



DATE: SEP 06 2011

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SUBJECT: PS-341 (bortezomib; Velcade®) and CC-5013 (lenalidomide, Revlimid®) NCI IND Safety Report, AE# 1800822

TO: Investigators Using Bortezomib (NSC 681239) and Lenalidomide (NSC 703813).

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies conducted under a U.S. IND to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agents. Please find attached a copy of an IND Safety Report recently submitted to the FDA for the CTEP-sponsored investigational agents bortezomib and lenalidomide.

The following must be completed by all investigators using bortezomib under NCI IND 58443 and lenalidomide under NCI IND 70116:

- Send a copy of this letter to your Institutional Review Board (IRB) of record according to your policies and procedures.
- File a copy of this letter in your protocol file.

If your study is not covered under INDs 58443 and 70116, it is strongly recommended that you follow the instructions above.

Please note that for Cooperative Group studies, the Cooperative Group Operations Office will provide instructions for IRB submissions, any patient notifications, etc.

Based on CTEP's assessment of the current information in light of previous experience with bortezomib and lenalidomide, there does not appear to be a change in the risk-benefit ratio for bortezomib and lenalidomide studies; therefore, CTEP is not requiring a protocol amendment at this time.

Please continue to report events according to the adverse event reporting guidelines in your protocol(s).

The attached Adverse Events Assessment describes the adverse event(s) (synopsis provided below), relevant previous experience under these INDs and/or NSCs, and the total number of patients enrolled in trials under these INDs and/or NSCs.

A 67-year-old male with mantle cell lymphoma experienced grade 4 choroidal effusion while on a phase 2 trial utilizing the investigational agents bortezomib and lenalidomide.

ADVERSE EVENTS ASSESSMENT

IND 58443	70116	ADVERSE EXPERIENCE REPORT NO.
NSC 681239	703813	IND Safety Report: # 1
PS-341 (bortezomib; Velcade®)	CC-5013 (lenalidomide, Revlimid®)	Event: Gr. 4: Eye disorders: Choroidal effusion
AE: 1800822		Protocol: CALGB-50501

The patient is a 67-year-old male with mantle cell lymphoma who experienced choroidal effusion while on a phase 2 trial utilizing the investigational agents bortezomib and lenalidomide. The planned protocol therapy the patient was assigned to is as follows:

Cycle = 21 Days
 Induction Therapy:
 Bortezomib: 1.3 mg/m² IV over 3-5 seconds on Days 1, 4, 8, and 11
 Lenalidomide: 20 mg PO QD on Days 1-14

The patient was diagnosed with mantle cell lymphoma in August 2009, and is status post chemotherapy. The patient began the investigational treatment on April 14, 2011, and received his last dose of bortezomib on May 9, 2011 (Cycle 2, Day 5), and his last dose of lenalidomide on May 11, 2011 (Cycle 2, Day 7).

On May 11, 2011 (Cycle 2, Day 7), the patient reported waking up with both eyes swollen and “glued shut”, with a “wallpaper pattern” of vision in 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 bilateral choroidal detachments with no evidence of intracranial metastases and evidence of a remote history of subdural hematoma, status post a craniotomy. While an infiltrating tumor would be the most likely cause of this process, the event was bilateral, no evidence of a tumor was found on the MRI, and the event occurred approximately one month after initiating therapy. It was felt that the patient’s choroidal effusions, detachment and glaucoma were due to the investigational therapy, and the patient was removed from the protocol.

On May 16, 2011, although the patient still could not read, his intraocular pressures had decreased from the high 40s mmHg to less than 10 mmHg (reference range: 10-21 mmHg), his vision had improved, and he was discharged on prednisone eye drops. On May 19, 2011, the patient's intraocular pressures were still less than 10 mmHg; his eye medications included Pred Forte®, atropine, NICOL®, and Muro 128® ointment. The patient’s vision would continue to be closely monitored for a recurrence, at which time the need for a biopsy will be considered.

The patient’s past medical history is significant for bilateral subdural hematoma, deep vein thrombosis, hypothyroidism, seasonal allergies, and craniotomy. Medication taken at the time of the event included levothyroxine.

There have been no other cases of choroidal effusion reported to the NCI as serious adverse events through AdEERS under the bortezomib NSC and/or IND, and no other cases of choroidal effusion reported to the NCI as serious adverse events through AdEERS under the lenalidomide NSC and/or IND.

To date, a total of 3,720 patients have been enrolled in NCI-sponsored clinical trials under the bortezomib IND and/or NSC, and a total of 2,803 patients have been enrolled in NCI-sponsored clinical trials under the lenalidomide IND and/or NSC.

In this case, it is felt that a possible causal relationship exists between the event and the investigational agents bortezomib and lenalidomide.

	Choroidal effusion
Bortezomib	Possible
Lenalidomide	Possible
Mantle cell lymphoma	Probable

Date: 8/26/11

Signature: John Wright M.D.
John J. Wright, M.D., Ph.D.
(IDB Monitor for bortezomib)

Date: 9/1/11

Signature: Howard J. Streicher
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If this assessment is changed, we will notify your office.

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