

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

Page 1

Mfr report #	WAES 0712USA09051
UF/Dist report #	
FDA Use Only	

A. Patient information			
1. Patient identifier Unk AN 61512 in confidence	2. Age at time of event: or 66 years Date of Birth: 07/09/1941	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 172 pounds

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 01/28/2008 (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) 12/20/2007	4. Date of this report (mm/dd/yyyy) 03/09/2009
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5. Describe event or problem
This is in follow-up to report(s) previously submitted on 1/7/2008; 2/12/2008; 2/28/2008; 3/5/2008; 4/14/2008; 4/24/2008; 7/23/2008; 8/21/2008; 9/11/2008; 9/17/2008; 9/24/2008; 12/5/2008; 1/29/2009; 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 66 year old white male with liver metastasis, chronic obstructive pulmonary disease (COPD), tobacco abuse, pain, hypertension, neutropenia, atrial fibrillation, peripheral vascular disease and a history of hip and leg surgery who on 10-DEC-2007, was randomized to a study, title as stated above.

On 10-DEC-2007, the patient was placed on blinded study therapy of either vorinostat 100 mg capsule, 400 mg daily

(Continued on Additional Page)

6. Relevant tests/laboratory data, including dates Refer to Additional Page
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7 Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc)
MEDICAL HISTORY: Hip surgery; Leg operation
CONCURRENT CONDITIONS: Pain; Metastases to liver; Tobacco abuse; Neutropenia; Chronic obstructive pulmonary disease; Atrial fibrillation; Hypertension; Peripheral vascular disorder

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 12/10/2007 - 12/19/2007
# 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 checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
	# 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 checked="" type="checkbox"/> <input 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)	
ADVAIR	11/19/2007-Cont
ANZEMET	12/13/2007-12/13/2007

(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
4. Date received by manufacturer (mm/dd/yyyy) 02/26/2009	3. Report source (check all that apply) <input type="checkbox"/> foreign <input checked="" type="checkbox"/> study <input type="checkbox"/> literature <input type="checkbox"/> consumer health professional <input type="checkbox"/> user facility <input type="checkbox"/> company representative <input type="checkbox"/> distributor <input type="checkbox"/> other
6. If IND, protocol # 0560084	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# 14	9. Mfr. report number WAES 0712USA09051

8. Adverse event term(s)
FEBRILE NEUTROPENIA; FEMUR FRACTURE; DEATH;
CELLULITIS; PNEUMONIA; ATRIAL FIBRILLATION; PLEURAL EFFUSION

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
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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**

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 (current staging: T2/N3/M1/stage IV)

Concomitant study therapy included paclitaxel, 200 mg/m² (total dose 382 mg) and carboplatin [AUC 6] total dose 600mg, administered intravenous (IV) on day 1 of each treatment cycle). Other concomitant therapy included acetaminophen (+) oxycodone hydrochloride (PERCOCET), clonazepam (KLONOPIN), fluticasone propionate (+) salmeterol xinafoate (ADVAIR INHALER), tiotropium bromide (SPIRIVA INHALER), albuterol sulfate (+) ipratropium bromide (DUONEB), warfarin (COUMADIN), furosemide (LASIX), verapamil, digoxin (DIGITEK), dolasetron mesylate (ANZEMET), dexamethasone (MSD), ranitidine hydrochloride (ZANTAC), diphenhydramine hydrochloride (BENADRYL) and methylprednisolone sodium succinate (SOLU-MEDROL).

On 20-DEC-2007 (Cycle 1 Day 11) the patient developed febrile neutropenia (grade 3) and respiratory distress (grade 2) (NSAE). The patient was presented to the emergency room (ER) with complaints of weakness, increased cough, productive sputum and some respiratory distress. The patient also complained of nausea and increased fever at home (temperature unknown) for 2 days. The patient was found to be neutropenic with white blood cell count (WBC) 0.2 and neutrophil count was unknown. On 20-DEC-2007 the patient was treated with levofloxacin (LEVAQUIN) for neutropenia. No further information was available. On 20-DEC-2007 chest X-ray revealed pleural effusion, blood hemoglobin test was 12.1gm/dl, sputum culture, blood culture and urine culture was negative-normal, white blood cell count was 0.2 K/uL and blood platelet count was $24 \times 10^3/L$, temperature 99.2, and lung sounds were decreased at the bases with scattered bronchi. The patient was found to be neutropenic. The patient was treated with filgrastim (NEUPOGEN) for neutropenia. On 21-DEC-2008 (Cycle 1, Day 12) the patient was hospitalised for febrile neutropenia (grade 3). Blinded study therapy was interrupted. The action taken regarding therapy with carboplatin and paclitaxel was none. The patient was treated with IV fluids, cefepime and levofloxacin (LEVAQUIN), IV. He was given oxygen support and duo-nebs. He was also placed in reverse isolation and started on filgrastim (NEUPOGEN) injections daily. On 24-DEC-2007, the patient was considered recovered with sequelae from febrile neutropenia (grade 3) and was discharged from the hospital. The discharge diagnosis was reported as non-small cell lung cancer with liver mets, chronic obstructive pulmonary disease (COPD), tobacco abuse, neutropenic fever and respiratory distress. On 24-DEC-2007 the patient also recovered from respiratory distress (grade 2) (NSAE). The patient had no further complaints of nausea, vomiting, or shortness of breath at discharge and her WBC count was 15,000.

