

MERCK RESEARCH LABORATORIES

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

Date: December 4, 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 # 0708USA04710, GENSTUDY # 056-0030, AN # 64501

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 0708USA04710
UF/Dist report #	
FDA Use Only	

A. Patient information

1. Patient Identifier Confidential AN 64501 in confidence	2. Age at time of event: or 32 years Date of Birth: 04/21/1975	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 200 lbs
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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 09/23/2007 (mm/dd/yyyy)	<input type="checkbox"/> Disability or Permanent Damage
<input checked="" 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) 08/23/2007	4. Date of this report (mm/dd/yyyy) 12/04/2008

5. Describe event or problem
This is in follow-up to report(s) previously submitted on 8/29/2007; 9/4/2007; 9/20/2007; 10/3/2007; 11/1/2007; 11/20/2007; 11/28/2007; 12/3/2007; 2/20/2008; 3/5/2008; 5/30/2008; 11/26/2008

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 32 year old white male who entered a study, title as stated above. On 09-JUL-2007, the patient was placed on cycle one blinded study therapy of either vorinostat, capsule, 400 mg or placebo, daily for 14 days, every 25 days, for the treatment of stage IIIB (with pleural effusion) and stage IV non-small cell lung cancer (initial diagnosis 05-MAY-2007; staging as of 26-JUN-2007: T2N2M1). Concomitant study therapy included carboplatin, AUC equivalent to 6 (206.4 mg) 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; Cough; Sensory neuropathy

C. Suspect medication(s)

1. Name (Give labeled strength & mfr/labeler)	
# 1 CAP 0683-blinded therapy 400 mg	# 2
(Continued on Additional Page)	
2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration) from/to (or best estimate)
# 1 Unk/DAILY/PO	# 1 07/09/2007 - 07/22/2007
# 2	# 2

4. Diagnosis for use (indication)	5. Event abated after use stopped or dose reduced.
# 1 Non-small cell lung cancer stage IV	yes <input type="checkbox"/> no <input checked="" type="checkbox"/> N/A <input type="checkbox"/> unk <input type="checkbox"/>
# 2	# 2 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
6. Lot #	7. Exp. Date
# 1	# 1
# 2	# 2
8. Event reappeared after reintroduction.	
yes <input type="checkbox"/> no <input type="checkbox"/> N/A <input checked="" type="checkbox"/> unk <input type="checkbox"/>	
# 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)
PARACODINA (DIHYDROCODEINE BITAR) 07/13/2007-Cont
WINADEINE F 08/13/2007-Cont
(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
4. Date received by manufacturer (mm/dd/yyyy) 11/27/2008	5. (A)NDA # IND # 58915
6. If IND, protocol # 0560030	STN # PMA/ 510(k) #
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# 12	Combination Product <input type="checkbox"/> Yes Pre-1938 <input type="checkbox"/> Yes OTC product <input type="checkbox"/> Yes
9. Mfr. report number WAES 0708USA04710	

8. Adverse event term(s)
CEREBROVASCULAR ACCIDENT; NON-SMALL CELL LUNG CANCER

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. <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**

