

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 0803USA03465

UF/Dist report #

FDA Use Onl

A. Patient information			
1. Patient identifier Confidential AN 55508 in confidence	2. Age at time of event: or Date of Birth 66 years 10/23/1941	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight 73 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) 03/18/2008	4. Date of this report (mm/dd/yyyy) 03/02/2009
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5. Describe event or problem
This is in follow-up to report(s) previously submitted on 3/28/2008; 4/14/2008; 4/21/2008; 5/2/2008; 5/9/2008; 5/23/2008; 5/30/2008; 6/12/2008; 7/3/2008; 8/1/2008; 8/28/2008; 1/23/2009; 1/26/2009; 2/6/2009

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 66 year old white female with hypercholesterolaemia, pain, constipation, fatigue, left shoulder pain, shortness of breath, cough and weight loss and a history of ductal carcinoma in situ, duodenal ulcer, hysterectomy, left lower lung lobectomy (13-NOV-2003), left breast lesion excision (08-APR-1997) and radiotherapy to left breast (1997) who on 11-FEB-2008 was placed on cycle 1 of study therapy with blinded therapy, with either vorinostat, capsule 400 mg or

(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.)
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MEDICAL HISTORY: Ductal carcinoma in situ; Duodenal ulcer; Radiotherapy; Hysterectomy; Lung lobectomy; Lesion excision
CONCURRENT CONDITIONS: Hypercholesterolaemia; Weight decreased; Nausea; Cough; Pain; Fatigue; Breath shortness; Shoulder pain; Constipation

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 02/11/2008 - 02/17/2008
# 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 checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
	# 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 <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"/>

10. Concomitant medical products and therapy dates (excluded treatment of event)	
COLOXYL WITH SENNA	02/11/2008 - Cont
EMEND	03/11/2008 - 03/11/2008

(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
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 checked="" type="checkbox"/> company representative	
<input type="checkbox"/> distributor	
<input type="checkbox"/> other:	

4. Date received by manufacturer (mm/dd/yyyy) 01/16/2009	5. (A)NDA # IND # 58915
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6. If IND, protocol # 0560020	STN # PMA/ 510(k) #
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7. Type of report	Combination Product <input type="checkbox"/> Yes <input type="checkbox"/> No
<input type="checkbox"/> 5-day <input type="checkbox"/> 30-day	Pre-1938 <input type="checkbox"/> Yes <input type="checkbox"/> No
<input type="checkbox"/> 7-day <input type="checkbox"/> Periodic	OTC product <input type="checkbox"/> Yes <input type="checkbox"/> No
<input type="checkbox"/> 10-day <input type="checkbox"/> Initial	
<input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up# 14	

9 Mfr. report number WAES 0803USA03465

8. Adverse event term(s) NEUTROPENIA; PLEURAL EFFUSION; HYPOMAGNESAEMIA; HYPOKALAEMIA

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
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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**

placebo for the treatment of non-small cell lung cancer (diagnosed 13-NOV-2003; current staging 03-JAN-2008; primary tumor T4; nodal involvement NX; distant metastases M1; overall stage IV). Concomitant study therapy included carboplatin, AUC equivalent to 6 (450 mg), administered IV and paclitaxel, 200 mg/m² (246 mg), administered IV, both initiated on 15-FEB-2008. Other concomitant therapy included atorvastatin calcium (LIPITOR), acetaminophen, docusate sodium (+) senna (COLOXYL WITH SENNA), dexamethasone (manufacturer unknown), aprepitant (MSD), loratadine, ranitidine and tropisetron. On 06-MAR-2008 the patient experienced a cough (NSAE) that was not related to the study therapy.

