

**MERCK RESEARCH LABORATORIES**  
Division of Merck & Co., Inc.  
West Point, Pennsylvania 19486

December 16, 2008

Re: 0683-blinded therapy

Dear Doctor:

This letter is to provide follow-up information on an adverse experience concerning 0683-blinded therapy which has been reported to you previously.

U.S. Food and Drug Regulations require sponsors of clinical studies conducted under an IND to notify the FDA of any serious and unexpected adverse experiences occurring in a clinical study filed under that IND when either the investigator or the sponsor believes that there is a reasonable possibility that the experience may have been drug related or if the drug relationship is unknown. The sponsor is also required to inform all investigators working with the particular drug under the IND.

In compliance with these requirements, the enclosed report has been submitted to the FDA and, because you are an investigator in a clinical study under this IND, a copy is enclosed for your information.

Please append this report to the Confidential Investigator's Brochure for the appropriate investigational product or to the Product Circular for the appropriate marketed product and retain in your files.

Please submit a copy of this report promptly (within less than 30 days of receipt) to your Institutional Review Board(s) even though the report may not involve a patient in your study.

This report does not necessarily reflect a conclusion by Merck or the FDA that the drug caused or contributed to the adverse experience. If you have any questions about this report, please contact the Merck monitor for your study.

Enclosure(s): WAES # 0712USA09142 GENSTUDY # 056-0084, AN # 61514

# MedWatch

# 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)

The FDA Medical Products Reporting Program

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Mfr report #	WAES 0712USA09142
UF/Dist report #	
	FDA Use On

### A. Patient information

1. Patient identifier Unk AN 61514 in confidence	2. Age at time of event: or 46 years Date of Birth: 04/29/1961	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight 177 pounds
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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) 12/21/2007

4. Date of this report (mm/dd/yyyy) 12/16/2008

5. Describe event or problem

This is in follow-up to report(s) previously submitted on 1/2/2008; 1/3/2008; 2/13/2008; 2/27/2008; 3/6/2008; 3/27/2008; 4/15/2008; 9/10/2008; 9/24/2008

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)

Initial and follow-up information has been received from an investigator concerning a 46 year old white female with Chronic obstructive pulmonary disease (COPD), pain, anorexia, nausea, fatigue and a sleep disorder who entered a study, title as stated above. On 10-DEC-2007, the patient was placed on cycle one blinded study therapy, capsule, of either vorinostat 400 mg or placebo, administered daily for 14 days every 3 weeks, for the treatment of non-small cell lung cancer. Concomitant study therapy included carboplatin, 600 mg (AUC equivalent to 6), administered IV on day 3 and

(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.)

CONCURRENT CONDITIONS: Pain; Sleep disorder; Nausea; Anorexia; Fatigue; Chronic obstructive pulmonary disease; Premedication; Tobacco user

### C. Suspect medication(s)

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

# 1 CAP 0683-blinded therapy Unk

# 2 carboplatin Unk

(Continued on Additional Page)

2. Dose, frequency & route used

# 1 Unk/Unk/PO

# 2 600 mg/1X/IV

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

# 1 12/10/2007 - 12/20/2007

# 2 12/13/2007 - 12/13/2007

4. Diagnosis for use (indication)

# 1 Non-small cell lung cancer

# 2 Non-small cell lung cancer

5. Event abated after use stopped or dose reduced.

yes no N/A unk

# 1

# 2

6. Lot #

# 1

# 2

7. Exp. Date

# 1

# 2

8. Event reappeared after reintroduction.

yes no N/A unk

# 1

# 2

9. NDC # or Unique ID

Unknown

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

BENADRYL 12/13/2007-12/13/2007

DECADRON (DEXAMETHASONE) 12/13/2007-12/13/2007

(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)

foreign

study

literature

consumer

health professional

user facility

company representative

distributor

other:

