: Safety Analysis

Results

- There were 109 patient deaths across all 4 studies.
 - Vast majority occurred > 28 days after the last oxaliplatin dose
- 20% of patients in the Phase 2 studies had a non-fatal, serious adverse event.
- 8% of patients across all 4 studies withdrew their study participation due to an adverse event.

Conclusions

- The adverse event assessment was difficult in such an end-stage population.
- All deaths were clearly or likely due to disease progression and expected in a population with very advanced and refractory metastatic solid tumors.
- Oxaliplatin's safety profile in the pediatric population is similar to that in adults.

Pediatric Exclusivity Studies: Safety Analysis

Deaths (n=109)

- All deaths in the Phase 1 studies (56) and in Study ARD5530 (26) were due to disease progression.
- 21 (78%) of the deaths in Study ARD5021 were due to disease progression.
 - 6 deaths classified as unknown/other causes
 - 1 seizure event due to progressive disease
 - 1 neurological event related to progressive disease
 - 1 did not have a reported cause of death
 - 3 had a status of death at follow-up and the cause and date of death were unknown

Pediatric Exclusivity Studies: Safety Analysis

Non-fatal Serious Adverse Events (SAEs)

- Phase 2 studies (oxaliplatin 130 mg/m² q 3 weeks)
 - SAEs reported in 18 (20 %) patients
 - Events reported by 2 or more patients
 - Headache (4), hypersensitivity reactions (3), convulsions (2), infection (2), peripheral sensory neuropathy (2)

Pediatric Exclusivity Studies: Safety Analysis

Non-fatal Serious Adverse Events (continued)

- Study DFI7434 (oxaliplatin 100 to 160 mg/m² q 3 weeks)
 - SAEs reported in 6 (23%) patients
 - Events reported by 2 or more patients
 - Sensory neuropathy (2)
- Study ARD5531 (oxaliplatin 40 to 100 mg/m² q 4 weeks)
 - SAEs reported in 25 (58%) patients
 - Events reported by 2 or more patients
 - Cohort 1 (17 patients): 2 patients each for disease progression, **dyaesthesia**, metastatic pain, pyrexia, urinary retention, vomiting
 - RD Cohort (8 patients): 2 patients each for superior vena cava occlusion, pyrexia, thrombocytopenia¹⁸

Pediatric Exclusivity Studies: Safety Analysis

Withdrawals

- 13 (8%) patient withdrawals due to an adverse event across all 4 studies
- Most common adverse events leading to withdrawal
 - Thrombocytopenia (3), hypersensitivity reactions (2)
- Adverse events associated with 1 patient withdrawal
 - Pain, dehydration, bone pain, metastatic pain, Horner's syndrome, urinary retention, pleural effusion, respiratory distress, hematoma, superior vena cava occlusion

Pediatric Exclusivity Studies: Labeling Changes

Pediatric Use

- Effectiveness of oxaliplatin in children has not been established.
- The pediatric patient population, study dosing, PK analysis, activity response, and most common adverse events are described for each of the 4 pediatric exclusivity studies.

Adverse Event Reports During the Post-Exclusivity Period

9/27/2006 – 10/27/2007

Raw Counts*	All Reports (US)	Serious (US)	Death (US)
Adults (≥ 17)	1387 (634)	1359 (609)	320 (118)
Pediatrics (0 to 16)	6 (1)	6 (1)	1 (1)
Age unknown	102 (53)	102 (53)	20 (10)
All ages	1495 (688)	1467 (663)	341 (129)

*May include duplicate cases

Source: Adverse Event Reporting System, FDA

Adverse Event Reports Since Marketing Approval

8/9/2002 – 10/27/2007

Raw Counts*	All Reports (US)	Serious (US)	Death (US)
Adults (≥ 17)	4693 (2313)	4456 (2143)	953 (345)
Pediatrics (0 to 16)	15 (8)	15 (8)	2 (2)
Age unknown	776 (382)	428 (261)	82 (35)
All ages	5484 (2703)	4899 (2412)	1037 (382)

*May include duplicate cases

Source: Adverse Event Reporting System, FDA

Pediatric Adverse Events Since Marketing Approval

- 15 raw count cases
- 7 cases excluded
 - Duplicate cases (3)
 - Miscoded cases involving patients ≥ 17 years old (4)
 - Included the 2 raw count death cases
- 8 remaining cases
 - 0 Deaths
 - 8 Serious adverse events

Serious Adverse Events

Since Marketing Approval (n=8 patients)

- Intussusception and pleural effusion (1)
- Seizure, tremors, and altered mental status (1)
- Elevated lipase (2)
- Sensory neuropathy (3)
- Allergic reaction (2)
- Hemorrhage, cerebral (1)

There were no new safety concerns after considering patients' concomitant treatments and underlying diseases.

Unlabeled Serious Adverse Events Since Marketing Approval

Intussusception and pleural effusion (1)

- 4 y.o. female with h/o refractory/relapsed solid tumor with liver metastases. Intussusception occurred 2 days after initial oxaliplatin and gemcitabine study treatment and resolved. Pleural effusion occurred 6 days later. Investigator reported events related to study medications, disease progression, and concomitant therapy (co-trimoxazole, allopurinol).

Seizure, tremors, and altered mental status (1)

- 10 y.o. child with h/o megaloblastoma and recurrent seizures. Concomitant medications included zonisamide.

Unlabeled Serious Adverse Events Since Marketing Approval

Elevated lipase (2)

- 16 y.o. female with a h/o metastatic Ewing's sarcoma. Two weeks after first oxaliplatin and irinotecan treatment had vomiting, diarrhea, abdominal tenderness, elevated lipase (1368 U/L), and elevated amylase (185 U/L). Treated with IV fluids and octreotide and recovered. **Investigator reported elevated lipase and amylase possibly related to oxaliplatin and irinotecan.**
- 15 y.o. female with a h/o metastatic renal cell cancer. Two weeks after first oxaliplatin and irinotecan treatment had diarrhea, nausea, vomiting, abdominal pain, and elevated lipase (634 U/L). D/c from hospital after IV fluids, octreotide, and other care. **Investigator reported elevated lipase possibly related to oxaliplatin and irinotecan treatment.**

Warnings and Precautions: Oxaliplatin Labeling

6.2 Postmarketing Experience

Liver and Gastrointestinal System Disorders:

Severe diarrhea/vomiting resulting in hypokalemia, colitis (including Clostridium difficile diarrhea), metabolic acidosis, ileus, intestinal obstruction, **pancreatitis**, veno-occlusive disease of liver also known as sinusoidal obstruction syndrome, and perisinusoidal fibrosis which rarely may progress.

Summary: Oxaliplatin

- This completes the one year post-exclusivity adverse event reporting.
- FDA recommends routine monitoring of oxaliplatin for adverse events in all populations.

Does the Advisory Committee concur?

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