

# 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 0805USA03080
UF/Dist report #	
	FDA Use Onl

<b>A. Patient information</b>			
1. Patient identifier Confidential AN 60007 in confidence	2. Age at time of event: or 65 years Date of Birth: 06/13/1942	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight 112 lbs
<b>B. Adverse event or product problem</b>			
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 06/27/2008 (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)	05/10/2008	4. Date of this report (mm/dd/yyyy)	02/25/2009
5. Describe event or problem			
This is in follow-up to report(s) previously submitted on 5/20/2008; 5/29/2008; 6/9/2008; 6/17/2008; 6/27/2008; 7/11/2008; 7/23/2008; 7/31/2008; 8/25/2008; 8/29/2008; 9/4/2008; 9/9/2008; 9/19/2008; 9/23/2008; 12/2/2008; 2/5/2009; 2/12/2009			
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 65 year old multi-racial female on chemotherapy and fluid replacement with chest pain, cough, urinary infection, dyspnoea, fatigue, fever, lymphopenia, pleural effusion and weight decreased on 02-APR-2008 was placed on blinded therapy of either vorinostat, capsule, 400 mg, or placebo once a day for the treatment of non-small cell lung cancer (04-MAR-2008, current staging 18-MAR-2008, T2/N1/M1/ stage IV).			
(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.)			
CONCURRENT CONDITIONS: Chest pain; Cough; Dyspnoea; Fatigue; Pleural effusion; Weight decreased; Fluid replacement; Gastritis prophylaxis; Urinary tract infection; Fever; Lymphopenia; Nausea prophylaxis			

<b>C. Suspect medication(s)</b>			
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/DAILY/PO		# 1 04/02/2008 - 04/15/2008	
# 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)			
[therapy unspecified] Unk -Unk			
chlorpheniramine maleate 04/29/2008-04/29/2008			
(Continued on Additional Page)			

<b>G. All manufacturers</b>	
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)	5. (A)NDA #
02/19/2009	IND # 58915
6. If IND, protocol #	STN #
0560117	PMA/510(k) #
7. Type of report	9. Mfr. report number
<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# 17	WAES 0805USA03080
8. Adverse event term(s)	
NEUTROPENIA; ACUTE RESPIRATORY DISTRESS SYNDROME; PNEUMOTHORAX	

<b>E. Initial reporter</b>		
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

Concomitant study therapy included paclitaxel, 200 mg/m<sup>2</sup> and carboplatin administered intravenous (IV) on day 1 of each treatment cycle. Other concomitant medication included ketoprofen, dexamethasone, ondansetron, ranitidine, chlorpheniramine maleate, prednisone, oral rehydration therapy, ciprofloxacin and "filgastrim".

It was also reported that on 11-APR-2008 the patient experienced diarrhea (non-serious). On 14-APR-2008 the patient experienced nausea, hyponatremia, hypokalemia, hyperbilirubinemia, increased alkaline phosphatase, thrombocytopenia, lymphopenia, neutropenia, leukopenia and a urinary infection (all non-serious). The patient's dose of blinded study therapy was reduced to 300 mg daily on 29-APR-2008 (reason not reported). On 30-APR-2008, the patient experienced constipation (non-serious). On 06-MAY-2008, the patient experienced oral candidiasis, thrombocytopenia, leukopenia, and hyponatremia, (all non-serious). On 10-MAY-2008 at 09:05, the patient experienced neutropenia (grade 4), neutrophils were  $0.5 \times 10^3/\text{ul}$  (on admission) and was hospitalized and also experienced leukopenia (non-serious) leukocytes were  $2 \times 10^3/\text{ul}$  and thrombocytopenia (non-serious). She had malaise without fever. "Her vital signs were 36.5 C her blood pressure was 120/80, 80/min, 20/min". Urine analysis showed leukocyturia was  $> 20$  cells/field. Other laboratory examinations revealed a platelet count of 8 and a hemoglobin of 10 g/dl. It was reported that the patient was doing well without other complications and was receiving prophylactic antibiotics. In the hospital the patient received ranitidine, ceftriaxone, amikacin sulfate (AMIKACINA), and filgrastim.

