

# 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

Page 1

|                  |                   |
|------------------|-------------------|
| Mfr report #     | WAES 0803USA03465 |
| UF/Dist report # |                   |
|                  | FDA Use On        |

### A. Patient information

|  |   |   |                     |
|--|---|---|---------------------|
| 1. Patient identifier<br>Confidential<br><br>AN 55508<br>in confidence | 2. Age at time of event:<br>or 66 years<br>Date of Birth 10/23/1941 | 3. Sex<br><input checked="" type="checkbox"/> Female<br><input type="checkbox"/> Male | 4. Weight<br>73 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) 03/18/2008  | 4. Date of this report (mm/dd/yyyy) 02/06/2009                   |   |  |

5. Describe event or problem  
This is in follow-up to report(s) previously submitted on 3/28/2008; 4/14/2008; 4/21/2008; 5/2/2008; 5/9/2008; 5/23/2008; 5/30/2008; 6/12/2008; 7/3/2008; 8/1/2008; 8/28/2008; 1/23/2009; 1/26/2009

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 66 year old white female with hypercholesterolaemia, pain, constipation, fatigue, left shoulder pain, shortness of breath, cough and weight loss and a history of ductal carcinoma in situ, duodenal ulcer, hysterectomy, left lower lung lobectomy (13-NOV-2003), left breast lesion excision (08-APR-1997) and radiotherapy to left breast (1997) who on 11-FEB-2008 was placed on cycle 1 of study therapy with blinded therapy, with either vorinostat, capsule 400 mg or

(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: Ductal carcinoma in situ; Duodenal ulcer; Radiotherapy; Hysterectomy; Lung lobectomy; Lesion excision  
CONCURRENT CONDITIONS: Hypercholesterolaemia; Weight decreased; Nausea; Cough; Pain; Fatigue; Breath shortness; Shoulder pain; Constipation

### C. Suspect medication(s)

|  |  |  |  |
|--|--|--|--|
| 1. Name (Give labeled strength & mfr/labeler)                                    |  | 3. Therapy dates (if unknown, give duration) from/to (or best estimate)  |  |
| # 1 CAP 0683-blinded therapy Unk   |  | # 1 02/11/2008 - 02/17/2008  |  |
| # 2  |  | # 2  |  |
| (Continued on Additional Page)   |  |  |  |
| 2. Dose, frequency & route used  |  | 3. Therapy dates (if unknown, give duration) from/to (or best estimate)  |  |
| # 1 Unk/Unk/PO   |  | # 1 02/11/2008 - 02/17/2008  |  |
| # 2  |  | # 2  |  |
| 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  |  | # 1 <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> |  |
| 6. Lot #   |  | 7. Exp. Date   |  |
| # 1  |  | # 1  |  |
| # 2  |  | # 2  |  |
| 9. NDC # or Unique ID  |  | 8. Event reappeared after reintroduction.  |  |
| Unknown  |  | yes no N/A unk   |  |
| # 1  |  | # 1 <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> |  |
| # 2  |  | # 2 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>            |  |
| 10. Concomitant medical products and therapy dates (excluded treatment of event) |  |  |  |
| COLOXYL WITH SENNA   |  | 02/11/2008-Cont  |  |
| EMEND  |  | 03/11/2008-03/11/2008  |  |
| (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) 01/16/2009  |  | 3. Report source. (check all that apply)                   |  |
| 6. If IND, protocol # 0560020   |  | <input checked="" type="checkbox"/> foreign                |  |
| 7. Type of report   |  | <input checked="" type="checkbox"/> study                  |  |
| <input type="checkbox"/> 5-day <input type="checkbox"/> 30-day  |  | <input type="checkbox"/> literature                        |  |
| <input type="checkbox"/> 7-day <input type="checkbox"/> Periodic  |  | <input type="checkbox"/> consumer                          |  |
| <input type="checkbox"/> 10-day <input type="checkbox"/> Initial  |  | <input checked="" type="checkbox"/> health professional    |  |
| <input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up# 13                                    |  | <input type="checkbox"/> user facility                     |  |
| 5. (A)NDA # 58915   |  | <input checked="" type="checkbox"/> company representative |  |
| STN #   |  | <input type="checkbox"/> distributor                       |  |
| PMA/510(k) #  |  | <input type="checkbox"/> other:                            |  |
| Combination Product <input type="checkbox"/> Yes  |  | 9. Mfr. report number                                      |  |
| Pre-1938 <input type="checkbox"/> Yes   |  | WAES 0803USA03465  |  |
| OTC product <input type="checkbox"/> Yes  |  |  |  |

