

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

05-FEB-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 # 0806USA01374 GENSTUDY # 056-0079, AN # 60010

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 0806USA01374
UF/Dist report #	
FDA Use On	

A. Patient information			
1. Patient identifier Confidential AN 60010 in confidence	2. Age at time of event: or 42 years Date of Birth: 01/01/1966	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight 79 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 checked="" type="checkbox"/> Death 06/23/2008 (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 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) 06/04/2008		4. Date of this report (mm/dd/yyyy) 02/05/2009	
5. Describe event or problem			
This is in follow-up to report(s) previously submitted on 11/24/2008; 1/7/2009			
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 42 year old Asian female with a history of tubal ligation and with adenocarcinoma, who on 26-MAY-2008 was randomized to a study, title as above.			
On 26-MAY-2008 the patient was placed on therapy with blinded therapy with either vorinostat, capsule, 400 mg or placebo administered on days 1-14 of cycle 1 (cycle equivalent to 25 days) for the treatment of non-small cell lung cancer (diagnosed 17-APR-2008; current staging (26-MAY-2008): T4/N3/M1; overall stage IV).			
(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: Tubal ligation CONCURRENT CONDITIONS: Adenocarcinoma; Premedication; Prophylaxis			

C. Suspect medication(s)			
1. Name (Give labeled strength & mfr/labeler)			
# 1 CAP 0683-blinded therapy Unk			
# 2 carboplatin 574 mg			
(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 05/26/2008 - 06/06/2008	
# 2 574 mg/1X/IV		# 2 05/30/2008 - 05/30/2008	
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 Non-small cell lung cancer		# 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 checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		# 2 <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	
10. Concomitant medical products and therapy dates (excluded treatment of event)			
ATIVAN		05/30/2008 - 06/01/2008	
DECMAX		05/29/2008 - 05/29/2008	
(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) 11/14/2008	3. Report source. (check all that apply)
6. If IND, protocol # 0560079	<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	5. (A)NDA #
<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# 2	IND # 58915 STN # PMA/ 510(k) # Combination Product <input type="checkbox"/> Yes Pre-1938 <input type="checkbox"/> Yes OTC product <input type="checkbox"/> Yes
8. Adverse event term(s)	9. Mfr. report number
NEUTROPENIA; THROMBOCYTOPENIA; GASTROENTERITIS; DEATH	WAES 0806USA01374

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		<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

Concomitant study therapy included carboplatin, AUC equivalent to 6 (574 mg) and paclitaxel, 200 mg/m² (240 mg) both administered intravenously on 30-MAY-2008.

Other concomitant therapy included: dexamethasone (DECMAX), granisetron hydrochloride (GRANISET) and dexamethasone (manufacturer unknown) for premedication for paclitaxel, ranitidine hydrochloride (RANTAC) and omeprazole (OMEZ), for vomiting prophylaxis, lorazepam (ATIVAN) for postchemotherapy medication, promethazine hydrochloride (PHENERGAN) and "effecorlin" for allergic reaction prophylaxis.