On 11-MAY-2008 the patient was not neutropenic and therefore was discharged in good condition. Laboratory examinations were as follows: hemoglobin of 10 g/dl, leukocytes of  $4 \times 10^3/\text{ul}$ , neutrophil count of  $2.2 \times 10^3/\text{ul}$ , and platelet count of  $8 \times 10^3/\text{ul}$ . At home, the patient received ("MAXICEF") for 7 days and ranitidine. Discharge diagnosis was thrombocytopenia (grade 4) anemia (grade 2) and no neutropenia. On 11-MAY-2008 patient received the last dose of study therapy. In follow up information it was reported that the physician interrupted the study medication due to neutropenia (grade 4) but the patient took one doses by misunderstanding until 11-MAY-2008. The event neutropenia (grade 4) resolved on 11-MAY-2008 (also reported as 10-MAY-2008).

On 13-MAY-2008, the patient had a scheduled visit for cycle 2 day 15. She had a volume increase of the left leg and dyspnea. The patient was hospitalized at 20:00 for adult respiratory distress syndrome (grade 3), hypoxia (grade 3) and dyspnea (grade 3). Vital signs were 36.5 deg C, blood pressure 120/80, 110/min, 24/min" and oxygen saturation of 84%. It was reported that the patient was still in evaluation. She received 3 liter of oxygen therapy one time dose for respiratory shortness and continued oxygen therapy. Her oxygen saturation was 95% with 4 liters oxygen therapy by nasal cannula. She had complete deep vein thrombosis (DVT) (non-serious) in the left leg (grade 2) and partial DVT (non-serious) in the right leg revealed in a ECO doppler. It was reported that the patient was being evaluated for possible pulmonary thromboembolism and was diagnosed in follow up with an onset of 13-MAY-2008. The patient also received treatment with enoxaparin sodium (CLEXANE (enoxaparin sodium)) 40 mg SC twice a day, filgastrim, enoxaparin sodium, lipebim, glycerine suppository and dexamethasone. In follow up it was reported that the patient did not require bronchoscopy because pleural effusion was noted in the chest x-ray.

The patient was treated with lactulose and glycerin for constipation. On 15-MAY-2008 the patient developed shortness of breath. On 17-MAY-2008 chest x-ray showed pleural effusion. In follow up report it was reported that patient had pleural effusion and her pleural biopsy was positive. The patient was in evaluation. The patient was treated with a chest drainage tube which improved the pneumothorax. Thoracentesis on 22-MAY-2008 was done and evacuated 4200 cc dark brown fluid. It was reported that the patient was still in respiratory distress oxygen saturation decreased with movement and effort. On 19-MAY-2008, the patient had a gammagraphy which was moderate probably due to lung thromboembolism. The patient had shortness of breath and on 25-MAY-2008 a chest drainage tube was placed for pneumothorax (25-MAY-2008 to 01-JUN-2008). On 25-MAY-2008 a chest x-ray showed a massive pneumothorax occurred following an injury to the chest wall by thoracentesis on 22-MAY-2008. On 26-MAY-2008 the chest x-ray showed improvement in pneumothorax.

On 27-MAY-2008 fluid was exudative for cytology laboratory test and the result showed the fluid was + malignant cells (abnorml). On 27-May-2008 the patient received ciprofloxacin 500 mg twice a day for respiratory infection. On 31-MAY-2008 the patient was placed on fluconazole 150 mg twice a day for oral candidiasis. On 01-JUN-2008 the patient recovered from the pneumothorax. On 05-JUN-2008 patient was treated with dexamethasone 4 mg daily IV for dyspnea and respiratory distress. On 07-JUN-2008 the patient was placed on furosemide 20 mg IV one time dose for the treatment of edema. On 09-JUN-2008 the patient discontinued from the study with a completed status. It was also reported that the patient experienced the following non-serious events: fatigue, blurred vision, hypoalbuminemia, alopecia, thrombocytopenia, hyponatremia, pleural effusion, respiratory infection and oral candidiasis. On 11-JUN-2008 patient was discharged.

Discharge diagnosis was respiratory distress (grade 3), thrombocytopenia (grade 4), anemia (grade 2), no neutropenia and pneumothorax resolved.

Action taken regarding study medication for neutropenia (grade 4) was discontinued, adult respiratory distress syndrome (grade 5) and pneumothorax (grade 2) was none.

