

# MedWatch

The FDA Medical Products Reporting Program

## Merck Human Health Division

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

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

Mfr report #	WAES 0801USA03882
UF/Dist report #	
	FDA Use Only

A. Patient information			
1. Patient identifier Confidential AN 61515 in confidence	2. Age at time of event: or 59 years Date of Birth: 04/15/1948	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight 141 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 checked="" 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)	01/03/2008	4. Date of this report (mm/dd/yyyy)	03/04/2009
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5. Describe event or problem  
This is in follow-up to report(s) previously submitted on 1/24/2008; 2/14/2008; 2/20/2008; 7/9/2008; 7/24/2008; 8/5/2008; 11/5/2008; 12/16/2008; 12/26/2008

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 59 year old white female with asthma, back pain, dry skin, insomnia, muscular leg cramps, nocturia, pain in right hip and varicose vein and a history of hysterectomy, nausea, lower lobe lung lobectomy and sinus surgery for nasal polyps who entered a study, title as stated above. On 20-DEC-2007, the patient was randomized and placed on vorinostat/blinded therapy, 400 mg or placebo once daily administered on days -4 through 10 of cycle 1 (cycle equivalent to 25 days) (or days 1 through 14) for each subsequent cycle )

(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: Hysterectomy; Nausea; Sinus operation; Nasal polyps; Lung lobectomy; Chemotherapy  
CONCURRENT CONDITIONS: Asthma; Back pain; Nausea prophylaxis; Dry skin; Insomnia; Leg cramps; Nocturia; Pain in hip; Varicose vein

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 12/20/2007 - 01/02/2008
# 2	

4. Diagnosis for use (indication)	5. Event abated after use stopped or dose reduced
# 1	Non-small cell lung cancer
# 2	
	yes no N/A unk
	# 1 <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>
	# 2 <input 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 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)	
ACTONEL	06/??/2007-Cont
ADVAIR	01/??/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
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 health professional	
<input type="checkbox"/> user facility	
<input type="checkbox"/> company representative	
<input type="checkbox"/> distributor	
<input type="checkbox"/> other:	

4. Date received by manufacturer (mm/dd/yyyy)	12/16/2008	5. (A)NDA #	
		IND #	58915
6. If IND, protocol #	0560018	STN #	
		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	9. Mfr. report number	WAES 0801USA03882
<input checked="" type="checkbox"/> 15-day	<input checked="" type="checkbox"/> Follow-up# 9		

8. Adverse event term(s)	FEBRILE NEUTROPENIA; PYREXIA
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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**

for the treatment of non small cell lung cancer (diagnosed on 19-JUN-2006; current staging 20-DEC-2007, T4/N3/M1/IV).

Concomitant study therapy included carboplatin 6 AUC and paclitaxel 200 mg/m2 (infusion form). Other concomitant therapy included risedronate sodium (ACTONEL), calcium, vitamin D and vitamin C, dexamethasone (MSD), ranitidine, ondansetron hydrochloride (ZOFTRAN), diphenhydramine hcl (BENADRYL), metoclopramide hydrochloride (MAXERAN), fluticasone propionate (+) salmeterol xinafoate (ADVAIR) and fluticasone propionate (FLONASE).

On 03-JAN-2008, the patient presented to the emergency department with fever of 38.6 C. The patient was admitted to the hospital for febrile neutropenia (grade 3). Laboratory evaluations revealed neutropenia of  $0.1 \times 10^9/L$ . Blood cultures were reported as normal and negative). On 04-JAN-2008, a chest x-ray showed no evidence of pneumonia and the urine culture was normal and negative). The patient was treated with ticarcillin disodium/ clavulanate potassium (TIMENTIN) 3.1 g IV every 4 hours and gentamicin 80 mg IV every 8 hours. A serum potassium test revealed a potassium level of 3 mmol/L (also reported as 3.3 mmol/L). She also received 60 mEq potassium IV on 04-JAN-2008. On 05-JAN-2008, the patient recovered. On 05-JAN-2008, the patient was discharged with no signs of neutropenia ( $1.5 \times 10^9/L$ ) or fever, or hypokalemia at discharge. Discharge diagnosis was febrile neutropenia (grade 3). The patient was seen in pulmonary oncology clinic on 09-JAN-2008. There was no new neutropenia or fever since event and the patient's condition was stable. On 20-FEB-2008, the patient called from home complaining of a fever (grade 1) of 38.6 C and a suggestion was made to take acetaminophen (TYLENOL). The absolute neutrophil count (ANC) was 20.66 GI/L and on 27-FEB-2008 it was 3.7 GI/L. The patient was reported to be on filgrastim (NEUPOGEN). The next day the patient returned to the clinic for blood cultures. Both blood and urine cultures came back negative. The patient was started on levofloxacin (LEVAQUIN) for 7 days. On 26-FEB-2008, the patient called saying the fever still persisted despite antibiotics and acetaminophen (TYLENOL). On 27-FEB-2008, the patient came back to the clinic with the fever (still persisting at 37.8 C as per patient), during the visit the fever was 36.5 C. The patient met with a physician from infectious disease department who prescribed atovaquone (MEPRON). During this time, the patient's 4th cycle was postponed from 27-FEB-2008 to 12-MAR-2008 since the fever resolved on atovaquone (MEPRON). Patient came back to clinic on 05-MAR-2008 and no other episode of fever was noted. The diagnosis was fever of unknown etiology. The investigator rationale for deeming this a medically significant event was because the event was out the norm and because intervention was required.

