

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 0802USA05927
UF/Dist report #	
FDA Use Only	

A. Patient information			
1. Patient identifier Confidential AN 59001 in confidence	2. Age at time of event: or 59 years Date of Birth: 06/21/1948	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 183 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) 02/06/2008		4. Date of this report (mm/dd/yyyy) 02/10/2009	
5. Describe event or problem			
This is in follow-up to report(s) previously submitted on 3/4/2008; 3/10/2008; 3/17/2008; 3/25/2008; 4/11/2008; 4/14/2008; 5/13/2008; 6/16/2008; 7/1/2008; 8/4/2008; 8/19/2008; 9/25/2008; 2/9/2009			
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)			
Information has been received from an investigator concerning a 59 year old Asian male on premedication prior to chemotherapy and pain relief, with diabetes mellitus and hypertension and a history of radiotherapy for a right lung mass 60 gy, right mediastinum 45 gy, and the right supraclavicular area 45 gy from 05-JUL-2007 to 27-SEP-2007) who entered a study, title as stated above. On 01-FEB-2008 the patient was placed on therapy with blinded therapy, capsule for the treatment of non-small cell lung cancer (dose not reported) (diagnosed			
(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: Radiotherapy CONCURRENT CONDITIONS: Diabetes mellitus; Hypertension; Pain			

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 02/01/2008 - 02/14/2008	
# 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 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)			
BENADRYL		02/05/2008-02/05/2008	
COMBIZAR		01/24/2008-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) 01/08/2009	3. Report source. (check all that apply)
6. If IND, protocol # 0560091	<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
7. Type of report	5. (A)NDA #
<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# 13	IND # 58915 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	9. Mfr. report number
WAES 0802USA05927	WAES 0802USA05927
8. Adverse event term(s)	
PERIPHERAL SENSORY NEUROPATHY; FATIGUE; PERIPHERAL SENSORY NEUROPATHY; CHRONIC OBSTRUCTIVE PULMONARY DISEASE; PERIPHERAL SENSORY NEUROPATHY; FATIGUE	

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.	
		yes 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**

10-JAN-2007; current staging IV, T2, N2, M1). Concomitant therapy included losartan potassium-HCTZ (COMBIZAR), metformin HCl (GLUCOPHAGE), glimepiride (NORIZEC), mefenamic acid, dexamethasone, diphenhydramine HCl (BENADRYL), ranitidine and ramosetron hydrochloride (NASEA). On 06-FEB-2008 the patient experienced sensory peripheral neuropathy (grade 2) (non-serious) and fatigue (grade 2) (non-serious), and recovered from both on 09-FEB-2008. On the 10-FEB-2008 day after paclitaxel and carboplatin was given, the patient developed sensory peripheral neuropathy (grade 3) and fatigue (grade 3) and was admitted to the hospital due to the persistence of symptoms. The patient was unable to walk without support. The patient was not able to report for work due to fatigue, and needed assistance to perform activities of daily living; no lab or diagnostic procedures were performed. Fatigue was not attributed to dehydration nor was there any significant decrease in blood count for the patient. He was advised to rest. Treatment for sensory peripheral neuropathy included gabapentin (NEURONTIN) and vitamin B complex. No prior symptoms of neuropathy related to the patient's diabetes mellitus was reported prior to chemotherapy. Symptoms were only apparent after the chemotherapy. No action was taken with study therapy. On 12-FEB-2008, the patient was discharged; the discharge diagnoses were peripheral neuropathy and generalized body weakness both secondary to paclitaxel. On 14-FEB-2008, Cycle 1 of blinded study therapy completed, and the patient had recovered from fatigue (grade 3), and was able to perform ADL's with minimal assistance. He was able to go back to work after a few days. On 19-FEB-2008, the patient developed the non-serious adverse event (NSAE) of neutropenia (grade 4). On 25-FEB-2008, the patient was considered to be recovered with sequelae from sensory peripheral neuropathy. On 26-FEB-2008, the patient was still recovering from peripheral neuropathy (decreased to grade 1), and a neutrophil count was normal.

