

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 0805USA04831 |
| UF/Dist report # | |
| | FDA Use Onl |

| A. Patient information | | | |
|--|--|---|----------------------|
| 1. Patient identifier Confidential AN 62529 in confidence | 2. Age at time of event: or 73 years Date of Birth: 09/29/1934 | 3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male | 4. Weight 191 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) 04/05/2008 | 4. Date of this report (mm/dd/yyyy) 02/12/2009 | | |
| 5. Describe event or problem This is in follow-up to report(s) previously submitted on 6/2/2008; 6/4/2008; 6/6/2008; 7/9/2008; 8/13/2008; 9/15/2008; 9/29/2008; 1/14/2009; 2/9/2009 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) Information has been received from an investigator concerning a 73 year old white male with breathlessness, and a history of computed tomography pulmonary angiogram, diagnostic arthroscopy of the knee and 2 varicose vein strippings of the left leg who entered a study, title as stated above. On 17-DEC-2007, the patient was originally diagnosed with adenocarcinoma, primary tumor T4, no nodal involvement, M1 distant metastasis, overall stage IV. From 31-MAR-2008 to 13-APR-2008, cycle 1, the patient received therapy with blinded therapy (either vorinostat 100 mg capsule, total daily dose 400 mg for 14 days every | | | |
| (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: Varicose veins stripping; Arthroscopy; Varicose vein CONCURRENT CONDITIONS: Breathlessness | | | |

| C. Suspect medication(s) | | | |
|--|--|--|--|
| 1. Name (Give labeled strength & mfr/labeler) | | | |
| # 1 CAP 0683-blinded therapy Unk | | | |
| # 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 03/31/2008 - 04/13/2008 | |
| # 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 type="checkbox"/> <input type="checkbox"/> <input checked="" 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) | | | |
| PRO-BANTHINE | | 12/24/2007-Cont | |
| albuterol | | 12/24/2007-Cont | |
| (Continued on Additional Page) | | | |

| G. All manufacturers | |
|--|--|
| 1. Contact office - name/address Merck Human Health Division Merck & Co., Inc. P.O. Box 4 West Point, Pa. 19486-0004 Attn: World Wide Product Safety | 2. Phone Number (215) 652-8071 |
| 4. Date received by manufacturer (mm/dd/yyyy) 02/03/2009 | 3. Report source. (check all that apply) <input checked="" type="checkbox"/> foreign <input checked="" type="checkbox"/> study <input type="checkbox"/> literature <input type="checkbox"/> consumer <input checked="" type="checkbox"/> health professional <input type="checkbox"/> user facility <input type="checkbox"/> company representative <input type="checkbox"/> distributor <input type="checkbox"/> other |
| 5. (A)NDA # IND # 58915 STN # PMA/ 510(k) # | 6. If IND, protocol # 0560035 |
| 7. Type of report <input type="checkbox"/> 5-day <input type="checkbox"/> 30-day <input type="checkbox"/> 7-day <input type="checkbox"/> Periodic <input type="checkbox"/> 10-day <input type="checkbox"/> Initial <input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up# 9 | 8. Adverse event term(s) DYSPNOEA; FEBRILE NEUTROPENIA |
| 9 Mfr. report number WAES 0805USA04831 | |

| E. Initial reporter | | | |
|--|--|---------------|--|
| 1. Name, address & phone # | | | |
| 2. Health professional? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO | | 3. Occupation | |
| 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**

3 weeks or placebo) for the treatment of bronchoalveolar carcinoma. Concomitant study therapy included paclitaxel 200 mg/m² IV every 3 weeks (total daily dose 420 mg), and carboplatin AUC 6 IV, every 3 weeks (total daily dose 666 mg) administered on day 1 of each treatment cycle. Other concomitant therapy included omeprazole, propantheline bromide (PRO-BANTHINE), ondansetron, dexamethasone IV (manufacturer unknown), salbutamol MDI, domperidone domperidone, cimetidine and chlorpheniramine maleate.

