

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 0805USA02256
UF/Dist report #	
	FDA Use On

A. Patient information			
1. Patient Identifier Unk AN 61527 in confidence	2. Age at time of event: or 55 years Date of Birth: 08/21/1952	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 209 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 checked="" 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)	02/11/2009
5. Describe event or problem			
This is in follow-up to report(s) previously submitted on 5/14/2008; 5/20/2008; 5/28/2008; 6/12/2008; 6/16/2008; 7/25/2008; 8/19/2008; 8/27/2008; 8/29/2008; 9/5/2008; 9/11/2008; 9/19/2008; 10/2/2008; 10/21/2008; 10/23/2008; 11/10/2008; 1/20/2009; 2/6/2009			

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 55 year old white male with fatigue, weakness in right hand, alopecia, anemia, cough, depression, dyspepsia, hyperglycaemia, hypertension, insomnia, occasional fungal topical infection and weight decreased and a history of radiotherapy (37.5 Gy from 30-JAN-2008 to 19-FEB-2008), gout, anorexia, metastases to brain and brain resection (17-JAN-2008) who on

(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: Gout; Metastases to brain; Anorexia; Brain operation; Radiotherapy CONCURRENT CONDITIONS: Fatigue; Depression; Hyperglycaemia; Insomnia; Dehydration; Fungal infection; Weight decreased; Hypertension; Dyspepsia; Cough; Hands weakness of; Alopecia; Anaemia

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 03/21/2008 - 04/03/2008
# 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 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 type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>
		# 2 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>

9. NDC # or Unique ID	10. Concomitant medical products and therapy dates (excluded treatment of event)
Unknown	BENADRYL 03/25/2008-03/25/2008 BENADRYL 04/23/2008-04/23/2008
(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)	3. Report source (check all that apply)
02/03/2009	<input type="checkbox"/> foreign <input checked="" type="checkbox"/> study <input type="checkbox"/> literature <input type="checkbox"/> consumer health professional <input type="checkbox"/> user facility <input type="checkbox"/> company representative <input type="checkbox"/> distributor <input type="checkbox"/> other:
6. If IND, protocol #	5. (A)NDA #
0560026	IND # 58915
7. Type of report	STN #
<input type="checkbox"/> 5-day <input type="checkbox"/> 30-day <input type="checkbox"/> 7-day <input type="checkbox"/> Periodic <input type="checkbox"/> 10-day <input type="checkbox"/> Initial <input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up# 18	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 0805USA02256

8. Adverse event term(s)
ANOREXIA; CHOLECYSTITIS; DEHYDRATION; PYREXIA; BACTERAEEMIA; FATIGUE

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-MAR-2008 was allocated/ randomized to a study, title as stated above.

On 21-MAR-2008 the patient was placed on cycle one blinded study therapy of either vorinostat, 400 mg daily for cycle 1 placebo administered on day(s) -4 through 10 of cycle 1 (cycle 1 equivalent to 25 days and each subsequent cycle 21 days) (or days 1 through 14 for each subsequent cycle) for treatment of non-small cell lung cancer (current staging 10-MAR-2008; T4;N2;M1;stage IV).

Concomitant study therapy included paclitaxel, 200 mg/m², administered IV over 3 hours on 25-MAR-2008 (412 mg) and 23-APR-2008 (355 mg) and carboplatin, administered IV over 30 minutes on 24-MAR-2008 (806 mg) and on 23-APR-2008 (652 mg) (day 1 of each treatment cycle.) Other concomitant therapy included lisinopril (manufacturer unknown), allopurinol, ondansetron, omeprazole, dexamethasone (manufacturer unknown), saline, diphenhydramine, ranitidine, lorazepam and prochlorperazine

