

# 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 0802USA02223
UF/Dist report #	
	FDA Use On

A. Patient information			
1. Patient identifier Confidential  AN 58005 in confidence	2. Age at time of event: or 68 years  Date of Birth: 07/22/1939	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight  194 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)	01/31/2008	4. Date of this report (mm/dd/yyyy)	03/05/2009
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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; 11/21/2008; 12/16/2008  
  
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 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))	
# 1 400 mg/DAILY/PO		# 1 12/07/2007 - 12/20/2007	
# 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 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"/>	
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)			
BARILUX		01/23/2008-01/23/2008	
BERODUAL		12/07/2007-Cont	
(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 #
02/24/2009	IND # 58915
6. If IND, protocol #	STN #
0560012	PMA/
7. Type of report	510(k) #
<input type="checkbox"/> 5-day <input type="checkbox"/> 30-day	Combination Product <input type="checkbox"/> Yes
<input type="checkbox"/> 7-day <input type="checkbox"/> Periodic	Pre-1938 <input type="checkbox"/> Yes
<input type="checkbox"/> 10-day <input type="checkbox"/> Initial	OTC product <input type="checkbox"/> Yes
<input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up# 8	9. Mfr. report number
	WAES 0802USA02223
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	

8. Adverse event term(s)
NEUTROPENIA

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

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 (ZOFTRAN) and clemastine fumarate (TAVEGIL) as chemotherapy prophylaxis.

On 31-JAN-2008, the patient developed neutropenia (grade 4) (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 (non-serious). Subsequently on 06-FEB-2008, the patient was hospitalized for neutropenia (grade 4). On 06-FEB-2008, the patient showed neutropenia (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. No blood cultures were drawn or a throat swab was performed prior to antibiotic therapy. The patient was treated with dipyrone (NOVALGIN) for pain, oxethazaine (TEPILTA), pantoprazole sodium (PANTOZOL) PO for dysphagia, xylometazoline hydrochloride (OTRIVEN) and amoxicillin (+) clavulanate potassium (AUGMENTAN) PO for paranasal sinusitis and was administered lenograstim (GRANOCYTE) IV 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). 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 patient experienced the following non-serious adverse events during the study protocol: stomatitis (grade 2) onset 06-FEB-2008 which was treated with amphotericin B (AMPHO-MORONAL) PO and resolved on 12-FEB-2008.

The reporting investigator felt that neutropenia (grade 4) was related to study therapy, carboplatin and paclitaxel. The reporting investigator felt that stomatitis (grade 2) was not related to study therapy.

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 &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  
 #2 carboplatin Unk  
 #2 carboplatin Unk  
 #3 paclitaxel Unk  
 #3 paclitaxel Unk  
 #3 paclitaxel Unk

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

#1 400 mg/DAILY/PO  
 #1 400 mg/DAILY/PO  
 #1 300 mg/DAILY/PO  
 #2 570 mg/1X/IV  
 #2 570 mg/1X/IV  
 #2 672 mg/1X/IV  
 #2 496 mg/1X/IV  
 #3 400 mg/1X/IV  
 #3 400 mg/1X/IV  
 #3 400 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  
 #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  
 #3 12/11/2007 - 12/11/2007  
 #3 01/03/2008 - 01/03/2008  
 #3 01/24/2008 - 01/24/2008

## 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  
 #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

## 5. Event abated after use stopped or dose reduced

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

## 6. Lot # (if known)

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

## 7. Exp date (if known)

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

## 8. Event reappeared after reintroduction

	YES	NO	N/A	UNK
#1			X	
#1			X	
#1			X	
#2			X	
#2			X	
#2			X	
#2			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 - 01/23/2008
FORTECORTIN	01/24/2008 - 01/24/2008
FORTECORTIN	01/25/2008 - 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