

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

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Mfr report #	WAES 0712USA08170
UF/Dist report #	
	FDA Use On

A. Patient information			
1. Patient identifier Confidential AN 51003 in confidence	2. Age at time of event: or 69 years Date of Birth: 09/14/1938	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 130 lbs

B. Adverse event or product problem	
1. <input checked="" type="checkbox"/> Adverse event and / or (check all that apply)	<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 checked="" 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) 12/15/2007	4. Date of this report (mm/dd/yyyy) 02/27/2009

5. Describe event or problem
This is in follow-up to report(s) previously submitted on 4/2/2008; 4/9/2008; 4/23/2008; 6/11/2008; 6/17/2008; 6/30/2008; 7/3/2008; 8/19/2008; 9/4/2008

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 69 year old male patient with anemia, decreased albumin, increased alkaline phosphatase and increased calcium who on 06-DEC-2007, was randomized to a study titled as stated above. On 26-SEP-2007, the patient was diagnosed with stage 4 adenocarcinoma (T4 N2 M1). On 03-DEC-2007, the patient was placed on cycle one of study therapy with vorinostat tablet, 400 mg, or placebo daily for the treatment of non-small cell lung cancer (NSCLC). Concomitant study therapy included IV carboplatin (AUC 6), 678 mg, and IV paclitaxel 200 mg/m2, 334 mg, both

(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: Anaemia; Albumin decreased; Alkaline phosphatase increased; Calcium increased

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 12/03/2007 - 12/17/2007 # 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
9. NDC # or Unique ID Unknown	8. Event reappeared after reintroduction. yes no N/A unk # 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"/>
10. Concomitant medical products and therapy dates (excluded treatment of event) CHLORPHENAMINE 12/06/2007-12/06/2007 TRAMAL 12/09/2007-12/12/2007 (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) 02/23/2009	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 health professional <input type="checkbox"/> user facility <input type="checkbox"/> company representative <input type="checkbox"/> distributor <input type="checkbox"/> other:
6. If IND, protocol # 0560016	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# 9	9. Mfr. report number WAES 0712USA08170

8. Adverse event term(s)
THROMBOCYTOPENIA; FEBRILE NEUTROPENIA

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

administered on 06-DEC-2007 (and both to be administered every 3 weeks) for the treatment of NSCLC. Other concomitant therapy included dexamethasone (manufacturer unknown), ondansetron, tramadol hydrochloride (TRAMAL), chlorpheniramine maleate (CHLORPHENAMINE) and etoricoxib. On 15-DEC-2007 the patient went to the emergency room due to epistaxis grade 1 and high fever (value not reported). In the physical exam he was asymptomatic without fever. The hematology showed hematology toxicity (decreased platelets [8]) and antibiotic prophylaxis was initiated. Other laboratory tests on that date revealed hemoglobin of 84.2 g/L. Blinded study therapy dose was reduced. The patient was hospitalized. Treatment initiated 15-DEC-2007 included IV ceftriaxone 2 g daily (stop date 17-DEC-2007); IV amikacin 800 mg daily (stop date 17-DEC-2007); IV ranitidine 50 mg daily (stop date 19-DEC-2007); IV platelets 6 units on 15-DEC-2007; and 300 mg filgrastim SC on 15-DEC-2007. As of 18-DEC-2007, the event was ongoing.

