

**MedWatch**

The FDA Medical Products Reporting Program

Mfr report #	WAES 0805USA01319
UF/Dist report #	
FDA Use Only	

**A. Patient information**

1. Patient identifier Unk AN 61535 in confidence	2. Age at time of event: or 66 years Date of Birth: 03/10/1942	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 211 lbs
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**B. Adverse event or product problem**

1.  Adverse event and/or  Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)

Death (mm/dd/yyyy)  Disability or Permanent Damage

Life-threatening  Congenital Anomaly/Birth Defect

Hospitalization-initial or prolonged  Other Serious (Important Medical Events)

Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of event (mm/dd/yyyy) 05/05/2008

4. Date of this report (mm/dd/yyyy) 03/23/2009

5. Describe event or problem

This is in follow-up to report(s) previously submitted on 5/12/2008; 5/28/2008; 6/6/2008; 6/16/2008; 7/31/2008; 8/5/2008; 8/13/2008; 9/2/2008; 10/8/2008; 10/13/2008; 12/29/2008; 1/5/2009; 2/13/2009; 3/19/2009

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 66 year old white male with benign prostatic hyperplasia, anorexia (grade 1), allergic reaction to cephalosprins, chronic sinusitis, intervertebral disc degeneration, diverticulitis, dyspnea on exertion (grade 2), elevated lactate dehydrogenase, elevated partial thromboplastin time (grade 2), erectile dysfunction, fatigue (grade 1), general osteoarthritis, vascular disease, genito urinary weak stream (grade 1),

(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: Necrotising fasciitis; Penicillin allergy; Rotator cuff repair; Benign neoplasm; Rotator cuff tear; Epistaxis; Left inguinal hernia; Carotid bruit; Dermatitis; Gout

CONCURRENT CONDITIONS: Benign prostatic hyperplasia; Allergic reaction to antibiotics; Intervertebral disc degeneration;

(Continued on Additional Page)

**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

# 1 Unk/Unk/PO

# 2

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

# 1 04/24/2008 - 05/06/2008

# 2

4. Diagnosis for use (indication)

# 1 Non-small cell lung cancer

# 2

5. Event abated after use stopped or dose reduced.

	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 type="checkbox"/>	<input type="checkbox"/>

6. Lot #

# 1

# 2

7. Exp. Date

# 1

# 2

8. Event reappeared after reintroduction.

	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 type="checkbox"/>	<input type="checkbox"/>

9. NDC # or Unique ID

Unknown

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

ACCURETIC 03/12/2008-05/11/2008

COMPAZINE 04/09/2008-Cont

(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)

foreign

study

literature

consumer

health professional

user facility

company representative

distributor

other:

4. Date received by manufacturer (mm/dd/yyyy) 03/12/2009

5. (A)NDA #

IND # 58915

STN #

PMA/510(k) #

Combination Product  Yes

Pre-1938  Yes

OTC product  Yes

9. Mfr. report number  
WAES 0805USA01319

8. Adverse event term(s)

THROMBOSIS; THROMBOSIS; PULMONARY EMBOLISM;  
PERIPHERAL ISCHAEMIA

**E. Initial reporter**

1. Name, address & phone #

2. Health professional?  
 YES  NO

3. Occupation

4. Initial reporter also sent report to FDA.  
 yes  no  unk

## B. Adverse event or product problem

## 5. Describe event or problem

hemoglobinemia (grade 1) hemorrhoids, hypertension, hyperlipidemia, intermittent hemoptysis (grade 1), intermittent insomnia (grade 1) lacunar infarction, low absolute lymphocyte count (grade 1), lower extremity neuropathy, metabolic syndrome, productive cough (grade 1) ceftriaxone sodium (ROCEPHIN) allergy, sensory neuropathy (grade 1) and tinnitus and a history of a benign neoplasm (large bowel), necrotizing fasciitis, anemia, aortic valve disorder, carotid bruit (right ear), epistaxis, dermatitis, gout, inguinal hernia (left groin), penicillin reaction, rotator cuff tear and rotator cuff repair who entered a study, title as stated above. On 24-APR-2008 the patient was randomized into study and placed on cycle 1 therapy with blinded therapy, (either vorinostat, 400 mg capsule, PO or placebo) administered on day(s) -4 through 10 of cycle 1 (cycle equivalent to 25 days) (or days 1 through 14 for each subsequent cycle) for the treatment of non-small cell lung cancer (original diagnosis 25-MAR-2008; stage IV adenocarcinoma ;current staging 09-APR-2008: (T2, N3, M1). Concomitant study therapy included carboplatin (999 mg) and paclitaxel, 200 mg/m<sup>2</sup> [2], (443 mg), both administered intravenously (IV) on 28-APR-2008 (day 1 of each treatment cycle). Other premedication included ondansetron hydrochloride (ZOFTRAN), dexamethasone sodium phosphate (manufacturer unknown), diphenhydramine hydrochloride and famotidine (manufacturer unknown). Concomitant medication included albuterol, atenolol, multivitamins (unspecified) and calcium antacids. On 05-MAY-2008, cycle 1, day 12, the patient developed thrombosis (grade 3) and peripheral artery ischemia (grade 3) and was hospitalized. It was reported that the patient had a progressively cyanotic right foot with elevation. The patient had complained of intermittent numbness and cyanosis since 30-APR-2008 and intermittent leg cramps since 28-APR-2008 after receiving chemotherapy treatment. Examination revealed weak pedal pulses bilaterally. Bilateral ultrasound of lower extremities on 05-MAY-2008 showed bilateral deep vein thrombosis, below the knee (BTK). The patient was anticoagulated with heparin infusion in D5W- 100 units/ml, enoxaparin sodium (LOVENOX) 100 mg, subcutaneous injection once a day and warfarin sodium (COUMADIN) alternating 5 mg/7.5 mg (discontinued on 22-MAY-2008). On 06-MAY-2008, acetaminophen (+) oxycodone hydrochloride, 5 mg, PO, PRN, was started for pain. Diagnostic test on 07-MAY-2008 showed mild-moderate disease in both legs and stent was placed on the same day. Therapy with enoxaparin was started on 07-MAY-2008, 100 mg, BID, SC for treatment of thrombosis and metoclopramide, 10 mg, PRN, was started on the same day for treatment of nausea. Furosemide was administered as diuretic on 08-MAY-2008. Therapy with enoxaparin continued with marked improvement in his plasminogen activator inhibitor (PAI). Factor Xa levels were not evaluated while the patient was on low molecular weight heparin (LMWH). On 12-MAY-2008 the patient was started on atorvastatin. Hydrochlorothiazide (+) quinapril hydrochloride (ACCURETIC) was also administered from 12-MAY-2008 to 27-MAY-2008 for the treatment of the patient's thrombosis/pulmonary embolism. The patient was discharged from the hospital recovered with sequelae on 14-MAY-2008. Discharge diagnoses were right lower extremity showed peripheral vascular disease; bilateral lower extremity deep vein thrombosis. Other discharge diagnoses included right lung adenocarcinoma; hyperlipidemia; coronary artery disease; hypertension; degenerative disc disease. International normalized ratio on 19-MAY-2008 was 1.6. On 19-MAY-2008, the patient was treated with cycle 2 at dose level -1 for paclitaxel, carboplatin, blinded therapy, per protocol. Therapy with vorinostat 300 mg or placebo was reduced on 19-MAY-2008 due to thrombosis. On 22-MAY-2008, the patient's international normalized ratio was 4.2 (target was 2). Acetaminophen (TYLENOL) was administered starting on 27-May-2008 for pain (continuing). On 05-JUN-2008, the patient called the site to report left arm swelling, redness, warmth and pain, which started on 04-JUN-2008 (day 3 after last study medication). The patient was on anticoagulation therapy with warfarin (started again on 23-MAY-2008) for previous clot to right leg. INR was 2.2 (grade 2, non-serious) on 04-JUN-2008. The patient was brought in for evaluation and ultrasound of upper extremities. Ultrasound of left arm showed clots in axillary vein. There was no access device, venous or otherwise in the affected limb. On 05-JUN-2008 the physician discontinued warfarin and started patient on enoxaparin, 150 mg subcutaneously (SQ). The patient was given injection teaching on 06-JUN-2008. It was reported that the patient's swelling, redness, warmth and pain decreased in intensity from 05-JUN-2008 to 06-JUN-2008. The patient continued on enoxaparin on an outpatient basis and was considered recovered with sequelae from thrombosis (grade 3).