8. Adverse event term(s)  
NEUTROPENIA; PLEURAL EFFUSION; HYPOMAGNEAEMIA;  
HYPOKALAEMIA

### 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.   |  |               |  |
| <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**

placebo for the treatment of non-small cell lung cancer (diagnosed 13-NOV-2003; current staging 03-JAN-2008; primary tumor T4; nodal involvement NX; distant metastases M1; overall stage IV). Concomitant study therapy included carboplatin, AUC equivalent to 6 (450 mg), administered IV and paclitaxel, 200 mg/m<sup>2</sup> (246 mg), administered IV, both initiated on 15-FEB-2008. Other concomitant therapy included atorvastatin calcium (LIPITOR), acetaminophen, docusate sodium (+) senna (COLOXYL WITH SENNA), dexamethasone (manufacturer unknown), aprepitant (MSD), loratadine, ranitidine and tropisetron. On 06-MAR-2008 the patient experienced a cough (NSAE) that was not related to the study therapy.

On 11-MAR-2008, the patient began cycle 2 of study therapy with vorinostat, capsule 300 mg or placebo, carboplatin, AUC equivalent to 5 (375 mg), administered IV and paclitaxel, 175 mg/m<sup>2</sup> (217 mg), administered IV. On 18-MAR-2008 (Cycle 2 Day 8) the patient developed pleural effusion (grade 2), neutropenia (grade 4) (also reported as grade 3), hypomagnesemia (grade 2) and hypokalemia (grade 4) and was hospitalized. The patient had a 2 days history of shortness of breath, limited mobility and decreased appetite. On admission an EKG showed sinus rhythm tachycardia, right ventricular strain and non-specific T-wave changes, blood tests revealed electrolyte abnormalities (potassium was 2.4), the patient was afebrile with a temperature of 36.6 C. On 18-MAR-2008, computed axial tomography chest pulmonary angiography revealed left pleural effusion and no scan evidence of pulmonary embolism and chest x-ray revealed left pleural effusion. Neutrophil count was 0.1, potassium was 3.0 and blood cultures were negative for infection. Blinded study therapy was discontinued and the patient was placed on therapy with gentamicin and clavulanate potassium (+) ticarcillin disodium (TIMENTIN) to cover sepsis because the patient was neutropenic. The patient was also placed on therapy with IV potassium, potassium chloride (SLOW-K), potassium bicarbonate (+) sodium bicarbonate (+) sodium phosphate, monobasic (PHOSPHATE-SANDOZ), potassium bicarbonate (+) potassium chloride (CHLORVESENT), and magnesium aspartate (MAGMIN). On 19-MAR-2008, the pleural effusion was drained of 200 ml of pleural fluid and the patient was reported to be feeling less shortness of breath. An accurate cell count was unable to be performed as the specimen was clotted. The patient's BF protein was 3.4 g/L which indicated an exudate fluid protein. Cytology of pleural fluid was negative for malignant cells and pleural fluid culture had no growth. On 20-MAR-2008 the patient was placed on potassium bicarbonate (+) potassium chloride (CHLORVESENT) for a decrease in potassium. On 22-MAR-2008, antibiotics ceased and the patient recovered from hypokalemia (GRADE 4). On 22-MAR-2008 the patient's potassium was 3.8. White blood cell growth factors were not given. On 23-MAR-2008 absolute neutrophil count was normal and the patient recovered from neutropenia (grade 4). On 25-MAR-2008 the patient recovered from pleural effusion (grade 2) and the patient was discharged from the hospital. Discharge diagnoses were pleural effusion, neutropenia, hypomagnesaemia and hypokalemia. On 30-MAR-2008, treatment therapy with magnesium aspartate (MAGMIN) was stopped. On 31-MAR-2008 and ECG was performed and showed sinus rhythm with non-specific T abnormality, left atrial abnormality, reversed arm leads, indeterminate axis, poor anterior R progression. On 31-MAR-2008, the patient recovered from hypomagnesaemia. The patient returned to clinic for review on 31-MAR-2008 and neutropenia remained normal, potassium was 4.1, magnesium was 0.77. No clinical symptoms presented. The patient was not restarted on study therapy. At the time of the report, the patient's shortness of breath improved. The patient's cough persisted. On 31-MAR-2008 the patient discontinued study medication due to adverse event. The status for the study was completed.