Additional follow up information from the investigator reported that since peripheral neuropathy is a known side effect of paclitaxel, the dose was adjusted for Cycle 2. On 28-FEB-2008, peripheral neuropathy resolved. On 29-FEB-2008, Cycle 2 of blinded study therapy was initiated for days 1-14 (cycle of 3 weeks), capsule, 400 mg or placebo, with a one time dose of paclitaxel administered at 150mg/m², 285 mg, IV, and a one time dose of carboplatin, 6 AUC, 695 mg, IV. The patient continued to recover from the events. Cycle 2 of blinded therapy completed on 13-MAR-2008. On 24-MAR-2004, Cycle 3 of blinded study therapy, 400 mg capsule or placebo, was initiated; a one time dose of paclitaxel was administered at 150 mg/m², 280 mg, IV and a one time dose of carboplatin, 6 AUC, 600 mg, IV. Cycle 3 completed on 06-APR-2008.

The reporting investigator felt that fatigue (grade 2) (non serious) (onset 06-FEB-2008) and the sensory peripheral neuropathy (grade 2) (non serious) (onset 06-FEB-2008) were not related to blinded study therapy of vorinostat or placebo.

The reporting investigator felt that fatigue (grade 3) was related to blinded study therapy of vorinostat or placebo, carboplatin, and paclitaxel; the dose of paclitaxel was reduced for Cycle 2 of therapy. The reporting investigator felt that sensory peripheral neuropathy (grade 3) (onset 10-FEB-2008) was not related to blinded study therapy of vorinostat or placebo or carboplatin, but was related to paclitaxel.

The investigator considered the NSAE of neutropenia to be an event of clinical interest and felt the event was related to blinded study therapy; therefore, the dose of blinded therapy was reduced.

Follow up information from the investigator, indicated that on 17-APR-2008, Cycle 4 of blinded study therapy, capsule, 400 mg, or placebo, was initiated; a one time dose of paclitaxel was administered at 150 mg/m², 280 mg, IV and a one time dose of carboplatin, 6 AUC, 660 mg, IV.

On 21-APR-2008, the patient had a tingling sensation on both hands and feet, that interfered with his activities of daily living (ADLs) and was admitted to the hospital. His vital signs were stable, with clear breathsounds. A chest x-ray showed right bullous peripheral emphysematous changes and partial cicatricial atelectasis with fibrotic lesion. No infiltrates noted in the official reading. On 22-APR-2008, the patient had dizziness, which persisted until the following day; neurological findings were normal.

On 24-APR-2008, (cycle 4, day 8) a head CT was performed, indicating a lacunar infarct left corona radiata, cerebocerebellar atrophy, no change from previous. The patient had dyspnea with wheezes on physical exam, and was referred to a pulmonologist for dyspnea, cough with phlegm. He was diagnosed with chronic obstructive pulmonary disease (COPD) exacerbation (grade 2). His sensory neuropathy was then improved to grade 2. Other labs were unremarkable, except for hemoglobin of 10g/dL, potassium 4.7 U/L, serum alanine aminotransferase test 17 U/L, white blood count 6.92, neutrophil 77.2, lymphocyte 19.6, and eosinophil 1.7. No other laboratory tests (ie sputum "gs.cs" nor blood cultures) done. Other labs (creatinine, serum aspartate aminotransferase test (AST), and sodium) were unremarkable. Treatment included vitamin B complex, tramadol hydrochloride (TRAMADOLOR) and gabapentin for sensory neuropathy (grade 3), betahistine hydrochloride (SERC) for dizziness, azithromycin, PO, and ciprofloxacin IV for obstructive pneumonia, and hydrocortisone for chronic obstructive pulmonary disease (COPD).

On 25-APR-2008 the patient was much improved, with paresthesia, but not interfering with ADLs, with minimal wheezing and decreasing phlegm. He was discharged the same day. The discharge diagnoses were: non small cell lung cancer, rule out obstructive pneumonia; COPD in acute exacerbation, improved; sensory neuropathy secondary to adverse drug reaction (ADR) from paclitaxel/carboplatin. Therapy with blinded study therapy continued.

On 02-MAY-2008, at a clinic evaluation, the patient was much improved, with sensory neuropathy decreased to grade 1. He had occasional whitish phlegm production. The physical exam showed only occasional rhonchi at the right upper "LF." A repeat CBC results as follows: hemoglobin 99, white blood count 2.33, neutrophils 0.56, monocytes 0.68, and eosinophil 0.02. On 05-MAY-2008 the patient completed and discontinued study medication due to progressive disease.

