

MedWatch

Merck Human Health Division

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MANDATORY reporting

Merck Facsimile of FDA Form 3500A
Approved by FDA (10/21/1993)

The FDA Medical Products Reporting Program

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Mfr report #	WAES 0805USA04831
UF/Dist report #	
FDA Use Only	

A. Patient information			
1. Patient identifier Confidential AN 62529 in confidence	2. Age at time of event: or 73 years Date of Birth: 09/29/1934	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 191 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 type="checkbox"/> Death (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)	04/05/2008	4. Date of this report (mm/dd/yyyy)	02/16/2009

5. Describe event or problem
This is in follow-up to report(s) previously submitted on 6/2/2008; 6/4/2008; 6/6/2008; 7/9/2008; 8/13/2008; 9/15/2008; 9/29/2008; 1/14/2009; 2/9/2009; 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 73 year old white male with breathlessness, and a history of computed tomography pulmonary angiogram, diagnostic arthroscopy of the knee and 2 varicose vein strippings of the left leg who entered a study, title as stated above. On 17-DEC-2007, the patient was originally diagnosed with adenocarcinoma, primary tumor T4, no nodal involvement, M1 distant metastasis, overall stage IV. From 31-MAR-2008 to 13-APR-2008, cycle 1, the patient received therapy with blinded therapy (either vorinostat 100 mg capsule, total daily dose 400 mg for 14 days every

(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: Varicose veins stripping; Arthroscopy; Varicose vein CONCURRENT CONDITIONS: Breathlessness

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 03/31/2008 - 04/13/2008 # 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
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 type="checkbox"/> <input type="checkbox"/>	
9. NDC # or Unique ID Unknown	

10. Concomitant medical products and therapy dates (excluded treatment of event) PRO- BANTHINE 12/24/2007-Cont albuterol 12/24/2007-Cont	
(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) 02/03/2009	5. (A)NDA # 21991 IND # 58915 STN # PMA/ 510(k) # Combination Product <input type="checkbox"/> Yes Pre-1938 <input type="checkbox"/> Yes OTC product <input type="checkbox"/> Yes
6. If IND, protocol # 0560035	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
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# 10	9. Mfr. report number WAES 0805USA04831

8. Adverse event term(s) DYSпноEA; 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**

3 weeks or placebo) for the treatment of bronchoalveolar carcinoma. Concomitant study therapy included paclitaxel 200 mg/m² IV every 3 weeks (total daily dose 420 mg), and carboplatin AUC 6 IV, every 3 weeks (total daily dose 666 mg) administered on day 1 of each treatment cycle. Other concomitant therapy included omeprazole, propantheline bromide (PRO-BANTHINE), ondansetron, dexamethasone IV (manufacturer unknown), salbutamol MDI, domperidone domperidone, cimetidine and chlorpheniramine maleate.

From 22-APR-2008 to 05-MAY-2008, the patient received cycle 2 study therapy with blinded therapy (either vorinostat 100 mg capsule, total daily dose 400 mg or placebo. Concomitant study suspect therapy included paclitaxel 200 mg/m² IV total daily dose 400 mg given on 22-APR-2008, and carboplatin AUC 6 IV, total daily dose 700 mg given on 22-APR-2008.

On 05-APR-2008, (cycle 1, day 6) the patient experienced intermittent shortness of breath (grade 1) and was hospitalized. On 19-MAY-2008 the patient experienced pneumonia (grade 2) and neutropenia (grade 4) which were non-serious. On 21-MAY-2008, (cycle 3, day 9) the patient was presented with increased shortness of breath and feeling "unwell" over last 2 days and one episode of diarrhea. Temperature on admission was 39.2 centigrade. Pulmonary embolism (PE) was suspected, but not confirmed. On 21-MAY-2008, the patient had a chest x-ray performed that revealed increased shadow of the left lung, no PE's. Admission note had provisional diagnosis of neutropenic sepsis. ?? pulmonary embolism (PE). Chest x-ray showed no PE's. Oxygen saturation was 88%. Pulmonary embolism was suspected, but not confirmed. Blood cultures were negative. Full blood count (FBC) revealed neutropenia with a neutrophil count of $0.1 \times 10^9/L$. He was admitted per neutropenic sepsis protocol with a diagnosis of febrile neutropenia (grade 4). He was started antibiotics: piperacillin sodium (+) tazobactam sodium (TAZOCIN) 4.5 g IV tid, vancomycin 1 gram IV bid, and gentamicin 440 mg IV daily. On 21-MAY-2008, he was given filgrastim 6 mg subcutaneously. He was placed on oxygen therapy. The patient's blood pressure was 110/56 and her pulse was 66. On 21-MAY-2008 through 23-MAY-2008 the patient was given paracetamol. Laboratory exams on 21-MAY-2008 included a serum creatinine protein of 205 mg/L, a white blood cell count was $0.9 \times 10^9/L$, albumin was 25 g/L, platelets were $112 \times 10^9/L$, serum sodium was 120 mmol/L, and troponin I was 0.22 ug/L. Last dose given of MK-683-blinded therapy or placebo was on 26-MAY-2008. On 22-MAY-2008 through 26-MAY-2008 the patient was given potassium bicarbonate (+) potassium chloride (SANDO K). On 23-MAY-2008, the patient received transfusion with 2 units, and his neutropenia (grade 4) (non-serious) resolved. Action taken regarding study therapy was none. As of 27-MAY-2008, the patient was still hospitalized. The patient was treated with ciprofloxacin for the neutropenic sepsis and clarithromycin for the febrile neutropenia (grade 4). The patient recovered from febrile neutropenia (grade 4) on 26-MAY-2008. The patient was discharged from the hospital on 29-MAY-2008 and will be seen 01-JUN-2008. A sputum sample had no significant growth. The patient was discharged on ciprofloxacin and clarithromycin. On 29-MAY-2008 the patient's neutrophils were 13.8. On 29-MAY-2008 the patient recovered from (grade 2) (NSAE). It was reported that the patient was still very weak. The discharge diagnoses were neutropenic sepsis and the source was left sided pneumonia. On 07-JUL-2008 the patient recovered from shortness of breath. On 16-JUN-2008 the patient discontinued study medication due to the physician's decision without receiving further chemo after discharge.