paclitaxel, 200 mg/m² (416 mg), both administered IV as a onetime dose per cycle and initiated on 13-JUL-2007. Other concomitant therapy included acetaminophen/codeine phosphate (WINADEINE F), vitamin B complex, dihydrocodeine bitartrate (PARACODINA), and tramadol HCl. On 02-AUG-2007, the patient was placed on cycle two blinded study therapy, which was completed on 15-AUG-2007. On 22-AUG-2007, the patient was placed on cycle three blinded study therapy. On 23-AUG-2007, at 14:20, the patient presented to an emergency room with an incapacity to move his left arm, difficulty speaking and right facial paralysis 15 minutes after he took his medication. The patient also presented with respiratory difficulty, and subsequently, was admitted to the intensive care unit (ICU). No history of substance abuse, cardiac disease or hypercoagulability was noted. Cerebral computed axial tomography (CT) was performed on the patient which revealed ischemic infarct of the right medium cerebral artery territory. The patient was diagnosed with cerebrovascular accident (grade 4). The patient was placed on supplemental oxygen and "anti-edema" measures. On 23-AUG-2007, blinded study therapy was discontinued. On 23-AUG-2008 the patient was treated with oxygen gas for dyspnea. On 24-AUG-2007, cerebral magnetic resonance imaging (MRI) performed on the patient revealed an ischemic lesion which compromised the right medial cerebral artery in its M2 portion, with little edema, but no hemorrhage and a transesophageal echocardiogram revealed an ejection fraction of 65 percent, and no intracavitary thrombi. The patient was reported as stable in the ICU, although, was agitated and tachycardic. Metabolic acidosis, systemic inflammatory response syndrome (SIRS) and paralysis persisted. It was also reported that the patient had difficulty swallowing, LVEF 65 percent, and subsequently, a nasogastric (NG) tube was inserted for feedings and speech therapy was initiated. The patient later developed an incapacity to walk, which was associated with the loss of strength in his left limb. On 24-AUG-2007, the patient was placed on therapy with enoxaparin sodium, 40 mg, administered SC daily for anticoagulation, ranitidine, 50 mg, administered IV three times a day for gastric upset prophylaxis, captopril, 50 mg, administered IV three times a day as an antihypertensive, dipyrone, 2,500 gm, administered IV four times a day for analgesia, and calcium carbonate. On 25-AUG-2007, the patient was placed on therapy with aspirin, 100 mg, administered orally once a day, for anticoagulation, haloperidol, 5 mg, administered IV daily as an antipsychotic, and was administered one dose of alprazolam, 250 mcg, IV for sedation. On 26-AUG-2007, the patient was placed on treatment therapy with citicoline ("COMPLEGEL NF"), 1,000 mg, administered IV, twice a day as a neuroprotector and lovastatin (manufacturer unknown), oral, 40 mg, daily for the treatment of elevated triglycerides. On 27-AUG-2007, captopril and haloperidol were discontinued. On 28-AUG-2007, the patient was placed on therapy with alprazolam, 500 mcg, once a day for sedation, and was administered dipyrone, 2 gm, IV, onetime dose for analgesia. On 29-AUG-2007, the patient was placed on therapy with oral hydroxyzine, 25 mg, daily as hypnotic therapy and was administered a onetime dose of dipyrone, 2 gm, IV for analgesia. On 30-AUG-2007, the patient was placed on therapy with amitriptyline (manufacturer unknown), oral, 125 mcg, administered daily as an antidepressant, and therapy with dipyrone was discontinued. On 03-SEP-2007, ranitidine and enoxaparin therapies were discontinued, and the patient was placed on therapy with oral omeprazole, 20 mg, daily for gastric upset prophylaxis. On 05-SEP-2007, hydroxyzine, alprazolam and amitriptyline therapies were discontinued. On 08-SEP-2007, a repeat MRI was performed on the patient and revealed the following: "a subacute infarct on the territory of the right middle cerebral artery, with alteration on the caliber of the internal carotid. In addition, there was a small epidural left frontal image," questionable metastasis. On 08-SEP-2007, the patient was discharged home. The discharge diagnosis was reported as CNS ischemia. A nursing assistant stayed with the patient during the day, not only to help with his care, but to administer therapy with IV citicoline. The patient was reported as gradually recovering with improved ability to swallow. The patient had also recovered some sensory sensation on the left lower extremity and gained some movements, although, was unable to stand up by himself. The patient had no sensory and no movement of the left upper extremity, and required oxygen for approximately 12 hours a day. The patient's condition gradually worsened, and the patient developed cardio-respiratory failure secondary to his lung cancer. On 23-SEP-2007, the patient experienced worsened dyspnea, became cyanotic and apneic. Attempts to resuscitate the patient were unsuccessful. On 23-SEP-2007, at 22:15, the patient died. The cause of death was reported as progression of non-small cell lung cancer. Cerebrovascular accident (grade 4) was ongoing at the time of the patient's death.

