

IND SAFETY REPORT: INITIAL WRITTEN REPORT

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

FAX: 301-796-9845

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1. IND NUMBER
59699
7921

2. AGENT NAME
BMS 247550 (Ixabepilone, Ixempra®)
Bevacizumab (rhuMAb VEGF)

3. DATE
October 24, 2011

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

5. REPORTER'S NAME, TITLE, AND INSTITUTION
Richard Piekarz, MD, PhD – Senior Investigator, Investigational Drug Branch, CTEP, DCTD, NCI
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8a. PROTOCOL NUMBER (AE #)
GOG-0086P (AE#1360883)

8b. AE GRADE: AE
Grade 4: Hypokalemia

9. PATIENT IDENTIFICATION
083-0086P-034

10. AGE
72 yrs

11. SEX
Female

12. PROTOCOL SPECIFIED

Cycle = 21 days:
No Prior Radiotherapy:
Ixabepilone: 30 mg/m² IV over 1 hour on Day 1 x 6 cycles
Carboplatin: AUC = 6 IV over 30 minutes on Day 1 x 6 cycles
Bevacizumab: 15 mg/kg IV over 30-90 minutes on Day 1 (starting with cycle 2 for those patients entering post surgery) x 6 cycles
Maintenance Therapy (Cycles 7+):
Bevacizumab: 15 mg/kg IV over 30-90 minutes on Day 1
(Note: Patients continue to receive maintenance treatment until disease progression or until adverse events prohibit further therapy)

Prior Radiotherapy:
Ixabepilone: 25 mg/m² IV over 1 hour on Day 1 x 6 cycles
Carboplatin: AUC = 5 IV over 30 minutes on Day 1 x 6 cycles
Bevacizumab: 15 mg/kg IV over 30-90 minutes on Day 1 (starting with cycle 2 for those patients entering post surgery) x 6 cycles
Maintenance Therapy (Cycles 7+):
Bevacizumab: 15 mg/kg IV over 30-90 minutes on Day 1
(Note: Patients continue to receive maintenance treatment until disease progression or until adverse events prohibit further therapy)

13. TREATMENT RECEIVED AND DATES

The patient started the investigational therapy on June 24, 2011, and received the last doses of ixabepilone, bevacizumab, and carboplatin on August 16, 2011 (Cycle 3, Day 1).

14. DESCRIPTION OF ADVERSE EVENT

The patient is a 72-year-old female with uterine cancer who experienced a grade 4 hypokalemia while on a phase 2 study using the investigational agents ixabepilone and bevacizumab in combination with carboplatin. On August 22, 2011, the patient was hospitalized for leakage of straw-colored ascites from her colostomy. She was removed from the protocol this same day, and on August 24, 2011, she was discharged. On August 29, 2011, the patient was re-admitted to the hospital for a prothrombin time (PT) greater than 200 seconds (reference range: 11.0-12.5 seconds). She had been taking between 5-7.5 mg of Coumadin® every other day. Laboratory results also revealed her serum potassium was decreased at 2.3 mEq/L (reference range: 3.5-5 mEq/L), in comparison to her baseline potassium of 4 mEq/L on June 22, 2011. Vitamin K and platelets were administered. On August 31, 2011, the

patient's international normalized ratio (INR) was 1.7 (reference range for anticoagulant therapy: 2.0-3.0), and she was discharged on Coumadin[®] 5 mg daily. On September 6, 2011, the patient was re-admitted to the hospital for a fever of 102° F. Abdominal fluid cultures showed *Escherichia coli*, *Klebsiella pneumoniae*, *Streptococcus viridans*, and *Streptococcus B*. She was given vancomycin, IV fluids, 4 units of plasma, and 1 unit of packed red blood cells. The patient underwent an exploratory laparotomy for debridement of fascia, and received subsequent abdominal washes and wound V.A.C.[®] care. On September 17, 2011, the patient's condition was stable and she was discharged. 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 ixabepilone = 2,796, and the number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 35,152. There have been 23 other cases of hypokalemia reported to the NCI through AdEERS as serious adverse events for ixabepilone, and 207 other cases of hypokalemia reported to the NCI through AdEERS as serious adverse events for bevacizumab, as summarized in the table below.

Adverse Event	Grade	Attribution
<i>Ixabepilone</i>		
Hypokalemia (n=23)	4	2 Unrelated, 2 Unlikely, 1 Possible
	3	6 Unrelated, 8 Unlikely, 4 Possible
<i>Bevacizumab</i>		
Hypokalemia (n=207)	4	12 Unrelated, 15 Unlikely, 3 Possible, 1 Probable
	3	55 Unrelated, 78 Unlikely, 37 Possible, 6 Probable

16. ASSESSMENT

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

	Hypokalemia
Ixabepilone	Possible
Bevacizumab	Unlikely
Carboplatin	Possible
Uterine cancer	Unlikely

17. COMMENTS

Medication taken at the time of the event included Coumadin[®].

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.