



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

## Memorandum

PID#           D040393

DATE:         July 11, 2005

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               Office of Counter-Terrorism and Pediatric Development

SUBJECT:      One Year Post-Pediatric Exclusivity Postmarketing Adverse Event Review  
               Carboplatin (Paraplatin<sup>®</sup>), NDA 19-880/SE8-019  
               Pediatric Exclusivity Approval Date: April 30, 2004

### EXECUTIVE SUMMARY

Carboplatin (Paraplatin<sup>®</sup>) was granted pediatric exclusivity for the sponsor's submission of full study reports regarding a phase 1 dose finding study and a phase 2 evaluation of children with relapsed or refractory solid tumors; from a safety perspective, the adverse events observed were consistent with those previously observed and described in the label.<sup>1</sup> There were no labeling changes effected as a result of the pediatric studies.

The FDA AERS database was searched for reports of adverse events occurring in association with the use of carboplatin in children aged 16 years and younger. The time period of interest was the one-year period following FDA Pediatric Exclusivity approval, April 30, 2004 through May 30, 2005. Forty-three reports were identified. The overall profile of adverse events observed in the pediatric reports is generally similar to that of the corresponding adult reports. Most events are either currently labeled or would not be unexpected in association with the disease or with concomitant treatments received by the child.

One case of blindness secondary to eye swelling and optic nerve atrophy was identified in a child with bilateral retinoblastoma who received subtenon<sup>2</sup> carboplatin, cryotherapy, and systemic

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<sup>1</sup> Clinical Review of NDA 19-880/SE8-019, Ramzi Dagher, Division of Oncology Drug Products, September 13, 2004.

<sup>2</sup> Subtenon is defined as injection through Tenon's capsule, the thin connective-tissue membrane ensheathing the eyeball.

chemotherapy. In addition, a search of the medical literature found a report of fibrotic complications and decreased ocular motility in children similarly treated.<sup>3</sup> This treatment regimen is under clinical study<sup>4</sup> by the Children's Oncology Group, which is evaluating the event-free survival and toxic effects of systemic chemotherapy, subtenon carboplatin, and local ophthalmic therapy in children with retinoblastoma.

## BACKGROUND

Carboplatin is a platinum alkylating agent that produces interstrand DNA cross-links; normal DNA synthesis is inhibited by this disruption of DNA conformation. The drug is approved for the treatment of advanced ovarian carcinoma and is used off-label for a broad range of oncologic indications. The major toxicities of carboplatin therapy include bone marrow suppression, vomiting, and anaphylactic-type reactions.

## AERS SEARCH RESULTS

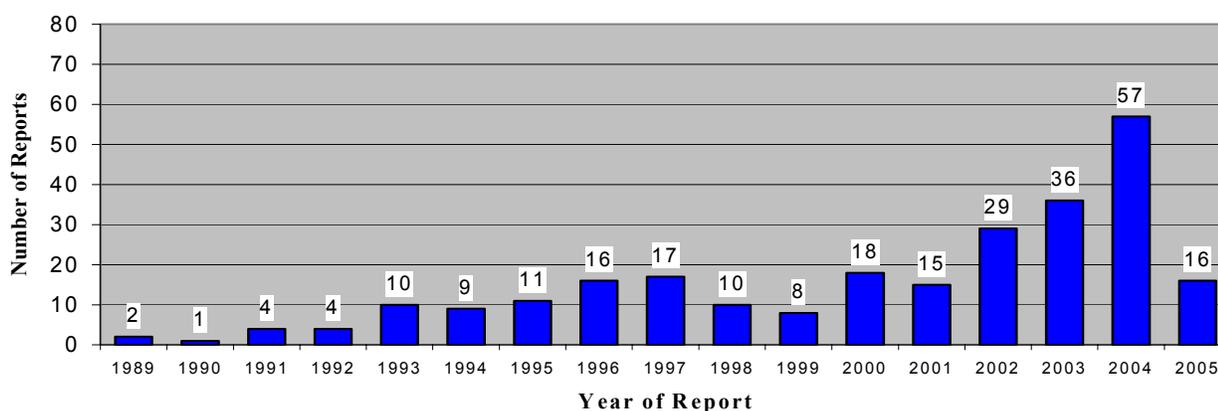
AERS Search Date: June 15, 2005  
Including all sources - U.S. & Foreign Reports