4. Date received by manufacturer (mm/dd/yyyy) 12/10/2008

5. (A)NDA #

IND # 58915

STN #

PMA/

510(k) #

Combination Product  Yes  No

Pre-1938  Yes  No

OTC product  Yes  No

6. If IND, protocol #

0560084

7. Type of report

5-day  30-day

7-day  Periodic

10-day  Initial

15-day  Follow-up# 9

9. Mfr. report number

WAES 0712USA09142

8. Adverse event term(s)

FEBRILE NEUTROPENIA

### 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

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

paclitaxel, 200 mg/m<sup>2</sup> (364 mg), administered IV on day 3; both initiated on 13-DEC-2007. Concomitant therapy included clonazepam (KLONOPIN), dronabinol (MARINOL), fentanyl (DURAGESIC), metoclopramide hydrochloride (REGLAN), dexamethasone (MSD), ranitidine hydrochloride (ZANTAC), diphenhydramine hydrochloride (BENADRYL) for pre-medication and acetaminophen (+) oxycodone hydrochloride (ENDOCET). On 21-DEC-2007, the patient developed neutropenic fever and shortness of breath and presented to an emergency room with increased shortness of breath. Other symptoms were weakness, cough with productive sputum and complaint of fever for 2 days. The patient's temperature was 99.2, white blood cell (WBC) count was 1.1, platelet count was 91,000 and breath sounds were decreased bilaterally with few scattered rhonchi. The patient was hospitalized with the diagnosis of neutropenic fever (grade 3) and respiratory distress. On 21-DEC-2007, study therapy was interrupted due to neutropenic fever. A Chest x-ray was performed on the patient and revealed pleural effusion. Blood and sputum cultures revealed gram positive cocci and therapy with intravenous cefepime, levofloxacin (LEVAQUIN) and ceftriaxone sodium (ROCEPHIN) was initiated. The patient was placed on reverse isolation and therapy with filgrastim (NEUPOGEN), injection, daily. Oxygen support at 2L/min via nasal cannula, albuterol sulfate (+) ipratropium bromide (DUONEB) with mucomyst added and IV fluids were administered. On 24-DEC-2007, the patient had no further complaints, WBC count was stable at 15. On 24-DEC-2007, the patient was discharged to home. The discharge diagnoses were reported as lung cancer, COPD, tobacco abuse and neutropenic fever. The patient was reported to be recovered from the febrile neutropenia on 25-DEC-2007. On 27-DEC-2007 the patient returned to the clinic for follow-up. She was improved after antibiotics and steroid therapy.

The investigator felt that neutropenic fever (grade 3) was related to blinded study therapy and study therapy with carboplatin and paclitaxel.

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 Comment: pleural effusion	12/25/2007			

## LABORATORY RESULTS

<u>Tests</u>	<u>Date</u>	<u>Value</u>	<u>Unit</u>	<u>Normal Range</u>
absolute neutrophil count	12/20/2007	500		2000 - 7800
WBC count	12/21/2007	1100	K/uL	4100 - 10900
body temp	12/21/2007	99.2		
platelet count	12/21/2007	91000	K/uL	140000 - 440000
blood culture Comment: gram + cocci	12/21/2007			
sputum culture Comment: gram + cocci	12/21/2007			
WBC count	12/24/2007	15		
WBC count	12/25/2007	0.2		

## C. Suspect medication(s)

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

#3 paclitaxel Unk

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

#3 364 mg/1X/IV

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

#3 12/13/2007 - 12/13/2007

## 4. Diagnosis for use (indication)

#3 Non-small cell lung cancer

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

YES NO N/A UNK

#3 X

6. Lot # (if known)

#3

7. Exp date (if known)

#3

8. Event reappeared after reintroduction

	YES	NO	N/A	UNK
#3				X

## C. Suspect medication(s)

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

DURAGESIC	11/28/2007 - 02/11/2008
ENDOCET	11/01/2007 - Cont
KLONOPIN	11/08/2007 - Cont
MARINOL	12/03/2007 - Cont
REGLAN	12/03/2007 - Cont
ZANTAC	12/13/2007 - 12/13/2007