On 11-MAR-2008, the patient began cycle 2 of study therapy with vorinostat, capsule 300 mg or placebo, carboplatin, AUC equivalent to 5 (375 mg), administered IV and paclitaxel, 175 mg/m² (217 mg), administered IV. On 18-MAR-2008 (Cycle 2 Day 8) the patient developed pleural effusion (grade 2), neutropenia (grade 4) (also reported as grade 3), hypomagnesemia (grade 2) and hypokalemia (grade 4) and was hospitalized. The patient had a 2 days history of shortness of breath, limited mobility and decreased appetite. On admission an EKG showed sinus rhythm tachycardia, right ventricular strain and non-specific T-wave changes, blood tests revealed electrolyte abnormalities (potassium was 2.4), the patient was afebrile with a temperature of 36.6 C. On 18-MAR-2008, computed axial tomography chest pulmonary angiography revealed left pleural effusion and no scan evidence of pulmonary embolism and chest x-ray revealed left pleural effusion. Neutrophil count was 0.1, potassium was 3.0 and blood cultures were negative for infection. Blinded study therapy was discontinued and the patient was placed on therapy with gentamicin and clavulanate potassium (+) ticarcillin disodium (TIMENTIN) to cover sepsis because the patient was neutropenic. The patient was also placed on therapy with IV potassium, potassium chloride (SLOW-K), potassium bicarbonate (+) sodium bicarbonate (+) sodium phosphate, monobasic (PHOSPHATE-SANDOZ), potassium bicarbonate (+) potassium chloride (CHLORVESENT), and magnesium aspartate (MAGMIN). On 19-MAR-2008, the pleural effusion was drained of 200 ml of pleural fluid and the patient was reported to be feeling less shortness of breath. An accurate cell count was unable to be performed as the specimen was clotted. The patient's BF protein was 34.0 g/L which indicated an exudate fluid protein. Cytology of pleural fluid was negative for malignant cells and pleural fluid culture had no growth. On 20-MAR-2008 the patient was placed on potassium bicarbonate (+) potassium chloride (CHLORVESENT) for a decrease in potassium. On 22-MAR-2008, antibiotics ceased and the patient recovered from hypokalemia (GRADE 4). On 22-MAR-2008 the patient's potassium was 3.8. White blood cell growth factors were not given. On 23-MAR-2008 absolute neutrophil count was normal and the patient recovered from neutropenia (grade 4). On 25-MAR-2008 the patient recovered from pleural effusion (grade 2) and the patient was discharged from the hospital. Discharge diagnoses were pleural effusion, neutropenia, hypomagnesemia and hypokalemia. On 30-MAR-2008, treatment therapy with magnesium aspartate (MAGMIN) was stopped. On 31-MAR-2008 and ECG was performed and showed sinus rhythm with non-specific T abnormality, left atrial abnormality, reversed arm leads, indeterminate axis, poor anterior R progression. On 31-MAR-2008, the patient recovered from hypomagnesemia. The patient returned to clinic for review on 31-MAR-2008 and neutropenia remained normal, potassium was 4.1, magnesium was 0.77. No clinical symptoms presented. The patient was not restarted on study therapy. At the time of the report, the patient's shortness of breath improved. The patient's cough persisted. On 31-MAR-2008 the patient discontinued study medication due to adverse event. The status for the study was completed.

The investigator felt that neutropenia (grade 4), hypomagnesemia (grade 2), and hypokalemia (grade 4) were related to blinded study therapy and pleural effusion (grade 2) was not related to blinded study therapy.

The investigator felt that pleural effusion (grade 2) was not related to carboplatin and paclitaxel.

The investigator felt that neutropenia (grade 4), hypomagnesemia (grade 2) and hypokalemia (grade 4) were related to carboplatin and paclitaxel.

The investigator felt that the cough (NSAE) was not related to blinded therapy or carboplatin and paclitaxel.

The patient was placed on the following medications during the study: enoxaparin sodium (CLEXANE) for prophylaxis for pulmonary embolism, blood transfusion for anemia, normal saline for dehydration, prochlorperazine maleate (STEMETIL) for nausea, and atropine sulfate (+) diphenoxylate hydrochloride (LOMOTIL) for diarrhea, KCL/potassium for hypokalemia, sandozphosphate for hypophosphatemia, and thiamine for malnourishment.

This is an amended report. The patient's BF protein was changed from 3.4g/L to 34 g/L.

