

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 0804USA06512
UF/Dist report #	
	FDA Use On

A. Patient information

1. Patient identifier Confidential AN 61529 in confidence	2. Age at time of event: or <u>77 years</u> Date of Birth: <u>06/28/1930</u>	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 134 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) <u>04/28/2008</u>	4. Date of this report (mm/dd/yyyy) <u>02/26/2009</u>

5. Describe event or problem
This is in follow-up to report(s) previously submitted on 5/9/2008; 5/27/2008; 6/9/2008; 6/20/2008; 7/9/2008; 7/16/2008; 7/18/2008; 8/11/2008; 9/5/2008; 9/19/2008; 9/25/2008; 10/30/2008; 12/23/2008

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 77 year old white male on thrombosis and eye infection prophylaxis, with angina pectoris, bilateral knee pain, anxiety, anemia, diarrhea, burning and itching anus, hypercholesterolemia, hypotension, dehydration, nausea, vomiting, arterial occlusion, carotid artery stenosis, chronic obstructive pulmonary disease, gastroesophageal reflux, hypertension and Paget's disease of bone and a history of abdominal aortic aneurysm, haemoptysis, non st segment elevation

(Continued on Additional Page)

6. Relevant tests/laboratory data, including dates

Refer to Additional Page

7. Type of report	5. (A)NDA #
<input type="checkbox"/> 5-day <input type="checkbox"/> 30-day	IND # <u>58915</u>
<input type="checkbox"/> 7-day <input type="checkbox"/> Periodic	STN # _____
<input type="checkbox"/> 10-day <input type="checkbox"/> Initial	PMAV _____
<input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up# <u>13</u>	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 0804USA06512

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>03/24/2008 - 04/06/2008</u>
# 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
# 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 checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
	# 2 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
10. Concomitant medical products and therapy dates (excluded treatment of event)	
APO-RAMIPRIL	01/31/2008-Cont
GARAMYCIN	04/10/2008-04/17/2008
(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) <u>12/09/2008</u>	3. Report source. (check all that apply)
6. If IND, protocol # <u>0560018</u>	<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# <u>13</u>	<input type="checkbox"/> user facility
	<input type="checkbox"/> company representative
	<input type="checkbox"/> distributor
	<input type="checkbox"/> other
	9. Mfr. report number
	WAES 0804USA06512

8. Adverse event term(s)
ASTHENIA; DEHYDRATION

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.

(Continued on Additional Page)

B. Adverse event or product problem**5. Describe event or problem**

myocardial infarction and stent placement who entered a study title as stated above. On 24-MAR-2008 the patient was placed on blinded therapy, with either vorinostat, capsule, 400 mg, or placebo, once a day for the treatment of non-small cell lung cancer (diagnosed 28-FEB-2008 current staging 28-FEB-2008, T4/N2/M1/stage IV). Concomitant study therapy included carboplatin IV 6 AUC and paclitaxel IV 200 mg/m². Concomitant therapy included atorvastatin calcium (LIPITOR), clopidogrel bisulfate (PLAVIX), ramipril (APO-RAMIPRIL), metoprolol tartrate (PMS METOPROLOL), aspirin, codeine, zopiclone (IMOVANE), senna (SENOKOT), gentamicinSO₄ (GARAMYCIN), hydrocortisone, clonazepam (RIVOTRIL), sodium chloride, oxazepam (SERAX), loperamide HCl (IMODIUM), and clopidogrel bisulfate (PLAVIX).

On 28-MAR-2008, the patient experienced fatigue (non-serious). On 28-APR-2008 the patient experienced generalized weakness (grade 3) (Cycle 2 Day 11) and was hospitalized. It was reported that this information was obtained from the patient's family saying that the patient was extremely weak, not eating, and had fallen. The family was advised to bring the patient to the emergency room. Upon arrival to the ER, blood tests were done which showed that the patient was neutropenic, thrombocytopenic and anemic. Vital signs showed that the patient was hypotensive (84/43). The patient was found to be dehydrated and also had diarrhea while in the ER. Cultures were also done and sent back negative. Yellow skin not observed during the assessment but the patient was pale. On 28-APR-2008 diagnostic laboratory testing included: absolute blood neutrophil (ANC) was $.4 \times 10^9/L$, hemoglobin (HGB) 89 g/L and white blood cell (WBC) $1.8 \times 10^9/L$; 29-APR-2008 ANC $2.2 \times 10^9/L$, HGB 116 g/L, and WBC 4.3; 30-APR-2008 HGB 110 g/L. The patient was treated with loperamide hydrochloride (IMODIUM) for the diarrhea. He also received a normal saline bolus for the hypotension and was infused with 2 units of packed red blood cells for anemia. Blinded therapy was interrupted. On 04-MAY-2008, the patient recovered. Upon return to the clinic on 08-MAY-2008, the patient was still weak but improving and had no complaints of diarrhea. Cycle 3 of chemotherapy was postponed for one week to allow the patient to become stronger and have a cat scan. On 15-MAY-2008, the patient received cycle 3 chemotherapy and will continue in the study. The patient was also placed on hydration cream for dry skin. No discharge summary was available.