On 04-JUN-2008, at 17:00, the patient developed gastroenteritis (grade 3), with watery diarrhea seven to eight times with no blood, the patient was not taking any medication which would lead to bleeding. Stool and urine culture shows no pathogen isolated. On 07-JUN-2008, at 13:00, the patient developed neutropenia (grade 4) and thrombocytopenia (grade 2). On 07-JUN-2008, the patient was hospitalized for neutropenia (grade 4), gastroenteritis (grade 3) and thrombocytopenia (grade 2). The patient was afebrile. On 07-Jun-2008 blood neutrophil count was 17 %, blood platelet count was 55000/cumm, serum sodium test was 129 meq/L and white blood cell count was 1160/cumm. Blood pressure was 90/70, pulse was 100/minutes, respiratory rate was 24/minutes and temperature was 99. The patient also had dehydration (grade 2). Study therapy was interrupted. The patient was treated with IV pints, piperacillin sodium (+) tazobactam sodium (ZOSYN), nitroimidazole (FLAGYL), amikacin, benzydamine hydrochloride (TANTUM), filgrastim (NUFIL SAFE), loperamide hydrochloride (IMODIUM), dextrose in normal saline (2 pints), normal saline (2 pints) and ringer's lactate (2 pints) with "kesol" added to each pint and ceftazidime (CEFTUM). On 09-Jun-2008, white blood cell count was 4510/cumm, blood neutrophil count was 42 percent and blood platelet count was 24,000/cumm. On 09-JUN-2008, the patient recovered from neutropenia (grade 4), gastroenteritis (grade 3) and recovered with sequelae from thrombocytopenia (grade 2) and was discharged from the hospital. On 09-JUN-2008 the patient experienced thrombocytopenia (grade 4) and the outcome was unknown. It was also reported that there was no diarrhea, no fever, and the patient was clinically better so she was discharged on 09-JUN-2008. All treatments were given for 3 days. Discharge diagnoses were neutropenia (grade 4), thrombocytopenia (grade 2) and gastroenteritis. On 20-JUN-2008, the patient was discontinued from study medication due to progressive disease. The patient was lost to follow-up. The patient's family reported to the investigator that the patient died 23-JUN-2008 at home. She was not on any treatment. There was no autopsy performed and the cause of death was unknown. The patients family did not mention any signs and symptoms after the hospital discharge.

The reporting investigator felt that gastroenteritis (grade 3) was related to blinded study therapy. Neutropenia (grade 4) and thrombocytopenia (grade 2) were not related to blinded study therapy and were related to carboplatin and paclitaxel. Dehydration (grade 2) was not related to paclitaxel and carboplatin. Death cause unknown was reported to be not related to study therapy and not related to paclitaxel and carboplatin.

The patient was placed on the following treatment medications during the study: benzydamine hydrochloride (TANTUM) for oral ulcer prophylaxis, cyanocobalamin (+) iron polymaltose (+) pyridixone (OROPER SYRUP) for nutritional support and for the treatment of dehydration.

This is an amended report, the unit measure of "/cumm" was added to the narrative and the laboratory data table.

Additional information is not expected.

This report is corrected as amended.

6. Relevant tests/laboratory data, including dates

DIAGNOSTIC TEST

Tests	Date	Value	Unit	Normal Range
blood pressure measurement	06/07/2008	90/70		

LABORATORY RESULTS

Tests	Date	Value	Unit	Normal Range
stool culture Comment: no pathogen isolated	06/04/2008			
urine culture Comment: no pathogen isolated	06/04/2008			
WBC count	06/07/2008	1160	/cumm	4000 - 11000
body temp	06/07/2008	99		
neutrophil count	06/07/2008	17	percent	40 - 75
platelet count	06/07/2008	55000	/cumm	150000 - 400000

serum creatinine	06/07/2008		
Comment: results not reported			
serum potassium	06/07/2008		
Comment: results not reported			
serum sodium	06/07/2008	129 meq/L	136 - 142
respiratory rate measurement	06/07/2008	24 /min	
total heartbeat count	06/07/2008	100 /min	
WBC count	06/09/2008	4510 /cumm	4000 - 11000
neutrophil count	06/09/2008	42 percent	40 - 75
platelet count	06/09/2008	24,000 /cumm	150000 - 400000

C. Suspect medication(s)

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

#3 paclitaxel 240 mg

2. Dose, frequency & route used

#3 240 mg/1X/IV

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

#3 05/30/2008 - 05/30/2008

4. Diagnosis for use (indication)

#3 Non-small cell lung cancer

5. Event abated after use stopped or dose reduced

	YES	NO	N/A	UNK
#3			X	

6. Lot # (if known)

#3

7. Exp date (if known)

#3

8. Event reappeared after reintroduction

	YES	NO	N/A	UNK
#3			X	

C. Suspect medication(s)

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

GRANiset	05/30/2008 - 05/30/2008
OMEZ	05/30/2008 - 06/03/2008
RANTAC	05/30/2008 - 05/30/2008
dexamethasone	05/30/2008 - 05/30/2008
promethazine hydrochloride	05/30/2008 - 05/30/2008