

IND SAFETY REPORT: INITIAL WRITTEN REPORT

TO: Division of Drug Oncology Products, Center for Drug Evaluation and Research, FDA

FAX: 301-796-9845

1. IND NUMBER
61010

2. AGENT NAME
CCI-779 (temsirolimus, Torisel®)

3. DATE
October 7, 2011

4. SPONSOR
Division of Cancer Treatment and Diagnosis, National Cancer Institute

5. REPORTER'S NAME, TITLE, AND INSTITUTION
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8a. PROTOCOL NUMBER (AE #)
ARST0921 (AE# 1844142)

8b. AE GRADE: AE
Grade 3: Small intestinal obstruction

9. PATIENT IDENTIFICATION
786237

10. AGE
18 years

11. SEX
Male

12. PROTOCOL SPECIFIED
Cycle = 21 days (maximum = 12 cycles):
Temsirolimus: 15 mg/m²/dose (0.5 mg/kg/dose if patients < 10 kg) IV over 30-60 minutes on Days 1, 8, and 15
Vinorelbine: 25 mg/m²/dose (0.83 mg/kg/dose if patient < 10 kg) IV over 6-10 minutes on Days 1 and 8
Cyclophosphamide: 1200 mg/m²/dose (40 mg/kg/dose if patient < 10 kg) IV over 30-60 minutes on Day 1

13. TREATMENT RECEIVED AND DATES

The patient began the investigational therapy on January 13, 2011, receiving the last dose of temsirolimus on March 4, 2011 (Cycle 2, Day 16), the last dose of vinorelbine on February 24, 2011 (Cycle 2, Day 8), and the last dose of cyclophosphamide on February 17, 2011 (Cycle 2, Day 1).

14. DESCRIPTION OF ADVERSE EVENT

The patient is an 18-year-old male with relapsed Stage 4 pelvic alveolar rhabdomyosarcoma who experienced a grade 3 small intestinal obstruction while on a phase 2 trial utilizing the investigational agent temsirolimus in combination with vinorelbine and cyclophosphamide. On July 27, 2011, the patient presented to the emergency room (ER) with a 2-day history of diffuse, non-radiating, and persistent abdominal pain, and an episode of a large loose non-bloody stool. He developed fever and an initial non-bilious emesis which later transitioned to a bilious emesis while in the ER. The patient had a temperature of 103.5 °F and his abdominal examination was tender to palpation with guarding. A CT scan of the abdomen was consistent with typhlitis with no evidence of pneumatosis or pneumoperitoneum. He was given IV morphine and IV methadone, and was started on IV Zofran®, ceftazidime, and Flagyl®. The patient was made NPO, and was admitted to the PICU for further evaluation. In the PICU, he received 2 liters of normal saline boluses, 2 units of packed red blood cells, and 6 units of platelets transfusion. The patient was also started on Dilaudid® as needed, meropenem, and vancomycin, and was continued on IV fluids. The possibility of an abdominal metastasis, shock bowel or sepsis was considered. A surgical consult was recommended. On August 19, 2011, the patient was removed from the protocol. Additional information has been requested from the investigational site. There is a reasonable possibility that the experience may have been caused by the drug.

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using temsirolimus = 3,017
There have been 31 other cases of small intestinal obstruction reported to the NCI through AdEERS as serious adverse events for temsirolimus.

Adverse Event	Grade	Attribution
Small intestinal obstruction (n=31)	3 2	8 Unrelated, 18 Unlikely, 2 Possible 1 Unrelated, 2 Unlikely,

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16. ASSESSMENT

In this case, it is felt that a possible relationship exists between the event and the investigational agent.

	<u>Small intestinal obstruction</u>
<u>Temsirolimus</u>	<u>Possible</u>
<u>Vinorelbine</u>	<u>Possible</u>
<u>Cyclophosphamide</u>	<u>Possible</u>
<u>Methadone</u>	<u>Possible</u>
<u>Relapsed rhabdomyosarcoma</u>	<u>Unlikely</u>

17. COMMENTS

Medications taken at the time of the event included Bactrim[®], methadone, hydrocodone-acetaminophen, gabapentin, lidocaine-prilocaine cream, Prevacid[®], Zoloft[®], and multivitamin.

AT THIS TIME, NO OTHER INFORMATION IS AVAILABLE. IF UPON FURTHER INVESTIGATION RELEVANT INFORMATION BECOMES AVAILABLE, THEN A FOLLOW-UP REPORT WILL BE SUBMITTED IN ACCORDANCE WITH 21CFR 312.32 (d) (2).

DISCLAIMER per 21 CFR 312.32 (e): THIS SAFETY REPORT DOES NOT NECESSARILY REFLECT A CONCLUSION OR ADMISSION BY THE CTEP IDB SENIOR INVESTIGATOR/SPONSOR THAT THE INVESTIGATIONAL AGENT/THERAPY CAUSED OR CONTRIBUTED TO THE ADVERSE EXPERIENCE BEING REPORTED.