

Merck Human Health Division

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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 0802USA00123
UF/Dist report #	
	FDA Use On

A. Patient information			
1. Patient identifier Confidential AN 63505 in confidence	2. Age at time of event: or 60 years Date of Birth: 02/15/1947	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 134 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 02/03/2008 (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 checked="" 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) 01/25/2008	4. Date of this report (mm/dd/yyyy) 03/24/2009

5. Describe event or problem
This is in follow-up to report(s) previously submitted on 2/11/2008; 2/18/2008; 2/22/2008; 2/26/2008; 2/29/2008; 3/17/2008; 3/26/2008; 5/13/2008; 5/27/2008; 7/2/2008; 7/23/2008; 7/30/2008; 1/15/2009; 1/26/2009; 2/19/2009; 3/2/2009

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 60 year old Asian male with a history of a closed tube thoracostomy (22-DEC-2007) who entered a study, title as stated above. On 08-JAN-2008 (visit 1A), the patient was screened to receive study therapy for the treatment of non-small cell lung cancer (diagnosed 13-DEC-2007, staging 23-JAN-2008, T3, N2, M1 stage IV (with progressive disease)).

(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: Thoracostomy CONCURRENT CONDITIONS: Metastases to bone; Bronchospasm; Wheezing; Airways obstruction; Dyspnoea; Pain; Restlessness

C. Suspect medication(s)			
1. Name (Give labeled strength & mfr/labeler) # 1 CAP 0683-blinded therapy Unk # 2 carboplatin Unk (Continued on Additional Page)			
2. Dose, frequency & route used # 1 Unk/Unk/PO # 2 Unk/Unk/IV		3. Therapy dates (if unknown, give duration from/to (or best estimate)) # 1 01/28/2008 - 02/03/2008 # 2 02/01/2008 - 02/01/2008	
4. Diagnosis for use (indication) # 1 Non-small cell lung cancer # 2 Non-small cell lung cancer		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 checked="" 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 checked="" type="checkbox"/> <input type="checkbox"/>	
9. NDC # or Unique ID Unknown			
10. Concomitant medical products and therapy dates (excluded treatment of event) ANSIMAR 01/26/2008-02/03/2008 APPEBON TABLETS 01/03/2008-01/25/2008 (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) 03/17/2009	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
6. If IND, protocol # 0560091	5. (A)NDA # IND # 58915 STN # PMA/ 510(k) # Combination Product <input type="checkbox"/> Yes Pre-1938 <input type="checkbox"/> Yes OTC product <input type="checkbox"/> Yes
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# 16	9. Mfr. report number WAES 0802USA00123

8. Adverse event term(s) NON-SMALL CELL LUNG CANCER; HAEMATURIA; PULMONARY EMBOLISM
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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**

On 22-JAN-2008, additional CT scans were done to document liver and adrenal metastases. He complained of additional knee and rib pains at this time and he was prescribed with morphine sulfate which relieved the bone pains. Total body bone scan was also requested. Other medicines were continued as needed. On 23-JAN-2008, he was able to undergo bone scanning, and results showed multiple bone metastases noted in posterior 5th right ribs, 5th-6th, 8th-9th left ribs, 7th thoracic, 5th lumbar vertebrae, both acetabulae, right ischium, whole right femur and the midshaft of the left femur.

The patient was experiencing severe bone pains (left and right ribs, back, hip, left and right legs) and intermittent dyspnea, agitation, aggravated by movement/ambulation not relieved with medication, thus opted for confinement. ECOG 0-1 at the time of admission. Chest findings were decreased breath sounds at the left lung field, occasional wheezing right lung field, otherwise unremarkable physical exam. No other laboratory tests (CT, VQ scan, d-dimer) were done. Medications were given and afforded temporary relief, tramadol, paracetamol, Duovent nebulization on PRN basis for dyspnea and Medrol tab on PRN basis for bronchospasm secondary to airway obstruction. Laboratory (CBC and blood Chem) results were unremarkable except for leukocytosis from CBC (26-JAN-2008) and azithromycin was given for 5 days. On 26-JAN-2008, the patient's alkaline phosphatase was 220 u/l, AST was 70 u/l, complete blood count (reported as WBC) was $15 \times 10^9/l$, and granulocytes were 86%. Hemoglobin was 12.7 g/dl, no blood transfusion done. On 26-JAN-2008, other laboratory tests done included alanine aminotransferase test (ALT): 41 u/L; albumin: 3.1g/dL; calcium: 8.6 mg/dL; creatinine: 0.5 mg/dL; erythrocytes: $4.32 \times 10^{12}/L$; hematocrit: 37.4%; lymphocyte: 9.7%; monocyte: 4.3%; potassium: 4.1 mmol/L; sodium: 133 mmol/L and thrombocyte: $373 \times 10^9/L$. The patient was given prophylactic antibiotic coverage although no clinical apparent signs of active infection were noted. The other consideration was leukocytosis secondary to malignancy. It was reported that there was no progression of NSCLC after screening only symptomatic progressive bone pains. Other labs were unremarkable.

