

**MedWatch**

The FDA Medical Products Reporting Program

Mfr report #	WAES 0709USA02327
UF/Dist report #	
FDA Use On	

**A. Patient information**

1. Patient identifier Confidential AN 61503 in confidence	2. Age at time of event: or 65 years Date of Birth: 03/17/1942	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 187 lbs
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**B. Adverse event or product problem**

1.  Adverse event and/or  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)	09/11/2007	4. Date of this report (mm/dd/yyyy)	03/05/2009
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5. Describe event or problem  
This is in follow-up to report(s) previously submitted on 9/24/2007; 10/19/2007; 10/29/2007; 10/31/2007; 11/16/2007; 11/20/2007; 1/25/2008; 2/29/2008; 8/20/2008; 9/4/2008; 9/17/2008; 9/22/2008; 9/26/2008; 10/29/2008; 11/14/2008; 12/31/2008; 1/23/2009; 2/26/2009

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 65 year old white male with alcohol use, anxiety, deafness, cough, cramps calf, fatigue, gout, heartburn, haemoptysis, insomnia, left and right eye cataract, myalgia, rash, taste changed, umbilical hernia, pain and a history of cerebral commotion, a thoracic CT scan, an abdominal CT scan, a cerebral CT scan, a bronchial biopsy and bronchoscopy who

(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: Commotio cerebri; Computerised tomogram thorax; Computerised tomogram abdomen; Brain computerised tomography; Bronchoscopy; Biopsy bronchus  
CONCURRENT CONDITIONS: Alcohol use; Anxiety; Cough; Cramps calf; Fatigue; Pain; Umbilical hernia; Premedication; Prophylaxis; Rash; Deafness;

(Continued on Additional Page)

**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 # 1 Unk/Unk/PO # 2 _____	3. Therapy dates (if unknown, give duration) from/to (or best estimate) # 1 08/31/2007 - 09/13/2007 # 2 _____
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4. Diagnosis for use (indication) # 1 Non-small cell lung cancer # 2 _____	5. Event abated after use stopped or dose reduced. 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 type="checkbox"/> <input type="checkbox"/>
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6. Lot # # 1 _____ # 2 _____	7. Exp. Date # 1 _____ # 2 _____
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9. NDC # or Unique ID Unknown	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 type="checkbox"/> <input type="checkbox"/>
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10. Concomitant medical products and therapy dates (excluded treatment of event) LOVENOX 10/27/2007-10/30/2007 PANTOLOC 08/31/2007-12/17/2007
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**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
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4. Date received by manufacturer (mm/dd/yyyy) 02/24/2009	5. (A)NDA # IND # 58915 STN # _____ PMA/510(k) # _____ Combination Product <input type="checkbox"/> Yes <input type="checkbox"/> No Pre-1938 <input type="checkbox"/> Yes <input type="checkbox"/> No OTC product <input type="checkbox"/> Yes <input type="checkbox"/> No
6. If IND, protocol # 0560019	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# 18
9. Mfr report number WAES 0709USA02327	

8. Adverse event term(s)  
FEBRILE NEUTROPENIA; FEBRILE NEUTROPENIA; FEBRILE NEUTROPENIA; PNEUMONIA

**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

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

on 31-AUG-2007 was allocated/randomized to a study, title as stated above.

On 31-AUG-2007, the patient was placed on blinded study therapy of either vorinostat 400 mg capsule, 400 mg daily or placebo administered on day(s) -4 through 10 of cycle 1 (cycle equivalent to 25 days) (or days 1 through 14 for each subsequent cycle) for treatment of non-small-cell lung cancer (initial diagnosis 06-JUN-2007; current staging 21-AUG-2007: T2/N2/M1/IV).