A. From marketing Approval date (March 3, 1989) to one year post-Pediatric Exclusivity Approval (May 30, 2005):

1. Counts of reports:

	All reports (U.S.)	Serious (U.S.)	Death (U.S.)
All ages	9,176 (5,552)	7,785 (4,351)	2,121 (1,018)
Adults ( $\geq 17$ years)	7,369 (4,215)	6,583 (3,573)	1,703 (725)
Peds (0-16 years)	263 (136)	209 (100)	41 (16)

**Reporting Trend for Pediatric Reports  
Time of Approval to One Year post-Pediatric Exclusivity Approval  
(March 3, 1989 to May 30, 2005)**



Top 20 reported event PTs and labeling status of events (underlined = unlabeled):

All ages:

<sup>3</sup> Mulvihill A, et al. Ocular motility changes after subtenon carboplatin chemotherapy for retinoblastoma. *Arch Ophthalmol* 2003; 121:1120-1124. Comment in: *Arch Ophthalmol* 2005; 123:128-129.

<sup>4</sup> Available from: <http://www.cancer.gov/clinicaltrials/COG-ARET0231>

Pyrexia (893), dyspnoea (853), vomiting (752), neutropenia (747), leukopenia (673), thrombocytopenia (660), dehydration (605), nausea (601), pneumonia (545), sepsis (484), anaemia (477), diarrhoea (471), hypersensitivity (449), asthenia (446), hypotension (436), haemoglobin decreased (319), pancytopenia (281), chest pain<sup>5</sup> (277), white blood cell count decreased (276), abdominal pain (266)

Adults:

Pyrexia (796), dyspnoea (760), vomiting (699), neutropenia (689), thrombocytopenia (591), leukopenia (583), dehydration (570), nausea (567), pneumonia (510), anaemia (444), diarrhoea (423), sepsis (411), asthenia (405), hypotension (364), haemoglobin decreased (302), white blood cell count decreased (263), hypersensitivity (256), pancytopenia (250), chest pain (246), abdominal pain (238)

Children:

Pyrexia (19), urticaria (19), sepsis (17), diarrhea (16), vomiting (15), cough (14), hypersensitivity (14), deafness<sup>6</sup> (13), bone marrow depression (12), dyspnoea (12), febrile neutropenia (12), pancytopenia (12), leukopenia (11), dehydration (10), rash (10), eye movement disorder (9), flushing (9), hypotension (9), cardiac failure (8), dermatitis (8), nausea (8), renal failure (8), renal failure acute (8), thrombocytopenia (8)

B. From Pediatric Exclusivity approval date, April 30, 2004 to May 30, 2005:

1. Counts of reports:

	All reports (U.S.)	Serious (U.S.)	Death (U.S.)
All ages	1429 (883)	1228 (716)	283 (147)
Adults (≥17 years)	1240 (760)	1109 (648)	246 (122)
Peds (0-16 years)	43 (15)	34 (11)	5 (2)

2. Top 20 reported event PTs and labeling status of events (underlined = unlabeled):

All ages:

Dyspnoea (144), nausea (131), vomiting (130), dehydration (126), neutropenia (90), pyrexia (90), febrile neutropenia (82), anaemia (81), diarrhoea (77), haemoglobin decreased (76), asthenia (73), pneumonia (70), platelet count decreased (67), sepsis (64), thrombocytopenia (64), hypotension (60), white blood cell count decreased (56), flushing (46), pancytopenia (46), death (44), erythema (44), fatigue (44)

Adults:

Dyspnoea (134), vomiting (127), dehydration (124), nausea (124), pyrexia (84), neutropenia (83), anaemia (80), haemoglobin decreased (75), febrile neutropenia (74), asthenia (71), diarrhoea (68), platelet count decreased (66), pneumonia (66), thrombocytopenia (63), sepsis (59), hypotension (56), white blood cell count decreased (55), pancytopenia (45), fatigue (40), flushing (38)

Children:

Urticaria (6), diarrhoea (4), febrile neutropenia (4), flushing (4), gastrointestinal disorder (4), nausea (4), pyrexia (4), bone marrow depression (3), confusional state (3), cough (3), disease

<sup>5</sup> Pain is labeled as a miscellaneous adverse effect.

