

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 0804USA03296
UF/Dist report #	
FDA Use On	

A. Patient information			
1. Patient identifier Confidential AN 55511 in confidence	2. Age at time of event: or 75 years Date of Birth: 08/30/1932	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight 132 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 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)	04/11/2008	4. Date of this report (mm/dd/yyyy)	02/24/2009
5. Describe event or problem			
This is in follow-up to report(s) previously submitted on 4/21/2008; 4/25/2008; 4/28/2008; 5/5/2008; 5/8/2008; 5/21/2008; 5/28/2008; 7/31/2008; 9/18/2008; 10/2/2008			
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 75 year old white female (weight 60 kg, height 153 cm) with chest pain, insomnia, dyspnoea exertional, dysuria, gastritis, pollakiuria, polydipsia, weight decreased (from 62 kg to 60 kg) and alkaline phosphatase increased who entered a study, title as stated above. On 18-FEB-2008, the patient was placed on therapy with blinded therapy, capsule, of either 400 mg, once a day or placebo x 14 days/25 days for the treatment of non-small cell lung cancer stage IV (diagnosed			
(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: Chest pain; Insomnia; Dyspnoea exertional; Dysuria; Pollakiuria; Polydipsia; Weight decreased; Alkaline phosphatase increased; Gastritis; Pain			

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/DAILY/PO		# 1 02/18/2008 - 02/29/2008	
# 2		# 2	
4. Diagnosis for use (indication)		5. Event abated after use stopped or dose reduced.	
# 1 Non-small cell lung cancer stage IV		yes no N/A unk	
# 2		# 1 <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
# 2		# 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 type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	
# 2		# 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)			
chlorpheniramine maleate		04/03/2008 - 04/03/2008	
dexamethasone		04/03/2008 - 04/03/2008	
(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 #
02/13/2009	IND # 58915
6. If IND, protocol #	STN #
0560047	PMA/510(k) #
7. Type of report	Combination Product <input type="checkbox"/> Yes <input type="checkbox"/> No
<input type="checkbox"/> 5-day <input type="checkbox"/> 30-day	Pre-1938 <input type="checkbox"/> Yes <input type="checkbox"/> No
<input type="checkbox"/> 7-day <input type="checkbox"/> Periodic	OTC product <input type="checkbox"/> Yes <input type="checkbox"/> No
<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# 10	WAES 0804USA03296

8. Adverse event term(s)
FEBRILE NEUTROPENIA; PNEUMONIA; SEPTIC SHOCK

E. Initial reporter			
1. Name, address & phone #			
2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA.	
<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO		<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**

21-SEP-2007; current staging 14-FEB-2008; T4/N2/M1/IV). Concomitant study therapy included carboplatin, 6 AUC, 621 mg on 22-FEB-2008, 6 AUC, 497.76 mg on 13-MAR-2008 and 6 AUC, 603 mg on 03-APR-2008 and paclitaxel, 200 mg/m2, 316 mg on 22-FEB-2008, 322 mg on 13-MAR-2008 and 318 mg on 03-APR-2008. Concomitant therapy included ketoprofen, gabapentin, diazepam, tramadol HCl, and ranitidine, dexamethasone, ondansetron, and chlorpheniramine maleate.

On 22-MAR-2008, the following laboratory test was performed quantity of urine protein (24 hours) results reported were 241 mg in 24 hours (normal range 0-150). On 11-APR-2008, the patient developed a fever. On 12-APR-2008, the patient went to the emergency room with dysuria, polykiuria and moderate cough. Physical examination findings showed temperature 39.5 C, CF 153, PA 80/60, and test results were as follows: hemoglobin 87, white blood cells 1.25 (febrile neutropenia grade 4 toxicity), neutrophil 25, platelets 98, quantity of hemoglobin 118 g/L (normal range 110-160) and chest x-rays (12-APR-2008, 16-APR-2008 and 20-APR-2008) showed multiple lesions poor defined in both lungs compatible with pneumonia (grade 2 toxicity) and was hospitalized. The patient started treatment with hydration, ceftriaxone IV, amikacin IV, filgastrim, metamizol IV, furosemide IV, spironolactone and oxygenotherapy.