From 22-APR-2008 to 05-MAY-2008, the patient received cycle 2 study therapy with blinded therapy (either vorinostat 100 mg capsule, total daily dose 400 mg or placebo). Concomitant study suspect therapy included paclitaxel 200 mg/m² IV total daily dose 400 mg given on 22-APR-2008, and carboplatin AUC 6 IV, total daily dose 700 mg given on 22-APR-2008.

On 05-APR-2008, (cycle 1, day 6) the patient experienced intermittent shortness of breath (grade 1) and was hospitalized. On 19-MAY-2008 the patient experienced pneumonia (grade 2) and neutropenia (grade 4) which were non-serious. On 21-MAY-2008, (cycle 3, day 9) the patient was presented with increased shortness of breath and feeling "unwell" over last 2 days and one episode of diarrhea. Temperature on admission was 39.2 centigrade. Pulmonary embolism (PE) was suspected, but not confirmed. On 21-MAY-2008, the patient had a chest x-ray performed that revealed increased shadow of the left lung, no PE's. Admission note had provisional diagnosis of neutropenic sepsis. ?? pulmonary embolism (PE). Chest x-ray showed no PE's. Oxygen saturation was 88%. Pulmonary embolism was suspected, but not confirmed. Blood cultures were negative. Full blood count (FBC) revealed neutropenia with a neutrophil count of 0.1x10⁹/L. He was admitted per neutropenic sepsis protocol with a diagnosis of febrile neutropenia (grade 4). He was started antibiotics: piperacillin sodium (+) tazobactam sodium (TAZOCIN) 4.5 g IV tid, vancomycin 1 gram IV bid, and gentamicin 440 mg IV daily. On 21-MAY-2008, he was given filgastrim 6 mg subcutaneously. He was placed on oxygen therapy. The patient's blood pressure was 110/56 and her pulse was 66. On 21-MAY-2008 through 23-MAY-2008 the patient was given paracetamol. Laboratory exams on 21-MAY-2008 included a serum creatinine protein of 205 mg/L, a white blood cell count was 0.9x10⁹/L, albumin was 25 g/L, platelets were 112x10⁹/L, serum sodium was 120 mmol/L, and troponin I was 0.22 ug/L. Last dose given of MK-683-blinded therapy or placebo was on 26-MAY-2008. On 22-MAY-2008 through 26-MAY-2008 the patient was given potassium bicarbonate (+) potassium chloride (SANDO K). On 23-MAY-2008, the patient received transfusion with 2 units, and his neutropenia (grade 4) (non-serious) resolved. Action taken regarding study therapy was none. As of 27-MAY-2008, the patient was still hospitalized. The patient was treated with ciprofloxacin for the neutropenic sepsis and clarithromycin for the febrile neutropenia (grade 4). The patient recovered from febrile neutropenia (grade 4) on 26-MAY-2008. The patient was discharged from the hospital on 29-MAY-2008 and will be seen 01-JUN-2008. A sputum sample had no significant growth. The patient was discharged on ciprofloxacin and clarithromycin. On 29-MAY-2008 the patient's neutrophils were 13.8. On 29-MAY-2008 the patient recovered from (grade 2) (NSAE). It was reported that the patient was still very weak. The discharge diagnoses were neutropenic sepsis and the source was left sided pneumonia. On 07-JUL-2008 the patient recovered from shortness of breath. On 16-JUN-2008 the patient discontinued study medication due to the physician's decision without receiving further chemo after discharge.

The reporting investigator felt that the febrile neutropenia (grade 4), shortness of breath, and pneumonia (NSAE) were related to MK-683-blinded therapy or placebo, carboplatin and paclitaxel. The reporting investigator also felt that the patient's neutropenia (grade 4) (non-serious) was related to therapy with MK-683-blinded therapy or placebo, carboplatin and paclitaxel. Action taken regarding carboplatin and paclitaxel was none.

