

**MERCK RESEARCH LABORATORIES**  
Division of Merck & Co., Inc.  
West Point, Pennsylvania 19486

December 22, 2008

Re: blinded therapy/MK-0683

Dear Doctor:

This letter is to provide follow-up information on an adverse experience concerning blinded MK-0683 which has been reported to you previously.

U.S. Food and Drug Regulations require sponsors of clinical studies conducted under an IND to notify the FDA of any serious and unexpected adverse experiences occurring in a clinical study filed under that IND when either the investigator or the sponsor believes that there is a reasonable possibility that the experience may have been drug related or if the drug relationship is unknown. The sponsor is also required to inform all investigators working with the particular drug under the IND.

In compliance with these requirements, the enclosed report has been submitted to the FDA and, because you are an investigator in a clinical study under this IND, a copy is enclosed for your information.

Please append this report to the Confidential Investigator's Brochure for the appropriate investigational product or to the Product Circular for the appropriate marketed product and retain in your files.

Please submit a copy of this report promptly (within less than 30 days of receipt) to your Institutional Review Board(s) even though the report may not involve a patient in your study.

This report does not necessarily reflect a conclusion by Merck or the FDA that the drug caused or contributed to the adverse experience. If you have any questions about this report, please contact the Merck monitor for your study.

Enclosure(s): WAES # 0802USA04821, GENSTUDY # 056-0096, AN # 63507

# Merck Human Health Division

For use by user-facilities,  
distributors and manufacturers for  
MANDATORY reporting

Merck Facsimile of FDA Form 3500A  
Approved by FDA (10/21/1993)

## MedWatch

The FDA Medical Products Reporting Program

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|                  |                   |
|------------------|-------------------|
| Mfr report #     | WAES 0802USA04821 |
| UF/Dist report # |                   |
|                  | FDA Use On        |

| A. Patient information   |  |   |                      |
|--|--|---|----------------------|
| 1. Patient identifier<br>Confidential<br>AN 63507<br>in confidence   | 2. Age at time of event:<br>or 64 years<br>Date of Birth: 11/23/1943 | 3. Sex<br><input checked="" type="checkbox"/> Female<br><input type="checkbox"/> Male | 4. Weight<br>132 lbs |
| B. Adverse event or product problem  |  |   |                      |
| 1. <input checked="" type="checkbox"/> Adverse event and/or <input type="checkbox"/> Product problem (e.g., defects/malfunctions)  |  |   |                      |
| 2. Outcomes attributed to adverse event (check all that apply)   |  |   |                      |
| <input type="checkbox"/> Death (mm/dd/yyyy)  |  | <input type="checkbox"/> Disability or Permanent Damage                               |                      |
| <input type="checkbox"/> Life-threatening  |  | <input type="checkbox"/> Congenital Anomaly/Birth Defect                              |                      |
| <input checked="" type="checkbox"/> Hospitalization-initial or prolonged   |  | <input type="checkbox"/> Other Serious(Important Medical Events)                      |                      |
| <input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices)  |  |   |                      |
| 3. Date of event (mm/dd/yyyy)  | 02/17/2008   | 4. Date of this report (mm/dd/yyyy)   | 12/22/2008           |
| 5. Describe event or problem   |  |   |                      |
| This is in follow-up to report(s) previously submitted on 2/29/2008; 3/20/2008; 3/26/2008; 4/15/2008; 5/5/2008; 8/29/2008; 11/7/2008; 11/12/2008; 12/5/2008; 12/15/2008  |  |   |                      |
| A Phase II/III Randomized, Double-Blind Study of Paclitaxel plus Carboplatin in Combination with Vorinostat (MK-0683) or Placebo in Patients with Stage IIIB (with pleural effusion) or Stage IV Non-Small-Cell Lung Cancer (NSCLC)  |  |   |                      |
| Initial and follow up information has been received from an investigator concerning a 64 year old Asian female with vomiting and a history of hemoptysis and toothache who entered a study, title as stated above who was randomized on 07-FEB-2008. On 07-FEB-2008, the patient was placed on blinded study therapy with either vorinostat, capsule, 400 mg or placebo administered on days -4 through 10 of cycle 1 (cycle equivalent to 25 days) for the treatment of non-small cell lung cancer (diagnosed on 11-NOV-2007, T2 N2 M1, stage 4 |  |   |                      |
| (Continued on Additional Page)   |  |   |                      |
| 6. Relevant tests/laboratory data, including dates   |  |   |                      |
| Refer to Additional Page   |  |   |                      |
| 7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)   |  |   |                      |
| MEDICAL HISTORY: Haemoptysis; Toothache<br>CONCURRENT CONDITIONS: Vomiting; Prophylaxis of nausea and vomiting   |  |   |                      |