The morning of 13-APR-2008, the patient developed hypotension 70/40. She was treated with intravenous fluids and intravenous therapies including: Hidroxyl-Etil-Almidon Solution, magnesium sulfate, dopamine, hydrocortisone, meropenem and vancomycin as the patient was diagnosed with septic shock (grade 4) probably due to pulmonary infection as the evolution was favorable. On 13-APR-2008 the patient also received ranitidine IV for gastritis until 21-APR-2008. Study therapy was not received April 13th through the April 17th 2008. Febrile neutropenia (grade 4) was treated with filgastrim (G-CSF) IV from 13-APR-2008 through 15-APR-2008. On 14-APR-2008, the patient had recovered from the event of febrile neutropenia (grade 4). Subsequently on 15-APR-2008, the patient's blood pressure was reported as 100/60, dopamine and filgastrim therapies were discontinued and the patient recovered from the septic shock (grade 4). On 17-APR-2008, urine fungus culture test was performed and the result was positive (abnormal). The patient had a normal temperature and blood pressure and was still receiving vancomycin and meropenem. On 17-APR-2008 dimenhydrinate IV was started as an antiemetic until 18-APR-2008. On 18-APR-2008 furosemide was started as a diuretic until 19-APR-2008. On 20-APR-2008, the patient had finished the 7 day course of antibiotics and the event of febrile neutropenia (grade 4) was controlled. Laboratory tests performed on 20-APR-2008 showed hemoglobin was 9.8, white blood cell count was 5,780, blood segmented neutrophil count was 70 and platelet count was 209,000. On 21-APR-2008, the patient was better, had recovered from pneumonia, oxygenotherapy was discontinued and the patient was discharged from the hospital. On 21-APR-2008 the patient's discharge diagnosis was febrile neutropenia (grade 4) and back pain (grade 2) treated with tramadol HCl (TRAMAL). As of 20-MAY-2008, the investigator decided to discontinue study medication (date not reported) and the patient had completed the study. The reporting investigator felt that febrile neutropenia (grade 4), septic shock (grade 4) and pneumonia (grade 2) were related to study therapy.

Febrile neutropenia (grade 4) was considered to be immediately life-threatening.

The patient had the following non-serious adverse experiences: cough; hyporexia was treated with meggestrol acetate (MEGACE), 20 ml, daily on 29-FEB-2008 to ongoing; dizziness; pain was treated with ketoprofen, 100 mg, BID from 23-FEB-2008 to 12-APR-2008, tramadol HCl 100 mg, TID from 07-MAR-2008 to 12-APR-2008; pain of left hemithorax; neutropenia; leukopenia; dyspepsia; diarrhea; increased alkaline phosphatase; proteinuria; fullness sensation; generalized itching; nausea; vomiting; back pain was treated with tramadol HCl, 50 mg, PRN; anemia; fever; gingival burning; flu; sweating; insomnia; generalized itching and fungal urinary tract infection was treated with fluconazole, 150 mg, daily from 19-APR-2008 to 21-APR-2008.