The reporting investigator felt that the febrile neutropenia (grade 4), shortness of breath, and pneumonia (NSAE) were related to MK-683-blinded therapy or placebo, carboplatin and paclitaxel. The reporting investigator also felt that the patient's neutropenia (grade 4) (non-serious) was related to therapy with MK-683-blinded therapy or placebo, carboplatin and paclitaxel. Action taken regarding carboplatin and paclitaxel was none.

Additional information is not expected.

This is an amended report. The local registration number was removed from the report.

This blinded study report was sent to NDA #21991 on 09-FEB-2009.

6. Relevant tests/laboratory data, including dates**DIAGNOSTIC TEST**

<u>Tests</u>	<u>Date</u>	<u>Value Unit</u>	<u>Normal Range</u>
electrocardiogram	03/25/2008		
Comment: sinus tachycardia-bundle branch block right			
chest X-ray	05/21/2008		
Comment: increased shadow on left lung			
electrocardiogram	05/21/2008		
Comment: sinus tachycardia-bundle branch block right			
blood pressure measurement		110/56	

LABORATORY RESULTS

<u>Tests</u>	<u>Date</u>	<u>Value Unit</u>	<u>Normal Range</u>
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WBC count	05/21/2008	0.9 10 ⁹ /L	4 - 11
Comment: low			
body temp	05/21/2008	39.2 C	
hemoglobin	05/21/2008	9.2 g/dL	13 - 18
Comment: low			
neutrophil count	05/21/2008	0.10 10 ⁹ /L	2 - 7.5
Comment: low			
platelet count	05/21/2008	112 10 ⁹ /L	150 - 450
Comment: low			
pulse oximetry	05/21/2008	88 %	
serum C-reactive protein	05/21/2008	205 mg/L	0 - 6
serum TnI	05/21/2008	0.22 ug/L	0 - 0.1
serum albumin	05/21/2008	25 g/L	30 - 51
serum sodium	05/21/2008	120 mmol/L	135 - 145
blood culture	05/21/2008		
Comment: negative normal			
neutrophil count		13.8	
total heartbeat count		66	

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

2. Dose, frequency & route used

#1 Unk/Unk/PO
 #1 Unk/Unk/PO
 #2 420 mg/1X/IV
 #2 400 mg/1X/IV
 #2 400 mg/1X/IV
 #3 666 mg/1X/IV
 #3 700 mg/1X/IV
 #3 648 mg/1X/IV

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

#1 04/22/2008 - 05/05/2008
 #1 05/13/2008 - 05/26/2008
 #2 04/04/2008 - 04/04/2008
 #2 04/22/2008 - 04/22/2008
 #2 05/13/2008 - 05/13/2008
 #3 04/04/2008 - 04/04/2008
 #3 04/22/2008 - 04/22/2008
 #3 05/13/2008 - 05/13/2008

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
#3
#3

7. Exp date (if known)

#1
#1
#2
#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)

chlorpheniramine maleate	04/04/2008 - Cont
cimetidine	04/04/2008 - Cont
dexamethasone	04/04/2008 - Cont
dexamethasone	04/04/2008 - Cont
domperidone	04/04/2008 - Cont
omeprazole	12/24/2007 - Cont
ondansetron	04/04/2008 - Cont