| C. Suspect medication(s)  |  |  |  |
|---|--|--|--|
| 1. Name (Give labeled strength & mfr/labeler)   |  |  |  |
| # 1 CAP 0683-blinded therapy Unk  |  |  |  |
| # 2 INJ carboplatin Unk   |  |  |  |
| (Continued on Additional Page)  |  |  |  |
| 2. Dose, frequency & route used   |  | 3. Therapy dates (if unknown, give duration) from/to (or best estimate)  |  |
| # 1 400 mg/DAILY/PO   |  | # 1 02/07/2008 - 02/20/2008  |  |
| # 2 684 mg/1X/IV  |  | # 2 02/13/2008 - 02/13/2008  |  |
| 4. Diagnosis for use (indication)   |  | 5. Event abated after use stopped or dose reduced.   |  |
| # 1 Non-small cell lung cancer  |  | yes no N/A unk   |  |
| # 2 Non-small cell lung cancer  |  | # 1 <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> |  |
| 6. Lot #  |  | 7. Exp. Date   |  |
| # 1   |  | # 1  |  |
| # 2   |  | # 2  |  |
| 8. Event reappeared after reintroduction.   |  | yes no N/A unk   |  |
| # 1   |  | <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>     |  |
| # 2   |  | <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>     |  |
| 9. NDC # or Unique ID   |  |  |  |
| Unknown   |  |  |  |
| 10. Concomitant medical products and therapy dates (excluded treatment of event)  |  |  |  |
| BENADRYL  |  | 02/13/2008 - 02/13/2008  |  |
| STEMETIL  |  | 02/13/2008 - 02/17/2008  |  |
| (Continued on Additional Page)  |  |  |  |
| G. All manufacturers  |  |  |  |
| 1. Contact office - name/address  |  | 2. Phone Number  |  |
| Merck Human Health Division<br>Merck & Co., Inc.<br>P.O. Box 4<br>West Point, Pa. 19486-0004<br>Attn: World Wide Product Safety |  | (215) 652-8071   |  |
| 4. Date received by manufacturer (mm/dd/yyyy)   |  | 5. (A)NDA #  |  |
| 12/12/2008  |  | IND # 58915  |  |
| 6. If IND, protocol #   |  | STN #  |  |
| 0560096   |  | PMA/510(k) #   |  |
| 7. Type of report   |  | Combination Product  |  |
| <input type="checkbox"/> 5-day <input type="checkbox"/> 30-day  |  | <input type="checkbox"/> Yes   |  |
| <input type="checkbox"/> 7-day <input type="checkbox"/> Periodic  |  | Pre-1938 <input type="checkbox"/> Yes  |  |
| <input type="checkbox"/> 10-day <input type="checkbox"/> Initial  |  | OTC product <input type="checkbox"/> Yes   |  |
| <input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up# 10                                    |  | 9. Mfr. report number  |  |
|   |  | WAES 0802USA04821  |  |
| 8. Adverse event term(s)  |  |  |  |
| HYPONATRAEMIA   |  |  |  |
| E. Initial reporter   |  |  |  |
| 1. Name, address & phone #  |  |  |  |
|   |  |  |  |
| 2. Health professional?   |  | 3. Occupation  |  |
| <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO   |  |  |  |
| 4. Initial reporter also sent report to FDA.  |  | yes no unk   |  |
| <input type="checkbox"/> yes <input type="checkbox"/> no  |  | <input checked="" type="checkbox"/> unk  |  |

FDA

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

**B. Adverse event or product problem****5. Describe event or problem**

Adenocarcinoma).

Concomitant suspect study therapy carboplatin AUC equivalent to 6 (684 mg), and paclitaxel 200 mg/m<sup>2</sup> (320), administered IV on day 1 of each treatment cycle. Other concomitant therapy included ondansetron HCL (ZOFRAN), diphenhydramine (BENADRYL), dexamethasone (manufacturer unknown), ranitidine, tramadol hydrochloride (TRAMAL) and prochlorperazine maleate (STEMETIL).

