

# 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 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

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)	4. Date of this report (mm/dd/yyyy)
09/11/2007	03/19/2009

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; 3/5/2009

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, hemorrhage pulmonary upper respiratory of the nose, 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

(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; Biopsy bronchus; Bronchoscopy; Computerised tomogram abdomen; Brain computerised tomography  
CONCURRENT CONDITIONS: Alcohol use; Anxiety; Cough; Cramps calf; Fatigue; Haemorrhage nasal; Deafness; Umbilical hernia; Taste changed; Pain;

(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
--	---

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"/>
--	---

6. Lot # # 1 # 2	7. Exp. Date # 1 # 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 type="checkbox"/> <input type="checkbox"/>
------------------------	----------------------------	--

9. NDC # or Unique ID Unknown
----------------------------------

10. Concomitant medical products and therapy dates (excluded treatment of event) LOVENOX 10/27/2007-10/30/2007 codeine 08/31/2007-12/17/2007
--

(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
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:	
4. Date received by manufacturer (mm/dd/yyyy) 03/12/2009	5. (A)NDA # IND # 58915 STN # PMA/ 510(k) # Combination <input type="checkbox"/> Yes Product <input type="checkbox"/> Yes Pre-1938 <input type="checkbox"/> Yes OTC product <input type="checkbox"/> Yes
6. If IND, protocol # 0560019	9. Mfr. report number WAES 0709USA02327

8. Adverse event term(s) BACTERAEemia; 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
--	---------------	--

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**

bronchial biopsy and bronchoscopy who on 31-AUG-2007 was 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, dolasetron mesylate and zopiclone.

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 bacteremia (grade 3). The patient's absolute neutrophil count (ANC) was  $0.02 \times 10^9/L$ ; platelet count 12,000. Eastern Cooperative Oncology Group (ECOG) rating was equivalent to 3. On 12-SEP-2007 the patient was hospitalized for bacteremia (grade 3). On 12-SEP-2007 hemoculture was positive and blood culture showed escheria coli (abnormal). On 12-SEP-2007 the patient was treated with IV antibiotics cefepime (MAXEPIME) and filgrastim (NEUPOGEN) for febrile neutropenia. The patient received 5 units of platelets for thrombocytopenia. On 13-SEP-2007 the patient was evaluated by a microbiologist. The patient was treated with metronidazole (FLAGYL) for bacteremia E. coli. 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). 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, (absolute neutrophil count) ANC was  $4.15 \times 10^9/L$  and platelet count was 123,000. On 17-SEP-2007 the patient recovered from bacteremia (grade 3). On 18-SEP-2007, the patient was discharged from the hospital. Discharge diagnosis was 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 started 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 07-OCT-2007 (Cycle 2, day 10) the patient presented to an emergency room with fever (38.7 degrees celcius), 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 developed neutropenia (grade 3) and was hospitalized. On 07-OCT-2007 chest x-ray revealed no particularity and urinalysis lab was normal and hemoculture test was negative. Blinded study therapy was interrupted. The patient was treated with cefepime (MAXEPIME) 2 gm, IV every 8 hours and filgrastim (NEUPOGEN) for febrile neutropenia. On 08-OCT-2007 the patient's ANC was  $0.32 \times 10^9/L$ . On 10-OCT-2007 the patient's ANC was  $5.08 \times 10^9/L$ . On 11-OCT-2007 the patient recovered from neutropenia (grade 4). 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) 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% O2 upon auscultation, the patient had some rale. On 25-OCT-2007 the patient developed pneumonia (grade 3) and was hospitalized. On 25-OCT-2007, the patient completed cycle 3 study therapy and received IV antibiotics cefepime (MAXEPIME) 2000 mg TID for febrile neutropenia and filgrastim (NEUPOGEN) injection "escalate" at 400 mg subcutaneously for febrile neutropenia (patient took filgrastim (NEUPOGEN) 300mg SC since 18-OCT-2007). The patient was also treated with albuterol sulfate (VENTOLIN) and ipratropium bromide (ATROVENT). On 26-OCT-2007 pulmonary x-ray was performed and the result was pulmonary surinfection. 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  $4.56 \times 10^9/L$ . The patient had no fever, dyspnea or asthenia. On 31-OCT-2007, the patient recovered from pneumonia (grade 3). Discharge diagnoses was pulmonary surinfection and febrile neutropenia.

The patient was to be evaluated for Cycle 4 on 08-NOV-2007 in an outpatient clinic. The patient was seen by a physician on 08-NOV-2007 and the physician decided to discontinue patient from study due to recurrent episodes of febrile neutropenia.

Other treatment medications administered for non-serious adverse events (NSAE) during the study were: sodium chloride for hyponatremia; sodium chloride (NACL 0.9%) (+) potassium chloride for hyponatremia and hypokalemia; potassium bicarbonate (+) sodium phosphate, monobasic (PHOSPHATE-NOVARTIS) for hyponatremia; potassium tablet and potassium phosphate for hypokalemia; vitamin B1 and folic acid for use of alcohol; oxazepam (SERAX) for insomnia; diphenhydramine

hydrochloride (BENEDRYL) for rash; acetaminophen (TYLENOL) for fever; benzydamine hydrochloride (TANTUM) for mucositis; gabapentin (NEURONTIN) for myalgia; aluminum hydroxide (+) magnesium hydroxide (MAALOX), pantoprazole sodium (PANTOLOC) and famotidine IV for heartburn; codeine elixir codeine phosphate (STATEX) and morphine syrup for cough; acetaminophen (+) oxycodone hydrochloride (PERCOCET) for thoracic pain; sodium chloride (NACL 0.9%) for hydration; oxygen inhalant and salbutamol for dyspnea; enoxaparin sodium (LOVENOX) for prophylactic use for phlebitis; docusate sodium, magnesium sulfate and sennosides for prophylaxis for constipation; magnesium hydroxide for prophylaxis of hypomagnesemia; hydrocortisone (+) diphenhydramine (+) nystatin (+) water (MAGIC MOUTHWASH) for prevention of mucositis;

The reporting investigator felt that bacteremia (grade 3), neutropenia (grade 4) and pneumonia (grade 3) was related to blinded study therapy, carboplatin and paclitaxel.

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		
X-ray	10/26/2008		
Comment: Pulmonary X-ray revealed pulmonary surinfection			

##### 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{3}	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{3}	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{3}	09/18/2007	22 mmol/L	12 - 31
platelet count	09/18/2007	207 10 <sup>9</sup> /L	140 - 150
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 $10^9/L$	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 $\times 10^9/L$	140 - 150
blood culture	10/07/2007		
Comment: hemoculture - negative			
absolute neutrophil count	10/08/2007	0.32 $\times 10^9/L$	1.8 - 7
platelet count	10/08/2007	35 $\times 10^9/L$	140 - 150
absolute neutrophil count	10/10/2007	5.08 $\times 10^9/L$	1.8 - 7
WBC count	10/25/2007	1.9	4.5 - 11.3
absolute neutrophil count	10/25/2007	0.1 $\times 10^9/L$	1.8 - 7
body temp	10/25/2007	39.1 C	
platelet count	10/25/2007	53 $\times 10^9/L$	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 $\times 10^9/L$	
white blood cell differential	09/12/2008	negative	

## 7. Other relevant history including preexisting medical conditions

Gout; Haemoptysis; Insomnia; Cataract

## C. Suspect medication(s)

## 1. Name (Give labeled strength &amp; 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 &amp; 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)

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
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
zopiclone	09/28/2007 - 10/29/2007