On 28-JAN-2008, physical findings were ECOG 0-1 with mild respiratory distress, coherent and conversant, ambulatory, decreased breath sounds at left lung field, no rales or wheezes at right lung field, otherwise unremarkable. On 28-JAN-2008, oral vorinostat or placebo was given with meals (witnessed dose), no adverse reaction noted. The following day, the patient remained on status quo. On 30-JAN-2008, the patient still had dyspneic episodes with O2 saturation in 92-95%. Additional aminophylline drip on 30-JAN-2008 started with relief of bronchospasm. Per CT scan (screening), noted mass effect in left hilar region, with possible compression of airways in the left upper lung. On 30-JAN-2008, an indwelling foley catheter was inserted for accurate urine output monitoring and to minimize straining and to make the patient more comfortable since he was in severe pain due to bone metastases. No gross hematuria noted during insertion. The patient was noted to have light tea colored urine. Dyspnea was relieved by aminophylline drip (as needed), hydrocortisone IV, and oxygen supplementation. Morphine IV was given round the clock for bone pains, with moderate improvement. Demerol was ordered for severe pain but was never given.

On 01-FEB-2008, physical findings were ECOG-1, ambulatory, coherent and conversant; no air entry noted at left lung field, with good air entry on right lung field, other findings were essentially normal. Urine red blood cells were innumerable (abnormal) and urinalysis found microscopic hematuria noted (no numerical value).

Chest CT, VQ scan and D-Dimer were not done, (+) symptomatic progressive bone pains.

Cycle 1 meds of paclitaxel (300 mg) and carboplatin (800 mg) were given on 01-FEB-2008 with no immediate adverse reaction. Concomitant therapy included dexamethasone (manufacturer unknown), diphenhydramine HCl (BENADRYL), ranitidine (ZANTAC), methylprednisone (MEDROL), azithromycin, fenoterol hydrobromide (+) ipratropium bromide (DUOVENT), ascorbic acid (+) buclizine hydrochloride (+) cyanocobalamin (+) pyridoxine hydrochloride (+) thiamine hydrochloride (APPEBON) with iron capsules, zolpidem, ramosetron hydrochloride, tramadol, paracetamol, methylprednisolone (MEDROL), terbutaline sulfate, albuterol sulfate (+) ipratropium bromide (COMBIVENT) and doxofylline (ANSIMAR) and (NASEA).

On 02-FEB-2008, the patient was noted to be comfortable, ambulatory but with slight body weakness and still with no air entry at left lung field, and had light tea-colored urine per urine bag. Aminophylline drip was discontinued and patient was hydrated via intravenous infusion (total urine output that day was 2100 cc/24 hrs). On the night of 02-FEB-2008, the patient had difficulty in breathing and was noted to be restless but coherent. BP was 130/90 mm/Hg. The patient was given zolpidem which relieved restlessness.

Two days after chemotherapy, the patient was noted to be dyspneic and agitated with transient cyanosis (O2 saturation fluctuating from 75% to 80% to 90%) at mid am on 03-FEB-2008. A few hours after, he was obtunded and with shallow breathing. He had increased abdominal girth with bloody urine in the catheter and decreased urine output (800 cc/8 hr shift). He was intubated for impending respiratory distress but had CP arrest during the process. Clinical impression at this time was acute respiratory distress secondary to carbon dioxide retention (grade 5) secondary to

severe pulmonary obstruction secondary to NSCLC, highly considering massive pulmonary embolism (grade 5) (diagnosed clinically) secondary to malignancy. During intubation patient had frothy secretions per orem and no air entry noted at the left lung field. NGT inserted with note of light brown aspirate amounting to 100-150 cc and no urine output was noted. After intubation, he had decreasing heart rate and eventually had CP arrest. CPR was performed for 45 minutes with no success. The patient was pronounced expired at 4:35 pm 03-FEB-2008. No autopsy was performed. Possible cause of death was acute respiratory distress secondary to carbon dioxide retention secondary to pulmonary obstruction, secondary to progressive NSCLC stage IV (with liver, adrenal and bone metastases). Massive pulmonary embolism secondary to malignancy, acute gross hematuria, etiology unknown which was probably related to study drugs (carboplatin + paclitaxel + vorinostat or matching placebo.)

