

MEMORANDUM

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

PID# D040224

DATE: June 2, 2005

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SUBJECT: ODS POSTMARKETING SAFETY REVIEW
Consult: One-Year Post Pediatric Exclusivity Postmarketing Adverse
Events Review
Drug: Irinotecan
NDA: 20-571
Pediatric Exclusivity Approval Date: March 10, 2004

Executive Summary

The AERS database was searched for reports of pediatric adverse events associated with the use of irinotecan. Overall, AERS contains 4506 reports (raw count) for all irinotecan products, including adult and pediatric reports. Pediatric reports constituted 85 (1.9%) reports. We focused on the one-year pediatric exclusivity period from March 10, 2004 to April 10, 2005 (extra one month lag-time for report entry). A total of 922 reports (raw count) were received during this period for all ages. Nine (raw count) of the 922 reports received in the pediatric exclusivity period involved pediatric patients.

Of the nine reports, we identified four unique pediatric cases (five were duplicates) during the pediatric exclusivity period. Three cases were domestic, and one was foreign. The four cases involved children between the ages of 5-15 years, three were of female gender. Two patients were hospitalized and one patient expired. One patient required intervention to prevent permanent impairment/damage. Reported events consisted of pulmonary fibrosis, paraneoplastic meningoencephalitis, hives, and neutropenia with or without fever. Two cases, one consisting of pulmonary fibrosis and a second of paraneoplastic meningoencephalitis, appear to be confounded. The last two cases, one of neutropenia with and without fever and a second of hives, are labeled events.

In conclusion, this review did not identify any unexpected safety concerns with the use of irinotecan in the pediatric population. We will continue to monitor reports of adverse events in the pediatric population receiving irinotecan to increase our understanding of its effects in children.

AERS Search Results

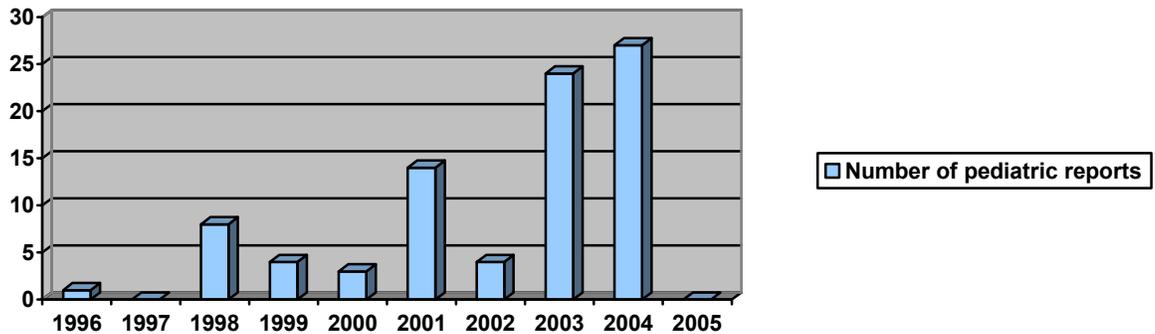
AERS Search Date: Searches for all (U.S. and foreign) cases during two time periods, (1) June 14, 1996 (approval date) to April 10, 2005, and (2) March 10, 2004 to April 10, 2005.

A. From FDA approval date, June 14, 1996, to May 2, 2004:

1. Counts of reports:

Age groups	All reports (US)	Serious (US)	Death (US)
All ages	4506 (2412)	4094 (2147)	944 (409)
Adults (≥ 17 yrs.)	4421 (2357)	4016 (2098)	934 (403)
Pediatrics (0-16 yrs.)	85 (55)	78 (49)	10 (6)

Table 1. Reporting trend for all pediatric reports from March 10, 2004 to April 10, 2005



2. Top 20 reported event PTs and labeling status of these events (underlined> denotes unlabeled events, events that are similar in nature in the product label are noted in parentheses):

All ages:

Diarrhea (1350), vomiting (701), neutropenia (694), dehydration (610), pyrexia [fever in product label (587)], nausea (486), leucopenia (422), abdominal pain (359), asthenia (314), thrombocytopenia (261), hemoglobin decreased [anemia (245)], pneumonia (232), dyspnea (230), hypotension (218), anorexia (204), febrile neutropenia [neutropenic fever (195)], anemia (191), sepsis (188), fatigue (183), pulmonary embolism [thromboembolism (176)]

