

# 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 0805USA04558
UF/Dist report #	
	FDA Use Onl

A. Patient information			
1. Patient identifier Confidential AN 64521 in confidence	2. Age at time of event: or 78 years Date of Birth: 11/17/1929	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight 136 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 checked="" type="checkbox"/> Death 08/26/2008 (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) 05/15/2008	4. Date of this report (mm/dd/yyyy) 03/20/2009
5. Describe event or problem	
This is in follow-up to report(s) previously submitted on 5/28/2008; 5/30/2008; 6/6/2008; 6/27/2008; 7/8/2008; 7/30/2008; 8/13/2008; 8/25/2008; 8/26/2008; 8/29/2008; 9/5/2008; 9/19/2008; 9/25/2008; 10/3/2008; 10/31/2008; 11/11/2008; 11/14/2008; 11/17/2008; 3/10/2009	

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 78 year old white female with sulfonamide allergy, hypoalbuminemia, lymphopenia, anemia, fatigue, fever, nausea, pain, thoracic pain, anorexia, cough, dyspnea, lost weight, pneumonia and hypertension and history of appendectomy, cholecystectomy, hysterectomy and salpingo-oophorectomy who on 10-MAY-2008 was randomized to a study, title as

(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: Appendectomy; Cholecystectomy; Hysterectomy; Salpingo-oophorectomy CONCURRENT CONDITIONS: Sulfonamide allergy; Hypertension; Fatigue; Anorexia; Cough; Dyspnoea; Weight decreased; Pain; Lymphopenia; Anaemia; Hypoalbuminaemia; Fever; Nausea; Chest pain; Pneumonia

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 05/10/2008 - 05/16/2008
# 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"/>
# 2	# 2 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>

6. Lot #	7. Exp. Date	8. Event reappeared after reintroduction.
# 1	# 1	yes no N/A unk
# 2	# 2	# 1 <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>
# 2	# 2	# 2 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>

9. NDC # or Unique ID	10. Concomitant medical products and therapy dates (excluded treatment of event)
Unknown	DYNASTAT 05/09/2008-05/11/2008 amikacin 05/14/2008-05/17/2008
(Continued on Additional Page)	

## G. All manufacturers

1. Contact office - name/address	2. Phone Number
Merck Human Health Division Merck & Co., Inc. P.O. Box 4 West Point, Pa. 19486-0004 Attn: World Wide Product Safety	(215) 652-8071
4. Date received by manufacturer (mm/dd/yyyy) 03/12/2009	3. Report source. (check all that apply)
6. If IND, protocol # 0560117	<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 # 58915	7. Type of report
IND # 58915	<input type="checkbox"/> 5-day <input type="checkbox"/> 30-day
STN #	<input type="checkbox"/> 7-day <input type="checkbox"/> Periodic
PMA/	<input type="checkbox"/> 10-day <input type="checkbox"/> Initial
510(k) #	<input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up# 19
Combination Product Pre-1938 OTC product	<input type="checkbox"/> Yes <input type="checkbox"/> Yes <input type="checkbox"/> Yes
9. Mfr. report number	8. Adverse event term(s)
WAES 0805USA04558	ACUTE RESPIRATORY DISTRESS SYNDROME; ATRIAL FIBRILLATION; EMBOLISM; PNEUMONIA; 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 stated above.**

On 10-MAY-2008, the patient was placed on blinded study therapy of 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 (diagnosed 30-APR-2008, date of staging 08-MAY-2008 T4/N2/M1/stage IV).

Concomitant study therapy on included paclitaxel, 200 mg/m<sup>2</sup> and carboplatin [AUC 6], administered intravenous (IV) on day 1 of each treatment cycle). Other concomitant therapy included ceftazidime, parecoxib sodium (DYNASTAT), phenyltoloxamine citrate, dexamethasone (manufacturer unknown), ondansetron, ranitidine, furosemide, omeprazole, amlodipine, captopril, amikacin, sodium chloride, clotrimazole topica, potassium chloride, chlorphenamine maleate and