On 03-JAN-2008, the patient was seen in the office and Cycle 2 Day 1 blinded study therapy capsule was started. Neutropenia resolved (WBC 8.2 and ANC 7.1). On 03-JAN-2008, the patient received carboplatin IV 6 AUC (dose 600 mg) and paclitaxel 200 mg/m² IV (dose 382 mg/m²). The last dose of carboplatin and paclitaxel the patient received prior to the event was on 03-JAN-2008 oral started the same day. The patient was presented with shortness of breath (SOB). The cause of pleural effusion was not addressed. Temperature was 97.5, blood pressure measurement was 101/68, pulse was 120, respiratory rate was 24, absolute neutrophil count (ANC) was 0.45 and oxygen saturation results were not documented. Neutrophil count was not available. On 08-JAN-2008, (Cycle 2 Day 6) the patient was admitted to the hospital with fractured left femoral (grade 3), worsening of atrial fibrillation (grade 3), recurrent pleural effusion (grade 3), pneumonia (grade 3) and cellulitis of the left leg (grade 3). The patient had a left femur X-ray performed and showed a fracture mid-shaft, left femur, severe osteopenia of bony structure, computed tomography guided thoracentesis was performed and 1200 CC of serous fluid, urine culture, sputum culture and blood culture was negative and a chest X-ray showed bibasilar infiltrates and effusions, left was greater than the right. An orthopedic consult determined that the patient was not a candidate for surgery due to left lower extremity cellulitis. The type of fracture was not specified. No further information about leg fracture treatment available. The patient had known soft tissue infection prior to admission. The patient had an infectious disease consultation. Diagnosis date was unknown. Previous cultures of soft tissue indicated MRSA. The patient was treated with vancomycin and piperacillin sodium (+) tazobactam sodium (ZOSYN). No blood culture lab results are available. It was only dictated in the hospital note, no further information will be available. On 08-JAN-2008 the patient also experienced phlebitis of the left arm with superficial venous thrombosis (grade 2) (NSAE), anemia (grade 2) (NSAE) and increased creatinine (grade 3) (NSAE). On 08-JAN-2008 the patient was treated with red blood cells for anemia (grade 2) (NSAE) and amiodarone for atrial fibrillation (grade 3). On 09-JAN-2008 the patient recovered from anemia (grade 2) (NSAE). On 10-JAN-2008 the patient developed anemia (grade 3) (NSAE) and was treated with red blood cells. On 10-JAN-2008 the patient had a transthoracic echocardiogram performed and revealed normal left ventricular systolic function, EF greater than 60%, no aortic stenosis, trace mitral regurgitation and mild to moderate tricuspid regurgitation. A chest x-ray also showed markedly improved from 08-JAN-2008 and the amount of fluid in the left chest was dramatically decreased. Details about the fluid are not available. On 11-JAN-2008 the patient recovered from anemia (grade 3) (NSAE). Electrocardioversion was not done since the patient was not on warfarin hcl (COUMADIN) therapy. Digoxin was increased and patient required more beta blocker/calcium channel blocker secondary to intermittent hypotension, names of medications are not listed. No specific doses were given. Digoxin was increased. Amiodarone started, furosemide hcl (LASIX) was given electrocardioversion

was not necessary due to meds given that are listed. No further information about the term more beta blockers was available. On 15-JAN-2008 the patient had a NSAE of thrombocytopenia. On 16-JAN-2008, the patient was discharged from the hospital for fracture left femoral (grade 3), worsening of atrial fibrillation (grade 3), recurrent pleural effusion (grade 3), pneumonia (grade 3) and cellulitis of the left leg (grade 3). The fractured left femur (grade 3) and recurrent pleural effusion (grade 3) persisted. Discharge diagnosis was left leg fracture, cellulitis of left leg with MRSA, phlebitis of the left arm with thrombosis, pneumonia, atrial fibrillation, mild renal failure, and recurrent pleural effusion; cellulitis of the left leg; pneumonia; atrial fibrillation and improved left pleural effusion. On 16-JAN-2008 the patient recovered from phlebitis of the left arm with superficial venous thrombosis (grade 2) (NSAE) and increased creatinine (grade 3) (NSAE). On 16-JAN-2008 the patient developed anxiety (grade 1) (NSAE) and was treated with alprazolam (XANAZ) and thrombocytopenia (grade 4) (NSAE). On 16-JAN-2008 the patient was treated with furosemide (LASIX) for atrial fibrillation (grade 3). On 16-JAN-2008 the patient recovered from thrombocytopenia (grade 4) (NSAE). At the time of reporting the patient did not recover from anxiety (grade 1) (NSAE). The patient was transferred to Transitional Care Unit for extended care. The investigator was unable to contact the patient or patient's family since 03-JAN-2008.