Follow up information indicated that the nurse reported that the patient was hospitalized in the emergency department on 26-MAY-2008. The patient had weakness (one week), oliguria, dyspnea, dizziness, nausea, vomiting, diarrhea for 4 days, dehydration and loss of appetite. Upon arrival to the emergency room, blood tests were done which showed that the patient was hypocalcemic, thrombocytopenic, and anemic. Vital signs showed that the patient was afebrile but hypotensive (80/40). The patient was hospitalized for dehydration post chemotherapy (grade 3) (cycle 3, day 12). Study therapy was interrupted. He was infused with 2 units packed red blood cells for anemia. On 26-MAY-2008 diagnostic laboratory testing included: ANC $1.6 \times 10^9/L$, chloride 94 mmol/L, creatinine 220 umol/L, HGB 90 g/L, sodium 129 mmol/L, urea 12 mmol/L and WBC $3.1 \times 10^9/L$. On 27-MAY-2008 the patient received therapy with metoclopramide hydrochloride (MAXERAN), dimenhydrinate (GRAVOL), pantoprazole sodium (PANTOLOC) for nausea and vomiting and "diltiazem", calcium carbonate, vitamin D, bacitracin ointment, and potassium chloride (K-DUR) for hypokalemia, and a normal saline bolus for dehydration and hypotension. It was reported that the patient was treated with magnesium hydroxide (PHILLIPS' MILK OF MAGNESIA) and ciprofloxacin hydrochloride (CIPRO) for the urinary tract infection. It was also reported that the patient was treated with chlorhexidine soap for prophylaxis of an infection on 27-MAY-2008. On 27-MAY-2008 diagnostic laboratory testing included ANC $3.1 \times 10^9/L$, HGB 115 g/L, potassium 3 mmol/L and WBC $5.2 \times 10^9/L$. The patient felt well, recovered well on fluids and was discharged home on 28-MAY-2008. On 28-MAY-2008 diagnostic laboratory testing included chloride 105 mmol/L, creatinine 131 mmol/L, HGB 116 g/L, potassium 4.8 mmol/L, sodium 137 mmol/L, urea and 8.2 mmol/L. A urine culture on 29-MAY-2008 showed that the patient had a UTI. Discharge diagnosis included dehydration post chemotherapy.

The patient returned to the clinic on 05-JUN-2008 and was still weak (grade 1) and was on antibiotics for the UTI. He has not had any repeat episodes as described above. The patient was later taken off study due to toxicities.

It was reported that on 26-JUN-2008 the patient discontinued the study due to the events.

It was also reported that the patient experienced non-serious events diarrhea, insomnia, loss of appetite, dry skin, fatigue, epigastric pain, bilateral knee pain, soft bowels, right eye pain, burning anal area pain, mouth pain, neutropenia, anemia, thrombocytopenia, hypotension, dizziness, dehydration, motor neuropathy, and right eye clear discharge.

The reporting investigator felt that generalized weakness (grade 3) and dehydration post chemotherapy (grade 3) were related to study therapy.

This is an amended report. The secondary suspect therapies of carboplatin and paclitaxel now reads infusion (form), IV. In the narrative blinded therapy now reads "with either vorinostat, capsule, 400 mg, or placebo." In the lab and narrative the hemoglobin result on 29-APR-2008 now reads 116g/L. In the narrative "normal saline bolus" added for dehydration and hypotension.

Additional information is not expected.

This is a corrected report, as amended.

