

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 0802USA04821

UF/Dist report #

FDA Use On

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 <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) 01/13/2009	
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			
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 vomiting and 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, T2 N2 M1, stage 4			
(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: Haemoptysis; Toothache CONCURRENT CONDITIONS: Vomiting; Prophylaxis of nausea and vomiting			

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 #		7. Exp. Date	
# 1		# 1	
# 2		# 2	
9. NDC # or Unique ID		8. Event reappeared after reintroduction.	
Unknown		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 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			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) 01/09/2009			3. Report source. (check all that apply)
6. If IND, protocol # 0560096			<input checked="" type="checkbox"/> foreign
7. Type of report			<input checked="" type="checkbox"/> study
<input type="checkbox"/> 5-day <input type="checkbox"/> 30-day			<input type="checkbox"/> literature
<input type="checkbox"/> 7-day <input type="checkbox"/> Periodic			<input type="checkbox"/> consumer
<input type="checkbox"/> 10-day <input type="checkbox"/> Initial			<input checked="" type="checkbox"/> health professional
<input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up# 13			<input type="checkbox"/> user facility
5. (A)NDA #			<input type="checkbox"/> company representative
IND # 58915			<input type="checkbox"/> distributor
STN #			<input type="checkbox"/> other:
PMA/510(k) #			
Combination Product <input type="checkbox"/> Yes			
Pre-1938 <input type="checkbox"/> Yes			
OTC product <input type="checkbox"/> Yes			
9. Mfr. report number			
WAES 0802USA04821			
8. Adverse event term(s)			
HYPONATRAEMIA			
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

Adenocarcinoma).

Concomitant suspect study therapy carboplatin AUC equivalent to 6 (684 mg), and paclitaxel 200 mg/m² (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). 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 19-FEB-2008 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). No other diagnosis was made. On 20-FEB-2008, the patient completed cycle 1 of study therapy. On 21-FEB-2008 patient experienced hyponatraemia (grade 1) (NSAE). On 21-FEB-2008 patient's serum sodium was 131 mmol/L. On 23-FEB-2008 the patient experienced hyponatremia (sodium was 127) (grade 3) (NSAE). On 27-FEB-2008, the patient's serum sodium level was 136 mmol/L.

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 20-FEB-2008 she recovered from hyponatremia with sequelae (grade 3) (NSAE). On 22-FEB-2008 patient recovered from hyponatremia with sequelae (grade 1) (NSAE). No other diagnosis was made. On 27-FEB-2008 she recovered from hyponatremia (grade 3) (NSAE). The patient was treated with cefepime for severe neutropenia (22-FEB-2008 to 28-FEB-2008).

On 29-FEB-2008 patient was discharged from the hospital. Discharge diagnosis was hyponatremia. On 05-MAR-2008, the patient was discontinued from the study due to the adverse event. Action taken for blinded study therapy for hyponatremia (grade 4) was none. Action taken for study therapy for hyponatremia (grade 1, NSAE) was none. Action taken for study therapy for hyponatremia (grade 3) (NSAE) was discontinued.

The reporting investigator felt that the hyponatremia (grade 4) was related to blinded study therapy and Hyponatremia (grade 1) (NSAE), Hyponatremia (grade 3) (NSAE), Hyponatremia (grade 3) (NSAE) were related to study therapy. The reporting investigator reported that hyponatremia (grade 4), Hyponatremia (grade 1), Hyponatremia (grade 3) (NSAE), Hyponatremia (grade 3) (NSAE) were related to therapy carboplatin, Paclitaxel. Action taken for therapy with carboplatin, Paclitaxel were discontinued.

Per the investigator the severe febrile neutropenia (reported as ECI previously) was no longer considered to be an SAE nor associate with this SAE.

Additional information is not expected.

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			

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
serum sodium	02/18/2008	110 mmol/L	135 - 145
Comment: hyponatremia grade 3			
serum sodium	02/18/2008	105 mmol/L	135 - 145
Comment: hyponatremia grade 3			
serum sodium	02/18/2008	115 mmol/L	135 - 145
Comment: hyponatremia grade 3			
serum sodium	02/19/2008	123 mmol/L	135 - 145
serum sodium	02/21/2008	131 mmol/L	135 - 145
serum sodium	02/23/2008	127 mmol/L	135 - 145
serum sodium	02/27/2008	136 mmol/L	135 - 145

C. Suspect medication(s)

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

#3 paclitaxel Unk

2. Dose, frequency & 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