

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

December 26, 2008

Re: blinded therapy/MK-0683

Dear Doctor:

This letter is to provide follow-up information on an adverse experience concerning blinded MK-0683 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 # 0801USA03882, GENSTUDY # 056-0018, AN # 61515

# 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

Page 1

Mfr report #	WAES 0801USA03882
UF/Dist report #	
	FDA Use On

A. Patient information			
1. Patient identifier Confidential AN 61515 in confidence	2. Age at time of event: or 59 years Date of Birth: 04/15/1948	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight 141 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 checked="" 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) 01/03/2008	4. Date of this report (mm/dd/yyyy) 12/26/2008

5. Describe event or problem  
This is in follow-up to report(s) previously submitted on 1/24/2008; 2/14/2008; 2/20/2008; 7/9/2008; 7/24/2008; 8/5/2008; 11/5/2008; 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 59 year old white female with asthma, back pain, dry skin, insomnia, muscular leg cramps, nocturia, pain in right hip and varicose vein and a history of hysterectomy, nausea, lung lobectomy and sinus surgery for nasal polyps who entered a study, title as stated above. On 20-DEC-2007, the patient was randomized and placed on vorinostat/blinded therapy, 100 mg capsule, 400 mg once daily administered on days -4 through 10 of cycle 1 (cycle equivalent to 25 days) (or days 1 through 14) for each subsequent cycle for the

(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: Hysterectomy; Nausea; Sinus operation; Nasal polyps; Lung lobectomy; Chemotherapy  
CONCURRENT CONDITIONS: Asthma; Back pain; Nausea prophylaxis; Dry skin; Routine health maintenance; Insomnia; Leg cramps; Nocturia; Pain in hip; Varicose vein

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 12/20/2007 - 01/02/2008	
# 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"/>	
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 type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>		# 2 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
10. Concomitant medical products and therapy dates (excluded treatment of event)			
ACTONEL		06/??/2007-Cont	
ADVAIR		01/??/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) 12/16/2008	3. Report source. (check all that apply)
6. If IND, protocol # 0560018	<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:
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# 8	5. (A)NDA # 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 0801USA03882	

8. Adverse event term(s)  
FEBRILE NEUTROPENIA; PYREXIA

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. yes 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

treatment of non small cell lung cancer. Concomitant study therapy included carboplatin 6 AUC and paclitaxel 200 mg/m<sup>2</sup>. Other concomitant therapy included risedronate sodium (ACTONEL), calcium, vitamin D and vitamin C, dexamethasone (MSD), ranitidine, ondansetron hydrochloride (ZOFRAN), diphenhydramine hcl (BENADRYL), metoclopramide hydrochloride (MAXERAN), fluticasone propionate (+) salmeterol xinafoate (ADVAIR) and fluticasone propionate (FLONASE). On 03-JAN-2008, the patient presented to the emergency department with fever of 38.6 C. The patient was admitted to the hospital for febrile neutropenia (grade 3). Laboratory evaluations revealed neutropenia of 0.1 x10<sup>9</sup>/L (also reported as 2 x 10<sup>9</sup>/L). Blood cultures were reported as normal and negative). On 04-JAN-2008, a chest x-ray showed no evidence of pneumonia and the urine culture was normal and negative). The patient was treated with ticarcillin disodium/ clavulanate potassium (TIMENTIN) 3.1 g IV every 4 hours and gentamicin 80 mg IV every 8 hours. A serum potassium test revealed a potassium level of 3 mmol/L (also reported as 3.3 mmol/L). She also received 60 mEq potassium IV on 04-JAN-2008. On 05-JAN-2008, the patient recovered. On 05-JAN-2008, the patient was discharged with no signs of neutropenia (1.5 x10<sup>9</sup>/L) or fever, or hypokalemia at discharge. Discharge diagnosis was febrile neutropenia (grade 3). The patient was seen in pulmonary oncology clinic on 09-JAN-2008. There was no new neutropenia or fever since event. On 20-FEB-2008, the patient called from home complaining of a fever (grade 1) of 38.6 C and a suggestion was made to take acetaminophen (TYLENOL). The absolute neutrophil count (ANC) was 20.66 GI/L and on 27-FEB-2008 it was 3.7 GI/L. The patient was reported to be on filgrastim (NEUPOGEN). The next day the patient returned to the clinic for blood cultures. Both blood and urine cultures came back negative. The patient was started on levofloxacin (LEVAQUIN) for 7 days. On 26-FEB-2008, the patient called saying the fever still persisted despite antibiotics and acetaminophen (TYLENOL). On 27-FEB-2008, the patient came back to the clinic with the fever (still persisting at 37.8 C as per patient), during the visit the fever was 36.5 C. The patient met with a physician from infectious disease department who prescribed atovaquone (MEPRON). During this time, the patient's 4th cycle was postponed from 27-FEB-2008 to 12-MAR-2008 since the fever resolved on atovaquone (MEPRON). Patient came back to clinic on 05-MAR-2008 and no other episode of fever was noted. The diagnosis was fever of unknown etiology. The investigator rationale for deeming this a medically significant event is because the event is out the norm and because intervention was required.