This is a consolidation of two reports concerning the same patient.

The adverse event code has been changed from obstructive pneumonia (grade 2) to chronic obstructive pulmonary disease (COPD) exacerbation (grade 2).

The investigator felt that sensory peripheral neuropathy (grade 3) (onset 21-APR-2008) was not related to blinded study therapy of vorinostat or placebo or carboplatin, but was related to paclitaxel; and that chronic obstructive pulmonary disease (COPD) exacerbation (grade 2) was not related to study therapy, carboplatin or paclitaxel.

Additional information is not expected.

It has been determined that WAES# 0804USA04829 is a duplicate of WAES # 0802USA05927. Therefore, WAES # 0804USA04829 is being deleted from our files and the reports consolidated into WAES # 0802USA05927.

This report no longer meets the criteria for submission because the relationship to study therapy has been changed to not related.

This is a corrected report, as amended.

6. Relevant tests/laboratory data, including dates

DIAGNOSTIC TEST

Tests	Date	Value	Unit	Normal Range
chest X-ray	04/21/2008			
Comment: right bullous emphysematous changes, partial cicatricial atelectasis w/fibrotic lesion				
neurological examination	04/22/2008			
Comment: normal				
head computed axial tomography	04/24/2008			
Comment: lacunar infarct left corona radiata, cerebrocerebellar atrophy, no change from previous				
diagnostic laboratory test	04/24/2008			
Comment: creatinine, AST, ALT, sodium, potassium and CBC were unremarkable.				

LABORATORY RESULTS

Tests	Date	Value	Unit	Normal Range
neutrophil count	02/26/2008			
Comment: normal				
absolute neutrophil count	04/15/2008	3	g/l	1.96 - 7.23
complete blood cell count	04/21/2008	10	g/dl	
serum alanine aminotransferase	04/23/2008	17	U/L	
Comment: slightly decreased				
serum potassium	04/23/2008	4.7	mmol/L	
WBC count	04/24/2008	6.92		
eosinophil count	04/24/2008	1.7		
hemoglobin	04/24/2008	10	g/dL	12 -
lymphocyte count	04/24/2008	19.6		
monocyte count	04/24/2008	1.3		
neutrophil count	04/24/2008	77.2		
WBC count	05/02/2008	2.33		
eosinophil count	05/02/2008	0.02		
hemoglobin	05/02/2008	99		
lymphocyte count	05/02/2008	1.05		
monocyte count	05/02/2008	0.68		
neutrophil count	05/02/2008	0.56		

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 INJ carboplatin Unk
 #2 INJ carboplatin Unk
 #2 INJ carboplatin Unk
 #2 INJ carboplatin Unk
 #3 INJ paclitaxel Unk
 #3 INJ paclitaxel Unk
 #3 INJ paclitaxel Unk
 #3 INJ paclitaxel Unk

2. Dose, frequency & route used

#1 Unk/Unk/PO
 #1 Unk/Unk/PO
 #1 Unk/Unk/PO
 #2 695 mg/1X/IV
 #2 695 mg/1X/IV
 #2 660 mg/1X/IV
 #2 660 mg/1X/IV
 #3 360 mg/1X/IV
 #3 285 mg/1X/IV
 #3 280 mg/1X/IV
 #3 280 mg/1X/IV

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

#1 02/29/2008 - 03/13/2008
 #1 03/24/2008 - 04/06/2008
 #1 04/17/2008 - 04/30/2008
 #2 02/05/2008 - 02/05/2008
 #2 02/29/2008 - 02/29/2008
 #2 03/24/2008 - 03/24/2008
 #2 04/17/2008 - 04/17/2008
 #3 02/05/2008 - 02/05/2008
 #3 02/29/2008 - 02/29/2008
 #3 03/24/2008 - 03/24/2008
 #3 04/17/2008 - 04/17/2008

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
 #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	
#3			X	

6. Lot # (if known)

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

7. Exp date (if known)

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

C. Suspect medication(s)

10. Concomitant medical products and therapy dates (exclude treatment of event)	
GLUCOPHAGE	01/??/2007 - Cont
NASEA	02/05/2008 - 02/05/2008
NORIZEC	01/??/2007 - Cont
dexamethasone	02/04/2008 - 02/05/2008
mefenamic acid	01/??/2008 - Cont
ranitidine	02/05/2008 - 02/05/2008