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>
physical examination Comment: CF	04/12/2008	153	
physical examination Comment: PA	04/12/2008	80/60	
chest X-ray Comment: multiple lesions poor defined in both lungs compatible with Pneumonia	04/12/2008		
blood pressure measurement	04/13/2008	70/40	
blood pressure measurement	04/15/2008	100/60	
chest X-ray	04/16/2008		

Comment: pneumonia

chest X-ray

04/20/2008

Comment: pneumonia

LABORATORY RESULTS

Tests	Date	Value	Unit	Normal Range
body weight measurement	02/04/2008	62	kg	
body height measurement	02/04/2008	153	cm	
body weight measurement	02/18/2008	61	kg	
body height measurement	02/18/2008	153	cm	
body weight measurement	02/22/2008	62	kg	
body weight measurement	02/29/2008	62	kg	
body weight measurement	03/07/2008	62	kg	
body weight measurement	03/13/2008	61	kg	
body weight measurement	04/03/2008	60	kg	
WBC count	04/12/2008	1.25		
body temp	04/12/2008	39.5	C	
hemoglobin	04/12/2008	87		
hemoglobin	04/12/2008	118	g/L	110 - 160
neutrophil count	04/12/2008	25		
platelet count	04/12/2008	98		
body weight measurement	04/12/2008	58	kg	
body weight measurement	04/17/2008	58	kg	
urine culture	04/17/2008	positive		
Comment: Abnormal				
WBC count	04/20/2008	9.8		
WBC count	04/20/2008	5,780		
hemoglobin	04/20/2008	9.8		
platelet count	04/20/2008	209000		
segmented neutrophil	04/20/2008	70		
body weight measurement	04/30/2008	58	kg	
body weight measurement	05/08/2008	58	kg	

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 INJ carboplatin Unk
 #2 INJ carboplatin Unk
 #2 INJ carboplatin Unk
 #3 paclitaxel 200 mg
 #3 paclitaxel 200 mg
 #3 paclitaxel 200 mg

2. Dose, frequency & route used

#1 Unk/DAILY/PO
 #1 Unk/DAILY/PO
 #1 Unk/DAILY/PO
 #1 Unk/DAILY/PO
 #1 Unk/DAILY/PO
 #2 621 mg/1X/IV
 #2 497.76 mg/1X/IV
 #2 603 mg/1X/IV
 #3 316 mg/Unk/Unk
 #3 322 mg/Unk/Unk
 #3 318 mg/Unk/Unk

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

#1 03/01/2008 - 03/02/2008
 #1 03/13/2008 - 03/26/2008
 #1 03/27/2008 - 04/02/2008
 #1 04/03/2008 - 04/12/2008
 #1 04/19/2008 - 04/22/2008
 #2 02/22/2008 - 02/22/2008
 #2 03/13/2008 - 03/13/2008
 #2 04/03/2008 - 04/03/2008
 #3 02/22/2008 - 02/22/2008
 #3 03/13/2008 - 03/13/2008
 #3 04/03/2008 - 04/03/2008

4. Diagnosis for use (indication)

#1	Non-small cell lung cancer stage IV
#1	Non-small cell lung cancer stage IV
#1	Non-small cell lung cancer stage IV
#1	Non-small cell lung cancer stage IV
#1	Non-small cell lung cancer stage IV
#2	Non-small cell lung cancer stage IV
#2	Non-small cell lung cancer stage IV
#2	Non-small cell lung cancer stage IV
#3	Non-small cell lung cancer stage IV
#3	Non-small cell lung cancer stage IV
#3	Non-small cell lung cancer stage IV

5. Event abated after use stopped or dose reduced

	YES	NO	N/A	UNK
#1	X			
#1	X			
#1	X			
#1	X			
#1	X			
#2				X
#2				X
#2				X
#3				X
#3				X
#3				X

6. Lot # (if known)

#1
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7. Exp date (if known)

#1
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 #3

8. Event reappeared after reintroduction

	YES	NO	N/A	UNK
#1			X	
#1			X	
#1			X	
#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)

diazepam	03/07/2008 - 04/12/2008
gabapentin	02/25/2008 - 04/12/2008
ketoprofen	02/23/2008 - 04/12/2008
ondansetron	04/03/2008 - 04/03/2008
ranitidine	04/03/2008 - 04/03/2008
ranitidine	04/11/2008 - 04/12/2008
tramadol hydrochloride	03/07/2008 - 04/12/2008