

# MedWatch

The FDA Medical Products Reporting Program

## 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)

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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)	02/27/2009
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; 2/16/2009; 2/26/2009			
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			
(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		3. Therapy dates (if unknown, give duration) from/to (or best estimate)	
# 1 Unk/Unk/PO		# 1 03/31/2008 - 04/13/2008	
# 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)			
PRO-BANTHINE		12/24/2007-Cont	
albuterol		12/24/2007-Cont	
(Continued on Additional Page)			

G. All manufacturers	
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 # 21991
02/03/2009	IND # 58915
6. # IND, protocol #	STN #
0560035	PMA/510(k) #
7. Type of report	Combination Product <input type="checkbox"/> Yes
<input type="checkbox"/> 5-day <input type="checkbox"/> 30-day	Pre-1938 <input type="checkbox"/> Yes
<input type="checkbox"/> 7-day <input type="checkbox"/> Periodic	OTC product <input type="checkbox"/> Yes
<input type="checkbox"/> 10-day <input type="checkbox"/> Initial	9. Mfr. report number
<input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up# 12	WAES 0805USA04831
8. Adverse event term(s)	
DYSPNOEA; FEBRILE NEUTROPENIA	
E. Initial reporter	
1. Name, address & phone #	
2. Health professional?	3. Occupation
<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
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

100 mg capsule, total daily dose 400 mg for 14 days every 3 weeks or placebo) for the treatment of bronchoalveolar carcinoma. Concomitant study therapy included paclitaxel 200 mg/m<sup>2</sup> IV and carboplatin AUC 6 IV, administered on day 1 of each treatment cycle. Other concomitant therapy included omeprazole, propantheline bromide (PRO-BANTHINE), ondansetron, dexamethasone IV and oral (manufacturer unknown), salbutamol MDI, domperidone, cimetidine and chlorpheniramine maleate.

On 05-APR-2008, (cycle 1, day 6) the patient experienced intermittent shortness of breath (grade 1). Cycle 3 study therapy was administered on 13-MAY-2008.

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 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). Oxygen saturation was 88%. 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 filgastrim 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) pneumonia (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 (grade 1). 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 (grade 1), 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 and on 26-FEB-2009.

## 6. Relevant tests/laboratory data, including dates

## DIAGNOSTIC TEST

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

## LABORATORY RESULTS

Tests	Date	Value Unit	Normal Range
WBC count Comment: low	05/21/2008	$0.9 \times 10^9/L$	4 - 11
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 <sup>9</sup> /L	2 - 7.5
Comment: low			
platelet count	05/21/2008	112 10 <sup>9</sup> /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  
#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