On 28-MAR-2008, the patient had vomiting (non-serious) and worsening fatigue (non-serious) with occasional constipation (non-serious) and myalgias (non-serious). On 31-MAR-2008, the patient developed a rash (non-serious), nausea (non-serious) and became dehydrated (non-serious). On 11-APR-2008, cycle 1, day 21 the patient experienced anorexia (grade 3) and fever (grade 1) and was hospitalized. The patient was treated with acetaminophen (11-APR-2008 to 13-MAY-2008) for fever. On 11-APR-2008, the patient developed fatigue (grade 3), which prolonged hospitalization. On 15-APR-2008 the patient was treated with naproxen sodium (ALEVE) (15-APR-2008 to 13-MAY-2008) for fever. On 16-APR-2008, cycle 1, day 26 the patient was thought to be dehydrated due to decreased fluid intake and was admitted for IV fluids. The patient had a weight loss of 5.2 kilograms. Sodium was 137 mmol/L. Vitals on admission were temperature was 99 F, pulse was 120, respiration was 20 and blood pressure was 104/78. The patient became dehydrated (grade 3), which prolonged hospitalization. The patient was administered a one time dose of 2 liters of 0.9% normal saline IV for dehydration (14-APR-2008 to 16-APR-2008). Blood cultures for infection was negative. The ANC was 4440u/L and the fever peaked at 101.9F. On 16-APR-2008, the patient experienced nausea (non-serious), oral leukoplakia (non-serious), halitosis (non-serious), disconjugated gaze (non-serious) and weight loss (non-serious). On 16-APR-2008 a chest CT was performed and results were stable disease. A chest X-ray was performed and was negative for infection. The patient had no history of syncope. On 16-APR-2008 a MRI of the head was performed and was negative for metastasis. Urine cultures for infection was negative. The patient was treated with pantoprazole (16-APR-2008 to 17-APR-2008) for dyspepsia (NSAE). On 17-APR-2008 nasopharyngeal swab was negative. The patient recovered from anorexia (grade 3), fatigue (grade 3), dehydration (grade 3), and fever on 17-APR-2008. On 17-APR-2008 the patient was discharged from the hospital. Discharge diagnosis was fever of unknown etiology, dehydration and anorexia. On 23-APR-2008 the patient received pre-medication of diphenhydramine, ranitidine and ondansetron prior to the beginning of cycle 2. On 23-APR-2008 the patient began cycle 2 of study therapy; blinded therapy was reduced to vorinostat 300mg or placebo, carboplatin 652 mg and paclitaxel was 355mg due to the SAE's of anorexia (grade 3), fatigue (grade 3) and dehydration (grade 3). On 30-APR-2008, the patient experienced fatigue (non-serious). On 05-MAY-2008 the patient developed pain (non-serious) and was treated with oxycodone (05-MAY-2008 to 13-MAY-2008). On 08-MAY-2008 cycle 2, day 15 the patient again developed fever (non-serious) and intermittent rigors (non-serious). On 08-MAY-2008 the patient had a computed axial tomography of the chest and abdomen and revealed cholecystitis. On 08-MAY-2008, the patient was admitted to the oncology unit for treatment of acalculous cholecystitis (grade 2) and bacteremia (grade 3) secondary to cholecystitis. Blood cultures was positive for gram negative rod, likely E.Coli. The patient had restaging scan which showed cholecystitis was on 08-MAY-2008. It was reported that the patient had a recent history of low grade fever, neutrophils WNL, pain in right upper quadrant. The patient did not have diarrhea, nausea, or vomiting. There was no tumor located near gallbladder. Abdominal pain was characterized by physician as "progressive, intermittent sharp right upper quadrant pain". Maximum temperature was 102F, total serum bilirubin test was 1.0, serum aspartate aminotransferase test (AST) was 39 and serum alanine aminotransferase test (ALT) was 1. On 10-MAY-2008, the patient was administered lidocaine 1% and had a laproscopic cholecystectomy with no complication. The patient recovered from acalculous cholecystitis (grade 3) and bacteremia (grade 3) on 10-MAY-2008. On 11-MAY-2008 the patient was administered amoxicillin (+) clavulanate potassium (AUGMENTIN) (11-MAY-2008 to 22-MAY-2008) for bacteremia. Hemoglobin was 8 g/dL (normal range 13.6-17.2). The patient was off treatment when the fever occurred and the event was considered resolved. On 12-MAY-2008, the patient experienced anaemia (grade 3) (non-serious) and was treated with a one time dose (2 litres) of blood transfusion IV. On 12-MAY-2008 the patient recovered from rigors-intermittent. On 13-MAY-2008 anemia (grade 3) (non-serious) was resolved and the patient was discharged. On 28-MAY-2008 the patient began cycle 3 of study therapy. Blinded study therapy was reduced to vorinostat 200mg or placebo, carboplatin 542.3mg and paclitaxel 297 mg respectively due to the SAE of acalculous cholecystitis. The patient's pain (grade 2) and fatigue (grade 2) persisted. On 09-JUL-2008 the patient recovered from fatigue (grade 2). The discharge diagnosis was fever and dehydration of unknown etiology, fatigue and acalculous cholecystitis bacteremia. Blinded study therapy dose was reduced because of anorexia, fatigue, dehydration and acalculous cholecystitis. On 18-JUN-2008 the patient began cycle 4 of study therapy. On 11-JUL-2008 the patient began cycle 5 of study therapy. On 30-JUL-2008 the investigator decided to discontinue study medication for the patient.

On 05-OCT-2008 the patient's gallbladder was removed.