On 15-MAY-2008 the patient came to the care intensity unit (CIU) with dyspnea, hypoxia, headache and an oxygen saturation of 85% with venturi mask 0.50 during oxygen saturation (oxygen mask with RETROVIR bag) at 10 liters. On 15-MAY-2008 (Cycle 1, Day 6) the patient was hospitalized with acute respiratory distress syndrome (grade 3). On 16-MAY-2008 (Cycle 1, Day 7) the patient was hospitalized in care intensity unit (CIU) due to atrial fibrillation (grade 3) with a "FC" (functional capacity test) at 160/min. The patient was diagnosed with adult respiratory distress syndrome (grade 1) which improved with oxygenotherapy (15-MAY-2008 to 05-JUN-2008) as needed (oxygen saturation 90% with venturi mask 0.50). At 17:40 she also received mechanical ventilation until 20-MAY-2008. On 16-MAY-2008 an electrocardiogram showed sinus rhythm and a radiography of the thorax showed inflammatory infiltrate and opacity right hemothorax. On 16-MAY-2008 the patient was treated with amiodarone (16-MAY-2008 to 17-MAY-2008) IV for heart arrhythmia. During oxygen administration the patient had a pneumonia for the two days prior to the initiation of this event and that the patient had taken ceftriaxone (03-MAY-2008 to 20-MAY-2008). She again had an oxygen saturation 88% and receipt of the oxygen mask with a reservoir bag at 15 liters. ARDS grade 3 worsened to grade 4. On 16-MAY-2008 the patient was treated with enoxaparin sodium (CLEXANE) (16-MAY-2008 to 20-MAY-2008) for atrial fibrillation (grade 3). On 17-MAY-2008 the patient was treated with vancomycin (17-MAY-2008 to 02-JUN-2008) IV for pneumonia. On 18-MAY-2008 the patient was treated with filgrastim (18-MAY-2008 to 23-MAY-2008) for neutropenia and leukopenia, imipenem for the treatment of pneumonia (18-MAY-2008 to 02-JUN-2008) and dexamethasone (18-MAY-2008 to 25-MAY-2008) (manufacturer unknown) for respiratory distress. Laboratory studies indicated that AGA: ph was 7.197, partial pressure of carbon dioxide in the artery (PCO<sub>2</sub>) was 32.8, partial pressure of oxygen in the artery (PO<sub>2</sub>) was 87.4, bicarbonate (HCO<sub>3</sub>) was 12.4 (also reported as 12mmol/l), TCO<sub>2</sub> was 13.4 (also reported as 13), oxygen saturation was 94.7 (also reported as 94) (MR 10 liters). ARDS grade 4 improved to grade 3. Subsequently, the patient recovered from atrial fibrillation (grade 3).

On 21-MAY-2008, the patient's oxygen saturation was 99%. On 21-MAY-2008 the patient was treated with amiodarone IV for heart arrhythmia. On 21-MAY-2008 the patient's mechanical ventilation tube was removed. It was reported that the patient was discharged on 23-MAY-2008 with a binasal cannula and was in stable condition. On 23-MAY-2008 the patient was treated with amiodarone tablets (23-MAY-2008 to 04-JUN-2008) for heart arrhythmia. On 26-MAY-2008 therapy with dexamethasone (26-MAY-2008 to 08-JUN-2008) (manufacturer unknown) IV was reduced for treatment of respiratory distress. Patient had no further atrial fibrillation. On 29-MAY-2008, (Cycle 1, Day 20) the patient entered the care intensity unit (CIU) with hypoxia (oxygen saturation of 87%). The patient received morphine (29-MAY-2008 to 30-MAY-2008) 9 mg daily IV and non invasive mechanical ventilation. On 29-MAY-2008 (Cycle 1, Day 20) a diagnosis of thromboembolism of the lung (grade 4) was confirmed by angioTEM. The patient was treated with enoxaparin sodium (CLEXANE) (30-MAY-2008 to 22-JUN-2008) for lung thromboembolism (grade 4). The patient started therapy with oxygen therapy and the patient saturation level was improving (SAT O<sub>2</sub> 96%). It was reported that the laboratory quantity of fibrin-D-dimer was 15. The patient recovered from lung thromboembolism (grade 4) on 30-MAY-2008. On 01-JUN-2008 the patient was treated with furosemide injection for liquid retention. On 02-JUN-2008 the patient was discharged. Discharge diagnosis was adult respiratory distress syndrome. Paroxysmal atrial fibrillation controlled and lung thromboembolism were controlled by anticoagulation. On 05-JUN-2008 the patient was treated with amiodarone tablets for heart arrhythmia and continued. On 09-JUN-2008 the patient recovered from adult respiratory distress syndrome (grade 1).

