

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

November 21, 2008

Re: MK-0683 – blinded therapy

Dear Doctor:

This letter is to provide follow-up information on an adverse experience concerning MK-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 # 0802USA02223, GENSTUDY # 0560012, AN # 58005

MedWatch

The FDA Medical Products Reporting Program

MERCK HUMAN HEALTH DIVISION

For use by user-facilities,
distributors and manufacturers for
MANDATORY reporting

Page 1

Merck Facsimile of FDA Form 3500A
Approved by FDA (10/21/1993)

Mfr report #	WAES 0802USA02223
UF/Dist report #	
FDA Use Onl	

A. Patient information

1. Patient identifier Confidential AN 58005 in confidence	2. Age at time of event: or <u>68 years</u> Date of Birth: <u>07/22/1939</u>	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 194 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 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>01/31/2008</u>	4. Date of this report (mm/dd/yyyy) <u>11/21/2008</u>

5. Describe event or problem
This is in follow-up to report(s) previously submitted on 2/15/2008; 3/13/2008; 5/12/2008; 5/30/2008; 6/13/2008; 7/31/2008

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 68 year old white male with vitamin D deficiency, asthma, chronic obstructive pulmonary disease (COPD), house dust mite allergy, allergic reaction to neomycin, arthrosis of great joints and right midfoot, dyspnea, diverticulosis, gout, hiatal hernia, pleural effusion, Raynaud's syndrome and productive cough (cough with sputum) and a history of bronchoscopy, whole body scan, lymph node puncture, computerized tomogram abdomen, computerised tomogram skull, deep vein thrombosis (DVT), inguinal hernia,

(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: Bronchoscopy; Computerised tomogram abdomen; Computerised tomogram head; Inguinal hernia; Scintigraphy; Whole body scan; Biopsy lymph gland; Pulmonary embolism; Pneumonia; Deep vein thrombosis CONCURRENT CONDITIONS: Vitamin D deficiency; Raynaud's syndrome; Pleural effusion; Hiatus

(Continued on Additional Page)

C. Suspect medication(s)

1. Name (Give labeled strength & mfr/labeler) # 1 <u>CAP 0683-blinded therapy Unk</u> # 2 _____ (Continued on Additional Page)	
2. Dose, frequency & route used # 1 <u>400 mg/DAILY/PO</u> # 2 _____	3. Therapy dates (if unknown, give duration) from/to (or best estimate) # 1 <u>12/07/2007 - 12/20/2007</u> # 2 _____
4. Diagnosis for use (indication) # 1 <u>Non-small cell lung cancer</u> # 2 _____	5. Event abated after use stopped or dose reduced. # 1 <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> N/A <input type="checkbox"/> unk # 2 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
6. Lot # # 1 _____ # 2 _____	7. Exp. Date # 1 _____ # 2 _____
8. Event reappeared after reintroduction. # 1 <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> N/A <input type="checkbox"/> unk # 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) BARILUX <u>01/23/2008-01/23/2008</u> BERODUAL <u>12/07/2007-Cont</u>	

(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) <u>11/19/2008</u>	3. Report source (check all that apply) <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:
5. (A)NDA # _____ 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 0802USA02223
6. If IND, protocol # <u>0560012.</u>	8. Adverse event term(s) NEUTROPENIA; MUCOSAL INFLAMMATION
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# <u>6</u>	

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

pneumonia, pulmonary embolism and pulmonary perfusion scintigraphy who entered a study, title as stated above. On 07-DEC-2007, the patient was placed on cycle one blinded study therapy of either vorinostat, capsule, 400 mg or placebo, PO administered daily for 14 days every 25 days for the treatment of non-small cell lung cancer (T4, N3, M0 Stage III B date of current staging 03-DEC-2007). Concomitant study therapy included carboplatin, 570 mg (AUC equivalent to 6) and paclitaxel, 200 mg, both administered IV on day one of each cycle. Other concomitant therapy included cholecalciferol (VIGANTOLETTEN), budesonide (+) formoterol fumarate (SYMBICORT), tiotropium bromide (SPIRIVA), ambroxol hydrochloride (MUCOSOLVAN), fenoterol hydrobromide (+) ipratropium bromide (BERODUAL), and metoclopramide ("MCP"). On 03-JAN-2008, the patient was placed on cycle two study therapy. On 04-JAN-2008, the patient was placed on therapy with esomeprazole magnesium (NEXIUM) for gastric prophylaxis. On 16-JAN-2008, cycle two study therapy was completed. On 23-JAN-2008, the patient was placed on therapy with dexamethasone sodium phosphate (FORTECORTIN) as chemotherapy prophylaxis, and administered barium sulfate (BARILUX) and iomeprol (IMERON) contrast medium for CT scan. On 24-JAN-2008, the patient was placed on cycle three study therapy, as well as therapy with ranitidine, ondansetron hydrochloride (ZOFRAN) and clemastine fumarate (TAVEGIL) as chemotherapy prophylaxis.