Hematuria, grade 1 was considered an other important medical event by the investigator.

Cause of death was reported as non-small cell lung cancer stage IV with progressive disease grade 5 and pulmonary embolism grade 5.

The action taken regarding therapy with carboplatin and paclitaxel was reported as reduced with the events of progression of NSCLCA, grade 5 and discontinued with the event of hematuria, grade 1.

The reporting investigator felt that acute gross hematuria grade 1 was related to study therapy; progression of non small cell lung cancer, grade 3; and pulmonary embolism, grade 5 were not related to study therapy of vorinostat or placebo, carboplatin and paclitaxel.

Additional information is not expected.

A 7 calendar day phone call was placed to FDA on 21-FEB-2008.

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>
bone scan Comment: See narrative	01/23/2008			
diagnostic urinalysis test Comment: rbc/ microscopic hematuria	02/01/2008			
blood pressure measurement	02/02/2008	130/90	mm/Hg	

LABORATORY RESULTS

<u>Tests</u>	<u>Date</u>	<u>Value</u>	<u>Unit</u>	<u>Normal Range</u>
WBC count	01/26/2008	15	10 ⁹ /l	5 - 10
hematocrit	01/26/2008	37.4	%	40 - 54
hemoglobin	01/26/2008	12.7	g/dl	
lymphocyte count	01/26/2008	9.7	%	20 - 40
monocyte count	01/26/2008	4.3	%	0 - 7
platelet count	01/26/2008	373	10x ⁹ /L	150 - 450
serum albumin	01/26/2008	3.1	g/dL	3.5 - 5
serum alkaline phosphatase	01/26/2008	220	u/l	38 - 126
serum aspartate aminotransferase	01/26/2008	70	u/l	17 - 59
serum calcium	01/26/2008	8.6	mg/dL	8.4 - 10.2
serum creatinine	01/26/2008	.5	mg/dL	.8 - 1.5
serum potassium	01/26/2008	4.1	mmol/L	3.5 - 5.1
serum sodium	01/26/2008	133	mmol/L	137 - 145
complete blood cell count	01/26/2008	15	10 ⁹ /l	5 - 10
red blood cell count	01/26/2008	4.32	10x ¹² /L	4.6 - 6.2
blood granulocyte count	01/26/2008	86	%	50 - 70
pulse oximetry Comment: 92-95%	01/28/2008			
urine RBC count Comment: innumerable-abnormal	02/01/2008			
serum alkaline phosphatase	02/??/2008	194	U/L	35 - 125
pulse oximetry Comment: fluctuating from 75 to 80%	02/03/2008			
serum blood urea nitrogen	02/03/2008	36	mg/dL	

C. Suspect medication(s)

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

#3 paclitaxel Unk

2. Dose, frequency & route used

#3 Unk/Unk/IV

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

#3 02/01/2008 - 02/01/2008

4. Diagnosis for use (indication)

#3 Non-small cell lung cancer

5. Event abated after use stopped or dose reduced

	YES	NO	N/A	UNK
#3			X	

6. Lot # (if known)

#3

7. Exp date (if known)

#3

8. Event reappeared after reintroduction

	YES	NO	N/A	UNK
#3			X	

C. Suspect medication(s)

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

BENADRYL	02/01/2008 - 02/01/2008
COMBIVENT	01/25/2008 - 02/03/2008
DUOVENT	01/03/2008 - Cont
MEDROL	01/17/2008 - 01/24/2008
MEDROL	01/25/2008 - 01/26/2008
NASEA	02/01/2008 - 02/01/2008
ZANTAC	02/01/2008 - 02/01/2008
acetaminophen	12/??/2007 - 01/24/2008
acetaminophen	01/25/2008 - 02/03/2008
azithromycin	01/26/2008 - 01/30/2008
dexamethasone	01/31/2008 - 02/01/2008
dexamethasone	02/01/2008 - 02/01/2008
terbutaline sulfate	01/25/2008 - 02/03/2008
tramadol hydrochloride	12/??/2007 - 01/24/2008
tramadol hydrochloride	01/25/2008 - 02/03/2008
zolpidem tartrate	02/02/2008 - 02/02/2008