

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

Date: 14-JAN-2009

Re: MK-0683/Blinded Therapy

Dear Doctor:

This letter is to provide follow-up information on an adverse experience concerning MK-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 # 0805USA04831, GENSTUDY # 056-0035 AN # 62529

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 0805USA04831
UF/Dist report #	
	FDA Use Only

A. Patient information			
1. Patient identifier Confidential AN 62529 in confidence	2. Age at time of event: or 73 years Date of Birth: 09/29/1934	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 191 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 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)	04/05/2008	4. Date of this report (mm/dd/yyyy)	01/14/2009
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5. Describe event or problem
This is in follow-up to report(s) previously submitted on 6/2/2008; 6/4/2008; 6/6/2008; 7/9/2008; 8/13/2008; 9/15/2008; 9/29/2008

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)

Information has been received from an investigator concerning a 73 year old white male with breathlessness, bronchoalveolar carcinoma, and a history of computed tomography pulmonary angiogram, diagnostic arthroscopy of the knee and 2 varicose vein strippings of the left leg who entered a study, title as stated above. On 17-DEC-2007, the patient was originally diagnosed with adenocarcinoma, primary tumor T4, no nodal involvement, M1 distant metastasis, overall stage IV. From 31-MAR-2008 to 13-APR-2008, cycle 1, the patient received therapy with blinded therapy (either vorinostat 100 mg capsule,

(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: Varicose veins stripping; Arthroscopy; Varicose vein
CONCURRENT CONDITIONS: Lung neoplasm malignant; Stomatitis; Breathlessness

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	3. Therapy dates (if unknown, give duration) from/to (or best estimate)
# 1 Unk/Unk/PO	# 1 03/31/2008 - 04/13/2008
# 2	# 2

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	# 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 #	7. Exp. Date	8. Event reappeared after reintroduction.
# 1	# 1	yes no N/A unk
# 2	# 2	# 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)
DIFFLAM 04/15/2008-Cont PRO-BANTHINE 12/24/2007-Cont
(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 #
01/06/2009	IND # 58915
6. If IND, protocol #	STN #
0560035	PMA/510(k) #
7. Type of report	Combination Product
<input type="checkbox"/> 5-day <input type="checkbox"/> 30-day	<input type="checkbox"/> Yes
<input type="checkbox"/> 7-day <input type="checkbox"/> Periodic	Pre-1938 <input type="checkbox"/> Yes
<input type="checkbox"/> 10-day <input type="checkbox"/> Initial	OTC product <input type="checkbox"/> Yes
<input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up# 7	9. Mfr. report number
	WAES 0805USA04831

8. Adverse event term(s)
DYSPNOEA; 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

total daily dose 400 mg for 14 days every 3 weeks or placebo) for the treatment of non-small cell lung cancer. Concomitant study therapy included paclitaxel 200 mg/m² IV every 3 weeks (total daily dose 400 mg), and carboplatin AUC 6 IV, every 3 weeks (total daily dose 666 mg) administered on day 1 of each treatment cycle. Other concomitant therapy included omeprazole, propantheline bromide (PRO-BANTHINE), ondansetron, fluconazole, ciprofloxacin, dexamethasone by mouth (manufacturer unknown), dexamethasone IV (manufacturer unknown), salbutamol MDI, cetirizine, benzydamine HCl (DIFFLAM), domperidone, cimetidine and chlorpheniramine maleate.

From 22-APR-2008 to 05-MAY-2008, the patient received cycle 2 study therapy with blinded therapy (either vorinostat 100 mg capsule, total daily dose 400 mg or placebo). Concomitant study suspect therapy included paclitaxel 200 mg/m² IV total daily dose 400 mg given on 22-APR-2008, and carboplatin AUC 6 IV, total daily dose 700 mg given on 22-APR-2008.

On 05-APR-2008, the patient experienced intermittent shortness of breath (grade 1). On 19-MAY-2008 the patient experienced pneumonia (grade 2) (NSAE). On 21-MAY-2008, the patient was presented with increased shortness of breath and feeling "unwell" over last 2 days and one episode of diarrhea. Temperature on admission was 39.2 centigrade. On 21-MAY-2008, the patient had a chest x-ray performed that revealed increased shadow of the left lung. Oxygen saturation was 88%. Pulmonary embolism was suspected, but not confirmed. Blood cultures were negative. Laboratory evaluation revealed neutropenia with a neutrophil count of $0.1 \times 10^9/L$. He was admitted per neutropenic sepsis protocol with a diagnosis of febrile neutropenia (grade 3). He was started antibiotics: piperacillin sodium (+) tazobactam sodium (TAZOCIN) 4.5 g IV tid, vancomycin 1 gram IV bid, and gentamicin 440 mg IV daily. On 21-MAY-2008, he was given filgastrim 6 mg subcutaneously. He was placed on oxygen therapy. The patient's blood pressure was 110/56 and her pulse was 66. On 21-MAY-2008 through 23-MAY-2008 the patient was given paracetamol. Laboratory exams on 21-MAY-2008 included a serum creatine protein of 205 mg/L, blood culutres were negative and normal, a white blood cell count was $0.9 \times 10^9/L$, albumin was 25 g/L, platelets were $112 \times 10^9/L$, serum sodium was 120 mmol/L, and tropinin I was 0.22 ug/L. Last dose given of blinded therapy was on 22-MAY-2008. On 22-MAY-2008 through 26-MAY-2008 the patient was given potassium bicarbonate (+) potassium chloride (SANDO K). On 23-MAY-2008, he received transfusion with 2 units. Action taken regarding study therapy was none. As of 27-MAY-2008, the patient was still hospitalized. The patient was treated with ciprofloxacin for the neutropenic sepsis and clarithromycin for the febrile neutropenia. The patient recovered from neutropenia on 26-MAY-2008. The patient was discharged from the hospital on 29-MAY-2008 and will be seen 01-JUN-2008. A sputum sample had no significant growth. The patient was discharged on ciprofloxacin and clarithromycin. On 29-MAY-2008 the patient's neutrophils were 13.8. On 29-MAY-2008 the patient recovered from pneumonia (grade 2) (NSAE). It was reported that the patient was still very weak. The discharge diagnoses were neutropenic sepsis and the source was left sided pneumonia. On 07-JUL-2008 the patient recovered from shortness of breath. On 16-JUN-2008 the patient discontinued study medication due to the physician's decision without receiving further chemo after discharge.