Fever (grade 1) was considered to be an other important medical event.

The reporting investigator felt that the fever and the febrile neutropenia, grade 3 were related to study therapy of vorinostat or placebo, carboplatin, and paclitaxel. It was reported that on 13-MAY-2008 the patient had a study visit. The patient completed oncology study medication.

This is a consolidation of 2 reports concerning the same patient.

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	01/04/2008		
Comment: No evidence of pneumonia - negative for pneumonia - Normal			

## LABORATORY RESULTS

<u>Tests</u>	<u>Date</u>	<u>Value</u> <u>Unit</u>	<u>Normal Range</u>
absolute neutrophil count	01/03/2008	.2 x 10 <sup>9</sup> /L	1.8 - 7.5
body temp	01/03/2008	38.6 C	
blood culture	01/03/2008		
Comment: Normal			
serum potassium	01/04/2008	3 mmol/L	3.5 - 5.5
serum potassium	01/04/2008	3.3 mmol/L	3.5 - 5.5
urine culture	01/04/2008		
Comment: Normal			
absolute neutrophil count	01/05/2008	1.5 x 10 <sup>9</sup> /L	1.8 - 7.5
absolute neutrophil count	02/20/2008	20.66 GI/L	
absolute neutrophil count	02/20/2008	21.2 x 10 <sup>9</sup> /L	1.8 - 7.5
body temp	02/20/2008	38.6 C	
absolute neutrophil count	02/27/2008	3.7 GI/L	
absolute neutrophil count	02/27/2008	3.6 x 10 <sup>9</sup> /L	1.8 - 7.5
body temp	02/27/2008	37.8 C	
Comment: 36.5 C per patient			
body temp	02/27/2008	36.5 C	

## C. Suspect medication(s)

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

#1 CAP 0683-blinded therapy Unk  
 #1 CAP 0683-blinded therapy Unk  
 #2 carboplatin Unk  
 #2 carboplatin Unk  
 #2 carboplatin Unk  
 #3 paclitaxel Unk  
 #3 paclitaxel Unk  
 #3 paclitaxel Unk

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

#1 Unk/Unk/PO  
 #1 Unk/Unk/PO  
 #2 670 mg/1X/IV  
 #2 619 mg/1X/IV  
 #2 681 mg/1X/IV  
 #3 338 mg/1X/IV  
 #3 338 mg/1X/IV  
 #3 338 mg/1X/IV

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

#1 01/16/2008 - 01/29/2008  
 #1 02/06/2008 - 02/19/2008  
 #2 12/24/2007 - 12/24/2007  
 #2 01/16/2008 - 01/16/2008  
 #2 02/06/2008 - 02/06/2008  
 #3 12/24/2007 - 12/24/2007  
 #3 01/16/2008 - 01/16/2008  
 #3 02/06/2008 - 02/06/2008

## 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)

BENADRYL	12/24/2007 - 12/24/2007
BENADRYL	02/06/2008 - 02/06/2008
DECADRON (DEXAMETHASONE)	12/23/2007 - 12/24/2007
DECADRON (DEXAMETHASONE)	12/25/2007 - 12/26/2007
DECADRON (DEXAMETHASONE)	12/27/2007 - 12/29/2007
DECADRON (DEXAMETHASONE)	02/05/2008 - 02/06/2008
DECADRON (DEXAMETHASONE)	02/07/2008 - 02/08/2008
DECADRON (DEXAMETHASONE)	02/09/2008 - 02/11/2008
FLONASE	01/13/2008 - Cont
MAXERAN	12/25/2007 - 12/29/2007
MAXERAN	02/07/2008 - 02/11/2008
ZOFRAN	12/24/2007 - 12/24/2007
ZOFRAN	02/06/2008 - 02/06/2008
ascorbic acid	01/09/2007 - Cont
calcium (unspecified)	06/??/2007 - Cont
ranitidine	12/24/2007 - 12/24/2007
ranitidine	02/06/2008 - 02/06/2008
vitamin d (unspecified)	06/01/2007 - Cont