Concomitant study therapy included paclitaxel, 200 mg/m<sup>2</sup> and carboplatin AUC equivalent to 6 administered intravenous (IV) on day 1 of each treatment cycle). Other concomitant therapy included dexamethasone (manufacturer unknown) famotidine (manufacturer unknown), diphenhydramine hydrochloride, ibuprofen, indomethacin (manufacturer unknown), codeine, pantoprazole sodium (PANTOLOC), dolasetron mesylate, hydrocortisone (+) diphenhydramine (+) nystatin (+) water (MAGIC MOUTHWASH) and magnesium sulfate.

On 11-SEP-2007 (Cycle 1, Day 12) the patient was presented to an emergency room with a fever of 38.2C, asthenia, diarrhea, hyponatremia, and myalgia. The patient was diagnosed with febrile neutropenia (grade 3) and was hospitalized. The following lab values were noted: absolute neutrophil count (ANC)  $0.02 \times 10^9/L$ ; platelet count 12,000. Eastern Cooperative Oncology Group (ECOG) rating was equivalent to 3. On 12-SEP-2007 hemoculture was positive and blood culture showed escheria coli (abnormal). The patient was placed on IV antibiotics cefepime (MAXEPIME) (12-SEP-2007 to 16-SEP-2007), IV, 2 gm, three times a day for febrile neutropenia, filgrastim (NEUPOGEN) (12-SEP-2007 to 14-SEP-2007) for febrile neutropenia, SC die, and received 5 units of platelets for thrombocytopenia. The patient was evaluated by a microbiologist. On 13-SEP-2007 patient's phosphate level was noted to be low (0.37 mmol/L) and was treated with potassium bicarbonate (+) sodium bicarbonate (+) sodium phosphate, monobasic (PHOSPHATE SANDOZ). Subsequently, the patient was treated with metronidazole (FLAGYL) (13-SEP-2007 to 16-SEP-2007) for febrile neutropenia; E. coli bacteremia. On 14-SEP-2007, the patient's potassium level was 3.0 mmol/L (non-serious) and was treated with phosphate potassium. On 16-SEP-2007, IV antibiotics were discontinued. On 17-SEP-2007, the following lab values were noted: ANC  $4.15 \times 10^9/L$ ; platelet count 123,000, and the patient was considered recovered from febrile neutropenia (grade 3). On 18-SEP-2007, the patient was discharged with the discharge diagnosis of E. coli septicemia secondary to febrile neutropenia. On 27-SEP-2007 the patient will be evaluated for Cycle 2 in the outpatient clinic. On 28-SEP-2007, the patient was placed on cycle 2 study therapy. Blinded study therapy was reduced to 200mg daily or placebo. On 05-OCT-2007, the patient's neutrophil count was noted to be 0.58. On 05-OCT-2007 the patient developed neutropenia (grade 3) (non-serious). On 07-OCT-2007 (Cycle 2, day 10) the patient presented to an emergency room with fever (38.7 degrees celsius), confusion, dysphagia, sore throat and chills. The patient's absolute neutrophil count was noted to be  $0.11 \times 10^9/L$  and the patient was hospitalized for febrile neutropenia (grade 4). Chest X-ray revealed no particularity and urinalysis lab was normal. Hemoculture test done on 07-OCT-2007 was negative. Blinded study therapy was interrupted. The patient was treated with cefepime (MAXEPIME) (07-OCT-2007 to 10-OCT-2007) 2 gm, IV every 8 hours and filgrastim (NEUPOGEN) (07-OCT-2007 to 09-OCT-2007) for febrile neutropenia. The patient's ANC was  $0.32 \times 10^9/L$  on 08-OCT-2007. The patient's ANC was  $5.08 \times 10^9/L$  on 10-OCT-2007. The patient recovered on 11-OCT-2007 and was discharged. The patient's discharge diagnosis was febrile neutropenia. Cycle 3 of blinded study therapy day 1 was initiated on 18-OCT-2007. On 19-OCT-2007 the patient was treated with filgrastim (NEUPOGEN) (19-OCT-2007 to 25-OCT-2007) for neutropenia. On 25-OCT-2007 (Cycle 3, Day 8), the patient presented to the emergency room due to fever (39.1 C), cough, dyspnea and asthenia. Control labs were performed and the patient had an ANC of  $0.1 \times 10^9/L$  (also reported as  $1.39 \times 10^9/L$  and white blood cell count was  $1.9 \times 10^9/L$ ). The patient had a respiration rate of 28 per minute and a saturation of 91% on 100%. At the auscultation, the patient had some rale. The patient was hospitalized for febrile neutropenia (grade 2) and pneumonia (grade 3). On 25-OCT-2007, the patient completed cycle 3 study therapy and received IV antibiotics cefepime (MAXEPIME) (25-OCT-2007 to 30-OCT-2007) 2000 mg TID for febrile neutropenia and on 26-OCT-2007 filgrastim (NEUPOGEN) injection "escalate" at 400 mg subcutaneously for febrile neutropenia. The patient was also treated with albuterol sulfate (VENTOLIN) and ipratropium bromide (ATROVENT). Chest x-ray was performed on 26-OCT-2007, the result was pneumonia, no pleural effusion. On 29-OCT-2007, the patient received a blood transfusion for anemia (NSAE). On 31-OCT-2007, the patient was discharged with an ANC of  $4.56 \times 10^9/L$ , no fever, dyspnea or asthenia. On 31-OCT-2007, the patient recovered from febrile neutropenia (grade 3) and pneumonia (grade 3). The patient's discharge diagnoses were pulmonary superinfection, febrile neutropenia and pneumonia. The patient will be evaluated for Cycle 4 on 08-NOV-2007 in an outpatient clinic.

