

**MERCK RESEARCH LABORATORIES**

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

Date: 30-DEC-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 #0712USA07938, GENSTUDY # 056-0028 AN # 62512

# 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 0712USA07938
UF/Dist report #	
	FDA Use Onl

A. Patient information			
1. Patient identifier Confidential  AN 62512  in confidence	2. Age at time of event: or <u>71</u> years  Date of Birth: <u>06/28/1936</u>	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight  163 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) <u>12/13/2007</u>		4. Date of this report (mm/dd/yyyy) <u>12/30/2008</u>	
5. Describe event or problem			
This is in follow-up to report(s) previously submitted on 12/26/2007; 1/22/2008; 1/25/2008; 2/15/2008; 6/3/2008; 7/3/2008; 7/28/2008; 8/1/2008; 8/12/2008; 8/26/2008; 9/12/2008; 9/30/2008; 10/2/2008; 12/23/2008			
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 71 year old white male with oedema, chronic obstructive pulmonary disease (COPD), diabetes mellitus, and benign prostate hyperplasia and a history of radiotherapy to holcraneal site (17-SEP-2007 to 04-OCT-2007), meniscus surgery and right hernia surgery who entered a study, title as stated above. On 12-NOV-2007, the patient was placed on cycle one blinded study 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: Meniscus operation; Herniotomy; Radiotherapy CONCURRENT CONDITIONS: Chronic obstructive pulmonary disease; Oedema; Premedication; Diabetes mellitus; Benign prostatic hyperplasia			

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 11/12/2007 - 11/25/2007	
# 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		# 1 <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	
# 2		# 2 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
10. Concomitant medical products and therapy dates (excluded treatment of event)			
dexamethasone		12/10/2007-12/10/2007	
dexchlorpheniramine maleate		12/10/2007-12/10/2007	
(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) <u>12/15/2008</u>	3. Report source. (check all that apply)
6. If IND, protocol # <u>0560028</u>	<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 type="checkbox"/> company representative <input type="checkbox"/> distributor <input type="checkbox"/> other
7. Type of report	5. (A)NDA # <u>58915</u>
<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# <u>14</u>	IND # <u>58915</u> 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 0712USA07938
8. Adverse event term(s)	
RECTAL PERFORATION; PROCEDURAL SITE REACTION; PROCEDURAL PAIN	

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, administered daily for 14 days (cycle equivalent to 25 days) for the treatment of non-small cell lung cancer (diagnosed 20-SEP-2007, current staging: T2/N1/M1; overall stage IV). Concomitant study therapy included carboplatin, 600 mg (AUC equivalent to 6) and paclitaxel, 200 mg/m<sup>2</sup>, 344 mg, both administered IV on 16-NOV-2007. Other concomitant medication included dexamethasone, repaglinide, tamsulosin, omeprazol, rantidine, dexchlorpheniramine maleate and lorazepam. On 25-NOV-2007, the patient completed cycle one blinded study therapy. On 10-DEC-2007, the patient was placed on cycle two study therapy. On 12-DEC-2007, the patient presented to an emergency room with abdominal pain and constipation for 4 days. The event resolved favorably in less than 24 hours with a "deposition." Neutrophils was 92.2%. On 13-DEC-2007, (Cycle 2, Day 4) the patient returned to the emergency room with a complaint of abdominal pain. After medical exploration, the patient was diagnosed with perforation of the rectum (grade 3) with an adjacent necrosis area and was hospitalized. Computed axial tomography revealed pneumoperitoneum. There was no colonoscopy performed prior to hospitalization. After the intestinal perforation was diagnosed the medical staff decided to carry out a surgery on 13-DEC-2007; (HARTMANN procedure). On 13-DEC-2007 a computed axial tomography was performed and did not demonstrate mechanical obstruction. The patient underwent rectum resection and Terminal Colostomy in FII for resolution of perforation of the rectum on 13-DEC-2007. There was free purulent fluid in Douglas and right parietocolic. Blinded study therapy was discontinued. He was treated with acetaminophen, "ceptriazone", hydrocortisone, pantoprazole, vitamin K, levofloxacin, butylscopolamine bromide (+) dipyrone (BUSCAPINA COMPOSITUM), domperidone, meperidine hydrochloride (DOLANTIN), "fitomenadione," acetylcysteine, enoxaparin sodium, dexamethasone and potassium ascorbate. On 09-JAN-2008 the patient was discharged as recovered. Discharge diagnosis was intestinal perforation in upper site of rectus. On 24-JAN-2008, (post therapy day 44) the patient went to the emergency department with pericostomy pain and erythema around it. There was no fever. The patient was hospitalized with pericostomy dermatitis with pain (grade 3). The patient was treated with acetaminophen, amoxicillin (+) clavulanate potassium (AUGMENTIN), and enoxaparin and colostomy care to improve erythema. The patient had satisfactory evolution with local treatment on erythema area. On 29-JAN-2008, the patient recovered and was discharged from the hospital. Discharge diagnosis was intestinal perforation in the upper site of the rectum with diverticulosis and diverticulitis, pericostomy dermatitis and pericostomy pain. On 30-JAN-2008 the patient presented for his medical review and was completely recovered. On 16-MAY-2008, it was reported that the patient was discontinued from the study and was lost to follow-up.

The reporting investigator felt that perforation of the rectum (grade 3) was possibly related to blinded study therapy, and not related to carboplatin or paclitaxel. The investigator reported that the patient hadn't any previous disease which would be the reason of the adverse event reported.

The reporting physician felt that pericostomy dermatitis with pain (grade 3) was not related to blinded study therapy, or study therapy with carboplatin and paclitaxel.

The patient developed the following non-serious adverse events during the study: hypoalbuminemia, hyponatremia, hyperglucemia, anemia, thrombocytopenia, neutropenia and constipation.

The patient was placed on the following treatment medications during the study: furosemide as a diuretic (14-DEC-2007), insulin for hyperglycemia (13-DEC-2007), and alfuzosin hydrochloride (indication not reported) (20-DEC-2007).

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>
computed axial tomography Comment: pneumoperitoneum	12/13/2007		

## LABORATORY RESULTS

<u>Tests</u>	<u>Date</u>	<u>Value</u> <u>Unit</u>	<u>Normal Range</u>
neutrophil count	12/12/2007	92 %	
pathology analysis Comment: see narrative	12/13/2007		

## C. Suspect medication(s)

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

#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  
 #2 600 mg/1X/IV  
 #2 600 mg/1X/IV  
 #3 344 mg/1X/IV  
 #3 344 mg/1X/IV

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

#1 12/10/2007 - 12/13/2007  
 #2 11/16/2007 - 11/16/2007  
 #2 12/10/2007 - 12/10/2007  
 #3 11/16/2007 - 11/16/2007  
 #3 12/10/2007 - 12/10/2007

## 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)

lorazepam	11/06/2007 - Cont
omeprazole	11/06/2007 - Cont
ranitidine	12/10/2007 - 12/10/2007
repaglinide	10/02/2007 - 12/12/2007
tamsulosin hydrochloride	10/02/2007 - Cont