

# Merck Human Health Division

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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 0802USA04821
UF/Dist report #	
FDA Use Only	

A. Patient information			
1. Patient identifier Confidential AN 63507 in confidence	2. Age at time of event or 64 years Date of Birth: 11/23/1943	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 (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 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) 02/17/2008	4. Date of this report (mm/dd/yyyy) 03/24/2009
5. Describe event or problem This is in follow-up to report(s) previously submitted on 2/29/2008; 3/20/2008; 3/26/2008; 4/15/2008; 5/5/2008; 8/29/2008; 11/7/2008; 11/12/2008; 12/5/2008; 12/15/2008; 12/22/2008; 12/26/2008; 1/5/2009; 1/13/2009; 2/20/2009; 2/23/2009; 3/5/2009	

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)

Initial and follow up information has been received from an investigator concerning a 64 year old Asian female with a history of hemoptysis and toothache who entered a study, title as stated above who was randomized on 07-FEB-2008. On 07-FEB-2008, the patient was placed on blinded study therapy with either vorinostat, capsule, 400 mg or placebo administered on days -4 through 10 of cycle 1 (cycle equivalent to 25 days) for the treatment of non-small cell lung cancer (diagnosed on 11-NOV-2007,

(Continued on Additional Page)

6. Relevant tests/laboratory data, including dates Refer to Additional Page
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7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) MEDICAL HISTORY: Haemoptysis; Toothache
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C. Suspect medication(s)			
1. Name (Give labeled strength & mfr/labeler)			
# 1 CAP 0683-blinded therapy Unk			
# 2 INJ carboplatin Unk (Continued on Additional Page)			
2. Dose, frequency & route used		3. Therapy dates (if unknown, give duration) from/to (or best estimate)	
# 1 400 mg/DAILY/PO		# 1 02/07/2008 - 02/20/2008	
# 2 684 mg/1X/IV		# 2 02/13/2008 - 02/13/2008	
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 Non-small cell lung cancer		# 1 <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	
# 2 <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6. Lot #	
# 1		7. Exp. Date	
# 2		# 1	
# 2		# 2	
9. NDC # or Unique ID Unknown		8. Event reappeared after reintroduction.	
# 1 <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>		yes no N/A unk	
# 2 <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>		# 1 <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	
# 2 <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>		# 2 <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	
10. Concomitant medical products and therapy dates (excluded treatment of event)			
BENADRYL		02/13/2008 - 02/13/2008	
STEMETIL		02/13/2008 - 02/17/2008	
(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
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:	
4. Date received by manufacturer (mm/dd/yyyy) 02/26/2009	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
6. If IND, protocol # 0560096	9. Mfr. report number WAES 0802USA04821

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

T2 N2 M1, stage 4 Adenocarcinoma).

Concomitant suspect study therapy carboplatin AUC equivalent to 6 (684 mg), and paclitaxel 200 mg/m<sup>2</sup> (320), administered IV on day 1 of each treatment cycle. Other concomitant therapy included ondansetron HCL (ZOFTRAN), diphenhydramine (BENADRYL), dexamethasone (manufacturer unknown), ranitidine, tramadol hydrochloride (TRAMAL) and prochlorperazine maleate (STEMETIL).

On 17-FEB-2008 (cycle 1, day 10) at 10:05 the patient experienced hyponatremia (grade 4) (sodium was 105 mmol/L). On 18-FEB-2008, (Cycle 1, day 11) the patient experienced fatigue and vomiting. Laboratory evaluation on 18-FEB-2008 revealed serum sodium was 115 mmol/L (also reported as 110 mmol/L), absolute neutrophil count (ANC) was 3687 mm<sup>3</sup>, and white blood count (WBC) was 4400/ul. Serum osmolality was not checked. On 18-FEB-2008 patient was admitted to the hospital. She was treated with 3 percent sodium chloride intravenously. On 18-FEB-2008 chest x-ray showed patient's lungs were clear and no evidence of pleural effusion. On 18-FEB-2008, the patient recovered from hyponatremia (grade 4) with sequelae. On 19-FEB-2008 at 00:36 patient experienced hyponatremia sodium was 123 (grade 3) (NSAE). She was treated with 5% dextrose in normal saline IV 80cc /hr (19-FEB-2008 to 27-FEB-2008). She had fever of 38.5 C. No EKG test done and patient had normal blood pressure. No hypotension and no tachycardia. No other diagnosis was made. On 20-FEB-2008, the patient completed cycle 1 of study therapy. On 20-FEB-2008 she recovered from hyponatremia with sequelae (grade 3) (NSAE). On 21-FEB-2008 patient experienced severe febrile neutropenia (grade 3) (Cycle 1, day 15) and hyponatraemia (grade 1) (NSAE). On 21-FEB-2008 patient's serum sodium was 131 mmol/L, white blood count was 1000/ul and neutrophil was 54% and absolute neutrophil count (ANC) was 660/mm<sup>3</sup> (also reported 594). No electrocardiogram was done and her blood pressure was normal (value not reported). The event of severe febrile neutropenia (grade 3) prolonged hospitalization for the earlier reported hyponatremia. On 22-FEB-2008 patient recovered from hyponatremia with sequelae (grade 1) (NSAE). No other diagnosis was made. No culture was done. The patient was treated with cefepime for severe neutropenia (22-FEB-2008 to 28-FEB-2008). On 23-FEB-2008 the patient experienced hyponatremia (sodium was 127) (grade 3) (NSAE), ANC was 594 /mm<sup>3</sup> and WBC was 1100/ul. On 27-FEB-2008, the patient's serum sodium level was 136 mmol/L. On 27-FEB-2008 she recovered from hyponatremia (grade 3) (NSAE) and had no fever. Her WBC was 5400/ul and ANC was 3709 /mm<sup>3</sup>. On 28-FEB-2008 the patient recovered from severe febril neutrpenia (grade 3) with sequelae.