On 11-JUN-2008, the patient was placed on cycle 2 blinded treatment of either vorinostat 300 mg or placebo, carboplatin AUC 5 and paclitaxel 175 mg per millileter. On 18-JUN-2008 (Cycle 2, Day 8) the patient's laboratory data revealed neutropenia (grade 3). Neutrophil count was 690 X 10<sup>3</sup>/uL (grade 3) and the patient was hospitalized. It was reported that the patient was asymptomatic and did not have a fever. On 22-JUN-2008 the patient presented with asthenia and poor general condition. The study therapy was interrupted and the patient was started on antibiotics and filgrastim. On 22-JUN-2008 the patient had a prolongation of hospitalization due to the neutropenia (grade 3). The patient started on "filgrastim" 300 mcg SC stat until 23-JUN-2008. The patient continued on antibiotics. Patient had no fever. On 23-JUN-2008, labs showed no neutropenia (results not reported) and the patient recovered from neutropenia (grade 3). On 24-JUN-2008, (Cycle

2, Day 14) the patient had ARDS (decreased oxygen saturation of 84%). She developed pneumonia (grade 3). It was reported that the patient clinically worsened with a suspected infection but improved with supportive therapy of 3 liters of oxygen and her oxygen saturation increased to 92%. The patient improved with support therapy patient had not a fever. On 24-JUN-2008 the patient was treated with levofloxacin (24-JUN-2008 to 29-JUN-2008) for infection. On 24-JUN-2008 chest X-ray showed opacity alveolus interstitial and pleural effusion right. On 25-JUN-2008 the patient was placed on meropenem (25-JUN-2008 to 09-JUL-2008) for infection. On 25-JUN-2008 blood neutrophil count was  $4.32 \times 10^3/\mu\text{L}$ . On 25-JUN-2008 and 26-JUN-2008 the patient was treated with a one time dose of packed red blood cells. Chest x-ray on 27-JUN-2008 showed opacity alveolus interstitial with consolidation areas. On 28-JUN-2008 the patient was treated with methylprednisone (28-JUN-2008 to 02-JUL-2008) for pneumonia (grade 3), ipratropium bromide (ATROVENT) (28-JUN-2008 to 29-JUN-2008) for respiratory distress (grade 3) and vancomycin (28-JUN-2008 to 08-JUL-2008) for respiratory infection. The patient was also treated with enoxaparin sodium (CLEXANE) (28-JUN-2008 to 17-JUL-2008) as an anticoagulant. On 01-JUL-2008, the patient recovered with sequelae from pneumonia (grade 3) (O2 saturation 95%, FI O2 0.21). Patient had no fever. Sputum culture was not obtained. The patient did not have myocardial infarction. She had an hypertension as risk factor for myocardial infarction.

On 16-JUL-2008 the patient began cycle 3 of study therapy. Blinded study therapy was reduced to vorinostat 200mg or placebo. On 19-AUG-2008, the patient was discharged from the hospital and the discharge diagnosis was distress respiratory. On 26-AUG-2008 (posttherapy day 28) the patient died of pneumonia (grade 5) in another institution and the signs and symptoms were not known. No autopsy was performed.

The patient was treated with acetaminophen (+) diclofenac, morphine and codeine phosphate (+) phenyltoloxamine citrate for pain; acyclovir for herpes virus infection; amikacin for pneumonia; amitriptyline hydrochloride and pregabalin (LYRICA) for neuralgia; clotrimazole, fluconazole and econazol for mycosis; dexamethasone INJ for premedication; erlotinib hydrochloride for lung neoplasm malignant; filgrastim for neutropenia; furosemide pulmonary congestion and fluid retention; glycerin for constipation; lactulose for constipation; omeprazole for gastric prophylaxis; potassium chloride for fluid retention; sodium chloride for fluid replacement.