The patient also experienced the following non serious events: loose stools intermittent, sputum increased and salty taste, slight blood in nasal mucus intermittent, blood in sputum, hair loss/alopecia, peripheral neuropathy, fatigue, body shivers and loss of appetite.

The reporting investigator felt that the febrile neutropenia, shortness of breath, and pneumonia (NSAE) were related to blinded study therapy, carboplatin and paclitaxel. Action taken regarding carboplatin and paclitaxel was none.

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>
electrocardiogram Comment: sinus tachycardia-bundle branch block right	03/25/2008		
chest X-ray Comment: increased shadow on left lung	05/21/2008		
electrocardiogram Comment: sinus tachycardia-bundle branch block right	05/21/2008		
electrocardiogram Comment: sinus tachycardia-bundle branch block right	06/02/2008		
ultrasound	06/02/2008		

Comment: calf- no DVT

electrocardiogram 06/16/2008
 Comment: sinus tachycardia-bundle branch block right

blood pressure measurement

110/56

LABORATORY RESULTS

<u>Tests</u>	<u>Date</u>	<u>Value</u> <u>Unit</u>	<u>Normal Range</u>
WBC count Comment: low	05/21/2008	0.9 10 ⁹ /L	4 - 11
body temp	05/21/2008	39.2 C	
hemoglobin Comment: low	05/21/2008	9.2 g/dL	13 - 18
neutrophil count Comment: low	05/21/2008	0.10 10 ⁹ /L	2 - 7.5
platelet count Comment: low	05/21/2008	112 10 ⁹ /L	150 - 450
pulse oximetry	05/21/2008	88 %	
serum C-reactive protein	05/21/2008	205 mg/L	0 - 6
serum TnI	05/21/2008	0.22 ug/L	0 - 0.1
serum albumin	05/21/2008	25 g/L	30 - 51
serum sodium	05/21/2008	120 mmol/L	135 - 145
blood culture Comment: negative normal	05/21/2008		
neutrophil count		13.8	
total heartbeat count		66	

C. Suspect medication(s)

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

#1 CAP 0683-blinded therapy Unk
 #1 CAP 0683-blinded therapy Unk
 #2 infusion (form) paclitaxel Unk
 #2 infusion (form) paclitaxel Unk
 #2 infusion (form) paclitaxel Unk
 #3 infusion (form) carboplatin Unk
 #3 infusion (form) carboplatin Unk
 #3 infusion (form) carboplatin Unk

2. Dose, frequency & route used

#1 Unk/Unk/PO
 #1 Unk/Unk/PO
 #2 420 mg/1X/IV
 #2 400 mg/1X/IV
 #2 400 mg/1X/IV
 #3 666 mg/1X/IV
 #3 700 mg/1X/IV
 #3 648 mg/1X/IV

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

#1 04/22/2008 - 05/05/2008
 #1 05/13/2008 - 05/26/2008
 #2 04/04/2008 - 04/04/2008
 #2 04/22/2008 - 04/22/2008
 #2 05/13/2008 - 05/13/2008
 #3 04/04/2008 - 04/04/2008
 #3 04/22/2008 - 04/22/2008
 #3 05/13/2008 - 05/13/2008

4. Diagnosis for use (indication)

#1 Non-small cell lung cancer
 #1 Non-small cell lung cancer
 #2 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
 #3 Non-small cell lung cancer

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)

albuterol	12/24/2007 - Cont
cetirizine hydrochloride	06/16/2008 - 06/22/2008
chlorpheniramine maleate	04/04/2008 - Cont
cimetidine	04/04/2008 - Cont
ciprofloxacin	04/11/2008 - Cont
ciprofloxacin	05/20/2008 - Unk
dexamethasone	04/04/2008 - Cont
dexamethasone	05/13/2008 - 05/16/2008
domperidone	04/04/2008 - Cont
fluconazole	04/11/2008 - Cont
fluconazole	05/20/2008 - Unk
omeprazole	12/24/2007 - Cont
ondansetron	04/04/2008 - Cont
ondansetron	05/13/2008 - 05/15/2008