Adults (>17 years):

Diarrhea (1317), neutropenia (694), vomiting (683), dehydration (585), pyrexia (569), nausea (478), leucopenia (420), abdominal pain (351), asthenia (312), thrombocytopenia (257), hemoglobin decreased [anemia (243)], pneumonia (228), dyspnea (223), hypotension (216), anorexia (197), febrile neutropenia [neutropenic fever (185)], sepsis (185), fatigue (183), anemia (182), pulmonary embolism [thromboembolism (175)]

Pediatrics (0-16 years):

Diarrhea (153), neutropenia (123), drug toxicity (75), febrile neutropenia [neutropenic fever (74)], vomiting (71), dehydration (50), nausea (40), pyrexia [fever (35)], abdominal pain (30), leucopenia (24), anemia (22), infection (22), hematotoxicity (21), thrombocytopenia (21), dyspnea (19), constipation (18), death (17), anorexia (15), asthenia (15), hemoglobin decreased (15)

B. From pediatric exclusivity approval date, March 10, 2004, to April 10, 2005:

1. Counts of reports

Age group	All reports (US)	Serious (US)	Death (US)
All ages	922 (521)	817 (467)	187 (91)
Adults (≥17 yrs.)	653 (521)	609 (467)	199 (91)
Pediatrics (0-16 yrs.)	9 (7)	9 (7)	2 (2)

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

All ages:

Diarrhea (242), vomiting (132), dehydration (122), nausea (115), neutropenia (109), febrile neutropenia [neutropenic fever (85)], asthenia (69), pyrexia [fever (67)], abdominal pain (61), fatigue (61), anemia (52), disease progression (48), anorexia (47), drug toxicity (47), pulmonary embolism [thromboembolism (45)], white blood cell count decreased [leucopenia (44)], dyspnea (42), hemoglobin decreased [anemia (41)], malignant neoplasm progression (41), pneumonia (40)

Adults:

Diarrhea (241), vomiting (128), dehydration (119), nausea (113), neutropenia (108), febrile neutropenia [neutropenic fever (83)], asthenia (69), pyrexia [fever (65)], fatigue (61), abdominal pain (59), anemia (51), drug toxicity (47), disease progression (46), anorexia (45), pulmonary embolism (44), white blood cell count decreased [leucopenia (44)], dyspnea (41), hemoglobin decreased [anemia (41)], malignant neoplasm progression (40), leucopenia (38)

Pediatrics:

Vomiting (4), dehydration (3), abdominal pain (2), anorexia (2), areflexia (2), convulsion (2), depressed level of consciousness (2), diplopia (2), facial paresis (2), hemiparesis (2), hypotonia (2), Third nerve paralysis (2), nausea (2), somnolence (2), urticaria (2), anemia (1), antibody test positive (1), blood immunoglobulin G increased (1), brain edema (1)

Postmarketing Review of All Pediatric Adverse Event Reports from March 10, 2004, to April 10, 2005

Our search of the AERS database yielded nine pediatric reports, five of which were duplicates. Two of the duplicate reports recorded death as an outcome. Thus, four unique pediatric cases were identified, three domestic and one foreign. One foreign case was reported domestically by another manufacturer.

The children in the four cases were between the ages of 5-15 years, and three were of female gender. Two patients were hospitalized, and one patient expired due to tumor progression. One patient required intervention to prevent permanent impairment/damage. The characteristics of the cases are as follows:

Table 2. Characteristics of pediatric cases during the one-year period after receiving pediatric market exclusivity

Selected characteristic	N=4
Age, years	
Range	5-15
Mean	10.3
Median	10.5
Gender	
Male	1
Female	3
Outcome	
Hospitalization	2
Death (due to disease progression)	1
Required intervention	1
Treatment indication	
Wilms' tumor	1
Neuroblastoma	1
Undifferentiated sarcoma	1
Astrocytoma	1
Adverse event	
Pulmonary fibrosis	1
Paraneoplastic meningoencephalitis	1
Hives	1
Neutropenia with and without fever	1

The cases are described below:

1. ISR #4330883, Domestic

A five year-old female patient started on irinotecan on December 1, 2003 for treatment of Wilms' tumor. Irinotecan was administered at 20 mg/m² for five days, repeated weekly per pediatric oncology protocol. She had received a total of two weeks of therapy. Additionally, she was also treated with radiation therapy (dose and frequency not provided) in 2002 and 2003. In the latter part of December 2003, she was admitted to the hospital and diagnosed with pulmonary fibrosis. Subsequently, the patient expired at an unknown date, secondary to tumor progression. No information on medical history or other concomitant medications were provided.

