

# MedWatch

The FDA Medical Products Reporting Program

## Merck Human Health Division

For use by user-facilities,  
distributors and manufacturers for  
MANDATORY reporting

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Merck Facsimile of FDA Form 3500A  
Approved by FDA (10/21/1993)

Mfr report # WAES 0711USA07005

UF/Dist report #

FDA Use Onl

A. Patient information			
1. Patient identifier Confidential AN 64503 in confidence	2. Age at time of event: or 61 years Date of Birth: 10/03/1946	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 180 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 checked="" type="checkbox"/> Death 11/24/2007 (mm/dd/yyyy)	<input type="checkbox"/> Disability or Permanent Damage
<input checked="" 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) 11/21/2007	4. Date of this report (mm/dd/yyyy) 03/02/2009

5. Describe event or problem  
This is in follow-up to report(s) previously submitted on 6/2/2008; 6/4/2008; 8/12/2008; 1/26/2009; 1/28/2009; 2/3/2009; 2/9/2009

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 61 year old white male with a target lesion into right adrenal gland, arterial hypertension, mediastinal lymph adenopathy and liver metastasis and a history of bronchoscopy who on 26-SEP-2007 was randomized to a study, title as stated above. Concomitant therapy included dexamethasone, ondansetron, cimetidine and diphenhydramine HCl.

On 26-SEP-2007, the patient was randomized to study and placed on therapy with blinded therapy with either

(Continued on Additional Page)

6. Relevant tests/laboratory data, including dates Refer to Additional Page
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7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc) MEDICAL HISTORY: Bronchoscopy CONCURRENT CONDITIONS: Malignant neoplasm of adrenal gland; Hypertension arterial; Lymphadenopathy mediastinal; Metastases to liver
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C. Suspect medication(s)			
1. Name (Give labeled strength & mfr/labeler) # 1 CAP 0683-blinded therapy 400 mg # 2 _____ (Continued on Additional Page)			
2. Dose, frequency & route used # 1 400 mg/DAILY/PO # 2 _____		3. Therapy dates (if unknown, give duration) from/to (or best estimate) # 1 09/26/2007 - 10/09/2007 # 2 _____	
4. Diagnosis for use (indication) # 1 Adenocarcinoma # 2 _____		5. Event abated after use stopped or dose reduced. 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"/>	
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) cimetidine 11/09/2007-11/09/2007 dexamethasone 11/08/2007-11/12/2007 (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) <input checked="" 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	
4. Date received by manufacturer (mm/dd/yyyy) 01/29/2009	5. (A)NDA # IND # 58915 STN # _____ PMA/ 510(k) # _____ Combination Product Pre-1938 <input type="checkbox"/> Yes <input type="checkbox"/> No OTC product <input type="checkbox"/> Yes <input type="checkbox"/> No
6. If IND, protocol # 0560042	7. Type of report <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# 7
9. Mfr. report number WAES 0711USA07005	

8. Adverse event term(s) HYPOTENSION
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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**

vorinostat, capsule, 400 mg, daily or placebo, administered orally on days 1-14 on cycle 1 (cycle equivalent to 25 days) for the treatment of adenocarcinoma (diagnosed 22-AUG-2007; Current Staging date 16-AUG-2007: IV, T2, N1, M1).

On 19-OCT-2007 the patient was administered a reduced dose of cycle 2 with either vorinostat, capsule, 300 mg, daily or placebo, carboplatin 850 mg, IV and paclitaxel 350 mg, IV.

On 09-NOV-2007 the patient was administered cycle 3 of with either vorinostat, capsule, 300 mg, daily or placebo, carboplatin 850 mg, IV and paclitaxel 175 mg/m<sup>2</sup> (375) mg, IV.

Concomitant study therapy included carboplatin, AUC equivalent to 6 (850 mg) and paclitaxel 200 mg/m<sup>2</sup> (400 mg) administered IV on day 1 of each treatment cycle.

On 16-NOV-2007 absolute neutrophil count was 4.01. Study medication was stopped by the patient independently on 20-NOV-2007. The patient's wife reported that on 21-NOV-2007, (cycle 3, day 13), the patient was hospitalized to the emergency care department with severe weakness, dizziness and low arterial pressure (80/40 mm Hg). The investigator indicated that the patient developed hypotension (grade 5) his condition was declining and therefore he was hospitalized. On 22-NOV-2007, (cycle 3, day 14) an active call to the patient was made as a reminder and necessity to come for delivery of analysis in the central laboratory. It was reported that the patient was not dehydrated and had not had any nausea, vomiting, diarrhea fever or infection. The patient did not receive any treatment specific to the hypotension. It was reported that the cardiac function was not assessed by the investigator because the patient was hospitalized to the emergency care department at another hospital. On 23-NOV-2007 the patient completed the study and discontinued study medication. On 24-NOV-2007, the patient died in the emergency care department by cardiovascular insufficiency. Pathomorphology diagnosis were listed as "cardiovascular and pulmonary insufficiency, NSCLC left lung with metastatic lung disease." It was also reported that the direct and dominant cause of death was cardiovascular and pulmonary insufficiency.

The reporting investigator considered hypotension, grade 5 to be immediately life-threatening.

The reporting investigator felt that hypotension, grade 5 was related to MK-0683 blinded study therapy but was not related to carboplatin or paclitaxel.

This is an amended report incorporating the current staging date of 16-AUG-2007 into the narrative.

Additional information is not expected.

A 7 calendar day telephone/facsimilie report was made to the FDA on 02-JUN-2008.  
This is amended as corrected.

**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: arterial pressure		80/40 mm Hg	

**LABORATORY RESULTS**

<u>Tests</u>	<u>Date</u>	<u>Value</u> <u>Unit</u>	<u>Normal Range</u>
absolute neutrophil count	11/16/2007	4.01	

**C. Suspect medication(s)****1. Name (Give labeled strength & mfr/labeler)**

- #1 CAP 0683-blinded therapy 300 mg
- #1 CAP 0683-blinded therapy 300 mg
- #2 infusion (form) carboplatin 850 mg
- #2 infusion (form) carboplatin 850 mg
- #2 infusion (form) carboplatin 850 mg
- #3 infusion (form) paclitaxel 400 mg
- #3 infusion (form) paclitaxel 350 mg
- #3 infusion (form) paclitaxel 375 mg

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

#1 300 mg/DAILY/PO  
 #1 300 mg/DAILY/PO  
 #2 850 mg/1X/IV  
 #2 850 mg/1X/IV  
 #2 850 mg/1X/IV  
 #3 400 mg/1X/IV  
 #3 350 mg/1X/IV  
 #3 375 mg/1X/IV

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

#1 10/19/2007 - 11/01/2007  
 #1 11/09/2007 - 11/20/2007  
 #2 09/30/2007 - 09/30/2007  
 #2 10/19/2007 - 10/19/2007  
 #2 11/09/2007 - 11/09/2007  
 #3 09/30/2007 - 09/30/2007  
 #3 10/19/2007 - 10/19/2007  
 #3 11/09/2007 - 11/09/2007

## 4. Diagnosis for use (indication)

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

## 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)

diphenhydramine hydrochloride	11/09/2007 - 11/09/2007
ondansetron	11/09/2007 - 11/09/2007