

MERCK RESEARCH LABORATORIES

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

Date: 29-JAN-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 # 0712USA09051, GENSTUDY # 056-0084 AN # 61512

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 0712USA09051**

UF/Dist report #

FDA Use On

A. Patient information			
1. Patient identifier Unk AN 61512 in confidence	2. Age at time of event: or 66 years Date of Birth: 07/09/1941	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 172 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 checked="" type="checkbox"/> Death 01/28/2008 (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)	12/21/2007	4. Date of this report (mm/dd/yyyy)	01/29/2009
5. Describe event or problem			
This is in follow-up to report(s) previously submitted on 1/7/2008; 2/12/2008; 2/28/2008; 3/5/2008; 4/14/2008; 4/24/2008; 7/23/2008; 8/21/2008; 9/11/2008; 9/17/2008; 9/24/2008; 12/5/2008			
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 66 year old white male with liver metastasis, chronic obstructive pulmonary disease (COPD), tobacco abuse, pain, hypertension, neutropenia, atrial fibrillation, peripheral vascular disease and a history of hip and leg surgery who on 10-DEC-2007, was randomized to a study, title as stated above.			
On 10-DEC-2007, the patient was placed on blinded study therapy of either vorinostat 100 mg capsule, 400 mg daily			
(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: Hip surgery; Leg operation CONCURRENT CONDITIONS: Pain; Metastases to liver; Tobacco abuse; Neutropenia; Chronic obstructive pulmonary disease; Atrial fibrillation; Hypertension; Peripheral vascular disorder			

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 12/10/2007 - 12/19/2007	
# 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 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 type="checkbox"/>	
10. Concomitant medical products and therapy dates (excluded treatment of event)			
ADVAIR		11/19/2007-Cont	
ANZEMET		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 #
01/21/2009	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# 12	WAES 0712USA09051
3. Report source (check all that apply)	
<input type="checkbox"/> foreign	
<input checked="" type="checkbox"/> study	
<input type="checkbox"/> literature	
<input type="checkbox"/> consumer 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; FEMUR FRACTURE; DEATH; CELLULITIS; PNEUMONIA; ATRIAL FIBRILLATION; PLEURAL EFFUSION	

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		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**

or placebo administered on day(s) -4 through 10 of cycle 1 (cycle equivalent to 25 days) (or days 1 through 14 for each subsequent cycle) for treatment of non-small cell lung cancer (current staging: T2/N3/M1/stage IV)

Concomitant study therapy included paclitaxel, 200 mg/m² (total dose 382 mg) and carboplatin [AUC 6] total dose 600mg, administered intravenous (IV) on day 1 of each treatment cycle). Other concomitant therapy included acetaminophen (+) oxycodone hydrochloride (PERCOCET), clonazepam (KLONOPIN), fluticasone propionate (+) salmeterol xinafoate (ADVAIR INHALER), tiotropium bromide (SPIRIVA INHALER), albuterol sulfate (+) ipratropium bromide (DUONEB), warfarin (COUMADIN), furosemide (LASIX), verapamil, digoxin (DIGITEK), levofloxacin (LEVAQUIN), dolasetron mesylate (ANZEMET), dexamethasone (MSD), ranitidine hydrochloride (ZANTAC), diphenhydramine hydrochloride (BENADRYL) and methylprednisolone sodium succinate (SOLU-MEDROL).

On 20-DEC-2007 the patient experienced respiratory distress (grade 2) (NSAE). The patient was presented to the emergency room (ER) with complaints of weakness, increased cough, productive sputum and some respiratory distress. The patient also complained of nausea and increased fever at home (temperature unknown) for 2 days. The patient was found to be neutropenic with white blood cell count (WBC) 0.2 and neutrophil count was unknown. No further information was available. On 20-DEC-2007 chest X-ray revealed pleural effusion, blood hemoglobin test was 12.1gm/dl, sputum culture, blood culture and urine culture was negative-normal, white blood cell count was 0.2 K/uL and blood platelet count was 24 X 10³/L, temperature 99.2, and lung sounds were decreased at the bases with scattered bronchi. The patient was found to be neutropenic. On 21-DEC-2008 (Cycle 1 Day 12) the patient had febrile neutropenia (grade 3) and was hospitalized. Blinded study therapy was interrupted. The action taken regarding therapy with carboplatin and paclitaxel was none. The patient was treated with IV fluids, cefepime and levofloxacin (LEVAQUIN), IV. He was given oxygen support and duo-nebs. The patient was also placed in reverse isolation and started on filgrastim (NEUPOGEN) injections daily. On 24-DEC-2007, the patient was considered recovered with sequelae from febrile neutropenia (grade 3) and was discharged from the hospital. The discharge diagnosis was reported as non-small cell lung cancer with liver mets, chronic obstructive pulmonary disease (COPD), tobacco abuse, neutropenic fever and respiratory distress. On 24-DEC-2007 the patient also recovered from respiratory distress (grade 2) (NSAE). The patient had no further complaints of nausea, vomiting, or shortness of breath at discharge and her WBC count was 15,000.