Physical exam on 08-NOV-2007 showed lungs to be clear auscultation. The patient was seen by a physician on 08-NOV-2007 and decided to discontinue patient from study. At the time of the report the patient had not recovered from neutropenia (grade 3) (non-serious).

Other treatment medications administered for non-serious adverse events (NSAE) during the study were: sodium chloride (12-SEP-2007) for hyponatremia; sodium chloride (NaCl 0.9%) (+) potassium chloride (13-SEP-2007 to 15-SEP-2007, 15-SEP-2007 to 18-SEP-2007) for hyponatremia and hypokalemia; potassium bicarbonate (+) sodium phosphate, monobasic (PHOSPHATE-NOVARTIS) (13-SEP-2007 and

continuing) for hyponatremia; potassium (14-SEP-2007 and continuing) tablet and potassium phosphate (14-SEP-2007 to 15-SEP-2007) for hypokalemia; vitamin B1 (12-SEP-2007, 13-SEP-2007 to 17-DEC-2007) and folic acid (12-SEP-2007 to 17-DEC-2007) for use of alcohol; oxazepam (SERAX) (15-SEP-2007) for insomnia; diphenhydramine hydrochloride (BENEDRYL) (15-SEP-2007) for rash. acetaminophen (TYLENOL) (12-SEP-2007 to 30-OCT-2007) for fever; benzydamine hydrochloride (TANTUM) (07-OCT-2007 to 10-OCT-2007) for mucositis; gabapentin (NEURONTIN) (12-SEP-2007 to 13-SEP-2007, 14-SEP-2007 and continuing) for myalgia; aluminum hydroxide (+) magnesium hydroxide (MAALOX) (27-OCT-2007) and famotidine IV (07-OCT-2007 to 10-OCT-2007) for heartburn; codeine elixir (14-SEP-2007 to 18-SEP-2007), codeine phosphate (27-OCT-2007 to 30-OCT-2007), STATEX (27-OCT-2007 to 30-OCT-2007) and morphine syrup (07-OCT-2007 to 10-OCT-2007) for cough; acetaminophen (+) oxycodone hydrochloride (PERCOCET) for thoracic pain (26-OCT-2007); sodium chloride (NACL 0.9%) (07-OCT-2007 to 10-OCT-2007, 26-OCT-2007 to 30-OCT-2007) for hydration; oxygen inhalant (25-OCT-2007 to 26-OCT-2007) and salbutamol (26-OCT-2007 and continuing) for dyspnea and zopiclone for insomnia (28-SEP-2007 to 29-OCT-2007); enoxaparin sodium (LOVENOX) (27-OCT-2007) for prophylactic use for phlebitis; docusate sodium (27-OCT-2007) and sennosides (27-OCT-2007) for prophylaxis for constipation and magnesium hydroxide (28-OCT-2007) for prophylaxis of hypomagnesemia.

