

**MERCK RESEARCH LABORATORIES**

Division of Merck & Co., Inc.

West Point, Pennsylvania 19486

Date: 23-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 # 0803USA03465, GENSTUDY # 056-0020 AN # 55508

# 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 0803USA03465
UF/Dist report #	
FDA Use Onl	

A. Patient information			
1. Patient identifier Confidential AN 55508 in confidence	2. Age at time of event: or 66 years Date of Birth: 10/23/1941	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight 73 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) 03/18/2008		4. Date of this report (mm/dd/yyyy) 01/23/2009	
5. Describe event or problem			
This is in follow-up to report(s) previously submitted on 3/28/2008; 4/14/2008; 4/21/2008; 5/2/2008; 5/9/2008; 5/23/2008; 5/30/2008; 6/12/2008; 7/3/2008; 8/1/2008; 8/28/2008			
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 female with hypercholesterolaemia, pain, constipation, fatigue, left shoulder pain, shortness of breath, cough and weight loss and a history of ductal carcinoma in situ, duodenal ulcer, hysterectomy, left lower lung lobectomy (13-NOV-2003), left breast lesion excision (08-APR-1997) and radiotherapy to left breast (1997) who on 11-FEB-2008 was placed on cycle 1 of study therapy with blinded therapy, with either vorinostat, capsule 400 mg or			
(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: Ductal carcinoma in situ; Duodenal ulcer; Radiotherapy; Hysterectomy; Lung lobectomy; Lesion excision CONCURRENT CONDITIONS: Hypercholesterolaemia; Weight decreased; Nausea; Premedication; Prophylaxis; Cough; Pain; Fatigue; Breath shortness; Shoulder pain; Constipation			

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 02/11/2008 - 02/17/2008	
# 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 checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <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 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"/>	
9. NDC # or Unique ID			
Unknown			
10. Concomitant medical products and therapy dates (excluded treatment of event)			
COLOXYL WITH SENNA		02/11/2008 - Cont	
EMEND		03/11/2008 - 03/11/2008	
(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) 03/19/2008		3. Report source. (check all that apply)	
5. (A)NDA # IND # 58915 STN # PMA/ 510(k) #		<input checked="" 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 checked="" type="checkbox"/> company representative <input type="checkbox"/> distributor <input type="checkbox"/> other	
6. If IND, protocol # 0560020		7. Type of report	
7. Type of report		Combination Product <input type="checkbox"/> Yes Pre-1938 <input type="checkbox"/> Yes OTC product <input type="checkbox"/> Yes	
<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# 11		9. Mfr. report number WAES 0803USA03465	
8. Adverse event term(s) NEUTROPENIA; PLEURAL EFFUSION; HYPOMAGNEAEMIA; HYPOKALAEMIA			
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**

placebo for the treatment of non-small cell lung cancer (diagnosed 13-NOV-2003; current staging 03-JAN-2008; primary tumor T4; nodal involvement NX; distant metastases M1; overall stage IV). Concomitant study therapy included carboplatin, AUC equivalent to 6 (450 mg), administered IV and paclitaxel, 200 mg/m<sup>2</sup> (246 mg), administered IV, both initiated on 15-FEB-2008. Other concomitant therapy included atorvastatin calcium (LIPITOR), acetaminophen, docusate sodium (+) senna (COLOXYL WITH SENNA), dexamethasone (manufacturer unknown), aprepitant (MSD), loratadine, ranitidine and tropisetron. On 06-MAR-2008 the patient experienced a cough (NSAE) that was not related to the study therapy.