The investigator felt that neutropenia (grade 4), hypomagnesaemia (grade 2), and hypokalaemia (grade 4) were related to blinded study therapy and pleural effusion (grade 2) was not related to blinded study therapy.

The investigator felt that pleural effusion (grade 2) was not related to carboplatin and paclitaxel.

The investigator felt that neutropenia (grade 4), hypomagnesaemia (grade 2) and hypokalaemia (grade 4) were related to carboplatin and paclitaxel.

The investigator felt that the cough (NSAE) was not related to blinded therapy or carboplatin and paclitaxel.

The patient was placed on the following medications during the study: enoxaparin sodium (CLEXANE) for prophylaxis for pulmonary embolism, blood transfusion for anemia, normal saline for dehydration, prochlorperazine maleate (STEMETIL) for nausea, and atropine sulfate (+) diphenoxylate hydrochloride (LOMOTIL) for diarrhea, KCL/potassium for hypokalemia, sandozphosphate for hypophosphatemia, and thiamine for malnourishment.

This is an amended report. The concomitant therapy tropisetron (21-FEB-2008) was deleted from the therapy screen and phosphate levels 0.70 mmol/L was deleted from the narrative and lab diagnostic screen.

Additional information is not expected.

This is a corrected report as amended.

#### 6. Relevant tests/laboratory data, including dates

##### DIAGNOSTIC TEST

| <u>Tests</u>   | <u>Date</u> | <u>Value</u> | <u>Unit</u> | <u>Normal Range</u> |
|--|-------------|--------------|-------------|---------------------|
| computed axial tomography<br>Comment: L pleural effusion no scan evidence of pulmonary embolism      | 03/18/2008  |              |             |                     |
| chest X-ray<br>Comment: L pleural effusion   | 03/18/2008  |              |             |                     |
| diagnostic laboratory test<br>Comment: blood: electrolyte abnormalities                              | 03/18/2008  |              |             |                     |
| electrocardiogram  | 03/18/2008  |              |             |                     |
| diagnostic pathological examination<br>Comment: pleural fluid cytology- negative for malignant cells | 03/19/2008  |              |             |                     |
| white blood cell scan<br>Comment: WBC growth factor not given  | 03/23/2008  |              |             |                     |
| diagnostic laboratory test<br>Comment: blood: returned to normal                                     | 03/23/2008  |              |             |                     |
| electrocardiogram<br>Comment: electrocardiogram T wave inversion sinus rhythm                        | 03/31/2008  |              |             |                     |

##### LABORATORY RESULTS

| <u>Tests</u>                                     | <u>Date</u> | <u>Value</u> | <u>Unit</u> | <u>Normal Range</u> |
|--|-------------|--------------|-------------|---------------------|
| body temp<br>Comment: afebrile                   | 03/??/2008  | 36.6         |             |                     |
| neutrophil count                                 | 03/18/2008  | 0.1          |             |                     |
| neutrophil count                                 | 03/18/2008  | 1            | 10x 10/L    | 2 - 7               |
| serum magnesium                                  | 03/18/2008  | 65           | mol/L       | 70 - 95             |
| serum potassium                                  | 03/18/2008  | 2.4          |             |                     |
| serum potassium                                  | 03/18/2008  | 3            | mmol/L      | 3.5 - 5.0           |
| blood culture<br>Comment: negative for infection | 03/18/2008  |              |             |                     |
| serum magnesium                                  | 03/19/2008  | 50           | mmol/L      | 70 - 95             |
| serum potassium                                  | 03/19/2008  | 25           | mol/L       | 35 - 50             |
| pleural fluid culture<br>Comment: no growth      | 03/19/2008  |              |             |                     |
| serum magnesium                                  | 03/20/2008  | 51           | mol/L       | 70 - 95             |
| serum potassium                                  | 03/20/2008  | 27           | mol/L       | 35 - 50             |
| serum magnesium                                  | 03/21/2008  | 41           | mol/L       | 70 - 95             |
| serum magnesium                                  | 03/21/2008  | 43           | mol/L       | 70 - 95             |
| serum potassium                                  | 03/21/2008  | 23           | mol/L       | 35 - 50             |
| serum potassium                                  | 03/21/2008  | 46           | mol/L       | 35 - 50             |
| serum magnesium                                  | 03/22/2008  | 62           | mol/L       | 70 - 95             |
| serum potassium                                  | 03/22/2008  | 3.8          |             |                     |
| absolute neutrophil count                        | 03/23/2008  | normal       |             |                     |
| neutrophil count                                 | 03/23/2008  | 1            | 10x 9/L     | 2 - 7               |
| serum magnesium                                  | 03/23/2008  | 57           | mol/L       | 70 - 95             |
| serum phosphorus                                 | 03/25/2008  | 0.70         | mmol/L      |                     |
| absolute neutrophil count                        | 03/31/2008  | normal       |             |                     |
| serum magnesium                                  | 03/31/2008  | 77           | mmol/L      | 70 - 95             |
| serum potassium                                  | 03/31/2008  | 4.1          | mmol/L      |                     |