<sup>6</sup> The current label states, "Clinically significant hearing loss has been reported to occur in pediatric children when carboplatin was administered at higher than recommended doses in combination with other ototoxic agents."

progression (3), dyspnoea (3), erythema (3), eye swelling (3), growth retardation (3), hallucination (3), infusion related reaction (3), lymph node abscess (3), portal vein thrombosis (3), pruritus (3), rash (3), rash maculo-papular (3), stem cell transplant (3), tremor (3), vasculitis (3)

POSTMARKETING REVIEW OF ALL PEDIATRIC ADVERSE EVENT REPORTS, APRIL 30, 2004 TO MAY 30, 2005

A. Demographics

N = 36 unduplicated cases

Gender: Male = 21  
Female = 14  
Unknown = 1

Ages: 0 – <1 month = 0  
1 month – 2 years = 11  
3 – 5 years = 12  
6 – 11 years = 7  
12 – 16 years = 5  
Unknown = 1

Report Source: U.S. = 13  
Foreign = 23

Outcomes: Death = 4  
Life threatening = 9  
Hospitalization = 6  
Required Intervention = 1  
Disability = 1  
Other = 10  
Unknown = 5

Indications: CNS malignancy = 13  
Neuroblastoma = 8  
Optic Nerve Glioma = 2  
Retinoblastoma = 2  
Other = 8  
Not specified = 3

- Eleven cases involved the use of carboplatin as part of the conditioning regimen for bone marrow or stem cell transplant.
- Most of the 36 cases did not report the dosage used.
- One case involved subtenon and intravenous administration for the treatment of retinoblastoma.

B. Comments regarding labeling status of the top 20 adverse events from Pediatric Exclusivity period and comparison with the adult adverse event profile.

The overall profile of adverse events observed in the pediatric reports is generally similar to that of the corresponding adult reports. Most events are currently labeled or would not be unexpected in association with the disease or with concomitant treatments received by the child. Every pediatric case that involved an unlabeled event occurred in the setting of multi-drug chemotherapy. Elimination of duplicate pediatric reports resulted in the counts of several unlabeled events being decreased, as described below.

Unlabeled events of interest

- Confusional state, hallucination, and tremor were experienced in only one child.  
ISR# 4506566, France: A 16 year-old female with a history of nephroblastoma, lung and bone metastases, and peritoneal carcinomatosis was hospitalized on day 11 with severe bone marrow aplasia after receiving treatment with ifosfamide, mesna, and etoposide on days 1-5, carboplatin on days 1-2, and pegfilgrastim on day 7. On day 21, she developed confusion, hallucinations, and trembling of the extremities. She was treated with methylene blue for two days and recovered without sequelae.<sup>7</sup> Bone marrow aplasia was treated with transfusions and resolved several weeks later.
- Growth retardation, lymph node abscess and vasculitis occurred in a single child.  
ISR# 4520742, United Kingdom: A 7 year-old female with rhabdomyosarcoma was placed on a combination of six chemotherapeutic agents including dactinomycin, vincristine, ifosfamide, carboplatin, epirubicin, and etoposide. The child experienced multiple episodes of extreme toxicity including neutropenic shock, severe gastrointestinal side effects, and an unusual maculopapular rash with features of vasculitis. She recovered from these events and ultimately showed no evidence of local disease or new metastases. Six months after treatment, she developed a recurrent lymph node abscess in her neck that was slow to resolve. After two years post-treatment, her growth velocity decreased; in addition to other clinical features, she was suspected of having Nijmegen breakage syndrome (NBS), a rare autosomal recessive chromosomal instability syndrome associated with a mutant DNA repair protein. NBS is characterized by immunodeficiency, microcephaly, dysmorphic features, and growth retardation. The diagnosis was confirmed by molecular analysis.<sup>8</sup>
- Portal vein thrombosis was experienced by two children.<sup>9</sup>  
ISR# 4607260, France: A 3.5 year-old male with localized medulloblastoma was treated with cisplatin, vincristine, carboplatin, cyclophosphamide, and etoposide followed by high-dose busulfan and thiotepa with stem cell transplant (SCT). The child developed hepatic veno-occlusive disease on day 24 post-SCT and portal vein thrombosis on day 51. Revascularization occurred after 13 days. The child died several months later of disease progression.  
  
ISR# 4607261, France: A 2.5 year-old female had metastatic medulloblastoma treated with cisplatin, procarbazine, vincristine, carboplatin, and cyclophosphamide followed by high-dose busulfan and thiotepa with SCT. She developed hepatic veno-occlusive disease on day 18 post-SCT and portal vein thrombosis on day 20. Revascularization occurred after 3 days. The child died several months later of disease progression.
- Blindness<sup>10</sup>  
ISR# 4677133, U.S. (includes follow-up information): A 6 month-old male with bilateral retinoblastoma was treated with systemic carboplatin, etoposide, and vincristine. The child

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<sup>7</sup> Signs of serious neurotoxicity, including confusion and hallucinations, are described in the ifosfamide labeling. Limited evidence indicates that signs of encephalopathy may be reversed by IV administration of methylene blue; the mechanism of ifosfamide encephalopathy and its possible responsiveness to methylene blue remain to be established (AHFS Drug Information 2005, accessed online June 27, 2005).