Fever (grade 1) was considered to be an other important medical event.

The reporting investigator felt that the fever and the febrile neutropenia, grade 3 were related to study therapy of vorinostat or placebo, carboplatin, and paclitaxel. It was reported that on 13-MAY-2008 the patient had a study visit. The patient completed oncology study medication.

This is an amended report.

The following changes were made to the narrative: The formulation for carboplatin and paclitaxel was added to the field. The lower lobe was added; 100 mg capsule was deleted from therapy with vorinostat/blinded therapy; non small cell cancer was (diagnosed on 19-JUN-2006; current staging 20-DEC-2007, T4/N3/M1/IV) was added; deleted value of neutropenia "also reported as  $2 \times 10^9/L$ ." In the laboratory screen on 28-FEB-2008 blood and urine culture were added as negative which was in the narrative.

Additional information is not expected.

The report is corrected as amended.

**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>
chest X-ray	01/04/2008			
Comment: No evidence of pneumonia - negative for pneumonia - Normal				

**LABORATORY RESULTS**

<u>Tests</u>	<u>Date</u>	<u>Value</u>	<u>Unit</u>	<u>Normal Range</u>
absolute neutrophil count	01/03/2008	.2 x 10	<sup>9</sup> /	1.8 - 7.5
body temp	01/03/2008	38.6	C	
blood culture	01/03/2008			
Comment: Normal				

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 01/04/2008  
 01/04/2008  
 01/04/2008

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 3 mmol/L 3.5 - 5.5  
 3.3 mmol/L 3.5 - 5.5

serum potassium  
 serum potassium  
 urine culture  
 Comment: Normal

absolute neutrophil count 01/05/2008  
 absolute neutrophil count 02/20/2008  
 absolute neutrophil count 02/20/2008  
 body temp 02/20/2008  
 absolute neutrophil count 02/27/2008  
 absolute neutrophil count 02/27/2008  
 body temp 02/27/2008  
 Comment: 36.5 C per patient

1.5 x 10<sup>9</sup>/L 1.8 - 7.5  
 20.66 GI/L  
 21.2 x 10<sup>9</sup>/L 1.8 - 7.5  
 38.6 C  
 3.7 GI/L  
 3.6 x 10<sup>9</sup>/L 1.8 - 7.5  
 37.8 C

body temp 02/27/2008  
 blood culture 02/28/2008  
 Comment: Negative  
 urine culture 02/28/2008  
 Comment: Negative

36.5 C

C. Suspect medication(s)

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

- #1 CAP 0683-blinded therapy Unk
- #1 CAP 0683-blinded therapy Unk
- #2 infusion (form) carboplatin Unk
- #2 infusion (form) carboplatin Unk
- #2 infusion (form) carboplatin Unk
- #3 infusion (form) paclitaxel Unk
- #3 infusion (form) paclitaxel Unk
- #3 infusion (form) paclitaxel Unk

2. Dose, frequency & route used

- #1 Unk/Unk/PO
- #1 Unk/Unk/PO
- #2 670 mg/1X/IV
- #2 619 mg/1X/IV
- #2 681 mg/1X/IV
- #3 338 mg/1X/IV
- #3 338 mg/1X/IV
- #3 338 mg/1X/IV

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

- #1 01/16/2008 - 01/29/2008
- #1 02/06/2008 - 02/19/2008
- #2 12/24/2007 - 12/24/2007
- #2 01/16/2008 - 01/16/2008
- #2 02/06/2008 - 02/06/2008
- #3 12/24/2007 - 12/24/2007
- #3 01/16/2008 - 01/16/2008
- #3 02/06/2008 - 02/06/2008

4. Diagnosis for use (indication)

- #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
- #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	
#2			X	
#2			X	
#2			X	
#3			X	
#3			X	
#3			X	

6. Lot # (if known)

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

7. Exp date (if known)

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

8. Event reappeared after reintroduction

	YES	NO	N/A	UNK
#1			X	
#1			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)

BENADRYL	12/24/2007 - 12/24/2007
BENADRYL	02/06/2008 - 02/06/2008
DECADRON (DEXAMETHASONE)	12/23/2007 - 12/24/2007
DECADRON (DEXAMETHASONE)	12/25/2007 - 12/26/2007
DECADRON (DEXAMETHASONE)	12/27/2007 - 12/29/2007
DECADRON (DEXAMETHASONE)	02/05/2008 - 02/06/2008
DECADRON (DEXAMETHASONE)	02/07/2008 - 02/08/2008
DECADRON (DEXAMETHASONE)	02/09/2008 - 02/11/2008
FLONASE	01/13/2008 - Cont
MAXERAN	12/25/2007 - 12/29/2007
MAXERAN	02/07/2008 - 02/11/2008
ZOFRAN	12/24/2007 - 12/24/2007
ZOFRAN	02/06/2008 - 02/06/2008
ascorbic acid	01/09/2007 - Cont
calcium (unspecified)	06/??/2007 - Cont
ranitidine	12/24/2007 - 12/24/2007
ranitidine	02/06/2008 - 02/06/2008
vitamin d (unspecified)	06/01/2007 - Cont