On 28-JAN-2008, (Cycle 2 Day 30) the patient died (grade 5). The cause of death was not reported. The site learned of the patient's death through radio obituary. It was unknown if autopsy was performed. The investigator has been unable to obtain a death certificate. The patient was lost to follow-up.

The investigator felt that the patient's death was not related to blinded study therapy, or study therapy with carboplatin, and/or paclitaxel.

The investigator felt that neutropenic fever (grade 3) was related to blinded study therapy and carboplatin and not related to paclitaxel.

The investigator felt that left fractured femur (grade 3), pneumonia (grade 3), cellulitis of the left leg (grade 3), worsening of atrial fibrillation (grade 3), recurrent pleural effusion (grade 3) and death (grade 5) were not related to blinded study therapy or study therapy with carboplatin and paclitaxel.

The investigator considered neutropenic fever to be an other important medical event.

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>
chest X-ray Comment: pleural effusion	12/20/2007			
computed axial tomography Comment: CT thoracentis done for pleural effusion 1200 CC of serous fluid	01/08/2008			
chest X-ray Comment: bibasilar infiltrates and effusions, left greater than right	01/08/2008			
chest X-ray Comment: see narrative	01/08/2008			
lower extremity X-ray Comment: fracture mid-shaft, left femur, severe osteopenia of bony structure	01/08/2008			
blood pressure measurement	01/08/2008	101/68		
transthoracic echocardiography Comment: see narrative	01/10/2008			

LABORATORY RESULTS

<u>Tests</u>	<u>Date</u>	<u>Value</u>	<u>Unit</u>	<u>Normal Range</u>
WBC count	12/20/2007	0.2	K/uL	4.8 - 10.8
body temp	12/20/2007	99.2		
hemoglobin	12/20/2007	12.1	gm/dl	12 - 16
platelet count	12/20/2007	24	$10^3/L$	150 - 400
blood culture Comment: negative-normal	12/20/2007			
sputum culture Comment: negative-normal	12/20/2007			
urine culture Comment: negative-normal	12/20/2007			
WBC count	12/24/2007	15,000		

WBC count	01/03/2008	8.2
neutrophil count	01/03/2008	7.1
absolute neutrophil count	01/08/2008	0.45
body temp	01/08/2008	97.5
blood culture	01/08/2008	
Comment: negative-normal		
total heartbeat count	01/08/2008	120
respiratory rate measurement	01/08/2008	24
sputum culture	01/08/2008	
Comment: negative-normal		
urine culture	01/08/2008	
Comment: negative-normal		

C. Suspect medication(s)

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

#1 CAP 0683-blinded therapy Unk
 #2 INJ paclitaxel Unk
 #2 INJ paclitaxel Unk
 #3 INJ carboplatin Unk
 #3 INJ carboplatin Unk

2. Dose, frequency & route used

#1 Unk/Unk/PO
 #2 382 mg/1X/IV
 #2 382 mg/1X/IV
 #3 600 mg/1X/IV
 #3 600 mg/1X/IV

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

#1 01/03/2008 - 01/16/2008
 #2 12/13/2007 - 12/13/2007
 #2 01/03/2008 - 01/03/2008
 #3 12/13/2007 - 12/13/2007
 #3 01/03/2008 - 01/03/2008

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)

ANZEMET	01/03/2008 - 01/03/2008
BENADRYL	12/13/2007 - 12/13/2007
BENADRYL	01/03/2008 - 01/03/2008
COUMADIN	11/19/2007 - 01/18/2008
DECADRON (DEXAMETHASONE)	12/13/2007 - 12/13/2007
DECADRON (DEXAMETHASONE)	01/03/2008 - 01/03/2008
DIGITEK	11/19/2007 - Cont
DUONEB	11/19/2007 - Cont
KLONOPIN	11/08/2007 - Cont
LASIX (FUROSEMIDE SODIUM)	11/19/2007 - 01/16/2008
PERCOCET	11/01/2007 - Cont
SOLU-MEDROL	12/13/2007 - 12/13/2007
SOLU-MEDROL	01/03/2008 - 01/03/2008
SPIRIVA	11/19/2007 - Cont
ZANTAC	12/13/2007 - 12/13/2007
ZANTAC	01/03/2008 - 01/03/2008
verapamil	11/19/2007 - Cont