On 11-MAR-2008, the patient began cycle 2 of study therapy with vorinostat, capsule 300 mg or placebo, carboplatin, AUC equivalent to 5 (375 mg), administered IV and paclitaxel, 175 mg/m<sup>2</sup> (217 mg), administered IV. On 18-MAR-2008 the patient developed pleural effusion (grade 2), neutropenia (grade 4) (also reported as grade 3), hypomagnesemia (grade 2) and hypokalemia (grade 4) and was hospitalized. The patient had a 2 days history of shortness of breath, limited mobility and decreased appetite. On admission an EKG showed sinus rhythm tachycardia, right ventricular strain and non-specific T-wave changes, blood tests revealed electrolyte abnormalities (potassium was 2.4), the patient was afebrile with a temperature of 36.6 C. On 18-MAR-2008, computed axial tomography chest pulmonary angiography revealed left pleural effusion and no scan evidence of pulmonary embolism and chest x-ray revealed left pleural effusion. Neutrophil count was 0.1, potassium was 2.4, phosphate was 0.70 mmol/L and blood cultures were negative for infection. Blinded study therapy was discontinued and the patient was placed on therapy with gentamicin and clavulanate potassium (+) ticarcillin disodium (TIMENTIN) to cover sepsis because the patient was neutropenic. The patient was also placed on therapy with IV potassium, potassium chloride (SLOW-K), potassium bicarbonate (+) sodium bicarbonate (+) sodium phosphate, monobasic (PHOSPHATE-SANDOZ), potassium bicarbonate (+) potassium chloride (CHLORVESENT), and magnesium aspartate (MAGMIN). On 19-MAR-2008, the pleural effusion was drained of 200 ml of pleural fluid and the patient was reported to be feeling less shortness of breath. An accurate cell count was unable to be performed as the specimen was clotted. The patient's BF protein was 3.4 g/L which indicated an exudate fluid protein. Cytology of pleural fluid was negative for malignant cells and pleural fluid culture had no growth. On 20-MAR-2008 the patient was placed on potassium bicarbonate (+) potassium chloride (CHLORVESENT) for a decrease in potassium. On 22-MAR-2008, antibiotics ceased and the patient recovered from hypokalemia (GRADE 4). On 22-MAR-2008 the patient's potassium was 3.8. White blood cell growth factors were not given. On 23-MAR-2008 absolute neutrophil count was normal and the patient recovered from neutropenia (grade 4). On 25-MAR-2008 the patient recovered from pleural effusion (grade 2) and the patient was discharged from the hospital. Discharge diagnoses were pleural effusion, neutropenia, hypomagnesaemia and hypokalemia. On 30-MAR-2008, treatment therapy with magnesium aspartate (MAGMIN) was stopped. On 31-MAR-2008, the patient recovered from hypomagnesaemia. The patient returned to clinic for review on 31-MAR-2008 and neutropenia remained normal, magnesium was 0.77. No clinical symptoms presented. The patient was not restarted on study therapy. At the time of the report, the patient's shortness of breath improved. The patient's cough persisted.

The investigator felt that neutropenia (grade 4), and hypomagnesaemia (grade 2), and hypokalaemia (grade 4) were related to blinded study therapy and pleural effusion (grade 2) was not related to blinded study therapy. The investigator felt that pleural effusion (grade 2), neutropenia (grade 4), and hypomagnesaemia (grade 2) were related to carboplatin and hypokalaemia (grade 4) was not related to carboplatin. The investigator felt that pleural effusion (grade 2), neutropenia (grade 4) were related to paclitaxel and hypomagnesaemia (grade 2) and hypokalaemia (grade 4) were not related to paclitaxel. The investigator felt that pleural effusion (grade 2) was not related to blinded study therapy but was related to carboplatin and paclitaxel. The investigator felt that the cough (NSAE) was not related to blinded therapy or carboplatin and paclitaxel.

The patient was placed on the following medications during the study: enoxaparin sodium (CLEXANE) for prophylaxis for pulmonary embolism, blood transfusion for anemia, normal saline for dehydration, prochlorperazine maleate (STEMETIL) for nausea, and atropine sulfate (+) diphenoxylate hydrochloride (LOMOTIL) for diarrhea, KCL/potassium for hypokalemia, sandozphosphate for hypophosphatemia, and thiamine for malnourishment.

Additional information is not expected.

This is an amended report. Concomitant therapy dexamethasone (manufacturer unknown), loratadine, ranitidine, tropisetron and aprepitant (MSD) were added to the therapy field. The date of current staging (03-JAN-2008) was added to the narrative. Phosphate levels 0.70 mmol/L and 0.94 mmol/L was removed from the narrative and lab section. The date of treatment therapy with magnesium aspartate (MAGMIN) was changed from 28-MAR-2008 to 30-MAR-2008. The NSAE's were removed from the narrative.