Additional information is not expected.

This is a corrected report 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>
computed axial tomography Comment: L pleural effusion no scan evidence of pulmonary embolism	03/18/2008			
chest X-ray Comment: L pleural effusion	03/18/2008			
diagnostic laboratory test Comment: blood: electrolyte abnormalities	03/18/2008			
electrocardiogram	03/18/2008			
diagnostic pathological examination Comment: pleural fluid cytology- negative for malignant cells	03/19/2008			
white blood cell scan Comment: WBC growth factor not given	03/23/2008			
diagnostic laboratory test Comment: blood: returned to normal	03/23/2008			
electrocardiogram Comment: electrocardiogram T wave inversion sinus rhythm	03/31/2008			

LABORATORY RESULTS

<u>Tests</u>	<u>Date</u>	<u>Value</u>	<u>Unit</u>	<u>Normal Range</u>
body temp Comment: afebrile	03/??/2008	36.6		
neutrophil count	03/18/2008	0.1		
neutrophil count	03/18/2008	1	10x 10/L	2 - 7
serum magnesium	03/18/2008	65	mol/L	70 - 95
serum potassium	03/18/2008	2.4		
serum potassium	03/18/2008	3	mmol/L	3.5 - 5.0
blood culture Comment: negative for infection	03/18/2008			
serum magnesium	03/19/2008	50	mmol/L	70 - 95
serum potassium	03/19/2008	25	mol/L	35 - 50
pleural fluid culture Comment: no growth	03/19/2008			
serum magnesium	03/20/2008	51	mol/L	70 - 95
serum potassium	03/20/2008	27	mol/L	35 - 50
serum magnesium	03/21/2008	41	mol/L	70 - 95
serum magnesium	03/21/2008	43	mol/L	70 - 95
serum potassium	03/21/2008	23	mol/L	35 - 50
serum potassium	03/21/2008	46	mol/L	35 - 50
serum magnesium	03/22/2008	62	mol/L	70 - 95
serum potassium	03/22/2008	3.8		
absolute neutrophil count	03/23/2008	normal		
neutrophil count	03/23/2008	1	10x 9/L	2 - 7
serum magnesium	03/23/2008	57	mol/L	70 - 95
serum phosphorus	03/25/2008	0.70	mmol/L	
absolute neutrophil count	03/31?/2008	normal		
serum magnesium	03/31/2008	77	mmol/L	70 - 95
serum potassium	03/31/2008	4.1	mmol/L	
total serum protein Comment: BF Protein		34.0	g/dL	

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
- #2 carboplatin Unk
- #2 carboplatin Unk
- #3 paclitaxel Unk
- #3 paclitaxel Unk

2. Dose, frequency & route used

#1 Unk/Unk/PO
 #1 Unk/Unk/PO
 #1 Unk/Unk/PO
 #2 450 mg/1X/IV
 #2 375 mg/1X/IV
 #3 246 mg/1X/IV
 #3 217 mg/1X/IV

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

#1 02/19/2008 - 02/20/2008
 #1 02/22/2008 - 02/24/2008
 #1 03/11/2008 - 03/18/2008
 #2 02/15/2008 - 02/15/2008
 #2 03/11/2008 - 03/11/2008
 #3 02/15/2008 - 02/15/2008
 #3 03/11/2008 - 03/11/2008

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
 #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
#3				X
#3				X

6. Lot # (if known)

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

7. Exp date (if known)

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

8. Event reappeared after reintroduction

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

C. Suspect medication(s)

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

EMEND	03/12/2008 - Cont
LIPITOR	07/01/2007 - Cont
acetaminophen	12/01/2007 - Cont
dexamethasone	03/09/2008 - 03/09/2008
dexamethasone	03/10/2008 - 03/10/2008
dexamethasone	03/11/2008 - 03/11/2008
loratadine	03/11/2008 - 03/11/2008
ranitidine	03/11/2008 - 03/11/2008
tropisetron	03/11/2008 - 03/11/2008