

# 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 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 <u>75 years</u>  Date of Birth: <u>08/30/1932</u>	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)	4. Date of this report (mm/dd/yyyy)
<u>04/11/2008</u>	<u>03/20/2009</u>

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; 2/24/2009; 3/4/2009; 3/10/2009; 3/17/2009

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 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 <u>02/18/2008 - 02/29/2008</u>
# 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 <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)  
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 #
<u>03/09/2009</u>	IND # <u>58915</u>
6. If IND, protocol #	STN #
<u>0560047</u>	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	
<input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up# <u>14</u>	9. Mfr. report number
	WAES 0804USA03296

3. Report source. (check all that apply)

foreign  
 study  
 literature  
 consumer  
 health professional  
 user facility  
 company representative  
 distributor  
 other:

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

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**

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/m<sup>2</sup>, 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 (manufacturer unknown), 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 and physical exam (PE) showed that she had a temperature of 39.5 C, CF 153, PA 80/60. She had moderate cough. At the time the patient did not require oxygen. The cough was resolved and the patient was stable without a fever, but she had back pain (grade 2). Test results were as follows: hemoglobin 87, white blood cells 1.25 (febrile neutropenia grade 4 toxicity), neutrophil 312.5xmm<sup>3</sup>, platelets 98, quantity of hemoglobin 118 g/L (normal range 110-160) and chest x-ray showed multiple lesions, poor defined in both lungs compatible with pneumonia (grade 2 toxicity). On 12-APR-2008, the patient was hospitalized. The patient started treatment with hydration, ceftriaxone IV, amikacin IV, filgastrim, metamizol IV, furosemide IV, spironolactone and oxygen.

The patient received oxygen 3L/min (oxygen saturation 95%) from when she entered the emergency room on 13-APR-2008 due to pneumonia. The morning of 13-APR-2008, the patient developed hypotension 70/40. She was treated with intravenous fluids and intravenous therapies including:

Hidroxy-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) 300 ug twice daily 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). The febrile neutropenia (grade 4) was reported as being "controlled". Subsequently on 15-APR-2008, the patient's blood pressure was reported as normal at 100/60 with a normal temperature also, dopamine and filgastrim therapies were discontinued. The patient was still on oxygen therapy and on vancomycin and meropenem. Laboratory results on 15-APR-2008 were hemoglobin: 96 g/L; white blood cell count: 7.41 and neutrophils 6298.5. The patient received oxygen therapy as suspect therapy. On 15-APR-2008 the patient recovered from the septic shock (grade 4). On 16-APR-2008, a second chest x-ray was performed and showed pneumonia. On 17-APR-2008, urine fungus culture test was performed and the result was positive (abnormal). 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 18-APR-2008, the patient recovered from pneumonia (grade 2).

On 20-APR-2008, the patient had finished the 7 day course of antibiotics. Laboratory tests performed on 20-APR-2008 showed hemoglobin was 9.8 gr/L, white blood cell count was 5,780 gr/L, blood segmented neutrophil count was 70% and platelet count was 209,000. On 20-APR-2008 chest x-ray showed heterogeneous opacities not well-defined contours located in both pulmonary fields, in relation to the inflammatory process bilaterally. On 21-APR-2008, the patient was better, had recovered from pneumonia, oxygen therapy was discontinued and the patient was discharged from the hospital. On 21-APR-2008 the patient's discharge diagnosis was febrile neutropenia (grade 4), pneumonia (grade 2); back pain (grade 2) treated with tramadol HCl (TRAMAL) and septic shock. 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) and pneumonia (grade 2) were related to blinded study therapy and to carboplatin and paclitaxel. The reporting investigator felt that septic shock (grade 4) was related to blinded study therapy and was not related to therapy with carboplatin or to paclitaxel.

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 megestrol 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.

This is an amended report. In the therapy screen the route and frequency of paclitaxel was added as 1x IV. In the narrative, the dose of filgstrim(G-CSF) was changed from 600 ug twice daily to 300 ug twice daily. Body weight was removed from the laboratory test section.

A 7 day call pertaining to this report was placed to FDA on 18-APR-2008.

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

## DIAGNOSTIC TEST

Tests	Date	Value	Unit	Normal Range
physical examination Comment: CF	04/12/2008	153		
physical examination Comment: PA	04/12/2008	80/60		
chest X-ray Comment: 1st: 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 Comment: 2nd: pneumonia	04/16/2008			
chest X-ray Comment: 3rd: pneumonia-heterogenous opacities not well-defined contours/ both pulmonary fields in relation	04/20/2008			

## LABORATORY RESULTS

Tests	Date	Value	Unit	Normal Range
WBC count	04/12/2008	1.25	gr/L	
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	312.5	xmm [3]	
platelet count	04/12/2008	98	x 10 <sup>3</sup> /L	
pulse oximetry Comment: O2 @ 3L/min	04/12/2008	95	%	
WBC count	04/15/2008	7.4		
hemoglobin	04/15/2008	96	g/L	
neutrophil count	04/15/2008	6298.5		
urine culture Comment: Abnormal	04/17/2008	positive		
WBC count	04/20/2008	9.8		
WBC count	04/20/2008	5,780	gr/L	
hemoglobin	04/20/2008	9.8	gr/L	
platelet count	04/20/2008	209000		
segmented neutrophil	04/20/2008	70	%	

## C. Suspect medication(s)

## 1. Name (Give labeled strength &amp; 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  
 #2 INJ carboplatin Unk  
 #2 INJ carboplatin Unk  
 #2 INJ carboplatin Unk  
 #3 infusion (form) paclitaxel 200 mg  
 #3 infusion (form) paclitaxel 200 mg  
 #3 infusion (form) paclitaxel 200 mg

## 2. Dose, frequency &amp; route used

#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/1X/IV  
 #3 322 mg/1X/IV  
 #3 318 mg/1X/IV

## 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 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  
 #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			
#2				X
#2				X
#2				X
#3				X
#3				X
#3				X

## 6. Lot # (if known)

#1  
 #1  
 #1  
 #1  
 #2  
 #2  
 #2  
 #3  
 #3  
 #3

## 7. Exp date (if known)

#1  
 #1  
 #1  
 #1  
 #2  
 #2  
 #2  
 #3  
 #3  
 #3

## 8. Event reappeared after reintroduction

	YES	NO	N/A	UNK
#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