On 09-JUN-2008, the patient reported for cycle 3 day 1 treatment (day 8 after last study medication) complaining of worsening dyspnea on exertion and worsening fatigue which started on 07-JUN-2008. Pulse oximetry on RA was 97% and 97-100% with walking test. Patient was sent for CT of chest with PE protocol which revealed bilateral segmental and subsegmental pulmonary emboli. The patient was admitted for heparin therapy and vascular consult. On 09-JUN-2008 therapy with heparin infusion D5W, 100 units/ml was started, and the patient was also given oxycodone for pain management (PRN; continuing).

On 10-JUN-2008 therapy with heparin infusion was discontinued, and therapy with enoxaparin (LOVENOX) 100 mg SQ twice daily was started, and was reported to be continued without further embolic or thrombotic events.

The patient was discontinued from study medications due to lack of efficacy and was considered recovered with sequelae. On 11-JUN-2008 the patient was discharged. Discharge diagnosis was pulmonary embolism and deep vein thrombosis. No action with study therapy was taken. The patient had multiple thrombotic episodes and continued with anticoagulation until his demise (no details provided). The patient's peripheral artery disease (PAD) did not cause any problems since the placement of the stents.

The patient was given psyllium husk (METAMUCIL) for constipation from 01-NOV-2007 and aspirin was given as antiplatelet and prophylaxis from 01-NOV-2007, both are reported to be continued.

The patient experienced the following events and received treatment medications as follows: (OCEAN NASAL SPRAY) inhalant for hemoptysis, non-serious) on 27-MAY-2008 and continues; folic acid as a supplement on 09-JUN-2008 and continues; docusate sodium for constipation, 09-MAY-2008 to 15-MAY-2008; senna for constipation, 09-MAY-2008 to 15-MAY-2008; on 09-JUN-2008, 1000 mcg of vitamin B-12 as a subcutaneous injection as a supplement; and a (MEDROL DOSE-PAK) as an anti-inflammatory from 10-JUN-2008 until 16-JUN-2008.

The reporting investigator felt that thromboses (grade 3) (05-MAY-2008 and 04-JUN-2008 and peripheral artery ischemia (grade 3) were related to blinded study therapy and were not related to paclitaxel or to carboplatin.

The investigator felt that the patient's pulmonary emboli (grade 3) was related to blinded study therapy and related to therapy with paclitaxel and carboplatin.

The investigator also considered that the patient's thrombosis (grade 3) (04-JUN-2008) and pulmonary emboli (grade 3) were related to warfarin sodium (COUMADIN) therapy.

The following non-serious adverse events were also reported: intermittent hemoptysis (12-MAY-2008; not recovered; not related), hemoptysis, R/T O2 (12-MAY-2008), hypertension r/t + meds (12-MAY-2008; recovered; not related), thrombocytopenia (27-MAY-2008; recovered 02-JUN-2008; related), hypotension (27-MAY-2008; recovered 02-JUN-2008; not related), "r/t overmed" (27-MAY-2008), leukocytopenia (02-JUN-2008; recovered 09-JUN-2008; related), hemoglobinemia (02-JUN-2008), INR, inc r/t anticoagulant w/warfarin sodium (COUMADIN) (02-JUN-2008; not recovered; not related), harsh wheezing, bilaterally (02-JUN-2008; not recovered; not related), shortness of breath, inc (09-JUN-2008; not recovered; not related), lymphopenia (09-JUN-2008; not recovered; related).

The reporting investigator felt that the patient's thrombosis (grade 3) (04-JUN-2008) was an other important medical event.

Additional information is not expected.