2. ISR #4420047 and 4425169, Domestic

A 12 year-old male with relapsed undifferentiated sarcoma was receiving an infusion of irinotecan 70 mg on August 2, 2004 when he developed hives half way through the infusion. Hives started on the trunk and back, and then progressed to the face. He also had developed a possible throat "lump", but had no shortness of breath,. His chest was clear and he had no change in vital signs. The hives receded after 60 minutes and irinotecan was restarted without problems. Subsequent to this incident, the patient started receiving premedications consisting of diphenhydramine, prednisone, and ranitidine just prior to the infusion. The infusions were then well-tolerated.

3. ISR #4531636 and 4493991, Domestic

A 10 year-old female patient participated in a clinical study on September 29, 2004 to receive temozolomide (TEM) 100 mg/m²/day and irinotecan (IRN) 30 mg/m²/day for treatment for recurrent stage IV neuroblastoma. She was previously treated with radiation and received an autologous stem cell transplant (ASCT) in 1999. After failing ASCT with recurrent disease, she received interleukin-12 (IL-12) as part of a clinical trial in August 2004, but IL-12 was discontinued due to lymphadenitis and fever. She received TEM+IRN from [redacted], and oral cefixime was given concurrently, dosed at 8mg/kg/day. On [redacted], the patient was seen in the clinic for a brief episode of diplopia. Neurologic exam was within normal limits and a CT scan of the head, with and without contrast, showed no abnormalities. She continued with TEM + IRN again on [redacted] and [redacted], when she was admitted for brief left arm and leg focal seizures, left facial weakness, and left hemiparesis. Her head scans were again negative and cerebrospinal fluid (CSF) findings were normal with negative cytology and negative cultures. Ophthalmology evaluation revealed neurologic deterioration. The CSF on [redacted] was normal, except for an elevated IgG and IgG synthesis. Paraneoplastic antibodies testing of the CSF demonstrated presence of anti-Hu antibody. The patient then continued with progressive neurologic deterioration culminating in death on [redacted]. Preliminary findings showed no tumor in the brain or spinal cord, but active tumor was present in the right inguinal nodes. Gross examination of the brain showed minimal swelling, some venous congestion, and mild thickening of the meninges, without exudates. Histology showed neuronophagia with lymphocytic infiltrates that were CD3 positive, with involvement more notable, but not limited to the medulla, pons, and midbrain. Similar changes were also observed in the basal ganglia and motor cortex. No demyelination was noted. An autopsy revealed paraneoplastic meningoencephalitis that involved the brain stem and correlated with the patient's clinical neurologic deterioration.

4. ISR #4321054 and 4316800, Foreign

A 15 year-old female patient with refractory astrocytoma started on irinotecan 26 mg (frequency not given) in July 2003 (precise date not stated). The patient then developed an infection with neutropenia on [redacted]. Filgrastim support was administered two days later and the neutropenia resolved on [redacted]. The patient then developed a fever and infection on [redacted] with anorexia occurring the following day, which resulted in a prolonged hospital stay. On [redacted], a fungal infection was diagnosed and fluconazole was given. Urine cultures were taken and were positive for *Escherichia coli* and vancomycin was prescribed. Fever and anorexia resolved on [redacted]. The second cycle of irinotecan was started on [redacted] and nine days later, the patient was again hospitalized with a fever, infection. Treatment with ranitidine, ciprofloxacin, and loperamide were given. The patient also presented with anemia and neutropenia on [redacted]. Filgrastim was administered and anemia resolved with treatment the next day. Ceftazidime and amikacin were also prescribed. Neutropenia resolved seven days after onset. The patient developed anorexia, which resolved three days later. Other concomitant medications included filgrastim, tropisetron, and omeprazole.