On 03-JAN-2008, the patient was seen in the office and Cycle 2 Day 1 blinded study therapy capsule was started. Neutropenia resolved (WBC 8.2 and ANC 7.1). On 03-JAN-2008, the patient received carboplatin IV 6 AUC (dose 600 mg) and paclitaxel 200 mg/m² IV (dose 382 mg/m²). The last dose of carboplatin and paclitaxel the patient received prior to the event was on 03-JAN-2008 oral started the same day. The patient was presented with shortness of breath (SOB). Temperature was 97.5, blood pressure measurement was 101/68, pulse was 120, respiratory rate was 24, absolute neutrophil count (ANC) was 0.45 and oxygen saturation results were not documented. On 08-JAN-2008, (Cycle 2 Day 6) the patient was admitted to the hospital with fractured left femoral (grade 3), worsening of atrial fibrillation (grade 3), recurrent pleural effusion (grade 3), pneumonia (grade 3) and cellulitis of the left leg (grade 3). The patient had a left femur X-ray performed and showed a fracture mid-shaft, left femur, severe osteopenia of bony structure, computed tomography guided thoracentesis was performed and 1200 CC of serous fluid, urine culture, sputum culture and blood culture was negative and a chest X-ray showed bibasilar infiltrates and effusions, left was greater than the right. An orthopedic consult determined that the patient was not a candidate for surgery. The patient was not a candidate for surgery due to left lower extremity cellulitis. No further information about leg fracture treatment available. The patient had known soft tissue infection prior to admission. The patient had an infectious disease consultation. Diagnosis date was unknown. Previous cultures of soft tissue indicated MRSA. The patient was treated with vancomycin and piperacillin sodium (+) tazobactam sodium (ZOSYN). No blood culture lab results are available. It was only dictated in the hospital note, no further information will be available. On 08-JAN-2008 the patient also experienced phlebitis of the left arm with superficial venous thrombosis (grade 2) (NSAE), anemia (grade 2) (NSAE) and increased creatinine (grade 3) (NSAE). The patient was treated with red blood cells for anemia (grade 2) (NSAE). On 09-JAN-2008 the patient recovered from anemia (grade 2) (NSAE). On 10-JAN-2008 the patient developed anemia (grade 3) (NSAE) and was treated with red blood cells. On 10-JAN-2008 the patient had a transthoracic echocardiogram performed and revealed normal left ventricular systolic function, EF greater than 60%, no aortic stenosis, trace mitral regurgitation and mild to moderate tricuspid regurgitation. A chest x-ray also showed markedly improved from 08-JAN-2008 and the amount of fluid in the left chest was dramatically decreased. Details about the fluid are not available. On 11-JAN-2008 the patient recovered from anemia (grade 3) (NSAE). The patient was treated with amiodarone was given for worsening of atrial fibrillation (grade 3). Electrocardioversion was not done since the patient was not on warfarin hcl (COUMADIN) therapy. Digoxin was increased and patient required more beta blocker/calcium channel blocker secondary to intermittent hypotension, furosemide hcl (LASIX) was administered. On 16-JAN-2008, the patient was discharged from the hospital for fracture left femoral (grade 3), worsening of atrial fibrillation (grade 3), recurrent pleural effusion (grade 3), pneumonia (grade 3) and cellulitis of the left leg (grade 3). The fractured left femur (grade 3) and recurrent pleural effusion (grade 3) persisted. Discharge diagnosis was left leg fracture, cellulitis of left

leg with MRSA, phlebitis of the left arm with thrombosis, pneumonia, atrial fibrillation, mild renal failure, and recurrent pleural effusion; cellulitis of the left leg; pneumonia; atrial fibrillation and improved left pleural effusion. On 16-JAN-2008 the patient recovered from phlebitis of the left arm with superficial venous thrombosis (grade 2) (NSAE) and increased creatinine (grade 3) (NSAE). On 16-JAN-2008 the patient developed anxiety (grade 1) (NSAE) and was treated with alprazolam (XANAZ) and thrombocytopenia (grade 4) (NSAE). On 16-JAN-2008 the patient recovered from thrombocytopenia (grade 4) (NSAE). At the time of reporting the patient did not recover from anxiety (grade 1) (NSAE). The patient was transferred to Transitional Care Unit for extended care. The investigator was unable to contact the patient or patient's family since 03-JAN-2008.