Additional information is not expected.

This is an amended report. The local registration number was removed from the report.

This is a corrected report. This blinded study report was sent to NDA #21991 on 09-FEB-2009.

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> |
|---|-------------|--------------|-------------|---------------------|
| electrocardiogram Comment: sinus tachycardia-bundle branch block right | 03/25/2008 | | | |
| chest X-ray Comment: increased shadow on left lung | 05/21/2008 | | | |
| electrocardiogram Comment: sinus tachycardia-bundle branch block right | 05/21/2008 | | | |
| blood pressure measurement | | 110/56 | | |

LABORATORY RESULTS

| <u>Tests</u> | <u>Date</u> | <u>Value</u> | <u>Unit</u> | <u>Normal Range</u> |
|--------------|-------------|--------------|-------------|---------------------|
|--------------|-------------|--------------|-------------|---------------------|

| | | | |
|--------------------------|------------|-------------------------|-----------|
| WBC count | 05/21/2008 | 39.2 C | |
| Comment: low | | | |
| body temp | 05/21/2008 | 9.2 g/dL | 13 - 18 |
| hemoglobin | 05/21/2008 | | |
| Comment: low | | | |
| neutrophil count | 05/21/2008 | 0.10 10 ⁹ /L | 2 - 7.5 |
| Comment: low | | | |
| platelet count | 05/21/2008 | 112 10 ⁹ /L | 150 - 450 |
| Comment: low | | | |
| pulse oximetry | 05/21/2008 | 88 % | |
| serum C-reactive protein | 05/21/2008 | 205 mg/L | 0 - 6 |
| serum TnI | 05/21/2008 | 0.22 ug/L | 0 - 0.1 |
| serum albumin | 05/21/2008 | 25 g/L | 30 - 51 |
| serum sodium | 05/21/2008 | 120 mmol/L | 135 - 145 |
| blood culture | 05/21/2008 | | |
| Comment: negative normal | | | |
| neutrophil count | | 13.8 | |
| total heartbeat count | | 66 | |

C. Suspect medication(s)

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

- #1 CAP 0683-blinded therapy Unk
- #1 CAP 0683-blinded therapy Unk
- #2 infusion (form) paclitaxel Unk
- #2 infusion (form) paclitaxel Unk
- #2 infusion (form) paclitaxel Unk
- #3 infusion (form) carboplatin Unk
- #3 infusion (form) carboplatin Unk
- #3 infusion (form) carboplatin Unk

2. Dose, frequency & route used

- #1 Unk/Unk/PO
- #1 Unk/Unk/PO
- #2 420 mg/1X/IV
- #2 400 mg/1X/IV
- #2 400 mg/1X/IV
- #3 666 mg/1X/IV
- #3 700 mg/1X/IV
- #3 648 mg/1X/IV

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

- #1 04/22/2008 - 05/05/2008
- #1 05/13/2008 - 05/26/2008
- #2 04/04/2008 - 04/04/2008
- #2 04/22/2008 - 04/22/2008
- #2 05/13/2008 - 05/13/2008
- #3 04/04/2008 - 04/04/2008
- #3 04/22/2008 - 04/22/2008
- #3 05/13/2008 - 05/13/2008

4. Diagnosis for use (indication)

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

5. Event abated after use stopped or dose reduced

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

6. Lot # (if known)

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

7. Exp date (if known)

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

8. Event reappeared after reintroduction

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

C. Suspect medication(s)

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

| | |
|--------------------------|-------------------|
| chlorpheniramine maleate | 04/04/2008 - Cont |
| cimetidine | 04/04/2008 - Cont |
| dexamethasone | 04/04/2008 - Cont |
| dexamethasone | 04/04/2008 - Cont |
| domperidone | 04/04/2008 - Cont |
| omeprazole | 12/24/2007 - Cont |
| ondansetron | 04/04/2008 - Cont |