It was reported that she died at home on 27-JUN-2008 due to respiratory distress and cardiac arrest. Her family reported the death of patient by telephone. Patient's mother said that she presented major respiratory distress and respiratory distress was handled with oxygen therapy at home.

Patient had an autopsy done and in the death certificate adult respiratory distress syndrome was reported as causality.

The reporting investigator felt that neutropenia (grade 4) was related to blinded therapy, carboplatin and paclitaxel. Adult respiratory distress syndrome (grade 5), pneumothorax (grade 2) were not related to blinded study therapy, carboplatin or 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>
Doppler echocardiography Comment: complete DVT left leg/partial DVT right leg	05/13/2008			
chest X-ray Comment: Pleural effusion	05/17/2008			
diagnostic laboratory test Comment: gammagraphy see narrative	05/19/2008			
thoracentesis Comment: was evacuated 4200 cc of dark brown fluid	05/22/2008			
chest X-ray Comment: massive pneumothorax	05/25/2008			
chest tube placement Comment: Pneumothorax	05/25/2008			
chest X-ray Comment: improve pneumothorax	05/26/2008			
diagnostic pathological examination Comment: Cytology of pleural effusion test showed + malignant cells (abnormal)	05/27/2008			
biopsy Comment: Pleural biopsy + ve before study therapy				

##### LABORATORY RESULTS

<u>Tests</u>	<u>Date</u>	<u>Value</u>	<u>Unit</u>	<u>Normal Range</u>
neutrophil count	05/09/2008	20	cells per	0 - 5
WBC count	05/10/2008	2 x 10 <sup>3</sup>	/ul	4.5 - 11
hemoglobin	05/10/2008	10	g/dl	12 - 16
neutrophil count Comment: On admission	05/10/2008	0.5 x 10 <sup>3</sup>	/ul	1.8 - 7.7
platelet count	05/10/2008	8 x 10 <sup>3</sup>	/ul	150 - 350
vital sign Comment: see narrative	05/10/2008			
WBC count	05/11/2008	4 x 10 <sup>3</sup>	/ul	4.5 - 11
body temp	05/11/2008	36.5	C	
hemoglobin	05/11/2008	10	g/dl	12 - 16
neutrophil count	05/11/2008	2 x 10 <sup>3</sup>	/ul	1.8 - 7.7
neutrophil count	05/11/2008	2.2 x 10 <sup>3</sup>	/ul	
platelet count	05/11/2008	8 x 10 <sup>3</sup>	/ul	150 - 350
pulse oximetry	05/13/2008	84	%	
vital sign Comment: see narrative	05/13/2008			

#### C. Suspect medication(s)

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

- #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/DAILY/PO  
 #2 586.32 mg/1X/Unk  
 #2 588.24 mg/1X/Unk  
 #3 298 mg/1X/Unk  
 #3 291.8 mg/1X/Unk

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

#1 04/29/2008 - 05/11/2008  
 #2 04/07/2008 - 04/07/2008  
 #2 04/29/2008 - 04/29/2008  
 #3 04/07/2008 - 04/07/2008  
 #3 04/29/2008 - 04/29/2008

## 4. Diagnosis for use (indication)

#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	
#2				X
#2				X
#3				X
#3				X

## 6. Lot # (if known)

#1  
 #2  
 #2  
 #3  
 #3

## 7. Exp date (if known)

#1  
 #2  
 #2  
 #3  
 #3

## 8. Event reappeared after reintroduction

	YES	NO	N/A	UNK
#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)

ciprofloxacin	04/14/2008 - 04/19/2008
dexamethasone	04/07/2008 - 04/07/2008
dexamethasone	04/29/2008 - 04/29/2008
dimenhydrinate	04/14/2008 - 04/19/2008
ketoprofen	03/31/2008 - Cont
ondansetron	04/07/2008 - 04/07/2008
ondansetron	04/29/2008 - 04/29/2008
ondansetron	04/29/2008 - 05/02/2008
prednisone	04/29/2008 - 05/04/2008
ranitidine	04/29/2008 - 04/29/2008
ranitidine	04/29/2008 - 05/06/2008
ranitidine	05/10/2008 - 05/11/2008
ranitidine	05/11/2008 - 05/13/2008
ranitidine	05/13/2008 - 06/08/2008