#### C. Suspect medication(s)

##### 1. Name (Give labeled strength & mfr/labeler)

- #1 CAP 0683-blinded therapy Unk
- #1 CAP 0683-blinded therapy Unk
- #1 CAP 0683-blinded therapy Unk
- #2 carboplatin Unk
- #2 carboplatin Unk
- #3 paclitaxel Unk
- #3 paclitaxel Unk

## 2. Dose, frequency &amp; route used

#1 Unk/Unk/PO  
 #1 Unk/Unk/PO  
 #1 Unk/Unk/PO  
 #2 450 mg/1X/IV  
 #2 375 mg/1X/IV  
 #3 246 mg/1X/IV  
 #3 217 mg/1X/IV

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

#1 02/19/2008 - 02/20/2008  
 #1 02/22/2008 - 02/24/2008  
 #1 03/11/2008 - 03/18/2008  
 #2 02/15/2008 - 02/15/2008  
 #2 03/11/2008 - 03/11/2008  
 #3 02/15/2008 - 02/15/2008  
 #3 03/11/2008 - 03/11/2008

## 4. Diagnosis for use (indication)

#1 Non-small cell lung cancer  
 #1 Non-small cell lung cancer  
 #1 Non-small cell lung cancer  
 #2 Non-small cell lung cancer  
 #2 Non-small cell lung cancer  
 #3 Non-small cell lung cancer  
 #3 Non-small cell lung cancer

## 5. Event abated after use stopped or dose reduced

|    | YES | NO | N/A | UNK |
|----|-----|----|-----|-----|
| #1 | X   |    |     |     |
| #1 | X   |    |     |     |
| #1 | X   |    |     |     |
| #2 |     |    |     | X   |
| #2 |     |    |     | X   |
| #3 |     |    |     | X   |
| #3 |     |    |     | X   |

## 6. Lot # (if known)

#1  
 #1  
 #1  
 #2  
 #2  
 #3  
 #3

## 7. Exp date (if known)

#1  
 #1  
 #1  
 #2  
 #2  
 #3  
 #3

## 8. Event reappeared after reintroduction

|    | YES | NO | N/A | UNK |
|----|-----|----|-----|-----|
| #1 |     |    | X   |     |
| #1 |     |    | X   |     |
| #1 |     |    | X   |     |
| #2 |     |    |     | X   |
| #2 |     |    |     | X   |
| #3 |     |    |     | X   |
| #3 |     |    |     | X   |

## C. Suspect medication(s)

- 10. Concomitant medical products and therapy dates (exclude treatment of event)

|               |                         |
|---------------|-------------------------|
| EMEND         | 03/12/2008 - Cont       |
| LIPITOR       | 07/01/2007 - Cont       |
| acetaminophen | 12/01/2007 - Cont       |
| dexamethasone | 03/09/2008 - 03/09/2008 |
| dexamethasone | 03/10/2008 - 03/10/2008 |
| dexamethasone | 03/11/2008 - 03/11/2008 |
| loratadine    | 03/11/2008 - 03/11/2008 |
| ranitidine    | 03/11/2008 - 03/11/2008 |
| tropisetron   | 03/11/2008 - 03/11/2008 |

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

06-FEB-2009

Re: 0683 Blinded Therapy

Dear Doctor:

This letter is to provide follow-up information on an adverse experience concerning 0683 Blinded Therapy 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.

The enclosed report, although not fulfilling the aforementioned reporting requirements, was submitted to the FDA because of the nature of the event. Because you are an investigator in a clinical study under the IND, a copy of the report 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 # 0803USA03465, GENSTUDY # 056-0020, AN # 55508