This is a corrected report as amended.

**6. Relevant tests/laboratory data, including dates**

## DIAGNOSTIC TEST

Tests	Date	Value	Unit	Normal Range
computed axial tomography Comment: L pleural effusion no scan evidence of pulmonary embolism	03/18/2008			
chest X-ray Comment: L pleural effusion	03/18/2008			
diagnostic laboratory test Comment: blood: electrolyte abnormalities	03/18/2008			
electrocardiogram	03/18/2008			
diagnostic pathological examination Comment: pleural fluid cytology- negative for malignant cells	03/19/2008			
white blood cell scan Comment: WBC growth factor not given	03/23/2008			
diagnostic laboratory test Comment: blood: returned to normal	03/23/2008			

## LABORATORY RESULTS

Tests	Date	Value	Unit	Normal Range
body temp Comment: afebrile	03/??/2008	36.6		
neutrophil count	03/18/2008	0.1		
neutrophil count	03/18/2008	1	10x 10/L	2 - 7
serum magnesium	03/18/2008	65	mol/L	70 - 95
serum phosphorus	03/18/2008	0.70	mmol/L	
serum potassium	03/18/2008	2.4		
serum potassium	03/18/2008	3	mmol/L	3.5 - 5.0
blood culture Comment: negative for infection	03/18/2008			
serum magnesium	03/19/2008	50	mmol/L	70 - 95
serum potassium	03/19/2008	25	mol/L	35 - 50
pleural fluid culture Comment: no growth	03/19/2008			
serum magnesium	03/20/2008	51	mol/L	70 - 95
serum potassium	03/20/2008	27	mol/L	35 - 50
serum magnesium	03/21/2008	41	mol/L	70 - 95
serum magnesium	03/21/2008	43	mol/L	70 - 95
serum potassium	03/21/2008	23	mol/L	35 - 50
serum potassium	03/21/2008	46	mol/L	35 - 50
serum magnesium	03/22/2008	62	mol/L	70 - 95
serum potassium	03/22/2008	3.8		
absolute neutrophil count	03/23/2008	normal		
neutrophil count	03/23/2008	1	10x 9/L	2 - 7
serum magnesium	03/23/2008	57	mol/L	70 - 95
serum phosphorus	03/25/2008	0.70	mmol/L	
absolute neutrophil count	03/31/2008	normal		
serum magnesium	03/31/2008	0.77	mmol/L	
serum potassium	03/31/2008	4.1		

## C. Suspect medication(s)

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

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

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

- #1 Unk/Unk/PO
- #1 Unk/Unk/PO
- #1 Unk/Unk/PO
- #2 450 mg/1X/IV
- #2 375 mg/1X/IV
- #3 246 mg/1X/IV
- #3 217 mg/1X/IV

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

#1 02/19/2008 - 02/20/2008  
 #1 02/22/2008 - 02/24/2008  
 #1 03/11/2008 - 03/18/2008  
 #2 02/15/2008 - 02/15/2008  
 #2 03/11/2008 - 03/11/2008  
 #3 02/15/2008 - 02/15/2008  
 #3 03/11/2008 - 03/11/2008

## 4. Diagnosis for use (indication)

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

## 6. Lot # (if known)

#1  
 #1  
 #1  
 #2  
 #2  
 #3  
 #3

## 7. Exp date (if known)

#1  
 #1  
 #1  
 #2  
 #2  
 #3  
 #3

## 8. Event reappeared after reintroduction

	YES	NO	N/A	UNK
#1			X	
#1			X	
#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)

EMEND	03/12/2008 - Cont
LIPITOR	07/01/2007 - Cont
acetaminophen	12/01/2007 - Cont
dexamethasone	03/09/2008 - 03/09/2008
dexamethasone	03/10/2008 - 03/10/2008
dexamethasone	03/11/2008 - 03/11/2008
loratadine	03/11/2008 - 03/11/2008
ranitidine	03/11/2008 - 03/11/2008
tropisetron	02/21/2008 - 02/21/2008
tropisetron	03/11/2008 - 03/11/2008