

## 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 <b>58443 70116</b>	2. AGENT NAME <b>PS-341 (bortezomib; Velcade®) CC-5013 (lenalidomide, Revlimid®)</b>	3. DATE <b>July 12, 2011</b>
4. SPONSOR <b>Division of Cancer Treatment and Diagnosis, National Cancer Institute</b>		
5. REPORTER'S NAME, TITLE, AND INSTITUTION <b>John Wright, MD, PhD-Associate Branch Chief for Investigational Therapeutics 2, Investigational Drug Branch, CTEP, DCTD, NCI Howard Streicher, MD-Senior Investigator for Investigational Therapeutics 3, Investigational Drug Branch, CTEP, DCTD, NCI</b>		6. PHONE NUMBER <b>301-496-1196</b>
		7. FAX NUMBER <b>301-402-0428</b>
8a. PROTOCOL NUMBER (AE #) <b>CALGB-50501 (AE# 1800822)</b>	8b. AE GRADE: AE <b>Grade 4: Eye disorders-Other: Choroidal effusion</b>	
9. PATIENT IDENTIFICATION <b>117251</b>	10. AGE <b>67 years</b>	11. SEX <b>Male</b>
12. DESCRIPTION OF ADVERSE EVENT <b>The patient is a 67-year-old male with mantle cell lymphoma who experienced grade 4 choroidal effusion while on a phase 2 study utilizing the investigational agents lenalidomide and bortezomib. He began the induction investigational therapy on April 14, 2011, and received his last dose of lenalidomide on May 11, 2011 (Cycle 2, Day 7), and the last dose of bortezomib May 9, 2011 (Cycle 2, Day 5). On May 11, 2011 (Cycle 2, Day 7), the patient reported waking up with both eyes swollen and "glued shut", and a "wallpaper pattern" of the right eye. He also had persistent low-grade fever and a "terrible" cough for several weeks. The patient presented to the clinic with a 24-hour history of bilateral orbital pain, as well as periorbital edema. It was initially felt that he had conjunctivitis, and Ilotycin® ointment was prescribed. On the same day, the ophthalmologist found the patient's visual acuity to be markedly decreased in both eyes. His diagnosis was bilateral acute angle closure glaucoma, secondary to diffuse choroidal edema/effusions. A maxillofacial CT scan showed postsurgical changes of the left parietal craniotomy and normal orbits. On May 12, 2011, the patient was admitted to the hospital, started on mannitol and IV Solu-Medrol®, and his investigational therapy was held. On May 13, 2011, a brain/brain stem MRI revealed postsurgical changes of the left frontoparietal craniotomy. Susceptibility weighted images demonstrated decreased signal in the left posterior cerebral subarachnoid space. No evidence of intercranial metastases was seen. These findings were compatible with bilateral choroidal detachments with a remote history of subdural hematoma, status post craniotomy. Although it was felt that his glaucoma was due to the investigational therapy, there was also concern that his symptoms could be due to lymphoma involvement of the eye. On May 16, 2011, the patient's condition had improved and he was discharged on prednisone eye drops. His follow-up appointments included oncology, ophthalmology, and radiation oncology. Additional information has been requested from the investigational site. There is a reasonable possibility that the experience may have been caused by the drugs.</b>		
13. DOSE, ROUTE, AND SCHEDULE: <b>Cycle = 21 days Induction Therapy: Bortezomib: 1.3 mg/m<sup>2</sup> IV over 3-5 seconds on Days 1, 4, 8, and 11 Lenalidomide: 20 mg PO QD on Days 1-14</b>		
14. DATES OF TREATMENT <b>The patient began the investigational therapy on April 14, 2011, and received his last dose of lenalidomide on May 11, 2011 (Cycle 2, Day 7), and the last dose of bortezomib on May 9, 2011 (Cycle 2, Day 5).</b>		
15. ACCRUAL AND IND EXPERIENCE <b>Number of patients enrolled in NCI-sponsored clinical trials using lenalidomide = 2803 and bortezomib = 3720. There have been no other cases of choroidal effusion reported to the NCI through AdEERS as serious adverse events for lenalidomide and no other cases of choroidal effusion reported to the NCI through AdEERS as serious adverse events for bortezomib.</b>		
16. COMMENTS: <b>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). <u>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.</u></b>		