Follow up information has been received concerning the white patient who developed thrombocytopenia (grade 4). On 15-DEC-2007 (Cycle 1, day 13), he complained of epistaxis (grade 1) and high fever; the physical exam was not contributory and the CBC count showed 8,000 /mm³ platelets. He was admitted at the hospital and was doing well without other complications. He received antibiotic prophylaxis and hematological support. The patient responded to 6 platelet transfusions from 15-DEC-2007 to 18-DEC-2007 respectively. On 17-DEC-2007, he required a red blood cell transfusion. He was not neutropenic. The cultures were negative and he was not bleeding. On 19-DEC-2007 he recovered and was discharged on 20-DEC-2007. Blood count on that date revealed 110,000 /mm³ platelets. His discharge diagnosis was thrombocytopenia grade 2 due to chemotherapy. He was seen in outpatient clinic on 22-DEC-2007 in rather good condition. New blood count showed 136,000 /mm³ platelets. On 02-JAN-2008 the patient started cycle 2 and received paclitaxel 336 mg IV, and carboplatin 670 mg IV. He also received blinded therapy from 02-JAN-2008 to 15-JAN-2008. On 23-JAN-2008 to 05-FEB-2008, the patient received cycle 3 of blinded therapy. On 23-JAN-2008, the patient received a dose of study therapy, paclitaxel, 338 mg as part of cycle 3 and omeprazole for prophylactic gastric protection. On 13-FEB-2008, the patient started cycle 4 and received blinded therapy. The patient also received a dose of concomitant study therapy which included IV carboplatin, 562 mg, and IV paclitaxel, 340 mg. On 12-MAR-2008, the patient was placed on cycle 5 blinded study therapy and study therapy, carboplatin (517 mg), paclitaxel (340 mg) and was given a dose of dexamethasone (20 mg) (manufacturer unknown), ranitidine (50 mg), ondansetron (16 mg) and chlorphen (10 mg). On 17-MAR-2008, he developed febrile neutropenia (grade 3), cough and asthenia (grade 3) (NSAE) and was hospitalized for febrile neutropenia (grade 3). Vital signs were reported as AP: 130/80, CR: 100x, BR: 20x and T: 39.0C (oral). It was reported that the patient had bilateral crackling sounds, pneumonia signs and his blood culture was reported as negative. Lab analysis showed grade 4 neutropenia and grade 3 plaquetopenia. On 17-MAR-2008 (Cycle 5, day 6), the patient's quantity of hemoglobin was 11 g/dL, quantity of neutrophil was 0 and quantity of platelets was 1. Blinded study treatment dose was reduced. Treatment with ceftazidime IV, 2 grams every 8 hours, amikacin 1 gram every 24 hours, filgrastim 300 mcg every 12 hours, ranitidine, paracetamol and fenoterol were started on 17-MAR-2008. On 18-MAR-2008, the patient's fever resolved and laboratory diagnostic studies performed included a quantity of hemoglobin 105g/L and quantity of platelets 24 10⁹/L. On 19-MAR-2008, the patient's asthenia resolved and laboratory diagnostic studies performed were quantity of hemoglobin 98 g/L, quantity of neutrophil was 9 10⁹/L and quantity of platelets 22 10⁹/L. On 20-MAR-2008, the patient was discharged home on ceftazidime, amikacin, filgrastim, ranitidine, flumicil and albuterol sulfate (+) ipratropium bromide (COMBIVENT) with a discharge diagnosis of neutropenia (grade 4), thrombocytopenia (grade 4), anemia (grade 2) and hyponatremia (grade 3). His quantity of hemoglobin was 99 g/L, platelets were 19 10⁹/L and neutrophils were 9 10⁹/L. On 23-MAR-2008, the patient's febrile neutropenia (grade 3) resolved although thrombocytopenia (grade 2) persisted. On 24-MAR-2008, the patient was restarted on blinded study therapy. On 02-APR-2008 the patient's quantity of neutrophil count was 1 10³/uL and quantity of hemoglobin was 9 g/dL. On 24-APR-2008, the patient's quantity of neutrophytes was reported as 60% and hemoglobin was 12 g/dL. On 14-MAY-2008, the patient completed study therapy.

The reporting investigator felt that thrombocytopenia (grade 4) and febrile neutropenia (grade 3) were related to blinded study therapy, paclitaxel and carboplatin.

Thrombocytopenia (grade 4) was considered to be immediately life threatening.

Additional information has been requested.

6. Relevant tests/laboratory data, including dates

DIAGNOSTIC TEST

Tests	Date	Value Unit	Normal Range
physical examination Comment: asymptomatic without fever	12/15/2007		
diagnostic laboratory test Comment: Grade 4 neutropenia and grade 3 plaquetopenia	03/17/2008		

LABORATORY RESULTS

Tests	Date	Value	Unit	Normal Range
hemoglobin	12/15/2007	84.2	g/L	130 - 180
Comment: abnormal				
platelet count	12/15/2007	8		150 - 450
Comment: abnormal				
platelet count	12/15/2007	8,000	/mm3	
platelet count	12/20/2007	110,000	/mm3	
platelet count	12/22/2007	136,000	/mm3	
stool occult blood	12/??/2007			
Comment: not bleeding				
blood culture	12/??/2007			
Comment: negative				
hemoglobin	03/17/2008	11	g/dl	13.5 - 17.5
neutrophil count	03/17/2008	0	10 ³ /uL	1.8 - 7.7
platelet count	03/17/2008	1	10 ³ /uL	4.5 - 11
vital sign	03/17/2008			
Comment: AP: 130/80, CR: 100, BR:20, T:39.0C				
blood culture	03/17/2008			
Comment: negative				
hemoglobin	03/18/2008	105	g/L	130 - 180
platelet count	03/18/2008	24	10 ⁹ /L	150 - 450
hemoglobin	03/19/2008	98	g/L	130 - 180
platelet count	03/19/2008	22	10 ⁹ /L	150 - 450
hemoglobin	03/20/2008	99	g/L	130 - 180
neutrophil count	03/20/2008	9	10 ⁹ /L	2.8 - 7.8
platelet count	03/20/2008	19	10 ⁹ /L	150 - 450
hemoglobin	04/02/2008	9	g/dl	13.5 - 17.5
neutrophil count	04/02/2008	1	10 ³ /uL	1.8 - 7.7
hemoglobin	04/04/2008	12		13.5 - 17.5
neutrophil count	04/04/2008	37	%	35 - 66
hemoglobin	04/08/2008	12	g/dl	13.5 - 17.5
neutrophil count	04/08/2008	33	%	35 - 66
hemoglobin	04/15/2008	12	g/dl	13.5 - 17.5
neutrophil count	04/15/2008	41	%	35 - 66
hemoglobin	04/24/2008	12	g/dL	13.5 - 17.5
neutrophil count	04/24/2008	60	%	35 - 66

C. Suspect medication(s)

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

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