On 31-JAN-2008, the patient developed neutropenia with CTC grade 3 (ANC 0.8 Giga/l). No fever was noted. On 06-FEB-2008, the patient completed cycle three study therapy. The patient was seen in the emergency room on 06-FEB-2008, (Day 14 of his third cycle). The patient presented to an emergency room suffering from a cold with complete obstruction of his nose and dysphagia due to mucositis as a consequence of neutropenia.

On 06-FEB-2008 the patient showed neutropenia with CTC grade 4 (ANC 0.4 Giga/l). Physical exam on 06-FEB-2008 revealed mucositis, sinusitis and an x-ray of the thorax on 07-FEB-2008 revealed no significant findings. Subsequently, the patient was hospitalized for neutropenia (grade 4) and mucositis (grade 3) which was reported as non-serious. The patient was treated with dipyrone (NOVALGIN) for pain, "Telpilta," pantoprazole sodium (PANTOZOL) for dysphagia, and amphotericin B (AMPHO-MORONAL) and xylometazoline hydrochloride (OTRIVEN) for paranasal sinusitis and was administered lenograstim (GRANOCYTE), SC for neutropenia (one injection on 07-FEB-2008). It was reported that study therapy was reduced due to the neutropenia. On 07-FEB-2008 lab values showed normal values (ANC 2.3 G/l). On 07-FEB-2008, the patient had recovered from mucositis (grade 3). The patient was discharged on 08-FEB-2008 with discharge diagnosis was grade IV neutropenia, grade I thrombocytopenia, mucositis and sinusitis. On 13-FEB-2008, the patient recovered from the symptoms (mucositis, sinusitis low ANC). On 15-FEB-2008, the patient was placed on cycle four of the study therapy. On 22-APR-2008 therapy with metoclopramide HCL (MCP) was stopped, and on 24-APR-2008 therapy with esomeprazole magnesium (NEXIUM) was stopped.

The reporting investigator felt that neutropenia (grade 4) was related to The reporting investigator felt that mucositis (grade 3) was not related to blinded study therapy or study therapy with carboplatin and paclitaxel.

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>
physical examination Comment: see narrative	02/06/2008		
X-ray Comment: no significant finding	02/07/2008		

LABORATORY RESULTS

<u>Tests</u>	<u>Date</u>	<u>Value</u> <u>Unit</u>	<u>Normal Range</u>
absolute neutrophil count Comment: CTC 3	01/31/2008	0.8 g/L	2.4 - 8.1
absolute neutrophil count Comment: CTC 4	02/06/2008	0.4 g/L	2.4 - 8.1
absolute neutrophil count	02/07/2008	2.3 g/L	2.4 - 8.1

7. Other relevant history including preexisting medical conditions

hernia; Gout; Diverticulosis; Asthma; Chronic obstructive pulmonary disease; House dust mite allergy; Dyspnoea; Allergic reaction to antibiotics; Arthrosis; Productive cough

C. Suspect medication(s)

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

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

2. Dose, frequency & route used

#1 400 mg/DAILY/PO
#1 400 mg/DAILY/PO
#1 300 mg/DAILY/PO
#1 400 mg/DAILY/PO
#2 570 mg/1X/IV
#2 570 mg/1X/IV
#2 672 mg/1X/IV
#2 496 mg/1X/IV
#2 570 mg/1X/IV
#3 400 mg/1X/IV
#3 400 mg/1X/IV
#3 400 mg/1X/IV
#3 255 mg/1X/IV
#3 355 mg/1X/IV

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

#1 01/03/2008 - 01/16/2008
#1 01/24/2008 - 02/06/2008
#1 02/15/2008 - 02/29/2008
#1 03/07/2008 - 03/20/2008
#2 12/11/2007 - 12/11/2007
#2 01/03/2008 - 01/03/2008
#2 01/24/2008 - 01/24/2008
#2 02/15/2008 - 02/15/2008
#2 03/07/2008 - 03/07/2008
#3 12/11/2007 - 12/11/2007
#3 01/03/2008 - 01/03/2008
#3 01/24/2008 - 01/24/2008
#3 02/15/2008 - 02/15/2008
#3 03/07/2008 - 03/07/2008

4. Diagnosis for use (indication)

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

6. Lot # (if known)

#1
#1
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7. Exp date (if known)

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

8. Event reappeared after reintroduction

	YES	NO	N/A	UNK
#1			X	
#1			X	
#1			X	
#1			X	
#2			X	
#2			X	
#2			X	
#2			X	
#2			X	
#3			X	
#3			X	
#3			X	
#3			X	

C. Suspect medication(s)

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

FORTECORTIN	01/23/2008 - 01/27/2008
IMERON	01/23/2008 - 01/23/2008
MCP	01/04/2008 - 04/22/2008
MUCOSOLVAN	11/26/2007 - 12/??/2007
NEXIUM	01/04/2008 - 04/24/2008
SPIRIVA	11/26/2007 - Cont
SYMBICORT	11/26/2007 - Cont
TAVEGIL	01/24/2008 - 01/24/2008
VIGANTOLETTEN	11/26/2007 - Cont
ZOFRAN	01/24/2008 - 01/25/2008
ranitidine	01/24/2008 - 01/24/2008