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>
blood pressure measurement	04/28?/2008	84/43	
diagnostic laboratory test Comment: cultures were negative	04/28?/2008		
diagnostic laboratory test Comment: neutropenic, thrombocytopenic and anemic	04/28?/2008		
blood transfusion Comment: hgb increased	04/29/2008		
diagnostic laboratory test Comment: mrsa, vre and vre culture- negative normal	04/29/2008		

LABORATORY RESULTS

<u>Tests</u>	<u>Date</u>	<u>Value</u> <u>Unit</u>	<u>Normal Range</u>
WBC count	04/28/2008	1.8 10 ⁹ /L	4 - 11
absolute neutrophil count	04/28/2008	.4 10 ⁹ /L	1.8 - 7.5
hemoglobin	04/28/2008	89 g/L	140 - 175
MRSA test Comment: negative	04/29/2008		
WBC count	04/29/2008	4.3 10 ⁹ /L	4 - 11
absolute neutrophil count	04/29/2008	2.2 10 ⁹ /L	1.8 - 7.5
hemoglobin	04/29/2008	116 g/L	140 - 175
hemoglobin	04/30/2008	110 g/L	140 - 175
WBC count	05/26/2008	3.1 10 ⁹ /L	4 - 11
absolute neutrophil count	05/26/2008	1.6 10 ⁹ /L	1.8 - 7.5
hemoglobin	05/26/2008	90 g/L	140 - 175
serum chloride	05/26/2008	94 mmol/L	98 - 108
serum creatinine	05/26/2008	220 mmol/L	55 - 120
serum sodium	05/26/2008	129 mmol/L	134 - 144
serum uric acid	05/26/2008	12 mmol/L	3.2 - 8.5
WBC count	05/27/2008	5.2 10 ⁹ /L	4 - 11
absolute neutrophil count	05/27/2008	3.1 10 ⁹ /L	1.8 - 7.5
hemoglobin	05/27/2008	115 g/L	140 - 175
serum potassium	05/27/2008	3 mmol/L	3.5 - 5.5
hemoglobin	05/28/2008	116 g/L	140 - 175
serum chloride	05/28/2008	105 mmol/L	98 - 108
serum creatinine	05/28/2008	131 mmol/L	55 - 120
serum potassium	05/28/2008	4.8 mmol/L	3.5 - 5.5
serum sodium	05/28/2008	137 mmol/L	134 - 144
serum uric acid	05/28/2008	8.2 mmol/L	3.2 - 8.5
urine culture Comment: lactose-neg coliform urinary tract infection	05/29/2008		

7. Other relevant history including preexisting medical conditions

disease of bone; Thrombosis prophylaxis; Anaemia; Diarrhoea; Burning anal; Anal pruritus; Eye infection; Hypotension; Dehydration; Nausea; Vomiting; Knee pain; Dry skin; Insomnia

C. Suspect medication(s)

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

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

2. Dose, frequency & route used

#1 Unk/DAILY/PO
 #1 Unk/DAILY/PO
 #2 368 mg/1X/IV
 #2 351 mg/1X/IV
 #2 350 mg/1X/IV
 #3 347 mg/1X/IV
 #3 340 mg/1X/IV
 #3 336 mg/1X/IV

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

#1 04/18/2008 - 04/28/2008
 #1 05/15/2008 - 05/26/2008
 #2 03/28/2008 - 03/28/2008
 #2 04/18/2008 - 04/18/2008
 #2 05/15/2008 - 05/15/2008
 #3 03/28/2008 - 03/28/2008
 #3 04/18/2008 - 04/18/2008
 #3 05/15/2008 - 05/15/2008

4. Diagnosis for use (indication)

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

5. Event abated after use stopped or dose reduced

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

6. Lot # (if known)

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

7. Exp date (if known)

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

8. Event reappeared after reintroduction

	YES	NO	N/A	UNK
#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)

IMODIUM	04/23/2008 - 04/23/2008
IMOVANE	04/03/2008 - Cont
LIPITOR	01/31/2008 - Cont
PLAVIX	01/31/2008 - Cont
PMS METOPROLOL	01/31/2008 - Cont
RIVOTRIL	04/17/2008 - 05/28/2008
SENOKOT (SENNA)	04/03/2008 - 05/27/2008
aspirin	01/01/2007 - 05/01/2008
codeine	04/03/2008 - 04/23/2008
hydrocortisone	04/10/2008 - 04/17/2008