The reporting investigator felt that febrile neutropenia (1st 2nd and 3rd occurrences) was related to blinded study therapy, carboplatin and paclitaxel and pneumonia (grade 3) was not related to blinded study therapy.

Additional information is not expected.

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

### DIAGNOSTIC TEST

Tests	Date	Value	Unit	Normal Range
chest X-ray	10/25/2007			
Comment: See Narrative				
blood transfusion	10/29/2007			

### LABORATORY RESULTS

Tests	Date	Value	Unit	Normal Range
free serum calcium	09/09/2007	1	mmol/L	1.15 - 1.3
serum sodium	09/09/2007	128	mmol/L	135 - 145
WBC count	09/12/2007	1	10 <sup>9</sup> /L	4.5 - 11.3
absolute neutrophil count	09/12/2007	0.02	10 <sup>9</sup> /L	1.8 - 7.00
body temp	09/12/2007	38.2	C	
free serum calcium	09/12/2007	1	mmol/L	1.15 - 1.3
neutrophil count	09/12/2007	3	%	1.8 - 7
platelet count	09/12/2007	12,000		
platelet count	09/12/2007	16	x10 <sup>9</sup> /L	140 - 150
serum sodium	09/12/2007	123	mmol/L	135 - 145
stool occult blood	09/12/2007			
Comment: positive				
blood culture	09/12/2007			
Comment: E. coli				
WBC count	09/13/2007	1	10 <sup>9</sup> /L	4.5 - 11.3
absolute neutrophil count	09/13/2007	1	10 <sup>9</sup> /L	1.8 - 7
platelet count	09/13/2007	40	x10 <sup>9</sup> /L	140 - 150
serum phosphorus	09/13/2007	0.37	mmol/L	
WBC count	09/14/2007	1	10 <sup>9</sup> /L	4.5 - 11.3
neutrophil count	09/14/2007	17	%	40 - 70
plasma HCO <sub>3</sub>	09/14/2007	16	mmol/L	12 - 31
platelet count	09/14/2007	23	10 <sup>9</sup> /L	140 - 150
serum calcium	09/14/2007	1	mmol/L	2.1 - 2.55
serum phosphorus	09/14/2007	1	mmol/L	.74 - 1.2
serum potassium	09/14/2007	3.0	mmol/L	3.5 - 5
WBC count	09/15/2007	5	10 <sup>9</sup> /L	4.5 - 11.3
neutrophil count	09/15/2007	46	%	40 - 70
plasma HCO <sub>3</sub>	09/15/2007	18	mmol/L	12 - 31
platelet count	09/15/2007	28	10 <sup>9</sup> /L	140 - 150
serum calcium	09/15/2007	1	mmol/L	2.1 - 2.55
serum phosphorus	09/15/2007	1	mmol/L	.74 - 1.2
serum potassium	09/15/2007	3	mmol/L	3.5 - 5
absolute neutrophil count	09/17/2007	4.15	10 <sup>9</sup> /L	1.8 - 7.00
neutrophil count	09/17/2007	56	%	40 - 10
platelet count	09/17/2007	123,000		
WBC count	09/18/2007	1	10 <sup>9</sup> /L	4.5 - 11.3
neutrophil count	09/18/2007	53	%	40 - 70
plasma HCO <sub>3</sub>	09/18/2007	22	mmol/L	12 - 31
platelet count	09/18/2007	207	10 <sup>9</sup> /L	140 - 150