Treatment medications administered for non-serious adverse events included sodium phosphate, dibasic (+) sodium phosphate, monobasic enema (FLEET) (07-MAY-2008), polyethylene glycol 3350 (MIRALAX) (08-MAY-2007 to 13-MAY-2008), docusate senna (07-MAY-2008 to 13-MAY-2008), piperacillin sodium (+) tazobactam sodium (ZOSYN) (09-MAY-2008 to 10-MAY-2008) for an antibiotic, 0.9% normal saline (25-APR-2008; 08-MAY-2008 to 13-MAY-2008) for hydration, morphine IV (08-MAY-2008 to 13-MAY-2008) for pain control, heparin injection (08-MAY-2008 to 13-MAY-2008) for prophylaxis for deep vein thrombosis (DVT), and pantoprazole (08-MAY-2008 to 13-MAY-2008) for dyspepsia, potassium chloride (11-MAY-2008).

The investigator felt that acalculous cholecystitis (grade 3) were related to blinded study therapy and study therapy with carboplatin and paclitaxel. Anorexia (grade 3) was not related to blinded study therapy or study therapy with carboplatin and paclitaxel. Bacteremia (grade 3) was not related to blinded study therapy and was not related to study therapy carboplatin and paclitaxel. Dehydration (grade 3), fatigue (grade 3) and fever (grade 1) were not related to study therapy and were related to study therapy carboplatin and paclitaxel.

Acalculous cholecystitis (grade 3) was considered to be an other important medical event.

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>
chest X-ray	04/16/2008			
Comment: negative for infection				
magnetic resonance imaging	04/16/2008			
Comment: head - negative for metastasis				
computed axial tomography	04/16/2008			
Comment: stable disease				
blood pressure measurement	04/16/2008	104/78		
diagnostic laboratory test	05/08/2008			
Comment: "restaging scan" showed cholecystitis; no tumor in gallbladder				
computed axial tomography	05/08/2008			
Comment: chest and abdomen showed cholecystitis				

LABORATORY RESULTS

<u>Tests</u>	<u>Date</u>	<u>Value</u>	<u>Unit</u>	<u>Normal Range</u>
absolute neutrophil count	04/16/2008	4440		
body temp	04/16/2008	101.9	F	
body temp	04/16/2008	99	F	
serum sodium	04/16/2008	137	mmol/L	
blood culture	04/16/2008			
Comment: negative for infection				
urine culture	04/16/2008			
Comment: negative				
respiratory rate measurement	04/16/2008	20		
total heartbeat count	04/16/2008	120		
upper respiratory culture	04/17/2008			
Comment: nasopharyngeal culture negative for influenza A,B,RSV				
body temp	05/08/2008	102	F	
serum alanine aminotransferase	05/08/2008	1		
serum aspartate aminotransferase	05/08/2008	39		
total serum bilirubin	05/08/2008	1.0		
blood culture	05/08/2008			
Comment: positive for gram neg bacteria				
blood culture	05/10/2008			
Comment: negative for growth				

C. Suspect medication(s)

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

- #1 CAP 0683-blinded therapy Unk
- #2 infusion (form) carboplatin Unk
- #2 infusion (form) carboplatin Unk
- #3 infusion (form) paclitaxel 200 mg
- #3 infusion (form) paclitaxel 175 mg

2. Dose, frequency & route used

#1 Unk/Unk/PO
#2 806 mg/1X/IV
#2 652 mg/1X/IV
#3 412 mg/1X/IV
#3 355 mg/1X/IV

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

#1 04/23/2008 - 05/06/2008
#2 03/25/2008 - 03/25/2008
#2 04/23/2008 - 04/23/2008
#3 03/25/2008 - 03/25/2008
#3 04/23/2008 - 04/23/2008

4. Diagnosis for use (indication)

#1 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

5. Event abated after use stopped or dose reduced

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

6. Lot # (if known)

#1
#2
#2
#3
#3

7. Exp date (if known)

#1
#2
#2
#3
#3

8. Event reappeared after reintroduction

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

C. Suspect medication(s)

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

DECADRON TABLETS	03/24/2008 - 06/21/2008
allopurinol	01/??/2007 - Cont
lisinopril	01/??/2007 - 05/08/2008
lorazepam	03/25/2008 - 07/30/2008
omeprazole	04/01/2008 - 06/18/2008
ondansetron	04/01/2008 - 07/09/2008
ondansetron	04/23/2008 - 04/23/2008
prochlorperazine	03/25/2008 - 07/30/2008
ranitidine	03/25/2008 - 03/25/2008
ranitidine	04/23/2008 - 04/23/2008
sodium chloride	04/01/2008 - 04/01/2008