

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 0805USA00867
UF/Dist report #	
FDA Use On	

A. Patient information

1. Patient identifier RB AN 12654 in confidence	2. Age at time of event: or 61 years Date of Birth:	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 172 lbs
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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 checked="" 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) 04/25/2008	4. Date of this report (mm/dd/yyyy) 02/26/2009

5. Describe event or problem
This is in follow-up to report(s) previously submitted on 5/13/2008; 6/26/2008; 8/1/2008

A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial of Oral Suberoylanilide Hydroxamic Acid (L-001079038) in Patients with Advanced Malignant Pleural Mesothelioma Previously Treated with Systemic Chemotherapy

Information has been received from an investigator concerning a 61 year old male with hypercholesterolemia, hypertension, dyspnea, pain and pulmonary embolism, and with a history of abdominal aortic aneurysm, chronic obstructive pulmonary disease, emphysema, malignant pleural mesothelioma, and shingles, who entered a study title as stated above. On 11-APR-2008 the patient was placed on blinded therapy, capsule, 300 mg, twice a day for the treatment of mesothelioma. Concomitant therapy included atorvastatin calcium (LIPITOR), atenolol, warfarin sodium (COUMADIN), prednisone and fentanyl.

(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: Pleural mesothelioma malignant; Shingles; Emphysema; Chronic obstructive pulmonary disease; Abdominal aortic aneurysm
CONCURRENT CONDITIONS: Hypercholesterolaemia; Hypertension; Dyspnoea; Pain; Pulmonary embolism

C. Suspect medication(s)

1. Name (Give labeled strength & mfr/labeler)		3. Therapy dates (if unknown, give duration) from/to (or best estimate)	
# 1 CAP 0683-blinded therapy Unk		# 1 04/11/2008 - 05/28/2008	
# 2		# 2	
2. Dose, frequency & route used		5. Event abated after use stopped or dose reduced.	
# 1 300 mg/BID/PO		yes no N/A unk	
# 2		# 1 <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
4. Diagnosis for use (indication)		# 2 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
# 1 Mesothelioma		8. Event reappeared after reintroduction.	
# 2		yes no N/A unk	
6. Lot #		# 1 <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	
# 1		# 2 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
# 2		# 1 <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	
7. Exp. Date		# 2 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
# 1			
# 2			
9. NDC # or Unique ID			
Unknown			
10. Concomitant medical products and therapy dates (excluded treatment of event)			
COUMADIN		Unk - Unk	
LIPITOR		Unk - Unk	

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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) 02/18/2009		3. Report source. (check all that apply)	
6. If IND, protocol # 0140041		<input 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:	
7. Type of report		5. (A)NDA #	
<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# 3		IND # 58915 STN # 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 0805USA00867	

8. Adverse event term(s)
DYSPNOEA; DYSPNOEA; ATRIAL FIBRILLATION

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

On 25-APR-2008 the patient experienced an abrupt onset of dyspnea (Grade 3) while ambulating outdoors. He was admitted to the hospital for management of dyspnea. Blinded therapy was interrupted. On presentation to the emergency room, temperature was 98.5, heart rate 121, respirations 46, blood pressure 131/100 and oxygen saturation 82% on room air and 94% on non-rebreather. During the emergency department course he suddenly had a rapid improvement in his clinical status with significant decrease in tachypnea, work of breathing, able to speak in full sentences and appeared significantly more comfortable. It was thought that he had a large mucus plug that he had cleared which was responsible for his shortness of breath, with which he initially presented. Physical examination (date unspecified) revealed heart rate 101, respirations 26, blood pressure 111/88 and oxygen saturation 93% on nasal cannula. In general the subject was mildly short of breath and appeared stable. Chest x-ray (date unspecified) showed new calcification in the left hemithorax. Electrocardiogram (EKG) on an unspecified date showed sinus tachycardia at 116, left atrial enlargement and no ischemic changes. Computed tomography (CT) on an unspecified date showed a large mass in the lower lobe of the left lung with extensive likely tumor growth up through the left lung. There was some external pressure on the left pulmonary artery from tumor burden, it was incomplete and obstructing the artery. However, in addition to this the left pulmonary artery appeared to have a large clot adjacent to it as well. There appeared to be right midsegmental pulmonary embolism as well. He was treated with albuterol, albuterol sulfate (+) ipratropium bromide (COMBIVENT), heparin, vancomycin and piperacillin sodium (+) tazobactam sodium (ZOSYN). He was transfused 2 units of packed red blood cells (RBC) for anemia. The subject recovered and was discharged from the hospital on 2 liters nasal cannula continuous oxygen on 28-APR-2008. Further information was expected from the site.

On 28-MAY-2008 blinded therapy was discontinued due to progressive disease. On 01-JUN-2008, the subject was admitted to the hospital with grade 3 dyspnea. The subject had an episode of atrial fibrillation grade 3 while hospitalized and was treated with diltiazem hydrochloride (CARDIZEM). On 10-JUN-2008 the patient was discharged home and continued on diltiazem hydrochloride (CARDIZEM) after discharge from the hospital. Subsequently, the patient recovered.

Follow up information indicated that the site was unable to obtain a discharge summary.

The reporting investigator felt that dyspnea (25-APR-2008) was related to study therapy and dyspnea (grade 3) (onset 01-JUN-2008) and atrial fibrillation were not related to the study drug.

Dyspnea (onset date 25-APR-2008) was considered to be disabling.

Additional information is 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>
blood pressure measurement Comment: see narrative	04/25/2008			
blood pressure measurement Comment: see narrative	04/25?/2008			
physical examination Comment: see narrative				
chest X-ray Comment: see narrative				
electrocardiogram Comment: see narrative				
chest computed axial tomography Comment: see narrative				

LABORATORY RESULTS

<u>Tests</u>	<u>Date</u>	<u>Value</u>	<u>Unit</u>	<u>Normal Range</u>
INR	04/25/2008			5.7
body temp Comment: see narrative	04/25/2008			
hematocrit	04/25/2008			28.4
platelet count	04/25/2008			281,000
pulse oximetry Comment: see narrative	04/25/2008			
pulse oximetry Comment: see narrative	04/25?/2008			
serum hemoglobin test	04/25/2008			9.6
respiratory rate measurement	04/25?/2008			

Comment: see narrative
• respiratory rate measurement 04/25/2008
Comment: see narrative
total heartbeat count 04/25/2008
Comment: see narrative
total heartbeat count 04/25/2008
Comment: see narrative
serum creatinine
serum hemoglobin test

C. Suspect medication(s)

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

atenolol	Unk - Unk
fentanyl	05/23/2008 - Unk
prednisone	04/25/2008 - Unk