The reporting investigator felt atrial fibrillation (grade 3) was related to blinded therapy, but was not related to paclitaxel, or carboplatin, adult respiratory distress syndrome (grade 3) was not related to blinded therapy, carboplatin although ARDS (onset 15-MAY-2008 was ruled out) and paclitaxel, and lung thromboembolism (grade 4) was not related to blinded therapy, carboplatin or paclitaxel. Neutropenia (grade 3) was related to blinded therapy, carboplatin, and paclitaxel. The reporting investigator felt that pneumonia (grade 5) and pneumonia (grade 3) were not related to blinded study therapy, carboplatin and paclitaxel.

Additional information is not expected.

#### 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: sinusal rhythm	05/16/2008		
diagnostic laboratory test	05/16/2008	13 mmol/l	21 - 25
diagnostic radiology Comment: inflammatory infiltrate and opacity right hemothorax	05/16/2008		
diagnostic laboratory test Comment: quantity of fibrin D dimer was 15	05/30/2008		
chest X-ray Comment: see narrative	06/24/2008		
chest X-ray Comment: see narrative	06/27/2008		

##### LABORATORY RESULTS

<u>Tests</u>	<u>Date</u>	<u>Value</u> <u>Unit</u>	<u>Normal Range</u>
pulse oximetry	05/15/2008	85 %	
pulse oximetry	05/15/2008	88 %	
arterial blood HCO{3}	05/16/2008	12 mmol/l	20 - 24
arterial blood PO{2}	05/16/2008	87.4	
arterial blood pCO{2}	05/16/2008	32.8	
pulse oximetry	05/16/2008	94 %	95 - 98

total serum carbon dioxide	05/16/2008	13.4 mmol/l	21 - 25
urine pH	05/16/2008	7.197	
pulse oximetry	05/21/2008	99 %	
pulse oximetry	05/29/2008	87 %	
pulse oximetry	05/29/2008	96 %	
neutrophil count	06/18/2008	690 X 10 <sup>3</sup> /uL	1.8 - 7.7
pulse oximetry	06/24/2008	84 %	
pulse oximetry	06/24/2008	92 %	
neutrophil count	06/25/2008	4.32 10 <sup>3</sup> /uL	
arterial blood O2 saturation	07/04/2008	95%	

### 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 Unk  
 #3 infusion (form) paclitaxel Unk  
 #3 infusion (form) paclitaxel Unk

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

#1 Unk/Unk/PO  
 #1 Unk/Unk/PO  
 #2 539 mg/1X/IV  
 #2 455 mg/1X/IV  
 #2 377 mg/1X/IV  
 #3 324.6 mg/1X/IV  
 #3 270 mg/1X/IV  
 #3 227 mg/1X/IV

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

#1 06/11/2008 - 06/21/2008  
 #1 07/16/2008 - 07/29/2008  
 #2 05/14/2008 - 05/14/2008  
 #2 06/11/2008 - 06/11/2008  
 #2 07/16/2008 - 07/16/2008  
 #3 05/14/2008 - 05/14/2008  
 #3 06/11/2008 - 06/11/2008  
 #3 07/16/2008 - 07/16/2008

#### 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  
#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)

amlodipine	01/01/2007 - Cont
captopril	05/02/2008 - 05/14/2008
ceftazidime	05/13/2008 - 05/17/2008
ceftriaxone sodium	05/03/2008 - 05/10/2008
chlorpheniramine maleate	05/14/2008 - 05/14/2008
clotrimazole	06/18/2008 - 06/24/2008
codeine phosphate (+) phenyltolol	05/12/2008 - 05/16/2008
dexamethasone	05/14/2008 - 05/14/2008
furosemide	05/26/2008 - 05/26/2008
glycerin	05/27/2008 - 05/27/2008
omeprazole	05/19/2008 - 06/01/2008
omeprazole	06/02/2008 - Cont
ondansetron	05/14/2008 - 05/14/2008
potassium chloride	05/16/2008 - 05/17/2008
ranitidine	05/09/2008 - 05/18/2008
sodium chloride	05/16/2008 - 05/17/2008