SUMMARY

The AERS database was searched for reports of adverse events occurring with the use of irinotecan in pediatric patients. We focused on the one-year period following the approval of pediatric exclusivity, March 10, 2004 to April 10, 2005. The profile of adverse events for pediatric patients was compared to that of the adult population. Nine (raw count) of the 922 cases received in the pediatric exclusivity period were reported in pediatric patients.

We identified four unique pediatric cases reported to FDA during the pediatric exclusivity period. The events included pulmonary fibrosis, paraneoplastic meningoencephalitis, hives, and neutropenia with and without fever.

Two cases appear to be confounded. In the case pertaining to pulmonary fibrosis, the patient received radiation therapy concurrently with irinotecan therapy, and then developed pulmonary fibrosis several weeks after starting irinotecan. Pulmonary fibrosis has been cited as a frequent complication of radiation therapy.¹ In the second confounded case, the patient, with positive for anti-Hu antibodies in the CSF, developed paraneoplastic meningoencephalitis while receiving irinotecan. Resultant paraneoplastic encephalitis has been reported in patients who have expressed anti-Hu antibodies as part of their neuroblastoma presentation.^{2,3} No literature currently exists on paraneoplastic encephalitis with irinotecan or IL-12 (patient's prior therapy).

The last two pediatric cases reported neutropenia and hives, both of which are labeled events in the product label. Neutropenia, complicated by fever, was observed in a phase 2 trial involving 170 children with refractory solid tumors, as described in the "Pediatric Use" under the "Precautions" section. The event occurred in 8.8% of patients (see Appendix 1).⁴ Hives is a dermatologic sign of a hypersensitivity reaction to this medication and is included under the "Warnings" and "Post-marketing Experience" sections of the label (see Appendix 1).

In conclusion, this review did not identify any unexpected safety concerns with the use of irinotecan in pediatric patients. We will continue to monitor reports of adverse events in the pediatric population receiving irinotecan to increase our understanding of its effects in children.

¹ Morgan GW, Breit SN: Radiation and the lung: a reevaluation of the mechanisms mediating pulmonary injury. *Int J Radiat Oncol Biol Phys* 1995: 361-9.

² Meyer JJ, Bulteau C, Adamsbaum C, Kalifa G. Paraneoplastic encephalomyelitis in a child with neuroblastoma. *Pediatr Radiol.* 1995; Suppl 1:S99-101.

³ Dalmau J, Graus F, Cheung NK et al. Major histocompatibility proteins, anti-Hu antibodies, and paraneoplastic encephalomyelitis in neuroblastoma and small cell lung cancer. *Cancer* 1995:99-109.

⁴ Irinotecan product label. Kalamazoo, MI: Pharmacia and Upjohn Company, December 2004. (Accessed May 13, 2005, at <http://www.fda.gov/cder/foi/label/2004/20571s023lbl.pdf>)

Appendix 1

WARNINGS

Hypersensitivity

Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been observed.

PRECAUTIONS

Pediatric Use

The effectiveness of irinotecan in pediatric patients has not been established. Results from two open-label, single arm studies were evaluated. One hundred and seventy children with refractory solid tumors were enrolled in one phase 2 trial in which 50 mg/m² of irinotecan was infused for 5 consecutive days every 3 weeks. Grade 3-4 neutropenia was experienced by 54 (31.8%) patients. Neutropenia was complicated by fever in 15 (8.8%) patients. Grade 3-4 diarrhea was observed in 35 (29.6%) patients. This adverse event profile was comparable to that observed in adults. In the second phase 2 trial of 21 children with previously untreated rhabdomyosarcoma, 20 mg/m² of irinotecan was infused for 5 consecutive days on weeks 0, 1, 3, and 4. This single agent therapy was followed by multimodal therapy. Accrual to the single agent irinotecan phase was halted due to the high rate (28.6%) of progressive disease and the early deaths (14%). The adverse event profile was different in this study from that observed in adults; in the most significant grade 3 or 4 adverse events were dehydration experienced by 6 patients (28.6%) associated with severe hypokalemia in 5 patients (23.8%) and hyponatremia in 3 patients (14.3%); in addition Grade 3-4 infection was reported in 5 patients (23.8%) (across all courses of therapy and irrespective of causal relationship).

Post-Marketing Experience

Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have also been observed (see [WARNINGS](#)).

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Concur:

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