	Date	Value	Reference Range
serum calcium	09/18/2007	1 mmol/L	2.1 - 2.55
serum potassium	09/18/2007	1 mmol/L	3.5 - 5
absolute neutrophil count	10/??/2007	2.1 10 <sup>9</sup> /L	1.96 - 7.23
Comment: cycle 2			
absolute neutrophil count	10/05/2007	0.58 10 <sup>9</sup> /L	1.96 - 7.23
Comment: cycle 2, Day 8			
absolute neutrophil count	10/07/2007	0.11 10 <sup>9</sup> /L	1.8 - 7
body temp	10/07/2007	38.7 C	
hemoglobin	10/07/2007	119 g/L	135 - 175
platelet count	10/07/2007	52 x10 <sup>9</sup> /L	140 - 150
blood culture	10/07/2007		
Comment: hemoculture - negative			
absolute neutrophil count	10/08/2007	0.32 X 10 <sup>9</sup> /L	1.8 - 7
platelet count	10/08/2007	35 x10 <sup>9</sup> /L	140 - 150
absolute neutrophil count	10/10/2007	5.08 X 10 <sup>9</sup> /L	1.8 - 7
WBC count	10/25/2007	1.9	4.5 - 11.3
absolute neutrophil count	10/25/2007	0.1 X 10 <sup>9</sup> /L	1.8 - 7
body temp	10/25/2007	39.1 C	
platelet count	10/25/2007	53 x10 <sup>9</sup> /L	140 - 150
pulse oximetry	10/25/2007	91 %	
respiratory rate measurement	10/25/2007	28 /minute	
blood culture	10/25/2007	negative	
hemoglobin	10/29/2007	86 g/L	135 - 175
absolute neutrophil count	10/31/2007	4.56 x 10 <sup>9</sup> /L	
white blood cell differential	09/12/2008	negative	

#### 7. Other relevant history including preexisting medical conditions

Taste changed; Myalgia; Gout; Heartburn; Haemoptysis; Insomnia; Cataract

### 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) carboplatin Unk
- #2 infusion (form) carboplatin Unk
- #2 infusion (form) carboplatin Unk
- #3 infusion (form) paclitaxel 200 mg
- #3 infusion (form) paclitaxel 150 mg
- #3 infusion (form) paclitaxel 200 mg

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

- #1 Unk/Unk/PO
- #1 Unk/Unk/PO
- #2 685 mg/1X/IV
- #2 560 mg/1X/IV
- #2 585 mg/1X/IV
- #3 388 mg/1X/IV
- #3 290 mg/1X/IV
- #3 294 mg/1X/IV

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

- #1 09/28/2007 - 10/09/2007
- #1 10/18/2007 - 10/25/2007
- #2 09/04/2007 - 09/04/2007
- #2 09/28/2007 - 09/28/2007
- #2 10/18/2007 - 10/18/2007
- #3 09/04/2007 - 09/04/2007
- #3 09/28/2007 - 09/28/2007
- #3 10/18/2007 - 10/18/2007

#### 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)

[therapy unspecified]	09/12/2007 - 10/12/2007
codeine	08/31/2007 - 12/17/2007
dexamethasone	10/17/2007 - 10/19/2007
diphenhydramine hydrochloride	09/04/2007 - 09/04/2007
diphenhydramine hydrochloride	09/28/2007 - 09/28/2007
diphenhydramine hydrochloride	10/18/2007 - 10/18/2007
docusate sodium	10/27/2007 - 10/28/2007
dolasetron mesylate	09/04/2007 - 09/04/2007
dolasetron mesylate	09/28/2007 - 09/28/2007
dolasetron mesylate	10/18/2007 - 10/18/2007
dolasetron mesylate	10/18/2007 - 10/18/2007
famotidine	09/04/2007 - 09/04/2007
famotidine	09/28/2007 - 09/28/2007
famotidine	10/18/2007 - 10/18/2007
ibuprofen	01/??/2007 - 12/17/2007
indomethacin	01/??/2007 - Cont
magnesium hydroxide	10/28/2007 - 10/30/2007
magnesium sulfate	09/12/2007 - 09/12/2007
sennosides	10/27/2007 - 10/28/2007