

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

December 05, 2008

Re: blinded therapy/MK-0683

Dear Doctor:

This letter is to provide follow-up information on an adverse experience concerning blinded MK-0683 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 # 0802USA04821, GENSTUDY # 056-0096, AN # 63507

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 0802USA04821
UF/Dist report #	
	FDA Use Onl

A. Patient information			
1. Patient identifier Confidential AN 63507 in confidence	2. Age at time of event: or 64 years Date of Birth: 11/23/1943	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight 132 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)	02/18/2008	4. Date of this report (mm/dd/yyyy)	12/05/2008
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5. Describe event or problem
This is in follow-up to report(s) previously submitted on 2/29/2008; 3/20/2008; 3/26/2008; 4/15/2008; 5/5/2008; 8/29/2008; 11/7/2008; 11/12/2008

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 64 year old Asian female with vomiting and a history of hemoptysis and toothache who entered a study, title as stated above who was randomized on 07-FEB-2008. On 07-FEB-2008, the patient was placed on blinded study therapy with either vorinostat, capsule, 400 mg or placebo administered on days -4 through 10 of cycle 1 (cycle equivalent to 25 days) for the treatment of non-small cell lung cancer (diagnosed on 11-NOV-2007, T2 N2 M1, stage 4 Adenocarcinoma).

(Continued on Additional Page)

6. Relevant tests/laboratory data, including dates	Refer to Additional Page
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7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

MEDICAL HISTORY: Haemoptysis; Toothache
CONCURRENT CONDITIONS: Vomiting

C. Suspect medication(s)	
1. Name (Give labeled strength & mfr/labeler)	
# 1 CAP 0683-blinded therapy Unk	
# 2 INJ carboplatin Unk	
(Continued on Additional Page)	

2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration from/to (or best estimate))
# 1 400 mg/DAILY/PO	# 1 02/07/2008 - 02/20/2008
# 2 684 mg/1X/IV	# 2 02/13/2008 - 02/13/2008

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"/>
	# 2 <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>

6. Lot #	7. Exp. Date	8. Event reappeared after reintroduction.
# 1	# 1	yes no N/A unk
# 2	# 2	# 1 <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>
		# 2 <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>

9. NDC # or Unique ID	Unknown
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10. Concomitant medical products and therapy dates (excluded treatment of event)	
BENADRYL	02/13/2008 - 02/13/2008
STEMETIL	02/13/2008 - 02/17/2008

(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)	5. (A)NDA #
11/26/2008	IND # 58915
6. If IND, protocol #	STN #
0560096	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	
<input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up# 8	9. Mfr. report number
	WAES 0802USA04821

8. Adverse event term(s)	
HYPONATRAEMIA	

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 suspect study therapy carboplatin AUC equivalent to 6 (684 mg), and paclitaxel 200 mg/m² (320), administered IV on day 1 of each treatment cycle. Other concomitant therapy included ondansetron HCL (ZOFTRAN), diphenhydramine (BENADRYL), dexamethasone (manufacturer unknown), ranitidine, tramadol hydrochloride (TRAMAL) and prochlorperazine maleate (STEMETIL).

On 13-FEB-2008, study therapy was discontinued. On 18-FEB-2008, (cycle 1, day 11) the patient experienced fatigue and vomiting and was hospitalized for hyponatremia (grade 4). Laboratory evaluation on 18-FEB-2008 revealed serum sodium was 105 mmol/L (also reported as 110 mmol/L) and white blood count was 4400/uL. She was treated with 3 percent sodium chloride intravenously. On 20-FEB-2008, the patient completed cycle 1 of study therapy. On 21-FEB-2008, the patient experienced severe febrile neutropenia (grade 3) (NSAE) which was treated with cefepime. On 21-FEB-2008 patient's serum sodium was 131 mmol/L. On 27-FEB-2008, the patient's serum sodium level was 136 mmol/L.

On 29-FEB-2008, the patient recovered from hyponatremia (grade 4) laboratory result not reported and was discharged from the hospital. Discharge diagnosis was hyponatremia. At the time of reporting, the patient had not recovered from the severe febrile neutropenia (NSAE). On 05-MAR-2008, the patient was discontinued from the study due to the adverse event. Action taken for blinded study therapy, carboplatin and paclitaxel was discontinued.

The reporting investigator felt that the grade 4 hyponatremia and severe febrile neutropenia (grade 4) (NSAE) were related to blinded study therapy, carboplatin, and paclitaxel.

Additional information is not expected.

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

<u>Tests</u>	<u>Date</u>	<u>Value</u>	<u>Unit</u>	<u>Normal Range</u>
serum sodium	02/17/2008	105	mmol/L	135 - 145
WBC count	02/18/2008	4400	/ul	4500 - 11000
serum sodium	02/18/2008	110	mmol/L	135 - 145
Comment: hyponatremia grade 3				
serum sodium	02/18/2008	105	mmol/L	135 - 145
Comment: hyponatremia grade 3				
serum sodium	02/18/2008	115	mmol/L	135 - 145
Comment: hyponatremia grade 3				
serum sodium	02/18/2008	105	mmol/L	135 - 145
Comment: hyponatremia grade 3				
serum sodium	02/19/2008	123	mmol/L	135 - 145
serum sodium	02/21/2008	131	mmol/L	135 - 145
serum sodium	02/23/2008	127	mmol/L	135 - 145
serum sodium	02/27/2008	136	mmol/L	135 - 145

C. Suspect medication(s)**1. Name (Give labeled strength & mfr/labeler)**

#3 paclitaxel Unk

2. Dose, frequency & route used

#3 320 mg/1X/IV

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

#3 02/13/2008 - 02/13/2008

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)

TRAMAL	02/13/2008 - Cont
dexamethasone	02/13/2008 - 02/13/2008
ondansetron	02/13/2008 - 02/13/2008
ondansetron	02/13/2008 - 03/04/2008
ranitidine	02/13/2008 - 02/13/2008