This is an amended report. The dose of enoxaparin (LOVENOX) on 10-JUN-2008 was changed from 100 mg SQ daily to 100 mg SQ twice daily.

#### 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>
venous ultrasound Comment: bilateral DVT's in lower extremities	05/05/2008			
physical examination Comment: weak pedal pulses bilaterally	05/05/2008			
diagnostic pathological examination Comment: revealed weak pedal pulses bilaterally	05/05/2008			
angioplasty Comment: --no residual stenosis with vigorous filling of the distal vasculature	05/07/2008			
diagnostic laboratory test Comment: PVR showed mild-moderate disease in both legs	05/07/2008			
diagnostic laboratory test Comment: ankle pressure/waveform, bilateral:mild disease at rest bilat. in legs	05/09/2008			
venous ultrasound Comment: left arm showed clots in axillary vein.	06/05/2008			
arterial ultrasound Comment: bilateral U/S: positive for DVT Left arm	06/05/2008			
chest computed axial tomography Comment: bilateral segmental and subsegmental PE's	06/09/2008			

##### LABORATORY RESULTS

<u>Tests</u>	<u>Date</u>	<u>Value</u>	<u>Unit</u>	<u>Normal Range</u>
INR	05/19/2008	1.6		
INR	06/04/2008	2.2		
pulse oximetry	06/09/2008	97	%	
pulse oximetry Comment: 97 to 100 with walking	06/09/2008		%	

## 7. Other relevant history including preexisting medical conditions

Diverticulitis; Erectile dysfunction; Haemorrhoids; Hypertension; Hyperlipidaemia; Lacunar infarction; Neuropathy; Drug hypersensitivity; Tinnitus; Dyspnoea; Anaemia; Aortic valve disease; Vascular disorder; Productive cough; Metabolic syndrome; Absolute lymphocyte count decreased; Insomnia; Haemoptysis; Haemoglobinaemia; Poor urinary stream; Osteoarthritis generalised; Fatigue; Partial thromboplastin time prolonged; Lactate dehydrogenase increased; Chronic sinusitis; Anorexia; Nausea; Breath shortness; Constipation; Antiplatelet therapy; Pain; Diuresis

## C. Suspect medication(s)

## 1. Name (Give labeled strength &amp; 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 200 mg  
 #4 warfarin Unk  
 #4 warfarin Unk

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

#1 Unk/Unk/PO  
 #2 999 mg/1X/IV  
 #2 817 mg/1X/IV  
 #3 443 mg/1X/IV  
 #3 379 mg/1X/IV  
 #4 5 mg/DAILY/PO  
 #4 5 mg/DAILY/PO

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

#1 05/19/2008 - 06/01/2008  
 #2 04/28/2008 - 04/28/2008  
 #2 05/19/2008 - 05/19/2008  
 #3 04/28/2008 - 04/28/2008  
 #3 05/19/2008 - 05/19/2008  
 #4 05/05/2008 - 05/22/2008  
 #4 05/23/2008 - 06/05/2008

## 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  
 #4 Thrombosis  
 #4 Thrombosis

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

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

## 6. Lot # (if known)

#1  
 #2  
 #2  
 #3  
 #3  
 #4  
 #4

## 7. Exp date (if known)

#1  
 #2  
 #2  
 #3  
 #3  
 #4  
 #4

## 8. Event reappeared after reintroduction

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

## C. Suspect medication(s)

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

METAMUCIL	01/01/2007 - Cont
ZOFRAN	04/09/2007 - Cont
ZOFRAN	04/28/2008 - 04/28/2008
albuterol	03/08/2008 - Cont
aspirin	01/01/2007 - Cont
atenolol	03/12/2008 - 05/12/2008
dexamethasone sodium phosphate	04/28/2008 - 04/28/2008
diphenhydramine hydrochloride	04/28/2008 - 04/28/2008
famotidine	04/28/2008 - 04/28/2008
fluticasone propionate (+) salme	04/24/2008 - Cont
gastrointestinal preparations (u	08/24/2007 - Cont
vitamins (unspecified)	08/24/2007 - Cont