

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

09-FEB-2009

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

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 0712USA09142
UF/Dist report #	
FDA Use Onl	

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

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)	4. Date of this report (mm/dd/yyyy)
12/21/2007	02/09/2009

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; 12/16/2008

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 (diagnosed 23-OCT-2007, current staging T3,N2,M1, stage IV).

(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	3. Therapy dates (if unknown, give duration) from/to (or best estimate)
# 1 Unk/Unk/PO	# 1 12/10/2007 - 12/20/2007
# 2 600 mg/1X/IV	# 2 12/13/2007 - 12/13/2007
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 Non-small cell lung cancer	# 1 <input checked="" 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 checked="" type="checkbox"/>

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	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)	5. (A)NDA #
12/12/2008	IND # 58915
6. If IND, protocol #	STN #
0560084	PMA/510(k) #
7. Type of report	Combination Product <input type="checkbox"/> Yes
<input type="checkbox"/> 5-day <input type="checkbox"/> 30-day	Pre-1938 <input type="checkbox"/> Yes
<input type="checkbox"/> 7-day <input type="checkbox"/> Periodic	OTC product <input type="checkbox"/> Yes
<input type="checkbox"/> 10-day <input type="checkbox"/> Initial	9. Mfr report number
<input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up# 10	WAES 0712USA09142
3. Report source. (check all that apply)	
<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:	

8. Adverse event term(s)
FEBRILE NEUTROPENIA

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.

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

Concomitant study therapy included carboplatin, 600 mg (AUC equivalent to 6), administered IV on day 3 and paclitaxel, 200 mg/m² (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, cycle 1 day 12, 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.

This is an amended report, the narrative has been updated with current staging and cycle information.

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 Unit</u>	<u>Normal Range</u>
chest X-ray	12/25/2007		
Comment: pleural effusion			

LABORATORY RESULTS

<u>Tests</u>	<u>Date</u>	<u>Value 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	12/21/2007		
Comment: gram + cocci			
sputum culture	12/21/2007		
Comment: gram + cocci			
WBC count	12/24/2007	15	
WBC count	12/25/2007	0.2	

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

#3 paclitaxel Unk

2. Dose, frequency & 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