On 17-FEB-2008 (cycle 1, day 10) at 10:05 the patient experienced hyponatremia (grade 4) (sodium was 105 mmol/L). On 18-FEB-2008, (cycle 1, day 11) the patient experienced fatigue and vomiting. Laboratory evaluation on 18-FEB-2008 revealed serum sodium was 115 mmol/L (also reported as 110 mmol/L). On 18-FEB-2008 patient was admitted to the hospital. She was treated with 3 percent sodium chloride intravenously. On 19-FEB-2008 patient experienced hyponatremia sodium was 123 (grade 3) (NSAE). She was treated with 5% dextrose in normal saline IV 80cc/hr (19-FEB-2008 to 27-FEB-2008). On 20-FEB-2008, the patient completed cycle 1 of study therapy. On 21-FEB-2008 patient experienced hyponatremia (grade 1) (NSAE). On 21-FEB-2008 patient's serum sodium was 131 mmol/L. On 23-FEB-2008 the patient experienced hyponatremia (sodium was 127) (grade 3) (NSAE). On 27-FEB-2008, the patient's serum sodium level was 136 mmol/L.

On 20-FEB-2008, the patient recovered from hyponatremia (grade 4) with sequelae. On 21-FEB-2008 patient recovered from hyponatremia (grade 3) (NSAE). On 23-FEB-2008 patient recovered with sequelae from hyponatremia (grade 1) (NSAE). On 27-FEB-2008 she recovered with sequelae from hyponatremia (grade 3) (NSAE). The patient was treated with cefepime for severe neutropenia (22-FEB-2008 to 28-FEB-2008).

On 29-FEB-2008 patient was discharged from the hospital. Discharge diagnosis was hyponatremia. On 05-MAR-2008, the patient was discontinued from the study due to the adverse event. Action taken for blinded study therapy for hyponatremia (grade 4) was discontinued. Action taken for study therapy for hyponatremia (grade 1, NSAE) was none. Action taken for study therapy for hyponatremia (grade 3) (NSAE) was discontinued. Action taken for study therapy for hyponatremia (grade 3) (NSAE) was none.

The reporting investigator felt that the hyponatremia (grade 4) was related to blinded study therapy and Hyponatremia (grade 1) (NSAE), Hyponatremia (grade 3) (NSAE), Hyponatremia (grade 3) (NSAE) were related to study therapy. The reporting investigator reported that hyponatremia (grade 4), Hyponatremia (grade 1), Hyponatremia (grade 3) (NSAE), Hyponatremia (grade 3) (NSAE) were related to therapy carboplatin, Paclitaxel. Action taken for therapy with carboplatin, Paclitaxel were discontinued.

Per the investigator the severe febrile neutropenia (reported as ECI previously) was no longer considered to be an SAE nor associate with this SAE.

Additional information is not expected.

**6. Relevant tests/laboratory data, including dates****LABORATORY RESULTS**

| Tests                         | Date       | Value | Unit   | Normal Range |
|-------------------------------|------------|-------|--------|--------------|
| serum sodium                  | 02/17/2008 | 105   | mmol/L | 135 - 145    |
| serum sodium                  | 02/18/2008 | 110   | mmol/L | 135 - 145    |
| Comment: hyponatremia grade 3 |            |       |        |              |
| serum sodium                  | 02/18/2008 | 105   | mmol/L | 135 - 145    |
| Comment: hyponatremia grade 3 |            |       |        |              |
| serum sodium                  | 02/18/2008 | 115   | mmol/L | 135 - 145    |
| Comment: hyponatremia grade 3 |            |       |        |              |
| serum sodium                  | 02/19/2008 | 123   | mmol/L | 135 - 145    |
| serum sodium                  | 02/21/2008 | 131   | mmol/L | 135 - 145    |
| serum sodium                  | 02/23/2008 | 127   | mmol/L | 135 - 145    |
| serum sodium                  | 02/27/2008 | 136   | mmol/L | 135 - 145    |

**C. Suspect medication(s)****1. Name (Give labeled strength & mfr/labeler)**

#3 paclitaxel Unk

**2. Dose, frequency & route used**

#3 320 mg/1X/IV

3. Therapy dates (if unknown, give duration) from/to (or best estimate)

#3 02/13/2008 - 02/13/2008

4. Diagnosis for use (indication)

#3 Non-small cell lung cancer

5. Event abated after use stopped or dose reduced

|    | YES | NO | N/A | UNK |
|----|-----|----|-----|-----|
| #3 | X   |    |     |     |

6. Lot # (if known)

#3

7. Exp date (if known)

#3

8. Event reappeared after reintroduction

|    | YES | NO | N/A | UNK |
|----|-----|----|-----|-----|
| #3 |     |    | X   |     |

C. Suspect medication(s)

| 10. Concomitant medical products and therapy dates (exclude treatment of event) |                         |
|---|-------------------------|
| TRAMAL  | 02/13/2008 - Cont       |
| dexamethasone   | 02/13/2008 - 02/13/2008 |
| ondansetron   | 02/13/2008 - 02/13/2008 |
| ondansetron   | 02/13/2008 - 03/04/2008 |
| ranitidine  | 02/13/2008 - 02/13/2008 |