On 28-JAN-2008, (Cycle 2 Day 30) the patient died (grade 5). The cause of death was not reported. The site learned of the patient's death through radio obituary. It was unknown if autopsy was performed. The investigator has been unable to obtain a death certificate. The investigator felt that the patient's death was not related to blinded study therapy, or study therapy with carboplatin, and/or paclitaxel.

The investigator felt that neutropenic fever (grade 3) was related to blinded study therapy, carboplatin and paclitaxel. The left fractured femur (grade 3), pneumonia (grade 3), cellulitis of the left leg (grade 3), worsening of atrial fibrillation (grade 3), recurrent pleural effusion (grade 3) and death (grade 5) was not related to blinded study therapy or study therapy with carboplatin and paclitaxel.

The investigator considered neutropenic fever to be an Other Important Medical Event.

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	12/20/2007			
Comment: pleural effusion				
computed axial tomography	01/08/2008			
Comment: CT thoracentis done for pleural effusion 1200 CC of serous fluid				
chest X-ray	01/08/2008			
Comment: bibasilar infiltrates and effusions, left greater than right				
chest X-ray	01/08/2008			
Comment: see narrative				
lower extremity X-ray	01/08/2008			
Comment: fracture mid-shaft, left femur, severe osteopenia of bony structure				
blood pressure measurement	01/08/2008	101/68		
transthoracic echocardiography	01/10/2008			
Comment: see narrative				

LABORATORY RESULTS

<u>Tests</u>	<u>Date</u>	<u>Value</u>	<u>Unit</u>	<u>Normal Range</u>
WBC count	12/20/2007	0.2	K/uL	4.8 - 10.8
body temp	12/20/2007	99.2		
hemoglobin	12/20/2007	12.1	gm/dl	12 - 16
platelet count	12/20/2007	24	10 ³ /L	150 - 400
blood culture	12/20/2007			
Comment: negative-normal				
sputum culture	12/20/2007			
Comment: negative-normal				
urine culture	12/20/2007			
Comment: negative-normal				
WBC count	12/24/2007	15,000		
WBC count	01/03/2008	8.2		
neutrophil count	01/03/2008	7.1		
absolute neutrophil count	01/08/2008	0.45		
body temp	01/08/2008	97.5		
blood culture	01/08/2008			
Comment: negative-normal				
total heartbeat count	01/08/2008	120		
respiratory rate measurement	01/08/2008	24		
sputum culture	01/08/2008			
Comment: negative-normal				
urine culture	01/08/2008			

C. Suspect medication(s)

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

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

2. Dose, frequency & route used

#1 Unk/Unk/PO
 #2 382 mg/1X/IV
 #2 382 mg/1X/IV
 #3 600 mg/1X/IV
 #3 600 mg/1X/IV

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

#1 01/03/2008 - 01/16/2008
 #2 12/13/2007 - 12/13/2007
 #2 01/03/2008 - 01/03/2008
 #3 12/13/2007 - 12/13/2007
 #3 01/03/2008 - 01/03/2008

4. Diagnosis for use (indication)

#1 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

5. Event abated after use stopped or dose reduced

	YES	NO	N/A	UNK
#1	X			
#2			X	
#2			X	
#3			X	
#3			X	

6. Lot # (if known)

#1
 #2
 #2
 #3
 #3

7. Exp date (if known)

#1
 #2
 #2
 #3
 #3

8. Event reappeared after reintroduction

	YES	NO	N/A	UNK
#1		X		
#2			X	
#2			X	
#3			X	
#3			X	

C. Suspect medication(s)

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

ANZEMET	01/03/2008 - 01/03/2008
BENADRYL	12/13/2007 - 12/13/2007
BENADRYL	01/03/2008 - 01/03/2008
COUMADIN	11/19/2007 - Cont
DECADRON (DEXAMETHASONE)	12/13/2007 - 12/13/2007
DECADRON (DEXAMETHASONE)	01/03/2008 - 01/03/2008
DIGITEK	11/19/2007 - Cont
DUONEB	11/19/2007 - Cont
KLONOPIN	11/08/2007 - Cont
LASIX (FUROSEMIDE SODIUM)	11/19/2007 - Cont
LEVAQUIN	12/20/2007 - 12/24/2007
PERCOCET	11/01/2007 - Cont
SOLU-MEDROL	12/13/2007 - 12/13/2007
SOLU-MEDROL	01/03/2008 - 01/03/2008
SPIRIVA	11/19/2007 - Cont
ZANTAC	12/13/2007 - 12/13/2007
ZANTAC	01/03/2008 - 01/03/2008
verapamil	11/19/2007 - Cont