On 29-FEB-2008 patient was discharged from the hospital. Discharge diagnosis was hyponatremia and severe febrile neutropenia. After discharge the patient had follow up on 05-MAR-2008 and she had no symptoms of febrile neutropenia. On 05-MAR-2008, the patient was discontinued from the study due to the adverse event. Action taken regarding blinded study therapy for hyponatremia (grade 4) was none and action taken for severe febril neutrpenia (grade 3) was discontinued. Action taken regarding study therapy for hyponatremia (grade 1, NSAE) and hyponatremia (grade 3, NSAE) was none.

The reporting investigator felt that the hyponatremia (grade 4), severe febril neutropenia (grade 3) were related to study therapy and were related to suspect therapy carboplatin, paclitaxel. Action taken for suspect therapy carboplatin, paclitaxe were discontinued.

This is an amended report. The formulation for dexamethasone was changed to IV instead of tablet. Serum sodium result of 105 mmol/L in the laboratory test section was changed from 18-FEB-2008 to 17-FEB-2008.

Additional information is not expected.

This report is a corrected report, as amended.

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

## DIAGNOSTIC TEST

<u>Tests</u>	<u>Date</u>	<u>Value Unit</u>	<u>Normal Range</u>
chest X-ray	02/18/2008		
Comment: Lungs are clear and no evidence of pleural effusion			
blood pressure measurement	02/19/2008		
Comment: normal			

## LABORATORY RESULTS

<u>Tests</u>	<u>Date</u>	<u>Value Unit</u>	<u>Normal Range</u>
serum sodium	02/17/2008	105 mmol/L	135 - 145
WBC count	02/18/2008	4400 /ul	4500 - 11000
absolute neutrophil count	02/18/2008	3687 mm <sup>3</sup>	1800 - 8200
serum sodium	02/18/2008	110 mmol/L	135 - 145
Comment: hyponatremia grade 3			
serum sodium	02/18/2008	115 mmol/L	135 - 145

Comment: hyponatremia grade 3

body temp	02/19/2008	38.5 C	
serum sodium	02/19/2008	123 mmol/L	135 - 145
WBC count	02/21/2008	1000 /ul	4500 - 11000
absolute neutrophil count	02/21/2008	660 mm3	1800 - 8200
neutrophil count	02/21/2008	54 %	
serum sodium	02/21/2008	131 mmol/L	135 - 145
WBC count	02/23/2008	1100 /ul	4500 - 11000
absolute neutrophil count	02/23/2008	594 mm3	1800 - 8200
serum sodium	02/23/2008	127 mmol/L	135 - 145
WBC count	02/27/2008	5400 /ul	4500 - 11000
absolute neutrophil count	02/27/2008	3709 mm3	1800 - 8200
serum sodium	02/27/2008	136 mmol/L	135 - 145

## C. Suspect medication(s)

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

#3 INJ paclitaxel Unk

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

#3 320 mg/1X/IV

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

#3 02/13/2008 - 02/13/2008

## 4. Diagnosis for use (indication)

#3 Non-small cell lung cancer

## 5. Event abated after use stopped or dose reduced

	YES	NO	N/A	UNK
#3	X			

## 6. Lot # (if known)

#3

## 7. Exp date (if known)

#3

## 8. Event reappeared after reintroduction

	YES	NO	N/A	UNK
#3			X	

## C. Suspect medication(s)

## 10. Concomitant medical products and therapy dates (exclude treatment of event)

TRAMAL	02/13/2008 - Cont
dexamethasone	02/13/2008 - 02/13/2008
ondansetron	02/13/2008 - 02/13/2008
ondansetron	02/13/2008 - 03/04/2008
ranitidine	02/13/2008 - 02/13/2008