<sup>8</sup> Meyer S, et al. Rhabdomyosarcoma in Nijmegen breakage syndrome: strong association with perianal primary site. *Cancer Genet Cytogenet* 2004; 154:169-174.

<sup>9</sup> Brise H, et al. Portal vein thrombosis during antineoplastic chemotherapy in children: Report of five cases and review of the literature. *Eur J Cancer* 2004; 40:2659-2666.

<sup>10</sup> Loss of vision, which can be complete for light and colors, is a labeled warning and has been reported after the use of carboplatin with doses higher than those recommended in the package insert. Vision appears to recover totally or to a significant extent within weeks of stopping these high doses.

also received subtenon carboplatin with laser and cryotherapy. Two months later, the mother reported he could not see from the subtenon-treated eye. Visual evoked potential testing was flat. The reporting physician attributed the event to the combination of cryotherapy and subtenon carboplatin, which caused swelling and increased pressure in the eye leading to optic nerve atrophy. The eye was subsequently enucleated due to persistent tumor.<sup>11</sup>

C. Summary and comment on fatal reports.

Two of the four deaths were related to disease progression, as described in the portal vein thrombosis cases above. A third fatal outcome involved a 10 month-old female with an atypical brain tumor who experienced cardiac arrest during infusion of stem cells; the child had been treated with carboplatin and thiotepa as part of the bone marrow conditioning regimen. The fourth case occurred in a 6 year-old male with pleuropulmonary blastoma who was treated with ifosfamide, etoposide, mesna, and carboplatin; the child developed acute and fatal myocarditis that was possibly related to ifosfamide therapy<sup>12</sup> or an infection.

SUMMARY

The FDA AERS database was searched for reports of adverse events occurring in association with the use of carboplatin in children aged 16 years and younger. The time period of interest was the one-year period following FDA Pediatric Exclusivity approval, April 30, 2004 through May 30, 2005. Thirty-six unduplicated cases were identified. The overall profile of adverse events observed in the pediatric reports is generally similar to that of the corresponding adult reports. Most events are currently labeled or would not be unexpected in association with the disease or with concomitant treatments received by the child. One case of blindness secondary to eye swelling and optic nerve atrophy was identified in a child with bilateral retinoblastoma who received subtenon carboplatin, cryotherapy, and systemic chemotherapy. In addition, a search of the medical literature found a report of fibrotic complications and decreased ocular motility in children similarly treated. This treatment regimen is under clinical study by the Children's Oncology Group, which is evaluating the event-free survival and toxic effects of systemic chemotherapy, subtenon carboplatin, and local ophthalmic therapy in children with retinoblastoma.

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<sup>11</sup> AERS and the medical literature were searched for additional adverse events associated with subtenon use of carboplatin. AERS identified three pediatric retinoblastoma cases, all reported by the same reporter on the same date, of orbital soft tissue atrophy that resulted in cosmetic deformity. In addition, there is one literature report that describes decreased ocular motility in 12 eyes of 10 consecutive children with retinoblastoma who received subtenon carboplatin. Four eyes required enucleation for uncontrolled tumor growth, whereas adequate tumor control was achieved in the other eight eyes. The authors noted subtenon carboplatin is associated with significant fibrosis of orbital soft tissues, rendering subsequent enucleations hazardous for potential spill of therapy-resistant tumor. [Mulvihill A, et al. Ocular motility changes after subtenon carboplatin chemotherapy for retinoblastoma. *Arch Ophthalmol* 2003; 121:1120-1124. Comment in: *Arch Ophthalmol* 2005; 123:128-129.]

<sup>12</sup> Ifosfamide has been reported to cause severe and fatal cardiac toxicity. [Zenaide M, et al. High-dose ifosfamide is associated with severe, reversible cardiac dysfunction. *Ann Intern Med* 1993; 118:31-36.]

Limitations of the Adverse Event Reporting System (AERS)

The voluntary or spontaneous reporting of adverse events from health care professionals and consumers in the U.S reflects underreporting and also duplicate reporting. For any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s). The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Therefore, counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing drug risk between drugs.

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