The reporting investigator felt that cerebrovascular accident (grade 4) and progression of non-small cell lung cancer (grade 5) were not related to the blinded study therapy.

The reporting investigator felt that cerebrovascular accident (grade 4) and progression of non-small cell lung cancer (grade 5) were not related to carboplatin or paclitaxel.

Cerebrovascular accident (grade 4) was considered to be immediately life-threatening.

Additional information is not expected.

A 7-calendar day phone call was made to the FDA on 28-AUG-2007.

This report no longer meets the criteria for submission because the relationship to the study drug therapy has changed.

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: increased pleural effusion on left side	06/27/2007			
thoracentesis Comment: small amount (60 mL) hemorrhagic fluid obtained	07/27/2007			
head computed axial tomography Comment: ischemia in the territory of the right medial cerebral artery	08/23/2007			
magnetic resonance imaging Comment: ischemic lesion which compromises the right medial cerebral artery	08/24/2007			
transesophageal echocardiography Comment: ejection fraction 65%; no intracavitary thrombi	08/24/2007			
chest X-ray Comment: disseminated alveolar infiltrates on right hemithorax.	08/24/2007			
chest X-ray Comment: Extensive pleural effusion on the left hemithorax	08/24/2007			
diagnostic laboratory test Comment: PCAT	08/25/2007	89	sec	93.7 - 93.8
diagnostic laboratory test Comment: PCAT-1	08/25/2007	57	sec	60.7 - 60.8
diagnostic laboratory test Comment: radius PCAT/PCAT-0 normal	08/25/2007		2 unit	
magnetic resonance imaging Comment: subacute infarct on the territory of the right middle cerebral artery	09/08/2007			
magnetic resonance imaging Comment: alteration on the caliper of the internal carotid. Small epidural left frontal image	09/08/2007			

LABORATORY RESULTS

<u>Tests</u>	<u>Date</u>	<u>Value</u>	<u>Unit</u>	<u>Normal Range</u>
neutrophil count	08/23/2007	89	%	
serum calcium	08/23/2007	2	mEq/l	2.3 - 2.58
serum chloride	08/23/2007	100	mEq/l	98 - 106
WBC count	08/24/2007	9900		4500 - 10000
serum chloride	08/24/2007	98	mEq/l	98 - 106
serum potassium	08/24/2007	4	mEq/l	3.5 - 5
serum sodium	08/24/2007	136	mEq/l	136 - 146
total serum bilirubin	08/24/2007	1	mg/dL	0 - 1
total serum protein	08/24/2007	7	mg/dL	6.4 - 8.3

C. Suspect medication(s)

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

#1 CAP 0683-blinded therapy 400 mg
 #1 CAP 0683-blinded therapy 400 mg
 #2 carboplatin Unk
 #2 carboplatin Unk
 #2 carboplatin Unk
 #3 paclitaxel Unk
 #3 paclitaxel Unk
 #3 paclitaxel Unk

2. Dose, frequency & route used

#1 Unk/DAILY/PO
 #1 Unk/DAILY/PO
 #2 206.4 mg/1X/IV
 #2 782 mg/1X/IV
 #2 887 mg/1X/IV
 #3 416 mg/1X/IV
 #3 408 mg/1X/IV
 #3 414 mg/1X/IV

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

#1 08/02/2007 - 08/15/2007
 #1 08/22/2007 - 08/23/2007
 #2 07/13/2007 - 07/13/2007
 #2 08/02/2007 - 08/02/2007
 #2 08/22/2007 - 08/22/2007
 #3 07/13/2007 - 07/13/2007
 #3 08/02/2007 - 08/02/2007
 #3 08/22/2007 - 08/22/2007

4. Diagnosis for use (indication)

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

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)
 tramadol hydrochloride 08/13/2007 - 08/13/2007
 vitamin b complex 07/19/2007 - Cont